SPRING 2022 NEWSLETTER

Official Newsletter of the ACCP Hem/Onc PRN

2021 - 2022 PRN OFFICERS

Chair:

Don Moore, PharmD, BCPS, BCOP, DLPA

Clinical Pharmacist Specialist
Hematology/Oncology
Levine Cancer Institute—Northeast
Atrium Health
Charlotte, NC

Chair - Elect:

Erin Hickey Zacholski, PharmD, BCOP

Clinical Pharmacist Specialist
Hematology/Oncology
VCU Health
Assistant Professor at VCU School of Pharmacy
Richmond, VA

Secretary/Treasurer:

Farah Raheem, PharmD, BCOP

Clinical Pharmacist Specialist
Hematology/Oncology
Mayo Clinic Arizona
Phoenix, AZ

GREETINGS FROM THE CHAIR

Hello everyone, I hope you are all doing well.

As I reflect on the first half of my time as Chair of our PRN, I am excited to see all of our various activities in full swing: our committees are up and running, monthly journal clubs, engagement on social media, and the start-up of our PRN Awards program! I want to thank you all making this a fun and engaging year with the PRN thus far.

As such, a call for PRN Officers for the 2022-2023 year will go out in the coming months. If you are considering running for office, please be on the lookout for emails or please feel free to reach out to me directly.

Herein, you will find our biannual newsletter to coincide with the ACCP Spring and Fall PRN reports. Our goal with the newsletter is to have a document that supports the needs of the PRN membership. Submissions may be made by clinicians, residents/fellows, or students. The newsletter is a way to highlight our members and showcase a variety of practice areas.

In this issue:

American College of Clinical Pharmacy

New Drug Update—Tebentafusp (Kimmtrak®)

By: Rachel Hartman, PharmD, PGY Pharmacy Resident, Hospital of the University of Pennsylvania,
Mentors: Brendan Mangan, PharmD, BCOP, Oncology Clinical Pharmacy Specialist and Christopher Tweed, PharmD, BCOP Oncology Clinical Pharmacy Specialist, Hospital of the University of Pennsylvania, Philadelphia, PA

Review of Uveal Melanoma

Uveal melanoma is the most common and only potentially fatal primary intraocular malignancy in adults[1]. Uveal melanoma has an annual incidence of six cases per million, with an average age of diagnosis of 60 years old. While pediatric cases of uveal melanoma are rare, younger patients are at a higher likelihood of iris melanomas and melanocytosis, and a lower risk of metastatic disease compared to older patients. It is not known whether gender-specific differences exist in uveal melanoma, but symptomatic patients are most commonly men[2]. From 1992-2000, an analysis conducted within the Surveillance, Epidemiology, and End Results (SEER) Program database reported the annual age-adjusted incidence (per million population) of uveal melanoma was 0.31 (black), 0.38 (Asian), 1.67 (Hispanic), and 6.02 (non-Hispanic white). When relative risks of non-Hispanic white population and the Hispanic population were combined, the overall white:black ratio was 18:1[3].

The development of uveal melanoma has been associated with early oncogenic mutations which affect pathways involved with the regulation of the cell cycle or the control of cell apoptosis[4]. Approximately 95% of cases arise from cells within the uveal tract with 90% located in the choroid, 7% in the ciliary body, and 3% in the iris[5,6]. While iris melanomas seldom metastasize and have been effectively treated by local excision, tumors of the choroid and ciliary body pose a serious threat to life[2]. Although uveal and cutaneous melanomas both originate from melanocytes, their underlying pathogenesis and clinical behavior differ significantly[7]. For many years, details of the molecular pathogenesis of uveal melanoma has remained elusive. A recent discovery indicates early disruption of the cell cycle and apoptotic control leads to malignant transformation and proliferation of uveal melanocytes. Eventually, the growing tumor encounters a critical bifurcation point where it then progresses along one of two genetic pathways with distinct genetic signatures (monosomy 3 and 6p gain) and metastatic propensity. Specific chromosomal alterations, such as loss of chromosome 8p, can hasten the onset of metastasis in susceptible tumors[8].

Uveal melanomas commonly present asymptomatically and are discovered during routine eye exams. One-half of patients will present with visual symptoms including flashes, floaters, or visual field defects. Choroidal melanomas appear as a mass deep within the retina, without retinal feeder vessels, and often lead to retinal detachment[9]. Vitreous hemorrhage, which obscures visualization of the tumor, may occasionally occur. In these instances, the tumor is only visible via ocular ultrasonography. Choroidal melanomas may present as pigmented (55%), non-pigmented (15%), or mixed (30%), and appear in one of three configurations including dome (75%), mushroom (20%), or diffuse (5%)[9]. Ciliary body melanomas present with prominent episcleral (sentinel) vessels, shallowing of the anterior chamber, unilateral lens changes, unilateral decreased or increased intraocular pressure, a large nodular ciliary body mass, and extraocular extension[10]. Iris melanomas can present as a gradually expanding pigmented mass (asymptomatic in the majority of the population), with a predilection for the inferior iris. They commonly have some degree of pigmentation, often presenting as a brown or yellow color[11]. Host pigmentation factors serve as strong predictors for uveal melanoma development, including light eye color, fair skin, and the propensity to sunburn[2]. Cutaneous nevi, cutaneous freckles, iris nevi, and ultraviolet light exposure have also all be associated with increased risk of uveal melanoma, and oculodermal melanocytosis most strongly predisposes patients to uveal melanoma, and is associated with a lifetime risk of 1 in 400[12,13].

Overall, clinical prognosis of uveal melanoma estimates 50% of patients dying within 10 to 15 years of diagnosis. Although local treatment for primary uveal melanoma is effective in preventing local recurrence in over 95% of cases, up to 50% of patients are at risk of metastatic disease. The high risk of metastatic disease is thought to be due to the formation of early micrometastases, followed by a variable latency period prior to overt metastatic disease[14]. The most common site of metastases in uveal melanoma is the liver, with a median survival of 2-4 months after development. While highest rate of metastases occurs within the first five years following diagnosis, recurrences up to 42 years following treatment have been recorded[2].

New Drug Update—Tebentafusp (Kimmtrak®) [Continued]

In general, there are no systemic therapies that have reliably improved the overall survival (OS) in patients with metastatic uveal melanoma[15]. No standard-of-care therapy has been firmly established, and participation in clinical trials should be prioritized for patients with metastatic disease. In contrast to cutaneous melanoma, where targeted agents and immune checkpoint inhibitors are the standard of care, little has proven to be effective in patients with metastatic uveal melanoma. Liver-directed therapy for patients with hepatic metastases has demonstrated responses with clinical utility. These therapies function by taking advantage of the blood supply in the liver to deliver treatments directly to the metastases via the hepatic artery[16]. Procedures including radiofrequency ablation, chemoembolization, immunoembolization, stereotactic radiation therapy, and intra-arterial hepatic chemoembolization can be performed as directed management of uveal melanoma hepatic metastases[16,17]. Systemic approaches include chemotherapy, immunotherapy, and molecularly targeted tyrosine kinase inhibitors[17]. For those who decline or are not eligible for clinical trials, combination immunotherapy with nivolumab plus ipilimumab is recommended over single-agent immunotherapy. Studies have suggested limited activity for this combination in patients with uveal melanoma, with a response rate of 17%, a median progression-free survival (PFS) of up to six months, and a median overall survival (OS) of up to 19 months[18-22]. Patients ineligible for combination nivolumab ipilimumab can be offered single-agent immunotherapy with a programmed cell death receptor 1 (PD-1) inhibitor. Unfortunately, efficacy of single agent immunotherapy is limited, with pembrolizumab demonstrating an objective response (OR) in 2 of 56 (4%) study patients, a PFS of 3 months, and an OS of 8 months[23]. The single-agent ipilimumab arm of the CheckMate 172 trial demonstrated a median OS of 13 months, and the 18-month OS was 35%[18].

Tebentafusp

Newly FDA-approved on January 26th, 2022, Tebentafusp (Kimmtrack®) is a novel form of immunotherapy based on the immune-mobilizing monoclonal T-cell receptor against cancer (ImmTAC) platform, which comprises a soluble T cell receptor specific for the glycoprotein 100 peptide and is fused to an anti-CD3 single-chain variable fragment[24,25]. The T-cell receptor binds to a gp100 peptide presented by HLA-A*02:01 on the surface of uveal melanoma tumor cells. Once bound, they recruit and activate polyclonal T-cells through CD3, to release inflammatory cytokines and cytolytic proteins, resulting in direct lysis of uveal melanoma tumor cells. HLA-A*02:01 is present on about half of all Caucasians, the population most affected by uveal melanoma[26].

