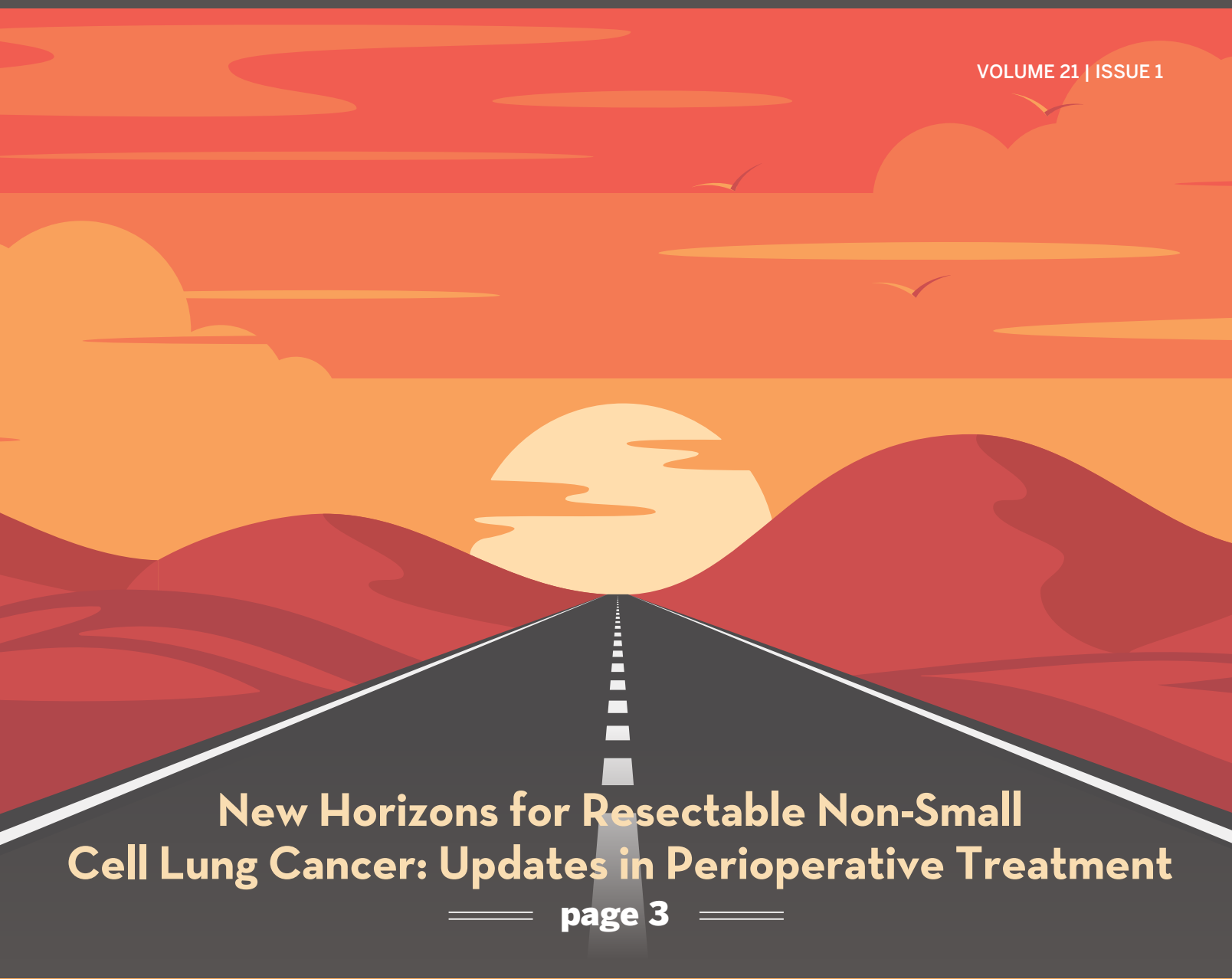
HOPA NEWS

Pharmacists Optimizing Cancer Care

VOLUME 21 | ISSUE 1



New Horizons for Resectable Non-Small Cell Lung Cancer: Updates in Perioperative Treatment

page 3

HOPA
Hematology/Oncology Pharmacy Association

VOLUME 21 | ISSUE 1

Send administrative correspondence or letters to the editor to HOPA, 555 East Wells Street, Suite 1100, Milwaukee, WI 53202, or e-mail info@hoparx.org.

HOPA News is published by the Hematology/Oncology Pharmacy Association.

HOPA
Hematology/Oncology Pharmacy Association

Pharmacists Optimizing Cancer Care®

CONTENTS

FEATURE

New Horizons for Resectable Non-Small Cell Lung Cancer: Updates in Perioperative Treatment

Jennifer Niccolai Martin, PharmD, BCOP
Hematology/Oncology Clinical Pharmacy Specialist
Allegheny Health Network Cancer Institute

Introduction

Lung cancer is the second most frequently diagnosed cancer and the leading cause of cancer death in the United States. Non-small cell lung cancer (NSCLC) is the most common type seen in the United States, accounting for 81% of all lung cancer diagnoses. In 2023, an estimated 238,240 new cases of lung and bronchial cancer will be diagnosed, and 127,070 deaths are estimated to occur because of the disease.[1,2] Although most are diagnosed at a metastatic or locally advanced stage, 25-30% are diagnosed at an early stage and may be eligible for resection.[3] New treatment options including immunotherapy and targeted therapy have drastically changed the landscape of advanced/metastatic NSCLC treatment, demonstrating improved survival rates and subsequently motivating expansion of these therapies to the perioperative setting.[4]

Historically, adjuvant platinum-based chemotherapy was the standard of care for patients with completely resected stage IB-IIIA NSCLC. The NCIC CTG JBR.10 trial and the ANITA trial compared adjuvant vinorelbine plus cisplatin versus observation. Both trials demonstrated prolonged overall survival (OS) and improved five-year survival rate with post-operative chemotherapy. The benefit was most observed in patients with stage II disease (JBR.10) and stage II-IIIA disease (ANITA), although no benefit was seen in stage I disease. These findings were further verified in the LACE meta-analysis published in 2008. The meta-analysis reported that postoperative cisplatin-based chemotherapy increased survival over 5 years with an absolute benefit of 5.4%.[1,5]

"The current expanding utilization of immunotherapy and targeted therapy to the neoadjuvant and adjuvant settings for resectable disease has shown promising outcomes in both safety and efficacy."

Neoadjuvant chemotherapy has historically been utilized to downstage stage III tumors with N2 involvement to obtain a resectable status. However, based on concerns about delaying surgery and lack of prospective data to support the use of preoperative systemic therapy, adjuvant chemotherapy has remained the standard.[1]

Until recently, advancements in early-stage lung cancer treatment were limited, with adjuvant platinum doublet chemotherapy remaining the mainstay of systemic therapy. The current expanding utilization of immunotherapy and targeted therapy to the neoadjuvant and adjuvant settings for resectable disease has shown promising outcomes in both safety and efficacy. Additionally, advancements in resectable NSCLC include integration of biomarker testing in the latest updates of clinical guidelines to determine eligibility for immunotherapy and targeted therapy. In the 2023 update, the National Comprehensive Cancer Network (NCCN) has expanded molecular testing criteria to include anaplastic lymphoma kinase (*ALK)* rearrangements, programmed death-ligand 1 (PD-L1) status, and epidermal growth factor receptor *(EGFR)* mutations for stages IB to IIIA or IIIB NSCLC (T3,N2).[1] Currently five targeted therapy- or immunotherapy-containing treatment options are United States Food and Drug Administration (FDA) approved for perioperative treatment of resectable NSCLC and are summarized in Table 1.

Adjuvant Targeted Therapy

The introduction of EGFR tyrosine kinase inhibitors (TKIs) in 2004 was a major development in the treatment of advanced and metastatic NSCLC and significantly improved survival of patients with sensitizing *EGFR* mutations (exon 19 deletions or L858 point mutations). The evaluation of these agents in early-stage NSCLC was a logical strategy when introducing precision medicine to curative intent treatment. ADAURA was an international, multicenter, phase III, double-blind, randomized controlled clinical study, evaluating osimertinib in patients with *EGFR*-sensitizing mutation-positive non-squamous NSCLC after complete tumor resection. Patients were randomized 1:1 to receive osimertinib 80 mg once daily or placebo for 3 years with a primary endpoint of disease-free survival (DFS).[4] At data cutoff, the 4-year DFS rate was 73% (osimertinib) and 38% (placebo) (hazard ratio [HR] 0.27, 95% confidence interval [CI] 0.21-0.34) in individuals with stage IB-IIIA disease.[6] The final analysis of OS (secondary endpoint) published in July 2023 demonstrated 5-year OS of 88% in the osimertinib group and 78% in the placebo group (HR 0.49, 95.03% CI 0.34-0.70, p<0.001).[7] Adjuvant osimertinib for a duration of 3 years was approved in 2021 and is recommended for *EGFR*-sensitizing mutation-positive stage IB-IIIA patients with NSCLC.[4]

ALK-positive NSCLC accounts for about 3-7% of cases, and targeted therapy provides a survival benefit in the metastatic setting. The efficacy of adjuvant alectinib, a highly selective, second-generation ALK inhibitor, was compared to adjuvant platinum-based chemotherapy in the phase III ALINA trial. Patients with completely resected, stage IB to IIIA *ALK*-positive NSCLC received alectinib 600 mg twice daily for 24 months or platinum-containing chemotherapy for four cycles. The primary endpoint was DFS, and secondary endpoints included OS and safety. The interim analysis presented at the European Society for

Table 1. Clinical trial efficacy data of the FDA-approved perioperative NSCLC regimens

Treatment	Therapy Setting	N	Median follow-up (months)	DFS Median (months)[a]	EFS Median (months)[a]	pCR (%)	HR (95% CI); p-value[a]
Osimertinib vs. placebo for 3 years following resection[4]	Adjuvant	682	44.2 osimertinib and 19.6 placebo	4 year: 73% with osimertinib vs. 38% with placebo	N/A	N/A	0.27; (0.21-0.34)
Atezolizumab every 3 weeks for 16 cycles or BSC following resection and CT[11]	Adjuvant	1005	32.2	NR with atezolizumab vs. 35.3 with BSC in PD-L1+ stage II-IIIA[b]	N/A	N/A	0.66 (0.50-0.88); 0.0039 in PD-L1+ stage II-IIIA[b]
Pembrolizumab every 3 weeks for 18 cycles following resection and CT[12]	Adjuvant	1177	35.6	56.6 with pembrolizumab vs. 42.0 with placebo	N/A	N/A	0.76 (0.63-0.91); 0.0014
Neoadjuvant nivolumab + CT for 3 cycles[14]	Neoadjuvant	358	29.5	N/A	31.6 with nivolumab + CT vs. 20.8 with CT alone	24.0% with nivolumab + CT vs. 2.2% with CT alone	EFS: 0.63 (97.38% CI, 0.43-0.91); 0.005 pCR: OR, 13.94 (99% CI, 3.49-55.75); 0.001
Pembrolizumab or placebo with CT for 4 cycles followed by surgery and pembrolizumab or placebo every 3 weeks for 13 cycles[16]	Perioperative	797	25.2	N/A	NR with pembrolizumab vs. 17.0 with placebo	18.1% with pembrolizumab vs. 4% with placebo	EFS: 0.58 (0.46 -0.72); <0.001 pCR: (95%CI 10.1-18.7); <0.0001

Legend
[a] Unless otherwise specified.
[b] FDA approved for patients with PD-L1 expression ≥ 1% and II-IIIA stage NSCLC
BSC best supportive care, *CT* chemotherapy, *DFS* disease-free survival, *EFS* event-free survival, *pCR* pathologic complete response, *NR* not reached, *OR* odds ratio, *PD-L1* programmed death-ligand 1

Medical Oncology (ESMO) Congress 2023 revealed a significant DFS benefit with alectinib as compared with platinum-based chemotherapy with favorable results for alectinib seen in both stage II-IIIA population (HR 0.24, 95% CI 0.13-0.45; p<0.0001) and the stage IB–IIIA intention-to-treat (ITT) population (HR 0.24, 95% CI 0.13-0.43; p<0.0001). Two-year DFS rates with alectinib and chemotherapy were 93.8% versus 63.0%, respectively, in the stage II–IIIA population and 93.6% versus 63.7%, respectively, in the ITT population. Grade 3–4 adverse events (AEs) were reported in 30% of patients receiving alectinib and 31% receiving chemotherapy.[8]

For individuals who are eligible for adjuvant targeted therapy, practitioners may reevaluate the need of cytotoxic chemotherapy. The ADAURA study allowed the option of sequential osimertinib after adjuvant chemotherapy, and there was no difference in terms of the 24-month DFS rate between patients who received adjuvant chemotherapy (55%) and those who did not (45%). Most patients with stage II to IIIA disease and approximately a quarter of patients with stage IB disease received adjuvant chemotherapy. Of patients who received adjuvant chemotherapy, 89% who received osimertinib and 49% who received placebo were alive and disease free at 24 months (HR 0.16); of the patients who did not receive adjuvant chemotherapy the percentages were 89% and 58% respectively (HR 0.23).[4,5]

Another question that arises from the use of targeted therapy in early-stage disease is the limited systemic options in the event of disease recurrence. Sparse data exist to support repeating targeted therapies within the same drug class for treatment of disease recurrence following adjuvant therapy.[5] The ADAURA trial reported that 33% of individuals in the osimertinib arm and 39% in the placebo arm received osimertinib as subsequent therapy for relapsed disease. The low rate of treatment with osimertinib at relapse was likely due to drug availability and consequently limited the evaluation of response and survival outcomes.[9] The ADJUVANT study evaluated adjuvant gefitinib in comparison with adjuvant cisplatin and vinorelbine (VP) for patients with *EGFR*-sensitizing mutations and collected subsequent therapy data for post hoc analysis. Study investigators found that 36.8% of patients in the gefitinib arm received subsequent EGFR-TKI, with a response rate of 46.4% and disease control rate of 82.1%, and 51.5% of patients in the VP arm received subsequent EGFR-TKI with a response rate of 22.9% and disease control rate of 65.8%. These findings indicate that NSCLC with an EGFR-sensitizing mutation maintains sensitivity to EGFR-TKIs at re-treatment.[10] Similar uncertainties remain

as to how to treat patients with resected *ALK*-positive NSCLC who relapse following adjuvant alectinib.

Adjuvant Immunotherapy

In recent years, neoadjuvant- and adjuvant-immunotherapy-containing regimens have gradually been adopted in early-stage NSCLC, with encouraging short- and long-term outcomes. The IMPOWER010 trial enrolled patients with stage IB (tumors ≥4 cm) to stage IIIA NSCLC to be randomized 1:1 to receive atezolizumab 1200 mg IV every 3 weeks for 16 cycles or best supportive care (BSC) following resection and cisplatin-based adjuvant chemotherapy. The primary endpoint, investigator-assessed DFS, was tested hierarchically: first, in the stage II–IIIA population subgroup whose tumors expressed PD-L1 on 1% or more of tumor cells; then, all patients in the stage II–IIIA population; and finally, ITT population (stage IB–IIIA). After a median follow-up of 32.2 months, atezolizumab treatment improved DFS compared with BSC for patients in the stage II–IIIA population whose tumors expressed PD-L1 on 1% or more of tumor cells (HR 0.66, 95% CI 0.50-0.88; p=0.0039) and in all patients in the stage II–IIIA population (HR 0.79, 95% CI 0.64-0.96; p=0.020). In the ITT population, the HR for DFS was 0.81 (95% CI 0.67-0.99; p=0.040) and did not cross the significance boundary. Atezolizumab is currently recommended in patients with II–IIIA stage NSCLC and PD-L1 expression ≥1% after complete resection and platinum-based chemotherapy.[11]

KEYNOTE-091 was a randomized, phase 3 trial evaluating pembrolizumab compared to placebo for the adjuvant treatment of patients with stage IB (tumor ≥ 4 cm) to IIIA NSCLC following resection and adjuvant chemotherapy. The primary outcomes were DFS in the overall population and in those whose tumors expressed PD-L1 (tumor proportion score [TPS] ≥50%). The median DFS in the overall population was 53.6 months for pembrolizumab versus 42.0 months for placebo. Adjuvant pembrolizumab significantly improved DFS (HR 0.76, 95% CI 0.63-0.91; p=0.0014) in patients with stage IB (≥4 cm) to IIIA NSCLC following surgical resection regardless of PD-L1 expression. The DFS difference in those with high PD-L1 expression (TPS ≥50%) did not reach statistical significance. Pembrolizumab was approved on January 26, 2023 for the adjuvant treatment, following resection and platinum-based chemotherapy, of stage IB, II, or IIIA NSCLC based on the results of KEYNOTE-091.[12]

Neoadjuvant and Perioperative Immunotherapy

Neoadjuvant systemic therapy for patients with early-stage NSCLC may allow for expeditious treatment of micrometastatic disease and the potential for downstaging tumors to improve surgical outcomes. Potential barriers to neoadjuvant therapy may include delays in local therapy and progression if disease is resistant to the systemic regimen. Patients with stage IB to IIIA NSCLC should be evaluated for preoperative systemic therapy and selected judiciously. According to current NCCN guidelines, neoadjuvant chemoimmunotherapy is the preferred recommendation for patients with stage IIIA disease without *ALK* or *EGFR* alterations.[1,13]

The phase III CheckMate 816 trial compared three cycles of neoadjuvant nivolumab plus platinum-doublet chemotherapy with chemotherapy alone. The primary endpoints were pathological complete response (pCR) and event-free survival (EFS), each assessed in the ITT population. Pathological CR was defined as no residual cancer cells in the resected primary tumor and lymph nodes. The median EFS was 31.6 months with nivolumab plus chemotherapy and 20.8 months with chemotherapy alone (HR 0.63, 97.38% CI 0.43-0.91; p=0.005). The percentage of patients with a pCR was 24.0% and 2.2%, respectively (OR, 13.94, 99% CI, 3.49-55.75; p<0.001). A benefit with nivolumab plus chemotherapy was seen across PD-L1 expression subgroups, with a greater EFS benefit in patients with a tumor PD-L1 expression level of ≥1%. However, these exploratory analysis subgroups were small, and analyses were not adequately statistically powered. The addition of nivolumab to chemotherapy did not result in more frequent delays or cancellations of surgery. Based on the results of CheckMate 816, neoadjuvant nivolumab with platinum doublet chemotherapy was approved for early-stage NSCLC in March 2022.[14]

Perioperative immunotherapy was introduced with the KEYNOTE-671 trial, which offered the opportunity for post-operative maintenance immunotherapy. Perioperative pembrolizumab was evaluated in a randomized, double-blind, phase 3 trial in patients with resectable II, IIIA, or IIIB (N2) NSCLC. Patients were randomized 1:1 to receive pembrolizumab or placebo with cisplatin-based chemotherapy for 4 cycles, followed by surgery and adjuvant pembrolizumab or placebo once every 3 weeks for up to 13 cycles. The primary endpoints were EFS and OS and secondary endpoints included major pathological response (≤10% viable tumor cells in resected primary tumor and lymph nodes), pCR, and safety. At the prespecified first interim analysis, the median follow-up was 25.2 months. EFS at 24 months was 62.4% in the pembrolizumab group and 40.6% in the placebo group (HR 0.58, 95% CI 0.46-0.72; p<0.001). The estimated 24-month overall survival was 80.9% in the pembrolizumab group and 77.6% in the placebo group (p=0.02, which did not meet the significance criterion). A major pathological response occurred in 30.2% of the participants in the pembrolizumab group and in 11.0% of those in the placebo group (95% CI 13.9-24.7; p<0.0001; threshold, p=0.0001), and a pCR occurred in 18.1% and 4.0%, respectively (95% CI 10.1-18.7; p<0.0001; threshold, p=0.0001). At this analysis, addition of perioperative pembrolizumab significantly improved EFS, major pathological response, and pCR as compared to neoadjuvant chemotherapy alone. Overall survival at this analysis did not differ significantly.[15] However, an updated analysis reported at the ESMO Congress 2023 showed statistically improved overall survival in the pembrolizumab arm (HR 0.72, 95% CI 0.56-0.93).[16] Pembrolizumab was approved in combination with platinum-containing chemotherapy as neoadjuvant treatment and with continuation of single-agent pembrolizumab as post-surgical adjuvant treatment for resectable (tumors ≥4 cm or node positive) NSCLC on October 16, 2023.

