PEER PERSPECTIVES
IN THE TREATMENT OF ALL

ISSUE 3 ALL

INSIDE THIS ISSUE:

- Reviewing the role of asparaginase therapy in the treatment of AYA patients with ALL/LBL
- Discussing AYA as a special population with unique treatment challenges, including perceptions of greater toxicities with asparaginase use
- Emphasizing the importance of using asparaginase-based protocols in AYA patients on clinical outcomes
- Exploring the efficacy, safety, and dosing schedules for an ALL/LBL asparaginase treatment option

FEATURING

Leidy Isenalumhe, MD, MS[a]
Director of Clinical Operations in the Department of Hematologic Malignancies, Moffitt Cancer Center, Tampa, Florida

> *"Asparaginase has been used in pediatric-based regimens for a very, very long time.[1] It is actually one of the backbones for ALL treatment.[1] Data have shown us that giving asparaginase-based regimens to adolescents and young adults helps with improving overall disease-free survival rates.[2,3]"*
>
> **— Leidy Isenalumhe MD, MS**

Peer Perspectives in ALL: *Asparaginase Therapy in AYA Patients*

ALL=acute lymphoblastic leukemia; AYA=adolescents and young adults; B-ALL=B-cell acute lymphoblastic leukemia; CI=confidence interval; DFS=disease-free survival; *E. coli*=*Escherichia coli*; IM=intramuscular; LBL=lymphoblastic lymphoma; NCI=National Cancer Institute; NSAA=nadir serum asparaginase activity; PEG=polyethylene glycol; Q48=every 48 hours; U=unit.

[a]Leidy Isenalumhe is a paid consultant of Jazz Pharmaceuticals. This content is intended for informational purposes only and is not a substitute for your clinical knowledge or professional judgment. The views and opinions expressed in this article are those of the author and Jazz Pharmaceuticals and do not necessarily reflect the opinions of the Moffitt Cancer Center.

PEER PERSPECTIVES IN THE TREATMENT OF ALL

WITH **LEIDY ISENALUMHE, MD, MS**

Q. What role does asparaginase play in the treatment plan for your AYA patients with ALL/LBL?

Asparaginase has been used in pediatric-based regimens for a very long time and is one of the backbones for ALL treatment.[1] When treating AYA patients, my approach is to typically give asparaginase-based therapy. There would have to be a contraindication or serious toxicity for us not to proceed with using asparaginase-based regimens in AYA patients. I think that there are enough data out there to show that asparaginase-based regimens may be safe to give to our patients and that outcomes can be better for AYA patients.[2-4] If we can provide these specific regimens to our pediatric patients while also managing them for toxicities, then we can do this in our AYA patients.[5]

Q. Can you expand on the importance of asparaginase-based regimens in AYA patients and how these regimens affect their clinical outcomes?

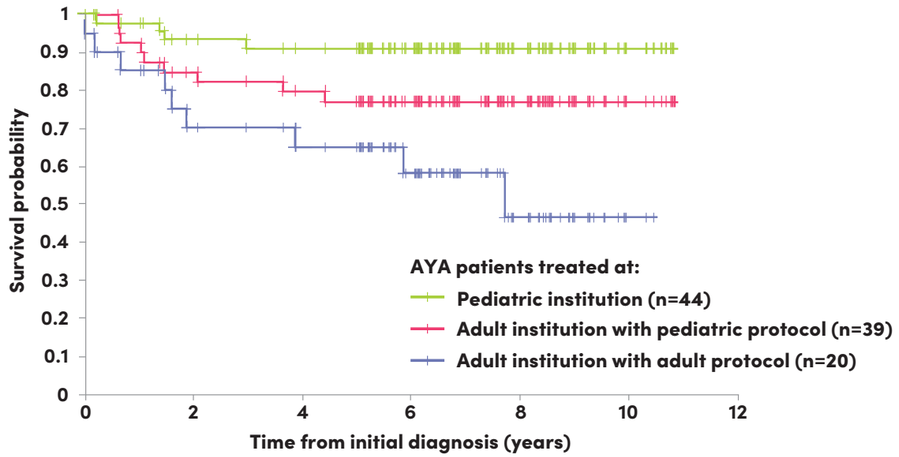
We know that asparaginase is associated with improved clinical outcomes, and this includes our AYA patients.[2,3] Removing asparaginase can worsen outcomes in these patients, and is something we see in practice often.[4] The current data show that asparaginase-based regimens in AYA patients result in greater disease-free survival and overall survival compared with AYA patients who receive less asparaginase as a result of using adult regimens.[2,3,6] We also know the importance of receiving all prescribed asparaginase doses, since missing asparaginase doses can negatively impact survival outcomes.[4]