Tebentafusp has shown a significant OS benefit among patients with systemic therapy-naïve metastatic uveal melanoma. A phase III trial was conducted in 378 previously untreated HLA-A*02:01-positive patients with metastatic uveal melanoma, with no prior liver-directed therapy (except surgery) and any level of lactate dehydrogenase (LDH)[27]. Patients were randomly assigned in a 2:1 ratio to receive tebentafusp or the investigator's choice of therapy (pembrolizumab, ipilimumab, or dacarbazine). Tebentafusp was administered via a dose-escalation strategy, with 20 mcg on day 1, 30 mcg on day 8, 68 mcg on day 15, and weekly thereafter. With a median follow-up of 14 months, tebentafusp was associated with an OS of 73% versus 59% in the control group (hazard ratio [HR], 0.51; 95% confidence interval [CI], 0.37 to 0.71; P<0.001). PFS was also significantly higher in the tebentafusp group than in the control group (31% vs. 19% at 6 months; HR for disease progression or death, 0.73; 95% CI, 0.58 to 0.94; P = 0.01). Throughout the trial, tebentafusp was well tolerated, with most treatment-related toxicities decreasing in frequency and severity after the first 3-4 doses. The PFS benefit and tumor response of tebentafusp were both low in comparison to the magnitude of survival benefit. Patients who received tebentafusp and had disease progression as the best response had longer survival compared to patients who had disease progression as the best response in the control group, implicating a clinically significant effect on outcomes, even if a patient had no radiographically significant decrease in tumor size.

The most common treatment-related adverse events in the tebentafusp group were cytokine-mediated events (due to T-cell activation) and skin-related events (due to glycoprotein 100-positive melanocytes), including rash (83%), pyrexia (76%), and pruritus (69%). Cytokine release syndrome (CRS), identified on the basis of pyrexia, hypotension, and hypoxia, occurred in 89% of the patients in the tebentafusp group. CRS most commonly occurred within the first few hours after the first three doses were administered. In most patients, the maximum grade of CRS was grade 1 (12%) or grade 2 (76%). Few patients (1%) had grade 3 cytokine release syndrome, and no grade 4 or 5 CRS events occurred. Patients with CRS during the trial were generally treated with antipyretic agents, intravenous fluids, glucocorticoids, or a combination of these therapies.

New Drug Update—Tebentafusp (Kimmtrak®) [Continued]

These events occurred in the hours after the first few doses; therefore, overnight monitoring of all the patients after the first three infusions was required. After this induction period, cytokine-mediated adverse events decreased in incidence and severity, and the extension of overnight monitoring beyond that required by the protocol was uncommon. Skin-related adverse events, presumably due to the recognition of gp100-expressing melanocytes by tebentafusp, were limited to the hours after administration of the first few doses. The onset of rash in the first week of treatment appeared to be associated with longer survival, suggesting skin inflammation may be a surrogate of activity against the tumor. Rash for clinical management decisions is not considered appropriate, given rash is not an independent predictor of OS; patients commonly have a rash at some point during treatment, and patients without a rash also can benefit from therapy. Overall, treatment with tebentafusp conferred longer overall survival compared to control therapy among previously untreated patients with metastatic uveal melanoma.

Tebentafusp is currently indicated for metastatic or unresectable HLA-A*02:01 positive uveal melanoma[25]. It is administered intravenously (IV) through a dedicated IV line and 0.2-micron inline filter via dose escalation, with 20 mcg IV on day 1, 30 mcg IV on day 8, 68 mcg IV on day 15, and then 68 mcg IV once weekly until disease progression or toxicity. It is recommended to ensure patients are euvolemic prior to initiating therapy. The first three infusions of tebentafusp are required to be administered in a healthcare setting, with immediate access to medications and resuscitation equipment to manage cytokine release syndrome. If no ≥ grade 2 hypotension events requiring medical intervention occur during or after the third infusion, subsequent doses of tebentafusp may be administered in the ambulatory care setting. No dosage adjustments for renal or hepatic impairment are currently recommended. It is recommended the infusion be completed within 4 hours of preparation24,25.

There are currently no contraindications to tebentafusp therapy. Medication warnings include hepatotoxicity, dermatologic toxicity, and CRS. Elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) were reported in over two-thirds of patients; the majority occurred within the first 3 tebentafusp infusions. In patients who had grade 3 or 4 transaminase elevations, most had improvement to ≤ grade 1 within seven days. Skin reactions include rash, pruritus, and cutaneous edema, and the majority or events have been grade 2 and grade 3 events. The median time to onset of skin reactions was 1 day, and median time to improvement to grade ≤1 is six days[25].

CRS is a systemic inflammatory response that can range from mild, flu-like symptoms to severe life-threatening manifestations of the overshooting inflammatory response[28]. Common mild symptoms include fever, fatigue, headache, rash, arthralgia, and myalgia. More severe cases are characterized by hypotension, high fever and progression to systemic inflammatory responses, circulatory shock, vascular leakage, disseminated intravascular coagulation, and multi-organ system failure. Common laboratory abnormalities include cytopenias, elevated creatinine and liver enzymes, deranged coagulation parameters, and high CRP. Respiratory symptoms can range from cough and tachypnea to acute respiratory distress syndrome (ARDS) requiring mechanical ventilation. Severe CRS is further characterized by cardiac dysfunction, renal dysfunction, and vascular leakage leading to peripheral and pulmonary edema. Neurologic symptoms can range from mild confusion with word-finding difficulty and headaches to aphasia, hemiparesis, seizures, and somnolence[28]. With regards to tebentafusp, the majority of CRS events begin the day of infusion, symptoms are primarily mild in nature, with a median time to resolution of two days[25].

Management of CRS is focused on grade- and risk-adapted strategies for monitoring and therapy[29]. Fever is commonly the first clinical sign that can signal CRS. Patients who develop fever should be frequently reassessed and outpatients should be admitted to the hospital for close observation. Low-grade CRS is treated symptomatically with antihistamines, antipyretic agents, and fluids[29,30]. If an infection cannot be ruled out, empiric antibiotic therapy should be promptly started[28]. For severe CRS, it is recommended to withhold tebentafusp until CRS and sequelae have resolved[24,25]. IV corticosteroids (methylprednisolone 2 mg/kg/day or equivalent) should be administered. Tebentafusp can be resumed at the same dose level (do not escalate dose if severe CRS occurred during initial dose escalation; resume escalation once dose is tolerated). Corticosteroids (dexamethasone 4 mg or equivalent) can be administered at least 30 minutes prior to the next dose as a premedication. For life-threatening CRS reactions, tebentafusp is recommended to be permanently discontinued. In clinical trials, there has been no incidence of grade 4 or 5 CRS events[24,25].

New Drug Update—Tebentafusp (Kimmtrak®) [Continued]

Given the previously stated considerations for CRS, hepatotoxicity, and dermatologic toxicity, monitoring parameters for tebentafusp include obtaining ALT, AST, and total bilirubin prior to tebentafusp initiation, as well as during treatment. Fluid status, vital signs, oxygenation level, as well as signs/symptoms of CRS should be monitored throughout therapy. Also monitor for skin reactions including rash, pruritus, and cutaneous edema. It is recommended to monitor patients during, and for at least 16 hours after completion of the first three infusions in a health care setting. If the first three infusions are tolerated, monitor for a minimum of 30 minutes following subsequent infusions. Prior to initiating therapy, pregnancy status should be verified in patients who could become pregnant. It is recommended to obtain hepatitis B virus (HBV) screening with hepatitis B surface antigen, hepatitis B core antibody, total IgG, and antibody to hepatitis B surface antigen prior to beginning systemic anticancer therapy[24,25].

Future Directions

Overall, the development of tebentafusp represents an important addition to the limited treatment options available for metastatic uveal melanoma. Tebentafusp is currently being further investigated for use in metastatic cutaneous melanoma. With an estimated study completion in January 2025, the phase Ib/II, multi-center, open-label study is investigating tebentafusp as a single agent and in combination with durvalumab and/or tremelimumab in metastatic cutaneous melanoma (NCT02535078)[31]. Future investigations involve evaluating efficacy of tebentafusp as an adjuvant therapy for patients whose genetic tumor profile indicates a high risk of developing metastatic disease, as well as a neoadjuvant therapy for primary uveal melanoma to reduce tumor size prior to radiotherapy or resection[32]. In conclusion, tebentafusp is a first-in-kind therapeutic agent that functions to redirect T cells against cancer cells, and has shown promising clinical activity in patients with metastatic uveal melanoma with superior survival rates in comparison to other available treatments.

