

HOPA NEWS

Pharmacists Optimizing Cancer Care

VOLUME 20 | ISSUE 1

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COMPANION DIAGNOSTIC
MOLECULAR ANALYSIS
TUMOR AGNOSTIC
PRECISION MEDICINE
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Pharmacists Optimizing Cancer Care®

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Putting All of Our Eggs in Basket Trials: New Tumor-Agnostic Approvals



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INTRODUCTION

Historically, cancers have been treated as separate entities with differing combinations of traditional systemic chemotherapy. Advances in the understanding of genetics, cancer, and molecular analysis over the last several decades have led to the identification of genetic alterations that drive different cancers' growth, known as driver mutations. These genetic alterations, while often rare, have led to the advent of immunotherapies and targeted therapies. Simultaneously, companion diagnostic assays have been co-developed and approved in parallel to the individual drugs, ensuring appropriate patient selection prior to prescribing and thus increasing efficacy and safety.¹ These therapies allow for a more precise approach to treatment and may circumvent some of the toxicities associated with conventional chemotherapy, albeit not without risks of their own.

Similar to most new oncologic treatments, initial clinical trials of cancer treatments specific to a given molecular profile were characterized by individual disease states (e.g., EGFR-mutated non-small cell lung cancer [NSCLC] or HER-2 positive breast cancer) and enrolled patients in the metastatic setting who had exhausted all other treatment options. Subsequent trials evolved to use a similar study design but included treatment-naïve patients either with advanced disease or as neoadjuvant/adjuvant therapy in patients with high risk but early-stage disease.² Recently, basket trials, which include patients with the same genetic mutation but differing tumor tissue of origin, are becoming more commonly used. These basket trials have led to the approval of tumor-agnostic therapies, or agents that have molecular targets for biomarker-defined diseases, without specificity for tumor histology. To date, six tumor-agnostic therapies (and their companion diagnostic assays) have been approved by the United States Food and Drug Administration (FDA). This represents a new shift in precision medicine and allows for a wider range of patients to be treated with more therapies.² Table 1 summarizes the supporting clinical trial data of the six tumor-agnostic therapies discussed below.

IMMUNOTHERAPY

Pembrolizumab

Pembrolizumab (Keytruda®) was the first tumor-agnostic therapy to gain FDA approval in May 2017 for the treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, as detected by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.³ The mismatch repair system serves to maintain genomic integrity and involves major pathways, such as apoptosis. When deficient, this leads to a phenomenon called microsat-

Table 1. Clinical trial efficacy data of the FDA-approved tumor-agnostic therapies

Medication	Genetic Target	Cancer Type ^a	N	Overall Response Rate n (%) (95% CI)	Duration of Response Range (mo.)
Larotrectinib	NTRK gene fusion	Salivary gland	12	10 (83) (52-98)	7.7 - 44.7+
		Soft tissue sarcoma	11	10 (91) (59-100)	3.6+ - 50.6+
Entrectinib	NTRK gene fusion	Sarcoma	13	6 (46) (19-75)	2.8 - 33.6+
Pembrolizumab	MSI-H or dMMR	Colorectal	90	32 (36) (26-46)	1.6+ - 22.7+
		Small cell lung	34	10 (29) (15-47)	4.1 - 32.5+
Dostarlimab	dMMR	Colorectal	69	25 (36) (25-49)	5.6 - 30.1+
		Endometrial	103	46 (45) (35-55)	2.6 - 35.8+
Dabrafenib + Trametinib	BRAF V600E	Biliary tract	48	22 (46) (31-61)	1.8 - 40
		High grade glioma	48	16 (33) (20-48)	3.9 - 44
Selpercatinib	RET gene fusion	Colorectal	10	2 (20) (3-56)	5.6 - 13.3
		Pancreatic adenocarcinoma	11	6 (55) (23-83)	2.5 - 38.3+

^aOnly tumor types with >20% of total patients represented

+Indicates ongoing response

BRAF = B-Raf proto-oncogene; dMMR = mismatch repair deficient; MSI-H = microsatellite instability-high; NTRK = neurotrophic receptor tyrosine kinase; RET = rearranged during transfection; TMB-H = tumor mutational burden-high;

ellite instability, ultimately causing downstream effects of somatic hypermutation and uncontrolled cell growth.⁴ This approval was based on a pooled analysis of five single-arm trials consisting of 149 patients. A total of 15 different MSI-H or dMMR tumor types were analyzed, with the most common being colorectal, endometrial, biliary, gastric or gastroesophageal junction, pancreatic, and small intestinal. The overall response rate (ORR) was 39.6% (95% CI, 31.7 – 47.9), with 11 patients (7.4%) experiencing a complete response and 48 patients (32.2%) experiencing a partial response. An objective response was obtained in at least one patient in all included tumor types, except for sarcoma, renal cell, bladder, and thyroid cancers, with the latter two having only one enrolled patient each that were not evaluable during follow-up. Small sample sizes limited the ability to calculate a 95% CI for the ORR for patients with breast, prostate, esophageal, retroperitoneal adenocarcinoma, and small cell lung cancers.⁵

Pembrolizumab gained a second tumor-agnostic approval in June 2020 for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H; defined as ≥ 10 mutations/megabase as determined by an FDA-approved test) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.³ Tumor mutational burden quantifies the number of acquired mutations per megabase of sequenced DNA. The higher the TMB, the higher the probability that a cancer cell might present a neoantigen to the immune system. In turn, this increases the likelihood that the immune system will be activated and respond to a checkpoint inhibitor.⁶ This approval was based off a subgroup analysis of 102 patients with tumors identified as TMB-H from the open-label KEYNOTE-158 trial. The patients with TMB-H status had only 9 unique cancer types, with the most common being small-cell lung cancer, cervical cancer, and endometrial cancer. The ORR was 29% (95% CI, 21 – 39), with 4 patients (4%) experiencing a complete response and 26 patients (25%) experiencing a partial response. An objective response was obtained in at least one patient in all included tumor types, except for mesothelioma cancer. Small sample sizes limited the ability to calculate a 95% CI for the ORR for patients with salivary and thyroid cancers.⁷

Dostarlimab

A second immunotherapy agent, dostarlimab-gxly (Jemperli®), gained FDA approval in August 2021 for adults with dMMR recurrent or advanced solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.⁸ This approval was based on a subgroup analysis of 209 patients who were identified as having dMMR tumors from the open-label GARNET trial. Patients with 14 different non-endometrial tumor types were

included, with the most common being colorectal, small intestinal, gastric, and pancreatic cancers. The ORR was 41.6% (95% CI, 34.9 – 48.6) with 19 patients (9.1%) experiencing a complete response and 68 patients (32.5%) experiencing a partial response. An objective response was obtained in at least one patient in all included tumor types, except for esophageal cancer and renal cell carcinoma. Small sample sizes limited the ability to calculate a 95% CI for the ORR for patients with biliary neoplasms, liver, ovarian, adrenal cortical, breast, genital neoplasm, and pleural cancers.⁹

NTRK GENE FUSION

Larotrectinib

The first small molecule tumor-agnostic therapy approved by the FDA was larotrectinib (Vitrakvi®) in November 2018 for the treatment of adult and pediatric patients with solid tumors that 1) have

a specific variant neurotrophic receptor tyrosine kinase (NTRK) resulting in production of a gene fusion without known acquired resistance mutations, 2) are either metastatic or where surgical resection is likely to result in severe morbidity, and 3) have no satisfactory alternative treatments or have progressed following treatment.¹⁰ NTRK gene fusions occur when portions of the chromosome containing the *NTRK1*, *NTRK2*, or *NTRK3* genes break off and join with genes on a separate chromosome. This leads to production of oncogenic TRK fusion proteins, which activate downstream signaling pathways and

cell proliferation.¹¹ This approval was based on the pooled results of patients with NTRK gene fusions from three different single-arm trials. The first 55 patients with NTRK fusion-positive cancer, regardless of age or tumor type, were grouped together. Specific eligibility criteria differed slightly between each trial but included patients that had locally advanced or metastatic solid tumors and had received standard therapy previously (if available). In this group, there were 17 unique tumor types, with the most common being salivary gland, soft tissue sarcoma, infantile fibrosarcoma, and thyroid. The ORR was 75% (95% CI, 61 – 85), with 7 patients (13%) experiencing a complete response and 34 patients (62%) experiencing a partial response. Of note, a complete or partial response was obtained in at least one patient in all included tumor types, except for cholangiocarcinoma, appendiceal carcinoma, breast, and pancreas, with the latter three types having only one patient enrolled. Small sample sizes limited the ability to calculate a 95% CI for the ORR for patients with melanoma or colorectal cancers.¹²

Entrectinib

Shortly after the approval of larotrectinib, entrectinib (Rozlytrek®) was approved in August 2019 for adults and pediatric patients 12 years or older with solid tumors that 1) have an NTRK gene fusion as detected by an FDA-approved companion diagnostic test without a known acquired resistance mutation, 2) are metastatic or where

"Tumor-agnostic directed therapy is a new strategy for precision medicine that allows for treatment directed at molecular targets across a variety of different tumor types."

FEATURE

surgical resection is likely to result in severe morbidity, and 3) have progressed following treatment or have no satisfactory alternative therapy.¹³ This approval was based on an integrated analysis of three single-arm phase 1-2 trials. A total of 54 adults with metastatic or locally advanced NTRK fusion-positive solid tumors were pooled to evaluate efficacy. Ten different tumor types were included, with the most common being sarcoma, NSCLC, mammary analogue secretory carcinoma, breast, thyroid, and colorectal. The ORR was 57% (95% CI, 43.2 – 70.8), with 4 patients (7%) experiencing a complete response and 27 patients (50%) experiencing a partial response. An objective response was obtained in at least one patient in all included tumor types, though small sample sizes limited the ability to calculate a 95% CI for the ORR for patients with thyroid, colorectal, neuroendocrine, pancreatic, cholangiocarcinoma, or gynecological cancers.¹⁴

BRAF V600E MUTATION

Dabrafenib and Trametinib

The combination of dabrafenib (Tafinlar®) and trametinib (Mekinist®) gained FDA-approval in June 2022 for the treatment of adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with a B-Raf proto-oncogene (BRAF) V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options.^{15,16} BRAF is a serine/threonine kinase that is part of the mitogen-activated protein kinase (MAPK) signaling pathway. V600E is a point mutation of the BRAF gene in which the amino acid valine (V) is substituted by glutamic acid (E) at amino acid 600, leading to constitutive activation of the MAPK pathway and increased cell proliferation and resistance to apoptosis.¹⁷ This approval was based on the pooled analysis of 131 adult patients with 13 different tumor types who were enrolled in one of two single-arm trials. The most common tumor types were biliary tract cancer, high-grade glioma (with seven different histologies included), low-grade glioma (with six different histologies included), and low-grade serous ovarian carcinoma. A complete or partial response was observed in 54 patients (41.2%). An objective response was observed in at least one patient in all included tumor types, except for pancreas adenocarcinoma, mixed ductal/adenoneuroendocrine carcinoma, neuroendocrine carcinoma of the colon, adenocarcinoma of the anus, and gastrointestinal stromal tumor. Differences were seen when stratified by histologic subtype in both high- and low-grade gliomas. Efficacy was also confirmed in a trial of 48 pediatric patients with high- and low-grade gliomas; the ORR was 25% (95% CI, 12 – 42).¹⁸⁻¹⁹

RET GENE FUSION

Selpercatinib

Selpercatinib (Retevmo®) is the most recently available tumor-agnostic therapy, gaining FDA-approval in September 2022 for adult patients with locally advanced or metastatic solid tumors with a rearranged during transfection (RET) gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.²⁰ Similar to NTRK gene fusions, RET gene fusions occur when the *RET* gene is fused to

another unrelated gene, leading to overproduction of the RET protein and a subsequent increase in cell proliferation.²¹ This approval was based on the open-label LIBRETTO-001 trial that enrolled 45 patients with non-NSCLC or thyroid RET fusion-positive advanced solid tumors. A total of 14 unique cancer types were included, with the most common being pancreatic, colon, salivary, sarcoma, and unknown. The ORR was 43.9% (95% CI, 28.5 – 60.3), with 2 patients (4.9%) experiencing a complete response and 16 patients (39%) experiencing a partial response. An objective response was obtained in at least one patient in all included tumor types, except for xanthogranuloma, pulmonary carcinosarcoma, rectal neuroendocrine, and carcinoma of the skin tumor types. The two patients enrolled with xanthogranuloma were not evaluable. Small sample sizes limited the ability to calculate a 95% CI for the ORR for patients with biliary neoplasms, liver, ovarian, adrenal cortical, breast, genital neoplasm, and pleural cancers.²²

DISCUSSION

Tumor-agnostic directed therapy is a new strategy for precision medicine that allows for treatment directed at molecular targets across a variety of different tumor types. All of the tumor-agnostic approvals to date are accelerated approvals, and continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials.