Estimated 3-year overall survival in CALGB patients aged 16 to 29 years[3]

Pediatric regimen:		Adult regimen:
73% (95% CI: 68%–78%)	vs	**58%** (95% CI: 52%–64%)

Specifically, recent studies, such as the CALGB 10403 trial, have shown better overall survival and event-free survival rates in AYA patients who were treated with full asparaginase-based protocols when compared with their historical controls.[3] Ultimately, the goal is for my AYA patients to be cured without having to experience a relapse.

OVERALL SURVIVAL FOR AYA PATIENTS WITH ALL TREATED BY LOCUS OF CARE AND PROTOCOL TYPE[6]



"Removing asparaginase and missing doses from treatment regimens can have negative outcomes, including lower disease-free survival.[2,4] I don't want to decrease the amount of asparaginase my patients are receiving. So, if they experience a hypersensitivity reaction, I will find an alternative to compensate for any potential lack of asparaginase in their protocol. Ultimately, the goal is for my AYA patients to be cured without having to worry about a relapse."

— Leidy Isenalumhe, MD, MS

Q. How often are pediatric protocols for asparaginase therapy used in AYA patients with ALL/LBL?

If my AYA patients are getting treated at a pediatric center, they will most likely be receiving an asparaginase-based treatment. I believe that is the standard for treatment in pediatric patients who have ALL/LBL. Additionally, when considering treatment options, I will show my patients the "for and against" arguments for these specific regimens by sharing the data. I will specifically show the data that supports the use of these regimens in AYA patients. Current data shows that AYA patients treated with asparaginase-based protocols have higher overall survival outcomes.[2,3,6]

I personally believe that asparaginase-based regimens make a difference for my AYA patients.

Q. What would you identify as unique challenges or factors of consideration when making treatment plans for your AYA patients?

It's important to remember that these patients have lives. They may have to support their families or have children that they are solely responsible for taking care of. We have to look at the schedule for the regimen they are on, when they need to come back for follow-up visits, and how often. Fertility is also something to consider within the AYA patient population. My AYA patients are sometimes concerned with how treatment may affect their likelihood to have children in the future. I will have these conversations early on to help address any misconceptions my patients may have regarding their treatment, while also making sure these regimens can be integrated into their lives.

Q. In your practice, what safety events do you look for when using asparaginase-based regimens in your AYA patients?

There is a perception that if patients are outside of the pediatric age group, and are younger than 39 years, they will experience an increase in toxicities with asparaginase, but data shows us that treatment with a pediatric regimen in AYA patients up to 40 years of age is feasible.[7] In my practice, I typically see toxicities like transaminitis, clotting, bleeding, and pancreatitis. Serious toxicities like these may impact continued asparaginase use in these patients and may result in discontinuation. It's important to remember that anyone receiving an asparaginase-based regimen may be at risk for toxicity and hypersensitivity, including our AYA patients, and should be managed appropriately.[2] Luckily, we have strong support from nurses who are well-trained in monitoring for and managing these safety events, including hypersensitivity reactions.

PEER PERSPECTIVES IN THE TREATMENT OF ALL

Q. How important is it for your patients to continue asparaginase-based regimens in the event of hypersensitivity?

It is very important for my patients to continue and maintain their asparaginase-based regimen. My decision to switch treatments based on hypersensitivity is fueled by my desire for my patients to receive and maintain all of their asparaginase doses.[2,8] I will always switch to another asparaginase-based option instead of rechallenging in cases of hypersensitivity so that patients can continue their regimen to compensate for any potential lack of asparaginase. If a patient experiences a hypersensitivity reaction due to a drug that is a part of their regimen, I typically will not give them that drug again. I would switch to an alternative asparaginase as soon as clinically possible, ideally within 48 to 72 hours, in order to continue the regimen.[9] We know the data tell us that missing asparaginase doses has a negative impact on disease-free survival.[4] For this patient population, removing asparaginase from their regimen can result in worse outcomes, which is why we prefer to switch them to an alternative asparaginase to continue the asparaginase regimen.[9]