References:

1. Spagnolo F, Caltabiano G, Queirolo P. Uveal melanoma. Cancer Treat Rev. 2012;38:549–53
2. Egan KM, Seddon JM, Glynn RJ, et al. Epidemiologic aspects of uveal melanoma. Surv Ophthalmol. 1988 Jan-Feb;32(4):239-51.
3. Hu DN, Yu GP, McCormick SA, et al. Population-based incidence of uveal melanoma in various races and ethnic groups. Am J Ophthalmol. 2005 Oct;140(4):612-7.
4. Singh M, Durairaj P, Yeung J. Uveal Melanoma: A Review of the Literature. Oncol Ther. 2018 Jun;6(1):87-104.
5. Krantz BA, Dave N, Komatsubara KM, MarrBP and CarvajalRD: Uveal melanoma: Epidemiology, etiology, and treatment of primary disease. Clin Ophthalmol 11: 279-289, 2017.
6. Damato B: Progress in the management of patients with uveal melanoma. the 2012 Ashton Lecture. Eye (Lond) 26: 1157-1172, 2012
7. Yonekawa Y, Kim IK. Epidemiology and management of uveal melanoma. Hematol Oncol Clin N Am. 2012;26:1170–84.
8. Landreville S, Agapova OA, Harbour JW. Emerging insights into the molecular pathogenesis of uveal melanoma. Future Oncol. 2008 Oct;4(5):629-36.
9. Shields CL, Manalac J, Das C, Ferguson K, Shields JA. Choroidal melanoma: clinical features, classification, and top 10 pseudomelanomas. Curr Opin Ophthalmol. 2014;25:177–85.
10. Demirci H, Shields CL, Shields JA, et al. Ring melanoma of the ciliary body: report on twenty-three patients. Retina. 2002 Dec;22(6):698-706; quiz 852-3.
11. Kersten RC, Tse DT, Anderson R. Iris melanoma. Nevus or malignancy? Surv Ophthalmol. 1985 May-Jun;29(6):423-33.
12. Bataille V, Sasieni P, Cuzick J, et al. Risk of ocular melanoma in relation to cutaneous and iris naevi. Int J Cancer. 1995 Mar 3;60(5):622-6.
13. van Hees CL, de Boer A, Jager MJ, et al. Are atypical nevi a risk factor for uveal melanoma? A case-control study. J Invest Dermatol. 1994 Aug;103(2):202-5.
14. Eskelin S, Pyrhönen S, Summanen P, et al. Tumor doubling times in metastatic malignant melanoma of the uvea: tumor progression before and after treatment. Ophthalmology. 2000 Aug;107(8):1443-9.
15. NCCN. Melanoma: Uveal. Version 2.2021.

New Drug Update—Tebentafusp (Kimmtrak®) [Continued]

16. Sato T. Locoregional management of hepatic metastasis from primary uveal melanoma. Semin Oncol. 2010 Apr;37(2):127-38.
17. Rule W, Timmerman R, Tong L, et al. Phase I dose-escalation study of stereotactic body radiotherapy in patients with hepatic metastases. Ann Surg Oncol. 2011 Apr;18(4):1081-7.
18. Nathan P, Ascierto PA, Haanen J, et al. Safety and efficacy of nivolumab in patients with rare melanoma subtypes who progressed on or after ipilimumab treatment: a single-arm, open-label, phase II study (CheckMate 172). Eur J Cancer. 2019 Sep;119:168-178.
19. Najjar YG, Navrazhina K, Ding F, et al. Ipilimumab plus nivolumab for patients with metastatic uveal melanoma: a multicenter, retrospective study. J Immunother Cancer. 2020 Jun;8(1):e000331.
20. Heppt MV, Amaral T, Kähler KC, et al. Combined immune checkpoint blockade for metastatic uveal melanoma: a retrospective, multi-center study. J Immunother Cancer. 2019 Nov 13;7(1):299.
21. Rapisuwon S, Izar B, Batenchuk C, et al. Exceptional response and multisystem autoimmune-like toxicities associated with the same T cell clone in a patient with uveal melanoma treated with immune checkpoint inhibitors. J Immunother Cancer. 2019 Mar 4;7(1):61.
22. Piulats JM, Espinosa E, de la Cruz Merino L, Varela M, et al. Nivolumab Plus Ipilimumab for Treatment-Naïve Metastatic Uveal Melanoma: An Open-Label, Multicenter, Phase II Trial by the Spanish Multidisciplinary Melanoma Group (GEM-1402). J Clin Oncol. 2021 Feb 20;39(6):586-598.
23. Algazi AP, Tsai KK, Shoushtari AN, et al. Clinical outcomes in metastatic uveal melanoma treated with PD-1 and PD-L1 antibodies. Cancer. 2016 Nov 15;122(21):3344-3353.
24. Tebentafusp. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: Lexicomp. Accessed February 16th, 2022.
25. Kimmtrak (tebentafusp) [prescribing information]. Conshohocken, PA: Immunocore Commercial LLC; January 2022.
26. Immunotherapy Drug Tebentafusp Improves Survival in Advanced Uveal Melanoma. NCI [Internet]. April 2021.
27. Nathan P, Hassel JC, Rutkowski P, et al. Overall Survival Benefit with Tebentafusp in Metastatic Uveal Melanoma. N Engl J Med. 2021 Sep 23;385(13):1196-1206.
28. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, et al. Cytokine release syndrome. *J Immunother Cancer*. 2018;6(1):56.
29. Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. Nat Rev Clin Oncol. 2018 Jan;15(1):47-62.
30. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014 Jul 10;124(2):188-95.
31. IMCgp100-201; ClinicalTrials.gov Identifier: NCT02535078.ClinicalTrials.gov.
32. Damato BE, Dukes J, Goodall H, et al. Tebentafusp: T Cell Redirection for the Treatment of Metastatic Uveal Melanoma. Cancers (Basel). 2019;11(7):971.

New Drug Update—Tebentafusp (Kimmtrak®)

Table 1. Tebentafusp (Kimmtrack®) Dose Modifications for Adverse Reactions[24,25]

Adverse Reaction	Severity	Tebentafusp Dose Modification
Cytokine Release Syndromes	**Moderate** (temperature ≥38°C with hypotension that responds to fluids [does not require vasopressors] or hypoxia requiring low flow nasal cannula [≤6 L/minute] or blow-by oxygen)	• If no improvement in hypotension and hypoxia within 3 hours or CRS worsens, escalate treatment and manage according to the next higher severity level. • For moderate persistent (lasting 2-3 hours) or recurrent CRS, administer corticosteroid premedication (eg, dexamethasone 4 mg or equivalent) at least 30 minutes prior to the next dose.
	Severe (temperature ≥38°C with hemodynamic instability requiring a vasopressor [with or without vasopressin] or worsening hypoxia or respiratory distress requiring high flow nasal canula [>6 L/minute oxygen] or face mask)	• Withhold tebentafusp until CRS and sequelae have resolved. • Administer IV corticosteroid (eg, methylprednisolone 2 mg/kg/day or equivalent). • Resume tebentafusp at the same dose level (do not escalate dose if severe CRS occurred during initial dose escalation; resume escalation once dose is tolerated). • For severe CRS, administer corticosteroid premedication (eg, dexamethasone 4 mg or equivalent) at least 30 minutes prior to the next dose.
	Life-threatening (temperature ≥38°C) **with:** Hemodynamic instability requiring multiple vasopressors (excluding vasopressin) Worsening hypoxia or respiratory distress despite oxygen administration requiring positive pressure	• Permanently discontinue tebentafusp. • Administer IV corticosteroid (eg, methylprednisolone 2 mg/kg/day or equivalent).
Skin Reactions	If skin reactions occur, treat with antihistamines and topical or systemic steroids (depending on severity and persistence of symptoms).	
	Grade 2 or 3	• Withhold tebentafusp until ≤ grade 1 (or baseline), then resume at the same dose level (do not escalate dose if grade 3 skin reactions occurred during initial dose escalation; resume escalation once dose is tolerated). • For persistent reactions not responding to oral steroids, consider IV corticosteroid (eg, methylprednisolone 2 mg/kg/day or equivalent).
	Grade 4	• Permanently discontinue tebentafusp. • Administer IV corticosteroid (eg, methylprednisolone 2 mg/kg/day or equivalent).
Other Adverse Reaction	**Grade 3**	Withhold tebentafusp until ≤ grade 1 (or baseline), then resume at the same dose level (do not escalate dose if other grade 3 adverse reaction occurred during initial dose escalation; resume escalation once dose is tolerated).
	Grade 4	Permanently discontinue tebentafusp.

ASCEMBL: A Phase 3, Open-Label, Randomized Study of Asciminib, a STAMP Inhibitor, vs. Bosutinib in CML after 2 or more prior TKIs

Summarized by: Daniel Do, PharmD Candidate 2023, University of Chicago College of Pharmacy
Mentor: Marco Martino, PharmD, MBA, BCPS, BCOP

Introduction

The World Health Organization (WHO) defines chronic myeloid leukemia (CML) as a myeloproliferative neoplasm with a chromosomal translocation t(9;22) forming the BCR-ABL1 fusion gene and the Philadelphia chromosome (Ph*), which causes an increase in granulocytes and bone marrow myeloid precursors1. The American Cancer Society (ACS) estimates that in 2022, there will be about 8,860 new cases diagnosed with CML and about 1,220 people will die of CML.