Two current studies of immunotherapy-containing perioperative regimens have reported interim results, and additional treatment options may be on the horizon. AEGEAN is a clinical trial evaluating

perioperative durvalumab in patients with stage II to IIIB (N2) NSCLC. In this trial, 802 patients were randomized to receive platinum-based chemotherapy plus durvalumab or placebo administered every 3 weeks for 4 cycles before surgery, followed by adjuvant durvalumab or placebo every 4 weeks for 12 cycles. Randomization was stratified according to disease stage (II or III) and PD-L1 expression (≥1% or <1%). Primary endpoints were EFS and pCR. The duration of EFS was significantly longer with durvalumab than with placebo; the stratified hazard ratio for disease progression, recurrence, or death was 0.68 (95%CI, 0.53-0.88; p=0.004) at the first interim analysis. At the 12-month landmark analysis, EFS was observed in 73.4% of the patients who received durvalumab as compared with 64.5% of the patients who received placebo. The incidence of pCR was significantly greater with durvalumab than with placebo (17.2% vs. 4.3% at the final analysis; difference, 13.0 percentage points; 95% CI, 8.7-17.6; p<0.001 at interim analysis of data from 402 patients). EFS and pCR benefit were observed regardless of stage and PD-L1 expression.[17] CheckMate 77T was presented at ESMO Congress 2023 with statistically significant and clinically meaningful EFS benefit for neoadjuvant nivolumab plus chemotherapy followed by surgery and adjuvant nivolumab for one year.[18]

Discussion

Recent FDA approvals and pending results from promising phase III studies are changing the landscape of early-stage NSCLC treatment outcomes, pushing beyond the humble 5-year absolute OS benefit of 5.4% per the LACE meta-analysis evaluating adjuvant cisplatin-based chemotherapy. Recent strategies, including molecular testing and incorporation of immunotherapy and targeted therapy, suggest improved outcomes for resectable NSCLC. Definitive answers regarding sequencing and duration of therapy are unclear. Understanding the data supporting these regimens and carefully identifying eligible patients is particularly critical as new options continue to emerge. The treatment selection is straightforward for patients eligible for targeted therapy (sensitizing *EGFR* mutations, *ALK*-positive), although adjuvant alectinib has not yet been FDA approved. The necessity and sequencing of adjuvant chemotherapy prior to targeted therapy deserves further evaluation. Inclusion of immunotherapy creates several opportunities for perioperative therapy. Both atezolizumab and pembrolizumab are approved for adjuvant NSCLC. Unlike adjuvant atezolizumab, pembrolizumab is approved for earlier-stage (stage IB) disease and is available to all patients regardless of PD-L1 expression. Treatment options exist for neoadjuvant nivolumab and chemotherapy or neoadjuvant pembrolizumab and chemotherapy with the option of adjuvant pembrolizumab following surgery. However, patients may not be eligible for immunotherapy if they have current or previously documented autoimmune diseases or current use of immunosuppressive agents. Certain oncogenic drivers (ie, *EGFR* exon 19 deletion or exon 21 L858R, *ALK* rearrangements) have been shown to derive less benefit from PD-1/PD-L1 inhibitors.[1]

Importantly, these recent approvals are based on surrogate endpoints and survival data is promising but remains immature. Currently, DFS or EFS, if significant, will have to serve as an OS surrogate until further follow-up of endpoints or new surrogate endpoints for OS are validated.[19,20] Additional areas of research may aid in patient selection by better predicting risk of recurrence. Presence of a postoperative circulating tumor DNA (ctDNA)-positive status is prognostic for a greater risk of disease recurrence or death. This biomarker has emerged as potentially useful for screening, diagnosis, treatment selection, postoperative minimal residual disease detection, response, and relapse. Minimal residual disease (MRD) may become part of clinical practice in predicting and monitoring the therapeutic effects of the NSCLC treatment to maximize immunotherapy efficacy and patient selection for adjuvant therapy.[5]

Conclusion

Pharmacists play a key role in identifying which patients may benefit from perioperative systemic therapy and regimen selection. By evaluating disease stage, presence of oncogenic driver mutations, and contraindications to immunotherapy, pharmacists can provide essential information needed at crucial decision points. Survival data and validation of surrogate endpoints from current studies will also improve the ability to utilize these treatments with confidence. ●●

REFERENCES

1. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer (Version 5.2023). https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed December 1, 2023.
2. Lung Cancer - Non-Small Cell - Statistics. Cancer.net. Published June 25, 2012. https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/statistics#:~:text=NSCLC%20is%20the%20most%20common%20type%20of%20lung. Accessed December 1, 2023.
3. Le Chevalier T. Adjuvant chemotherapy for resectable non-small-cell lung cancer: where is it going? Ann Oncol. 2010;21(Suppl 7):vii196–198.
4. Wu YL, Tsuboi M, He J, et al. Osimertinib in resected EGFR-mutated non–small cell lung cancer. N Engl J Med. 2020;383:1711-1723.
5. Duan J, Tan F, Bi N, et al. Expert consensus on perioperative treatment for non-small cell lung cancer. Transl Lung Cancer Res. 2022;11(7):1247-1267.
6. Herbst RS, Wu YL, John T, et al. Adjuvant osimertinib for resected EGFR-mutated stage IB-IIIA non-small-cell lung cancer: updated results from the phase III randomized ADAURA trial. J Clin Oncol. 2023;4(10):1830-1840.
7. Tsuboi M, Herbst RS, John T, et al. Overall survival with osimertinib in resected EGFR-mutated NSCLC. N Engl J Med. 2023;389:137-147.
8. Solomon BJ, Ahn JS, Barlesi F, et al. ALINA: A phase III study of alectinib versus chemotherapy as adjuvant therapy in patients with stage IB–IIIA anaplastic lymphoma kinase-positive (ALK+) non-small cell lung cancer (NSCLC). J Clin Oncol. 2019;37(15_suppl):TPS8569-TPS8569.
9. West H, Pennell NA. Lessons from ADAURA: Can we improve on a positive trial? Cancer. Published online ahead of print November 14, 2023.
10. Zhong WZ, Wang Q, Mao WM, et al. Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II-IIIA (N1-N2) EGFR-mutant NSCLC: final overall survival analysis of CTONG1104 phase III trial. J Clin Oncol. 2021;39(7):713-722.

11. Felip E, Altorki N, Zhou C, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. Lancet. 2021;398(10308):1344-1357.
12. O'Brient M, Paz-Ares L, Marreaud S, et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB–IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. Lancet Oncol. 2022;23(10): P1274-1286.
13. Chaft JE, Shyr Y, Sepesi B, Forde PM. Preoperative and postoperative systemic therapy for operable non-small-cell lung cancer. J Clin Oncol. 2022;40(6):546-555.
14. Forde PM, Spicer J, Lu S, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. N Eng J Med. 2022;386:1975-1985.
15. Wakelee H, Liberman M, Kato T, et al. Perioperative pembrolizumab for early-stage non–small-cell lung cancer. N Engl J Med. 2023;389:491-503.
16. ESMO 2023 update – KEYNOTE-671. The Cancer News. Published October 24, 2023. https://thecancernews.org/esmo-2023-update-keynote-671/?gclid=EAIaIQobChMIr7DN4ueZgwMVw1FyCh30ig9yEAAYASAAEgLoYvD_BwE. Accessed December 18, 2023
17. Heymach JV, Harpole DH, Mitsudomi T, et al. Perioperative durvalumab for resectable non–small-cell lung cancer. N Engl J Med. 2023;389:1672-1684.
18. Cascone T, Awad MM, Spicer JD, et al. LBA1 CheckMate 77T: Phase III study comparing neoadjuvant nivolumab (NIVO) plus chemotherapy (chemo) vs neoadjuvant placebo plus chemo followed by surgery and adjuvant NIVO or placebo for previously untreated, resectable stage II–IIIb NSCLC. Ann Oncol. 2023;34:S1295-S1295.
19. Cameron RB, Hines J, Torri V, et al. What is the ideal endpoint in early-stage immunotherapy neoadjuvant trials in lung cancer? Ther Adv Med Oncol. 2023;15: 17588359231198446.
20. Zhao F. Surrogate end points and their validation in oncology clinical trials. J Clin Oncol. 2016;34(13):1436-1437.

Reflection on Personal Impact and Growth

Then and Now

Karen M. Fancher, PharmD, BCOP
Associate Professor of Pharmacy Practice, Duquesne University School of Pharmacy
Clinical Pharmacy Specialist - Oncology, University of Pittsburgh Medical Center Passavant

I completed my residencies in 1999-2001. As I approach 25 years as a practicing pharmacist, I'm honored to share some thoughts I had then alongside some thoughts I have now.

Then: The pockets of my lab coat have ripped again. I shouldn't be surprised, because I have to cram my paperback copy of Lexi-Drugs, my solar-powered calculator, and all the index cards with my notes in there every day. My feet already hurt from the "cute shoes" I decided to wear today, even though I know I will be standing for the next four hours on rounds. I hope that I'm ready and sound confident when the attending physician asks for my recommendation in front of the whole team. I only had to say "I don't know" a few times yesterday – maybe I'm making progress.

Now: I'm not sure where my lab coat is these days since I only wear it when it gets cold in my office. I grab my iPad and my travel coffee mug and I'm ready for rounds to begin. I catch a glimpse of my reflection in a window, and I sigh when I see that I'm overdue to color my graying hair AGAIN. I patiently explain the appropriate dosing of rasburicase to the brand-new fellow while I simultaneously verify orders and answer messages on Teams. I politely but firmly argue with the attending when I disagree with the proposed plan. I add the following to my to-do list: re-read that lymphoma trial, check if we have enough methylene blue, and look up that new "flozin" drug.

"I hope that I eased her mind, even if for only a few moments."

Then: My preceptor says that I'm ready to counsel a patient by myself. I'm not sure that I agree. My heart is racing, and my hands are shaking. What if I don't remember to say everything I'm supposed to? The patient is much older than I am, and he can see that although I can relay the information, I don't really *know* what I'm talking about. I rationally answer all his questions, and I formally shake his hand as I leave. I hope that I eased his mind, even if for only a few moments.

Now: I have a whole entourage with me today: three APPE students, a PGY2 oncology resident, and a PY1 student who asked to shadow me. I'm about to counsel a patient with breast cancer. She's my own age and we have met several times before – I have shared with her that I, too, had breast cancer a few years ago. We breeze through my standard questions and she's kind to my learners, but today I sense something else from her. I ask the students to step out of the room, and when we are alone, she shyly asks me what sort of reconstructive surgery I had. We deliberate the finer points of silicone implants, and we hug before I head off to my next patient. I hope that I eased her mind, even if for only a few moments.

Then: I'm giving my first inservice to the pharmacy department tomorrow. There might be seven people there! I hope I'm prepared – I've spent many hours in the library researching my topic, and I have diligently typed out all my notes on the one and only desktop computer that all the residents share. I still need to make a few more copies of my handout, so I need to remember to bring change for the Xerox machine in the morning. I hope that I will sound professional and knowledgeable. I won't sleep well tonight because I'm really nervous and I want everything to go well.

Now: I'm presenting another webinar for Pharmacy Times tomorrow evening. They tell me there are already over 700 people registered! I know the data cold and don't need any notes. The moving graphics on the screen are very impressive and will add a lot to my presentation. We've practiced with the audience response questions that are embedded in the slides; I just need to remember which icon to click as I'm talking. I hope that I will sound conversational and approachable. I won't sleep well tonight because I'm a little nervous and I want everything to go well.

Then: I stop at the grocery store on my way home from work. Thank goodness I live alone, because I'm broke and my pantry is completely bare! My pager goes off as I am deciding what cereal to

Reflection on Personal Impact and Growth

eat for dinner. The pager only shows the number that I need to call back, so I abandon my half-full cart to go find a pay phone. I make a call to the pharmacy department to get a patient's tacrolimus level, then call my preceptor to review my plan, then page the medical resident with my recommendation. When I finally head back into the store 45 minutes later, my cart is long gone. I start my shopping over. I throw a pint of ice cream in my cart because it's been a long day and I deserve it.

Now: I stop at the grocery store on my way home from work. My son is now over six feet tall and he eats every meal like it's his last, so I'd better get the industrial size of everything. And my daughter will be home from college this weekend, so I want to cook all her favorites. My watch buzzes with a message about a patient's platelet level. I voice text "Decrease to 2 BID" and the attending replies with a thumbs-up emoji. I throw a pint of ice cream in my cart because it's been a long day and I deserve it.

Then: I really need to talk to Mike, my mentor. I'm still so unsure as to what the next step in my career should be. I want to hash out the pros and cons of each of my options. I don't know how to start my cover letter and I should ask him to review my CV… again. I'm not confident that I am ready for any of this. This is all so daunting, but Mike has everything figured out! He will help me navigate my path. I'm so lucky to have people to ask for help and advice.

Now: Four of my APPE students have asked me to proofread their letters of intent, and I'm participating in a CV workshop for PY3 students this afternoon. My favorite former resident wants to have coffee to discuss a possible move into industry, and I just agreed to review a colleague's materials for her promotion to Associate Professor. Exactly when did I become the adult in the room? My application to the HOPAmbassador program was accepted, and the first training session is next week. And I need to RSVP for Mike's retirement party.

Then and Now:

I get into my car at the end of another week. The sun is setting as I say a short prayer for all the patients and students that have touched my heart. I'm exhausted, but I thank the cosmos for leading me to a job I love, and where my work hopefully makes some small difference. I am at peace that I am exactly where I am meant to be. I turn the car stereo up loud, and sing along with Sting as I drive towards whatever lies ahead. ●●

Impact of the Inflation Reduction Act on Medicare Part D Out-Of-Pocket Costs for Oral Cancer Therapies

Matthew Smith, PharmD, CSP
Pharmacist, Mayo Clinic Specialty Pharmacy
Instructor in Pharmacy, Mayo Clinic College of Medicine

Introduction

"Medicare will make my 'chemo' prescriptions cheaper for me now, right?" As with many questions related to oral cancer therapies these days, my initial answer is, "It depends."

Much has been written about the need for legislative change to address uncapped out-of-pocket (OOP) prescription costs and associated financial toxicity for Medicare Part D patients. Provisions in the Inflation Reduction Act (IRA) of 2022 attempt to address these concerns and reduce medication costs for Medicare itself. However, it is also aimed to promote clean energy and raise government revenue through increased IRS funding and corporate taxes.

The IRA redesigns the Medicare Part D cost structure for all stakeholders, with the potential to dramatically alter the landscape for Medicare patients in need of oral cancer medications and other expensive prescriptions by capping patient annual OOP costs. In the near term, a government report estimates that beginning in 2025, the IRA will reduce patient OOP expenses by $7.4 billion dollars annually, impacting 18.7 million enrollees.[1]

"The IRA will make two major changes visibly benefiting many of our patients: (1) it removes the 5% catastrophic phase coinsurance in 2024 and (2) it reduces the MOOP to $2,000 in 2025."

Many variables determine how much an individual patient pays OOP, including the specific Medicare plan(s), medication, dose/dosage form, diagnosis code, Medicare Part B vs. Part D coverage, preferred pharmacy status, and the patient's mix of other brand/generic prescriptions sequenced over various coverage phases throughout the calendar year. Additionally, patient financial documentation is needed to assess eligibility for independent foundation grants, manufacturer patient assistance programs (PAP), or even Medicare "Extra Help" (aka Low-Income Subsidy [LIS]).

With multiple changes and a phased implementation, the full effects of the IRA on medication costs won't be seen for years. As such, the answer to our patient's question may change over time as well.

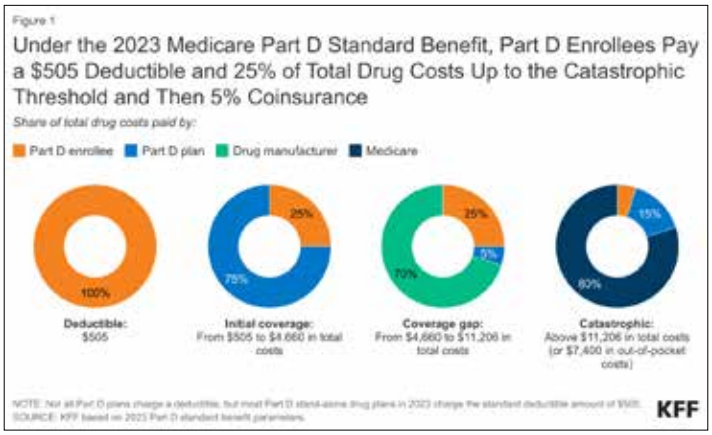
Medicare Part D

Medicare Part D prescription coverage first became available January 1, 2006, authorized under the Medicare Prescription Drug, Improvement, and Modernization Act of 2003.[2] Medicare Part D plans are provided through private companies contracted with Medicare, and sold as either stand-alone Prescription Drug Plans (PDPs) for patients with Medicare Part A/B, or as bundled Medicare Advantage Plans (aka Medicare Part C) usually with a Medicare Advantage Prescription Drug plan (MA-PD), which combine hospital, medical, and prescription coverage.

