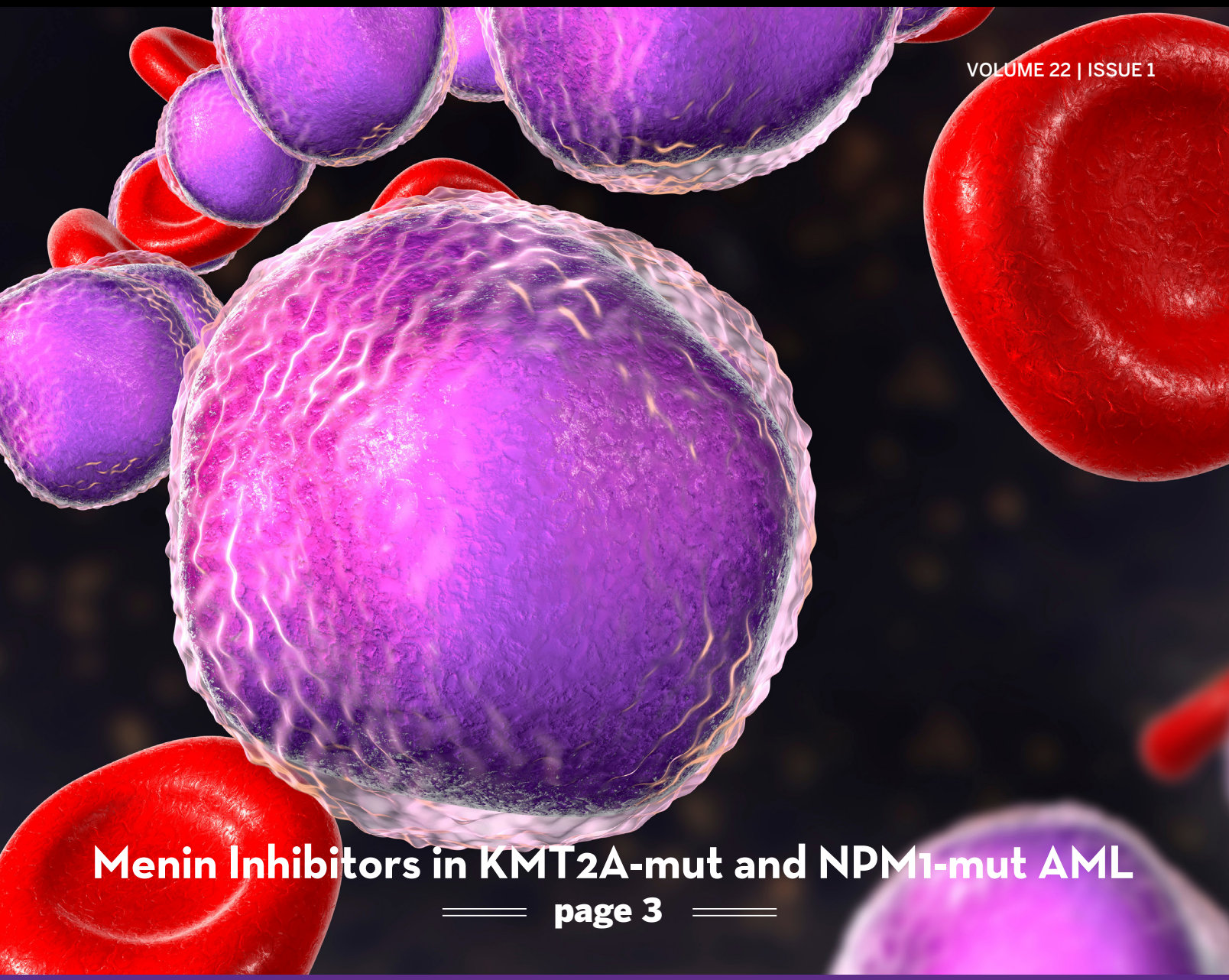
HOPA NEWS

Pharmacists Optimizing Cancer Care

VOLUME 22 | ISSUE 1



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FEATURE

Menin Inhibitors in KMT2A-mut and NPM1-mut AML

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Overview of Acute Leukemia

Acute leukemia is an aggressive hematologic malignancy with a variety of molecular and genetic dysregulations. Increased understanding of genomic alterations and subsequent risk stratifications have expanded treatment options and allowed for the utilization of targeted therapies for both acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)[1]. However, patients with relapsed or refractory AML (R/R AML) have a poor prognosis with less than 20% of these patients alive after 5 years[2]. Outcomes further become less favorable with specific genetically heterogeneous types of AML, such as lysine N-methyltransferase 2A (KMT2A) mutated AML, which confer a higher risk of relapse and mortality[3]. Treatment options to achieve complete remission (CR) prior to allogeneic hematopoietic stem cell transplant (HSCT), and the only curative option in R/R leukemia, are limited by treatment intensity[4].

"In addition to the relapsed or refractory setting, menin inhibitors have the potential to be used in earlier lines of therapy either as monotherapy or in combination with other therapies."

Role of Menin in KMT2A and Nucleophosmin (NPM1)-mutated Acute Leukemia

Menin, a nuclear scaffold protein, has previously been identified to have leukemic oncogenic properties as it plays a key role in the regulation of hematopoiesis and proliferation of white blood cell precursors[5]. Menin's ability to bind with lysine KMT2A forms a KMT2A fusion protein that translocates to the nucleus and upregulates transcription of proto-oncogenes homebox (HOXA and HOXB), cofactor myeloid ecotropic virus insertion site 1 genes (MEIS1), and additional genes PBX3, MEF2C, and CDK6. KMT2A rearrangements occur in up to 10% of acute leukemias in children and adults. Menin's role in oncogenesis has also been implicated in another form of acute leukemia, nucleophosmin 1 (NPM1) mutated AML[6,7]. NPM1-mutated AML presents a similar gene expression to KMT2A-mutated AML where HOX and MEIS1 are also overexpressed, albeit the exact mechanism for NPM1 inducing HOX1 and MEIS1 overexpression requires further elucidation[7].

Subsequent studies evaluating the loss of function in menin binding found an attenuated oncogenicity of KMT2A fusion proteins and reversed the higher expression of HOX A/B and MEIS 1 genes that correlated with pluripotent stem cells[6]. The characterization and understanding of KMT2A on leukemia biology over the past decade, and the recent developments in the protein menin has catalyzed the development of a class of therapeutic agents, menin inhibitors, to target the menin-KMT2a complex and downregulation of proto oncogenes[8].

First in Human Studies and FDA Approval

On November 15, 2024, the menin inhibitor revumenib (Revuforj) received FDA approval for relapsed or refractory acute leukemia with a lysine methyltransferase (KMT2A) translocation in adult and pediatric patients aged one year and older[9]. This first in class approval for revumenib was based on the results of the open label, single arm, phase I/II trial AUGMENT-101 (NCT04065399)[10]. AUGMENT-101 evaluated revumenib administered in 28 day continuous cycles in 94 patients for safety endpoints and 57 patients for efficacy. The primary efficacy endpoints for the study were the rate of CR or CR with partial hematologic recovery (CRh). Secondary efficacy end points included overall response rate (ORR), duration of remission (DOR), and overall survival (OS).

Patients were included in the study if they had primary refractory (persistent leukemia following intensive induction chemotherapy) or relapsed refractory (unresponsive to most recent salvage treatment) KMT2Ar acute leukemia of any lineage, with no restriction on the number of types of prior therapies. Patients were also eligible regardless of transplant status, as long as those with post-transplant relapse were at least Day +60 post HSCT.

Of the 94 patients initially assessed during phase 1, 78 patients (83.0%) were diagnosed with AML, 14 (14.9%) were diagnosed with ALL, and two (2.1%) were diagnosed with acute leukemia of ambiguous lineage. The majority of patients (75.5%) were age 18 and older and heavily pretreated, with 28 patients (29.8%) receiving two lines of prior therapy and 41 (43.6%) receiving at least three lines of prior therapy. During phase 2 analysis, 49 patients (86.0%) were diagnosed with AML, seven (12.3%) were diagnosed with ALL, and one (1.8%) was diagnosed with acute leukemia of ambiguous lineage. Once again, the majority of patients were adults and heavily pretreated; 44 patients (77.2%) were age 18 and older, 14 patients received two lines of prior therapy (24.6%), and 26 (45.6%) received at least three lines of prior therapy.

Treatment related adverse events were highly prevalent, resulting in a dose reduction for 9.6% of patients and discontinuation for 12.8% of patients. Grade 3 or higher adverse events included febrile neutropenia in 35 patients (37.2%), differentiation syndrome in 15 patients (16.0%), and QTc prolongation in 13 patients (13.8%). No

patients discontinued treatment secondary to differentiation syndrome or QTc prolongation. The median time to initial onset and median duration of the initial event of differentiation syndrome were 10 days (range of 3-41 days) and 12 days (range of 3-31 days). Grade 5 adverse events within 30 days of the last dose of revumenib occurred in 14 of 94 patients (14.9%)..

With a median follow up of 6.1 months (range, 0.3-18.6) for the efficacy population, 13 patients (22.8%) achieved CR/CRh (P = .0036) with an ORR of 63.2% (95% CI, 49.3 to 75.6). The median time to CR/CRH was 1.9 months. The median DOR was 6.4 months (95% CI, 3.4 to not reached). Median OS was 8.0 months (95% CI, 4.1 to 10.9). Median time to first ORR was 0.95 months. Of the patients who achieved CR/CRh, 14 (38.9%) received an allogeneic HSCT and seven of those patients resumed revumenib after transplant. Although the study authors reported observed responses across subgroups of patients with or without prior transplant, R/R disease, and varying numbers of prior lines of treatment, the study ultimately was not powered for analysis across subgroups.

Clinical Pearls of Revumenib[11]

Revumenib is available in oral tablet form and the recommended dose is dependent upon patient weight and concomitant CYP3A4 inhibitors. For patients weighing 40 kg or more, recommendations are for flat dosing of 270 mg orally twice daily without concomitant use of strong CYP3A4 inhibitors, or160 mg orally twice daily with concomitant use of strong CYP3A4 inhibitors. For patients weighing less than 40 kg, the recommended dose is dependent on the patient's BSA; 160 mg/m2 orally twice daily without concomitant use of strong CYP3A4 inhibitors or 95 mg/m2 orally twice daily with concomitant use of strong CYP3A4 inhibitors. Dose reduction recommendations for CYP3A4 drug drug interaction were supported by pharmacokinetic findings that revumenib AUC and Cmax is increased by 2-fold following concomitant use of multiple doses of strong CYP3A4 inhibitor azoles (posaconazole, voriconazole, and itraconazole). Dose modifications are only required for concomitant strong CYP3A4 inhibitors as studies using moderate CYP3A4 inhibitors fluconazole and isavuconazole did not result in clinically significant changes in revumenib concentrations. For patients unable to swallow whole tablets, the tablets may be crushed, dispersed in water, and administered within 2 hours of preparation. Also of note, the drug manufacturer specifically recommends for revumenib to be taken in either a fasted state or with a low-fat meal. The package labeling insert includes a box warning for differentiation syndrome. Recalling specifically back to the AUGMENT 101 trial, all instances of differentiation syndrome were treated with corticosteroids, and hydroxyurea was added for associated leukocytosis in six patients.

Table 1. Augment-101 Demographics and Efficacy

Parameter	Efficacy Population (n=57)	Safety Population (n=94)
Age, median (range)	34 (1.3 - 75)	37 (1.3 -75)
Sex, n (%) Male	 24 (42.1)	 38 (40.4)
Acute Leukemia Type, n(%) AML ALL ALAL	 49 (86) 7 (12.3) 1 (1.8)	 78 (83) 14 (14.9) 2 (2.1)
Co-occurring mutations, n(%) RAS FLT3 TP53	 9 (15.8) 5 (8.8) 4 (7)	 12 (12.8) 7 (7.4) 5 (5.3)
Prior Venetoclax, n(%)	41 (71.9)	61 (64.9)
Prior HSCT, n(%)	26 (45.6)	47 (50)
Responses Overall response rate, n(%) CR + CRh CRc MRD negativity Rate Within CR + CRh Within CRc	 36 (63.2) 13 (22.8) 25 (43.9) 7/10 (70) 15/22 (68.2)	-

Table 2. Augment-101 Safety

Parameter	Efficacy Population (n=57)	Safety Population (n=94)
Any Adverse Event, n(%)	-	93 (98.9)
AE occurred in ≥ 20% of patients, n(%) Nausea Febrile Neutropenia Diarrhea Edema Vomiting Neutropenia Transaminitis Differentiation Syndrome Hypokalemia Epistaxis Qtc prolongation Thrombocytopenia Rash Anemia Constipation Decreased Appetite Fatigue	-	 42 (44.7) 36 (38.3) 33 (35.1) 30 (31.9) 30 (31.9) 29 (30.9) 28 (29.8) 27 (28.7) 26 (27.7) 26 (27.7) 25 (26.6) 24 (25.5) 22 (23.4) 22 (23.4) 21 (22.3) 21 (22.3) 21 (22.3) 20 (21.3)
Any grade ≥ 3 AE, n (%)		86 (91.5)

AML: Acute Myeloid Leukemia; ALL: Acute Lymphoblastic Leukemia; ALAL: Acute Leukemia of Ambiguous Lineage; HSCT: Hematopoietic Stem Cell Transplantation; CR: Complete Response; CRh: CR with Partial Hematologic Recovery; CRc: Composite Complete Remission
MRD: Minimal Residual Disease; AE: Adverse Event

Future Directions of Menin Inhibitors

The recently announced FDA approval of revumenib provides an alternate treatment option to attempt to bridge adult and pediatric patients with R/R AML, ALL, and mixed lineage leukemia (MLL)[9]. In addition to the relapsed or refractory setting, menin inhibitors have the potential to be used in earlier lines of therapy either as monotherapy or in combination with other therapies[12].

The BEAT AML (NCT03013998) is an open label phase 1b dose escalation and expansion trial and substudy of the BEAT AML

master trial[13]. BEAT AML evaluated the safety and recommended dose of revumenib in combination with azacitidine and venetoclax in patients with newly diagnosed AML with NPM1m or KMT2aR who are not eligible to receive intensive induction therapy. The dose levels investigated were DL1a (113 mg orally every 12 hours for 28 days) or DL2a (163 mg orally every 12 hours for 28 days). There were 13 patients aged ≥ 60 years that were analyzed (n=7 in escalation DL1a, n=6 in escalation DL2a). Ten patients achieved CR, two achieved CRh, and one achieved CRi with a composite CR rate of 100%. Twelve patients were tested by flow cytometry and none had measurable residual disease.

Drug manufacturer Syndax has announced upcoming results for additional studies evaluating revumenib in the relapsed or refractory setting for AUGMENT 102 (NCT05326516) and the phase I/II SAVE trial (NCT05360160)[14]. In AUGMENT 102, revumenib is being studied in combination with fludarabine/cytarabine in patients with relapsed/refractory acute leukemias harboring KMT2A rearrangement, KMT2A amplification, NPM1c, or NUP98r mutations. Other ongoing trials evaluating the use of revumenib in combination with induction chemotherapy (NCT06226571) and with midostaurin (NCT06313437) in acute myeloid leukemia. Another ongoing trial is evaluating the use of revumenib in combination with gilteritinib for patients with concurrent FLT3 mutations (NCT06222580) in R/R AML.