These broad approvals that occur without regard to tumor of origin may provide patients with additional treatment options, especially in those with rare tumor types that otherwise may not be studied in phase 3 clinical trials. While this may benefit select patients, discernment should be used in identifying candidates for these agents, as not all tumor types are studied and approvals are specific to the type of variant (e.g., BRAFV600E point mutations but not BRAFV600D point mutations). In addition, the sample sizes in the basket trials are relatively small, ranging from approximately 40 to 200 patients, due to the low prevalence of variants. When looking at individual tumor types, the sample sizes are even smaller, with approvals of some disease states being based on evaluation of zero to only a few patients, and in some cases, without any objective responses. Additionally, an acceptable efficacy endpoint, most often either ORR or progression-free survival (which are surrogate measures for overall survival), can vary significantly across tumor types and clinical stages, making interpretation challenging.

It is important for pharmacists to critically evaluate the literature and weigh the risks and benefits of initiating tumor-agnostic therapies. A crucial first step is to ascertain whether the relevant basket trial included any participants with the patient's tumor type, and if so, to critically evaluate the trial design and efficacy endpoints. The next step is to evaluate whether the efficacy compares favorably to other standard-of-care treatments or off-label options, which are often single-agent chemotherapy regimens. As previously mentioned, although some of these immunotherapies and targeted therapies may circumvent the toxicity profiles of traditional chemotherapy agents, they are not without their own adverse effects. Shared decision-making should be used with the patient to determine a treatment of choice. Lastly, cost should be taken into

account, as these therapies may not be economically feasible for the patient and the healthcare system.

CONCLUSION

In conclusion, 6 tumor-agnostic therapies and their companion diagnostic assays are FDA-approved to date. This shift in precision medicine may offer additional treatment options to patients with rare tumor types and genomic alterations that may not otherwise be

studied in clinical trials. Pharmacists can play a key role in identifying which patients may benefit from these agents. Prior to prescribing of these therapies, it is essential to 1) ensure the variant harbored matches the tumor-agnostic indication, 2) evaluate whether available trials have included the tumor type of interest, and 3) assess the treatment on a case-by-case basis, taking into account patient-specific characteristics, other treatment options, and cost. ●●

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Reflections from a Life-long Oncology Pharmacist: “Unconditional Care”



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Oath of a Pharmacist

I promise to devote myself to a lifetime of service to others through the profession of pharmacy. In fulfilling this vow:
I will consider the welfare of humanity and relief of suffering my primary concerns.

I will promote inclusion, embrace diversity, and advocate for justice to advance health equity.

I will apply my knowledge, experience, and skills to the best of my ability to assure optimal outcomes for all patients.

I will respect and protect all personal and health information entrusted to me.

I will accept the responsibility to improve my professional knowledge, expertise, and self-awareness.

I will hold myself and my colleagues to the highest principles of our profession’s moral, ethical and legal conduct.

I will embrace and advocate changes that improve patient care.

I will utilize my knowledge, skills, experiences, and values to prepare the next generation of pharmacists.

I take these vows voluntarily with the full realization of the responsibility with which I am entrusted by the public.

Adopted by AACP and APhA (November 2021)

Reflections on Day 1 of a student pharmacist after taking the Oath of a Pharmacist:

Better pay attention in school so I can provide lifetime devotion of unconditional care to all individuals at the best of my ability...

Reflections on first day of APPE:

Wow!! I am actually going to take care of patients in real life. Better not screw up and pay attention so I can deliver unconditional care and not disappoint my preceptors and the medical team.

Reflections on my last day of APPE:

Wow!! Time flies this year. I really loved APPE more, especially oncology because I really get to know the patients and their families. They are so kind even when they are facing such a serious situation in their lives...amazing!!! I also appreciate the significance of interprofessional team care and the devotion of oncology health-care providers in giving unconditional care. I must learn more in my residency so I can give better unconditional care, just like how many of the medical team members have shown me.

Reflections on my last day of residency:

I am grateful that I got matched to the University of California Irvine Medical Center (UCIMC) residency program because the program design allowed me sufficient space to personalize my training. I rotated through various specialty oncology teams. My oncology preceptor, Dr. Tom Billups, supported my desire to take care of 2 patients with cancer throughout the year so I can truly understand what it takes to deliver unconditional longitudinal care and to confirm my commitment to be an oncology pharmacist.

Reflections on my end-of Year 1 as an oncology pharmacist:

Began my career as the first Gyn-Onc pharmacist at UCIMC and serving as a preceptor for student pharmacists. Working with a surgical oncology team that also manages their patients’ chemotherapy provided plenty of opportunities for this young pharmacist to learn about post-op care in addition to the conventional oncology care. Of course, attending daily patient rounds at 6:30 AM was precious. Thank you, Dr. Philip DiSaia for making all these experiences possible for me.

≡ Reflection on Personal Impact and Growth ≡

Reflections on my fifth year as an oncology pharmacist:

On top of now serving both medical oncology and gyn-oncology patients, the process of creating an infusion center pharmacy in the newly built NCI-designated Chao Comprehensive Cancer Center at UCI was one of the most rewarding experiences. The independence to develop an innovative pharmacy practice model for the oncology pharmacy team to provide comprehensive direct patient care in both ambulatory and inpatient settings was rewarding and appreciated by patients and the medical team. The interprofessional approach optimized the unconditional care delivered to the patients and caregivers. The pharmacy became a reference and training site that embraced and advocated change for continual improvement of patient care. Thank you, Drs. Steven Armentrout, Lewis Slater, and Frank Meyskens for your mentorship and support.

Reflection on my tenth year as an oncology pharmacist:

The growth as a practitioner was undeniable in the last 10 years... grateful... The new opportunity to grow in clinical research presented excitement for another chapter of my professional development. Entered my first full time academia appointment as a founding faculty of Western University College of Pharmacy satisfied my growing passion for research. I also founded the Pharmaceutical Science Committee at SWOG to supplement my learning dimension in research and expand my horizon to deliver unconditional care to patients, young colleagues, and peers.

Reflection on my twentieth year as an oncology pharmacist:

After working with an oncology surgeon to manage the patients on year-long adjuvant interferon therapy and clinical trials as a faculty-in-residence at UCIMC, I transitioned to an oncology private practice office to initiate a full-service clinical trial program. The ability to personalize investigative treatment options to patients in the community setting is priceless, not to mention another lifetime learning reward and the pleasure to share all these innovative, entrepreneurial and leadership events to learners who I worked with.

Reflection on my thirtieth year as an oncology pharmacist:

These last 10 years presented the most mobile phase of my personal and professional growth, including position and institutional changes that resulted in a bold move to take on a founding ad-

ministrative position at Chapman University School of Pharmacy. Perhaps a mid-life crisis? One of the most profound events that occurred was creating a stand-a-lone referral based oral chemotherapy management clinic, which resulted in my next phase of growth in elevating my viewpoint to broader professional issues, such as general population safety and professional responsibility.

Since my semi-retirement in early 2020, I reflected on my accomplishments and contributions to my profession in the last thirty-some years. I wonder if I have fulfilled the oath I took on my first day of pharmacy school. Did I consider the welfare of humanity and relief of suffering my primary concerns? Did I promote inclusion, embrace diversity, and advocate for justice to advance health equity? Did I apply my knowledge, experience, and skills to the best of my ability to assure optimal outcomes for all patients? Did I respect and protect all personal and health information entrusted to me? Did I accept the responsibility to improve my professional knowledge, expertise, and self-awareness? Did I hold myself and my colleagues to the highest principles of our profession's moral, ethical and legal conduct? Did I embrace and advocate changes that improve patient care? Did I utilize my knowledge, skills, experiences, and values to prepare the next generation of pharmacists?

I believe I did, and I think it is because of all the Unconditional Care I have received from, shared with, and provided to all my encounters as a life-long oncology pharmacist. I also came to recognize that I have embraced the oath starting with a very focused personal goal to fully embody the oath to my patients, collaborators, learners, and global professional issues as I grow professionally. As I am being asked to impart my "advice," I cherish the valuable lessons I learned from the late Randy Pausch "The Last Lecture" published in 2008 on his end-of-life reflections as a young computer science professor about *living* (in red) and add on my personal thoughts.

Be adventurous and just do it

Seizing every moment and do the best you can with it

It never hurts to ask because you never know if that may promote your personal and/or professional growth, even self-discovery for research ideas

Enabling the dreams of others because you will be amazed at the joy that will bring when you are surrounded by successful people ●●

Expansion of Oral Oncology Pharmacy Management through a Collaborative Practice Agreement at St. Luke's Cancer Institute



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The oral oncology medically integrated pharmacy (MIP) program at St. Luke's Cancer Institute (SLCI; formerly Mountain States Tumor Institute) was established subsequent to an oncology pharmacy resident project in 2009-2010. The department that was originally staffed with 1.0 pharmacist full-time equivalent (FTE) and 0.5 technician FTE has expanded exponentially over the last decade, and is currently staffed with 5.5 pharmacist FTEs, 6 technician FTEs, and 1.0 pharmacy manager FTE. A 1.4 nurse FTE has also been allocated to manage patients receiving their prescriptions through external specialty pharmacies or through drug manufacturers.

Services through the oral oncology MIP are offered to patients receiving care at the five SLCI sites under the care of sixteen medical oncologists who serve more than 3,500 total patients across Idaho and the surrounding states. Pharmacists are physically integrated within four of the five sites to provide in-person clinical services in addition to operating as a liaison with the dispensing pharmacy. Once a new oral oncology treatment plan is entered within the electronic health record (EHR), the plan is manually sent by the provider team to the oral oncology pharmacy team's pool. The prescription is first clinically reviewed by a pharmacist, who then contacts the patient to introduce services and address any upfront questions or concerns. Technicians then initiate benefits investigation, including prior authorizations, referrals for financial assistance, and insurance-specific fulfillment requirements. Pharmacists then communicate with the patient next steps, complete medication counseling, provide weekly follow up for the first month through contacting patients or reviewing provider visit notes, and then follow up prior to the initiation of every treatment cycle for patients receiving their prescriptions through the St. Luke's pharmacy. While the majority of patient follow up attempts are completed over the phone, with the expanded integration of pharmacists within the various clinics, the team is now able to increase the proportion of in-person visits with patients.

In an attempt to streamline workflow and prevent delays in treatment initiation and continuation, the oral oncology MIP established a collaborative practice agreement (CPA) as an oncology pharmacy resident pilot project in 2018. Implementing the oral oncologic CPA was facilitated by a decade of great oncology pharmacist and provider experience with a CPA for management of antiemetic

regimens. Through the latter, infusion center pharmacists completed an antiemetic risk assessment for every patient receiving a new cancer treatment regimen and prescribed appropriate antiemetics for clinic and at-home use. They also followed up with every subsequent treatment cycle and made the necessary adjustments to antiemetic regimens. This CPA served as the cornerstone for establishing provider-pharmacist trust within the Cancer Institute sites.