All Medicare Part D plans are required to at least meet the coverage of the standard plan design, but plan sponsors can add enhanced benefits, alter plan design and copay structure, and use formularies and utilization management strategies to differentiate plan offerings. Premiums for PDPs and MA-PDs vary significantly, with many patients choosing to enroll in plans with enhancements.[3] LIS also alters coverage, with $11.20 or less copays (in 2024) for those with both very low income and limited assets.[2]

The standard benefit design from 2006 through 2023 had no patient maximum OOP (MOOP) and included 4 phases: Deductible, Initial Coverage, Coverage Gap (Donut Hole), and Catastrophic (Figure 1).[4] Patients pay 100% of the Deductible, followed by 25% in the Initial phase. The Affordable Care Act of 2010 instituted the Coverage Gap Discount Program for brand products and gradually "closed the Donut Hole" between 2011 and 2020, reducing the Coverage Gap OOP to 25%.[5-7] After reaching the annual True Out-Of-Pocket (TrOOP) spending threshold, patients pay 5% in the Catastrophic phase. The dollar amounts needed to hit each stage have increased dramatically since inception.[8-9]

Figure 1[4]



Brands vs. Generics in the Coverage Gap:
The Coverage Gap Discount Program requires brand name manufacturers to pay 70% of the medication cost in the Coverage Gap. Generics differ from Figure 1 as the manufacturer pays nothing, with the plan responsible for 75% instead of 5%. Patients pay 25% for brands or generics, but manufacturer payments also get credited toward TrOOP. In other words, for every $100 in coverage gap claims, patients pay $25 in actual OOP and get TrOOP credit for $95 for a brand, but $25 for generic. This pushes patients through the Coverage Gap faster with brands, and paradoxically results in larger total Coverage Gap patient OOP responsibility for generics. The IRA removes this counterintuitive affordability barrier in 2025.

Medicare D – Cancer Therapies:
The extreme cost of most brand oral cancer therapies causes many patients to hit all 4 coverage phases in the first month. In 2023, that meant at least $3,000 OOP month one, followed by an uncapped ~$500 to $1,500+ per month Catastrophic phase coinsurance. The resulting patient OOP responsibility for one calendar year could commonly range from $10,000 to $20,000+.

The IRA will make two major changes visibly benefiting many of our patients: (1) it removes the 5% catastrophic phase coinsurance in 2024 and (2) it reduces the MOOP to $2,000 in 2025. Additional important changes are included below.

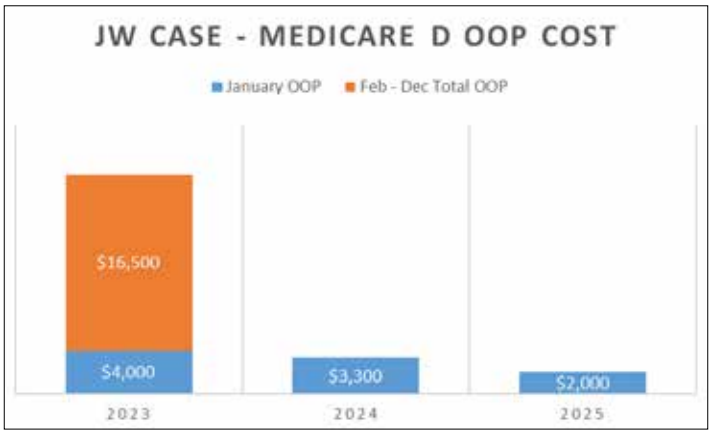
Key Changes from IRA[4,10-13]

2023	2024	2025	2026 and beyond
• $35 copay cap on covered insulins • $0 copay on covered vaccines • Penalties for manufacturers increasing prices faster than inflation	• Elimination of 5% Catastrophic phase coinsurance • MOOP range ~ $3,300 to $8,000 (depending upon brand/generic mix) • Expansion of LIS	• $2,000 MOOP • Medicare Prescription Payment Plan • Manufacturer Discount Program replaces Coverage Gap Discount	• Implementation of Maximum Fair Price

Patient Cases – Did the IRA lower oral cancer therapy OOP costs?

YES:
JW's brand name medication costs $30,000/month. His household annual income is $100,000 (507% of the 2023 Federal Poverty Level (FPL)), which exceeds limits for LIS, foundation grants, and PAP. In January 2023, he paid ~$4,000, followed by $1,500/month thereafter. His total OOP costs for this prescription for 2023 were ~$20,500.[14] He will hit the MOOP with his first prescription in 2024 (~$3,300) and in 2025 ($2,000) (Figure 2). JW saves ~$17,200 in 2024 and $18,500 in 2025 compared to 2023.

Figure 2



NO:
PN's brand name cancer medication costs $15,000/month. Her household income is $65,000 (~330% of 2023 FPL). In January 2023, she couldn't afford the initial $3,300 + $750/month OOP. She qualified for the manufacturer's PAP program, receiving the medication at no cost for all of 2023. Due to the IRA, the manufacturer reduced PAP eligibility for 2024 to 300% of the FPL and denied her re-enrollment. No grants were available in January 2024, so she puts the $3,300 MOOP cost on a credit card to continue therapy. For January 2025, she opts into the Medicare Prescription Payment Plan. Her Medicare plan bills her $2,000 MOOP at $166.66 each month for 2025. Unintended consequences of the IRA resulted in PN's increased OOP costs and financial toxicity via PAP program changes.

MAYBE:
RS's generic abiraterone 250 mg (#120/month) would have cost him a total of ~$9,500 for all of 2023 through his current Medicare Part D plan.[15-16] He discussed options with his care team, including skipping insurance by using GoodRx or Mark Cuban Cost Plus Drug Company (MCCPDC). He chose to use MCCPDC, paying ~$125 per month (~$1,500 for the year) saving ~$8,000 in 2023.[17] During open enrollment for 2024, RS uses the Medicare Plan Finder to look for a new PDP, finding options with estimated annual OOP abiraterone costs ranging from $880.63 to the $8,000 MOOP.[18] RS switches to a new PDP, saving >$600 in 2024 over MCCPDC. However, the savings from Medicare plan shopping are not specifically attributable to the IRA. Since bypassing insurance using a cash-based option doesn't count toward his MOOP, assessing IRA-specific savings will depend upon his other prescription costs relative to the MOOP combined with cash spending. If in 2025 he was using MCCPDC for abiraterone ($1,500) and he met his Medicare Part D MOOP ($2,000) from his other prescriptions, his combined total prescription costs would be $3,500 instead of a total of $2,000 if using Medicare Part D for all meds. Savings in this case vary dramatically based on an expert evaluation of all options, a willingness to make plan/pharmacy changes, and total prescription costs.

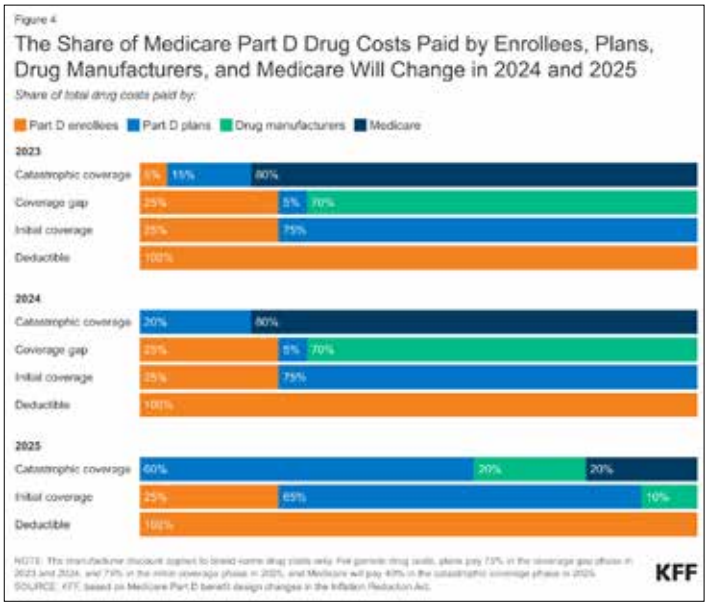
IT'S COMPLICATED:

CJ starts on a combination regimen with a brand oral targeted therapy, capecitabine, and an infused targeted therapy. She has traditional Medicare Part A/B, Medigap, plus a stand-alone PDP. Her oral targeted therapy is covered by Medicare Part D, while her capecitabine and infusions are covered by Medicare Part B (80%) and Medigap supplement (20%). During open enrollment, she switches to a $0 premium Medicare Advantage Plan with enhanced benefits including dental, vision, and hearing.[19] Her oral targeted therapy is covered under the MA-PD, saving on this med by hitting the 2024 Medicare D MOOP. However, her capecitabine and infused therapies are no longer covered by Medicare Part B/Medigap, but instead by her Medicare Part C plan with a separate in-network cap at $6,300 for 2024. Prior authorizations and a switch to an in-network provider are required, delaying her infusions while establishing with a new provider.[20] Total costs of care from all parts of Medicare plus premium costs must be factored in when assessing plan changes, particularly when switching from Medicare Part A/B/Medigap to a Medicare Advantage Plan.

Future Implications

Medicare Part D cost sharing redesign: (Figure 3)[4]

Figure 3[4]



Massive savings are predicted for Medicare from Maximum Fair Price negotiations and shifting liability in the Catastrophic phase from Medicare reinsurance to insurance plans and brand manufacturers.[4,20-22] While price negotiations for selected meds haven't been finalized yet, California Congresswoman Katie Porter's office published a report detailing the rising launch prices of cancer therapies. As launch prices aren't subject to any limits, continued rapid escalations are projected. The report also included an example illustrating the IRA's dramatic shift in cost from patients and Medicare reinsurance to insurance plans and manufacturers (Table 1).[23]

Table 1

2022	Total claim	Patient	Plan	Manufacturer	Medicare Reinsurance
January	$16,020	$3,222	$4,113	$4,113	$4,571
February	$16,020	$801	$2,403	$0	$12,816
March	$16,020	$801	$2,403	$0	$12,816
April	$16,020	$801	$2,403	$0	$12,816
May	$16,020	$801	$2,403	$0	$12,816
June	$16,020	$801	$2,403	$0	$12,816
July	$16,020	$801	$2,403	$0	$12,816
August	$16,020	$801	$2,403	$0	$12,816
September	$16,020	$801	$2,403	$0	$12,816
October	$16,020	$801	$2,403	$0	$12,816
November	$16,020	$801	$2,403	$0	$12,816
December	$16,020	$801	$2,403	$0	$12,816
Annual Total	$192,240	$12,033	$30,546	$4,113	$145,547

2025	Total claim	Patient	Plan	Manufacturer	Medicare Reinsurance
January	$16,020	$2,000	$9,628	$2,500	$1,892
February	$16,020	$0	$9,612	$3,204	$3,204
March	$16,020	$0	$9,612	$3,204	$3,204
April	$16,020	$0	$9,612	$3,204	$3,204
May	$16,020	$0	$9,612	$3,204	$3,204
June	$16,020	$0	$9,612	$3,204	$3,204
July	$16,020	$0	$9,612	$3,204	$3,204
August	$16,020	$0	$9,612	$3,204	$3,204
September	$16,020	$0	$9,612	$3,204	$3,204
October	$16,020	$0	$9,612	$3,204	$3,204
November	$16,020	$0	$9,612	$3,204	$3,204
December	$16,020	$0	$9,612	$3,204	$3,204
Annual Total	$192,240	$2,000	$115,360	$37,744	$37,136
IRA Change	$0	-$10,033	+$84,814	+$33,631	-$108,411

Cumulative long-term effects of all provisions will take years to determine. Legal challenges, lobbying, negotiations, and subsequent Congressional actions may also impact the trajectory of these changes. Intertwined stakeholders face potential consequences from adjustments made with competing priorities.

Patients:

- $2,000 OOP remains unaffordable for many
- PAP income limits slashed – more barriers to approval[24-25]
  - PAP denials below the LIS FPL threshold (150%)
  - Delays in therapy initiation while pursuing LIS/Medicaid eligibility
  - LIS/Medicaid denial proof needed for PAP appeal
- Smaller independent foundation grant sizes[26], if available at all
- Misunderstanding Medicare Payment Plan process, risks/benefits[27]
- Fewer PDP choices and/or higher premiums[28]
- Continued trend toward Medicare Advantage plan enrollment[28]
  - Limited provider networks
  - Increased Prior Authorization barriers, formulary restrictions, step therapy requirements[29]

Manufacturers:

- Via PhRMA[29-30]
  - Reduced new and post approval R&D
  - "Pill penalty" – move away from small molecule development
  - PBM utilization management strategies – Reduced access, higher cost tier placements or coverage exclusions of certain products
- Rebates vs. lower list prices[21]
- Increased launch prices[23]
- $2,000 MOOP disincentivizes providing PAPs

Payers[28]:

- Increased plan liability
- Reduced plan profitability
- Need to raise premiums or drop plans

Providers:

- Lower medication costs = smaller margin in dollars
  - Maximum Fair Price[31]
  - Lower list price with reduced manufacturer discounts/rebates
- Reimbursement below acquisition costs
- Increased shift to Medicare Advantage plan enrollment
  - Increased PBM utilization management barriers
  - Loss of patients no longer in-network

Pharmacist To Do List – IRA edition:

- Relearn your (Medicare) ABCs – expert advice is essential
- Prescribe/dispense with intent to minimize costly waste – $0 copay doesn't mean it's FREE!
- Reassess patient-level effects of skipping insurance – yesterday's savings may be tomorrow's additional OOP costs
- Expect fewer patients to qualify for PAP – assess alternatives, advocate for support
- Stay informed and ready to adapt – macro changes, but individualized impacts

Conclusion

The IRA's healthcare provisions are set to cap annual prescription OOP costs for Medicare Part D patients, particularly those taking extremely expensive oral cancer medications. However, contested manufacturer price negotiations, combined with dramatically redesigned Medicare Part D cost responsibilities, may result in unintended consequences impacting stakeholders for years to come. With billions of dollars at stake, there are certain to be winners, losers, and a continued need for expert assistance to overcome new barriers to ensure patients can affordably receive their medications.

"Medicare will make my 'chemo' prescriptions cheaper for me now, right?" For many patients, we'll soon be able to say "YES!" Unfortunately, given the complexities of cancer care across all parts of Medicare and early signs of patients unable to afford therapy without assistance falling through the cracks, "It depends" is likely to remain my initial answer for the foreseeable future. ●●

REFERENCES:

1. Sayed BA. —Inflation reduction act research series— Medicare Part D enrollee out-of-pocket spending: recent trends and projected impacts of the inflation reduction act. ASPE Office of Health Policy. Accessed November 20, 2023. aspe-part-d-oop.pdf (hhs.gov)
2. Part D / prescription drug benefits. Center for Medicare Advocacy. Accessed November 20, 2023. https://medicareadvocacy.org/medicare-info/medicare-part-d/
3. Medicare Part D prescription drug benefit. Congressional Research Service. Accessed November 20, 2023. https://crsreports.congress.gov/product/pdf/R/R40611/21
4. Changes to Medicare Part D in 2024 and 2025 under the Inflation Reduction Act and how enrollees will benefit. KFF. Accessed November 20, 2023. https://www.kff.org/medicare/issue-brief/changes-to-medicare-part-d-in-2024-and-2025-under-the-inflation-reduction-act-and-how-enrollees-will-benefit/
5. What kind of discount can we expect in the Medicare Part D Donut Hole or Coverage Gap? Q1Medicare.com. Accessed November 20, 2023. https://q1medicare.com/faq/FAQ.php?faq=medicare-part-d-donut-hole-discount-rates-by-year&faq_id=470
6. Will the Coverage Gap or Donut Hole just close up and go away? Q1Medicare.com. Accessed November 20, 2023. https://q1medicare.com/faq/FAQ.php?faq=did-coverage-gap-or-donut-hole-close-go-away&faq_id=471&category_id=118
7. Closing the Medicare Part D Coverage Gap: trends, recent changes, and what's ahead. KFF. Accessed November 20, 2023. www.kff.org/medicare/issue-brief/closing-the-medicare-part-d-coverage-gap-trends-recent-changes-and-whats-ahead/
8. Costs in the coverage gap. Medicare.gov. Accessed November 20, 2023. https://www.medicare.gov/drug-coverage-part-d/costs-for-medicare-drug-coverage/costs-in-the-coverage-gap
9. 2024-2006 Medicare Part D standard benefit model plan parameters. Q1Medicare.com. Accessed November 30, 2023. https://q1medicare.com/PartD-TheMedicarePartDOutlookAllYears.php
10. Saving money with the prescription drug program. Medicare.gov. Accessed November 20, 2023. www.medicare.gov/about-us/prescription-drug-law
11. Explaining the prescription drug provisions in the Inflation Reduction Act. KFF. Accessed November 20, 2023. www.kff.org/medicare/issue-brief/explaining-the-prescription-drug-provisions-in-the-inflation-reduction-act/
12. Fact sheet: Medicare prescription payment plan. CMS.gov. Accessed November 20, 2023. www.cms.gov/files/document/medicare-prescription-payment-plan-fact-sheet.pdf