Recently, the Food & Drug Administration (FDA) granted accelerated approval to asciminib (Scemblix) for patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML), previously treated with two or more tyrosine kinase inhibitors (TKIs), as well as for adult patients with Ph+ CML with the T315I mutation. The usual mechanistic approaches of current TKI therapy in treating CML involves the binding of the drug to the ATP binding site of BCR-ABL1 oncoprotein. Asciminib introduces a novel ap- proach to treating CML by binding allosterically to the BCR-ABL1 oncoprotein and earning the title of being the first Specifically Tar- geting the ABL Myristoyl Pocket (STAMP) inhibitor. This new mechanism of action allows asciminib to be a potential alternative for patients who experience treatment inefficacy, resistance or intolerance to the other TKIs.

Study Objective

This is a phase 3, multicentered, open-label, superiority study where patients with chronic myeloid leukemia in chronic phase(CML- CP) previously treated with ≥2 TKIs were recruited and then randomized in a 2:1 ratio, to receive asciminib 40 mg twice daily or bosutinib 500 mg once daily. The study aims to compare the major molecular response (MMR) rate for asciminib vs bosutinib, which is defined as a 3-log reduction or a BCR-ABL1 = 0.1%4.

Study Design

Patients were eligible to be recruited into the study is they were: diagnosed of CML-CP ≥ 18 years of age, patients must meet all of the laboratory values at the screening visit prior to start of therapy, BCR-ABL1 ratio > 0.1% on the international scale (IS) for patients intolerant to the most recent TKI therapy, prior treatment with a ≥ 2 ATP-binding site TKIs, failure or intolerance to most re- cent TKIs in the treatment of CML. Intolerance is defined as consistent grade 3 or 4 toxicities that cannot be managed through dose adjustments or other means.

Patients were deemed ineligible for the trial if they have a detected T315I or V299L mutation at any time prior to study entry, previous treatment or plan of future treatment with a hematopoietic stem-cell transplantation, cardiac abnormalities, severe and/or uncontrolled concurrent medical disease, women of child-bearing potential unless they are using highly effective methods of contraception during dosing and for 3 days after last dose of ABL001 and one month after the last dose of bosutinib.

The patients were randomized into two arms, where they received either asciminib 40 mg twice daily orally without food or bosutinib 500 mg once daily with food and followed for 96 weeks. In order to test for the primary endpoint, a total sample size of 222 patients was planned. This will allow a 90% power to detect a 20% difference in the MMR rates at week 24 with a significance level of 0.05. Power was achieved as 233 patients were enrolled and analyzed with a split of a 2:1 ratio (157 patients randomized to asciminib and 76 patients to bosutinib).

ASCEMBL (Continued)

Outcomes

The primary endpoint measured in the study was the rate of MMR at week 24 without failing treatment as defined by the protocol.

The secondary endpoints measured in the study was the rate of MMR at week 96 without failing treatment as defined by the protocol, time to achieve MMR, duration of MMR, time to achieve complete cytogenetic response (CCyR), duration of CCyR, time to treatment failure, progression-free survival, overall survival, safety and tolerability profile, and pharmacologic parameters.

Efficacy Results

The study was able to meet its primary objective with a MMR rate at week 24 of 25.5% with asciminib compared to 13.2% with bosutinib. When accounting for the MCyR status at baseline, the difference in MMR was 12.2% (95% CI, 2.19-22.30; 2-sided P=0.029).

More patients on asciminib than on bosutinib achieved BCR-ABL1 IS ≤10% at week 12 and week 24; with 63.1% vs 43.4% and 49.0% vs 23.7% respectively. More patients also achieved MR4 (BCR-ABL1 ≤0.01%) and MR4.5 (BCR-ABL1 ≤0.0032%) with asciminib com- pared to bosutinib at week 24 at 10.8% vs 5.3% and 8.9% vs 1.3% respectively.

The cumulative incidence of MMR by week 24 comparing asciminib vs bosutinib was 25.0% vs 12.0% respectively. The CCyR rate at week 24 in patients without CCyR at baseline was 40.8% vs 24.2% with asciminib vs bosutinib respectively. When accounting for the MCyR status at baseline, the difference in CCyR rates at week 24 was 17.3% (95% CI, 3.62-30.99).

Of the patients who failed to reach MMR at week 24 and had to discontinue treatment, 10 patients were using asciminib vs 4 patients who were using bosutinib.

Safety Results

When comparing all-grades of adverse events (AEs) between asciminib and bosutinib, it occurred in 140 patients (89.7%) and 73 (96.1%) patients, respectively, Grade ≥3 AEs occurred in 79 (50.6%) and 46 (60.5%) patients, respectively. Lastly, treatment-related AEs occurred in 99 (63.5%) and 67 (88.2%) patients, respectively.

The percentage of patients who experienced AEs severe enough to lead to discontinuation was lower with asciminib compared to bosutinib at 5.8% and 21.1% respectively. The most common AEs that lead to treatment discontinuation were thrombocytopenia (all-grade, 3.2%; grade ≥3, 3.2%) for asciminib and increased alanine aminotransferase (ALT) (all-grade, 5.3%; grade ≥3, 3.9%) for bosutinib. When comparing the need for ≥1 dose reductions in asciminib vs bosutinib, there were 33 patients (21.2%) vs 32 patients (42.1%), respectively. When comparing the need for ≥1 dose interruptions due to AEs in asciminib vs bosutinib, there were 60 patients (38.5%) and 43 patients (56.6%), respectively.

Conclusion

In conclusion, this study shows that patients taking asciminib (40 mg twice daily) compared to bosutinib showed superior efficacy in rate of achieving MMR at week 24, and a more tolerable safety profile if the patients have a diagnosis of CML-CP, have tried and failed therapy with ≥2 TKIs, and lacked the T315I or V299L mutation. As a newly approved TKI with a novel mechanism of action, designated to be the first STAMP inhibitor, asciminib offers patients and prescribers a more effective and tolerable option compared to bosutinib.

ASCEMBL (Continued)

Conclusion (continued)

Further studies into asciminib's place in therapy for different patient subgroups would strengthen recommendation of the drug as a chemotherapy option. Asciminib's efficacy and safety as an earlier line of therapy or as an alternative in patients resistant (either from mutation or inefficacy) to other TKIs are possible avenues to explore.

References

1. Haznedaroğlu İC, Kuzu I, İlhan O. WHO 2016 Definition of Chronic Myeloid Leukemia and Tyrosine Kinase Inhibitors. Turk J Hae- matol. 2020;37(1):42-47. doi:10.4274/tjh.galenos.2019.2019.0241

2. American Cancer Society. Key Statistics for Chronic Myeloid Leukemia 2022. https://www.cancer.org/cancer/chronic-myeloid- leukemia/about/statistics.html. Accessed February 22, 2022.

3. Réa D, Mauro MJ, Boquimpani C, et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. Blood. 2021;138(21):2031-2041. doi:10.1182/blood.2020009984

4. Cortes J, Quintás-Cardama A, Kantarjian HM. Monitoring molecular response in chronic myeloid leukemia. Cancer. 2011;117 (6):1113-1122. doi:10.1002/cncr.25527

Trastuzumab-Deruxtecan for HER2-Mutant Non-Small-Cell-Lung Cancer: A Review of the DESTINY-Lung01 Trial [1]

By Mark Pulver, PharmD. Candidate Class of 2023, University of Illinois at Chicago
Mentor: Dr. Kirollos S. Hanna, PharmD, BCPS, BCOP, Oncology Pharmacy Manager, M Health Fairview

Background

Lung cancer is the leading cause of cancer deaths worldwide with non-small-cell lung cancer (NSCLC) comprising 85% of lung cancers [2]. Human epidermal growth factor receptor 2 (HER2) is a common tumor marker that is found in a wide variety of different types of cancers. Therapies such as trastuzumab, a HER2 directed antibody, have become a mainstay in therapy in both breast and gastric cancers expressing HER2. In the setting of NSCLC, only approximately 2% of tumors feature mutation of HER2 while up to 35% demonstrate HER2 overexpression [3,4]. Some evidence suggests however that HER2 mutations may be more important in tumorigenesis than overexpression [4]. Mutations of HER2 are most often seen in female patients, non-smokers, and adenocarcinomas [4]. Some evidence does suggest that HER2 overexpression may be associated with worse prognosis in NSCLC [5].
Trastuzumab deruxtecan is an antibody-drug conjugate with a humanized anti-HER2 mAb and a linked topoisomerase I inhibitor. Currently, trastuzumab deruxtecan is approved in the United States for the treatment of HER2 overexpressing breast cancer and overexpressing metastatic gastric adenocarcinomas. The following study assessed the efficacy and safety of Trastuzumab deruxtecan in the setting of metastatic, HER2 mutant, NSCLC refractory to standard treatment [1]. These results are based on one of the two cohorts studied in this trial.