The oral oncologic CPA pilot initiation included creating clinical activities to be performed by pharmacists under the CPA, determining criteria for data collection, identifying a physician champion and specific physicians at a single site to participate in the pilot, and providing pharmacist and physician education. The CPA clinical activities included dose adjustment based on indication, toxicity, hepatic, and/or renal function, dose rounding to the nearest pill

size, prescription renewal based on prescriber notes, and ordering of laboratory tests and exams per recommended baseline and monitoring parameters.¹ These clinical activities were in alignment with the 2018 recommendations for pharmacy best practices in management of oral anticancer agents issued by the Hematology/Oncology Pharmacy Association.² After 3 months of implementation, the pilot data were presented at relevant institution committees for site-wide approval of the CPA, and an additional 3-month post-CPA implementation data was collected for continued evaluation of impact. The CPA implementation resulted in a statistically significant reduction in prescription mean turnaround time (7 minutes in pilot group versus 3,311

minutes in control group; $p < 0.0001$), and physicians communicated satisfaction with pharmacist interventions.¹ In the initial phases of CPA implementation, > 70% of pharmacist interventions included ordering prescription renewals. Dose-adjustment for toxicities such as diarrhea, nausea, vomiting, hand and foot syndrome, neutropenia, thrombocytopenia, rash, and neurotoxicity encompassed 8% of the interventions. Other interventions included ordering complete blood counts, comprehensive metabolic panels, tumor lysis syndrome labs, and electrocardiograms for toxicity monitoring. In addition, there were a few dose adjustments completed to account for drug interactions, renal function, and rounding to nearest pill size. Positive feedback and appreciation of the oral oncology services provided at St. Luke's incorporated new prescriber hires who vocalized extreme satisfaction with the instituted CPA, especially as it pertains to management of more complicated medications that

"In anticipation of potential barriers to getting unanimous multi-site provider approval, identifying the right provider champion as well as the pilot provider group was instrumental in getting other providers' buy-in."

require compliance with Risk Evaluation and Mitigation Strategy programs such as lenalidomide and pomalidomide.

In anticipation of potential barriers to getting unanimous multi-site provider approval, identifying the right provider champion as well as the pilot provider group was instrumental in getting other providers' buy-in. The pilot provider group was selected based on prescription volumes, accessibility, and consent to participate in the project. In addition, clear and detailed provider communication on every intervention performed was sent out. From a legal perspective, the Idaho Board of Pharmacy was consulted regarding required contract terms, parties, and other specifics while drafting the CPA, and a legal document that was already established on a health system level for other non-oncology CPA initiatives was employed as a starting point. From a logistical standpoint, some barriers to the utmost utilization of activities enabled through the CPA are related to insurance contracts resulting in restriction of prescription fulfillment to specific external specialty pharmacies. As a result of the successful implementation of the oral anti-cancer CPA at St. Luke's, the team was granted an Association of Community Cancer Centers (ACCC) innovator award in 2020 which allowed the opportunity to further share a detailed stepwise approach to development and implementation of a CPA based on the institution-specific experience.³

This CPA has facilitated expansion of clinical practice within the St. Luke's oral oncology MIP with the development of pharmacist-led clinical initiatives pertaining to medication and

class-specific in-depth toxicity management. Two ongoing quality improvement projects focus on the development of an initial risk assessment and subsequent management of side effects associated with Bruton Tyrosine Kinase inhibitors and implementation of appropriate monitoring parameters for Cyclin-Dependent Kinase 4/6 inhibitors.

The CPA has been further expanded into a global oncology CPA that encompasses management of oral anticancer agents, antiemetics, infusion reactions, over-the-counter medications, supportive care, anticoagulants, and, more recently, biosimilar conversions. For instance, pharmacists through the CPA are now able to convert any medication ordered, whether that be at initiation or continuation of therapy, to an available biosimilar per guidance from the system pharmacy and therapeutics committee and per payor preference, when applicable.

While CPA term and signature requirements can vary per state, after consulting with the Idaho Board of Pharmacy, this CPA is to be signed by an oncology physician representative (SLCI medical director) and an oncology pharmacy representative (SLCI oncology pharmacy director) and is to be renewed every three years. At this point, the oral oncology CPA activities are restricted to the adult cancer population at SLCI. Future targeted advancements focus on the expansion of CPA services to the pediatric hematology and oncology management teams. Another area to be explored is around reimbursement for these pharmacy services which are not currently billed within the health system. ●●

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Pharmacist Contributions to Quality Improvement in Oncology Care Presented at the ASCO Quality Care Symposium 2022



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Introduction

Quality improvement initiatives may target health care access, cost, policy, patient experience, technology, and safety.¹ Oncology pharmacists are constantly involved in quality improvement projects to further optimize patient care. The 2022 American Society of Clinical Oncology (ASCO) Quality Care Symposium was focused on highlighting the latest advances in quality improvement in oncology. Below are four abstracts presented at the ASCO Quality Care Symposium to capture the quality improvement initiatives led by oncology pharmacists and enhance the quality of care provided to patients with cancer.

Outcomes of a Quality Improvement Project Aimed at Improving Delivery of New Anticancer Drug Education to Nursing in an Academic-Community Hybrid Model²

Proper new anticancer medication education is critical for infusion center staff. An interdisciplinary team which included pharmacy, medical oncology, and nursing, measured nurses' comfort level administering new oncology drugs at Dana Farber Cancer Institute (DFCI). In an initial survey, nearly one-third of nursing staff indicated that they were "somewhat uncomfortable or very uncomfortable" according to survey results. In 2022, the team completed a series of pilot interventions with Plan-Do-Study-Act (PDSA) methodology to improve nursing comfort level. Throughout the 6-month period, the team focused on staff education and information communication. During this period, the team provided pharmacy-driven education materials that were more accessible by posting them on the DFCI intranet webpage and streamlined new drugs commu-

nication workflow by establishing monthly nursing and pharmacy huddles. With these interventions, the post-intervention survey revealed that more than 75% of nurses felt "extremely comfortable" or "somewhat comfortable" administering new anticancer agents, and the result remained sustainable.

Using Real-World Data to Quantify Chemotherapy Waste at Mayo Clinic³

Chemotherapy waste is an ongoing issue that adds a significant cost burden in the United States. The discrepancy between the desired doses to compound and the supplied vial drug volume results in billions of dollars' worth of wasted drugs in the reconstitution and compounding process. The goal of this study was to reduce drug waste using automated chemotherapy dose rounding. From January 1, 2019 to December 31, 2021, data for biologic and oncolytic medications were gathered using the electronic health record (EHR).

Waste associated with medications prepared and administered were selected and analyzed and the percent of each prepared dose with associated waste was calculated. Using the cost listed in the EHR at administration time, the total cost of drug administered and wasted was calculated. Over the three-year period, there was a documented 446,832 doses dispensed, with 47,626 (10.7%) of documented waste. The drugs with documented waste totaled \$114,323,203 with wasted drugs accounting for \$25,086,608 (21.9%) of that total.

While strict dose rounding policies are already in place, drug waste is still a concern at Mayo Clinic. This study supports

the need to create cost-savings solutions to reduce waste and costs associated with weight-based dosing of agents, mandating pharmaceutical companies for appropriate vial sizes, and development of standardized multidose vials. Additionally, the use of closed-system transfer devices to reduce waste, an in-depth evaluation of beyond-use-dating with primary literature for possible extended vial life, or requiring pharmaceutical company reimbursement for wasted drug are possible areas of opportunity for cost-savings.

Improving Cardiac Monitoring in Patients with Early-Stage Breast Cancer Receiving Cardiotoxic Chemotherapy in a Multidisciplinary Cancer Center⁴

In the early-stage breast cancer setting, patients commonly receive anthracyclines and anti-Her2 directed therapies. The cardiotoxicity that can result from these agents has led to the establishment of cardio-oncology. To properly address cardiovascular toxicity induced by anti-cancer medication, integration of healthcare professionals,

"The discrepancy between the desired doses to compound and the supplied vial drug volume results in billions of dollars' worth of wasted drugs in the reconstitution and compounding process."

including pharmacists, is required. A team of pharmacists studied the utilization of these prevention efforts in their early-stage breast cancer patients receiving cardiotoxic chemotherapy.

In a retrospective analysis, investigators compared utilization of strain imaging and rate of follow-up echocardiogram monitoring in two groups: January 2019 – July 2020 and August 2020 – December 2021. Myocardial strain imaging in conjunction with echocardiography became more readily available and implemented in all relevant chemotherapy plans at this institution in July 2020, hence the time mark for comparison. Rates of strain echocardiogram use improved from 26.3% to 97.9% following July 2020. Follow up echocardiograms were compared separately for those receiving trastuzumab versus anthracycline-based chemotherapy. Rates of follow up echocardiograms in those receiving trastuzumab based therapy were similar before and after July 2020 at rates of 91.8% and 87.5%. Rates of follow up echocardiograms in those receiving anthracycline-based therapy reached the goal of improving to greater than 50% but was lower than the trastuzumab group at 57%. The authors concluded that implementing a standardized cardiac monitoring program for breast cancer patients was successful. The investigators anticipate benefits such as enhanced detection of cardiotoxicity, utilization of cardio-oncology services, and collaboration with survivorship programs.⁴

Levine Cancer Institute Financial Toxicity Control Program: Expanding the Program to Reduce Fiscal Vulnerability to Patients⁵

The term “financial toxicity” refers to the burden of out-of-pocket costs for cancer care treatment. Specifically, a major contributor to financial toxicity to patients is insurance company denials for treatment coverage. The Levine Cancer Institute looked to expand their financial toxicity program by inserting pharmacy technicians who

were fully trained in the program into an additional site’s treatment team. The pharmacy technicians ensured proper prior authorizations were performed and medication denial reports were appropriately analyzed. Additionally, the program aimed to identify the main problem for the denials to improve and avoid the recurrent issues the institution was facing from insurance payers.

In the results of the study, the Levine Cancer Institute Financial Toxicity Tumor Board saw an overall decrease in denials from insurance payers over the one-year period. The investigators found a 48% decrease in financial toxicity for patients compared to the year prior to the study. When looking at the number of denials from insurance payers from the one-year period, the investigators saw a decrease from 16-18 denials per month to 3-4 denials per month. Overall, the Levine Cancer Institute’s financial toxicity program saw additional savings for patients of over 5 million dollars. The investigators concluded that the pattern of financial toxicity in patients’ care can be decreased with the use of trained pharmacy technicians in the financial toxicity program by decreasing the number of denials and out of pocket costs for patients and ensuring insurance companies are held accountable for their obligations.

Conclusion

Routine roles of the oncology pharmacy team have a primary effect on quality metrics and can be of value in providing clinical support to the care team to improve cancer outcomes and quality of life. Of all healthcare professionals, pharmacists have a core knowledge of medications that allows for broad proficiency regarding the entire medication management system. This authority comes along with the compelling reason for oncology pharmacists to expand their roles to include quality and process improvement initiatives, as seen consistently in regional and national publications and presentations. ●●

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Novel Bispecific Antibodies for the Treatment of Multiple Myeloma and Non-Hodgkin Lymphoma



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Background

Multiple myeloma and non-Hodgkin lymphoma (NHL) are two of the most common types of blood cancer with an estimated 34,470 and 80,470 new cases in 2022.¹ There are a plethora of available treatments for relapsed/refractory (R/R) disease but with each relapse, duration of remission decreases and rates of mortality rise.^{2,3} Bispecific antibodies (BsAbs) represent an emerging type of immunotherapy with blinatumomab being the first product approved to treat B-cell acute lymphoblastic leukemia. Recently, investigational products have shown promising response rates in patients with R/R myeloma and R/R NHL. BsAbs target CD3 on the surface of T-cells and tumor specific markers on the surface of malignant cells, bringing T-cells and malignant cells into proximity, thereby causing T-cell activation and lysis of the malignant cells. This article will summarize and discuss the literature for these novel myeloma and NHL targeting BsAbs.

Multiple Myeloma

Multiple myeloma is characterized by malignant proliferation of plasma cells in the bone marrow which results in marrow failure, bone destruction, and end-organ damage.⁴ Although many patients obtain deep and durable remissions with induction therapy, relapse is inevitable in this incurable disease. With each relapse and subsequent treatment, the duration of remission decreases and rates of mortality rise.² The poor prognoses of these patients have led researchers to investigate novel treatment modalities, including BsAbs.

Teclistamab: On October 25th, 2022, the US Food and Drug Administration (FDA) granted accelerated approval to teclistamab for use in adult patients with R/R multiple myeloma after failure of at least four prior lines of therapy.⁵ As a bispecific antibody (BsAb), teclistamab brings T-cells into contact with myeloma cells expressing

B-cell maturation antigen (BCMA), a surface protein unique to plasma cells. Accelerated approval for teclistamab was based upon the results of the MajesTEC-1 study.⁶ MajesTEC-1 was a phase 1/2, open-label, single-arm, multi-center study that included 165 triple-class R/R myeloma patients. Patients had received a median of five prior lines of therapy and median time between diagnosis and the first dose of teclistamab was six years. Nearly a quarter of patients had at least one high-risk cytogenetic abnormality, such as del(17p), t(4;14), or t(14;16). Eighty-one percent of patients had undergone previous hematopoietic stem cell transplant (HSCT) and nearly 90% of patients were refractory to their last available line of therapy. Following a step-up dosing protocol, patients received teclistamab subcutaneously once weekly at a dose of 1.5 mg/kg until disease progression, unacceptable toxicity, withdrawal, or the end of the two-year study period.