13. Smoothing Part D out-of-pocket costs under the Inflation Reduction Act. Penn LDI. Accessed November 20, 2023. www.ldi.upenn.edu/our-work/research-updates/smoothing-part-d-out-of-pocket-costs-under-the-inflation-reduction-act/
14. 2023 PDP-planner: Medicare Part D Donut Hole calculator. Q1Medicare.com. Accessed November 19, 2023. https://q1medicare.com/PartD-PartDCoverageGapCalculator2023.php
15. Pockros B, Shabet C, Stensland K, Herrel L. Out-of-pocket costs for prostate cancer medications substantially vary by Medicare Part D plan: an online tool presents an opportunity to mitigate financial toxicity. Urol Pract. 2023;10(5):467-475. doi:10.1097/UPJ.0000000000000421
16. Gupta A, Antonarakis ES, Blaes AH, Booth CM, Dusetzina SB. Evaluation of Medicare coverage and estimated out-of-pocket costs for generic abiraterone products. JAMA Netw Open. 2022;5(9):e2231475. doi:10.1001/jamanetworkopen.2022.31475
17. Abiraterone acetate. Mark Cuban Cost Plus Drug Company. Accessed November 21, 2023. www.costplusdrugs.com/medications/abiraterone-acetate-250mg-tablet/
18. Medicare plan finder. Medicare.gov. Accessed November 21, 2023, using zip code 55901 and selecting a local CVS pharmacy and a mail order option. https://www.medicare.gov/plan-compare/#/?year=2024&lang=en
19. Top advantages & disadvantages of Medicare Advantage. Value Penguin. Accessed November 21, 2023. https://www.valuepenguin.com/advantages-disadvantages-medicare-advantage
20. Medicare Advantage in 2023: premiums, out-of-pocket limits, cost sharing, supplemental benefits, prior authorization, and star ratings. KFF. Accessed November 21, 2023. https://www.kff.org/medicare/issue-brief/medicare-advantage-in-2023-premiums-out-of-pocket-limits-cost-sharing-supplemental-benefits-prior-authorization-and-star-ratings/
21. Explaining the prescription drug provisions in the Inflation Reduction Act. KFF. Accessed November 20, 2023. https://www.kff.org/medicare/issue-brief/explaining-the-prescription-drug-provisions-in-the-inflation-reduction-act/.
22. Part D redesign under the Inflation Reduction Act. Milliman. Accessed November 20, 2023. https://www.milliman.com/en/insight/part-d-redesign-under-ira-potential-financial-ramifications
23. Skyrocketing – how big pharma exploits launch prices to cash in on cancer. Katie Porter. Accessed November 21, 2023. https://porter.house.gov/uploadedfiles/skyrocketing_-_how_big_pharma_exploits_launch_prices_to_cash_in_on_cancer.pdf
24. Pfizer RxPathways updates. Pfizer RxPathways. Accessed November 20, 2023. https://www.pfizerrxpathways.com/updates
25. AZ&Me prescription savings program 2024 income eligibility requirements and Medicare re-enrollment process. AZ&Me. Accessed November 20, 2023. https://www.azandmeapp.com/prescriptionsavings/?screenName=showImpProgramUpdatesPage&showNotifications=false
26. Everything you need to know about Medicare reforms. PAN Foundation. Accessed November 30, 2023. https://www.panfoundation.org/everything-you-need-to-know-about-medicare-reforms/
27. Part D out-of-pocket smoothing policy raises implementation questions. Avalere. Accessed November 30, 2023. https://avalere.com/insights/part-d-out-of-pocket-smoothing-policy-raises-implementation-questions
28. Medicare Part D in 2024: a first look at prescription drug plan availability, premiums, and cost sharing. KFF. Accessed November 30, 2023. https://www.kff.org/medicare/issue-brief/medicare-part-d-in-2024-a-first-look-at-prescription-drug-plan-availability-premiums-and-cost-sharing/
29. Inflation Reduction Act's unintended consequences. PhRMA. Accessed November 21, 2023. https://phrma.org/en/Inflation-Reduction-Act
30. One year later: IRA's unintended consequences are becoming reality. PhRMA. Accessed November 21, 2023. https://phrma.org/Blog/One-year-later-IRAs-unintended-consequences-are-becoming-reality
31. IRA Medicare Part B negotiation shifts financial risk to physicians. Avalere. Accessed November 30, 2023. https://avalere.com/insights/ira-medicare-part-b-negotiation-shifts-financial-risk-to-physicians

Oncology Pharmacists Contribute to Quality Improvement: Select Presentations from the 2023 ASCO Quality Care Symposium

Yun Man, PharmD, BCOP
Medication Use Quality and Policy Specialist
Dana-Farber Cancer Institute
Boston, MA

Kelly Gaertner Brandt, PharmD, BCOP, BCPS
Scientific Director, Oncology
Clinical Care Options

In the constantly evolving healthcare landscape, oncology pharmacists have become pivotal drivers of transformative changes in patient care through their contributions to leading quality improvement (QI). This article explores their invaluable efforts to enhance the quality and efficiency of healthcare processes, spotlighting their QI initiatives. Select abstracts presented at the 2023 American Society of Clinical Oncology (ASCO) Quality Symposium are highlighted, including summaries of strategies, collaborative efforts, and impactful interventions from these pharmacist-led teams.

Update of Oncology Organizational Partnership Expanding ASCO Quality Training Program to Oncology Pharmacists[1]

The Hematology/Oncology Pharmacy Association (HOPA) collaborated with the ASCO Quality Training Program (QTP) to offer a one-day workshop focused on introducing tools and frameworks used in oncology QI to HOPA members. Specifically tailored for oncology pharmacists, the workshop aimed to empower participants to lead or engage in QI activities. To assess the workshop's impact, Schwemm and colleagues conducted a survey before and after participation. Between 2019 and 2022, a total of 124 members from 83 different institutions took part in four workshops. The post-participation survey, with an 83% response rate, revealed an average increase of 3.3 points in knowledge and 3.1 points in competency on a scale of 1 to 10. Ninety-nine percent of participants expressed an extreme likelihood or very high likelihood of recommending someone to participate in the workshop, and that they were continuing to use the skills gained in their practice. Three months after the workshop, 84% of respondents reported applying the acquired skills. Additionally, 80% had either initiated or were planning to develop a QI project. The authors concluded that the positive feedback from participants highlighted their enhanced abilities to facilitate and improve the quality of care for cancer patients.

"By evaluating existing processes, identifying areas for improvement, and dedicating themselves to the continuous optimization of patient care, pharmacists play a pivotal and lasting role in enhancing the quality of healthcare delivery."

Enhancing Policy Communication: Establishing a Formal Channel for Disseminating Policy Updates to Improve Staff Access and Engagement[2]

Institutional policies are the cornerstone of daily operations for staff, offering essential guidance to fulfill their roles and responsibilities. Man and colleagues identified a lack of engagement with policy updates within their institution, leading to an initiative with the goal of keeping pharmacy staff well-informed and providing easy access to the most recent policies. This project utilized a rapid cycle improvement methodology. Initially, baseline data on pharmacy policy access logs were collected before the intervention. Subsequently, diagnostic data were gathered through surveys focusing on staff members' familiarity with policy management system navigation, awareness of policy updates, and preferred communication channels for receiving updates. Through strategic interventions, including the establishment of a formal communication channel and improved accessibility to policy documents, the policy access rate had a two-fold increase compared to the pre-intervention rate. A Statistical Process Control (SPC) chart was employed to continuously monitor the process change over time, ensuring the sustainability of the result. The authors concluded that this project exemplifies the effectiveness of systematic QI in ensuring that essential policies are readily accessible to staff.

Annual Cost and Implementation of Remote Oncology Pharmacist Order Review within a Network of Community Oncology Practices[3]

Koselke and colleagues aimed to evaluate the annual cost-avoidance demonstrated by the United States Oncology Network's ClinReview program, which involved clinical and quality interventions. A retrospective, observational review of the interventions and associated time documented by this team of 6 centralized oncology clinical pharmacists providing remote services to community oncology practices, was conducted over a 6-month period. Categories of clinical interventions included: treatment plan reviews, identification of orders in need of dose modifications, symptom management recommendations, clinical consultations, entering regimens, and performing drug interaction reviews. Previously validated studies were used to assign cost-avoidance values to the interventions. During the study period, 10,195 interventions were documented. The most common interventions included med-

ication regimen/dosing change (62%), treatment plan management (24%), and symptom management (11%), with averages of 9.5, 8.8, and 14.4 associated minutes per intervention, respectively. The annualized cost avoidance from the ClinReview program was determined to be $2,247,818. Considering the cost of pharmacist time, the annualized net cost-avoidance was calculated to be $1,896,164. The authors concluded that incorporating the ClinReview program into community oncology practices results in significant quality, safety, and financial benefits.

Improving Timely Initiation of Oral Chemotherapy in an Outpatient Malignant Hematology Practice[4]

After identifying that 59% of patients receiving oral chemotherapy for hematologic malignancy were starting cycle 2 or 3 of therapy on time, Mejaki and colleagues aimed to increase the on-time initiation of cycle 2 or 3 to >90%. Using QI methodology and tools learned at the ASCO QTP, a multidisciplinary team set out to improve processes related to timely initiation of oral chemotherapy. Plan Do Study Act (PDSA) cycles were used to evaluate the performance of the interventions and the system's reaction to change. The internal benchmark used to define improvement was documentation of an on-time initiation (within 3 days before or after the anticipated cycle start date) of cycle 2 or 3 of oral chemotherapy within the practice site. PDSA Cycle #1 involved implementation of a pharmacist-generated communication process and led to an improvement in on-time starts to 87%. Following an optimization of staff education resources, PDSA Cycle #2 exceeded the on-time goal for the evaluated month with an increase in on-time starts to 92%. The authors concluded that implementation of a new pharmacist communication workflow and optimization of process education resources improved mean on-time cycle 2 or 3 oral chemotherapy starts to 89%.

Conclusion

These studies highlight various ways in which pharmacists can positively impact patient care through QI projects. By evaluating existing processes, identifying areas for improvement, and dedicating themselves to the continuous optimization of patient care, pharmacists play a pivotal and lasting role in enhancing the quality of healthcare delivery. Pharmacists' contributions are instrumental in advancing the field of oncology pharmacy practice and shaping a more effective healthcare system. ●●

REFERENCES

1. Schwemm A, Morris A, Mackler E, et al. Update of ongoing organizational partnership expanding ASCO quality training program to oncology pharmacists. JCO Oncol Pract 19, 2023 (Suppl 11; abstr 377).
2. Man Y, Xu FW, Scullion B. Enhancing policy communication: establishing a formal channel for disseminating policy updates to improve staff access and engagement. JCO Oncol Pract 19, 2023 (Suppl 11; abstr 43).
3. Koselke E, Carroll M, Cho J, et al. Annual cost and implementation of remote oncology pharmacist order review within a network of community oncology practices. JCO Oncol Pract 19, 2023 (Suppl 11; abstr 30).
4. Mejaki B, Williams M, Graff J, et al. Improving timely initiation of oral chemotherapy in an outpatient malignant hematology practice. JCO Oncol Pract 19, 2023 (Suppl 11; abstr 374).

Emerging Non-Hormonal Pharmacologic Therapies for the Management of Vasomotor Symptoms

Farah Raheem, PharmD, BCOP
Clinical Pharmacy Specialist, Outpatient Oncology
Mayo Clinic

Background

Vasomotor symptoms (VMS) are a collective term for hot flashes and night sweats caused by loss of thermoregulation due to declining estrogen levels during menopause.[1] Breast cancer treatment strategies including chemotherapy, surgical or chemical ovarian suppression, and antiestrogen therapy can induce menopause in young female patients. Induced menopause often leads to intense symptoms including VMS. Hot flashes are reported as one of the most common and bothersome menopausal symptoms in breast cancer survivors. Treatment-induced hot flashes affect 65-85% of breast cancer survivors.[2,3] Of the endocrine therapies used in breast cancer, tamoxifen can cause more frequent and severe hot flashes in up to 80% of patients.[4] Hot flashes in breast cancer survivors have a substantial negative impact on daily activities and overall quality of life, which can affect adherence to treatment.[5-9] This clinical pearl provides an updated review of VMS management in patients with breast cancer with a focus on emerging potential pharmacologic approaches.

Current Management Strategies

Nonpharmacologic options of VMS, including weight loss (if overweight), acupuncture, physical activity, lifestyle modifications (e.g., avoiding caffeine and alcohol, dressing in layers, etc.), and integrative therapies such as yoga and hypnosis, can help manage hot flashes, though effectiveness may be limited in patients with moderate to severe symptoms.[10]

Menopausal hormone therapies (MHT) are relatively contraindicated in survivors of hormone sensitive tumors including breast cancer, thus limiting this pharmacologic class as a therapeutic option.[10] Furthermore, data on the efficacy and safety of phytoestrogens and other supplements or herbal products for the management of VMS in survivors of breast cancer are limited and recommendations cannot be made for their use. Products containing phytoestrogens may theoretically have a negative impact on breast cancer disease recurrence, and their use should be discouraged in the absence of clinical evidence.

Nonhormonal pharmacologic agents that are currently available for the management of hot flashes in patients with cancer include selective serotonin and serotonin/norepinephrine reuptake inhibitors (venlafaxine, desvenlafaxine, escitalopram, citalopram), neuropathic pain relievers (gabapentin, pregabalin), certain antihypertensives (clonidine), and certain anticholinergic agents (oxybutynin).[10] To date, venlafaxine has been the most well studied and is shown to be the most effective of the serotonin and norepinephrine reuptake inhibitors for managing VMS in patients with breast cancer with the reported reduction in hot flash frequency >60%.[11,12]

"Fezolinetant is an attractive agent for the management of hot flashes in postmenopausal women, especially in patients with hormone sensitive tumors including breast cancer and those with other contraindications to MHT (e.g., history of stroke or venous thromboembolism)."

Novel Non-Hormonal Therapeutic Approaches for the Management of VMS

In recent years, researchers have identified a new pathway implicated in the pathophysiology of VMS, which involves the KNDy signaling pathway that innervates the thermoregulatory control center in the hypothalamus.[13] The KNDy—**K**isspeptin/**N**eurokinin B/**Dy**norphin—neurons play a role in regulating reproductive hormone levels and other neuroendocrine functions including thermoregulation, circadian rhythms, and sleep.[14-16] Specifically, Neurokinin B (NKB)-mediated activation of neurokinin-3 receptors (NK3R) was shown to modulate body temperature by activating heat dissipation effectors leading to cutaneous vasodilation, which is experienced as hot flashes.[15] Under normal physiologic conditions, the KNDy neurons are stimulated by NKB and inhibited by estrogen.[13] This balance is disrupted when estrogen levels decline in menopause resulting in unopposed activation and overexpression of NK3Rs, which leads to hot flashes.[14,15] These preclinical findings translated well into the clinical setting based on the positive results of the phase III clinical trials demonstrating efficacy of the first-in-class NK3R antagonist, fezolinetant (Veozah™) for the management of hot flashes in postmenopausal women.[17,18]

Fezolinetant 45 mg daily was approved by the United States (U.S.) Food and Drug Administration (FDA) in May 2023 for the treatment of moderate to severe hot flashes.[19] The approval is supported by results from the BRIGHT SKY™ program, which consisted of three phase III clinical trials that enrolled over 2800 women in the U.S., Canada, and Europe.[20] While SKYLIGHT 1 and 2 evaluated the safety and efficacy of fezolinetant, SKYLIGHT 4 characterized long-term safety of the agent.[17,18,21]

In the SKYLIGHT 1 and 2 clinical trials, 1028 postmenopausal females (40 to 65 years) with ≥7 moderate to severe hot flashes per day were randomized (1:1:1) to once daily placebo, fezolinetant 30

mg, or fezolinetant 45 mg for 12 weeks. After the initial 12 weeks, patients in the active treatment arms continued with their assigned doses of fezolinetant, and those in the control arm were re-randomized to fezolinetant 30 mg or 45 mg daily for a 40-week active treatment period (Figure 1). Moderate symptoms were defined as sensation of heat with sweating that is not interrupting activities. Severe symptoms were defined as sensation of heat with sweating interfering with activities. The co-primary endpoint was mean change in daily frequency and severity of hot flashes at weeks 4 and 12.[17,18]

Key exclusion criteria included any history of malignancy, concomitant use of strong or moderate CYP1A2 inhibitors, active liver disease, and baseline estimated glomerular filtration rate (eGFR) ≤59 mL/minute/1.73 m^2 at screening. Approximately 80% of participants self-identified as white and 14-19.8% as Black. About 20% of patients had a prior oophorectomy. Efficacy results are summarized in Table 1. Both fezolinetant doses led to improvement in frequency and severity of hot flashes when compared to placebo. Mean percentage change in hot flash frequency was >50% in the fezolinetant 45 mg arm at weeks 4 and 12, compared to 30-45% in the placebo arm. By week 12, more patients in the fezolinetant 45 mg arm achieved at least a 50% reduction in VMS frequency (57-60.5%) compared to fezolinetant 30 mg (45-50%).[17, 18] The notable placebo effect in the SKYLIGHT 1 and 2 studies is in line with that observed in historical studies of VMS.[22]

Improvement in frequency and severity of hot flashes with fezolinetant was observed as early as 1 week from treatment initiation. Improvement continued through week 12 and was sustained at week 52 though the magnitude of benefit plateaued beyond week 12.[17,18] The key secondary outcome of patient-reported sleep disturbance was not different with fezolinetant of any dose versus placebo in SKYLIGHT 1 but was significantly improved for fezolinetant 45 mg in SKYLIGHT 2. The exploratory endpoint of patient reported Menopause-Specific Quality of Life was significantly improved from baseline to weeks 4 and 12 with any fezolinetant dose versus placebo.[17,18]

Long-term safety of fezolinetant was investigated in SKYLIGHT 4, a phase III, randomized, double-blind, 52-week study in which 1830 postmenopausal women were randomized to placebo, fezolinetant 30 mg, or fezolinetant 45 mg once daily (1:1:1). The primary endpoint was treatment emergent adverse events (TEAEs) and endometrial changes (hyperplasia and malignancy).[21] Demonstrating endometrial safety is an FDA requirement of any treatment intended for managing menopause symptoms with preset endometrial hyperplasia or malignancy incidence limits of ≤1% with an upper bound of one-sided 95% confidence interval (CI) ≤ 4%.[23]

TEAEs occurred in 64.1% of patients in the placebo arm, 67.9% in the fezolinetant 30 mg arm, and 63.9% in the fezolinetant 45 mg arm.[21] The relatively high rate of AEs in the placebo arm is noteworthy. Headache and COVID-19 were the most commonly reported TEAEs with similar incidence across all treatment and placebo arms. Overall, fezolinetant was well tolerated. The majority of AEs were mild, and treatment discontinuation due to AEs was uncommon and occurred in 4.3%, 5.6%, and 4.6% in the placebo, fezolinetant 30 mg, and fezolinetant 45 mg arms, respectively.[21]

Endometrial hyperplasia occurred in one patient in the fezolinetant 45 mg arm (0.5%; upper 95% CI, 2.3%). Endometrial malignancy occurred in one patient in the fezolinetant 30 mg arm (0.5%; upper 95% CI, 2.2%).[21] These findings are within the FDA's prespecified limits.[23] The impact of the drug on the endometrium is not expected as fezolinetant is a centrally acting, non-estrogen containing agent.[13]

Elevations in liver function tests (LFTs) ≥3 times the upper limit of normal were reported in 1% of patients in the placebo arm, 1.4% in the fezolinetant 30 mg arm, and 2% in the fezolinetant 45 mg arm. Elevations in LFTs were asymptomatic, transient, and reversible while on treatment or upon dose interruption or discontinuation. There was no indication of drug-induced liver injury.[21]

Table 1. Efficacy Results of Fezolinetant for the Management of Hot Flashes[17,18]

		SKYLIGHT 1			SKYLIGHT 2		
Analysis Timeline	Outcomes	Placebo (n = 175)	Fezolinetant 30mg (n = 173)	Fezolinetant 45mg (n = 174)	Placebo (n = 167)	Fezolinetant 30mg (n = 166)	Fezolinetant 45mg (n = 167)
Frequency of daily VMS							
Week 4	Mean change	-3.01	-5.18	-5.21	-3.72	-5.53	-6.26
	Mean % change	30%	48%	51%	33.60%	51.60%	55.16%
	P value	–	<0.001	<0.001	–	<0.001	<0.001
Week 12	Mean change	-3.58	-5.95	-6.28	-4.97	-6.83	-7.50
	Mean % change	35%	56%	61%	45.35%	58.64%	64.27%
	P value	–	<0.001	<0.001	–	<0.001	<0.001
Severity of daily VMS							
Week 4	Mean change	-0.23	-0.40	-0.42	-0.32	-0.47	-0.61
	P value	–	0.003	<0.001	–	0.021	<0.001
Week 12	Mean change	-0.33	-0.54	-0.51	-0.48	-0.64	-0.77
	P value	–	0.007	0.019	–	<0.05	<0.001

VMS, vasomotor symptoms

NK3 Receptor Antagonists in Development

Another promising NK3R antagonist in development is elinzanetant, which is a nonselective neurokinin-1 receptor (NK1R)/NK3R pseudo-irreversible antagonist with greater potency at the NK1 receptor.[24] Elinzanetant was initially developed for the management of addiction disorders.[13] In a phase II clinical trial, elinzanetant appears to be effective in the management of VMS in postmenopausal women.[25] The potent effect of elinzanetant on NK1 receptors may be beneficial for improving sleep impairment associated with menopause and there is an ongoing study assessing this (NCT06112756). Elinzanetant is also being investigated for the management of treatment-induced hot flashes in patients with breast cancer (NCT05587296). This study is not currently recruiting, and the results are highly anticipated. Other agents currently in development for the management of VMS include the first generation NK3R antagonists osanetant (hot flashes in men with prostate cancer, NCT05647447) and SJX-653 (NCT04278872).