Methods

The DESTINY-Lung01 trial was a multicenter, open-label, two-cohort, phase 2 study to evaluate the efficacy and safety of trastuzumab deruxtecan in patients with HER2-overexpressing or mutant NSCLC. Patients were included in the trial if they had unresectable or metastatic NSCLC which had relapsed during, or refractory to, standard treatment. Patients also had to have one measurable lesion defined by the RECIST criteria and an ECOG score of 0 or 1. HER2 mutations were confirmed via tissue samples analyzed by a local laboratory adhering to CLIA standards. Patients with asymptomatic brain metastases not receiving glucocorticoids or anticonvulsants were included. Those who had been treated with a HER2 antibody with or without drug conjugate were excluded from the trial but prior use of HER2 TKI were included. Additionally, patients with a history or suspected of interstitial lung disease were excluded from the trial.
The primary endpoint of the DESTINY-Lung01 trial was confirmed objective response per the RECIST criteria. Secondary endpoints included the duration of response, disease control (defined as partial response, complete response, or stable disease at 6 weeks), and progression free and overall survival. Adverse drug events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (grade 1-5, 5 being death). Specifically, cases of interstitial lung disease of pneumonitis were adjudicated by an independent committee. Trastuzumab deruxtecan was dosed at 6.4 mg/kg with efficacy and safety results being assessed for all patients receiving at least one dose of trastuzumab deruxtecan.

Results

The average patient in the DESTINY-Lung01 trial was a 60-year-old, white female having failed prior platinum-based therapy with anti-PD/PDL1 treatment. A total of 91 patients were enrolled for treatment. Of the 91 patients included in the trial, 50 patients had an objective response (55%; 95% CI, 44 to 65). Among the 50 patients with objective response, 1 had a complete response (1%) and 49 had a partial response (54%). Overall, 92% of patients (95% CI, 85 to 97) had a reduction in tumor size and disease control.

The duration of response was 9.3 months (95% CI, 5.7 to 14.7), progression free survival was 8.2 months (95% CI, 6.0 to 11.9), and overall survival was 17.8 months (95% CI, 13.8 to 22.1). Among patients with CNS metastasis at baseline (33 patients) progression free and overall survival were 7.1 months (95% CI, 5.5 to 9.8) and 13.8 months (95% CI, 9.8 to 20.9) respectively. A

DESTINY-Lung01 Trial (Continued)

Results (continued)

All 91 patients had at least one adverse event during the trial. Most of the adverse events occurring in patients were grade 1 or 2 with common events including gastrointestinal and hematologic events, decreased appetite, and alopecia. The most common grade 3 events were neutropenia (19%) and anemia (10%). Thirteen patients had grade 5 events, of which two were drug related. Twenty-three patients (25%) discounted therapy related to adverse drug events including 12 cases (13%) of pneumonitis and 5 cases (5%) of interstitial lung disease. Analysis of adjudicated events of interstitial lung disease found occurrence in 24 patients (26%) with 4 patients having grade 3 response and 2 patients having grade 5 responses.

Discussion

The DESTINY-Lung01 trial demonstrated the anticancer activity of trastuzumab-deruxtecan in HER2 mutant refractory NSCLC. Of patients treated with trastuzumab-deruxtecan, 55% achieved a response to chemotherapy with an average duration of response of 9.3 months and overall survival of 17.8 months. Studies demonstrating a positive association with HER2 expression and worsening prognosis are variable but overall 5-year survival of NSCLC is 15% for all stages [1]. Trastuzumab-deruxtecan demonstrated a clinical benefit in an area of treatment that lacks many clinical options at this moment.
The safety of trastuzumab-deruxtecan was consistent with prior clinical trials with 49% of patients experiencing a grade 3 or higher adverse event, which tended to be hematologic or gastrointestinal in nature. The incidence of interstitial lung disease was not predictable and occurred in 26% patients, so it is important to monitor as this may potentially be fatal.
One weakness of this study is the lack of a comparator group which requires further investigation. Additionally further investigation is needed to assess the efficacy of trastuzumab-deruxtecan in patients having received prior HER2 targeted therapy.

References

1. Li BT, Smit EF, Goto Y, et al. Trastuzumab Deruxtecan in HER2-Mutant Non-Small-Cell Lung Cancer. N Engl J Med. 2022;386(3):241-251. doi:10.1056/NEJMoa2112431
2.Mar N, Vredenburgh JJ, Wasser JS. Targeting HER2 in the treatment of non-small cell lung cancer. Lung Cancer. 2015;87(3):220-225. doi:10.1016/j.lungcan.2014.12.018
3. Oh DY, Bang YJ. HER2-targeted therapies - a role beyond breast cancer. Nat Rev Clin Oncol. 2020;17(1):33-48. doi:10.1038/s41571-019-0268-3
4. Mazières J, Peters S, Lepage B, et al. Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. J Clin Oncol. 2013;31(16):1997-2003. doi:10.1200/JCO.2012.45.6095
5. Thibault C, Khodari W, Lequoy M, Gligorov J, Belkacémi Y. HER2 status for prognosis and prediction of treatment efficacy in adenocarcinomas: a review. Crit Rev Oncol Hematol. 2013;88(1):123-133. doi:10.1016/j.critrevonc.2013.03.003

How to Hematology/Oncology: Our Top 5 Tips for Building Student Interest and Engagement in Hematology/Oncology Topics

By: Linda Allworth, Pharm.D. Candidate at UNC Eshelman School of Pharmacy; Matthew Peery, Pharm.D. PGY1 Pharmacy Resident at VCU Health; Erin Hickey Zacholski, Pharm.D., BCOP, Hematology/Oncology Clinical Specialist at VCU Health and Assistant Professor at VCU School of Pharmacy

Over the past few years, the ACCP Student Chapter at the UNC Eshelman School of Pharmacy has grown. Our student leaders noticed that a large proportion of student members had interest in specific clinical areas, and this led to the creation of a more focused space to explore those passions. In spring 2021, we started two Student Practice and Research Networks (S-PRNs), one for hematology/oncology and one for critical care. Designed after ACCP's PRN groups, the goal of S-PRNs is to focus on bringing together students to foster clinical exploration and growth. As one of the original founders and the current student leader of the hematology/oncology PRN, I know it has been a long journey to building student interest and engagement. These are the top 5 tips I have learned throughout the process.

1. **Be interactive!**
   Our most popular event was also our most interactive one! The National ACCP Hematology/Oncology PRN Learner's Committee put together an "Oncology Pharmacy Resources Bootcamp" workshop and we shared the presentation as well as the "break out room" activity with members who were unable to experience the original event. Everyone loved the experience and the hands-on engagement that the "break out room" activity provided. "... it was an awesome idea and I did not expect how effective it would be, especially since that was the first time many of us even saw those databases." - Jorden Mandel, PharmD Candidate.

2. **Keep the playing field level!**

   Before the Oncology Pharmacy Resources Bootcamp workshop, we had tried another event that included a few cases to work though. Students who had more exposure to hematology/oncology through an elective class (only offered PY3 spring) were able to work though the cases faster which seemed to leave the younger students with no prior hematology/oncology exposure discouraged. Remember to focus on the process of learning and understanding and not the speed at which students learn. If possible, aim for layered learning in group events so those with more experience can share their knowledge. If you do decide to give out prizes for individual competitions make sure each student has an equal chance at winning!

3. **Share different types of learning opportunities!**

   Hematology/Oncology is a large field and we realized that some students were overwhelmed and unsure where to start their learning journey. We found that it was meaningful to share information about national organizations (such as HOPA) and encourage membership in the National ACCP PRN. Through this we were able to advertise national journal clubs and CE learning opportunities that went beyond the topics we had explored in our local events. We've also started collaborating with other organizations within the school to encourage new opportunities. Recently we teamed up with the Carolina Association of Pharmacy Students at UNC to provide education about bone marrow transplant and hold a Be The Match swabbing event!

4. **Focus on Key Concepts and Connections!**

   Depending on the day (and topic) some students remain engaged, and others begin to get lost quickly. Returning the focus on key concepts after diving into specific details can help promote retention and give students a chance to re-focus before moving on. Our members have really enjoyed seeing the connections between our events and what they might experience in clinical practice on immersion.

How to Hematology/Oncology (Continued)

5. Give It Time and Don't Give Up!

With students leaving and returning from immersion (IPPEs) each semester, it was very difficult to establish consistent attendance at our events early on. Now, almost a year later, we have a core group of students that show up every time. Get creative with your advertising strategies and don't be discouraged if turnout is low in the beginning.