At median follow-up of 14.1 months (range, 0.3-24.4), 63% (95% CI, 55.2-70.4) of patients had an overall response, with very good partial responses or better in 58.8% and complete responses (CR) or better in 39.4% of patients.⁶ Median progression free survival (PFS) and overall survival (OS) were 11.3 months (95% CI, 8.8 to 17.1) and 18.3 months (95% CI, 15.1 to not estimable), respectively.⁶

Limitations of this early phase study include a single arm study population with no comparator group. Without a comparator group, it is unfair to compare

the efficacy of teclistamab with other treatment options. Patients with International Staging System stage I disease and without extramedullary involvement had higher response rates compared with those with a higher disease burden. The phase 3 MajesTEC-3 trial is currently enrolling and compares the combination of teclistamab and daratumumab to either daratumumab, pomalidomide, dexamethasone (DPd) or daratumumab, bortezomib, dexamethasone (DVd) in R/R disease.⁷

Treatment-related toxicity was reported in all patients with 94.5% of patients experiencing a grade 3 or higher event. The most common adverse events were cytokine release syndrome (CRS), neutropenia, and infections. The majority of CRS was low grade and occurred during the step-up dosing period. Low grade neurotoxicity was less frequent and commonly presented as headache. Five deaths were deemed to be related to teclistamab, due to progressive multifocal leukoencephalopathy, COVID-19 infection, hepatic failure, and streptococcal pneumonia. Teclistamab is available through the TECVAYLI Risk Evaluation and Mitigation Strategy (REMS) program, and it is recommended all patients be observed for 48 hours after administration of all step-up doses, including the first treatment dose. Black box warnings for teclistamab include the risk of CRS and neurotoxicity.

"BsAbs represent a novel treatment approach for patients with difficult-to-treat hematologic malignancies."

Alternative Investigational Myeloma Targeting BsAbs: Numerous other BsAbs are currently being investigated for the treatment of multiple myeloma. REGN5458, elranatamab, AMG701, and TNB-383B are investigational agents targeting BCMA. Talquetamab and cevostamab are also under development and target novel cell surface markers GPRC5D and FcRH5, respectively.⁸ Commonly shared adverse events include low grade CRS and infections. Ongoing BsAbs trials in myeloma are presented in Table 1.

Non-Hodgkin Lymphoma

Despite advances in treatment, management of R/R NHL remains a challenge.³ Treatment options are especially limited for patients who are ineligible for or who have relapsed after autologous stem cell transplant or chimeric antigen receptor (CAR) T-cell therapy. The poor prognoses of these patients have led researchers to investigate novel treatment modalities, including BsAbs.

Epcoritamab: Epcoritamab is a BsAb for CD3 and CD20 that has shown activity against CD20+ malignant B-cells in the phase 1/2 EPCORE-NHL1 study.⁹ Seventy-three patients with R/R NHL were enrolled at ten sites globally. During the phase 1 study, patients received escalating doses of subcutaneous epcoritamab between 0.0128 mg and 60 mg which led to identification of a 48 mg target dose to be carried into the phase 2 expansion of the study. A June 2022 update presented at the European Hematology Association (EHA) meeting provided information on 157 patients in the phase 2 dose expansion cohort.¹⁰ After initial step-up dosing, epcoritamab was administered weekly for 12 weeks, biweekly for 24 weeks, then once every 28 days until disease progression or unacceptable toxicity. Twenty-four-hour hospitalization was required for the first full

dose. Patients had received a median of three prior lines of therapy and 38.9% of patients had received prior CAR T-cell therapy.

At a median follow-up of 10.7 months, the overall response rate (ORR) was 63% with 39% complete response (CR).¹⁰ Patients who received prior CAR T-cell therapy had similar ORR and CR of 54% and 34%, respectively. The median duration of response was 12 months.

The most common adverse events were CRS, fatigue, and neutropenia. The majority of CRS was low grade and occurred after the first full dose. Neurotoxicity was less common but did occur in 6.4% of patients and led to one death.

Despite the excitement of these novel therapies and mechanism, some limitations exist, including small dataset, absence of comparator arms, limited information on sequencing, and results not being completely released.

Alternative Investigational Lymphoma Targeting BsAbs: Similarly, several BsAbs are currently being investigated for the treatment of NHL. Mosunetuzumab, odronextamab, and glofitamab are investigational agents that also target CD20.¹¹ Like other BsAbs, commonly shared adverse events include CRS and neutropenia. Ongoing BsAbs trials in lymphoma are presented in Table 1.

Treatment Considerations

Accessibility: Unlike CAR T-cell therapy, BsAbs are available “off the shelf” through normal drug distribution channels. Patients requiring urgent treatment do not have to undergo cell collection and expansion which can delay CAR T-cell treatment for weeks. Increased availability may lead to selection bias for BsAb therapy over CAR T-cell therapy.

Table 1. Select Ongoing Trials of Investigational Bispecific Antibody Therapy

BsAb	NCT identifier	Phase	Indication	Target	Estimated Completion
Elranatamab	NCT04649359	2	R/R MM	CD3-BCMA	June 2022
	NCT05020236	3	R/R MM		October 2024
REGN5458	NCT05137054	1b	R/R MM	CD3-BCMA	May 2026
	NCT03761108	1/2	R/R MM		May 2023
TNB-383B	NCT03933735	1	R/R MM	CD3-BCMA	August 2025
Talquetamab	NCT03397999	1	R/R MM	CD3-GPRC5D	July 2022
	NCT04634552	2	R/R MM		August 2023
Cevostamab	NCT03275103	1	R/R MM	CD3-FCRH5	December 2025
Epcoritamab	NCT04628494	3	R/R DLBCL	CD3-CD20	May 2024
	NCT03625037	1/2a	R/R B-NHL		July 2025
Mosunetuzumab	NCT05389293	2	Untreated FL	CD3-CD20	December 2024
	NCT05207670	2	Untreated B-NHL		
Odronextamab	NCT02290951	1	R/R B-NHL, Untreated CLL, R/R CLL	CD3-CD20	December 2025
	NCT03888105	2	R/R B-NHL		February 2028
Glofitamab	NCT04914741	1/2	Untreated DLBCL, High-Grade BCL	CD3-CD20	July 2025

BsAb: bispecific antibody; MM: multiple myeloma; R/R: relapsed/refractory; B-NHL: B-cell non-Hodgkin Lymphoma; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; CLL: chronic lymphocytic leukemia

Challenges with BsAb administration include initial step-up dosing and monitoring requirements for CRS and neurotoxicity. Large tertiary centers can admit patients for observation or may have remote outpatient monitoring programs while small centers may not have the capability for the required monitoring. Nine-day inpatient admissions for teclistamab step-up doses may further strain already short-staffed hospital units as well as contribute to reimbursement issues. As providers gain comfort with these novel therapies, many centers will likely develop outpatient observation protocols to offset these issues. Indefinite and frequent dosing schedules may also present challenges to patients in regards to travel and quality of life. The high costs associated with these indefinite therapies may also limit utilization for some patients.

Toxicity: BsAb therapies have been associated with significant toxicities including CRS, neurotoxicity, and infections. Due to CRS and neurotoxicity related to teclistamab, a REMS program ensures that providers, healthcare settings, and pharmacies undergo training and certification to manage such adverse events. CRS is commonly observed and high-grade events are mitigated through step-up dosing and corticosteroid pre-medication. Infections, including pneumonia and COVID-19, were common in many of the studies and may be prevented with antimicrobial prophylaxis, vaccinations, and IVIG per institutional protocol.

Sequencing: While data on sequencing of these novel therapies is still maturing, studies in both myeloma and NHL have shown responses in patients receiving BsAb after progressing on CAR T-cell therapy.^{10,12} As data matures and more BsAbs become available, BsAb use after CAR T-cell therapy may be an option for these difficult to treat patients. BsAb use prior to CAR T-cell therapy is also an area still under investigation. Preliminary data show CAR T-cell response rates may be lessened in patients who received prior BsAb, but more data are needed to confirm these results.^{13,14} These lessened responses may also be due in part to selection bias, as the disease has become more challenging to treat and patients are less likely to respond in subsequent lines of therapy. Similar trends were seen when blinatumomab was administered prior to CAR T-cell therapy.¹⁵

Conclusion

BsAbs represent a novel treatment approach for patients with difficult-to-treat hematologic malignancies. Recent data showed promising response rates and led to the approval of teclistamab, the first BsAb for patients with R/R myeloma. Numerous alternative BsAbs are under investigation and may provide heavily pre-treated patients promising options in the future. As data mature and these therapies become available, BsAb therapy will likely become incorporated into the treatment paradigms of both MM and NHL. ●●

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Three Perspectives on Non-Traditional Clinical Roles in Hematology/Oncology Pharmacy



Kelley D. Carlstrom, PharmD, BCOP
CEO and Founder, KelleyCPharmD, LLC

Oncology Pharmacist Entrepreneur

Several years after achieving the vision I initially had for my career, I was surprised to find myself asking “is this it?” I loved my job, especially working with patients. And despite that, something felt off. That disconnect allowed my brain to turn on discovery mode, to seek out new ideas and opportunities.

During this time, I recognized that my professional experience up until then gave me only a very narrow viewpoint of oncology pharmacy. I had invested time developing my personal brand and because of this I was able to interact with many different types of oncology pharmacists. Many shared that they wanted to be good at their job but were struggling to fully understand oncology. It really hit home when one told me she went home at night and worried she had harmed a patient. No one wants to work under that kind of pressure.

These interactions showed me that there wasn't a good solution in the marketplace for these pharmacists and if I wanted to help them, I had to create it. This initial spark of an idea led me down a path that I never knew existed, let alone imagined myself walking - becoming a pharmacist entrepreneur.

Ironically, the path to entrepreneurship for me was a lot like the path to oncology for my clients. You're in an unfamiliar place with strangers that speak a language you've never heard. You're consuming content from a variety of sources and aren't sure how the pieces fit together - there isn't a clear plan to follow.

As I was developing my business model, I had to determine how I would structure my programs to meet the needs of my clients and myself; no one wants to build a business they don't enjoy working in! Additionally, I knew my experienced colleagues had valuable knowledge and loved educating but needed an avenue that allowed them to share their knowledge in a fun and innovative way, and one that paid them for their expertise. These insights led me to hire my peers to review and curate oncology resources that live inside an online course. And since consuming content is only one part of learning oncology, they are also a resource for questions. When I began this model, I was pleasantly surprised to learn that the experts got as much out of the interactions as my clients did!

As a solo entrepreneur, I am responsible for all aspects of my business, which is both exhausting and energizing. I function in every role in the org chart and must balance them all. I select, use, and troubleshoot the technology that powers my business. I manage revenue, expenses, and payroll. I am the recruiter that seeks out other expert oncology pharmacists to support my programs. I write email, social media, and program content, design graphics, and create new offers. And everything else that must be done.

Running a business is like putting together a puzzle, one that you don't know what the final picture is supposed to look like. Although this may sound intimidating, it has been the most fascinating and enjoyable part of the process for me!

I have learned a lot on this journey and the most transformational lesson would be learning to take risk. I, like most pharmacists, was very risk averse. I planned, calculated, triple checked, and made decisions based on what was the safe bet. And I had to completely change that mentality to survive as an entrepreneur. Even if running a business isn't in your future, learning to take more risk in your career can open doors you never knew existed.



Shannon Hough, PharmD, BCOP
Director of Clinical Content and ClinReview for The US Oncology Network

Director of Clinical Content and ClinReview

In my role as director of Clinical Content and the ClinReview program, I use my oncology specialty training to expand oncology pharmacist services offered within community oncology physician practices. We know that most cancer patients seek care within their communities, and oncology pharmacists have value in these settings.