Clinical Pearls and Recommendations

There is an unmet need for safe, effective, non-hormonal alternative therapy for the management of VMS in breast cancer survivors. Fezolinetant is an attractive agent for the management of hot flashes in postmenopausal women, especially in patients with hormone sensitive tumors including breast cancer and those with other contraindications to MHT (e.g., history of stroke or venous thromboembolism).

Fezolinetant met its primary endpoint of reducing the frequency and severity of moderate to severe hot flashes in postmenopausal women, but importantly, the mean percentage change in hot flash frequency was >50% with fezolinetant 45 mg at weeks 4 (mean change, 50-55%) and 12 (mean change, 60-64%). A reduction in hot flash frequency by more than 50% is considered clinically meaningful and should be required in clinical studies for an agent to be considered active.[22,27]

Furthermore, improvement in patient-reported sleep disturbance at week 12 was seen with fezolinetant 45 mg in the non-selected patient population. This is clinically relevant as moderate to severe VMS are associated with sleep impairment including poor sleep quality and difficulty staying asleep in nearly 50% of menopausal women.[28] The mechanism explaining sleep improvement with fezolinetant could be due to the KNDy pathway's role in circadian rhythm and sleep.[15] Sleep improvement with fezolinetant is also likely due to reducing VMS.[17,18] Further studies are needed to investigate the efficacy of fezolinetant for sleep impairment associated with menopause in healthy women and in patients with breast cancer.

Due to its recent approval and the fact that patients with breast cancer were excluded from clinical trials, fezolinetant's position in treatment guidelines is yet to be determined and strong recommendations for its use for the management of VMS in breast cancer survivors cannot be made at this time. However, given its relative favorable safety profile, lack of estrogenic effect, and absence of clinically relevant drug-drug interactions with endocrine treatment used for breast cancer (e.g., tamoxifen or aromatase inhibitors), fezolinetant could be a potential option for the management of moderate to severe hot flashes in breast cancer survivors whose symptoms are not adequately controlled with current standard-of-care, dose-optimized pharmacologic agents (e.g., venlafaxine, gabapentin, etc.) or in those who are intolerable to available therapies.

Given the lack of FDA approval in patients with breast cancer and the absence of treatment guideline endorsement, access to fezolinetant in this patient population outside of clinical trials is likely to be challenging. If fezolinetant is prescribed, it is important to obtain baseline LFTs (alanine transaminase [ALT], aspartate aminotransferase [AST], total and direct serum bilirubin) and at 3, 6, and 9 months or more often if clinically indicated.[19] Fezolinetant is contraindicated in patients with underlying severe liver disease (i.e., cirrhosis) or severe renal impairment.[19] Fezolinetant dosing, interactions, and other pharmacologic properties are outlined in Table 2.

Given that the currently available pharmacologic options for managing moderate to severe VMS in patients with breast cancer are limited by side effects (e.g., sedation, anticholinergic adverse events, etc.), significant drug-drug interactions, potential pharmacogenomic variability, and concern for withdrawal if stopped abruptly (e.g., venlafaxine), there is a substantial unmet need for investigating alternative nonhormonal therapies with novel mechanism of action such as NK3R antagonists in this patient population. With such significant need, there exist opportunities for oncology pharmacist-led investigator-initiated studies of fezolinetant for the management of VMS in patients with breast cancer.

Figure 1. SKYLIGHT 1 and 2 Clinical Trials Design[17,18]

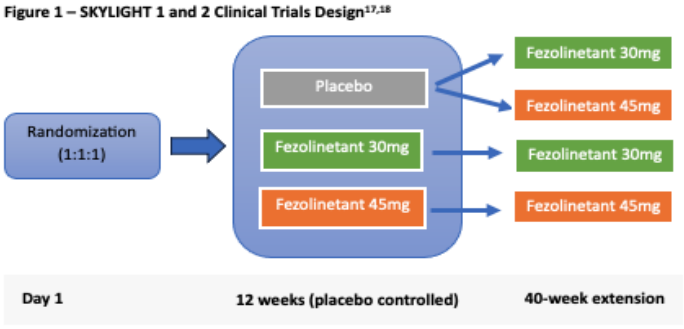


Table 2. Fezolinetant Dosing, Interactions, Mechanism, and Other Properties[19]

Pharmacologic Class	Neurokinin 3 receptor (NK3R) antagonist
Mechanism of Action	Modulates the KNDy neuronal activity in the thermoregulatory center by blocking neurokinin B binding on neurokinin 3 receptor. *Fezolinetant has high affinity to NK3R (>450-fold higher than binding affinity to NK1 or NK2 receptors).*
Indication	Treatment of moderate to severe hot flashes caused by menopause
Dosage Form	45 mg tablet, film-coated, size 7 mm
Dose	1 tablet (45 mg) daily with or without food. Do not cut or crush tablet.
Dose Adjustment	Renal – no dose adjustment necessary for eGFR ·30 mL/minute/1.73 m^2 Hepatic – prior to treatment Contraindicated if mild to moderate impairment (Child-Pugh class A or B) due to increase in fezolinetant exposure. Contraindicated (not studied) if severe impairment (Child-Pugh class C). Do not initiate treatment if ALT, AST, and/or total bilirubin ·2x ULN. Hepatotoxicity during treatment: Hold treatment if ALT, AST, and/or total bilirubin ·2x ULN.
Contraindications	Known Cirrhosis Severe renal impairment (eGFR 15 to < 30 mL/minute/1.73 m^2) or ESRD (eGFR < 15 mL/minute/1.73 m^2) Concomitant CYP1A2 inhibitors (weak, moderate, or strong)
PK/PD	Half-life ~ 9.6 hours Primarily metabolized by CYP1A2 and to a lesser extent by CYP2C9 and CYP2C19 Urine excretion 76.9% (1.1% unchanged) and 14.7% in feces (0.1% unchanged)
Drug Interactions	Substrate of CYP1A2 (major), CYP2C19 (minor), CYP2C9 (minor), P-glycoprotein (minor). *Avoid all CYP1A2 inhibitors (weak, moderate, or strong).*
Warnings	Hepatic transaminase elevation (do not initiate treatment if LFTs >2x ULN). LFT elevation >3x ULN occurred in 2.3% of patients. LFT elevation was asymptomatic, and levels returned to baseline with dose continuation, interruption, or discontinuation. No bilirubin elevation >2x ULN was observed.
Adverse Events	Abdominal pain (4%), diarrhea (4%), insomnia (4%), back pain (3%), and hepatic transaminase elevation (2%).
Monitoring	LFTs and bilirubin (total and direct) prior to initiating treatment, at 3 months, 6 months, and 9 months after treatment initiation or more frequently as clinically indicated.

ESRD, end-stage renal disease; KNDy, kisspeptin/neurokinin B/dynorphin; LFT, liver function test; PK/PD, pharmacokinetics and pharmacodynamics; ULN, upper limit of normal

REFERENCES:

1. Deecher DC, Dorries K. Understanding the pathophysiology of vasomotor symptoms (hot flushes and night sweats) that occur in perimenopause, menopause, and postmenopause life stages. Arch Womens Ment Health. 2007;10(6):247-57.
2. Kontos M, Agbaje OF, Rymer J, Fentiman IS. What can be done about hot flushes after treatment for breast cancer? Climacteric. 2010;13(1):4-21.
3. kChang HY, Jotwani AC, Lai YH, et al. Hot flashes in breast cancer survivors: frequency, severity and impact. Breast. 2016;27:116-121.
4. Nolvadex® (tamoxifen) prescribing information. AstraZeneca Pharmaceuticals; 2003.
5. Carpenter JS, Johnson D, Wagner L, Andrykowski M. Hot flashes and related outcomes in breast cancer survivors and matched comparison women. Oncol Nurs Forum. 2002;29(3):E16–25.
6. Otte JL, Carpenter JS, Russell KM, Bigatti S, Champion VL. Prevalence, severity, and correlates of sleep-wake disturbances in long-term breast cancer survivors. J Pain Symptom Manage. 2010;39(3):535–47.
7. Savard J, Davidson JR, Ivers H, Quesnel C, Rioux D, Dupere V, et al. The association between nocturnal hot flashes and sleep in breast cancer survivors. J Pain Symptom Manage. 2004;27(6):513–22.
8. Stan D, Loprinzi CL, Ruddy KJ. Breast cancer survivorship issues. Hematol Oncol Clin North Am. 2013;27(4):805–27.
9. Montagna E, Zagami P, Masiero M, et al. Assessing predictors of tamoxifen nonadherence in patients with early breast cancer. Patient Prefer Adherence. 2021; 15: 2051–2061.
10. National Comprehensive Cancer Network. Survivorship (v1.2023). Accessed on November 1 2023 from: https://www.nccn.org/professionals/physician_gls/pdf/survivorship.pdf
11. Bordeleau L, Pritchard KI, Loprinzi CL, et al. Multicenter, randomized, cross-over clinical trial of venlafaxine versus gabapentin for the management of hot flashes in breast cancer survivors. J Clin Oncol. 2010;28:5147-5152.
12. Loprinzi CL, Kugler JW, Sloan JA, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. Lancet. 2000;356(9247):2059-63.
13. Depypere H, Lademacher C, Siddiqui, et al. Fezolinetant in the treatment of vasomotor symptoms associated with menopause. Expert Opin Investig Drugs. 2021;30(7):681-694.
14. Rance NE, Krajewski SJ, Smith MA, et al. Neurokinin B and the hypothalamic regulation of reproduction. Brain Res. 2010;1364:116–128.
15. Mittelman-Smith MA, Williams H, Krajewski-Hall SJ, et al. Role for kisspeptin/neurokinin B/dynorphin (KNDy) neurons in cutaneous vasodilatation and the estrogen modulation of body temperature. Proc Natl Acad Sci USA. 2012;109(48):19846–19851.
16. Jayasena CN, Comninos AN, Stefanopoulou E, et al. Neurokinin B administration induces hot flushes in women. Sci Rep. 2015;16(5):8466.
17. Lederman S, Ottery FD, Cano A, et al. Fezolinetant for treatment of moderate-to-severe vasomotor symptoms associated with menopause (SKYLIGHT 1): a phase 3 randomised controlled study. Lancet. 2023;401(10382):1091-1102.

18. Johnson KA, Martin N, Nappi RE, et al. Efficacy and safety of fezolinetant in moderate to severe vasomotor symptoms associated with menopause: a phase 3 RCT. J Clin Endocrinol Metab. 2023;108(8):1981-1997.
19. Veozah (fezolinetant) [prescribing information]. Northbrook, IL: Astellas Pharma US, Inc; May 2023.
20. CISION PR Newswire. Astellas initiates phase 3 clinical trials for fezolinetant in postmenopausal women with vasomotor symptoms. Available at https://www.prnewswire.com/news-releases/astellas-initiates-phase-3-clinical-trials-for-fezolinetant-in-postmenopausal-women-with-vasomotor-symptoms-300896688.html. Accessed on November 25, 2023.
21. Neal-Perry G, Cano A, Lederman S, et al. Safety of fezolinetant for vasomotor symptoms associated with menopause: a randomized controlled trial. Obstet Gynecol. 2023;141(4):737-747.
22. Sloan JA, Loprinzi CL, Novotny PJ, Barton DL, Lavasseur BI, Windschitl H. Methodologic lessons learned from hot flash studies. J Clin Oncol. 2001;19(23):4280-90.
23. U.S. Food and Drug Administration. Draft guidance document. Estrogen and estrogen/progestin drug products to treat vasomotor symptoms and vulvar and vaginal atrophy symptoms—recommendations for clinical evaluation. 2003. Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/estrogen-and-estrogenprogestin-drug-products-treat-vasomotor-symptoms-and-vulvar-and-vaginal-atrophy. Accessed November 25, 2023.
24. Ridler K, Gunn RN, Searle GE, et al. Characterising the plasma-target occupancy relationship of the neurokinin antagonist GSK1144814 with PET. J Psychopharmacol. 2014;28(3):244–253.
25. Trower M, Anderson RA, Ballantyne E, et al. Effects of NT-814, a dual neurokinin 1 and 3 receptor antagonist, on vasomotor symptoms in postmenopausal women: a placebo-controlled, randomized trial. Menopause. 2020;27(5):498–505.
26. Dawson LA, Porter RA. Progress in the development of neurokinin 3 modulators for the treatment of schizophrenia: molecule development and clinical progress. Future Med Chem. 2013;5(13):1525–1546.
27. Newton KM, Carpenter JS, Guthrie KA, et al. Methods for the design of vasomotor symptom trials: the menopausal strategies: finding lasting answers to symptoms and health network. Menopause. 2014;21:45-58.
28. Thurston RC, Chang Y, Buysse DJ, Hall MH, Matthews KA. Hot flashes and awakenings among midlife women. Sleep. 2019;42(9):zsz131.

Establishing a Residency Wellness Program

Becca LaRue, PharmD, BCOP
Clinical Pharmacy Specialist, Hematology/Oncology/Cellular Therapy
Rush University Medical Center

As a new practitioner early in my career as a hematology/oncology (heme/onc) pharmacist, I was eager to get involved in our postgraduate year (PGY)-2 oncology residency program and pay it forward to the next generation of oncology pharmacists. I became one of the residency program coordinators and worked closely with the Residency Program Director (RPD) to keep the program running smoothly while always thinking of ways to improve. One of the improvement ideas came from this very section of HOPA News in the year 2020. I read an article published by Dr. Rorabaugh and two PGY-2 residents at the time, Dr. Stewart and Dr. Yingling, that outlined a Pharmacy Residency Wellness Program that was implemented at West Virginia University Medicine.[1] After reading this article I was extremely motivated to implement something similar at my institution as I thought, "wow, what a great idea; I wish I had something like this when I was in residency!"

"After three successful years of the Hematology/Oncology PGY-2 Wellness Program, the PGY-1 and other PGY-2 programs at Rush have created similar programs to increase wellness in all of our pharmacy residents."

Although the evidence is much more robust for our medical colleagues, we are starting to see more documented evidence of the effects of stress on pharmacy residents. Williams and colleagues reported that depressive symptoms of pharmacy residents were higher than both medicine residents and the general population.[2] Another article published by Le and colleagues found a statistically significant correlation between high levels of perceived stress reported by pharmacy residents and medication errors.[3] Aside from the evidence, I think we can all agree that focusing on wellness and mental health as we begin our careers in hematology/oncology is extremely beneficial to lay the groundwork for taking care of ourselves and our patients.

At the beginning of the pandemic in June 2020, the Rush Hematology/Oncology PGY-2 Wellness Program was created with a mission to educate pharmacy residents about wellness and provide them with the tools necessary to increase their overall wellness and combat burnout as they begin their pharmacy career. This program brings together pharmacy residents and their preceptors for monthly wellness activities throughout each year.

I started with a proposal to the PGY-2 RPD outlining my vision for the wellness program which included a mission statement, a twelve-month outline of events (Table 1), surveys, a PowerPoint overview for orientation, and a wellness goal setting form (Figure 1). The first month is devoted to an overview of the program and wellness resources available as well as goal setting. I tell my residents that these are the easiest goals to write—and

Table 1: PGY-2 Residency Wellness Program

Month	Wellness Activity
July	Baseline wellness surveys Discussion with wellness coordinator regarding importance of personal wellness Wellness goal setting
August	30-60 minute session with psychology/palliative colleagues regarding dealing with death and dying
September	Exercise (group fitness class, step challenge)
October	Mindfulness and meditation
November	Appointment at Rush Center for Wellness
December	Midpoint wellness surveys Formal wellness goal check in and reflection on first half of the year
January	Happy hour or dinner at a new local restaurant with preceptor group (bonus if your area has a restaurant week!)
February	Give back (volunteer outing or activity with preceptor group)
March	Happy hour with preceptors focused on career transition and interview advice
April	Focus on gratitude (encourage residents and colleagues to send email to a coworker's boss, give direct positive feedback to someone at work, or nominate someone for an award)
May	Share and tell (residents and preceptors share something that they are proud of reflecting back on the year)
June	Final wellness surveys Final wellness goal review and reflection Feedback on the program and ways to improve for the next year

yet possibly the most difficult to achieve—but they are just as important to focus on. I give example goals such as, "call a family member/friend from home once a week", "watch The Bachelor every Monday", or "go to the doctor and the dentist at least once this year." I also have the resident fill out baseline wellness surveys that we will repeat halfway through the year and again at the end of the residency year when we check in on these goals and reflect. For the remaining nine months of the year, I try to have a list of event options to send to residents each month to let them pick from. Then, as the wellness coordinator, I plan and set everything up so that there is no added stress to the resident. Some examples of activities in which we have participated include: a step challenge, group fitness class, happy hours, trip to a local museum, dealing with death and dying interdisciplinary discussion, preceptor advice for career transitions and job interviews, positive self-talk, meditation, volunteer activities, focus on gratitude and giving positive feedback to colleagues at work, sharing your "happy place" pictures via email, personal coaching sessions, and visiting our institution's Clinical Wellness Center.