It is imperative to build student interest and engagement in clinical specialty topics such as hematology/oncology, especially when students may not be exposed to such learning early in their school curriculum. Our S-PRN leaders get the most questions about internships and career opportunities from students who are unsure about what area of pharmacy most interests them. One member remarked that "The Heme/Onc PRN has been a great way to explore the role of a pharmacist in oncology. The PRN has also provided opportunities to learn about the specialty beyond what is covered in the curriculum. I am looking forward to attending future events!" - Sara Jubas, PharmD Candidate. We hope that you can implement these tips to hold successful events and build student interest and engagement in the future.

Asparaginase Therapeutic Drug Monitoring

By: Olivia White, PharmD, PGY-1 Pharmacy Resident, Duke University Hospital
Mentor: Jennifer Thackray, PharmD, BCPS, BCPPS, Pediatric Hematology/Oncology Clinical Pharmacist, Memorial Sloan Kettering Cancer Center

Asparaginase Overview

Asparaginase is an essential chemotherapeutic agent used for pediatric acute lymphoblastic leukemia (ALL) treatment.[1] Additionally, this agent is used in adult patients with ALL based on pediatric-inspired regimens.[2] Asparaginase therapy has demonstrated a significant overall survival benefit in this patient population, and thus it is used as part of several multi-agent, first-line treatment regimens for ALL.[1,2] Asparaginase is an enzyme that actively hydrolyzes L-asparagine into ammonia and aspartic acid. Through this mechanism, the agent starves leukemic cells of exogenous asparagine, which is necessary for protein synthesis. By doing this, the leukemic cells are stalled in the G_1 phase, leading to cell apoptosis.
Asparaginase is unique in nature due to the original product being derived from bacteria. With this formulation being foreign to the human body, asparaginase therapy has been associated with rates of hypersensitivity reactions as high as 76%.[3] Despite hypersensitivity reactions (HSR) and infusion-related reactions (IRR) being a common complication of therapy, the demonstrated survival benefit in this population necessitates the use of this agent. In response to HSRs, patients may develop neutralizing antibodies (NA). NAs may also develop without any clinical manifestations, which is known as 'silent inactivation'. The clinical presentation of an IRR may closely align with the clinical presentation of a HSR, thus making it nearly impossible to delineate between one reaction and the other.

There are currently four formulations of asparaginase in the US market. Due to the high rate of adverse events, the original asparaginase formulation (l-asparaginase) has been replaced by the pegylated version, pegaspargase (Oncaspar®). By favoring this formulation, HSRs are estimated to decrease to ~30%. Another long-acting asparaginase formulation that was FDA-labeled in 2018 for the treatment of pediatric ALL in combination with multi-agent chemotherapy is calaspargase pegol-mknl (Asparlas®). This formulation is only available in the US and only approved for patients < 22 years of age. Adult studies are planned (NCT 04817761), but are currently ongoing. Calaspargase pegol-mnkl is designed with a succinimidyl carbonate (SC) linker that affords a longer half-life and duration of action as compared to pegaspargase (succinimidyl succinate [SS] linker). Both long-acting asparaginase formulations are E.coli-derived and therefore may not be substituted for the other in the event of a HSR.

In addition to the long-acting, E.coli-derived formulations of asparaginase (pegaspargase and calaspargase pegol-mnkl), there are two short-acting formulations that are derived from different sources. These two formulations include asparaginase Erwinia chrysanthemi (Erwinaze®) and a recombinant product, asparaginase Erwinia chrysanthemi-rywn (Rylaze®). These two formulations are recommended for patients that develop an HSR to a long acting E.coli-derived product or for those who demonstrate confirmed silent inactivation (presence of NAs without a clinical HSR).

Generic (Trade) Name	Half-life	Dosing Schedule	Indication	Other Names	Clinical Pearls
LONG-ACTING *E. COLI*-DERIVED FORMULATIONS					
Pegaspargase (Oncaspar®)	5.3 days (IV) 5.8 days (IM)	<22 yr: 2,500u/m^2 IM/IV every 14-21 days ≥ 22 yr: 2,000u/m^2 IV/IM every 14-21 days	First line	SS-PEG' 'peg-asparginase'	Succinimidyl succinate (SS) linker
Calaspargase pegol-mknl (Asparlas®)	16.1 days (IV)	<22 yr: 2,500u/m^2 IM/IV every 14-21 days ≥ 22 yr: 2,000u/m^2 IV/IM every 14-21 days	First line (age ≤ 21 years old)	CAL-PEG' 'SC-PEG'	Succinimidyl carbonate linker (SC)

Asparaginase Therapeutic Drug Monitoring (Continued)

Generic (Trade) Name	Half-life	Dosing Schedule	Indication	Other Names	Clinical Pearls
SHORT-ACTING *E. COLI*-DERIVED FORMULATIONS					
Asparaginase *Erwinia chrysanthemi* (Erwinaze®)	16 hours	25,000 units/m^2 IM/IV 3 times weekly x 6 doses for every planned long-acting dose	Second line		Currently on national shortage
Asparaginase *Erwinia chrysanthemi* (recombinant)-rywn (Rylaze®)	18.2 hours	24 mg/m^2 IM (only) every 48 hours x 6 doses for every planned long-acting dose	Second line	'RC-P' 'recombinant crisantaspase' 'JZP-458'	Long shelf-life (33 months): Recombinant technology via *Pseudomonas fluorescens* platform

Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) has been explored in patients receiving asparaginase for two specific purposes. First, due to the high risk of HSR and IRRs, TDM may be implemented to delineate between the two. Patients with a true HSR will have NAs present and patients with an IRR will not. Hopefully through this, we can determine if therapy may be continued or if there is a need to change formulations. Secondly, through TDM, we hope to monitor for silent inactivation of asparaginase in patients.

Due to the risk of HSRs and IRRs associated with asparagine use, it is natural to consider the administration of pre-medications to prevent these adverse events. However, this is currently of clinical controversy[4,5,6]. Pre-medications would halt or mitigate the HSR/IRR that could cause discomfort to the patient; however, it would also potentially mask the formation of NAs, leaving clinicians unsure about the efficacy of the drug. Per the 2022 NCCN Guidelines for both adult and pediatric ALL patients, pre-medications may be considered prior to asparaginase administration. This is largely driven by the desire to reduce the number of patients switched to a short-acting formulation. The reason clinicians find this significant is due to the ongoing asparaginase *Erwinia chrysanthemi* shortage. Since our primary alternative option is currently in low supply and silent inactivation is generally thought to be of low incidence compared to the rate of IRRs, the guidelines allow for the administration of pre-medications if deemed clinically necessary.

Nadir serum asparaginase activity (NSAA) levels are believed to be correlated with asparagine depletion and it is generally thought that a threshold of 0.1 IU/mL defines clinical significance and therefore efficacy of the asparagine product. NSAA levels aid clinicians in determining the presence of NAs in patients with or without clinical manifestations of an IRR/HSR because it is assumed the reason for low NSAA levels (in the 7-10 days following a dose) is due to the presence of NAs (anti-asparaginase antibodies). Measuring asparaginase activity levels is the least technically complex with the highest reproducibility and reliability. The assessment is used by completing a reaction with indooxine to measure asparaginase activity. Thus, through this assay, the patients can have an estimated concentration of asparaginase present. Availability of NSAA levels is supported by two laboratories in the US: Granger Genetics and Next Molecular Analytics. The turnaround time is 2-4 days.

In general, a NSAA of ≥ 0.1 IU/mL (drawn 7-10 days following pegaspargase administration) is interpreted as a desirable level of activity and therefore is deemed adequate for asparagine depletion. Other cutoffs exist in the literature and are typically based on the length between drug administration, formulation administered, and lab variability. Based on the half-life of the administered formulation, the timing of obtaining the level can differ. It is generally accepted for pegaspargase, a 7-day level can define efficacy of treatment (NSAA level ≥ 0.1 IU/mL). However, some institutions may draw a NSAA level later as well (Day 14) to ensure levels ≥ 0.1 IU/mL for the entire 14 day period following a dose.

Asparaginase Therapeutic Drug Monitoring (Continued)

Consensus Guideline Recommendations for NSAA Assessments[7]:
1. The best and most reliable indicator for asparaginase efficacy is a nadir serum asparaginase activity (NSAA) level.
2. NSAA levels ≥ 0.1 IU/mL seem to be a safe target level to ensure therapeutic benefit.
3. Although useful, anti-asparaginase antibodies and asparagine measurements are difficult laboratory assays and have not been validated for routine clinical use.

HSRs are characterized based on the Common Terminology Criteria for Adverse Events v4.03 (CTCAE) classification. Studies have demonstrated that HSRs and antibody formation can be associated with any grade of reaction and thus any grade reaction should be considered clinically significant. The guideline recommendations and associated reactions are listed below for your reference.