Additional menin inhibitors under development include ziftomenib and bleximenib[8]. Ziftomenib is a menin-KMT2A interaction inhibitor, targeting NPM1-mutated and KMT2A-rearranged AML. Following the results of KOMET-001, a multinational, open-label, multi-cohort, phase 1/2 clinical trial of ziftomenib in adults with R/R AML, the FDA granted breakthrough therapy designation by the FDA in relapsed/refractory NPM1-mutant AML[15]. Preliminary data from KOMET-001 showed for patients treated at the phase 2 dose of 600 mg, nine (25%) of 36 patients with KMT2A rearrangement or NPM1 mutation had CR or CRh. Seven (35%) of 20 patients with NPM1 mutation treated at the recommended phase 2 dose had a complete remission. The KOMET-008 study, announced at the 2023 American Society of Hematology conference, will be evaluating safety, tolerability, and preliminary efficacy of ziftomenib when combined with standard of care regimens (gilteritinib, FLAG-IDA (fludarabine, cytarabine, granulocyte-colony stimulating factor, and idarubicin), or low-dose cytarabine) for the treatment of either NPM1-mutated or KMT2A-rearranged R/R AML[17]. Bleximenib (JNJ-75276617) is a menin-KMT2A inhibitor evaluating adult patients with R/R AML harboring KMT2A or NPM1 mutations. An ongoing Phase 1, multicenter, open-label study of JNJ-75276617(NCT04811560) is evaluating 58 adult patients diagnosed with R/R AML and ALL with KMT2A or NPM1 mutations[17]. There was a reduction in bone marrow disease burden in 26 (63%) of the 41 pts with disease. Menin inhibitors are a novel breakthrough therapy for patients with acute leukemia and this drug class will continue to evolve with the future studies evaluating novel drug combinations added to menin inhibitors, as well as studying menin inhibitors in frontline leukemia therapy (NCT05886049). ●●

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Powering Through Uncertainty and Doubt: My Journey as a Non-Traditional PGY2 Oncology Resident

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Around this time five years ago, I was about a third of the way through my PGY1 residency. As I prepared for Midyear, I remember feeling so overwhelmed that I began second-guessing my decision to pursue a PGY2 immediately after completing PGY1. In less than three years, I had moved from Saudi Arabia to Canada, followed by a cross-border move to the United States, and then a cross-country relocation from San Diego, CA, to Columbus, GA. By the time I started my PGY1 residency, I was utterly exhausted. Adding to this whirlwind of transitions, I had been married for less than a year and longed for some downtime to enjoy my first year of marriage.

Despite my uncertainty and doubts, and with the unwavering support of my husband, family, and friends, I pushed through and pursued a PGY2 in Medication Use Safety and Policy (MUSP) immediately after PGY1. However, that decision was driven by circumstance rather than a carefully laid plan. My true passion was oncology, but at the time, pursuing that dream simply wasn't possible.

Fast forward to today: I am now pursuing my second PGY2 in my field of choice—oncology, a discipline that resonates deeply with me on a personal level. Reflecting on my journey, I realize it has been anything but linear. In this essay, I will share insights into my non-traditional path and the lessons I have learned along the way.

A Wish Is Not a Plan

My journey toward oncology began in middle school, shaped by a deeply personal and transformative experience. When my younger brother was diagnosed with a brain tumor, our family faced what felt like an impossible reality. With few options available, we moved to London, UK, so he could participate in an experimental trial—our only hope at the time. The months that followed were fraught with fear and uncertainty, but they also brought an unexpected gift: the trial succeeded, and my brother recovered. What began as a traumatic chapter in our lives ended with gratitude and inspiration. It was during that time that I first felt the pull toward oncology, realizing how deeply the field could impact not just patients but entire families.

That early desire stayed with me, guiding my path as I pursued my PharmD and made the bold move to North America to chase my dream of practicing oncology at the highest level. Yet, while my wish was clear, my plan was not. I started in Vancouver, Canada, drawn by the comfort of having family nearby as I adjusted to a new country. However, I quickly realized the limited opportunities for oncology residencies in the area and struggled to gain traction with the few programs that seemed like a good fit. It became clear that I needed to pivot.

> **"I realized that a wish may spark a journey, but it's not enough to see it through."**

This realization led me to the bridge-to-residency program at the University of California, San Diego. Moving to a city where I had no connections felt overwhelming, but I sought out local communities online and found a supportive family willing to rent me a room. Their kindness gave me the courage to take the leap. At UCSD, I gained clinical skills and made invaluable connections, but I still lacked a deliberate plan. Much of what I achieved—like securing an oncology investigational drug service internship—came down to luck rather than intention.

That realization was pivotal. A wish may spark a journey, but it's not enough to see it through. I knew I had to move beyond navigating passively and start shaping my path with purpose. This shift in mindset became the first step in turning my dream into reality.

A Plan Is Not a Sentence

Before starting my PGY1 residency, I crafted a detailed plan to achieve my oncology career goals. My plan focused on strengthening my clinical knowledge, refining my skills, and gaining as much oncology exposure as possible to become a competitive PGY2 candidate.

The first months of PGY1 went well, though not without challenges. By Midyear, the signs of burnout became hard to ignore. Years of relentless change, international moves, and the demands of residency had taken their toll. Adding to this, my family dynamics shifted when my husband found a career opportunity in Atlanta, GA. After much thought, we decided to focus on Atlanta, which meant letting go of out-of-state PGY2 opportunities. Unfortunately, the only oncology PGY2 program in Atlanta that I

Reflection on Personal Impact and Growth

was interested in had already early-committed its slots, leaving me at an impasse.

Faced with this unexpected reality, I had to pivot—again. Instead of pursuing a PGY2 immediately, I chose to enter the workforce and postpone my plans. Around this time, the Residency Program Director of an Atlanta-based MUSP program offered me a post-match interview. While medication safety had never been part of my plan, I recognized its potential to enhance my clinical profile. The decision to pursue the program was also made easier thanks to a generous scholarship that more than offset the financial impact of forgoing a traditional pharmacist role.

After completing the PGY2 MUSP residency, I transitioned to two PRN roles in pain management and internal medicine, which offered the flexibility I needed as a new mother. Pain management, in particular, felt like the closest connection to oncology I could find at the time. Though this wasn't part of my original plan, I viewed it as a logical step forward.

Rejection: Not Always a Setback

Three years later, I believed my credentials and experience in pain management, internal medicine, and medication safety—combined with my BCPS certification—were more than enough to resume my pursuit of an oncology career. I applied for an inpatient oncology specialist position and made it through two screening interviews. However, less than a week before the final on-campus interview, I received a devastating call: I was no longer a contender for the position. The reason? The job required a PGY2 in oncology to qualify under a Collaborative Practice Agreement. The rejection was hard to stomach; I felt devastated and was stuck in a cycle of helplessness and self-doubt, questioning whether I had made the right decisions in my career path.

My husband, however, helped me reframe the situation. "You can sit here and cry, or you can do something about it," he said. "Why don't you pursue a PGY2 in oncology?" His words challenged me to confront my fears and reminded me that success and fulfillment often lie on the other side of fear. We spoke about my responsibilities as a wife and mother and agreed that we could manage as a team. We also spoke about the financial implications of me losing two thirds of my paycheck, and, again, we determined that we could manage. Despite all of that, the fear was still real. But now, I was determined to get to the other side of it.

I reached out to my network for support and letters of recommendation, completed shadowing sessions with the Emory oncology team, and submitted my application. Four months later, I matched with my dream program (Emory) and was absolutely overjoyed.

Hindsight Reflections and Parting Thoughts

Looking back, I see how the detours, though unexpected, made my journey more formative and rewarding. By the time I started my PGY2 in Oncology, I had a solid foundation and a clear sense of what I needed to accomplish. Rather than approaching the program in exploration mode, I arrived with specific goals and a clear plan for how to achieve them. The unplanned turns have also equipped me with unique skills that continue to shape my clinical practice today. For example, I am more attentive to safety risks and more appreciative of the value of continuous improvement than I could have been without my Med. Safety background. I am also a better clinician than I could have been without my pre-PGY2 clinical experiences.

Beyond the direct career benefits that my non-traditional journey afforded me, I am thankful for so many life lessons that I learned along the way. Here are a few that I hope will resonate with some of you.

- ***Support Systems Matter***: Success is rarely a solo effort. Building and nurturing relationships with mentors, colleagues, and loved ones is essential.
- ***Ask for Help***: Don't hesitate to seek guidance. Most people are willing to help if you show genuine interest and effort.
- ***Focus on Your Growth***: Comparing yourself to others is unproductive. Instead, track your progress and focus on becoming a better version of yourself.
- ***Embrace Uncertainty***: Outcomes may not always meet expectations, but effort is what truly counts. I've come to remind myself, "I owe my best effort, not a guaranteed result."
- ***Take Action***: Clarity about your goals and purpose makes a difference. Don't let fear or doubt hold you back—focus on your "why," and the "how" will follow. ●●

Review of Operationalizing Bispecific Therapies: From Engaging T-cells to Care Teams

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I am the chair of the HOPA Practice Management Committee this year, and the committee is transitioning from an annual conference to quarterly webinars. Thanks to Drs. Emile Aschenbrenner, Grace Baek, Megan May, and Anna Rivard, the first Practice Management Committee webinar was successfully given in November on operationalizing bispecific T-cell therapies. The presentation featured breakout rooms, allowing participants and panelists to discuss challenges such as transitions of care and the implementation of toxicity management. Additionally, the webinar discussed how academic and community hospitals approach implementation of bispecific antibodies (BsAbs). Below is a summary of the presentation.

"BsAbs can target multiple antigens and redirect immune effector cells."

Overview of BsAbs and Safety Considerations

Currently, there are nine FDA-approved oncology bispecific antibodies.[1,2] The first BsAb approval was blinatumomab for relapsed or refractory Philadelphia chromosome-negative B-cell precursor acute lymphocytic leukemia. Recently, blinatumomab also became the first BsAb to be recommended in a front-line setting.[3] The other BsAbs (elranatamab-bcmm, epcoritamab-bysp, glofitamab-gxbm, mosunetuzumab-axgb, talquetamab-tqvx, tarlatamab-dlle, tebentafusp-tebn, and teclistamab-cqyv) have been approved by the FDA for second-line or later therapy.[1] BsAbs can target multiple antigens and redirect immune effector cells. Recent innovations have enhanced their efficacy while reducing immunogenicity. Additionally, BsAbs currently in clinical trials have novel mechanisms such as trispecific targets. Most BsAbs received approval based on Phase 1/2 trials, and survival data has yet to mature.[1,4] These agents are akin to the new immunotherapy in oncology, though they are not without toxicity.

Safety of BsAbs can range from cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), cytopenias, infections, and antigen-specific toxicity. The incidence of all-grade CRS ranges from 51 to 89%, with 0.5 to 4.2% of patients experiencing grade 3 or higher, typically after the first or second administration of step-up therapy. Once CRS diagnosis is confirmed, the median duration is approximately two days. Neurotoxicity is another safety consideration, with all-grade neurotoxicity occurring in 1 to 9% of patients, with 0 to 3% being grade 3 or higher. The median time to onset of neurotoxicity can be up to 29.5 days, with a usual duration of about 2 days. The exception to this is tarlatamab-dlle, with a median duration of 33 days.[2,5-11] Due to the risks of CRS and neurotoxicity, some drug manufacturers recommend monitoring as described in Table 1.[12-19]

Lastly, infections are a significant concern with BsAbs, specifically the BCMA-targeted BsAbs (elranatamab-bcmm, teclistamab-cqyv), which have infection rates of 70 to 80%. In contrast, other BsAbs have lower infection rates: GPRC5D (talquetamab-tqvx) 34-47%, CD-20 targeted 20-45%, and solid tumors less than 10%.[2,4-11]

Operational Considerations

Site of Care

Because of these complexities, operationalizing BsAbs at institutions is challenging. Each site must determine where they are going to treat a patient for step-up: outpatient-in-a-bed, outpatient, or inpatient. Because of the continuous monitoring required for some BsAbs, outpatient-in-a-bed or inpatient status is the easiest site to monitor patients closely. However, choosing a hospital site brings challenges that include bed availability, staffing, education to all appropriate staff, and potential financial toxicity for the site.[20] Discussion with the expert panel during the Practice Management webinar revealed that institutions that have had more experience

Table 1: Manufacturer Recommended BsAb Monitoring[12-19]

Indication	Multiple Myeloma			Lymphoma			Melanoma	Small Cell Lung Cancer
BsAb Therapy	**Elranatamab-bcmm (Elrexfio®)**	**Talquetamab-tqvx (Talvey®)**	**Teclistamab-cqyv (Tecvayli®)**	**Epcoritamab-bysp (Epkinly®)**	**Glofitamab-gxbm (Columvi®)**	**Mosunetuzumab-axgb (Lunsumio®)**	**Tebentafusp-tebn (Kimmtrak®)**	**Tarlatamab-dlle (IMDELLTRA®)**
Hospital Monitoring	48 hours after C1D1 step-up dose, 24 hours after C1D4 step-up dose	48 hours after admin of all doses within step-up dosing schedule	48 hours after admin of all doses within step-up schedule	24 hours after 1st 48mg dose (C1D15)	24 hours after 1st 2.5mg step-up and all step-up doses if CRS from prior	If grade 2-3+ CRS on previously administered dose	First 3 infusions: Monitor at least 16 hours after infusion	C1D1, C1D8 monitor for 22 hours in "appropriate healthcare setting"

CRS= cytokine release syndrome

with BsAbs are moving to outpatient or outpatient-in-a-bed status for step-up therapy.

Completing outpatient step-up may be financially advantageous for the hospital and convenient for patients, but it requires resources for patient monitoring such as caregivers or additional onsite, telephone, or virtual visits. Frequency of monitoring for CRS and neurotoxicity also needs to be determined.[20] Webinar experts from different institutions discussed how their institution came up with outpatient monitoring that best fit each site. The BsAb monitoring ranged from none to up to 48 hours after a step-up dose, mostly defined by each BsAb package insert.

Transitions of Care

When administering BsAbs in the outpatient, inpatient or outpatient-in-a-bed status, transitions of care must be communicated effectively between teams. Some information to be incorporated into handoffs includes doses administered, premedications given prior to BsAb administration, CRS or neurotoxicity grading and timing if they occurred, and treatments administered for CRS or neurotoxicity. Additionally, if patients are referred from community providers or other locations within the system, the step-up site must determine how many doses they will monitor before sending the patient back to the referring provider.[20] All sites discussed in the webinar had common transitions of care processes that included standardization of electronic ordering of BsAbs between settings, REMS code documentation in the electronic medical record (EMR), utilization of warm handoffs between employees, standardized patient and caregiver education, and EMR flow sheet tracking. One difference between sites included the use of different teams for prior authorizations based on site of administration. For example, one site used one team to authorize BsAbs given outpatient-in-a-bed status and another team for BsAbs given outpatient. Another outlier process included a single site that used an EMR alert to identify patients receiving BsAbs.[20]

Patient Access

Access to these medications poses another challenge, particularly for patients from rural settings. Considerations for increasing access include the distance from a hospital/clinic, accessibility of transportation, housing availability and local support, caregiver education, availability of trained staff at local clinics, and the availability of treatment for CRS or neurotoxicity in local clinics and hospitals.[20] One site participating in the webinar discussed giving patients a prescription for dexamethasone prior to administration of BsAbs so that patients experiencing CRS or neurotoxicity symptoms could take dexamethasone on their way to the hospital. Additionally, a different site discussed a defined location that patients must stay within during step-up therapy in case they need to go to the hospital (e.g. being within 45 minutes of the hospital).