> *"We advocate by showing the important data. We know that receiving decreased amounts of asparaginase may lead to inferior survival rates.[4] We just have to show the data while continuing to educate our AYA patients that these regimens truly make a difference."*
>
> **— Leidy Isenalumhe, MD, MS**

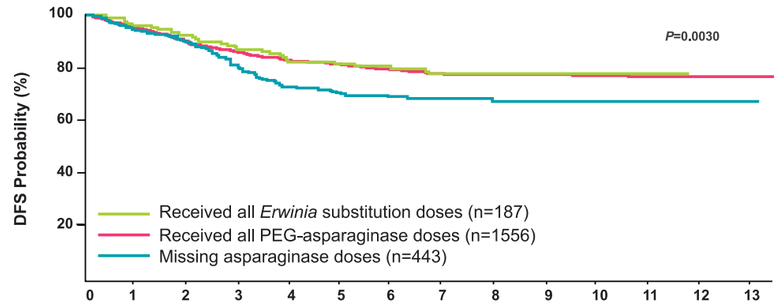
Q. How does RYLAZE differ from other asparaginases?

Unlike *E. coli* asparaginase, RYLAZE is derived from *Erwinia* and has minimal immunologic cross-reactivity to *E. coli*-derived asparaginases.[10] Therefore, my patients who may have developed a hypersensitivity reaction to *E. coli*-derived asparaginase can switch to an alternative asparaginase to continue their regimen.[9]

Q. How does RYLAZE allow your AYA patients to maintain asparaginase regimens?

Treatment with an alternative *Erwinia* asparaginase has been crucial in replacing any potential missed asparaginase doses so they can receive all prescribed doses based on their protocol.[4,11] This is really important as it helps to allow for completion of their regimen. In a compassionate-use trial, 147 AYA patients were switched to *Erwinia* asparaginase following hypersensitivity to *E. coli* asparaginase.[12] Hypersensitivity to *Erwinia* asparaginase was reported in 10.9% of patients ≥16 years of age to <40 years of age (n=16/147) compared with 15.1% in patients ≤10 years of age (n=81/537).[12] The majority of AYA patients (73%) were able to complete their planned course of asparaginase therapy with *Erwinia* asparaginase.[12] Adverse event profiles with asparaginase-based regimens have also been evaluated in AYA patients to determine whether age-related increases in certain toxicities may limit the use of pediatric asparaginase-based regimens in AYA patients.[7]

DISEASE-FREE SURVIVAL OF NCI HIGH-RISK B-ALL PATIENTS STRATIFIED BY ASPARAGINASE RECEIVED[4]



OPTIMIZED DOSING PROVIDES SUSTAINED ASPARAGINASE ACTIVITY THROUGHOUT THE ENTIRE COURSE OF TREATMENT[13]

Proportion of patients with NSAA ≥0.1 U/mL by simulation[13]

RYLAZE IM Dosing Options	Trough Sampling Time	Proportion With NSAA ≥0.1 U/mL (95% CI)[a]
Q48 25 mg/m²	48 hours	96.0% (94.4%-97.2%)
Monday morning, Wednesday morning, and Friday afternoon 25/25/50 mg/m²	Friday afternoon: 58 hours after 25 mg/m² Wednesday morning dose[b]	91.6% (90.4%-92.8%)
	Monday morning: 67 hours after 50 mg/m² Friday afternoon dose[c]	91.4% (90.1%-92.6%)

[a]Based on 2000 virtual subjects.[13]
[b]Based on maximum interval of 58 hours between the Wednesday morning and Friday afternoon doses.[13]
[c]Based on maximum interval of 67 hours between the Friday afternoon and Monday morning doses.[13]
Activity of ≥0.1 U/mL has been demonstrated to correlate with asparagine depletion and serum levels that predict clinical efficacy.[1,14]

Approved dosing is based on the RYLAZE AALL1931 Study.[10,13] In collaboration with Children's Oncology Group, the AALL1931 study was an open-label, multicohort, multicenter trial that evaluated the efficacy and safety of RYLAZE administered intramuscularly as part of a multiagent chemotherapeutic regimen for 167 ALL and LBL patients aged 1-25 years with hypersensitivity to *E. coli* asparaginase, to demonstrate that at least 90% of patients could achieve and maintain NSAA≥0.1 U/mL.[10,13]