CTCAE Criteria by Grade		Management Recommendations[1,2,7]
1	Transient flushing or rash, drug fever < 38 degrees, no intervention	Monitor NSAA level within 7 days, switch preparations as indicated
2	Intervention or interruption, symptomatic treatment, prophylaxis for ≤ 24 hours	
3	Prolonged reaction, symptom recurrence following initial improvement, hospitalization	Switch asparaginase preparations without need to check NSAA levels (neutralizing antibodies usually present)
4	Life-threatening; urgent intervention	

If a switch to a short-acting asparaginase formulation is clinical indicated (overt HSR or Day 7 NSAA < 0.1 IU/mL), either product is appropriate for use.

If silent inactivation is suspected, TDM strategies are fairly similar. Silent inactivation is named due to the development of neutralizing anti-drug antibodies without the presence of a clinical HSR. Through this production, drug is then rendered ineffective without the development of overt allergic symptoms, thus making it 'silent' in nature. Per the 2016 consensus guidelines, screening for silent inactivation should be considered in all patients undergoing therapy for ALL with asparaginase. Especially, this is believed to be true in patients undergoing therapy for relapsed leukemia or those with specific gaps of care. It is generally recommended to obtain the NSAA level within 7 days of the first dose. If the level is detectable, but < 0.1 IU/mL, activity should then be rechecked at day 14 to ensure adequate NSAA levels were maintained. If NSAA levels are <0.1 IU/mL following the day 14 level, this could potentially be considered due to silent inactivation or accelerated clearance. The mechanism of accelerated clearance and its management is generally less understood; however, switching to a short-acting agent is an option some clinicians use in practice.

For those receiving asparaginase *Erwinia chrysanthemi*, monitoring for these patients would occur at the 48-hour mark, based on the formulation's shorter half-life. However, pre-medications are not recommended prior to asparaginase *Erwinia chrysanthemi* and therefore monitoring NSAA levels is not routine.

Asparaginase Therapeutic Drug Monitoring (Continued)

Consensus Guideline Recommendations for Silent Inactivation Monitoring[7]:	
1	Although the rate of silent inactivation is rare, all patients should undergo TDM for silent inactivation 7 days after administration of pegaspargase.
2	Silent inactivation is defined as a day 7 level below 0.1 IU/mL and is thought to be due to the formation of neutralizing antibodies.
3	Measure NSAA levels within 7 days of the first dose of pegaspargase in induction and following every reinduction after a gap in asparaginase administration.
4	Determined by the planned pegaspargase schedule, consider confirmation of a low or undetectable level prior to switching from long-acting to short-acting formulations.

When switching to a short-acting alternative preparation due to either a clinically overt HSR or NSAA level < 0.1 IU/mL, in is critical to consider the differences in the products available. Asparaginase *Erwinia chrysanthemi* has been on and off shortage in the United States for several years due to complications with manufacturing. It may be given IV or IM on a Monday-Wednesday-Friday schedule, potentially making it more patient and ambulatory care clinic friendly. Asparaginase *Erwinia chrysanthemi*-rywn is the newest formulation to the market. This product is administered every 48 hours x 6 doses, potentially making this more difficult for outpatient clinics to coordinate with weekend hours, especially with the potential for anaphylaxis with drug administration. However, due to the persistent shortage of asparaginase *Erwinia chrysanthemi*, many hospitals have extended their formulary, ambulatory clinic hours, and weekend staff to accommodate. Therefore, when considering therapeutic alternatives to pegaspargase, it is key to consider administration schedule and availability of this product.

In conclusion, data supporting TDM of NSAA levels with pegaspargase continues to grow, especially in those patients receiving pre-medications. Based on current guidance, ongoing drug shortages, and developed monitoring strategies, all patients with ALL receiving asparaginase should receive TDM monitoring. However, there are still plenty of opportunities for continued growth and therapeutic optimization. These specifically include continued pharmacokinetic analyses of the asparaginase formulations to ensure proper dosing and monitoring strategies. With these studies in addition to continued TDM efforts, we can hopefully optimize patient's chemotherapeutic regimens to provide individualized, patient-centered medicine.

References

1. Brown P, Inaba H, et al. Pediatric Acute Lymphoblastic Leukemia. NCCN. 2021 Oct; 1.2022.
2. Brown P, Bijal S, et al. Acute Lymphoblastic Leukemia. NCCN. 2022 Jan; 4.2021.
3. Marini BL, Brown J, Benitez L, et al. A single-center multidisciplinary approach to managing the global Erwinia asparaginase shortage. Leuk Lymphoma. 2019 Dec;60(12):2854-2868.
4. Cooper SL, Young DJ, Bowen CJ, et al. Universal premedication and therapeutic drug monitoring for asparaginase-based therapy prevents infusion-associated acute adverse events and drug substitutions. Pediatr Blood Cancer. 2019 Aug;66(8):e27797.
5. Losasso M, Bostrom B, Messinger Y. Retrospective cohort study monitoring PEG-asparaginase activity in acute lymphoblastic leukemia patients with and without premedication. F1000Res. 2019 Jul 4;8:1007.
6. Stock W, Luger SM, Advani AS, et al. A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403. Blood. 2019 Apr 4;133(14):1548-1559. doi: 10.1182/blood-2018-10-881961. Epub 2019 Jan 18. Erratum in: Blood. 2019 Sep 26;134(13):1111.
7. Van der Sluis IM, Vrooman LM, Pieters R, et al. Consensus expert recommendations for identification and management of asparaginase hypersensitivity and silent inactivation. Haematologica. 2016 Mar;101(3):279-85.
8. Kloos RQH, Pieters R, Jumelet FMV, et al. Individualized Asparaginase Dosing in Childhood Acute Lymphoblastic Leukemia. J Clin Oncol. 2020 Mar 1;38(7):715-724.
9. Asselin B, Rizzari C. Asparaginase pharmacokinetics and implications of therapeutic drug monitoring. Leuk Lymphoma. 2015;56(8):2273-80.

A Day in the Life of an Oncology Pharmacy Resident

By: Emily Viehl, PharmD, PGY2 Oncology Pharmacy Resident, Froedtert & the Medical College of Wisconsin, Milwaukee, WI
Mentor: Farah Raheem, PharmD, BCOP, Clinical Oncology Pharmacist, Mayo - Clinic, Phoenix, AZ

Background & Education

I was born and raised in a suburb of Chicago, Illinois, received my undergraduate degree from the University of Wisconsin – Madison, and made my way back to Chicago for my Doctor of Pharmacy degree at the University of Illinois at Chicago (UIC) College of Pharmacy. Upon graduation, I stayed on at UIC as a PGY1 pharmacy practice resident then went on to Froedtert & the Medical College of Wisconsin for my PGY2 in oncology. My path seems clear-cut now, but it wasn't always. Choosing oncology, specifically, was not an easy decision. The truth is that I spent 3 years in pharmacy school having no direction in what I wanted to do until I was assigned to rotate through the hematology/BMT service at UIC as an APPE student. Later, I realized that this was the only rotation during which I was truly excited to wake up and go to each day. I loved the interprofessional teamwork, the patients I cared for, and the rapidly evolving oncological therapies that continue to improve patients' lives. Now, as a current PGY2 oncology pharmacy resident, I'm here to share what a typical day looks like working as a pharmacy resident in this field.

Mentorship

When I was a student and a PGY1 resident, I met many people who have made a positive impact on my academic and future career and helped me grow professionally. Mentors can be officially assigned to you during your training, but I recommend finding individuals who inspire you, motivate you, and are willing to offer advice and guidance throughout your career. I was afforded the opportunity of working with many mentors at UIC who helped in my decision-making for residency programs and oncology as a career as well as supported me every step of the way. At Froedtert, I have assigned an official mentor to ensure I am meeting expectations and support my PGY2 journey. However, I was lucky to also have met numerous unofficially assigned mentors, including preceptors, who have been such a big part of my professional growth as a trainee and a future clinical oncology pharmacist. They have shared with me job opportunities, reviewed my CV, invested in my success, and challenged me to grow and excel. Take advantage of the opportunities afforded to you as a trainee to build a network of life-long mentors and colleagues and continue to build on these relationships even after leaving your training site. I am certain that regardless of where I end up, I will be able to reach out to my mentors from residency for continued guidance and support. Your current mentors will one day be your colleagues and those relationships will become increasingly important as you kick start your career after residency.

Day-To-Day Activities & Life-Work Balance

The easiest way to describe my day-to-day activities is to say that they can be both similar and different each day. Clinical rotations are a constant daily activity. This week, I am rotating through the outpatient hematology and bone marrow transplant clinic. I interpreted tacrolimus levels and made recommendations to the providers for dose adjustments, called patients for adherence and toxicity monitoring of oral chemotherapy, and attempted to answer a litany of questions from nurses and providers. I did what feels like a hundred other things today, too. Some are more exciting, like preparing for my lecture at the pharmacy school about chronic leukemias and working on data collection for my research project. Some activities can be mundane, like filling out Pharmacademic evaluations, preparing for topic for the next day, documenting duty hours, and renewing my pharmacist license. I also called my mom, made myself dinner and watched the newest bachelor episode. The day-to-day life of a pharmacy resident is a constant balance between meeting your residency requirements, taking care of patients, and taking care of yourself. The balance is far from perfect each day, but it's important to remember that the other things matter, too.