Development of Standardized BsAb Monitoring and Management

Another key aspect of operationalizing BsAbs is developing guidelines for BsAb toxicity management and prevention. Success hinges on assembling a knowledgeable team, including a physician lead, department chair, oncology pharmacist, advanced practitioner, and a nurse. This interdisciplinary team can then be tasked with training other employees, implementing the site guidelines and standard operating procedures, and helping to manage patients when appropriate. Additionally, a monitoring protocol should be established. This should include, as appropriate, complete blood counts, complete metabolic panel, magnesium, phosphorus, C-reactive protein, ferritin, lactate dehydrogenase, pregnancy testing, transthoracic echocardiogram, baseline neurologic evaluations including immune effector cell encephalopathy (ICE) score, baseline disease progression via imaging, bone marrow evaluation, baseline lumbar puncture, and consideration of age-appropriate vaccinations prior to therapy. Nursing monitoring should include frequent vital signs, such as every 15 minutes for the first hour, every 30 minutes for 2 hours, and then hourly. Nurses should also regularly assess ICE scores, ideally at every shift if inpatient, or upon any neurologic changes. Any new onset or changes in CRS or neurotoxicity grading should be reported to the provider immediately.[20-24] Variations in practice for monitoring CRS and neurotoxicity include frequency of vitals (every 2 or 4 hours), frequency of neurologic checks (shift changes, every 4 or 8 hours), whether to require a provider review prior to starting tocilizumab and dexamethasone, use of automatic referrals to specialists like neurology or neuro-ICU, methods to alert the financial team, and information in the CRS or neurotoxicity order set, such as medication cost differences or prechecking specific orders like brain MRIs.[20] Once a guideline has been established and sites decide where to administer BsAbs, implementation methods need to be determined. Generally, most organizations build toxicity scoring into the EMR.[21-23]

For treatment of CRS, sites must have at least two doses of tocilizumab available, as mandated by certain REMS requirements. Some institutions may prophylactically give tocilizumab based on study data showing possible benefit in reducing rates of CRS.[25] Lastly, decisions regarding anti-infective prophylaxis protocol should be standardized across the organization (Table 2).[26]

Staff Education

Education of medical staff on BsAbs is another operational challenge. Key stakeholders to identify may include:

- Core care team (team prescribing and following patients to prevent and manage side effects)
- Pharmacists, nurses, and pharmacy technicians in several settings, including inpatient (intensive care, medical units, oncology, and emergency), ambulatory oncology, and infusion
- Scheduling team
- Prior authorization teams

Clinical education of these teams may include toxicities, interventions, prophylaxis, expectations for monitoring and follow-up, counseling points for when patients should seek care, monitoring algorithm, written CRS and neurotoxicity protocols, and a list of approved bispecific T-cell engager therapies. Operational education may include EMR order sets, process for escalating care, REMS program requirements, required duration of admits and outpatient dosing intervals, and billing codes.[21,27-29]

Table 2: BsAb Anti-Infective Prophylaxis Guidance[26]

Indication	Duration/Instructions
VZV/HSV Prophylaxis	Continue while on active therapy and for at least 18 months after treatment
PJP Prophylaxis	Continue while on active therapy or until CD4 >200 cells/uL (whichever is longer)
Bacterial Prophylaxis	Start when ANC · 0.5 or ANC < 1 expected to last · 1 week Continue until ANC > 0.5 for 3 consecutive days without growth factor support
Fungal Prophylaxis	Start when ANC <0.5 Continue until ANC > 0.5 for 3 consecutive days without growth factor support
Neutropenia (ANC <1000)	Growth factor PRN use for neutropenia Avoid use during dose escalation phase, given risk of aggravating CRS
Hypogammaglobulinemia	IgG levels monitored monthly with disease markers Give IVIG monthly if IgG < 400 mg/dL
Vaccines	No change in vaccination strategy

ANC=absolute neutrophil count; HSV= Herpes simplex virus; PJP= Pneumocystis jiroveci pneumonia; VZV=Varicella zoster virus

Financial Toxicity

Lastly, financial evaluations should occur prior to administering BsAbs. In 2023, BsAb Wholesale Acquisition Cost (WAC) pricing ranged from $9,715 per weekly treatment to $360,500 for a full treatment course.[30] As discussed earlier, identifying if your site is going to do step-up inpatient, outpatient-in-a-bed, or outpatient administration affects the financial coverage of these medications. Inpatient has higher financial risk since medications may not be reimbursed separately and instead grouped into a diagnosis related code. If inpatient is the site of administration, consider including the Medicare New Technology Add-on Payments (NTAP) and outlier payments, if available. For commercial insurance, collaborate with your financial team to understand the specific reimbursement of those plans and to verify how many nights patients can stay as an outpatient, as well as reimbursement policies under these conditions. If outpatient-in-a-bed or observation status is considered, Medicare requires a maximum two-midnight rule. If a patient stays longer than two nights, the encounter will be billed as an inpatient and covered under Medicare Part A rather than Part B. Lastly, if a patient has CRS or neurotoxicity and is admitted, consider other diagnosis related codes to help cover the cost of tocilizumab or any other treatments.[31]

Overall, the implementation and operationalization of bispecific antibodies across organizations can be challenging. There are several factors to consider both before and during therapy as discussed in this article and the referenced webinar. However, having a standardized operational and clinical approach is necessary to ensure that patients have safe and efficient access to BsAbs. ●●

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Pharmacist Contributions to Quality Improvement in Oncology Care: ASCO Quality Care Symposium 2024

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Introduction

Quality improvement (QI) initiatives aim to improve patient care through a variety of methods including increased health care access, improved patient experience, and advances in technology[1]. The 2024 American Society of Clinical Oncology (ASCO) Quality Care Symposium highlighted the latest advances in QI in oncology. Below are four research abstracts, led by oncology pharmacists, which demonstrate efforts aimed at enhancing the quality of care provided to patients with cancer.

Quality improvement project to reduce inpatient chemotherapy usage on a solid tumor oncology service[2].

Administration of inpatient chemotherapy for treatment of solid tumors is often avoided due to its correlation with increased length of hospital stays, healthcare costs, and morbidity. In select circumstances, inpatient chemotherapy may be warranted due to toxicity monitoring or need for timely treatment. In order to evaluate the usage of inpatient chemotherapy, Dreher and colleagues implemented Plan-Do-Study-Act (PDSA) cycles with a focus on education and policy initiatives on an inpatient oncology solid tumor service at a large academic medical center.

> **"Oncology pharmacists play a critical role in multidisciplinary teams working on QI projects."**

The PDSA cycles followed standard processes with the aim to reduce inappropriate inpatient chemotherapy administration. The approach focused on two components: education regarding inpatient chemotherapy indications and creation of a committee tasked to review requests for inpatient chemotherapy. The committee is composed of personnel with clinical backgrounds as well as representatives from operations, quality and safety, and ethics. Review requests are sent from inpatient teams to the committee and the patient case is reviewed for performance status, if the desired chemotherapy regimen will be clinically beneficial, and barriers to discharge and outpatient administration. To evaluate the outcomes of these interventions, data was collected from the electronic medical record for all patients admitted to the inpatient oncology service for 8.5 months before and after implementation of the first PDSA cycle. Prior to the first PDSA cycle, 111 admissions (11.9%, n=82 patients) of the total 930 admissions during the study time frame received inpatient chemotherapy. Following PDSA cycle 1, 57 (6.4%, n=35 patients) of the 889 admissions (n=557 patients) received inpatient chemotherapy ($p<0.001$). Similar proportions of patients received chemotherapy within 14 or 30 days of death pre- and post-PDSA cycle. Average hospital length of stay decreased from 11.1 days to 8.8 days ($p<0.001$).

Results from the implementation of this PDSA cycle suggest benefits to patients by reducing hospital length of stay and potential healthcare associated costs. Based on the results of this PDSA, future efforts will target limiting inpatient end-of-life chemotherapy and improving transitions of care.

Improving dihydropyrimidine dehydrogenase genotyping (DPYD) prior to initiation of fluoropyrimidine-based chemotherapy at a community-based hospital: A quality improvement initiative[3].

DPYD testing is often utilized to identify patients at increased risk of experiencing side effects from fluoropyrimidine chemotherapy. Despite well-established benefits and guideline recommendations, testing utilization is inconsistent in healthcare systems. Muzlera and colleagues implemented a quality improvement project aimed to increase DPYD testing for patients receiving fluoropyrimidine-based chemotherapy regimens from 65% to 95% during the study period (July 2023-July 2024).

Baseline characteristics, including frequency of DPYD testing and testing turnaround time (from May 1, 2023, to August 4, 2023), on 126 patients were collected via chart review. Subsequently, a multidisciplinary team including medical oncology residents, pharmacists, nurses and clinical informaticists identified barriers to implementation. The team used PDSA cycle methodology, Ishikawa diagrams, and process mapping to identify barriers. A p-chart was used to analyze results. Baseline DPYD testing occurred in 65% of patients with identified barriers including a lack of standard workflow and need for education on the importance of testing. PDSA cycles included educational sessions with medical oncologists and nurses as well as the implementation of a best-practice advisory in the electronic medical record. The percentage of eligible patients who received DPYD testing increased to 95.8% following these PDSA cycles. Two months following intervention, turnaround time for testing results had not changed from baseline.

By utilizing a PDSA cycle, creation of a standard workflow, and education on the benefits of DPYD testing in eligible patients, testing utilization increased from 65% to 95.8% during the study period. Future research efforts will describe fluoropyrimidine

prescribing patterns in patients at increased risk of toxicity due to decreased DPYD activity and analyze treatment outcomes.

Improving discharge times for patients admitted for allogeneic transplantation[4].

Timely patient discharge from the hospital may improve patient and provider satisfaction, decrease healthcare costs, expedite incoming admissions, and optimize the utilization of healthcare resources. Between January - December 2022, Maheshwari and colleagues at University of Virginia (UVA) Health recorded 0% of patients admitted for allogeneic stem cell transplant (allo-SCT) discharging by noon despite anticipated discharge. A multidisciplinary team consisting of licensed providers, pharmacists, nurses, and other key collaborators worked together to improve discharge times. The goal of the study was to increase the percentage of patients discharged by noon to 20%.

The most common perceived sources of delay included medication delivery time, complex medication issues, and delay in placing the discharge order. These survey results were combined with baseline data, process mapping, pareto charts, and priority matrix to determine an action plan. The first PDSA cycle was performed October - December 2023 with a focus on placing the discharge order and following a discharge checklist. The checklist was implemented as a smart phrase in the electronic health record (EHR) and utilized in daily progress notes during the admission. The second PDSA cycle was performed January - May 2024 and continued the use of the smart phrase from PDSA 1. PDSA 2 also focused on standardizing the responsibilities of all individuals involved in discharging the patients.

There were no patients discharged prior to noon with PDSA 1, but there was some improvement in placing earlier discharge orders and discharge time. PDSA 2 increased the percentage of patients discharged by noon to 14.3% with significant improvement in time of discharge order placement ($p \leq 0.0001$) and discharge time ($p \leq 0.022$). The team is planning to continue implementing future PDSA cycles, including a focus on medication delivery time to get closer to their 20% goal.

Coordinating expensive, difficult-to-obtain prophylactic medications before discharge: A quality improvement project in an academic stem cell transplant unit[5].

Antimicrobial prophylaxis is key in reducing morbidity and mortality rates in patients undergoing allo-SCT. Michaels and colleagues at UVA Health reported 21% of new allo-SCT patients discharging without posaconazole or isavuconazonium +/- letermovir prescriptions between July 2022 and July 2023. These patients were required to receive daily oral drug administration at the infusion center until these prescriptions could be filled after discharge, which led to increased healthcare costs, burden on clinical staff, medication nonadherence, and patient frustration. The aim of this study was to decrease the percentage of allo-SCT patients discharging without appropriate prophylactic agents in-hand from 21% to 10% by November 2024.

The team used PDSA methodology to reach their study goal. The first implemented intervention required prescriptions for prophylactic agents to be ordered 10 days prior to the planned admission to initiate the prior authorization (PA) process and allow more time for financial assistance and pharmacy logistics. This was assessed by Time to Affordable Medication (TAM), defined as days from prescription PA request to paid claim with a copay that the patient was able and willing to pay or access to free drug or assistance program. The baseline TAM prior to intervention was an average of 7.5 days. After implementation of PDSA cycle 1 in November 2023, TAM was decreased to 4.3 days for the first 35 prescriptions. A decrease in variation was also demonstrated through the statistical process control (SPC) upper control limit decreasing from 26.3 to 13.3 days. The reason for some prescriptions requiring 10 or more days to process was due to free drug applications. All patients received their prescriptions at discharge and 0% required drug administration at the infusion center. The team attained their study aim but will continue evaluating the process and ensuring sustainability.

Conclusion

Oncology pharmacists play a critical role in multidisciplinary teams working on QI projects. They provide expertise in medication management, ensuring treatment regimens are safe, effective, and personalized for all patients. It is important for oncology pharmacists to continue participating in QI projects to optimize processes, enhance patient care, and improve outcomes.

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Navigating IV Iron Formulation Options Amidst the Iron Sucrose Shortage

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Recently a national shortage of iron sucrose, a commonly used IV iron formulation, has created challenges in managing iron deficiency anemia (IDA), particularly in hospitals and infusion centers where it is the preferred product. Iron sucrose is widely used due to its well-established safety profile data and preferred cost-benefit ratio compared to other iron preparations.[1] In general, providers surveyed during medication shortages reported that decreased supply can lead to treatment delays and adjustments in therapy. There is concern that these potentially could lead to less effective therapies or increase in adverse reactions.[2] Previous literature on shortages highlight the critical role of supply chain management and inventory planning in ensuring that patients receive timely and appropriate treatment. Similar to other shortages, hospitals may need to consider adjusting iron administration protocols, expanding the use of other formulations, or exploring new approaches to managing iron deficiency in order to maintain optimal care for patients.

"With the current shortage of iron sucrose, navigating alternative treatment options for iron deficiency anemia can be challenging."

Background and History of Use

Iron deficiency anemia is the most common micronutrient deficiency worldwide affecting nearly 1.2 billion individuals.[3] This condition causes a decrease in hemoglobin production, limiting the ability of red blood cells to transport oxygen.[3] There are multiple causes including blood loss, malabsorption, chronic diseases, and increased iron requirements. Specific conditions that increase iron loss include heavy menstrual bleeding, irritable bowel syndrome, and chronic kidney disease (CKD).[3,4] Iron deficiency is typically treated with iron replacement, either by mouth (PO) or intravenously (IV). PO is the preferred option in stable patients although its gastrointestinal side effects and the extended duration required to replenish iron stores may result treatment failures necessitating the use of IV iron agents. IV formulations are typically reserved to treat patients that have failed PO iron supplements or need rapid red blood cell count improvements (Hgb < 7).[4,5] Traditionally their use was limited due to higher rates of infusion reactions, however in recent years these agents have become more popular across various disease states.[5]

Current available options

Currently, there are six formulations of IV iron available for use, including iron gluconate, iron sucrose, ferric carboxymaltose, ferumoxytol, ferric derisomaltose, and low-molecular-weight iron dextran.[5] While these products differ in their molecular structure (and therefore iron content and reaction risk), all are considered effective for the treatment of IDA. Each formulation offers distinct advantages and limitations, such as differences in dosing, frequency, adverse reactions, and price (Table 1). For example, ferric carboxymaltose and ferric derisomaltose allow for larger doses and fewer infusions, making them preferred options for rapid iron repletion and reduced chair times. Comparatively iron sucrose requires more frequent dosing but is often used by centers due to lower costs. This is typically why options like ferric derisomaltose, shown to be superior to iron sucrose in raising hemoglobin levels within 2 weeks [13], are less commonly used compared to iron sucrose due to cost-benefit ratio.