Keep an Open Mind and Stay Connected

I first learned about this position from a colleague. I wasn't actively looking for a new job, but after having a trial of remote work during the pandemic, I became more interested in a remote position. This role was posted on the [McKesson careers website](#), and I knew mostly of [McKesson](#) as a distributor. I had no idea that they also support [The US Oncology Network](#), the largest network of its kind of independent community oncologists dedicated to providing high-quality cancer care. I was excited to learn about this while researching and interviewing for the position.

When I started at McKesson, my role was as director of Clinical Content. Our team creates and maintains a regimen library for oncology treatments in [iKnowMedSM](#), Ontada's oncology-based electronic health record (EHR). [Ontada](#) is McKesson's oncology real-world data and evidence, clinical education, and provider technology business. We also maintain the content for a clinical decision support tool ([Clear Value PlusSM](#)), which includes clinical pathways for many cancer types ([Value Pathways powered by NCCN](#)). The team also creates patient education materials and a robust financial counseling tool ([Regimen Profiler](#)). In addition to these day-to-day activities, we also work together with practice leaders on network-wide Pharmacy & Therapeutics subcommittees dedicated to pharmacy operations, clinical care standardization, oral chemotherapies, and the integration of technology into care. Each year, we identify medication-use initiatives for implementation at practices in The Network. All of these activities support the delivery of high-quality care to patients at the practices in The US Oncology Network.

Jobs Can Evolve, Even on Your First Day

In addition to the things mentioned above, when I had my very first meeting with my new boss, he proposed a new service to consider developing. He suggested that a program which provided oncology practices with a strong oncology-trained pharmacist remotely may be useful to The Network. Some areas were not familiar with the value of this training and experience or weren't able to recruit these types of pharmacists to their geographic area.

Over the past two years, this idea has blossomed into the [ClinReview program](#), which now supports nine community oncology practices and employs seven pharmacists. Pharmacists use an EHR to provide clinical assessments of patient treatment plans, provide education to practice teams, are involved in committee work, improve financial performance of the practices, and more—also from their home offices.

Varied Oncology Backgrounds Adds Depth to Teams

The pharmacists I work with today came to oncology practice in a variety of training and experience pathways. Some were trained in a PGY-1 pharmacy practice residency; some also completed a PGY-2 oncology residency. Some pharmacists did not complete residency training but gained oncology experience in their prior work and formal or informal mentorship programs. Most pharmacists on the team are board-certified. This variety of prior experiences and common oncology passion strengthens our program offerings.



Kathleen M. Sullivan, PharmD, BCOP

Safety Evaluator, Oncology U.S Food & Drug Administration

FDA Oncology Safety Evaluator

My current position is an oncology safety evaluator (SE) in the Division of Pharmacovigilance (DPV) within the Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research (CDER) at the U.S. Food and Drug Administration (FDA). I learned about the SE role during an elective pharmacy school rotation at the FDA. I liked the work and CDER's mission, so I looked for career opportunities after completing additional clinical training. While I was finishing my PGY2 oncology pharmacy residency, I applied for an SE position on the oncology team in DPV because I wanted to impact public health globally.

SEs work on multi-disciplinary, therapeutic-focused teams to identify and assess safety signals in the postmarketing setting for marketed drug and therapeutic biological products. In these teams, our assessments of available evidence inform a drug-event causal association and recommend regulatory actions to protect public health.

As an SE, I am assigned a group of oncology drugs and am responsible for screening safety data from multiple sources to detect and assess new safety signals for these drugs. This work is important because many new oncology drugs are approved to meet an unmet medical need and are done so using expedited approval pathways that often contain fewer clinical trial participants enrolled over shorter time periods. Our knowledge of the complete safety profile of the drug evolves throughout the life cycle of the drug and I contribute to that knowledge base. I help apply a risk-based approach to screen adverse event reports submitted to the FDA through the MedWatch program or by pharmaceutical companies. We also monitor published medical literature case reports, postmarketing studies, and other sources for new safety information.

After identifying a safety signal, we evaluate the safety signal to inform a drug-event causal association. We develop a case definition for the adverse event and conduct a causality assessment. To assess causality, we consider variables such as temporal relationship, positive dechallenge/rechallenge, alternative etiologies, biologic plausibility and others. A multi-disciplinary team then considers the totality of evidence from all relevant data sources (e.g., clinical trials, case reports, preclinical models) and the need for any regulatory action. The most common regulatory action is addition of the new adverse reaction in the United States Prescribing Information (USPI), such as the Warnings and Precautions or Adverse Reactions sections, depending on the strength of the causal association and clinical importance. The FDA may also issue a Drug Safety Communication to further heighten the public and clinicians' awareness of the new safety issue. At times, we may publish some of our work and one recent example is our assessment of alpelisib associated colitis in [JAMA Oncology](#). (*JAMA Oncol.* 2022;8[10]:1503-1505)

I enjoy multiple aspects of my job and feel fortunate to be able to apply my oncology pharmacotherapy knowledge to advance public health globally through identification and communication of new safety information related to oncology products. If you would like to learn more about this type of work, please feel free to contact me at Kathleen.Sullivan@fda.hhs.gov or Sara Camilli at Sara.Camilli@fda.hhs.gov. ●●

How to Write a Research Grant



Benjamin Andrick, PharmD, BCOP

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Assistant Professor, Clinical Research, Center for Pharmacy
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Geisinger, Danville, PA

Background

Grant writing can be perceived as intimidating, particularly when an individual is new to the process. I recall early in my career it being an almost mythical, ultimate manifestation of research. However, I would encourage grant writers to approach it like all new journeys, by putting one foot in front of the other and breaking it into smaller, manageable steps. I concur with the advice shared by many mentors; grant writing is an art where practice makes perfect. Thus, I hope in this short review to share some tips and tricks to help empower researchers to step into the world of grant writing to advance their research endeavors.

Before even looking into funding opportunities and writing a fully-fledged grant, a primary investigator (PI) should start by completely developing their research question, methodology for examination, as well as hypothesis. When applying for grants, reviewers will be assessing if the study question is clearly articulated and if the corresponding study design and methodology are scientifically sound. Such items are often explicitly requested in the grant application. Additionally, knowing the feasibility and operational components to conduct the study are necessary for budgeting and creating a timeline. Numerous publications and review articles have been written on how to identify a research question and design study methodology, which I would encourage the reader to review.¹⁻³ I have personally found the principles of FINER and PICOT to be a great starting point when brainstorming a research project.⁴

Summary Document (Letter of Intent)

The next step is to outline the research project into a 1- or 2-page summary document. Some grants, including HOPA's, require a letter of intent application. It should be concise to leave the reader with a thorough understanding of the research question's importance and study design, your study team's qualifications, and how the results will impact the scientific community or clinical practice. A mentor once described this as the "elevator speech on paper" for your research project. This step is imperative to move from the often "messy" brainstorming process to a more formalized document outlining the project.

It is helpful to outline the study team members and their respective roles, including information on their investigator status (primary investigator, co-investigator, administrative staff, etc.) For example, the biostatistician may serve as a co-investigator who will oversee conducting the statistical inquiries and assist with manuscript preparation. As a new investigator, I found this step was critical to ensure the study team was clear on each other's roles and expectations for the project.

The document should contain information regarding background, specific aims and hypothesis, study methodology, statistical plan, justification of the evaluation, and relation to the grant sponsor's mission. I will comment on each of these areas in the following sections in more detail under the "Writing the Grant" section below.

Identifying a Target Grant for Submission

Following the creation of a summary document (letter of intent), the PI should work to identify a target grant for submission. Grant funding opportunities are often shared as funding opportunity announcement (FOA). Additionally, there are requests for applications (RFA), which are the same premise as FOAs but often more specific for research questions. There are numerous opportunities to identify possible sponsors for your research project, including government, non-profit, and private organizations. I would encourage PIs to routinely search the web and subscribe to email listservs which routinely share RFAs. The PI should be looking for a specific RFA in the vein

of their own project by noting the sponsor's mission and vision. For the National Institutes of Health (NIH) grant process in particular, the reader should take the time to review the types of grants and their requirements, as well as the process in more detail.⁵

The PI must read the RFA closely for instructions on how to write and apply for the grant, including due dates and formatting guidelines. The RFA will delineate the timeline for submission, when the grant will be awarded (paid to study team), and how the grant will be administered (onetime payment versus payment for study milestones). This information may be key if you are on timeline for a research project or for faculty tenure/re-appointment. The RFA will also contain clues on what exactly the grant sponsor is looking for in submissions to meet their aim as an institution. Failure to notice such minute detail may spell disaster for your grant submission.

"When applying for grants, reviewers will be assessing if the study question is clearly articulated and if the corresponding study design and methodology are scientifically sound. Such items are often explicitly requested in the grant application."

Writing the Grant

Grants tend to have the following format as outlined by the NIH structure: specific aims and research strategy with subsections on significance, innovation, and approach.⁶ Additionally, one needs to prepare their biographical sketch and a project summary which serves as an “abstract” for the grant, which I would recommend writing last. Formatting for the following section is key and I would recommend the reader review sample grants posted by the NIH.⁷

Figure 1 graphically outlines the various sections of a grant that will be discussed further below.

Figure 1. Grant Writing Section Example Outline

<p>Specific Aims Brief introductory information Aim 1. Example Aim 1 Aim 2. Example Aim 2</p> <p>Research Strategy</p> <p>Significance Detailed background justifying significance of the project</p> <p>Innovation Point 1 for why project is innovative Point 2 for why project is innovative Point 3 for why project is innovative</p> <p>Approach Aim 1. Example Aim 1 Aim 1.1 Aim 1.2 Preliminary Results and Expected Outcomes Potential Problems and Alternatives Aim 2. Example Aim 2 Preliminary Results and Expected Outcomes Potential Problems and Alternatives</p> <p>Statistical Analysis & Justification</p> <p>Budget</p> <p>Timeline</p>
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Specific Aims

Specific aims delineate goals or deliverables for each hypothesis of the research question. A possible example aim might be “Identify risk factors which exist at the time of cancer diagnosis and characterize their association with development of diabetes.” Thus, specific aims are often thought of as objectives for the research project.

For more complex or multifaceted projects, there may be distinct study questions which break the project into sequential phases. For example, a specific aim may entail developing a dataset of patients with a certain characteristic as part 1, determining the efficacy of the query in part 2, and building a new model to test against a standard model in part 3. Such a project might have one major specific aim with sub-aims. It’s common for specific aims to have sub-objectives (Aim 1.1, 1.2, etc.). Each specific aim should be thought of as a deliverable. Thus, the study team should clearly

articulate what will be the result or deliverable of each specific aim and describe in detail.

Before writing out each specific aim, it is common to have 3-5 paragraphs of introduction or background information on the project. There may be some overlap between this section and the Research Strategy Significance section. That is fine and can be used as opportunity to re-iterate (in different words) key points. When stating the actual specific aim, be sure to use a direct, strong verb to start the aim. Examples include “confirm, identify, predict, demonstrate.” Additionally, it is common to highlight the specific aim in bold, to help it stand out to the reader. A good practice is then to include a comment on the rationale for why the selected aim was chosen and very brief outcome to be expected.

Research Strategy: Significance

This section is akin to the background section of a research manuscript. The goal is to provide the grant reviewer an adequate background to understand why the study question is significant, often to clinical practice. This section should be no longer than 1 to 1.5 pages; thus, it must be very concise and comprehensive. When writing the background, assume the reviewer has no prior knowledge of this topic to explain your study question and gain reader buy-in. I would encourage the author to start with the “catch line” by stating the problem in a manner which will capture their interest. If pursuing with a specific grant sponsor, such as a pharmacy association, it would be pertinent to relate your research question and results back to the mission and vision of the grant sponsor’s organization and their goals. This section should finish with a few strong, non-passive writing style sentences on how and why your study is important and should receive funding.

Research Strategy: Innovation

This portion of the grant submission is focused on highlighting how the project is truly innovative or stand out from previously completed research. The body of this section will include pertinent references to previous research completed. I would encourage writers to focus on using the following questions to guide writing this section: 1) Why does this research question matter? 2) What previous research has been done in this area? 3) What are deficits or missing pieces from previous investigations that your project will address? 4) How is your team and study design prepared to conduct the proposed study design? Format this section to start with an objective statement (that aligns with your specific aims) and then detail how your team is uniquely positioned to address the objective. Often this section is broken up into a paragraph or sub-section format. Each section should contain one “novel” aspect of the project with accompanying justification.