A Day in the Life of an Oncology Pharmacy Resident (Continued)

Challenges & Resilience

The previous paragraph probably implies that every day is straightforward and that motivation is always easy to come by. It absolutely is not. Residency has constantly challenged me intellectually, emotionally, and physically. There is a frequent juxtaposition as a resident between being a learner and a teacher; autonomy and dependence; compliments and critique. It is exhausting. You'll hear people refer to resilience as a buzz word for how, we as learners, need to get through the residency years. I wish I had a perfect recipe for how to be resilient and motivated and cheerful all the times. The reality is that we are human beings who handle stress and cope with challenging situations differently. The best advice I can provide is to listen to your own needs, find your own motivation, and give yourself some grace when things don't work out as planned. For myself, it is being intentional with scheduled PTO days, having a routine for my work days, and maintaining contacts with friends and co-residents to lean on during tough times.

Looking Ahead

With only 4 months left of my oncology residency, it is easy to get lost in thinking about life after residency. I don't know exactly what that will look like yet, but I'm unbelievably excited. I chose this career path for a reason and I know I made the right decision. Despite the challenges and the countless sleepless nights, this residency prepared me to become an independent and a competent oncology pharmacist. PGY2 is meant to challenge you, help you grow personally and professionally, and make you uncomfortable at times. Those times when I was most uncomfortable, though, were the times I learned the most and became the pharmacist I am today. I'm excited for the future of oncology and oncology pharmacy practice. There are a multitude of areas where we can make a huge impact in patient care, research, drug development, and academia.

Activities and Announcements

Promotions

Sarah M Hayes: Hematology/Oncology Clinical Pharmacy Specialist, North Memorial Health, Minneapolis, MN
Deborah Hass: Retired after 42 years of practice at many different locations throughout the United States; mostly recently West Coast University Los Angeles
Lisa Holle: Clinical Professor, UConn School of Pharmacy
Roshawn Watson: Senior Director, Clinical Development, Bicycle Therapeutics
Olivia White: PGY-2 Oncology Pharmacy Resident at Duke University Hospital

Awards

Onye Ononogbu: Completion of ACCP Research and Scholarship Certificate Program
Jennifer Thackray: Institute for Safe Medication Practices (ISMP) Cheers Award – KIDs List Collaborative, Commissioned by the Pediatric Pharmacy Association

Publications

Katie Gatwood:

Bobbitt LJ, Satyanarayana G, Van Metre Baum L, Nebhan CA, Kassim AA, **Gatwood KS**. Evaluation of healthcare-associated infection rates in patients with hematologic malignancies and stem cell transplantation during the coronavirus disease 2019 (COVID-19) pandemic. Antimicrobial Stewardship & Healthcare Epidemiology. 2022;2(1):e11.

Kirollos Hanna:

- **Hanna KS**. Larson S, Nguyen J, et al. The Role of Enfortumab Vedotin and Sacituzumab Govitecan for Advanced Bladder Cancer. *Am J Health Syst Pharm*. 2021: zxab464 [epub ahead of print]
- **Hanna KS,** Larson S, Nguyen J, et al. Updates in the management of relapsed/refractory multiple myeloma: *J Oncol Pharm Pract.* 2021; 27(6):1477-1490.

Sarah Hayes:

- Acquisto N, Beavers CJ, Bolesta S, Buckley MS, Finch CK, **Hayes SM**, Johnson ST, Kane-Gill SL, Lat I. ACCP White Paper: Development and Application of Quality Measures of Clinical Pharmacist Services Provided in Inpatient/Acute Care Settings. *Journal of the American College of Clinical Pharmacy* 2021; 4(12): 1601-1617.
- **Hayes SM**, Wiese C, and Schneidewend RJ. Tumor Lysis Syndrome Following a Single Dose of Nivolumab for Relapsed Small-Cell Lung Cancer. *Case Reports in Oncology* 2021; 14: 1652-1659.

Donald C. Moore:

- **Moore DC**, Elmes JB, Gebru T, Lavery LA, Pellegrino A, Plesca D. Implementation, utilization, and evaluation of a pharmacist-driven romiplostim dosing service for patients with immune thrombocytopenia at a multisite cancer centre. *J Oncol Pharm Pract.* 2022. Manuscript published online ahead of print.
- Arnall JR, Maples KT, Harvey RD, **Moore DC.** Daratumumab for the treatment of multiple myeloma: a review of clinical applicability and operational considerations. *Ann Pharmacother.* 2021. Epub ahead of print.
- Crawford J, **Moore DC**, Morrison VA, Dale D. Use of prophylactic pegfilgrastim for chemotherapy-induced neutropenia in the US: a review of adherence to present guidelines for usage. *Cancer Treat Res Commun.* 2021; 29:100466.
- **Moore DC**, Soni AC, Hu B, Smith ET, Levine J, Moyo TK, Jacobs R, Ghosh N, Park SI. Rituximab, lenalidomide, and ibrutinib in relapsed/refractory primary cutaneous diffuse large B-cell lymphoma, leg type. *Br J Haematol.* 2021. Epub ahead of print.
- Ciolek AM, Arnall J, **Moore DC**, Palkimas S, Der-Nigoghossian J, Dane K. Eptacog beta for bleeding treatment and prevention of congenital hemophilia A and B with inhibitors: a review of clinical data and implications for clinical practice. *Ann Pharmacother.* 2021. Epub ahead of print.
- **Moore DC.** Bruton tyrosine kinase inhibitors for Waldenström macroglobulinemia: a review. *J Oncol Pharm Pract.* Epub ahead of print.

Onye Ononogbu:

Apostolidou E, Lachowiez C, Juneja H, Qiao W, **Ononogbu O**, et al. Clinical outcomes of patients with newly diagnosed acute lymphoblastic leukemia in a county hospital system. *Clin Lymphoma Myeloma Leuk.* 2021; Epub ahead of print.

Activities and Announcements (Continued)

Publications (continued)

Farah Raheem:

Raheem F, Ofori H, Simpson L, Shah V. Abemaciclib: the first FDA approved CDK4/6 inhibitor for the adjuvant treatment of HR+ HER2- early breast cancer. *Ann Pharmacother.* 2022. Epub ahead of print.

Presentations

Sarah Hayes: Rodgers JE, **Hayes SM**, Skersick P. Practical Considerations in Cardio-Oncology Drug Interactions: A Case-Based Series. International Cardio-Oncology Society (ICOS) International Weekly Webinar Series.

Donald Moore:

- "Updates on Immunotherapy and Best Pharmacy Practice for Multiple Myeloma," American College of Clinical Pharmacy/ American Society of Health-System Pharmacy BCOP Clinical Session. December 15, 2021.
- "Drug Interactions Relevant in Hematology/Oncology Patients," Area Health Education Center (AHEC) 29th Annual Wilson Medical Center Pharmacy Continuing Education Symposium. Virtual. November 11, 2021.
- "Updates in the Management of Acquired Thrombotic Thrombocytopenic Purpura," Atrium Health Clinical Pharmacy Symposium. Charlotte, NC. November 9, 2021.
- "New Drug Updates: Investigational Therapeutics in the Pipeline," JADPRO Live. Virtual. October 16, 2021.
- "Management of Immune Thrombocytopenia: Examining New Therapies and Advancements in Treatments – Featuring a Patient Perspective," *Pharmacy Times* Continuing Education™. Live Virtual Symposium. Cranbury, NJ. September 30, 2021.
- "A review of the Bruton Tyrosine Kinase inhibitors in B-cell malignancies," The Journal of the Advanced Practitioner in Oncology (JADPRO) Podcast. Virtual. August 2021.
- **Georgeann Vandyke:** ASHP Podcast "ISMP targeted medication safety practices for hospitals"

Other Notable Achievements

Kirollos Hanna: elected to serve on the NCCN Advanced or Metastatic Bladder Cancer Quality Initiative Request for Proposals Development Team under the NCCN's Oncology Research Program

Facebook and Twitter Pages

Follow us on Facebook and on Twitter or @HemOnc_ACCP for our posts!

Please send Claire Schumann (claire.schumman@nm.org) and David Quach (david2quach@gmail.com) articles and ideas you would like to see posted! If you have ideas for greater social media engagement we would especially enjoy hearing from you!

Ideas for the Newsletter

Please submit any ideas you may have for improving the newsletter to the PRN leadership or email Jared Vega (jvega@cedarville.edu) and David Quach (david2quach@gmail.com). If you would like to be featured in the fall edition, whether it be a member spotlight, or a clinical write-up, let us know!

Thank you!

The PRN leadership thanks everyone who has served on our various committees as well as our members who engages on a regular basis!