Hypersensitivity Reaction Risk

The rapid iron repletion that IV iron produces has been shown to be more beneficial than PO, however the infusion reactions that have been seen with these agents tends to limit the use of these products.[14] The most common reaction seen with IV iron is known as a Fishbane reaction. Fishbane reactions are physiologically different and less severe than anaphylactic reactions, however the mechanism is not fully understood. These reactions typically present with acute chest, back and joint pain without presentation of other symptoms like hypotension.[15] Fishbane reactions occur in roughly 1 in 100 patients[15] while anaphylaxis with IV iron use is rare, only occurring with <1:200000 administrations.[16] Regardless of the cause, if an infusion reaction is observed in a patient during administration, the infusion should be stopped and held for a minimum of 15 minutes and patient is to be assessed on severity of reaction.[17] If the reaction is mild, or a Fishbane-type reaction, infusions may be restarted back at 50% of the original rate upon resolution of symptoms.[15,17,] If reactions are severe and require rescue with intervention (corticosteroids), IV iron should not be restarted and patient should be observed for up to 24 hours depending on severity of reaction.[15,17] Premedication can be considered in patients with high risk factors for infusion reactions (e.g., prior reaction to IV iron) however data to support empiric premedication use in IV iron remains sparse. A study in 2022 showed that premedications may not be necessary and may even cause harm, specifically first-generation antihistamines which may exacerbate hypotension, converting minor reactions to more major concerns.[18]

Table 1: IV Iron Dose Recommendations and Pricing

	Ferric Gluconate	Iron Sucrose	Ferric Carboxyl-maltose	Ferumoxytol	Low molecular weight Iron dextran	Ferric derisomaltose
Brand	Ferrlecit[7]	Venofer[8]	Injectafer[9]	Feraheme[10]	INFeD[11]	Monoferric[12]
Test dose required	No	No	No	No	Yes	No
Typical single dose infusion	125-250 mg	200-400 mg	750 mg	510 mg	1000 mg	1000 mg
Infusion time	1-2 h	0.25-2.5 h (dose dependent)	15 min	15 min	1-2+ h (no faster than 50 mg/min)	20 min
Recommended premedication[6]	Consider if: • Previous IV iron reaction • Severe respiratory or cardiac disease • Older age (>65 years) • Treatment with beta-blockers or ACE inhibitors • History of multiple drug allergies, eczema, anxiety disorder, mastocytosis, or systemic inflammatory disease					
WAC Pricing (per 1000 mg) Cardinal Health December 3rd 2024	~$500.00	~$300.00	~$550.00 (750 mg)	~$350.00	~$350.00	~$2,300

The primary means of preventing iron reactions lies in the pharmacology of the products. Early IV formulations consisted of high molecular weight iron dextran formulations (HMWID). These formulations were known to have toxic reactions that limited the use of these products. It is thought that free circulating iron contributes to hypersensitivity reactions and the reduction in free iron in these newer formulations has been shown to reduce reactions.[19,20,21] Newer formulations of iron use alternative carbohydrate shells, binding iron more tightly, improving the side effect profile.[3] A retrospective review in 2006 showed that adverse reactions were significantly more frequent in the HMWID group finding iron sucrose, ferric gluconate, low molecular weight iron dextran and HMWID with absolute rates of life-threatening adverse events occurring in 0.6, 0.9, 3.3 and 11.3 per million, respectively.[22] In addition to using lower molecular weight formulations, slow infusion times have also been shown to reduce the amount of labile iron in order to reduce reaction risk.[21]

Dosing, Administration and Choice of Agent

Across products, the dosing for IV iron generally remains consistent and is determined by the severity of iron deficiency and the patient's response to therapy.[23,4] The severity of iron depletion is assessed through serum ferritin levels, which are considered the most sensitive and specific test for evaluating IDA. A serum ferritin level of < 35 µg per liter is considered specific for IDA.[24,25] However, it is important to consider that in patients with pro-inflammatory conditions, ferritin levels can be elevated. Therefore, additional tests should be used to assess iron deficiency in such cases which often includes measuring transferrin saturation (TSAT). In these situations, a higher ferritin cutoff combined with a TSAT of < 30%, is recommended to evaluate IDA.[24]

Once IDA is diagnosed, dosing is determined based on the specific iron agent used as noted in Table 1. While iron deficiency calculations such as the Ganzoni formula are available, this is typically not utilized in practice and has previously been shown to underestimate iron requirements in studies [23,26]. Instead, dosing is typically based on the package insert and Kidney Disease Improving Global Outcomes (KDIGO) guidelines, which suggest a cumulative IV iron dose of 1000 mg for adult patients.[23] A 2015 study found that patients with various etiologies for IDA generally have an average iron depletion of 1000 to 1500 mg, which aligns with the recommendations in the prescribing information for these products.[23]

The choice of agent influences the number of infusions needed since the dose of iron allowed in each infusion is different for each agent. Additionally adverse effect profile plays a role. Low molecular weight iron dextran has the ability to be utilized as a total dose infusion up to 1000 mg in 1 hour which allows larger doses to be administered within one infusion.[27] However, this agent has been shown to carry a higher risk of hypersensitivity and also side effects of hypophosphatemia.[28,29] Ferric gluconate and iron sucrose have shown lower rates of infusion reactions however require more infusions to complete therapy when compared to iron dextran.[28] Ferric gluconate has a max dose of 125mg per package insert but doses of 250 mg over 1 hour have been shown to be safe.[30] Iron sucrose has the most robust data and a study in 2005 showed that 1000 mg of iron sucrose in given in either two doses of 500 mg or five doses of 200 mg over 14 days was more effective than PO iron.[31] An alternative administration of iron sucrose can be utilized with doses less than 200 mg given undiluted over 2 to 5 minutes over 5 separate infusions.[31] Ferric carboxylmaltose and ferumoxytol are options that allow for more rapid infusion rates, however ferumoxytol has also been shown to have higher reaction risk.[28,32,33,34]

Typically, the patient is given the maximum dose recommended by the package insert, and treatment is repeated every 1 to 2 weeks until a satisfactory response is achieved.[4] It is important to keep in mind the patient's deficiency needs and the dosing schedule requirements when determining the appropriate agent.

Institutional Experience

At the authors' institution, due to the recent shortage, a decision was made to transition from iron sucrose to ferric gluconate in both the inpatient and infusion clinic settings. However, following the switch, an increase in reaction rates was observed in patients, prompting a closer examination of IV iron administration protocols and premedication practices. Due to the perceived higher risk of reaction from the ferric gluconate, providers were independently premedicating patients with acetaminophen and antihistamines (including diphenhydramine). Reactions including hypotension, tachycardia, diaphoresis, and shock were reported. Further investigation determined that reactions were worsening due to the diphenhydramine addition aligning with previously documented findings in the literature.[6,15] As a result, institutional guidelines were revised, replacing diphenhydramine with cetirizine in premedication regimens.

In addition to an increase in the frequency and severity of reactions due to changes in iron formulation and premedication, reports of increased reaction with the current generic brand carried were also noted. In order to reduce reaction risk, a change between generic manufacturers of ferric gluconate were pursued. Anecdotal reaction risk declined, and ferric gluconate has remained well tolerated; premedication is not routinely used, however when pursued second-generation antihistamines (ie: cetirizine) or steroids are utilized.

The story at our institution supports previously published literature regarding the impact of drug shortages on patient care.[2] As pharmacies and providers are forced to use alternative products, not only are there potentially higher costs incurred, there are also challenges in terms of medication coverage, provider buy-in and development of adverse effects. Due to the observed increased reaction risk, providers were initially resistant to the change. Continued investigation of adverse events, education on cost and premedication use helped to ensure that we were able to continue to provide IV iron through the use of ferric gluconate, a safe and cost-effective alternative.

Conclusion

Overall, IV iron is an effective treatment option for patients with severe or refractory iron deficiency anemia who do not respond to PO iron or other therapies. Over the years, these agents have evolved to offer a safer side effect profile, allowing for faster repletion of iron stores compared to PO formulations, which often require months of treatment. IV iron agents are especially beneficial for patients with chronic conditions, such as chronic kidney disease, inflammatory bowel disease, or those undergoing chemotherapy, who may experience poor absorption of PO iron or intolerance to it.

With the current shortage of iron sucrose, navigating alternative treatment options for IDA can be challenging. However, despite the differences in dosing and potential side effects, IV iron agents as a class are generally considered both safe and highly effective for managing IDA, particularly in patients who require rapid restoration of iron levels.[4] Education of providers and nurses is essential to ensure safe use of all iron products, and institutions should be prepared to address any differences observed in terms of adverse effects. With proper monitoring and tailored treatment plans, these alternatives offer an effective solution, ensuring that patients continue to receive optimal care despite the supply disruptions. ●●

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"What I Wish I Knew"

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The transition from PGY2 to first post-residency role is a significant adjustment. Whether you are planning to stay on staff at your training site or heading to a new institution, joining an inpatient unit or starting up a new clinic, or forging your way in management, academia, or industry, you'll be stepping out of the role in which you've been entrenched for the past year and starting your next chapter. As you are preparing for this next exciting step, we asked three newer practitioners, "*What do you wish you knew as a freshly graduated resident entering into your first post-residency role?*". Below is the shared wisdom from Drs. Socha, Schultz, and Hardler.

"...and it's important to allow for space to trial and error, to learn, to make mistakes and to grow into your new role."

Dr. Kaylee Socha, PharmD, BCOP
Clinical Oncology Pharmacist, Gynecologic Oncology

From the time I graduated high school, I had a goal of becoming an oncology pharmacist. This goal required countless hours in the library, involvement in extracurricular activities, and applying for a pharmacy technician job to gain experience during undergrad, all to increase my chances of being accepted to pharmacy school. Fast forward to pharmacy school, and I had the goals of matching with a PGY1 and PGY2 residency program to gain further training and expertise specific to oncology / hematology. Those ten years always felt like "go, go, go" - many everyday life activities were put on the backburner to focus on my career. Then, more quickly than you expect, you reach the end of residency training and accept a job. This job doesn't have the structure and evaluations that we as students/residents have grown accustomed to. I think this can be difficult for some, me included.

Post residency, I accepted a position at Mayo Clinic, the same institution at which I completed my PGY2, as an inpatient hematology/oncology pharmacist. One major shift that this entailed was the fact that the preceptors I had the year before were now my colleagues/peers. In hindsight, I wish I had embraced this change earlier as it would have taken away some of the self-induced stress I put on myself of feeling I should be an expert now that I completed my training. It is okay to continue to ask for help and not know the answers to every question. Lean on the people around you when needed! Also, be mindful of the projects and responsibilities you say yes to; it is okay to take time to focus on your personal life outside of pharmacy while you adjust to life post residency.

Dr. Syndey Schultz, PharmD
Inpatient Clinical Oncology Pharmacist

When I graduated residency, I wish I knew that it was okay to say "no" – in fact, I would highly encourage it! When I started my first post-residency role, I was bombarded with opportunities left and right. From joining a committee, to precepting residents and students, to joining research endeavors, to providing formal interdisciplinary education, you name it, the opportunity was there. Having not fully shed my resident mindset, I said "yes" to the first opportunity that came my way simply so I could dive in, get involved, and not feel behind.

Unfortunately, what ended up happening is that I was stuck dedicating hours each month to a project that I wasn't actually invested in and I had to say "no" to other, better suited, opportunities that came along. My recommendation to all new or recent residency graduates is to say "no". Instead, allow time to build a healthy work-life balance ensuring that you can dedicate time to personal interests, hobbies and cultivating relationships with friends and family. Allow time to hone your craft as an independent clinical pharmacist. This is the first time in your career that you are working independently without a preceptor; this is your time to figure out exactly what kind of practicing pharmacist you want to be and it's important to allow for space to trial and error, to learn, to make mistakes and to grow into your new role. Instead, allow time to observe and fully explore all the opportunities available before committing. You may discover committees or projects that you never knew existed. All of this will foster an environment where when the perfect opportunity comes along you are well positioned to confidently say "yes!".

Michael Hardler, PharmD, BCOP
Hematology/Oncology Clinical Pharmacist

The most anxiety-inducing part of starting my first post-residency role was feeling like I should know everything...or at least more than I did. I just KNEW I didn't know enough — you know? Let me tell you, that's not, or at least should never be, what is most important – even at top institutions. Imposter syndrome will kick you when you're down, but you have to get back up. Some days you'll feel like anyone else could do better, but your patients have *you*, not someone else. Don't let negativity distract you from the privilege of patient care that you've worked so hard to earn. If all you ever do

for your patients is give respect and kindness, you will be integral to their care.

In your pursuit of excellent patient care, prioritize taking care of yourself. If you're not taking care of yourself, you won't be able to help others (for very long). Trying to put everyone else's oxygen mask on before your own in a flight emergency will only ensure your patient-care days end sooner than they should. If you don't help yourself first, you're putting your dependents at risk.

After moving halfway across the country, I've realized the importance of finding a community that builds you up. Don't assume your community must center around your pharmacy colleagues. As fun as we are, diversifying your village will make it – and you – stronger. Sign up for a random intramural sport, join a book club, or commission a carrier pigeon to that quirky resident to join the upcoming Dungeons & Dragons campaign. Making personal connections inside and outside of work is one of the most impactful things you can do for your patients because it will keep you fit to care for them for years to come.

Lastly, never underestimate the importance of kindness. Your role is crucial, but it's no more important than anyone else's. Show appreciation for everyone's efforts, regardless of their role. On tough days, take a breath and help a nurse find that elusive melatonin. A simple greeting to a caregiver, a smile or compliment to a child clutching their parent's leg, or a cheeky comment to a new dad about the local coffee options ("Sorry, buddy, they're all bad!") are powerful contributions to the healing environment. Kindness will always yield more than you expect, so give it all you've got. Good luck out there – I believe in you! ●●

Thank You for Your Feedback!

We are incredibly grateful to the 760+ members who shared insights in our 2024 membership survey! Your feedback is invaluable in helping HOPA leadership shape future programs, products, and services.

Through your input, the Board gained a deeper understanding of what HOPA means to you, the benefits you find most impactful, and how you engage with our communications. We also gained insight into your overall perception of HOPA and our organization's reputation in the industry.

Two areas of high importance were continuing education and professional networking. While education remains one of our strongest offerings, we recognize the need to enhance networking opportunities. We are actively working on new initiatives to help you build meaningful connections and expand your professional network.

The survey also showed that the majority of members are satisfied or very satisfied with our current benefits. However, we understand that the value of these benefits varies depending on where you are in your career. Across all levels, there is a strong demand for more accessible continuing education, mentorship, networking, and career development. We also know that you count on HOPA to continue to raise awareness of the many roles of the oncology pharmacist.

Looking ahead, we recognize the challenges and emerging trends that will shape oncology pharmacy practice over the next five years. The very issues you identified are at the forefront of the HOPA Board's discussions, and we are working closely with our dedicated volunteers to address them—ensuring you have the resources and support needed to serve your patients effectively.

We hear you, and we are committed to helping you stay informed and engaged with your organization! I encourage you to connect with HOPA through social media, webinars, live education, and networking events throughout the year.