Research Strategy: Approach

This section is the meat and potatoes of the summary document and the heart of the grant. The study team should clearly articulate exactly how they are going to design and conduct the study. Do not skimp on the details on this section. The author should consider the perspective of the grant reviewer when writing this section. This section should make clear to the reviewer how your project design

FEATURE (continued)

and conduct will meet the highest level of scientific merit. If you are going to do conduct a study survey for example, and have previously done so, you can highlight your previous work with study surveys as justification of experience.

The outline format should be based around your previously stated specific aims, starting with the first aim. Briefly explain in 3-5 sentences details about how the aim will be assessed, and then provide a subsection with experimental design where you will outline how to test the specific aim. Next, you will list a preliminary result and expected outcome. This is where you can explain more about your proposed hypothesis. If you have previously done work in a space methodologically, you could highlight examples here to demonstrate that you can conduct the work. Finally, you must provide a section on potential problems and alternatives. The PI should give serious thought to this section and use it to preemptively address any concerns a reviewer might have about the methodology and assessment plan. Reflection and forethought are incredibly valuable in this section for the reviewer. Additionally, the PI should be honest about where limitations of the project may exist.

This process above should be repeated for each specific aim. Note that you only need one section on experimental/statistical design, expected outcome, and potential problems and alternatives per major specific aim. When possible, consider using preliminary data (pictures, figures, etc.) to help break up the text and add to your credibility to complete the project.

Statistical Justification/Plan for Evaluation

This section should highlight exactly what you are going to do with all that hard-earned data the grant sponsor is funding you to acquire. The author should again outline exactly what statistical analysis is planned and why. Try to be pre-emptive in asking yourself questions a grant reviewer may ask when reading the document. The study team should also think about how the results will be shared and articulate them here. If results will be shared at a conference as a podium or poster presentation, list which aims will be included and plans for publication.

Proposed Study Timeline

By this point in the writing process, the PI and study team should have a very good understanding of the proposed project. I would encourage the PI to meet with the entire study team as a group to develop the timeline. The PI should outline each step in the project. Examples of key milestones to consider outlining are IRB approval, when data collection starts and stops, when data analysis will occur, and writing up and sharing results. The PI should ask the team members responsible for each aspect of the project how long they anticipate it will take to complete their portion. It is a common mistake to give an aggressive estimate, but you must resist that urge. Encourage your team to provide plenty of wiggle room and space to breathe. Remember, no research project has ever gone exactly according to plan. However, the timeline dates you set for deliverables may be non-negotiable once agreed upon. Be reasonable and don't drag out the project but remember that giving yourself time to complete a quality project is paramount.

References

This line is self-explanatory but should not be overlooked in the writing process. I would strongly encourage writers to utilize citation software when writing the manuscript. When merging versions from various team members, it may require time some time to organize the citations; however, it is well worth the work. The PI should investigate if the grant funder has a specific citation format and ensure this section follows the corresponding guidance.

Budget

Creating the budget can often be daunting the first time, and I would encourage a new grant writer to consult with your institutional grant office or a team that previously has done grant work. Considerations will need to include salary support (time and effort), research supplies, fees for statistics and data analysis if applicable. Conducting research at your site may incur indirect expenses (lights, office supplies, etc.), thus understanding how such expenses are covered by the funder is important. Finally, this step is an opportunity in the grant process to pause and reflect on the entire project to ensure you have appropriate funding to support completion of the project.

Phone a Friend for an Outsider Perspective and Review

I think this is perhaps the MOST important step in grant writing process and writing in general. By this point, you likely have spent hours reviewing, refining, and editing your grant submission. I would strongly encourage that you share with a trusted friend, peer, or mentor for an outside review. Ideally, the reviewer should be someone with a strong editorial background (spelling, grammar, etc.) who does not directly work with you or the project. Such an outside perspective is key, as the grant reviewer will share a similar perspective. Thus, ask your independent reviewer to ask critical questions and add commentary beyond an editorial review. Many institutions may offer such a service through their grant funding office.

Post Notification of Award

If you do not get awarded the grant by the sponsor, do not dismay! This is more common than you might think. Akin to research manuscript submissions, many grants do not receive funding upon their first submission. Often, grant reviewers will provide you feedback on the submission. Take this as an opportunity to review their comment and edits. Such revisions will help to make the next submission even stronger and more likely to be funded. Be sure to keep moving forward and submit the project to another RFA. If you have a truly great research project (and if you are still reading, then I am sure you do!) then keep at it and continue to submit!

If you received funding, congratulations! Now the real work of conducting the project begins. Be sure to routinely correspond with the grant funding organization for updates and to provide deliverables by pre-determined milestones.

Conclusions

I hope the reader has found this commentary on how to approach grant writing useful and is now ready to submit a grant of their own! Grant writing is an art which requires practice and refinement over time for which there is no better remedy than practice. ●●

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Patient Perspectives on Oral Cancer Therapy



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Introduction

While cancer medicine has employed orally administered therapies for decades, continued breakthroughs over the last twenty years in next-generation sequencing (NGS) and an increased demand for personalized medicine strategies have resulted in a paradigm shift in treating many malignancies. Despite the predominance of small molecular inhibitors in the oral cancer therapy landscape, there continue to be new approvals for oral cytotoxic chemotherapy, hypomethylating agents, and hormonal therapies. In 2010, there were nine new FDA approvals for cancer treatments, of which five were for oral therapies.¹ As the world entered the global COVID-19 pandemic in 2020, there were 13 FDA approvals for novel oral cancer therapies.² These approvals continued to increase from 2020 to 2021 and showed few signs of slowing down despite the global COVID-19 pandemic.

Oral cancer therapy offers a host of advantages for patients, providers, and the healthcare system. For patients, the convenience of oral administration means decreased travel and waiting times at infusion centers for intravenous (IV) therapies that can span hours. Acute adverse reactions are also less likely with oral agents compared with cytotoxic chemotherapy or monoclonal antibody infusions. Providers and institutions that utilize oral cancer therapies may see lower patient loads in ambulatory infusion centers and inpatient services, offering those spaces instead for patients who require parenteral therapy or extended observation periods.

While pharmacists are keenly aware of the logistical nightmares associated with specialty medication acquisition, insurance delays, and other barriers to therapy, it's important to consider the viewpoints of others. In this article, we invite you to hear from Sandra

Zori, who serves on HOPA's Patient Advisory Panel, regarding her perspective and personal experience with oral cancer treatment. Given the limited time we have with patients at the bedside, we often prioritize what is most important for patients to know; here, we have the opportunity to hear directly from a patient's viewpoint. The guidance provided is based on discussions with Sandra who shared her insight to make our interactions both meaningful and relevant.

The Patient's Side of the Story

While patients are more familiar with IV chemotherapies and cancer treatments, oral therapies are less familiar. *Is it just as good, or maybe even better than IV chemotherapy? Will I feel just as sick on oral cancer therapy compared to IV chemotherapy? What happens if I forget to take the medicine? Does this mean things are turning for the worse?* As the questions pile up when transitioning therapies, patients must also cope with the strenuous emotional and physical trial of receiving news of a cancer progression or relapse. Providers and pharmacists can maximize our knowledge and expertise to ease patients' transition to these new therapies.

The success of oral cancer therapy is dependent on many variables, some of which may be proactively addressed. Medication counseling should include a thorough review of medication administration with written instructions, an overview of possible and expected adverse events with their respective management, drug-drug interactions review along with answering questions about supplements or herbal products, and addressing the patient's past and present concerns to set patients up for success. Having been previously diagnosed with breast cancer, Sandra discussed starting capecitabine with her local oncologist as a bridge to starting a clinical trial.

"It's a common misconception that oral therapies are going to be much better tolerated than IV therapy – a line of thinking that may do our patients a disservice."

It's important to mention that Sandra isn't your typical cancer patient - she's also a former pharmacist! Although she had some insight into the clinical perspective of cancer therapy, her personal experience suggests that until you go through something yourself, things may not always immediately click. Sandra recalls being told what she could expect while taking capecitabine: *Ten pills a day. Take it for two weeks before taking a one-week break. Take the medicine with some food. Twice a day and try not to miss any doses. Side effects this, this, and that.* Despite a prior course of IV chemotherapy, Sandra's experience with capecitabine turned out to be tougher than she had initially anticipated. With each passing cycle, she watched as her gastrointestinal symptoms progressively worsened from loose stools to eventually being fearful of leaving her home for extended periods of time. Developing moderate-to-severe hand-foot syndrome compounded with the deterioration in quality of life she felt due to prior chemotherapy-induced peripheral neuropathy.

We often find ourselves printing off patient education materials that discuss the adverse effects associated with chemotherapy. Pharmacists play such a key role in providing education in the setting of busy clinics and limited time. We can lend our expertise by setting reasonable expectations for patients. For Sandra, she may have benefitted from knowing about the potential for a reduced quality-of-life, which may have affected whether she took additional time off from work to better manage her symptoms or discussed temporary dose adjustments with her oncologist. In certain practices, clinical pharmacists are involved in conducting follow-up visits with patients and evaluating their tolerance to therapy. It's a common misconception that oral therapies are going to be much better tolerated than IV therapy – a line of thinking that may do our patients a disservice. Growing our clinical experience is paramount to understanding the spectrum of adverse effects that should be addressed during clinic visits and reinforcing all patients with at-home or pharmacotherapeutic supportive care interventions may improve the experience and tolerance of oral cancer therapies to patients. If providers indicate that patients are developing intolerance to oral cancer therapy, that's our invitation as clinical pharmacists to dive in and flex our expertise in managing adverse effects. While many encounters occur in the clinic, the utilization of telemedicine is on the rise amongst healthcare providers. While it may be more technologically cumbersome or involve more hands-on engagement, video conferencing may be preferred over telephone calls to capture the physical appearance of a patient and assess their tolerance to therapy. Nevertheless, there is an active role that each of us can play in promoting the safety and care of patients.

Every pharmacist knows: medications don't work when patients are not taking them. The same obviously goes for orally administered cancer therapy. Unlike most IV therapies, oral cancer therapy is taken in the convenience of one's own home and while many medication regimens for chronic diseases may be straightforward, cancer therapies can be a bit more complicated. While various practices and institutions may have designated education materials to provide to patients, providing more tailored guidance and tools may help reinforce key aspects of safe and effective medication delivery. Some patients may benefit from a personalized calendar that indicates when they should take treatment, while others want

to use mobile phone apps that set reminders when it's time to take their next dose. The key is to listen to and understand the needs of each individual patient - and that may involve us going a bit off-script and coming up with unconventional methods to assist our patients. HOPA even has their own collaboration with several other oncology practice societies that provide patient-centered handouts on the various oral cancer therapies that are utilized across malignancies. Fortunately, they cover those essential issues like what to do about missed doses, home medication storage, potential drug interactions, and how to take the medicine. The vast portion of the handouts are focused on adverse effects that may occur during treatment as well as some solutions to manage them.

Adding to the patient's stress of a complex regimen is the fear that if they aren't taking it exactly as prescribed, it may not have the needed effectiveness to fight the cancer. It may be helpful to remind patients that sometimes, delivering healthcare can be more like an art rather than an exact science. Patients and providers should extend themselves the grace associated with a steep learning curve that is cancer medicine. Instead of zeroing on the exact time (to the second) of when to take our medicines, it may be helpful to remind patients about general principles related to missed doses or forgetting to take it with (or without) food as instructed. By tailoring our interactions to the individual needs of patients, we can better equip our patients to be advocates of their own care and improve the delivery of safe and effective healthcare.