When comparing the adverse event profile experienced by patients ≥16 years of age in the COG AALL0232 trial with that of AYA patients enrolled in the CALGB 10403 trial, similar toxicities were observed in both cohorts, with no correlation between increased rate of serious (Grade 3 or 4) toxicities and not completing treatment.[7] These outcomes suggest pediatric-inspired regimens are tolerable in AYA patients up to 40 years of age.[7]

RYLAZE's 25-25-50 mg/m² IM dosing regimen also allows for patients to avoid weekend infusions, which can be challenging for patients who have complicated schedules, like my AYA patients.[13] So in addition to helping support completion of asparaginase regimens, RYLAZE offers flexibility with the approved dosing options.[10,13]

> *"If a patient were to experience a hypersensitivity reaction to* E. coli *asparaginase, we switch to RYLAZE. This is so patients can continue to receive all asparaginase doses since we know how important that is for clinical outcomes."*
>
> **— Leidy Isenalumhe, MD, MS**

Indication

RYLAZE is indicated as a component of a multi-agent chemotherapeutic regimen given by intramuscular injection for the treatment of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) in adult and pediatric patients 1 month or older who have developed hypersensitivity to *E. coli*-derived asparaginase.

IMPORTANT SAFETY INFORMATION

Contraindications

RYLAZE is contraindicated in patients with: history of serious hypersensitivity reactions to *Erwinia asparaginase*, including anaphylaxis; history of serious pancreatitis during previous asparaginase therapy; history of serious thrombosis during previous asparaginase therapy; history of serious hemorrhagic events during previous asparaginase therapy; or severe hepatic impairment.

RYLAZE®
asparaginase erwinia chrysanthemi (recombinant)-rywn
for injection 10mg/0.5mL per vial

Please see additional Important Safety Information on page 7. Please CLICK HERE for full Prescribing Information.

RECOMMENDED DURATION OF RYLAZE DOSING TO REPLACE ONE LONG-ACTING ASPARAGINASE DOSE[13]

When RYLAZE Is Administered	Recommended Duration of RYLAZE to Replace 3 Weeks of Asparaginase Coverage (Calaspargase Products)	Recommended Duration of RYLAZE to Replace 2 Weeks of Asparaginase Coverage (Pegaspargase Products)
25 mg/m^2 intramuscular every 48 hours	Replace 1 dose of calaspargase pegol products with 11 doses of RYLAZE	Replace 1 dose of pegaspargase products with 7 doses of RYLAZE
25 mg/m^2 intramuscular on Monday morning and Wednesday morning, and 50 mg/m^2 intramuscular on Friday afternoon*	Replace 1 dose of calaspargase pegol products with 9 doses of RYLAZE	Replace 1 dose of pegaspargase products with 6 doses of RYLAZE

*Administer the Friday afternoon dose 53 to 58 hours after the Wednesday morning dose.[13]

The table above shows the number of RYLAZE dosages recommended for the intended duration of treatment for replacement of:

-3 weeks of asparaginase coverage (1 dose of calaspargase pegol products) or

-2 weeks of asparaginase coverage (1 dose of pegaspargase products)

See the full prescribing information for the long-acting asparaginase product to determine the total duration of administration of RYLAZE as replacement therapy.[13]

Q. When your patients experience hypersensitivity to *E. coli* asparaginase, how often do you switch to RYLAZE?

When patients receiving treatment with *E. coli* asparaginase experience a hypersensitivity, they are switched to receiving RYLAZE. We don't rechallenge again in these patients. I am still careful when introducing RYLAZE into a patient's regimen because they may still experience hypersensitivity when on it.[2,13]

Q. How do you, along with other physicians, advocate for the importance of utilizing and maintaining asparaginase-based regimens so that AYA patients receive all doses?

I advocate by specifically showing the data on the importance of these regimens on disease-free survival. We also advocate for the use of asparaginase-based protocols by partnering with different community institutions to help comanage patients. This is because community centers may not have the resources (resources for checking labs, access to asparaginase-based regimens, etc) needed to treat AYA ALL patients. We do well in comanaging these patients together and making sure that they are on an asparaginase-based regimen where they can continue to receive all their doses. In recent years, there has been increased education on why these regimens make a difference in outcomes for AYA patients, but there is still more education needed.