Dr. Aaron Krapfl was the first PGY-2 pharmacy resident to complete this program and is now one of the inpatient clinical pharmacy specialists in hematology/oncology at Rush and continues to participate in the program from the preceptor side. Reflecting on his experience with the program, he stated, "*The wellness program provided a great avenue for stress relief throughout a busy residency year. The program enabled me to take part in fun and informative activities and forced me to take my mind off of daily work and projects. These activities also helped develop strong relationships with preceptors and coworkers that carried over to form an even better workplace environment*." Some of Aaron's favorite events included rooftop curling in the winter, a group Pilates class, and visiting Rush's Wellness Center and encouraging his co-residents to do so as well.

The wellness program, although initiated to focus on pharmacy residents, has truly made an impact on all members involved. It has been a nice way to instill wellness practices into our trainees while refocusing preceptors on their own wellness as well. After three successful years of the Hematology/Oncology PGY-2 Wellness Program, the PGY-1 and other PGY-2 programs at Rush have created similar programs to increase wellness in all of our pharmacy residents. We strongly believe that clinicians who take care of themselves can better care for our patients.

Tips from a pharmacy residency wellness coordinator:

- Use your connections at work. Want to have a session on dealing with death and dying? Reach out to your psychosocial oncology service to see if there are any clinicians that would be willing to help lead an interdisciplinary discussion. Search your institution's website for already established wellness resources and put them into your introduction presentation so residents have all this information in one place as a resource.
- No wellness event is too small, and it is ok to skip planning a wellness event one month if it is causing stress…as this is the opposite effect desired.
- Give options to your resident(s) for activities each month and ask them for ideas as well. It is nice when you can find events that match up with the interests of your resident(s) and everyone learns more about each other in the process.
- Strategically plan less time-consuming wellness activities during a busy month for your resident(s). If they have a research project deadline and a busy inpatient service one month, maybe your event is working on positive self-talk and thinking of a mantra to say to yourself at work. At the end of the month touch base and see if that practice was helpful or not. ●●

Figure 1

GOAL #1: _____

GOAL #2: _____

GOAL #3: _____

Additional Goals (if desired): _____

Resident Name (Print): _____

Resident Signature: _____

Wellness Coordinator Signature: _____

REFERENCES:

1. Rorabaugh K, Stewart A, Yingling S. Pharmacy residents' mental wellness: why and how to prioritize resilience in residency. HOPA News. 2020;17(1): 13-20.
2. Williams E, Martin SL, Fabrikant A, Wang A, Pojasek M. Rates of depressive symptoms among pharmacy residents. Am J Health Syst Pharm. 2018;75(5):292-297.
3. Le HM, Young SD. Exploring the relationship between environmental stressors, pharmacy residents stress and medication errors. J Psychol Cognition. 2017;2(3):192-197.

The Rapidly Evolving Landscape of Hormone Receptor Positive Early-Stage Breast Cancer: A More Tailored Approach

Jordan Hill, PharmD, BCOP
Clinical Pharmacy Specialist
WVU Medicine Cancer Institute

Over the last several months, a substantial amount of exciting data has been presented and published in the early-stage breast cancer landscape, especially for hormone receptor positive (HR+) disease. The updates have been wide-ranging including targeted therapies, chemotherapy, immunotherapy, fertility and pregnancy, and symptom management.

In June 2023, the highly anticipated initial results of the NATALEE trial examining adjuvant ribociclib for high-risk early-stage HR+ breast cancer were presented at the American Society of Clinical Oncology (ASCO) Annual Meeting. In contrast to monarchE, which only included very high-risk patients, NATALEE included intermediate to high-risk patients – including node negative patients if their tumor was 2 cm or larger and had one additional high-risk feature such as grade 2 with either a high Ki67 or high oncotype, or grade 3 disease. NATALEE randomized 5,101 patients 1:1 to receive ribociclib 400 mg for 3 weeks on, 1 week off for 3 years with a non-steroidal aromatase inhibitor (AI) or a non-steroidal aromatase inhibitor alone. Though approximately 30% of patients had node-negative disease, the majority of patients (60%) were stage 3 and almost all patients (88%) were high enough risk to receive chemotherapy. At the second-interim analysis, NATALEE met its primary endpoint of significantly improving invasive disease-free survival (iDFS) with 45% of patients in the combination arm still receiving ribociclib.[1] The final iDFS analysis was presented at the December 2023 San Antonio Breast Cancer Symposium (SABCS). At this time point, only 21% of patients were still receiving ribociclib. The 3-year iDFS rates were 90.7% for ribociclib + AI versus 87.6% for AI alone with a relative risk reduction of approximately 25% (hazard ratio [HR] 0.749, 95% confidence interval [CI]: 0.628-0.892; p = 0.0006). Similarly, distant disease-free survival (DDFS) was improved with 3-year DDFS rates of 92.9% and 90.2%, respectively (HR 0.749, 95% CI: 0.623-0.900; p = 0.001). From a safety perspective, 19.5% of patients discontinued therapy early due to adverse events with the most frequent reason being hepatotoxicity. Dose-dependent toxicities such as neutropenia and QT prolongation were less frequent in NATALEE compared to metastatic trials with ribociclib; however, 26% of patients in the ribociclib arm experienced liver-related adverse events with 9% experiencing grade ≥3 elevations in liver enzymes, highlighting the importance of close monitoring and management in these patients.[2] In addition to final iDFS results for NATALEE, a genomic profiling examination from monarchE was also presented at SABCS. This biomarker analysis sought to identify patients more likely to benefit from adjuvant abemaciclib; however, the authors found that adjuvant abemaciclib maintained iDFS benefit across all subpopulations including various RNA molecular subtypes (luminal A, luminal B, basal-like), 21-gene expression scores, and genomic alterations, concluding, for now, high clinical risk is still the best way to identify patients most likely to benefit from abemaciclib.[3] In addition to biomarker data at SABCS, 5-year follow-up data and dose reduction data were presented for adjuvant abemaciclib at the 2023 European Society for Medical Oncology (ESMO) Congress. The 5-year iDFS continued to show a sustained benefit from abemaciclib, reducing the risk for invasive disease by 32% (HR 0.680; 95% CI: 0.599-0.772) with similar reduction in DDFS (HR 0.675; 95% CI: 0.588-0.774), and importantly, for the 53% of patients requiring a dose reduction, iDFS and DDFS rates were similar to those maintained at full dose with improved patient retention in those receiving a dose reduction.[4,5]

"While not practice changing for most HR+ positive patients, these trials do help validate the practice of treating high-risk, low ER (< 10%) positive patients as triple negative, and with longer follow-up and event-free survival data, they may change the standard of care in very high-risk HR+ early-stage breast cancer patients."

While adjuvant CDK 4/6 inhibitors continue to show benefit in high-risk early-stage HR+ breast cancer, the use of anthracyclines remains controversial. In April 2023, a meta-analysis by the Early Breast Cancer Trialists' Collaborative Group evaluating anthracycline-containing and taxane-containing chemotherapy regimens was published in The Lancet.[6] This analysis of 15 trials found a 14% reduction in recurrence for taxane regimens including an anthracycline compared to those without. It is important to note that this reduction was primarily driven by the addition of anthracyclines when given concomitantly with docetaxel and cyclophosphamide, whereas sequential anthracycline and taxane regimens did not show significant reductions in risk compared to docetaxel and cyclophosphamide, which is the primary mode of administration for these regimens. Additionally, the largest hazard ratios (and widest confidence intervals) seen in the subgroup analysis were for patients with HR+ node negative disease and those with well differentiated tumors, leaving very conflicting results for this subset of patients compared to the trial's overall result.

Even though immunotherapy is standard in the neoadjuvant triple negative landscape, it is a newer development in the management of early-stage HR+ breast cancer with both pembrolizumab and nivolumab showing promising efficacy in the neoadjuvant setting for patients with very high-risk disease. KEYNOTE-756 demonstrated significantly improved pathologic complete response (pCR) rates with the addition of pembrolizumab to chemotherapy for patients with high-risk, high-grade, early-stage HR+ breast cancer. The absolute difference in pCR rates was 8.5% for the entire population (p=0.00005), with differences in improvements observed depending on nodal status – 9.3% absolute difference for node positive compared to 3.8% for node negative. Additionally, more significant differences were seen for patients with programmed death-ligand 1 (PD-L1) positive tumors (with combined positive score [CPS] ≥1) compared to PD-L1 negative – 9.8% and 4.5% respectively, and that difference continued to improve with higher levels of PD-L1 expression (13.2% if PD-L1 ≥10% and 17.4% if PD-L1 ≥20%). More dramatic differences were also observed for patients with lower levels of ER positivity (<10%).[7] Similarly, CheckMate 7FL also demonstrated significantly higher pCR rates with the addition of nivolumab to standard chemotherapy in high-risk, early-stage, HR+ breast cancer with an absolute difference of 10.7% in the overall population. Also similar to KEYNOTE-756, the absolute differences in pCR were more pronounced in PD-L1 positive patients with the greatest improvements in the PD-L1 ≥20% subgroup. While larger differences were also seen in lower ER positivity, the reported cutoff was different – with an absolute difference in pCR rates of 29.3% in patients with ER ≤50%.[8] In both trials, more than 80% of patients were node positive and almost all patients had grade 3 disease. While not practice changing for most HR+ positive patients, these trials do help validate the practice of treating high-risk, low ER (<10%) positive patients as triple negative, and with longer follow-up and event-free survival data, they may change the standard of care in very high-risk HR+ early-stage breast cancer patients.

Several exciting publications and presentations have recently occurred for younger premenopausal women with early-stage HR+ breast cancer. The POSITIVE trial was published in June 2023, showing temporary interruptions in endocrine therapy do not increase the short-term risk of breast cancer events (defined as ipsilateral or locoregional invasive disease, distant recurrence, or contralateral invasive breast cancer). Stage I-III HR+ breast cancer patients aged 42 years and younger who had received 18-30 months of endocrine therapy were permitted to interrupt endocrine therapy for up to two years and assisted reproductive technology (ART) was allowed. The 3-year incidence of breast cancer events was 8.9% in the treatment-interruption group and 9.2% in the external control cohort (patients from SOFT and TEXT trials represented the external control) with an adjusted hazard ratio of 0.81 (95% CI, 0.57 to 1.15). The 3-year incidence of distant recurrences was 4.5% versus 5.8%, respectively, with a hazard ratio of 0.70 (95% CI: 0.44 to 1.12). Pregnancy outcomes were also evaluated. Among patients with pregnancy status available, 74% had at least one pregnancy during the study; 54% of patients became pregnant within the first 12 months, which is higher than the percentages reported among women of similar age without breast cancer. Additionally, no increased risk of breast cancer events was associated with pregnancy.[9] At the 2023 SABCS, further data from the POSITIVE trial was presented, including time to pregnancy, fertility preservation, and use of ART. The only factor significantly impacting time to pregnancy was age < 35 compared to women ages 35-39 (HR 0.74; 95% CI: 0.59-0.95) and women ages 40-42 (HR 0.4; 95% CI: 0.29-0.56). Higher pregnancy rates were seen in patients who had embryo or oocyte cryopreservation, and importantly, those patients undergoing ovarian stimulation (for either embryo/oocyte cryopreservation after diagnosis or ART after trial enrollment) did not have an increase in breast cancer events, although follow-up is short and details of ovarian stimulation (such as proportion of patients receiving letrozole for stimulation) was not provided.[10]
The second exciting publication for younger patients with HR+ breast cancer was in the symptom management space. Younger women receiving endocrine therapy tend to experience more symptoms from endocrine therapy than older women, and some of the most common side effects are vasomotor symptoms. While the SKYLIGHT 1 and SKYLIGHT 2 trials investigating the efficacy of fezolinetant, a neurokinin 3 receptor antagonist, did not enroll patients with breast cancer or a history of breast cancer, they both found significantly reduced frequency and severity of vasomotor symptoms from a non-hormonal treatment.[11,12] This is an exciting addition to the current options that may have intolerable side effects for some women.

In compilation, these updates continue to demonstrate the importance of tailored approaches to the management of early-stage breast cancer. Even within the context of HR+ disease, patients have very different risks of recurrence, and therefore, require different management strategies tailored to their individual risk. ●●

REFERENCES:

1. Slamon DJ, Stroyakovskiy D, Yardley DA, et al. Phase III NATALEE trial of ribociclib + endocrine therapy as adjuvant treatment in patients with HR-POSITIVE/HER22 early breast cancer. Presented at: 2023 American Society of Clinical Oncology Annual Meeting; June 2-6, 2023. Abstract LBA500.
2. Stroyakovsky D, Yardley D, Huang CS, et al. Ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) as adjuvant treatment in patients with HR+/HER2· early breast cancer: final invasive disease-free survival (iDFS) analysis from the NATALEE trial. Presented at: San Antonio Breast Cancer Symposium; December 5-9, 2023; San Antonio, TX. GS03-03.
3. Turner N, Reis-Filho J, Goetz M, et al. Genomic and transcriptomic profiling of primary tumors from patients with HR+, HER2-, node-positive, high-risk early breast cancer in the monarchE trial. Presented at: San Antonio Breast Cancer Symposium; December 5-9, 2023; San Antonio, TX. GS03-06.
4. Harbeck N, Rastogi P, O'Shaughnessy J, et al. Adjuvant abemaciclib plus endocrine therapy for HR+, HER2-, high-risk early breast cancer: results from a preplanned monarchE overall survival interim analysis, including 5-year efficacy outcomes. Annals of Oncology (2023) 34 (suppl_2): S1254-S1335. 10.1016/annonc/annonc1358.

5. J, Cicin I, Testa L, et al. Impact of dose reductions on efficacy of adjuvant abemaciclib for patients with high-risk early breast cancer (EBC): analyses from the monarchE study. Annals of Oncology (2023) 34 (suppl_2): S278-S324. 10.1016/annonc/annonc1297.
6. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Anthracycline-containing and taxane-containing chemotherapy for early-stage operable breast cancer: a patient-level meta-analysis of 100 000 women from 86 randomised trials. Lancet. 2023;401(10384):1277-1292.
7. Cardoso F, O'Shaughnessy J, McArthur H, et al. Phase 3 study of neoadjuvant pembrolizumab or placebo plus chemotherapy, followed by adjuvant pembrolizumab or placebo plus endocrine therapy for early-stage high-risk ER+/HER2- breast cancer: KEYNOTE-756. Presented at: San Antonio Breast Cancer Symposium; December 5-9, 2023; San Antonio, TX. GS01-02.
8. Loi S, Curigliano G, Salgado R, et al. Biomarker results in high-risk estrogen receptor positive, human epidermal growth factor receptor 2 negative primary breast cancer following neoadjuvant chemotherapy ffl nivolumab: an exploratory analysis of CheckMate 7FL. Presented at: San Antonio Breast Cancer Symposium; December 5-9, 2023; San Antonio, TX. GS01-01.
9. Partridge AH, Niman SM, Ruggeri M, et al. Interrupting endocrine therapy to attempt pregnancy after breast cancer. N Engl J Med. 2023;388:1645-1656.
10. Azim H, Niman S, Partridge A, et al. Fertility preservation and assisted reproductive technologies (ART) in breast cancer (BC) patients (pts) interrupting endocrine therapy (ET) to attempt pregnancy. Presented at: San Antonio Breast Cancer Symposium; December 5-9, 2023; San Antonio, TX. GS02-11.
11. Lederman S, Ottery FD, Cano A, et al. Fezolinetant for treatment of moderate-to-severe vasomotor symptoms associated with menopause (SKYLIGHT 1): a phase 3 randomised controlled study. Lancet. 2023;401(10382):1091-1102.
12. Johnson KA, Martin N, Nappi RE, et al. Efficacy and safety of fezolinetant in moderate to severe vasomotor symptoms associated with menopause: a phase 3 RCT. J Clin Endocrinol Metab. 2023;108(8):1981–199.

Hill Day From the Eyes of HOPA's Patient Advisory Panel

Michael Leung PharmD, BCOP
Clinical Pharmacy Specialist
The University of Texas MD Anderson Cancer Center

Morgan Kelly

Kathleen Sellick

HOPA has been a longstanding advocate for clinical teams to incorporate a hematology/oncology pharmacist in the care of patients with cancer. As part of this work, HOPA is committed to speaking with members of congressional offices in Washington, D.C. to understand the role of hematology/oncology pharmacists and the current landscape of cancer care in the United States. HOPA's Advocacy team coordinated two Hill Day events this year, a virtual Hill Day in May 2023 and an in-person Hill Day in September 2023, where HOPA members, lobbyists, and even Patient Advisory Panel members were able to meet with and share their perspectives and personal stories with congressional staff. Two of our current Patient Advisory Panelists share their experiences at HOPA Hill Day.

"While many pharmacists in HOPA work on the front-lines of health care or influence the landscape of drug development and research, we may often forget about the importance of advocacy."

Morgan Kelly, an oncology pharmacist and HOPA member, is a returning member of the Patient Advisory Panel. Diagnosed with Hodgkin lymphoma in 2013, Morgan worked at the cancer center where she received her care in Augusta, GA in 2014. She brings with her a unique perspective as both a patient and a hematology/oncology pharmacist.

Kathleen Sellick joins the HOPA Patient Advisory Panel as one of our newest members, providing her perspective as a caregiver for cancer patients. With a long 30-year history in hospital administration, Kathleen most recently served as the President and CEO of Rady Children's Hospital in San Diego, CA and also previously as the Executive Director of UW Medical Center in Washington. This expertise equipped her to advocate fiercely for her late mother who was treated for non-small cell lung cancer and also for her late husband who was treated for glioblastoma.

Hill Day: The Virtual / Reality Experience

A resident of South Carolina, Morgan first participated in HOPA's Virtual Hill Day in May 2023 with several other HOPA leaders, meeting with congressional office staff from North Carolina and South Carolina. Morgan was able to share concerns related to oral chemotherapy parity with intravenously administered medications as well as the ever-changing list of medications that rotate through the drug shortages list, both of which limit patient access to sometimes life-saving medications. Over the span of a single day, Morgan was able to meet with 10 different groups of congressional staff to share her stories and HOPA's public policy positions. This experience facilitated her confidence and comfort when she visited Washington, D.C. in September 2023. Now equipped with a better understanding of the rhythm of these meetings, it was an easy transition for the team as they split off into smaller groups to cover more ground across the different congressional offices. One thing that impressed Morgan was the proficiency in which congressional staff were acquainted with the issues discussed. While not every meeting included a Congress member or Senator, each meeting included someone who was intimately involved in the workings of developing bills and implementing plans that would affect how our federal government operates. In participating in Hill Day, Morgan discovered a greater appreciation for the legislative process and the grand scale of how bills are proposed, developed, discussed, and finally taken to a vote.