Overall, we must consider each individual patient as a whole. Oncology pharmacists have the expertise and are uniquely positioned to improve the care of patients on oral oncolytics at every step of the patient care continuum. Standards for pharmacists' involvement in the management of patients on oral oncolytics have been previously addressed and can be incorporated in oncology practices to further enhance the role of the pharmacist on the oncology healthcare team.³ In cases like Sandra's, it is imperative that we listen to the concerns of our patients and address their questions and set appropriate expectations. When we are able to equip each patient with the tools needed to be knowledgeable about their own care, we invite them in as a key member on the treatment team alongside healthcare providers and increase the quality of care. ●●

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Real-world Analysis of Tumor Lysis Syndrome in Patients Started on Venetoclax Combination for Acute Myeloid Leukemia



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Background

Venetoclax is an oral antineoplastic agent that selectively inhibits the anti-apoptotic B-cell lymphoma 2 (BCL-2) protein, restoring the apoptotic process of malignant cells.¹ In combination with either a hypomethylating agent (HMA) or low-dose cytarabine (LDAC), venetoclax has shown favorable results in treatment naïve (TN) patients with acute myeloid leukemia (AML) who are unfit for intensive induction chemotherapy.^{2,3} Off-label experience in the relapsed/refractory (R/R) AML setting, including post-allogeneic hematopoietic cell transplantation (HCT), is growing and thus expanding the use of venetoclax-based therapies.^{4,5}

Tumor lysis syndrome (TLS) is an oncologic emergency resulting from the rapid breakdown of tumor cells, presenting as laboratory changes (hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia) and, in some cases, clinical manifestations such as acute renal injury, cardiac arrhythmias, and seizures. The risk of TLS varies by disease and patient characteristics, with risk categories for TLS development in AML being stratified by white blood cell (WBC) count and lactate dehydrogenase (LDH) levels.⁶

Prescribing information for venetoclax recommends hospitalization for dose ramp-up with frequent monitoring for patients with TN AML due to the risk of TLS.⁷ Experience in venetoclax-combination clinical trials for AML report a 1-6% risk of TLS, where all patients were hospitalized and received intravenous (IV) hydration and anti-urate therapy as prophylaxis.² With the expanding utilization of venetoclax-based therapies for AML, little is known regarding the real-world risk of TLS outside of a tightly controlled clinical trial. Specifically, the risk in the R/R population is even less documented in the literature.

The purpose of this study was to determine the real-world risk of developing TLS with initiation and dose ramp-up of venetoclax for AML. The ramp-up is often done in the inpatient setting, which is costly and may put patients at risk for hospital-acquired

complications. With this data, the goal was to develop a safe strategy to avoid hospitalization for the sole purpose of venetoclax ramp-up.

Methods

This study was a single-center, retrospective review of adult patients with a diagnosis of AML who were initiated on venetoclax with either an HMA or LDAC from November 2017 to May 2020. The primary outcome was the incidence of TLS, defined by the Cairo-Bishop classification for laboratory and clinical TLS. Secondary outcomes included identifying risk factors for the development of TLS and reviewing the length of hospital admission, as well as hospital-acquired complications (including intensive care unit [ICU] admissions, infections, falls, blood clots, and delirium).

Results

One hundred thirteen patients were included. Relapsed/refractory AML represented 56% of the population, with twenty-one patients undergoing a prior HCT. Just over half the patients were electively admitted to the hospital for venetoclax ramp-up, while the remainder were admitted for another reason (typically consequences of acute leukemia) and subsequently started on venetoclax while inpatient. Two patients were initiated on venetoclax with the partner agent in the outpatient setting. All patients in the study received some form of TLS prophylaxis.

Ten total patients (8.8%) experienced TLS, four of which were directly admitted for venetoclax ramp-up. Neither of the two patients who started venetoclax in the outpatient setting experienced TLS. All cases of TLS that occurred were laboratory TLS, including 10 cases of hyperphosphatemia (median 5.3 mg/dL, range: 4.5-6), nine with hypocalcemia (median 6.8 mg/dL, range: 5-7) and one with hyperuricemia that did not require treatment. Six of the patients received sevelamer for treatment of hyperphosphatemia. Laboratory TLS resolved in all 10 cases, and no patient in the study experienced clinical TLS.

For the secondary outcomes, the variables that were significantly more common in the TLS group are outlined in Table 1. There

"The purpose of this study was to determine the real-world risk of developing TLS with initiation and dose ramp-up of venetoclax for AML."

Table 1. Secondary Outcomes: Potential Risk Factors for Development of TLS

	TLS (n=10)	No TLS (n=103)	p-value
Hepatic dysfunction, n (%)	3 (30)	10 (9.7)	0.024
High TLS risk stratification, n (%)	4 (40)	1 (1)	< 0.001
Baseline WBC (n) - median [IQR]	16.2 [6.3-60.7]	2.7 [1.3-11.6]	< 0.001
Baseline LDH (n) - median [IQR]	794 [434-1556]	293 [220-452]	0.013

were no other significant between-group differences noted for all other variables tested, including TN versus R/R AML, molecular, or cytogenetic risk.

The median length of admission was similar in those who developed TLS versus those who did not (9.5 days vs. 8 days, $p = 0.57$). When comparing those who were electively admitted for venetoclax ramp-up as compared to patients who were admitted for other reasons and subsequently started on venetoclax, the median length of stay was 5 days [IQR 4–9] versus 13 days [IQR 9–28]. Of the patients directly admitted for venetoclax ramp-up, 13% developed a hospital-acquired complication. These complications occurred more frequently in those admitted for another reason, due to higher rates of ICU admission and infections, but there were no significant differences in rates of falls, blood clots, and delirium between the two groups (Table 2).

Discussion and Key Takeaways

The risk of TLS with venetoclax initiation is variably described in the literature which has led to the practice of admitting patients to the hospital for dose ramp-up for intensive monitoring and intervention. Prior to its use in AML, venetoclax was approved in patients with chronic lymphoblastic leukemia (CLL), a malignancy that is highly sensitive to venetoclax where its use is associated with rapid tumor cell death.^{1,8} The practice of admitting patients for drug initiation originated from the CLL trials and has since been largely adopted in the AML population.⁹ In AML, however, the risk of TLS is likely minor compared to CLL and may not require as extensive of monitoring.

In this study, the rates of TLS were consistent with those previously reported in the literature (1-6%); however, all occurrences

were laboratory TLS only without clinically significant signs or symptoms or impact on hospital length of stay. Dose ramp-up of venetoclax typically occurs over three to four days, where patients are often electively admitted to the hospital for drug initiation. This is inconvenient for the patient and costly to the healthcare system. In this analysis, there were no significant differences in hospital-acquired complications except for ICU admission in patients admitted for complications of leukemia and those who were elective admissions for venetoclax. This reveals that undesired and unanticipated hospital-acquired complications can occur as a result of admission for dose ramp-up, which may otherwise be avoided with outpatient initiation in these clinically stable individuals.

TLS was uncommon in this study and manifested as minor lab abnormalities. Those patients who present with elevated WBC counts or are considered high-risk individuals for TLS should be admitted for dose ramp-up. Otherwise, this study's findings support that initiation of venetoclax is potentially safe and feasible in the outpatient setting with close monitoring and administration of appropriate TLS prophylaxis. This approach to ambulatory initiation of venetoclax in low-risk individuals would prevent avoidable hospital-acquired complications from inpatient admissions.

The full manuscript for the research highlighted above can be found at:

Abernathy KM, Perciavalle MA, Gatwood KS, et al. Real-world analysis of tumor lysis syndrome in patients started on venetoclax combination for acute myeloid leukemia. *J Oncol Pharm Pract.* 2022 Aug 9; online ahead of print. doi: 10.1177/10781552221118635. ●●

Table 2. Secondary Outcomes: Hospital-acquired Complications by Reason for Admission

	Direct admission for venetoclax ramp-up (n=60)	Admission for other reason (n=51)	p-value
Hospital-acquired complications, n (%)	8 (13)	17 (33)	0.012
Infection	4 (6.7)	10 (19.6)	0.041
Fall	1 (1.7)	0	0.35
Blood clot	1 (1.7)	1 (2)	0.91
Delirium	3 (5)	7 (14)	0.11
ICU admission	0	5 (9.8)	0.013

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Corticosteroid Controversy Continues with Immune Checkpoint Inhibitors



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Introduction

Corticosteroids are the main treatment for immune-related adverse events (irAEs) recommended by the National Comprehensive Cancer Network® (NCCN®), the American Society of Clinical Oncology (ASCO), and the Society for Immunotherapy of Cancer (SITC). In general, it is recommended to utilize systemic corticosteroid treatment until the symptoms improve to grade 1 followed by a prolonged taper over four to six weeks.^{1,2,3} Systemic corticosteroids come with their own toxicities such as gastritis, mental status changes, and hyperglycemia for acute high-dose use. Common toxicities from long term use include increased risk of infections, type 2 diabetes, gastrointestinal dysfunction, weight gain, insomnia, hypertension, osteoporosis, lower extremity edema, mental status changes, and muscle weakness.^{4,5}

Can we shorten the corticosteroid taper duration?

Immune-related adverse events can rebound during corticosteroid tapers.

However, there may be the opportunity to decrease the dose and/or duration of the steroid taper or to use biologics more frequently which may allow patients who are clinically appropriate for a challenge to do so earlier in the regimen.

Immune checkpoint inhibitor (ICI)-induced nephritis has responded to corticosteroids with high percentages of patients achieving full or partial recovery.^{6,7} A single-center retrospective cohort study was completed at Massachusetts General Hospital Cancer Center to evaluate the time to renal recovery in patients with ICI-induced nephritis. They compared a rapid corticosteroid taper starting at 60 mg (or 1mg/kg) daily to 10 mg daily within 3 weeks versus standard of care 6 weeks. There were no significant differences in the time to renal recovery between the two groups ($p=0.092$).⁸ These findings prompt us to consider if other irAEs would be responsive to a shortened course of corticosteroids.

ASCO recommends tapering steroids for four to six weeks for immune-mediated colitis (IMC) but notes clinicians can consider a shorter taper of steroids in patients also treated with biologics.² A retrospective review was performed at the University of Texas MD Anderson Cancer Center to evaluate the efficacy of early selective immunosuppressive therapy (SIT) with infliximab or vedolizumab. In their analysis of steroid duration, they compared patients who received steroids < 6 weeks and began SIT within 10 days of IMC onset to patients who received steroids > 6 weeks and began SIT greater than 10 days after IMC onset. The patients who initiated treatment within 10 days and had shorter courses of corticosteroids had a statistically shorter duration of symptoms

($p<0.001$), had fewer steroid tapering attempts ($p<0.001$), were hospitalized less frequently ($p<0.001$) and for a shorter duration ($p=0.034$).⁹ Both ASCO and NCCN guidelines recommend utilizing SIT in colitis after 72 hours without improvement, but if this means we can potentially shorten the duration of steroids and reduce hospitalizations, should we strengthen the guideline recommendation to utilize SIT?

Can we utilize lower doses of corticosteroids than what is recommended in current guidelines?

A multicenter retrospective cohort study of adult patients treated at Dana-Farber/Brigham and Women's Cancer Center and Massachusetts General Cancer Center examined the effect of corticosteroid dos-

ing on the time to alanine aminotransferase (ALT) normalization, the need for additional immunosuppression, and steroid-related complications. Their study concluded that initial treatment of grade 3 or higher ICI-hepatitis using 1 mg/kg/day methylprednisolone equivalents provided similar hepatitis outcomes with reduced risk of steroid-related complications when compared to doses > 1.5 mg/kg/day of methylprednisolone equivalents. Only 20% of patients required corticosteroid dose escalations and these patients were also more likely to require a second immunosuppressive agent ($p<0.001$).¹⁰ This study demonstrates that starting on the low end of the dosing range recommended by ASCO/SITC guidelines for grade 3 hepatitis can be effective.

NCCN, ASCO, and SITC guidelines recommend 0.5-1 mg/kg/day of prednisone for grade 2 hepatitis and 1-2 mg/kg/day of prednisone for grade 3 hepatitis, with a taper over 4-6 weeks.^{1,2,3} A recent update to The European Society of Medical Oncology (ESMO) guidelines for irAE-associated hepatitis recommends the same

"All of these studies suggest that the impact on ICI efficacy is not the same for all patients on concomitant corticosteroids. Instead, these studies indicate the prognostic factor for decreased efficacy is the palliative indication of the corticosteroids."

corticosteroid dosing for grade 2 and 3 hepatitis, however, they differ in their taper recommendation and offer a shortened corticosteroid taper of 2 weeks for grade 2 hepatitis.¹¹ These findings give rise to the question, is there an opportunity to trial a shorter taper or even lower dose of corticosteroid for grade 3 hepatitis or other irAEs?