> *"RYLAZE has been crucial in replacing potentially missed doses, and its approved dosing options make it so that my AYA patients can receive all prescribed doses based on their protocol. This is really important as it helps to allow for completion of their regimen."*[10,13]
>
> **— Leidy Isenalumhe, MD, MS**

IMPORTANT DOSING INFORMATION

Recommended Premedication

Premedicate patients with acetaminophen, an H-1 receptor blocker (such as diphenhydramine), and an H-2 receptor blocker (such as famotidine) 30-60 minutes prior to administration of RYLAZE to decrease the risk and severity of hypersensitivity reactions.

Recommended Monitoring and Dosage Modifications for Adverse Reactions

Monitor patient's bilirubin, transaminases, glucose, and clinical examinations prior to treatment every 2-3 weeks and as indicated clinically. If results are abnormal, monitor patients until recovery from the cycle of therapy. If an adverse reaction occurs, modify treatment according to Table 2 in the accompanying full Prescribing Information.

Indication

RYLAZE is indicated as a component of a multi-agent chemotherapeutic regimen given by intramuscular injection for the treatment of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) in adult and pediatric patients 1 month or older who have developed hypersensitivity to *E. coli*-derived asparaginase.

IMPORTANT SAFETY INFORMATION

Contraindications

RYLAZE is contraindicated in patients with: history of serious hypersensitivity reactions to *Erwinia asparaginase*, including anaphylaxis; history of serious pancreatitis during previous asparaginase therapy; history of serious thrombosis during previous asparaginase therapy; history of serious hemorrhagic events during previous asparaginase therapy; or severe hepatic impairment.

Warnings and Precautions

Hypersensitivity Reactions

Hypersensitivity reactions after the use of RYLAZE occurred in 29% of patients in clinical trials, and it was severe in 6% of patients. Anaphylaxis was observed in 2% of patients after intramuscular administration. Discontinuation of RYLAZE due to hypersensitivity reactions occurred in 5% of patients. Hypersensitivity reactions were higher in patients who received intravenous asparaginase erwinia chrysanthemi (recombinant)-rywn. The intravenous route of administration is not approved.

In patients administered RYLAZE intramuscularly in clinical trials, the median number of doses of RYLAZE that patients received prior to the onset of the first hypersensitivity reaction was 12 doses (range: 1-64 doses). The most commonly observed reaction was rash (19%), and 1 patient (1%) experienced a severe rash.

Hypersensitivity reactions observed with L-asparaginase class products include angioedema, urticaria, lip swelling, eye swelling, rash or erythema, blood pressure decreased, bronchospasm, dyspnea, and pruritus.

Premedicate patients prior to administration of RYLAZE as recommended. Because of the risk of serious allergic reactions (e.g., life-threatening anaphylaxis), administer RYLAZE in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (e.g., epinephrine, oxygen, intravenous steroids, antihistamines). Discontinue RYLAZE in patients with serious hypersensitivity reactions.

Pancreatitis

Pancreatitis, including elevated amylase or lipase, was reported in 20% of patients in clinical trials of RYLAZE and was severe in 8%. Symptomatic pancreatitis occurred in 7% of patients, and it was severe in 6% of patients. Elevated amylase or lipase without symptomatic pancreatitis was observed in 13% of patients treated with RYLAZE. Hemorrhagic or necrotizing pancreatitis have been reported with L-asparaginase class products.

Inform patients of the signs and symptoms of pancreatitis, which, if left untreated, could be fatal. Evaluate patients with symptoms compatible with pancreatitis to establish a diagnosis. Assess serum amylase and lipase levels in patients with any signs or symptoms of pancreatitis. Discontinue RYLAZE in patients with severe or hemorrhagic pancreatitis. In the case of mild pancreatitis, withhold RYLAZE until the signs and symptoms subside and amylase and/or lipase levels return to 1.5 times the ULN. After resolution of mild pancreatitis, treatment with RYLAZE may be resumed.