If you'll be in Portland for HOPA 2025, I'd love to hear more about how we can make your HOPA experience even better!

Anne N. Krolikowski, CAE
Executive Director

Updates in EGFR-Mutated NSCLC

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Lung cancer is the second most common malignancy in both men and women. Despite numerous recent advancements in the care of patients with lung cancer, it continues to be the leading cause of cancer-related death in the United States. In 2024, it is estimated that there will be approximately 125,000 deaths and 234,000 new diagnoses.[1,2] In non-small cell lung cancer (NSCLC), there have been numerous advancements in biomarker driven therapies that have improved outcomes for patients. Example mutations/targets include EGFR mutations, ALK and ROS1 rearrangements, MET alterations and amplification, BRAF mutations, and many others.[3]

Classical EGFR mutations (Exon 19 deletion and L858R point mutations) occur in 10-15% of patients with NSCLC from Western populations and 50% of patients of Asian descent. These are the most common targetable mutations seen in this patient population. Until recently, the third generation EGFR tyrosine kinase inhibitor (TKI) osimertinib has been the first-line treatment option for metastatic EGFR mutated NSCLC followed by chemotherapy in those with disease progression. Osimertinib and the other EGFR inhibitors significantly improved the progression free survival (PFS) and overall survival (OS) of patients with EGFR-mutated NSCLC. These advancements were previously limited to the more common sensitizing mutations in the metastatic setting; however, in recent years there have been a number of new developments: using osimertinib in the adjuvant setting as well as the addition of new treatment options in metastatic disease, including the new oral EGFR inhibitor lazertinib and the EGFR-MET bispecific antibody amivantamab.[3]

"There have been rapid developments in the treatment of EGFR-mutated NSCLC in recent years, and further developments are expected as we gain more information regarding the biology of the disease."

Adjuvant Osimertinib ADAURA[5,6]

Approximately 30% of NSCLCs are diagnosed with limited and potentially resectable disease (stage I, II, or IIIA) with the primary modality of therapy being surgery and adjuvant chemotherapy.[4] Given the effectiveness of osimertinib in the metastatic setting, additional studies of its role in localized EGFR-mutated NSCLC. The ADAURA trial was a double-blind, randomized, phase 3 clinical trial that evaluated the efficacy and safety of osimertinib in patients with resected, EGFR-mutated (Exon 19 deletions and L858R mutations) NSCLC, stages II to IIIA. Patients received either osimertinib 80 mg once daily or placebo for three years or until disease recurrence. Patients were allowed to receive standard adjuvant chemotherapy before randomization, but this was not mandatory for all patients and was left at the discretion of the treating physician and/or patient. The primary outcome was disease-free survival (DFS). At data cutoff, the 4-year DFS rate was 70% in patients on osimertinib and 29% in patients receiving placebo. The DFS hazard ratio (HR) was 0.27 (95% confidence interval [CI] 0.21 to 0.34) in the overall population. This benefit was seen in the overall population and was consistent across all predefined subgroups, including whether patients had received adjuvant chemotherapy. In 2023, OS data was published and showed that the 5-year OS was 88% in the osimertinib group and 78% in the placebo group (HR for death, 0.49; 95.03 CI, 0.34 to 0.70; P<0.001). Based on this data, the FDA approved osimertinib to be given for three years as adjuvant therapy after tumor resection for patients with NSCLC with classical EGFR mutations.

Advanced NSCLC with EGFR Exon 19 del and L858R Mutations FLAURA2[7]

The FLAURA2 trial was an international, randomized, open-label trial in which previously untreated patients with advanced EGFR-mutated (exon 19 deletion or L858R mutation) NSCLC received either osimertinib 80 mg once daily alone or osimertinib 80 mg plus platinum doublet chemotherapy (pemetrexed and carboplatin or cisplatin) for four cycles followed by pemetrexed plus osimertinib maintenance therapy. The primary outcome was PFS. The median follow-up was 19.5 months in the osimertinib-chemotherapy group and 16.5 months in the osimertinib monotherapy group. At 24 months, 57% (95% CI, 50 to 63) of the patients in the osimertinib-chemotherapy group and 41% (95% CO. 35 to 47) of those in the osimertinib monotherapy group were alive and progression free. Investigator-assessed PFS was significantly longer in the combination group with a median PFS of 25.5 months versus 16.7 months (HR for disease progression or death: 0.62; 95% CI, 0.49 to 0.79; P<0.001). This benefit was consistent across all prespecified subgroups with a particular benefit attributed to patients with brain metastases at baseline. In these patients, the median PFS was 24.9 months in the combination group versus 13.8 months in the monotherapy group (HR for disease progression or death, 0.47; 95% CI, 0.33 to 0.66). The differences in toxicities were significant in the combination group, however, with 64% of patients experiencing grade 3 or higher adverse events versus 27% in patients receiving osimertinib. These were primarily driven by anticipated hematologic adverse events caused by chemotherapy. At this time, OS data is immature. This raises the question as to whether the benefits in PFS outweigh

Table 1. Clinical Trial Data of New Treatments in EGFR mutated NSCLC

Trial Name	Treatment	Place in Therapy	N	Median follow-up (months)	Median DFS rate (%)	Median PFS (months)	HR (95% CI); p-value	Rate of Grade ≥ 3 Toxicities (%)
ADAURA[5]	Osimertinib vs placebo x 3 years	Adjuvant (after tumor resection)	682	44.2 and 19.6	4 year: 73 vs. 38	N/A	0.27; (0.21 – 0.34)	20 vs 13
FLAURA2[7]	Osimertinib plus CT[a] vs CT	First-line; Advanced EGFR NSCLC (Exon 19 del or L858R)	557	19.5 and 16.5	N/A	25.5 vs 16.7	0.62; (0.49 – 0.79); p<0.001	64 vs 27
MARIPOSA[8]	Amivantamab + lazertinib vs osimertinib vs lazertinib	First-line; Advanced EGFR NSCLC (Exon 19 del or L858R)	1074	22	N/A	23.7 vs 16.6 vs 18.5	Amivantamab + lazertinib vs osimertinib: 0.70; (0.58 – 0.85); p<0.001	Amivantamab + lazertinib vs osimertinib: 75 vs 43
MARIPOSA-2[11]	CT vs CT + amivantamab vs CT + amivantamab + lazertinib	Second-line; Advanced EGFR NSCLC (Exon 19 del or L858R)	657	8.7	N/A	4.2 vs 6.3 vs 8.3	CT + amivantamab vs CT: 0.48; (0.36 – 0.64); p<0.001	48 vs 72 vs 92
PAPILLON[16]	Amivantamab + CT vs CT	First-line: Advanced EGFR NSCLC Exon 20 insertion	308	14.9	N/A	11.4 vs 6.7	0.40; (0.30 – 0.53); p<0.001	75 vs 54

[a]Chemotherapy consisted of carboplatin at area under the curve (AUC) 5 plus pemetrexed 500 mg/m² every 3 weeks for four cycles followed by pemetrexed 500 mg/m² every 3 weeks maintenance

CI confidence interval, *CT* chemotherapy, *DFS* disease-free survival, *HR* hazard ratio, *NSCLC* non-small cell lung cancer, *PFS* progression-free survival

the added toxicities, especially since patients who receive osimertinib monotherapy often go on to receive chemotherapy after disease progression.

MARIPOSA[8]

MARIPOSA was an international, randomized, phase 3 clinical trial that assessed previously untreated EGFR mutated (exon 19 deletion or L858R mutation), advanced NSCLC to receive amivantamab plus lazertinib, osimertinib, or lazertinib alone. Amivantamab is an EGFR-MET bispecific antibody that has both immune cell-mediated activity along with ligand blocking and receptor degradation. Lazertinib is a CNS active, third generation EGFR TKI with known efficacy against EGFR-mutated NSCLC. The rationale for combining these two agents is to proactively target common resistance mechanisms that arise in patients being treated with osimertinib, such as MET amplification.[9] The primary endpoint was PFS in the amivantamab-lazertinib group versus the osimertinib group. At a median follow-up of 22 months, the median PFS was 23.7 months (95% CI, 19.1 to 27.7) in the amivantamab-lazertinib group versus 16.6 months (95% CI, 14.8 to 18.5) in the osimertinib group (HR for progression or death, 0.70; 95% CI, 0.58 to 0.85; P<0.001). OS data could not be estimated in either group at the time of analysis. Grade 3 or higher adverse events were reported in 75% of patients receiving amivantamab-lazertinib versus 43% of patients receiving osimertinib. The most common of these toxicities at all grades seen in the combination group included paronychia (68%), infusion-related reactions (63%), and rash (62%). 10% of patients in the amivantamab-lazertinib group discontinued all trial agents compared to 3% in the osimertinib group. Based on the MARIPOSA trial, the FDA approved amivantamab and lazertinib for the first-line treatment of locally advanced or metastatic NSCLC with EGFR exon 19 or L858R mutations.[10] An important clinical pearl to note was the incidence of venous thromboembolism (VTE) seen in the amivantamab-lazertinib group. VTE events were reported in 37% of patients in the combination group versus 9% in the osimertinib group, with the majority of these events occurring in the first four months of treatment. As a result, it is recommended to initiate VTE prophylaxis in all patients starting amivantamab and lazertinib for the first four months of treatment.

MARIPOSA-2[11]

The treatment of advanced EGFR mutated NSCLC after progression on osimertinib is another area of unmet need. As discussed previously, most patients treated with osimertinib first-line may develop a heterogenous group of resistance mechanisms with the most common being alterations in MET.[9] Guidelines previously recommended platinum-based chemotherapy with carboplatin and pemetrexed in this setting with a historical median PFS of 4.4 months in one prior study.[12,13] As amivantamab has both EGFR and MET activity, it has the potential to overcome this common resistance mechanism. MARIPOSA-2 was an international, randomized, phase III clinical trial that investigated treatment of adults with locally advanced or metastatic EGFR-mutated (Exon 19 deletion or L858R mutation) NSCLC with disease progression on or after osimertinib with one of three arms: chemotherapy alone, chemotherapy plus amivantamab, or chemotherapy plus amivantamab plus lazertinib. Chemotherapy consisted of carboplatin plus pemetrexed for four cycles. The primary endpoint was PFS. Partway through the study, patients in the amivantamab-lazertinib-chemotherapy arm received a modified regimen in which lazertinib was started after comple-

tion of carboplatin due to hematologic toxicity; therefore data on this regimen was limited at the time of publication. The median PFS was 6.3 months (95% CI 5.6 – 8.4 months) in the amivantamab-chemotherapy arm, 8.3 months (95% CI 6.8 – 9.1 months) in the amivantamab-lazertinib-chemotherapy arm, and 4.2 months (95% CI 4.0 – 4.4 months) in the chemotherapy arm. PFS was significantly longer in the amivantamab-chemotherapy arm compared to chemotherapy (HR for disease progression or death 0.48, 95% CI 0.36 – 0.64, P<0.001). This benefit was also seen when comparing amivantamab-lazertinib-chemotherapy compared to chemotherapy alone (HR for disease progression or death 0.,44, 95% CI 0.35 – 0.56, P<0.001). Benefits were consistent across all pre-defined subgroups, including in patients with brain metastases at baseline with an intracranial PFS of 12.5 months (95% CI, 10.8 months to not estimable) in the amivantamab-chemotherapy arm, 12.8 months (95% CI, 11.1 to 14.3 months) in the amivantamab-lazertinib-chemotherapy arm, and 8.3 months (95% CI 7.3 to 11.3 months) in the chemotherapy arm. Toxicities were greater in the combination arms. Grade 3 or higher adverse events were reported in 72% of patients treated with amivantamab-chemotherapy, 92% with amivantamab-lazertinib-chemotherapy, and 48% with chemotherapy. The most common of these toxicities were neutropenia, thrombocytopenia, anemia, and leukopenia. Patients receiving amivantamab had the expected increase rates of infusion-related reactions, paronychia, rashes, and stomatitis. Dose interruptions, reductions, and discontinuations due to adverse events occurred in 65%, 41%, and 18% of patients treated with amivantamab-chemotherapy, amivantamab-lazertinib-chemotherapy, and chemotherapy alone respectively. Similar to the MARIPOSA study, patients treated with lazertinib experienced an increased risk of VTE (22% in the amivantamab-lazertinib-chemotherapy arm vs 10% in the amivantamab-chemotherapy arm vs 5% in the chemotherapy arm). Given similar outcomes were seen amongst the two experimental arms along with lesser toxicities (until additional information on a modified regimen is available), chemotherapy plus amivantamab is now recommended per the NCCN guidelines for advanced EGFR mutated NSCLC after progression on osimertinib.[12]

Advanced NSCLC with EGFR Exon 20 Insertion Mutation

EGFR exon 19 deletions and L858R mutations comprise approximately 85-90% of all EGFR mutations seen in NSCLC. Exon 20 insertions are rarer yet have been found to be the third most common activating mutation within EGFR-mutated NSCLC, seen in approximately 9% of cases. Exon 20 insertion mutations are associated with intrinsic resistance to traditional EGFR TKIs.[13,14] Due to this resistance, historically chemotherapy has been the recommended first-line treatment followed by single-agent amivantamab upon progression. This was based on the CHRYSALIS trial, which was a phase I, open-label, dose-escalation, and dose-expansion study that trialed amivantamab in patients with metastatic NSCLC with EGFR exon 20 insertion who had progressed on prior platinum therapy. The study overall concluded that amivantamab was able to demonstrate a 40% overall response rate (95% CI, 29 to 51) with a PFS of 8.3 months (95% CI, 6.5 to 10.9).[12,13,15]

PAPILLON[16]

The PAPILLON study was a phase 3, international, randomized trial assigning patients with untreated, advanced NSCLC with EGFR exon 20 insertion mutations to receive either amivantamab plus chemotherapy or chemotherapy alone. The chemotherapy regimen was carboplatin plus pemetrexed for four cycles followed by pemetrexed maintenance until disease progression. The primary outcome was PFS as determined by blinded independent central review. At a median follow-up of 14.9 months, the median PFS was 11.4 months (95% CI, 9.8 to 13.7) in the amivantamab-chemotherapy group and 6.7 months (95% CI, 5.6 to 7.3) in the chemotherapy group (HR for disease progression or death, 0.40; 95% CI, 0.30 to 0.53; P<0.001). At the 18 month analysis, the PFS was reported in 31% of patients in the amivantamab-chemotherapy group and in 3% of patients receiving chemotherapy alone. OS data was not mature as of the time of publication. Patients receiving amivantamab experienced more frequent grade 3 adverse events, 75% vs 54% in those receiving chemotherapy alone. Consistent with previous studies, amivantamab was associated with higher rates of infusion-related reactions (42%), paronychia (59%), and rash (54%). Amivantamab plus chemotherapy is now approved by the FDA and recommended by guidelines for the treatment of locally advanced or metastatic NSCLC harboring the EGFR Exon 20 insertion mutation as frontline therapy.

Discussion/ Future Directions

EGFR-directed therapy has revolutionized the treatment of NSCLC. Recent clinical trials have increased the number of therapeutic options both in the front line setting and in those who progress on osimertinib alone. Several key questions remain. Osimertinib's favorable toxicity profile and CNS activity continue to make it an excellent treatment option for many patients, particularly those who may be unable to tolerate the additional toxicities associated with chemotherapy or amivantamab. OS data from the FLAURA2, MARIPOSA, MARIPOSA-2, and PAPILLON trials will further elucidate the benefit of these new regimens/agents and how they compare to the previous standard of care.