There is no doubt that irAEs can be severe and life-threatening, but the one-size fits all recommendations for the duration of steroid taper leaves opportunities for more robust studies as the utilization of checkpoint inhibitors continues to expand into earlier stages of cancer treatment. Furthermore, will similar outcomes be achieved trialing lower doses of corticosteroids in other irAEs? Additional studies evaluating these two opportunities would be beneficial for patients to reduce corticosteroid exposure while receiving appropriate treatment for their irAEs.

Another area of controversy is baseline and concurrent corticosteroid administration with ICIs. A physiologic dose of corticosteroids is approximately 7.5 mg of prednisone; therefore, doses \leq 10 mg of prednisone have been deemed acceptable.^{12,13,14,15,16} Patients receiving $>$ 10 mg of prednisone equivalent prior to and concurrently with ICIs have been excluded from trials thus far.

Do corticosteroids impact efficacy when administered prior to and shortly after administration of ICIs?

Although the mechanisms of corticosteroids are not fully elucidated, there is a theory regarding the potential mechanism of corticosteroids early administration in ICI treatment. In cancer, there is a state of CD-8+ T-cell dysfunction that is associated with the expression of PD-1 inhibitory receptors. A study in rats found PD-1 positive CD-8+ T-cells underwent self-renewal but mainly differentiated into terminally exhausted CD-8+ T-cells. When these mice were treated with PD-1 blockade, there was a proliferative burst, almost exclusively of CD-8+ T-cells, resulting in restoration of their function. It is likely the benefit of ICI is largely derived from this initial burst in CD-8+ T-cells upon initiation of therapy. Therefore, there is concern that corticosteroid use at baseline and shortly after initiation of ICI therapy would blunt this T-cell burst and decrease the benefit.¹⁷ If true, the administration of corticosteroids after this CD-8+ T-cell burst would not impact ICI efficacy. There are a few retrospective studies indicating that corticosteroid use prior to and within 30 days of initiation of ICIs could impact efficacy.

A retrospective review at Memorial Sloan Kettering and Gustave Roussy in France reviewed 640 patients treated with single agent ICI. Ninety patients were on \geq 10 mg of prednisone for various indications, including dyspnea, fatigue, and brain metastasis. The ORR, PFS, and OS were significantly decreased in the corticosteroid group compared to the control group who were on $<$ 10 mg of prednisone or no steroids ($p=0.02$, $p=0.001$, $p<0.001$, respectively). They did find that timing of discontinuation of the steroids had a varying impact on PFS and OS. When patients discontinued their corticosteroids at least one day prior to initiation of the ICI, they had an intermediate PFS and OS. The best PFS and OS were seen in patients who had no corticosteroids within 30 days of ICI initiation. Early use of corticosteroids was associated with decreased efficacy,

despite adjusting for smoking history, performance status, and history of brain metastases.¹⁸

Another retrospective review adds additional evidence that the timing of corticosteroid initiation impacted ICI efficacy. A retrospective review of 247 patients with metastatic disease treated with ICI was conducted at Ochsner Medical Center in New Orleans, LA. This review evaluated the timing of corticosteroids relative to ICI initiation. Patients were divided into two groups: patients that started corticosteroids within 2 months and patients who started corticosteroids \geq 2 months after ICI initiation. Patients treated with corticosteroids \geq 2 months after ICI initiation had a statistically significant longer PFS (HR = 0.30, $p<0.001$) and OS (HR 0.34, $p<0.001$) than those who received corticosteroids $<$ 2 months after ICI initiation. ORR for patients who started corticosteroids $<$ 2 months after ICI therapy was also lower at 14.7% vs 39.8% in patients who started corticosteroids \geq 2 months after initiation of ICI therapy ($p<0.001$). This was consistent in subgroup analyses of patients treated with corticosteroids for irAEs and non-irAEs (both $p<0.0001$) and were adjusted for treatment type, tumor type, brain metastases, and irAEs. Based on these results, authors concluded that differences in outcomes were influenced by the timing of corticosteroid initiation relative to the start of ICI therapy and were consistent across corticosteroid indications.¹⁹

These studies indicate that the use of corticosteroids prior to and shortly after administration of ICIs impacts ICI efficacy. Is this the case for all patients? Even though results in the previous two studies were adjusted for a number of confounding factors, including corticosteroid indication, there are additional studies that suggest that the impact on efficacy is not the same for all patients.

Are corticosteroids directly impacting ICI efficacy for all patients? What is the true prognostic factor impacting ICI efficacy?

There are a number of studies supporting the theory that steroids for palliation is the prognostic factor impacting ICI efficacy and less likely the amount, duration, or timing of concurrent corticosteroids. A retrospective review at the Dana-Farber Cancer Institute consisted of 650 patients with non-small-cell lung cancer treated with single agent ICI. Out of 650 patients, 93 were on anywhere from 10-150 mg of steroids per day. Patients were categorized based on indication. Palliative indications included brain metastasis, cancer-related dyspnea, pain from bone metastasis, and cancer-related anorexia. Nonpalliative indications included pneumonitis from prior treatment, chronic obstructive pulmonary disease, autoimmune disease, and iodinated contrast prophylaxis. Authors found that patients on corticosteroids for nonpalliative indications had a similar PFS and OS compared to patients who were on $<$ 10 mg of prednisone equivalent (PFS 4.6 vs 3.4 months, respectively, $p=0.24$; OS 10.7 vs 11.2 months, respectively, $p=0.77$). Patients on corticosteroids for palliation had significantly lower outcomes than the $<$ 10 mg prednisone group (PFS 1.4 vs 3.4 months, respectively, $p<0.001$; OS 2.2 vs 11.2 months, respectively, $p=0.001$).²⁰

A meta-analysis reviewed 16 studies that included 4045 patients treated for melanoma, NSCLC, and other various histotypes. ICIs

NEW SECTION: CLINICAL CONTROVERSIES (continued)

included nivolumab, pembrolizumab, atezolizumab, durvalumab, and ipilimumab alone or in combination. Steroids were administered for various supportive care reasons (e.g., dyspnea, pain, brain edema, fatigue) and to treat irAEs. Authors found that concomitant use of steroids in patients treated with ICIs was associated with a 34% higher risk of progression or death (HR=1.34; 95% CI: 1.02-1.76; $p=0.03$). A subgroup analysis evaluated the reason for using steroids and found that the supportive care subgroup was associated with a worse prognosis (HR=2.51, 95% CI: 1.41-4.43; $p<0.01$). Conversely, the outcome was not compromised in patients taking steroids for irAEs.²¹

A retrospective review was conducted on 413 pretreated advanced NSCLC patients at Gustave Roussy evaluating the introduction of corticosteroids within the first 8 weeks of ICI initiation according to clinical indication. Most patients received single-agent ICI. Authors found that PFS and OS were significantly lower in the cancer-related symptoms group compared to non-cancer-related symptoms. Furthermore, the PFS and OS were not significantly different between the steroid-naïve population and the steroid group for non-cancer-related symptoms (all $p<0.0001$). The median daily dose of prednisone equivalent was 40 mg for cancer-related symptoms and 50 mg for unrelated indications, which adds to the evidence that the dose of corticosteroids is less likely to be a factor impacting ICI efficacy.²²

Another retrospective review in NSCLC patients was conducted in Sweden evaluating concomitant corticosteroids based on reason and timing. Patients were divided into three subgroups: steroids for non-cancer-related symptoms, steroids for cancer-related symptoms, and steroids for the management of irAEs. These three groups were further categorized into two groups: patients who

received corticosteroids within 2 weeks before and 2 days after ICI initiation and patients who received steroids anytime (≥ 2 days after ICI initiation) during their treatment course. Authors found that only steroid administration for palliation of cancer-related symptoms was an independent predictor for shorter OS (HR = 2.7; 95% CI 1.5-4.9). Timing of steroid administration did not affect OS ($p = 0.456$).²³

All of these studies suggest that the impact on ICI efficacy is not the same for all patients on concomitant corticosteroids. Instead, these studies indicate the prognostic factor for decreased efficacy is the palliative indication of the corticosteroids. A prospective randomized controlled trial evaluating baseline and concurrent corticosteroid use would be difficult to conduct. Retrospective reviews thus far provide growing evidence that patients on corticosteroids for cancer-related palliation had decreased efficacy likely due to an already poorer prognosis and not necessarily from the use of corticosteroids concurrently with ICI. Patients who have extensive disease requiring corticosteroids for symptom management may have limited benefit from ICI therapy. The reason for the reduced benefit is likely due to the characteristics of their disease since it takes weeks to months for ICIs to start working. Therefore, patients with extensive, rapidly progressing disease may not have enough time to really benefit from ICIs. So, the next question is, do these patients derive any benefit from ICIs? Or would they benefit more from alternative treatments, such as chemotherapy, considering their own toxicities and efficacy? Future studies evaluating outcomes of patients with extensive disease on ICI versus chemotherapy could provide insight on the optimal therapy for patients who need corticosteroids for palliation of their disease-related symptoms. ●●

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Board Update

You Matter



Heidi D. Finnes, PharmD, BCOP, FHOPA
HOPA President (2022-2023)

*Senior Manager, Pharmacy Cancer Research
Director, Pharmacy Shared Resources, Mayo Clinic Cancer Center
Assistant Professor of Pharmacy, Mayo Clinic Alix School of Medicine
Rochester, MN*

It is hard to believe it has been nearly a year since I gave my first address as HOPA President. Since my Incoming President Speech at last year's Annual Conference, I have been fortunate to watch HOPA leaders, members, and staff embrace the mantra, You Matter.

You Matter to Each Other.

I am reminded of this every time I attend a committee, subcommittee, or task force meeting and observe the exceptional teamwork. It is also evident in our annual award nominations and as we celebrate each new class of HOPA Fellows, which we are preparing to do once again during Annual Conference 2023 (AC23) in Phoenix this year.

You Matter to the Field of Oncology Pharmacy.

Our members make a difference in clinical practice, in academia, within Industry, and throughout the growing field of hematology/oncology pharmacy. Thank you all for being dedicated stewards of HOPA's mission.

You Matter to People Being Treated for Cancer.

Even as we roll out a new three-year Strategic Plan, our vision and mission remain the same: To support hematology/oncology pharmacists, and ensure everyone being treated for cancer has an oncology pharmacist as an integral part of their care team.

You Matter to our Strategic Partners.

From ASCO to Stupid Cancer, the connections we make matter and we truly are stronger together. I am proud of how well you represent HOPA within your institutions and as you interact with other organizations focused on optimizing cancer care.

You Matter to Me.

Serving as HOPA President has been a highlight of my career. Thank you for your ongoing contributions to our association and to oncology pharmacy. Together, we have accomplished so much this year:

The HOPAmbassadors Task Force is launching a new program that will expand our reach. Soon, a small group of members will be

trained in telling the HOPA story and giving voice to the important role of hematology/oncology pharmacists.

The Wellness Task Force has created an official HOPA Well-Being Statement to acknowledge the critical need to mitigate risk factors of burnout. The group has been charged with creating well-being initiatives with interventions aimed at individual wellness and organizational efforts to optimize cancer care. Their work thus far has culminated in the Wellness Toolkit published on hoparx.org.

The Diversity, Equity and Inclusion Committee has put into action many tactics to ensure HOPA remains an accepting, welcoming, and diverse organization. Award nominations, board elections, and committee compositions are all facilitated with an eye toward diversity. A forthcoming DEI Toolkit will provide self-assessments and resources for creating equity in cancer care.

HOPA Town Halls have brought together members who are interested in learning more about advocacy, wellness, and how to become more involved as HOPA committee members and leaders.

A new Strategic Plan for 2023-2026 has been rolled out. In it, you will find our new strategic imperatives where Education, Professional Practice, Quality Research, and Advocacy & Awareness are grounded in Organizational Excellence. Special thanks to the Board of Directors, other volunteer leaders, and staff who participated in the collaborative process led by 2B Communications & Strategy Group.

Enhancements to the HOPA Committee Structure are being made to go along with the new Strategic Plan. We will share more about this, including a new Advisory Group model, with you at AC23 on March 29-April 1 at the Phoenix Convention Center.

I hope to see you at AC23 where, in addition to all the great science and networking, I will have the privilege of introducing you to your next HOPA President, LeAnne Kennedy. See you in sunny Phoenix!





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SAVE THE DATE!

HOPA Practice Management 2023 is Heading to Austin!

Two days of CE and networking opportunities in an amazing city filled with
live music.

November 9-10, 2023

Details to come.