Kathleen first participated in HOPA's Hill Day in Washington, D.C. in September 2023. While in her capacity as a hospital administrator, she has advocated extensively with members of Congress. She was particularly struck by how well HOPA's lobbyists and staff conducted Hill Day. HOPA's advocates were well-informed and briefed on the organization's public policy positions as well as key talking points. Like Morgan, Kathleen felt her Hill Day experience was particularly meaningful because of how they were able to meet with staffers who understood the issues being discussed and those who would be able to do something about issues like drug shortages and oral chemotherapy drug parity. Because caregivers are new to the HOPA Patient Advisory Panel, Kathleen was able to share her unique caregiver experience in advocating for greater representation for hematology/oncologist pharmacists as well as for increased access to life-saving medications for patients with cancer.

We are Agents of Change

One common theme between Kathleen's and Morgan's experiences was their desire for HOPA members to understand the importance of advocacy. It's the shared belief that our voices need to be heard in congressional offices. One of the deepest human needs is that of connectedness and community – to feel as though we understand one another and empathize with others. Both Kathleen and Morgan recognized that one of the integral moments of their experi-

ences was when they started asking congressional staff whether they knew family or friends affected by cancer. In doing so, they appealed to the human desire to help those around them. For some people, cancer may have been a diagnosis they faced personally, while for others, it may have been a close loved one that they were caring for. It's important to establish that human connection with those in positions of power so that they might understand what it is that we as hematology/oncology pharmacists strive to achieve. Kathleen, Morgan, and countless others who participated in Hill Day created relationships with congressional offices and established the common feeling of wanting to help their own loved ones. They also encouraged and asked these lawmakers and officials to sign on to specific legislative bills as they passed through both the House of Representatives and the Senate.

While many pharmacists in HOPA work on the front-lines of health care or influence the landscape of drug development and research, we may often forget about the importance of advocacy. Like Morgan and Kathleen have both shared, advocacy is where change can happen on a greater scale. It is the difference in ensuring equitable access to potentially curative medications for cancer care or helping entire populations of patients see paradigm-changing advances in medical care. My only personal experiences with advocacy came in the form of participating in the University of Maryland's Legislative Day while I was a student there nearly ten years ago. Over the span of four hours, students and faculty from the school spoke with state legislators on the importance of pharmacists in direct patient care and in the interest of promoting public health. In speaking with both Kathleen and Morgan, I was reminded of those experiences and how they allowed me to better understand the landscape of healthcare and some of the unique challenges faced by patients undergoing treatment for cancer. The excitement and passion with which Morgan and Kathleen shared their advocacy experience with me renewed my own intent to identify opportunities to impact policies on both a local and national level. Both Kathleen and Morgan immediately recognized that congressional staff were interested in knowing where each of the HOPA representatives participating in Hill Day lived. As elected officials, they work for their constituents and want to hear what we believe to be important issues.

Next Steps

Following the experiences at Hill Day, it's reasonable to wonder, "*What's next? Where do we go from here?*" As Kathleen reminds us, "show up, speak up and vote!" Whether it be in local, state, or national elections, our voice matters. Our elected officials should listen to and represent our voices on the national scale and vote as their constituents demand. Our role as pharmacists can be to educate ourselves on healthcare-related bills and platforms that promote the work of pharmacists and patient safety. As members of HOPA, we are already well-aware of the value and care we provide on a daily basis. As a matter of fact, our patients, colleagues, and peers all probably recognize the important roles we play in the many facets of healthcare. Why not look into opportunities to call and speak with your own local elected officials? Why not share the work you are doing on an everyday basis and talk about the impact you have on the people around you? In her closing remarks to me, Morgan shares that "if I can take what I have learned and pay it forward, it will have been worth it." On a small scale, her role as an oncology infusion pharmacist allows her to impact patients directly. On a larger scale, she recognizes how participating with HOPA at Hill Day expands that impact on a national policy level. As we begin this new year, ask yourself how you might push your own influence and voice to advocate for patients and hematology/oncology pharmacy. ●●

Cardiac Safety of Pegylated Liposomal Doxorubicin After Conventional Doxorubicin Exposure in Patients With Sarcoma and Breast Cancer

Maher Alhaja, PharmD
Clinical Hematology/Oncology Pharmacist
Kaiser Permanente

Background

The existence of a dose-dependent cardiotoxicity correlating with lifetime cumulative doses of doxorubicin has been well established.[1,2] Early studies of administration of the medication evinced a possible correlation, with further study ultimately impacting prescriber guidelines and United States Food and Drug Administration (FDA) labeling.[3] However, there is limited evidence on the cardiac safety of high cumulative doses of pegylated liposomal doxorubicin (PLD) in patients with sarcoma and breast cancer (BC) who have had previous exposure to conventional doxorubicin in the adjuvant setting. The purpose of this study was to evaluate the risk of cardiotoxicity associated with PLD administration in patients with prior exposure to conventional doxorubicin. Given that many patients with sarcoma and BC receive conventional doxorubicin in earlier settings and may require PLD in later lines of treatment, it is vital to assess the risk of cardiotoxicity in this population.

"Given that many patients with sarcoma and breast cancer receive conventional doxorubicin in earlier settings and may require pegylated liposomal doxorubicin in later lines of treatment, it is vital to assess the risk of cardiotoxicity in this population."

Methods

This was a single-center, observational, retrospective cohort study conducted in patients ≥18 years with sarcoma or BC who were exposed to conventional doxorubicin from an earlier line of treatment before PLD between January 2010 to May 2022 at the University of California San Francisco, Helen Diller Family Comprehensive Cancer Center. Patients were evaluated for the presence of cardiac toxicity at any point in their treatment course. Cardiac toxicity was defined as ≥10% decrease in left ventricle ejection fraction (LVEF) or a new diagnosis of heart failure within six months after PLD cessation.

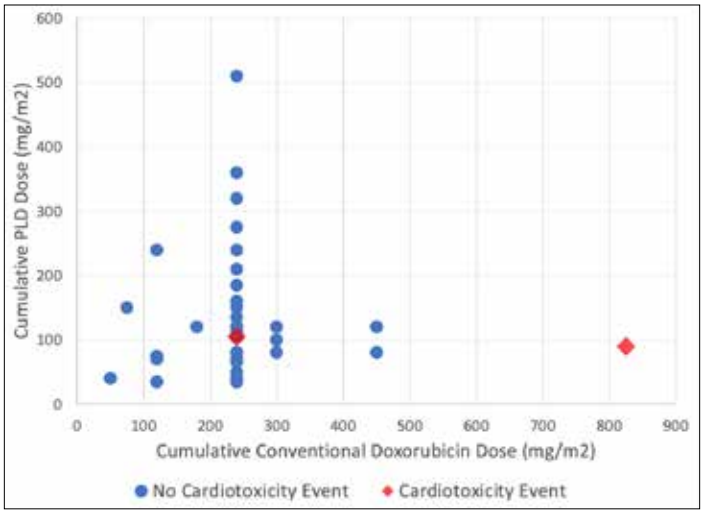
Results

During the study period from January 2010 to May 2022, 494 patients receiving PLD were screened, and 50 patients met inclusion criteria: eight (16%) sarcoma and 42 (84%) BC patients. Patients were excluded if they were participating in clinical trials, had a primary cancer diagnosis other than sarcoma or BC, or were receiving PLD without prior conventional doxorubicin exposure. There were a total of 7 sarcoma types, including leiomyosarcoma (n=2, 25%), liposarcoma (n=1, 12%), osteosarcoma (n=1, 12%), Kaposi sarcoma (n=1, 12%), unclassified spindle sarcoma (n=1, 13%), rhabdomyosarcoma (n=1, 13%), and malignant peripheral nerve sheath tumor (n=1, 13%), with leiomyosarcoma being the most common type. BC receptor status was HR+/HER2- (n=29, 69%), HR-/HER2- (n=10, 24%), HR+/HER2+ (n=2, 5%), and HR-/HER2+ (n=1, 2%).

The mean age at the time of PLD initiation in the sarcoma and breast cohorts was 55 years and 54 years, respectively. Fifty percent of patients in the sarcoma group were female, and most patients in the BC group were female (98%). All sarcoma patients were Caucasian, while the BC group included Caucasian (76%), Asian (15%), Black (2%), Other (1%), and Unknown (5%). One patient in the sarcoma group and none of the patients in the BC group had a past medical history of heart failure. The median lifetime cumulative conventional doxorubicin dose was higher in sarcoma patients (450 mg/m^2 with a maximum dose of 825 mg/m^2) compared to breast patients (240 mg/m^2 with a maximum dose of 300 mg/m^2). Dexrazoxane administration during conventional doxorubicin treatment occurred in three sarcoma patients (38%) and none of the BC patients. Prior or concurrent exposure to cardiotoxic agents while on PLD was observed in three sarcoma patients and in four BC patients. These agents included ifosfamide, pazopanib, trastuzumab, pertuzumab, everolimus, and ribociclib.

The median lifetime cumulative PLD dose in patients with sarcoma and BC was 105 mg/m^2 in both groups, with a maximum of 150 mg/m^2 and 510 mg/m^2, respectively. The mean baseline LVEF before PLD initiation was 60% and 63% in sarcoma patients and BC patients, respectively. None of the sarcoma or BC patients received dexrazoxane while on PLD. Of the 42 patients in the BC group, 22 had available echocardiogram results while receiving PLD, and three patients experienced a 10% or greater decline in LVEF. The mean time to LVEF decline from PLD initiation was five months in these patients. The mean cumulative PLD dose in BC patients with a >10% decrease in LVEF was 177 mg/m^2. One patient in the BC group developed heart failure within six months after stopping PLD. A LVEF decrease of 10% or more was not observed in the sarcoma group. One sarcoma patient had a previous diagnosis of heart failure prior to PLD initiation. Patient-specific lifetime cumulative dosing of conventional doxorubicin and PLD and whether the patient experienced a cardiotoxicity event is shown in Figure 1.

FIGURE 1: Cardiotoxicity Associated With Cumulative Doxorubicin and PLD Dose



Discussion and Conclusion

Limited data exist evaluating the cardiac safety of PLD in sarcoma and BC patients following previous exposure to conventional doxorubicin. The study results do not appear to suggest an increased incidence of cardiotoxicity in these patients. Among the 50 patients included in this study, three patients with BC experienced ≥10% decrease in LVEF, but none in the sarcoma group, despite the higher lifetime cumulative doxorubicin dose. The small sarcoma sample size (n=8) and the receipt of dexrazoxane during conventional doxorubicin (38%) may have contributed to no observations of ≥10% decrease in LVEF. It is possible that other external factors have a bearing on the incidence of cardiotoxicity, such as the history of administered medications and prior radiation exposure. The most common cardiotoxic agents used in the BC group were trastuzumab, pertuzumab, and ribociclib. Among the three patients with BC who had a greater than 10% decrease in LVEF, only one patient developed clinical manifestations of heart failure within six months of PLD cessation. Notably, this patient had a history of prior radiation within six months of heart failure diagnosis and previous exposure to everolimus, which has been associated with cardiac dysfunction.[4]

Although patients with sarcoma did not experience ≥10% decline in LVEF, one patient with a prior diagnosis of heart failure did have a cardiomyopathy event within six months of PLD cessation. This patient was able to receive three cycles of PLD prior to the cardiac event. It is uncertain if PLD was the sole contributing factor for this cardiac event, as this patient had a lower baseline LVEF of 50-55% and was previously on pazopanib, another known agent that may cause cardiotoxicity.[5,6] The most common cardiotoxic agents used in the sarcoma group were pazopanib and ifosfamide.

This study has several limitations, including a small sample size, a retrospective nature relying on accurate documentation, a single-center and observational study design, and the inconsistency of LVEF monitoring due to variations in clinical practice among providers. Additional research is needed with a greater representation of each type of cancer and a larger sample size to further validate our findings. A multicenter retrospective study or meta-analysis study is likely necessary to obtain enough power to draw stronger conclusions.

PLD administration in patients with sarcoma and BC and prior exposure to conventional doxorubicin was found to have an incidence of cardiotoxicity of 6%. Despite LVEF declines, only 2% of patients manifested clinical heart failure. At the time of this writing, there remain many lingering questions regarding the long-term safety of administration, and future studies or meta-analyses are likely necessary to confirm the safety of PLD use after conventional doxorubicin. ●●

REFERENCES:

1. Khouri MG, Douglas PS, Mackey JR, et al. Cancer therapy-induced cardiac toxicity in early breast cancer. Circulation. 2012;126(23):2749-2763. doi:10.1161/circulationaha.112.100560
2. Harris L, Batist G, Belt R, et al. Liposome-encapsulated doxorubicin compared with conventional doxorubicin in a randomized multicenter trial as first-line therapy of metastatic breast carcinoma. Cancer. 2002;94(1):25-36. doi:10.1002/cncr.10201
3. Adriamycin [package insert]. New York, NY: Pfizer, Inc. Published March 2020. Accessed: July 4, 2023: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/050467s078,050629s030lbl.pdf.
4. Nayernama A, Waldron P, Salaam T, et al. Postmarketing safety review of everolimus and cardiac failure or left ventricular dysfunction. J Clin Onc. 2016;34(15):S18226. doi:10.1200/JCO.2016.34.15_suppl.e18226
5. Karaağaç M, Eryılmaz MK. Pazopanib-induced fatal heart failure in a patient with unresectable soft tissue sarcoma and review of literature. J Oncol Pharm Pract. 2020;26(3):768-774. doi:10.1177/1078155219875797
6. Justice CN, Derbala MH, Baich TM, et al. The impact of pazopanib on the cardiovascular system. J Cardiovasc Pharmacol Ther. 2018;23(5):387-398. doi:10.1177/1074248418769612

Who's on First, What's on Second? Clinical Conundrums in Chronic Lymphocytic Leukemia

Diana Mansour, PharmD, BCOP
Oncology Pharmacy Specialist
Outpatient Transplant and Cellular Therapies/Malignant Hematology
WVU Medicine

Spencer K. Yingling, PharmD, BCOP
Oncology Pharmacy Specialist
Outpatient Transplant and Cellular Therapies/Malignant Hematology
WVU Medicine

Background

With an estimated 18,740 new cases in 2023, chronic lymphocytic leukemia (CLL) accounts for nearly one quarter of all newly diagnosed leukemias each year.[1,2] While asymptomatic patients with early-stage disease (Rai 0, Binet A) are managed with active surveillance, patients with symptomatic intermediate and high-risk disease require treatment. According to the International Workshop on CLL (iwCLL), indications for pharmacologic intervention include progressive symptoms such as leukocytosis, progressive or symptomatic lymphadenopathy, hepatosplenomegaly, marrow failure, symptomatic or functional extra-nodal involvement, steroid refractory autoimmune cytopenia, and/or disease-related constitutional symptoms.[3]

Apart from allogeneic stem cell transplantation, for which most patients are ineligible, CLL is incurable. Therefore, treatment goals focus on improving quality of life and extending survival. In the dynamic arena of CLL treatment, two main therapeutic approaches have emerged as prominent contenders. On one side are continuous Bruton's tyrosine kinase inhibitors (BTKi), celebrated for their remarkable ability to selectively target malignant B cells, thus disrupting CLL progression at its core. BTKi have garnered substantial attention due to their impressive efficacy, improved tolerability profiles, and ease of oral administration, making them a frontrunner in the first-line treatment race. On the opposing side, the combination of venetoclax and obinutuzumab (VenO) has taken the spotlight in offering a potent dual assault on CLL cells via fixed treatment duration. The progression-free survival (PFS) and/or overall survival (OS) benefits of these regimens have shifted the frontline treatment landscape away from traditional chemoimmunotherapy toward targeted therapies. Given the median age of diagnosis of 70 years, many patients with CLL have comorbidities that qualify them as "unfit" and making targeted therapies more appealing than traditional chemoimmunotherapy which carries risks of cytopenias, infection, and secondary malignancies.[4]

"While some patients may prefer a time-limited approach with VenO, others may be enticed by the ability to receive treatment from the comfort of their own homes with an oral BTKi."

Additionally, traditional chemoimmunotherapy has demonstrated decreased activity in patients with poor prognostic markers, such as TP53 mutation, del(17q), del(11q), and unmutated immunoglobulin heavy-chain variable region gene (IGHV) status.[5] However, each of the targeted frontline treatment options also come with adverse events and logistical considerations that must be evaluated when initiating therapy. With the availability of multiple treatment regimens approved in the frontline treatment of CLL, the sequencing of these therapies has been called into question. Selection of first-line treatment for patients with CLL must consider disease prognostic factors, patient preference, functional status, comorbidities, and long-term impact on subsequent treatment options.

The clash of these compelling perspectives underscores the complexity of CLL management, leaving clinicians and patients grappling with the pivotal decision of choosing the most suitable treatment path. Diana and Spencer utilize both regimens for treatment initiation in clinical practice and will make a case for each regimen as the preferred frontline therapy.

BTKi-based Therapy

By covalently binding to cysteine 481 (C481) of Bruton's tyrosine kinase, BTKi, including ibrutinib, acalabrutinib, and zanubrutinib, irreversibly inhibit the enzyme, thereby blocking B-cell receptor signaling, ultimately preventing proliferation and survival of CLL cells. The first-generation agent, ibrutinib, is the most potent inhibitor but also has lower kinase selectivity and more off-target effects. Second-generation inhibitors, acalabrutinib and zanubrutinib, offer higher specificity for the BTK enzyme and, as a result, improved tolerability.[6] Table 1 outlines the significant clinical trials paving the way for BTKi use in upfront CLL treatment.