Research is ongoing to gain a greater understanding regarding mechanisms of acquired resistance to osimertinib. There are off-target resistance mechanisms such as MET amplification or the rise of other pathways such as ROS1, HER2/3, RET, KRAS, BRAF, and others. Mutations can also occur on the EGFR gene, developing mutations such as C79X as an example. Histologic transformations are also possible, where NSCLC can transform into a small cell carcinoma. The heterogeneity of resistance mechanisms highlights the need for additional tumor profiling at the time of disease progression which may assist in guiding further treatment.[17]

Conclusion

There have been rapid developments in the treatment of EGFR-mutated NSCLC in recent years, and further developments are

expected as we gain more information regarding the biology of the disease. Additional time to determine OS benefit of these new treatment options will better define their place in therapy. There will be greater complexities as clinicians must apply treatment concepts in multiple settings and utilize individualized patient factors on a case-by-case basis. Pharmacists are vital to ensuring that patients undergo appropriate biomarker testing, work with the interdisciplinary team to ensure the most appropriate therapy for patients at each line of therapy, and support patients through adverse events. ●●

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From Dreams to Reality: Celebration of the Inaugural Patient Advocacy Summit

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HOPA's Patient Outreach and Education Committee (POEC) dreamt of a way to bring key stakeholders together to identify barriers and propose solutions to optimize cancer care. Over several years, the committee planned, discussed, and debated, which ultimately culminated in the inaugural Patient Advocacy Summit on September 24th, 2024, in conjunction with HOPA's annual Hill Day in Washington, DC. With valuable input from the Patient Advisory Panel, the summit was created to identify current needs within the advocacy space that HOPA could address in collaboration with advocacy partners, patients, caregivers, and industry partners. Bringing these key stakeholders together provided a platform to share ideas to improve oncology care and decrease barriers to access.

The members of the Patient Advisory Panel became our biggest advocate and source of expertise when developing the topics to discuss at the summit. The following three topics were chosen: screening recommendations, side effect management & over the counter (OTC)/supplement use guidance, and fertility & sexual health. The panel further supported our efforts by volunteering attendance and sharing personal stories when introducing the topics and throughout the discussion at their tables. We are truly thankful for their efforts to make this summit relevant to our patients by representing the patient and caregiver voice. Patient advocacy group partners were selected based on their fit and representation in the areas of the three selected topics. We were fortunate to have representation from the American Cancer Society (ACS), Stupid Cancer, Leukemia & Lymphoma Society (LLS), CancerCare, Cancer Support Community, Patient Empowerment Network, and National LGBT Cancer Network.

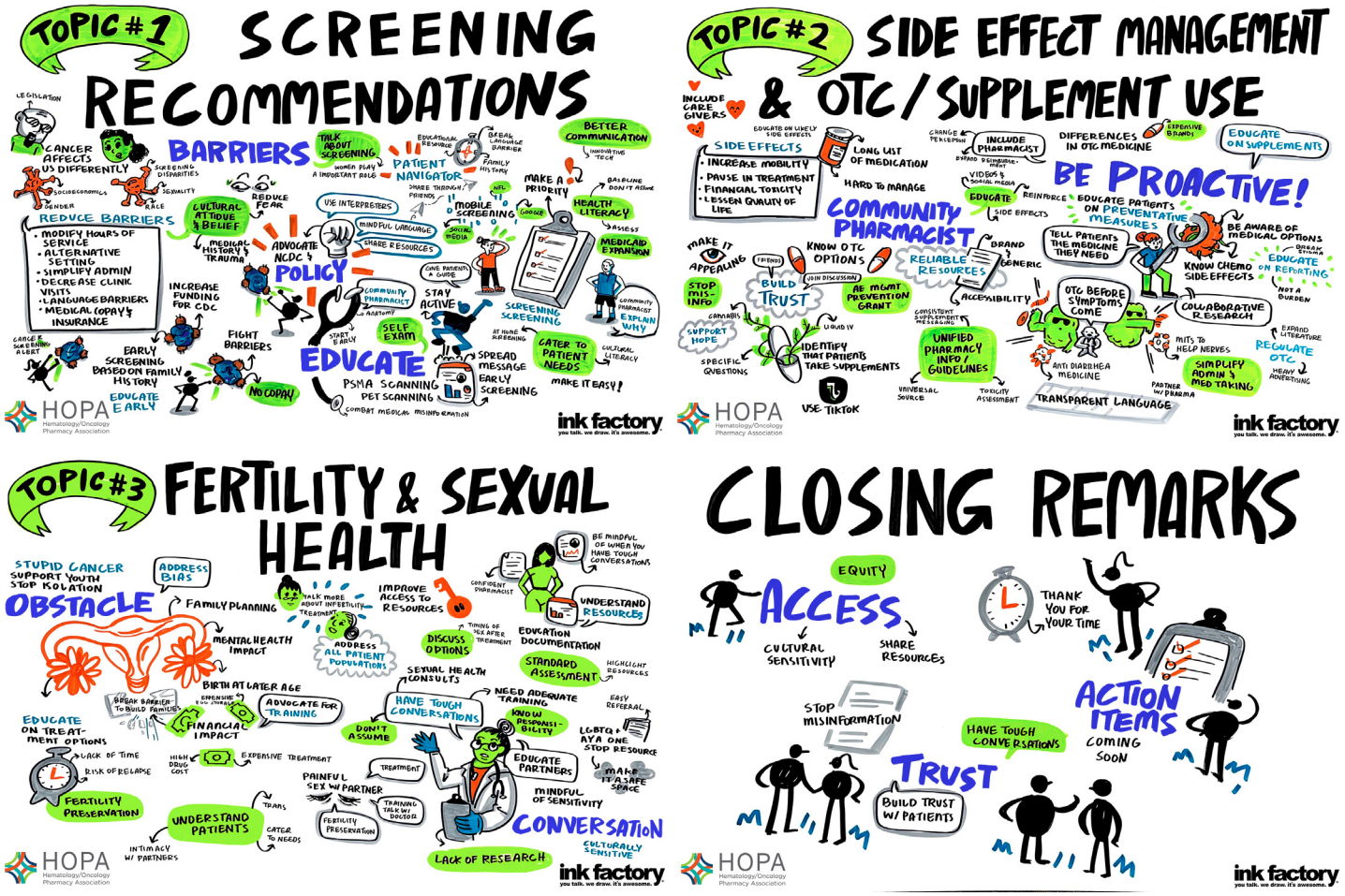
We are also grateful for the attendance from industry partners, HOPA board members, and other HOPA pharmacist members who were able to offer their expertise and perspective throughout the half-day summit. It was through the generous support of the HOPA Executive Board and industry partners who helped to deliver this concept to reality. Together, each table was composed of a patient/caregiver, a patient advocacy group representative, an industry partner, a HOPA board member, and a pharmacist. Discussion points were summarized throughout the summit by the creative skill of a visual note taker that we are excited to share through the remainder of this article.

> **"OTC and supplement use can be limited through misinformation and lack of reliable sources for dosing and drug interactions."**

Screening Recommendations

As oncology healthcare professionals, we are well versed in the need to screen at-risk populations for early signs of various cancers. However, the primary discussion at the summit addressed the gaps in education and communication to the general public, current barriers to access, social or cultural disparities, and considerations that can be addressed to increase screening. One recommendation for increasing screening education was to target local communities, especially at a young age. One participant suggested repeated public health education throughout middle and high school to highlight cancer screening benefits and recommendations. Other participants suggested the role of social media to increase screening recognition and access. Discussions around accessibility to screening looked at identifying other healthcare professionals that may be able to assist with public education, including community pharmacists and other outpatient providers.

One notable barrier to access identified from the summit included lack of understanding in screening recommendations. Some participants stated that recommendations may have too much healthcare verbiage or not be available in multiple languages, which can limit patient understanding of screening recommendations. To expand access, it's important to consider who we are trying to target and how they best receive communications and education. Other notable barriers included lack of community pharmacist involvement, medical misinformation about recommendations or modalities, differences in statewide or institutional practices, or limited insurance coverage. A recommendation for decreasing disparities and increasing cultural considerations was to increase funding for patient navigators/advocates who are culturally sensitive and speak a patient's native language. Action items from the screening discussion included developing a HOPA screening summary sheet that could be used by both pharmacists and patients and partnering with community pharmacists to reach and educate more patients on cancer screening recommendations.



Shown: visual notes taken in real-time during Patient Advocacy Summit, September 24, 2024."

Side Effect Management & OTC/Supplement Use Guidance

Much of the discussion around side effect management was focused on educating patients on the importance of being honest with physicians and healthcare providers. Patients fear being denied treatment if they experience side effects from a particular agent or regimen. Healthcare providers may be able to circumvent this by having better adverse effect management and expanding literature for adverse effects and supportive care management for various oncologic treatments. One major barrier identified for side effect management included lack of pharmacist reimbursement for clinical services and counseling, which limits the ability of pharmacists to reach the patients who need it most. A takeaway point from discussion and an area for improvement in the next few years could be creating side effect management guidelines or references to help increase access to patients and providers.

OTC and supplement use can be limited through misinformation and lack of reliable sources for dosing and drug interactions. One suggestion from the summit was to increase knowledge about how supplements may impact cancer treatment, as many patients may be influenced by misinformation from sources that are not regulated. Additionally, patients may not be aware that something they are taking over-the-counter is considered a supplement and may have an impact on their treatment. Some action items from the OTC/supplement discussion include partnering with other advocacy organizations to survey pharmacists and healthcare providers about awareness and utilization of supplements during active cancer treatment. Proactively discussing the use of supplements and OTC products from pharmacists and providers may facilitate effective medication use.

Fertility & Sexual Health

Despite an ever-increasing number of cancer survivors and a higher prevalence of patients under the age of 50, education and resources for sexual health and fertility are lacking. Oncology pharmacist, Liz R. Eubanks shared the following testimony from one of her patients at the summit. In 2021, Alexa Balazar was newly married. She and her husband had just purchased their first home when her world was turned upside down with an ALL diagnosis. The treatment that would save her life would also leave her infertile. The intense chemotherapy and constant pain coupled with anxiety and depression all but destroyed Alexa's plans for a family. But during a brief respite prior to her bone marrow transplant, "I advocated for myself

to undergo a round of IVF, despite the low chances of success". Today, two stored embryos are her hope for the future.

After personally experiencing the high cost of fertility preservation, Alexa knew she had to do more for other couples who may not have the resources to overcome the prohibitive expense. Alexa's non-profit, *Gifting Joy*, now provides oncofertility assistance for individuals who need it.

Body image, sexual health, and intimacy play an integral part in return to normalcy and quality of life for patients of all ages. Conversations around these subjects are often overlooked or avoided and under addressed. Barriers identified at the summit included a paucity of information on drug levels and drug exposure, cultural beliefs around sex, and limited resources for the LGBTQ+ population. Disparities may exist between community sites and academic sites.

Suggestions for better education and communication centered around increasing pharmacists' confidence with updated resources, toolkits and standardized assessments for sexual health. Other suggestions included providing patients with helpful facts about the safety and timing of sex and intimacy during and after treatment and reversible and irreversible side effects. Patients may need information regarding the levels of chemotherapy in body fluids and discussions should also address the fear of 'passing on cancer' and genetic counseling.

In February of 2024, NCCN released a statement urging policy makers to allow equitable access to fertility preservation as part of cancer care. ASCO and NCCN publish guidelines on fertility preservation. Resources and grants are available when insurance does not cover certain procedures. Websites and tools exist to increase knowledge and comfort level around sensitive conversations. Summit discussions highlighted the need for pharmacists to avail ourselves of resources, educate our patients and take a more holistic approach to care, especially when it comes to sexual health.

Overall, the Summit was well received and provided ample opportunity to discuss challenges, identify opportunities, and build new bridges between oncology professionals. Thanks to all the HOPA POEC members who worked tirelessly to help realize the Summit. POEC is grateful for the support of the following advocacy groups: ACS Cancer Action Network, LLS, CancerCare, Cancer Support Community, Stupid Cancer, Patient Empowerment Network and National LGBT Cancer Network. A special thanks to the patients who graciously gave their time, shared their stories, and provided us with invaluable insight. POEC members will now focus on developing short- and long-term deliverables in response to needs identified. The Summit clearly demonstrated that there is room for POEC to grow, improve, and continue to make a difference in the lives of people with cancer. ●●

The Benefits of a Clinical Oncology Pharmacy Technician

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Background

As the level of services provided by pharmacists have increased, there has been a call by both the American Society of Health-System Pharmacists (ASHP) and the Hematology/Oncology Pharmacy Association (HOPA) for a similar expansion of services provided by pharmacy technicians.[1] In response to the call for the expansion of pharmacy technician roles and to improve transitions of care, the Adult Academic Medical Center at Indiana University Health implemented a pharmacy technician-driven comprehensive meds-to-beds program that includes pharmacy-provided medication histories, evaluation of access to discharge medications, facilitation of prior authorization and/or financial assistance process, and delivery of discharge medications directly to bedside for patients admitted to and discharged from the hematology/oncology or the bone marrow transplant (BMT) units. The purpose of this study was to evaluate if this new initiative was providing a positive impact on pharmacy and patient related metrics.

"Implementation of roles like the clinical oncology pharmacy technician position is one such way to meet the call by ASHP and HOPA to expand the role of pharmacy technicians.[1]"

Methods

This was a single-center, quasi-experimental study at a 1,296 bed NCI-designated, comprehensive academic cancer center with a hospital-based retail pharmacy. The institutional review board at Indiana University approved this study and granted a waiver of informed consent. The retail pharmacy was a 340B eligible, Utilization Review Accreditation Commission (URAC) accredited specialty pharmacy. There were three inpatient, oncology-focused service lines consisting of the hematology, medical oncology, and BMT, each with a dedicated clinical pharmacist and located on either the 28-bed adult hematology/oncology or the 13-bed BMT units. The clinical oncology pharmacy technician role was a new 40-hour per week position filled by a single individual who worked weekdays from 7:30 am until 4 pm.

All encounters were for patients at least 18 years of age and admitted to the hematology/oncology or the BMT units. Encounters with a discharge date between April 1, 2016, and March 31, 2017, were included in the pre-technician cohort. Encounters with a discharge date between April 1, 2018, and March 31, 2019, were included in the post-technician cohort. Encounters were excluded if the patient was discharged to inpatient hospice care or if they expired during the hospital encounter.

After implementation of the clinical oncology pharmacy technician position, patients were offered enrollment in the meds-to-beds program at the time of the pharmacy-department provided admission medication history. For those who enrolled in the program, all new outpatient prescriptions were sent to the institution's retail pharmacy prior to discharge. The clinical oncology pharmacy technician obtained all necessary prior authorizations, communicated co-pay amounts to patients, and enrolled patients in assistance programs when needed. On the day of discharge, medications were filled at the retail pharmacy and delivered directly to the patient at bedside. If discharge was planned to occur outside of clinical oncology technician coverage hours, prescriptions were delivered to bedside and stored by nursing personnel until discharge. If counseling was required, it was performed by the service-based clinical pharmacist.

The primary endpoint was prescription capture rate. This was defined as the percentage of total newly prescribed discharge medications on each inpatient encounter that were ultimately dispensed by the institution's retail pharmacy within the 7-day period prior to discharge. Revenue is in United States Dollars (USD) and was not adjusted for inflation over the study period. The secondary endpoints were change in discharge medication revenue for the institution's retail pharmacy, percentage of medication histories completed by a member of the pharmacy department (pharmacist, student pharmacist, or pharmacy technician), hospital length of stay, 30-day readmission rates including unplanned readmissions, and unit-based patient satisfaction scores.