Thrombosis

Serious thrombotic events, including sagittal sinus thrombosis and pulmonary embolism, have been reported in 1% of patients following treatment with RYLAZE. Discontinue RYLAZE for a thrombotic event, and administer appropriate antithrombotic therapy. Consider resumption of treatment with RYLAZE only if the patient had an uncomplicated thrombosis.

Hemorrhage

Bleeding was reported in 25% of patients treated with RYLAZE, and it was severe in 2%. Most commonly observed reactions were bruising (12%) and nose bleed (9%).

In patients treated with L-asparaginase class products, hemorrhage may be associated with increased prothrombin time (PT), increased partial thromboplastin time (PTT), and hypofibrinogenemia. Consider appropriate replacement therapy in patients with severe or symptomatic coagulopathy.

Hepatotoxicity, including Hepatic Veno-Occlusive Disease

Elevated bilirubin and/or transaminases occurred in 75% of patients treated with RYLAZE in clinical trials, and 26% had Grade ≥3 elevations. Elevated bilirubin occurred in 28% of patients treated with RYLAZE in clinical trials, and 2% had Grade ≥3 elevations. Elevated transaminases occurred in 73% of patients treated with RYLAZE in clinical trials, and 25% had Grade ≥3 elevations.

Hepatotoxicity, including severe, life-threatening, and potential fatal cases of hepatic veno-occlusive disease (VOD), have been observed in patients treated with asparaginase class products in combination with standard chemotherapy, including during the induction phase of multiphase chemotherapy. Do not administer RYLAZE to patients with severe hepatic impairment. Inform patients of the signs and symptoms of hepatotoxicity.

Evaluate bilirubin and transaminases prior to each cycle of RYLAZE and at least weekly during cycles of treatment that include RYLAZE, through four weeks after the last dose of RYLAZE. Monitor frequently for signs and symptoms of hepatic VOD, which may include rapid weight gain, fluid retention with ascites, hepatomegaly (which may be painful), and rapid increase of bilirubin. For patients who develop abnormal liver tests after RYLAZE, more frequent monitoring for liver test abnormalities and clinical signs and symptoms of VOD is recommended. In the event of serious liver toxicity, including VOD, discontinue treatment with RYLAZE and provide supportive care.

Adverse Reactions

The most common adverse reactions (incidence >20%) with RYLAZE are abnormal liver test, nausea, musculoskeletal pain, infection, fatigue, headache, febrile neutropenia, pyrexia, hemorrhage, stomatitis, abdominal pain, decreased appetite, drug hypersensitivity, hyperglycemia, diarrhea, pancreatitis, and hypokalemia.

Use in Specific Populations

Pregnancy and Lactation

RYLAZE can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective non-hormonal contraceptive methods during treatment with RYLAZE and for 3 months after the last dose. Advise women not to breastfeed during treatment with RYLAZE and for 1 week after the last dose.

RYLAZE®
asparaginase erwinia chrysanthemi (recombinant)-rywn for injection 10mg/0.5mL per vial

"We have a lot of experience with managing toxicities. There's enough data out there to show that it may be safe to prescribe RYLAZE in AYA patients, and that the outcomes are better in those receiving treatment with an asparaginase-based regimen than in those who are not. It takes a lot of patient education and a lot of nursing support to be able to manage treatment with an asparaginase-based regimen, but it's very doable. If they are able to prescribe an asparaginase-based regimen in pediatrics while also managing potential toxicities, then we can do it in our AYA patients as well."

— Leidy Isenalumhe, MD, MS

LEARN MORE ABOUT A TREATMENT OPTION FOR YOUR AYA PATIENTS WITH ALL OR LBL AT

RYLAZEPRO.COM

Leidy Isenalumhe is a leading expert in ALL and LBL in the adolescent and young adult population.

Leidy Isenalumhe, MD, MS, is a board-certified hematologist-oncologist at H. Lee Moffitt Cancer Center and Research Institute in Tampa, Florida, where she serves as Director of Clinical Operations and Co-Director of Inpatient Outpatient Service in the Department of Hematologic Malignancies. She received her medical degree from Albany Medical College and her master's in clinical and biomedical investigation from the University of Southern California. Her research primarily focuses on lymphomas and leukemias. Dr Isenalumhe is a member of the American Society of Hematology, for which she chairs the Career Development Sessions and the Hematology Review Course Task Force.

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