RESONATE-2 was the first frontline study to assess a BTKi in CLL, but the study received criticism as it was felt that chlorambucil alone was not an adequate comparator arm.[7,8] The PFS benefit of ibrutinib in the frontline setting was reaffirmed in A041202. Notably, no additional PFS or OS benefit was observed with the addition of rituximab to ibrutinib.[9] Acalabrutinib entered the frontline treatment arena in ELEVATE-TN. The PFS benefit of acalabrutinib was maintained across all high-risk subgroups. While a post-hoc analysis found a PFS benefit of acalabrutinib plus obinutuzumab over acalabrutinib alone, this study was not powered to detect a difference between the two acalabrutinib-based arms.[10,11,12] The SEQUOIA trial then compared zanubrutinib to bendamustine-rituximab (BR) in the frontline setting and demonstrated improvement of PFS for zanubrutinib compared with BR with a shorter duration of follow-up.[13]

Table 1. Notable Frontline BTKi Studies in CLL

Trial Name	Patient Population	Treatment Arms	Efficacy Outcomes	Select Grade 3 or Higher Adverse Events[4]
RESONATE-2[7,8]	269 untreated CLL patients ≥65 years with high-risk cytogenetics except del (17p)	Ib (n=136) vs. Chl (n=133)	7-year PFS: 59% (Ib) vs. 9% (Chl) Median follow-up at 82.7 months: Median OS – not reached (Ib) vs. 89 months (Chl); HR 0.453 (CI 0.276–0.743)	Neutropenia: 10% (Ib) vs. 18% (Chl) Bleeding: 4% (Ib) vs. 2% (Chl) Diarrhea: 4% (Ib) vs. 0% (Chl) Atrial fibrillation: 1.5% (Ib) vs. UK (Chl) Hypertension: 4% (Ib) vs. 0% (Chl)
ALLIANCE-A041202[9]	547 untreated CLL patients ≥65 years with high-risk cyto-genetics	BR (n=183) vs. Ib (n=183) vs. IbR (n=182)	48-month PFS: 47% (BR) vs. 76% (Ib) vs. 76% (IbR) 48-month OS: 84% (BR) vs. 85% (Ib) vs. 86% (IbR)	Neutropenia: 40% (BR) vs. 15% (Ib) vs. 21% (IbR) Bleeding: 0% (BR) vs. 2% (Ib) vs. 4% (IbR) Diarrhea: Not Reported Atrial fibrillation: 3% (BR) vs. 9% (Ib) vs. 6% (IbR) Hypertension: 15% (BR) vs. 29% (Ib) vs. 33% (IbR)
ELEVATE-TN[10, 11, 12]	535 treatment-naïve CLL patients ≥65 years or ≤65 years with comorbidities, with high-risk cyto-genetics	A (n=179) vs. AO (n=179) vs. CO (n=177)	Median follow-up 58.2 months: Median PFS: NR (A-containing arms) vs. 27.8 months (CO) (p < 0.0001) 60-month OS: 84% (A) vs. 90% (AO) vs. 82% (CO)	Neutropenia: 9.5% (A) vs. 29.8% (AO) vs. 41.4% (CO) Bleeding: 2% (A) vs. 2% (AO) vs. 0% (CO) Diarrhea: 0.6% (A) vs. 4.5% (AO) vs. 1.8% (CO) Atrial fibrillation*: 4% (A) vs. 3% (AO) vs. 1% (CO) Hypertension: 2% (A) vs. 3% (AO) vs. 3% (CO)
SEQUOIA[13]	590 treatment-naïve CLL patients ≥65 years or ineligible for fludarabine, cyclophosphamide rituximab (FCR), and without del(17p)	Z (n=241) vs. BR (n=238)	Median follow-up 26.2 months: PFS: NR (Z) vs. NR (BR); HR 0.42 (95% CI 0.28–0.63), p < 0.0001 24-month OS: 94.3% (Z) vs. 94.6% (BR)	Neutropenia: 12% (Z) vs 51% (BR) Bleeding: 4% (Z) vs 1.8% (BR) Diarrhea: 1% (Z) vs 1% (BR) Atrial fibrillation: 0.4% (Z) vs 1.3% (BR) Hypertension: 6.3% (Z) vs 4.8% (BR)

Legend: *CLL* chronic lymphocytic leukemia, *UK* unknown, *NR* not reached, *Ib* ibrutinib, *Chl* chorambucil, *HR* hazard ratio, *CI* confidence interval, *BR* bendamustine-rituximab, *IbR* ibrutinib-rituximab, *A* acalabrutinib, *AO* acalabrutinib-obinutuzumab, *CO* chlorambucil-obinutuzmab, *Z* zanubrutinib
*= Any grade

BCL2 Inhibitor-based Therapy

In contrast to BTKi which were continued until progression/intolerability, venetoclax, an oral B-cell lymphoma 2 (BCL-2) inhibitor, was studied as a fixed duration therapy in the frontline setting. Table 2 highlights clinical trial data for the combination of venetoclax and obinutuzumab. While cross trial comparisons are inappropriate, it is noted that patients with del(17p) and TP53 had shorter PFS rates with VenO versus frontline BTK inhibitor studies.[14,15]

Pros and Cons of BTKi and Venetoclax-based Therapies

The time-limited approach of VenO is appealing to many patients and clinicians. Additionally, undetectable minimal residual disease (uMRD) is associated with improved PFS and OS with CLL treatment.[16] As evidenced by higher rates of uMRD in the VenO arm of CLL14, venetoclax is a potent inducer of apoptosis. While this agent allows for deep molecular responses, it presents the challenge of tumor lysis syndrome and is administered with a 4-week initial ramp up to decrease the risk of this adverse event. Frequent trips to the infusion center for intravenous obinutuzumab administration, supportive care requirements, and stringent monitoring (requiring inpatient admission for initial ramp up doses in high-risk patients) are the major pitfalls of this regimen.[17]

Due to their improved safety profiles, zanubrutinib and acalabrutinib (+/- obinutuzumab) are presented as preferred frontline BTKi treatment options in the CLL National Comprehensive Cancer Network (NCCN) guidelines.[17] BTKi may be preferred in patients with TP53 mutations as well as those who prefer less frequent visits to healthcare facilities. While BTKi are often presented as

Table 2. Frontline venetoclax-based regimen for CLL

Trial Name	Patient Population	Treatment Arms	Efficacy Outcomes	Grade 3 or Higher Adverse events[4]
CLL14[14,15]	432 treatment-naïve CLL adult patients with comorbidities and high-risk cytogenetics	VenO (n=216) vs. CO (n=216)	5-years PFS: 62.6% (VenO) vs. 27% (CO) 5-year OS: 81.9% (VenO) vs. 77% (CO); HR 0.72 (95% CI 0.48–1.09), p = 0.12	Neutropenia: 52.8% VenO vs. 48.1% CO Bleeding: Not Reported Diarrhea: 4.2% (VenO) vs. 0.5% (CO) Atrial fibrillation: Not Reported Hypertension: Not Reported

Legend: *VenO* venetoclax-obinutuzumab

a simple oral medication taken at home, it is an important role of the pharmacist to discuss frequency of dosing and additional supportive care medications that may be needed. The NCCN guidelines recommend considering herpes simplex virus (HSV) and Pneumocystis jirovecii pneumonia (PCP) prophylaxis in patients receiving BTKi, which may contribute significantly to patients' pill burden.[15] As previously mentioned, the adverse effects of BTKi are associated with off-target activity with major tolerability concerns being atrial fibrillation and increased bleeding from C-terminal Src kinase (CSK) and Tec inhibition, respectively. Patients with underlying atrial fibrillation/flutter, pre-existing hypertension, and other cardiovascular disorders may be at greater risk for cardiovascular complications.[4] Moreover, epidermal growth factor receptor (EGFR) inhibition may induce diarrhea/rash. Lastly, due to changes in the CXCR4 pathway, providers should be aware and patients should be counseled that BTKi can result in a transient increase in lymphocyte counts, but this does not represent disease progression.[18,19]

Frontline Triplet Therapy

While frontline triplet therapy (BTKi-Ven-antiCD20 monoclonal antibody) has achieved higher uMRD compared to VenO, PFS and response rates were similar in the short follow up. Additionally, the triplet regimen carries a greater chance for adverse events. While it is not currently an approved regimen, it is postulated that frontline triplet therapy may achieve a deep molecular remission but may also limit subsequent lines of treatment.[4,20]

Sequencing

Along with the previously mentioned considerations for first-line CLL therapy, prior first-line therapy, duration of remission, and acquired treatment resistance are also important factors for relapsed/refractory CLL/small lymphocytic lymphoma (SLL) treatment options. While optimal sequencing of therapy has not been identified, second-line regimens generally involve the use of a first-line regimen that has not previously been tried.[17] Additionally, pirtobrutinib, a highly selective BTKi with minimal off-target activity, is a novel agent that non-covalently binds to BTK, thus possibly overcoming covalent BTKi resistance. On December 1, 2023, pirtobrutinib was granted an accelerated United States Food and Drug Administration (FDA) approval for the treatment of adult patients with CLL/SLL who have received at least two prior lines of therapy, including a BTKi and BCL-2 inhibitor, based on the phase I/II BRUIN Trial.[21,22]

Conclusion

A one size fits all approach to CLL treatment does not exist, and there are still many unresolved questions that need answered when discussing first line treatment. Figure 1 highlights these uncertainties. While some patients may prefer a time-limited approach with VenO, others may be enticed by the ability to receive treatment from the comfort of their own homes with an oral BTKi. Pharmacists practicing in malignant hematology must discuss unique logistical concerns, adverse effects, and drug interactions for both treatment strategies with patients and providers alike. Additionally, once a regimen is selected, patient education, medication access, appropriate monitoring, supportive care, side effect management, and adherence assessments become invaluable roles of the pharmacist in CLL treatment. While frontline treatment of CLL has improved dramatically over the course of the last decade, management of newer targeted treatment options requires teamwork between pharmacists, providers, and patients. ●●

Figure 1. Unresolved questions for first line CLL treatment[4]

Preferred BTKi?	Should an anti-CD20 mAb be added to a BTKi?	Continuous BTKi or fixed-duration venetoclax-based therapy?	Optimal therapy for TP53 mutation?
Acalabrutinib and zanubrutinib preferred to ibrutinib in NCCN guidelines based on tolerability	Ibrutinib: no signficiant benefit with rituximab Acalabrutinib: underpowered to detect survival benefit with obinutuzumab Zanubrutinib: monotherapy only	Patient preference, comorbidities, concomitant medications	Targeted therapies preferred to chemoimmunotherapy BTKi may be preferrable to venetoclax-based treatment

REFERENCES:

1. Key Statistics for Chronic Lymphocytic Leukemia. American Cancer Society. Updated January 12, 2023. https://www.cancer.org/cancer/types/chronic-lymphocytic-leukemia/about/key-statistics.html. Accessed November 4, 2023.
2. Cancer Stat Facts: Leukemia — Leukemia — Chronic Lymphocytic Leukemia (CLL). National Cancer Institute: surveillance, epidemiology, and end results program. https://seer.cancer.gov/statfacts/html/clyl.html. Accessed November 4, 2023.
3. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood. 2018;131(25):2745-2760. doi:https://doi.org/10.1182/blood-2017-09-806398
4. Bennett R, et al. Unresolved questions in selection of therapies for treatment-naïve chronic lymphocytic leukemia. J Hematol Oncol. 2023;16(1):72. doi:10.1186/s13045-023-01469-7
5. Bewarder M, Stilgenbauer S, Thurner L, Kaddu-Mulindwa D. Current treatment options in CLL. Cancers (Basel). 2021;13(10):2468. doi:10.3390/cancers13102468
6. Palma M, Mulder TA, Österborg A. BTK inhibitors in chronic lymphocytic leukemia: biological activity and immune effects. Front Immunol. 2021;12:686768. doi:10.3389/fimmu.2021.686768
7. Burger J, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. N Engl J Med 2015; 373:2425-2437.

8. Barr PM, Owen C, Robak T, et al. Up to 8-year follow-up from RESONATE-2: first-line ibrutinib treatment for patients with chronic lymphocytic leukemia. Blood Advances. 2022;6(11):3440-3450. https://doi.org/10.1182/bloodadvances
9. Woyach JA, et al. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. N Engl J Med. 2018;379(26):2517-2528. doi: 10.1056/NEJMoa1812836
10. Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial [published correction appears in Lancet. 2020 May 30;395(10238):1694]. Lancet. 2020;395(10232):1278-1291. doi:10.1016/S0140-6736(20)30262-2
11. Sharman JP, Egyed M, Jurczak W, et al. Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naïve chronic lymphocytic leukemia. Leukemia. 2022;36(4):1171-1175. doi:10.1038/s41375-021-01485-x
12. Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib ffl obinutuzumab versus obinutuzumab + chlorambucil in treatment-naïve chronic lymphocytic leukemia: five-year follow-up of ELEVATE-TN. J Clin Oncol. 2022;40(16_suppl):7539-7539. doi: https://doi.org/10.1200/jco.2022.40.16_suppl.7539
13. Tam CS, Brown JR, Kahl BS, et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial [published correction appears in Lancet Oncol. 2023 Mar;24(3):e106]. Lancet Oncol. 2022;23(8):1031-1043. doi:10.1016/S1470-2045(22)00293-5
14. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. N Engl J Med. 2019;380(23):2225-2236. doi:10.1056/NEJMoa1815281
15. Al-Sawaf O, Zhang C, Tandon M, et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2020;21(9):1188-1200. doi:10.1016/S1470-2045(20)30443-5
16. Fresa A, Autore F, Galli E, et al. Treatment options for elderly/unfit patients with chronic lymphocytic leukemia in the era of targeted drugs: a comprehensive review. J Clin Med. 2021;10(21):5104. doi:10.3390/jcm10215104
17. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Chronic lymphocytic leukemia/small lymphocytic lymphoma, v1.2024. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf
18. Christensen BW, Zaha VG, Awan FT. Cardiotoxicity of BTK inhibitors: ibrutinib and beyond. Expert Rev Hematol. 2022;15(4):321-331. doi:10.1080/17474086.2022.2067526
19. O'Brien SM, Brown JR, Byrd JC, et al. Monitoring and managing BTK inhibitor treatment-related adverse events in clinical oractice. Front Oncol. 2021;11:720704. doi:10.3389/fonc.2021.720704
20. Davids MS, Lampson BL, Tyekucheva S, et al. Acalabrutinib, venetoclax, and obinutuzumab as frontline treatment for chronic lymphocytic leukaemia: a single-arm, open-label, phase 2 study. Lancet Oncol. 2021;22(10):1391-1402. doi:10.1016/S1470-2045(21)00455-1
21. Thompson PA, Tam CS. Pirtobrutinib: a new hope for patients with BTK inhibitor-refractory lymphoproliferative disorders. Blood. 2023;141(26):3137-3142. doi:10.1182/blood.2023020240
22. Mato AR, Woyach JA, Brown JR, et al. Pirtobrutinib after a covalent BTK inhibitor in chronic lymphocytic leukemia. N Engl J Med. 2023;389(1):33-44. doi:10.1056/NEJMoa2300696

Board Update

So Many Accomplishments in Such Little Time

LeAnne Kennedy, PharmD, BCOP, CPP, FHOPA
HOPA President (2023-2024)
Oncology Clinical Manager
Atrium Health Wake Forest Baptist
Winston-Salem, NC

It's March in North Carolina, where there is a nearly two-hour increase in sunlight between the first and last day of the month. In many ways, that steady ramp up to a new season runs parallel to HOPA's committee year.

20th Annual Conference and Anniversary Celebration

Right now, committees are gearing up to ensure Annual Conference 2024 has all the great science you want, continuing education you need, and networking you cherish. I hope you will join me on April 3-6 in Tampa, Florida for our 20th Annual Conference and Anniversary Celebration.

Annual Call for Volunteers

Our annual call for committee volunteers opens soon. If you are new to HOPA or have not served on a committee before, be sure to apply in the Volunteer Activity Center on hoparx.org. We need members with interest and expertise in education and professional development, external affairs, industry relations, leadership development, and quality research, as well as those with a passion for advocacy.

Year 1 of 2023-2026 Strategic Plan

As we prepare for a new committee year, many of you are working hard to advance or finish initiatives from the current year. To say there has been an abundance of noteworthy work is an understatement. Some of our key 2023-2024 initiatives are outlined below.

Advocacy & Awareness

Drug shortages, oral chemo parity, and the role of the hematology/oncology pharmacist continue to be priorities. The Oral Parity Bill was reintroduced in the House and Senate and HOPA members spoke to the offices of elected officials during virtual HOPA Hill Day in the spring and in-person in the fall.

The newly combined Patient Outreach & Education Committee has curated and updated all HOPA's patient-facing resources and made them more accessible on the HOPA website. They are also planning a HOPA Patient Advocacy Summit.

Education

Educational updates and user-experience enhancements for Core Competency were completed in summer of 2023. In addition to the nearly 30% discount on education courses for HOPA members, the Core Competency Task Force also set tiered pricing for developing countries to make the learning as accessible as possible.

Our BCOP annual releases continue to ensure there are many opportunities throughout the year to earn BCOP credit through HOPA. In addition, strong partnerships with Pharmacy Times Continuing Education and the FDA's Oncology Center of Excellence, for example, give members even more learning opportunities.

Professional Practice

Thanks to our highly engaged members, we have added four new Special Interest Groups: Breast Cancer, Gynecologic Cancers, Classical Hematology, and Precision Health in Oncology. This brings our total number of SIGs to 18, all of whom use the recently enhanced HOPA Central to network and crowd source ideas. We are currently seeking facilitators and moderators for each SIG which gives another opportunity for leadership experience.

The Leadership Subcommittee launched the latest Mentorship cohort of seven pairs of mentors and mentees. We have also seen an increase in informal mentorship within committees and workgroups and through opportunities like Conference Buddies.

Quality Research

POPBC is on track to complete their Workload Unit Project in May of this year and have already begun to outline their next project. The Quality Oversight Committee is currently planning a White Paper on the Pharmacist's Role in Oncology Quality. The Oral Chemotherapy Collaborative is developing standards for oral anticancer agents.

HOPA continues to support pharmacist-led cancer research through the HOPA Research Fund. In 2023, 100% of HOPA Board Members donated to the fund and we are planning a 20th Anniversary campaign later this year where HOPA will match up to $20,000 of individual donations.

One easy way to support the HOPA Research Fund is to purchase HOPA gear, where 100% of proceeds go directly into the fund! We recently added new items to our online such as dri-fit tees, fleeces, insulated mugs, a dog bandana, and much more – including some items with the HOPA2024/20th Anniversary logo. I have to say, the prices are reasonable while still raising funds to support member research. Visit printyourcause.com or find a link on our website.

Thank you to all our members for supporting and/or participating in pharmacist-led cancer research and for all the resources, best practices, and thought leadership you bring to our profession. I truly am amazed at all that you have done this year. It has been an honor to serve as HOPA President and I look forward to introducing your next President, Jolynn Sessions during HOPA2024. ●●

HOPA
Hematology/Oncology
Pharmacy Association

555 East Wells Street, Suite 1100
Milwaukee, WI 53202
hoparx.org

HOPA WELCOMES YOU TO

OUR 20TH ANNIVERSARY CONFERENCE

APRIL 3-6, 2024
TAMPA CONVENTION CENTER
TAMPA, FLORIDA!

All of the great topics, speakers and networking you've come to expect from HOPA's annual conference. ***There's more!*** Expect many exciting 20th anniversary activities throughout the conference!

HOPA2024
20 Years of Optimizing Cancer Care

VISIT HOPARX.ORG