Descriptive statistics were analyzed for each cohort. Chi-square or Fisher's exact test was used to assess statistical significance among categorical variables, as appropriate. Continuous variables were evaluated utilizing Student's t-test to determine statistical significance for normally distributed continuous data, and the Mann-Whitney U test was used for non-parametric data. An *a priori* p-value of <0.05 was considered statistically significant. Statistical analyses were performed using JMP 11 (SAS Institute Inc, Cary, NC).

Results

There were 727 unique patients in the pre-technician and 715 unique patients in the post-technician cohorts. The median age was lower (54 vs. 61 years, $p<0.001$) and there was a higher percentage of male patients (62 vs. 52.3%, $p<0.001$) in the pre- compared to post-technician cohort. There was no difference in race/ethnicity or insurance type. A total of 2,928 inpatient encounters were evaluated in the study and 1,169 and 1,112 were included in the pre- and post-technician cohort, respectively. The complete demographics, including primary cancer diagnoses, are detailed in Table 1.

Table 1: Demographics

Measure	Pre-technician cohort	Post-technician cohort	P value
Unique patients, n	727	715	-
Age in year, median (IQR)	54 (41-65)	61 (56-68)	<0.001
Male sex, n (%)	451 (62)	381 (52.3)	<0.001
Race/Ethnicity, n (%)			0.26
White, non-Hispanic	616 (84.7)	622 (86.9)	
White, Hispanic	20 (2.7)	10 (1.4)	
Black/African American	63 (8.7)	61 (8.5)	
Other/Unknown	28 (3.9)	22 (3.1)	
Insurance type, n (%)			0.08
Medicare/Medicaid	439 (60.4)	405 (56.6)	
Commercial	248 (34.1)	281 (49.3)	
Other/None	40 (5.5)	29 (4.1)	
Unique inpatient encounters, n	1,169	1,112	-
Oncology encounters, n (%)	425 (36.4)	345 (31)	0.007
Primary discharge diagnosis, n (%)			<0.001
Adenocarcinoma	106 (24.9)	51 (14.8)	
Germ cell tumor	93 (21.9)	36 (10.5)	
Sarcoma	61 (14.4)	42 (12.1)	
Renal cell carcinoma	35 (8.2)	18 (5.1)	
Other/Unknown	130 (30.6)	198 (57.5)	
Metastatic disease	288 (67.8)	279 (81)	<0.001
Hematology encounters, n (%)	437 (37.4)	447 (40.2)	0.17
Primary discharge diagnosis, n (%)			0.29
Acute leukemia	245 (56.1)	236 (52.8)	
Lymphoma	96 (22)	95 (21.3)	
Multiple myeloma	44 (10.1)	62 (13.9)	
Benign hematology condition	26 (5.9)	20 (4.5)	
Other/Unknown	26 (5.9)	34 (7.6)	
Bone marrow transplant encounters, n (%)	307 (26.3)	320 (28.8)	0.18
Primary discharge diagnosis, n (%)			0.02
History of autologous transplant	177 (57.7)	159 (49.7)	
History of allogeneic transplant	119 (38.8)	134 (41.9)	
Other/Unknown	11 (3.6)	27 (8.4)	

IQR: Interquartile Range

The discharge prescription capture rate was lower (42.7% vs. 78.5%, p<0.001) in the pre- compared to post-technician cohort as displayed in Table 2. The corresponding discharge medication revenue generated by discharge prescriptions filled at the institution's retail pharmacy increased from $314,639.46 in the pre- to $422,129.20 in the post-technician cohort. The was an increase in median revenue for the retail pharmacy per discharge ($0 vs. $11.41, p<0.001) and percentage of encounters with at least one prescription dispensed from the institution's retail pharmacy (27.9 vs. 64.3%, p<0.001) in the pre- compared to post-technician cohort.

Total medication histories performed by the pharmacy department increased (27.5 vs. 64.4%, p<0.001) in the pre- compared to post-technician cohort. The clinical oncology pharmacy technician completed 70% of the total medication histories in the post-technician cohort. There was a decrease in the percentage of medication histories performed by pharmacists from the pre- to post-technician cohorts (43.8 to 12.7%, p<0.001). There was no difference observed in hospital length of stay, rate of 30-day readmissions, rate of unplanned readmissions, or reason for unplanned readmission as depicted in Table 3. Overall, patient satisfaction scores were lower for the hematology/oncology unit based on 128 and 398 survey responses from the pre- compared to post-technician cohort (79 vs. 88%, p<0.001). Overall, patient satisfaction scores were also lower for the BMT unit based on 44 and 84 survey responses from the pre- compared to post-technician cohort (77 vs. 84%, p=0.02).

Discussion

This is one of the largest studies describing an expanded role for pharmacy technicians in the oncology patient population and the associated benefits for the health-system. Increasing the retail pharmacy discharge prescription capture rate to 78.5% from 42.7% ensured that more patients with cancer had appropriate access to discharge medications. Coupled directly to this increase in capture rate was an increase in retail pharmacy revenue and increase in overall patient satisfaction scores, which provides financial and quality-based justifications for the clinical oncology pharmacy technician position.

Table 2: Prescription Capture Rate and Retail Pharmacy Revenue

Measure	Pre-technician cohort (n=1,169)	Post-technician cohort (n=1,112)	P value
Overall discharge prescription capture rate, % Oncology encounters capture rate Hematology encounters capture rate Bone marrow transplant encounters capture rate	42.7 47 29.6 52	78.5 77 76.7 81.5	<0.001 <0.001 <0.001 <0.001
Overall newly prescribed discharge prescriptions, n Oncology encounters discharge prescriptions Hematology encounters discharge prescriptions Bone marrow transplant encounters discharge prescriptions	3,988 1182 1395 1411	3,152 940 1101 1111	-
Discharge prescriptions dispensed from institution's retail pharmacy, n Oncology encounters dispensed prescriptions Hematology encounters dispensed prescriptions Bone marrow transplant encounters dispensed prescriptions	1,702 555 413 734	2,475 724 845 906	-
Discharge encounters with at least 1 prescription dispensed from institution's retail pharmacy, n (%)	338 (27.9)	715 (64.3)	<0.001
Discharge prescriptions per encounter, median (IQR)	0 (0-1)	1 (0-3)	<0.001
Discharge prescriptions per encounter, mean (range)	1.2 (0-18)	2.2 (0-26)	*
Discharge prescription revenue per encounter, median (IQR), USD	0 (0-8.81)	11.41 (0-59.25)	<0.001
Discharge prescription revenue per encounter, mean (range), USD	268.88 (0-11,474.87)	379.27 (0-21,577.59)	*
Discharge prescriptions per encounter in those using institution's retail pharmacy, median (IQR)	3 (2-6)	3 (2-4)	0.03
Discharge prescriptions per encounter in those using institution's retail pharmacy, mean (range)	4.3 (1-18)	3.5 (1-26)	*
Discharge prescription revenue per encounter in those using institution's retail pharmacy, median (IQR) in USD	194.55 (42.25-712.71)	35.00 (12.82-209.90)	<0.001
Total discharge revenue, USD	314,639.50	422,129.18	-

* Mean with range is displayed only to help demonstrate distribution of data

Table 3: Secondary Endpoints

Measure	Pre-technician cohort (n=1,169)	Post-technician cohort (n=1,112)	P value
Pharmacy completed medication histories, n (%)	753 (64.4)	1,022 (91.9)	<0.001
Oncology technician completed medication histories, n (%)	0	778 (70.0)	-
Pharmacist completed medication histories, n (%)	512 (43.8)	141 (12.7)	<0.001
Hospital length of stay, days, median (IQR)	5 (5-16)	6 (4-16)	0.70
Readmissions within 30 days, n (%)	401 (34.3)	402 (36.2)	0.52
Unplanned readmissions within 30 days, n (%)	192 (16.4)	202 (18.2)	0.69
Reason for unplanned readmission, n (%)	-	-	0.22
Infection	63 (32.8)	54 (26.7)	-
Pain	33 (17.2)	26 (12.9)	-
Nausea/vomiting/diarrhea	27 (14.1)	31 (15.3)	-
Altered mental status	11 (5.7)	17 (8.4)	-
Other	54 (28.1)	74 (36.6)	-

Previous studies have also found increases in prescription capture rates in a variety of specialty patient populations when meds-to-beds programs were implemented. A study evaluating pediatric patients with asthma demonstrated an increase in the percentage of patients with meds in hand from 0% to 75%.[2] A study evaluating patients with cancer demonstrated an increase in capture rate by cancer center's retail pharmacy from 18.6% to 40.9%.[3] The results in this manuscript support these previous findings and specifically highlight the role an oncology pharmacy technicians can play.

Implementation of roles like the clinical oncology pharmacy technician position is one such way to meet the call by ASHP and HOPA to expand the role of pharmacy technicians.[1] Traditionally, oncology pharmacy technicians have been tied directly to working in intravenous sterile compounding areas. Within health-systems,

nearly 96% of pharmacy technicians perform sterile compounding activities.[4] This direct patient facing role as described has the potential to increase technician job satisfaction by tying responsibilities more directly to a desire to help patients, the primary motivator for health-system based pharmacy technicians.[4]

The results of this study showed no difference in the rate of total readmissions, unplanned readmissions, and reason for unplanned readmission. There may already be high levels of adherence due to the known severity of their diagnosis and understanding that non-adherence with drug therapy may lead to acute physical consequences or a lack of cancer treatment. The lack of difference in length of stay is thought to be attributed to the recurring scheduled inpatient chemotherapy admissions, which accounted for 80% of total admissions. These patients were often only admitted because it was required based on the administration complexities of the given cancer treatment and many of these admissions were of a fixed, predetermined duration.

It is important to note that this was a single-center retrospective analysis including patients who received services before and after the implementation of a new program. Given the retrospective design, only existing data collected as a part of routine care was available. This is particularly true in relation to patient reported and quality of life outcomes. Adherence rates were not collected or analyzed in this study. Clinical pharmacists completed the discharge medication reconciliation, including prescribing of discharge medications, in both cohorts—limiting missing supportive care medications as well as potentially mitigating any medication discrepancies that were present on admission.

Conclusion

The overall capture rate of discharge prescriptions, revenue for the institution's retail pharmacy, and overall patient satisfaction scores significantly increased following the implementation of expanded, inpatient clinical pharmacy technician provided services.

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Frontline Use of Immunotherapy in PD-L1 Negative Gastric/GEJ Adenocarcinoma and ESCC: Should We Stop the Kitchen Sink Approach?

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Introduction

Clinical outcomes for patients with unresectable or metastatic gastric, gastroesophageal junction (GEJ), and esophageal cancer remain poor with five-year survival rates below 10%.[1,2] Treatment resistance and complex symptom management make these tumors challenging to treat and new advances are urgently needed.

In March 2021, the United States Food and Drug Administration (FDA) approved the use of pembrolizumab in combination with fluoropyrimidine- and platinum-based chemotherapy for adults with advanced or metastatic esophageal or GEJ cancer, including both adenocarcinoma and squamous cell carcinoma (SCC), following the positive results from the KEYNOTE-590 trial.[3,4] In April 2021, nivolumab was also approved for this patient population in combination with fluoropyrimidine- and platinum-based chemotherapy, based on the results of the CHECKMATE-649 trial.[5,6] These were significant landmark FDA approvals, as immunotherapy (IO) had previously been considered effective only for patients with microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumors, and potentially as a second-line treatment for esophageal squamous cell carcinoma (ESCC). Nivolumab was also later approved in May 2022 for first-line treatment of advanced or metastatic ESCC based on the results of the CHECKMATE-648 trial and pembrolizumab was approved in November 2023 for first-line treatment of advanced or metastatic HER-2 negative gastric or GEJ adenocarcinoma following the KEYNOTE-859 trial.[7,8]

Following the FDA approvals, many oncologists began treating all patients with first-line IO in combination with chemotherapy regardless of patients' markers for IO benefit, such as programmed death-ligand 1 (PD-L1) expression, due to the overall trend towards improved outcomes across all patients in the published trials. This marked the first new treatment strategy for this disease in many years, following the introduction of human epidermal growth factor receptor 2 (HER-2) inhibitors, and there was widespread hope that the novel treatment regimen could enhance efficacy against this challenging cancer. With the countless reports of patients having an unexpected complete response to IO across different tumor types, there was hope for those rare outlier patients who defy the odds, even while understanding the statistical likelihood of limited response in these upper gastrointestinal malignancies.[9]

More recently, long-term subgroup analyses have been published highlighting superior outcomes in certain subsets of patients, prompting the question of whether we should continue treating all patients with combination therapy or "the kitchen sink approach."

"Following the FDA approvals, many oncologists began treating all patients with first-line IO in combination with chemotherapy regardless of patients' markers for IO benefit..."

In September 2024, the FDA's Oncologic Drugs Advisory Committee (ODAC) met to discuss the use of IO combination indiscriminately with chemotherapy in the first-line setting of gastric and GEJ adenocarcinoma and ESCC. The consensus was to avoid the use of IO combination therapy in PD-L1 negative patients, also known as those with a Combined Positive Score (CPS) <1. However, the FDA labeling of nivolumab and pembrolizumab remain unchanged and recommendations vary between guidelines. Consequently, the approach to treating PD-L1 negative patients remains highly controversial and varies depending on whom you ask.

Outcomes & Guidelines

I. Gastric & GEJ Adenocarcinoma

The National Comprehensive Cancer Network's (NCCN) treatment recommendations vary by CPS status. Currently for HER-2 negative, microsatellite stable (MSS), advanced or metastatic gastric adenocarcinoma, the NCCN recommendation is to treat first line with nivolumab plus chemotherapy (category 1 for CPS ≥5), pembrolizumab plus chemotherapy (category 1 for CPS ≥10 and category 2B for CPS 1-9), or chemotherapy alone. For the first-line treatment of HER-2 negative advanced or metastatic adenocarcinoma of the esophagus or GEJ, the NCCN recommends nivolumab plus chemotherapy (category 1 for CPS ≥5 and category 2B for CPS <5) or pembrolizumab plus chemotherapy (category 1 for CPS ≥10 and category 2B for CPS 1-9).

The NCCN recommendations followed the CHECKMATE-649 trial, which compared first-line treatment with nivolumab plus chemotherapy to chemotherapy alone in advanced or metastatic HER-2 negative gastric, GEJ, and esophageal adenocarcinoma. The trial originally also included an arm with nivolumab and ipilimumab

treatment alone, but it was closed due to lack of benefit. Overall survival (OS) and progression free survival (PFS) were improved in the overall population with nivolumab plus chemotherapy. Median OS was about two months longer with the addition of nivolumab [hazard ratio (HR) 0.80; 99.3% confidence interval (CI) 0.68-0.94]. Subgroup analysis by CPS demonstrated that median OS was improved with nivolumab plus chemotherapy, although not statistically significant for the CPS <1, <5, and <10 groups.[5,6] This has supported the notion that there are a select group of IO responders driving the positive conclusions made in combination IO studies.

The KEYNOTE-859 trial, which compared pembrolizumab plus chemotherapy to chemotherapy alone in patients with previously untreated advanced or metastatic HER-2 negative gastric or GEJ adenocarcinoma, also found variation based on CPS. While median OS was about 1.5 months longer for the overall population with pembrolizumab plus chemotherapy (HR 0.78; 95% CI 0.70-0.87), the benefit was not significant for CPS <1.[8]

Similar findings with lack of significant benefit in PD-L1 negative tumors have been reported with tislelizumab plus chemotherapy in the RATIONALE-305 trial, which is currently pending FDA review for first-line treatment.[10]

Lastly, with respect to the HER-2 positive population, KEYNOTE-811 led to the approval of pembrolizumab with standard trastuzumab plus chemotherapy for those with MSS, HER-2 positive gastric and GEJ adenocarcinoma regardless of CPS in May 2021. In this trial, treatment-naïve unresectable or metastatic HER-2 positive patients with gastric and GEJ adenocarcinoma had been randomized to receive trastuzumab + chemotherapy + pembrolizumab or placebo. The pembrolizumab group had an objective response rate of 74% (95% CI 66%-82%) compared with 52% (95% CI 43%-61%) among patients who received placebo (P <0.0001).[11]

Table 1: OS by CPS (Gastric & GEJ adenocarcinoma)

CPS	Median OS (months): *IO + Chemotherapy*	Median OS (months): *Chemotherapy Alone*	HR (95% CI)
CHECKMATE-649			
CPS <1	13.1	12.5	0.95 (0.74-1.24)
CPS ·1	14.0	11.3	0.76 (0.67-0.87)
CPS <5	12.4	12.3	0.95 (0.80-1.12)
CPS ·5	14.4	11.1	0.70 (0.60-0.81)
CPS <10	12.4	12.5	0.91 (0.79-1.06)
CPS ·10	15.0	10.9	0.65 (0.55-0.78)
KEYNOTE-859			
CPS <1	12.7	12.2	0.92 (0.73-1.17)
CPS ·1	13.0	11.4	0.73 (0.65-0.83)
CPS <5	12.0	11.4	0.85 (0.73-0.98)
CPS ·5	14.0	11.5	0.70 (0.60-0.82)
CPS <10	11.7	11.2	0.86 (0.75-0.98)
CPS ·10	15.7	11.8	0.64 (0.52-0.77)

OS: overall survival; CPS: combined positive score; GEJ: gastroesophageal junction; PD-L1: programmed death-ligand 1; IO: immunotherapy (checkpoint inhibitor); HR: hazard ratio; CI: confidence interval

However, five-year analyses revealed that the median OS and median PFS benefit were only statistically significant in the group with CPS ≥1.[12] Publication with more in-depth subgroup analyses by CPS score is still pending. Nevertheless, while one may speculate potential synergy between IO and directed therapies, current studies continue to suggest that IO does not provide substantial benefit in those with negative PD-L1.

II. Esophageal Squamous Cell Carcinoma

ESCC histology is historically more responsive to IO in comparison to adenocarcinoma.[13,14] For the first-line treatment of MSS unresectable or metastatic ESCC, the NCCN recommends nivolumab plus chemotherapy (category 1 regardless of CPS), pembrolizumab plus chemotherapy (category 2A for CPS ≥ 10 and category 2B for CPS <10), chemotherapy alone, or nivolumab plus ipilimumab.

The KEYNOTE-590 trial compared pembrolizumab plus chemotherapy to chemotherapy alone as first-line treatment for advanced or metastatic esophageal and GEJ adenocarcinoma (27%) or SCC (73%). Five-year outcome data revealed an improvement in median OS for the overall population with the addition of pembrolizumab [12.3 months vs. 9.8 months; HR 0.72 (95% CI 0.62-0.84)] with 10.6% OS compared to 3.0%. Median OS was similar between the treatment groups for CPS <1 and <10 with no significant benefit. Median OS was significantly improved with the addition of pembrolizumab in the CPS ≥1 and ≥10 groups, which was about 3 months longer OS in the ≥1 group and 5 months longer in the ≥10 group.[3,4] A limitation of the study is the inclusion of both adenocarcinoma and SCC histologies and the subsequent grouped outcome analyses. While the trial was not powered to identify differences in the small subgroup with adenocarcinoma, the large portion of SCC participants allow us to draw stronger conclusions of IO benefit in this group, which is notably incremental the higher the CPS.

The CHECKMATE-648 trial was a phase 3 trial exclusive to ESCC patients with previously untreated, unresectable or metastatic disease. Patients were randomized 1:1:1 to chemotherapy, nivolumab plus chemotherapy, or nivolumab plus ipilimumab. Improved OS and PFS were seen in the nivolumab plus chemotherapy group compared to chemotherapy alone in the overall population. Interestingly, increased OS was also seen in the overall population in the nivolumab plus ipilimumab cohort compared to chemotherapy alone, suggesting that ESCC can be responsive to IO without chemotherapy. Subgroup analysis by CPS found worse median OS with nivolumab plus chemotherapy compared to chemotherapy alone in the CPS <1 group (9.9 vs. 12.1 months). Median OS was about 2.5 months higher in the CPS <5 and CPS <10 groups, although not significant. Median OS was significantly improved with the addition of nivolumab in the CPS ≥1, ≥5, and ≥10 groups with about 4 months longer OS for all groups.[7]

Similar findings with lack of significant benefit in PD-L1 negative tumors were also reported with tislelizumab plus chemotherapy in the RATIONALE-306 trial which is currently pending FDA review.[15]

The NCCN includes PD-1 inhibitors nivolumab (category 1) and tislelizumab (category 1) as potential second-line options for ESCC regardless of PD-L1 status, as well as pembrolizumab

(category 1 for CPS of ≥10). Single-agent treatment demonstrated benefit regardless of PD-L1 status, although similar trends towards better outcomes with higher PD-L1 expression were seen for all agents.[16,17,18] Therefore, a patient could still be considered to receive IO in the second-line setting if they did not receive it upfront. Generally, SCC histology across tumor type tend to have more PD-L1 positivity, compared to adenocarcinoma which are more often PD-L1 negative.[19,20,21] Not surprisingly, about half of the ESCC patients in the KEYNOTE-590 and CHECKMATE-648 trials were CPS ≥10 and <10% were CPS <1.

Table 2: OS by CPS (ESCC)

CPS	Median OS (months): IO + Chemotherapy	Median OS (months): Chemotherapy Alone	HR (95% CI)
KEYNOTE-590 (ESCC only)			
CPS <1	11.4	11.4	1.00 (0.54-1.85)
CPS ·1	12.6	9.8	0.69 (0.56-0.85)
CPS <10	10.5	11.1	0.99 (0.74-1.32)
CPS ·10	13.9	8.8	0.57 (0.43-0.75)
CHECKMATE-648			
CPS <1	9.9	12.1	0.98 (0.50-1.95)
CPS ·1	13.8	9.8	0.69 (0.56-0.84)
CPS <5	12.0	9.4	0.74 (0.52-1.04)
CPS ·5	15.2	11.1	0.69 (0.55-0.87)
CPS <10	12.1	9.7	0.78 (0.60-1.01)
CPS ·10	16.1	11.6	0.63 (0.47-0.84)

OS: overall survival; CPS: combined positive score; ESCC: esophageal squamous cell carcinoma; PD-L1: programmed death-ligand 1; IO: immunotherapy (checkpoint inhibitor); HR: hazard ratio; CI: confidence interval

Discussion

Thus far, all studies have demonstrated significantly improved outcomes with the addition of IO to chemotherapy. However, the benefit is not statistically significant in subgroup analyses of PD-L1 negative patients, with some trials suggesting similar or potentially worse outcomes. These conclusions are a bit more nuanced when evaluating based on histology. Specifically, the outcomes in PD-L1 negative gastric and GEJ adenocarcinoma suggest a trend towards improved outcomes, while there does not appear to be any benefit in PD-L1 negative ESCC. Meanwhile, the clinical outcomes are unarguably improved in patients with higher PD-L1 expression across all trials and histologic classes. This emphasizes the role that PD-L1 expression plays when determining the risk versus benefits of adding first-line IO to chemotherapy. However, there is no clear PD-L1 expression cutoff, and to complicate this further, some trials utilize CPS, while others use tumor proportion score (TPS) or tumor area positivity (TAP) to characterize PD-L1 expression.

While most patients tend to tolerate PD-1 inhibitors well without the typical consequences of chemotherapy, such as cytopenia and nausea, there is still a rare risk of potentially severe and life-threatening immune-related side effects that must be taken into consideration. Patients with baseline comorbidities such as systemic lupus erythematosus, Crohn's disease, rheumatoid arthritis, and pulmonary fibrosis, are already at higher propensity for severe side effects. Patients with these baseline conditions that can be exacerbated should especially avoid IO where there is limited potential benefit. We must also keep in mind the high cost of immune-checkpoint inhibitors compared to chemotherapy alone. While cost varies widely in the United States based on insurance plan, it is estimated that a single 200 mg dose of pembrolizumab may cost $11,337.36 out of pocket in 2024 versus $5,907 for a dose of common chemotherapy doublet FOLFOX.[22] This can result in substantial financial toxicity and undue hardships on patients who may not necessarily see benefit from adding IO.

In the last years we have become more biomarker-driven in our treatment decisions. Aside from PD-1 positivity, patients with gastric, GEJ, and esophageal cancer should now also be screened for HER-2 and claudin 18 isoform 2 (CLDN18.2) status. Eligible patients that are considered HER-2 positive should receive upfront treatment with combination chemotherapy and HER-2 inhibitor trastuzumab.[11,12] The first-in-class CLDN18.2-inhibitor zolbetuximab was recently FDA-approved in October 2024 and is now indicated for first-line treatment in CLDN18.2-positive patients in combination with chemotherapy.[23,24] It is not yet known which target is the most important driver of tumor growth and we will be learning more in the years to come on the optimal sequencing of biomarker-driven therapies in the setting of patients that are positive for PD-L1, HER-2, and CLDN18.2. We may even start to see all three targeted therapies given in combination with chemotherapy as a quintet. Nonetheless, due to the lack of significant benefit in the PD-L1 negative patients in clinical trials with PD-1 inhibitors, these patients should instead be treated with HER-2 or CLDN18.2-inhibitors when eligible due to known benefits.

In conclusion, we agree with ODAC's vote against the use of PD-1 inhibitors in combination with chemotherapy as first-line treatment for patients with PD-L1 negative unresectable and metastatic gastric and GEJ adenocarcinoma and ESCC due to lack of significant clinical benefit and risk of severe toxicities. These patients may instead be eligible for chemotherapy alone or other targeted treatments if HER-2 or CLDN18.2-positive. However, it is difficult to devise a "one size fits all" approach as there was still a trend towards improved outcomes in the PD-1 negative gastric and GEJ adenocarcinoma patients, although not statistically significant, which alludes to some possible benefit in certain patients. Therefore, we think it is reasonable to consider the use of PD-1 inhibitors in select patients, such as younger, fit patients without significant comorbidities and lack of other actionable targets. Further investigations into the tumor immune microenvironment may help refine methods for more accurately identifying patients who are likely to respond to IO. ●●

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Board Update

The Value of Support Networks

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When I chose "Courage" as HOPA's theme for 2024-2025, I had no idea how crucial bravery and resilience would be in the months to come. Here in Asheville, North Carolina, we are still recovering from the impact of Hurricane Helene, and for me, it is a reminder that every HOPA member is also a member of your own community and family.

When I see neighbors rallying to help each other, it reminds me of HOPA members bringing to life our mission of supporting each other as oncology pharmacists. Now is the perfect time for us to come together, too, because HOPA 2025 is right around the corner!

Join us for HOPA 2025 in Portland!

I hope to see you for Annual Conference 2025 on April 9-12 in Portland, Oregon for education, knowledge-sharing, and perhaps most important, networking!

This year's John G Kuhn Keynote Speaker is Carolyn Taylor, Founder and Executive Director of Global Focus on Cancer. The Incoming President's Address will be delivered by Robert Mancini, PharmD, BCOP, FHOPA. You also won't want to miss the celebration of HOPA Award winners and the new FHOPA class.

Special to this conference is the *Big Idea Pitch*, which is the culmination of one of my priorities for the year: Innovation in oncology pharmacy. Five Big Idea teams will do a LIVE presentation of how they intend to advance oncology pharmacy practice. Be there to see their Big Ideas come to life – and the resources needed to implement their idea.

Councils Lead the Charge

Council leaders recently provided the HOPA Board with updates on initiatives that fall under each strategic pillar. As always, we are pleased with the work being done and amazed at how much can be accomplished by our dedicated volunteers and staff.

- **Education Council** – Education committees published useful tools, created or reimagined programs, and maintained more than the status quo on existing educational products. A new Virtual Practice Management format was created with highly concentrated (60-90 minutes) single-topic sessions presented quarterly. The Oncology Case Series was launched as an interactive webinar series for hematology/oncology residents and clinicians to discuss topics less likely to be included in every residency program.

  The Pediatric Oncology Pharmacy Toolkit was published and is available to all members under Resources on our website.
- **Professional Practice Council –** From shoring up the mentorship rubric to completing a membership drive, our professional practice committees have been very productive. In addition to facilitating the Member Awards nominations (43 total) and managing FHOPA applications (6 were chosen), professional practice committees focused on how to best feature current and past leaders. Please watch our website for personal reflections from HOPA leaders.
- **Research & Quality Council** – The Oral Chemo Collaborative (OCC) drafted practice standards, and an implementation guide is in the works. OCC also completed their qualitative interviews with oncology/pharmacy providers and a corresponding white paper is in development.

  The Practice Outcomes and Professional Benchmarking Committee (POPBC) created a task-valuation survey, which was completed by 500+ oncology pharmacists, and has a forthcoming manuscript. The Research Grant Reviewers (RGRs) streamlined their application submission and review processes. Grant funds were awarded through the HOPA Research Fund Award and the call for Early Career Research Grant Applications were open at the time of this writing.

  The Quality Oversight Committee (QOC) is working on a white paper about the role of pharmacists in quality improvement. QOC has also formed an EMR/IT workgroup to explore how data is used in quality improvement.
- **Advocacy & Awareness Council** – The Patient Outreach and Education Committee (POEC) hosted a successful HOPA Patient Advocacy Summit last fall in Washington DC and is already planning one for 2025. The Public Policy Committee (PPC) will soon send out a drug shortages survey and are busy compiling billing guidance by each state. POEC and PPC are co-planning an Advocacy Update during HOPA 2025.

Annual Call for Volunteers

By the time you read this, we will have begun our annual call for volunteers. Committees help fulfill our mission and your individual contributions help ensure that everyone going through cancer treatment has an oncology pharmacist by their side.

If your time is limited, please watch for calls for HOPA's new micro-volunteer positions throughout the year. We are excited to offer more volunteer opportunities with varied time commitments. Whether in quick bursts or through in-depth work, we thank you, our volunteers, for everything you do! See you in Portland next month. ●●

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HOPA 2025

Together we can reach new heights

We look forward to seeing you at HOPA 2025!

April 9-12, 2025 in Portland, Oregon at the Oregon Convention Center.

Early bird registration opens mid-December 2024! *Watch for details on hoparx.org.*

We are hard at work to make your HOPA 2025 experience complete!

Come for the cutting-edge science and industry-leading presenters and stay for plenty of HOPA networking and events.

Plus, use your complimentary transit pass to get out and explore Portland!

ABOUT THE HOPA 2025 VENUE:

- Open spaces and natural light set the scene for meaningful meet-ups with colleagues and friends!
- The **Oregon Convention Center's** commitment to sustainability sets HOPA up for our "greenest" conference to date
- The venue is a short walk or quick MAX Light Rail ride away from the hotel