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July/August 2023

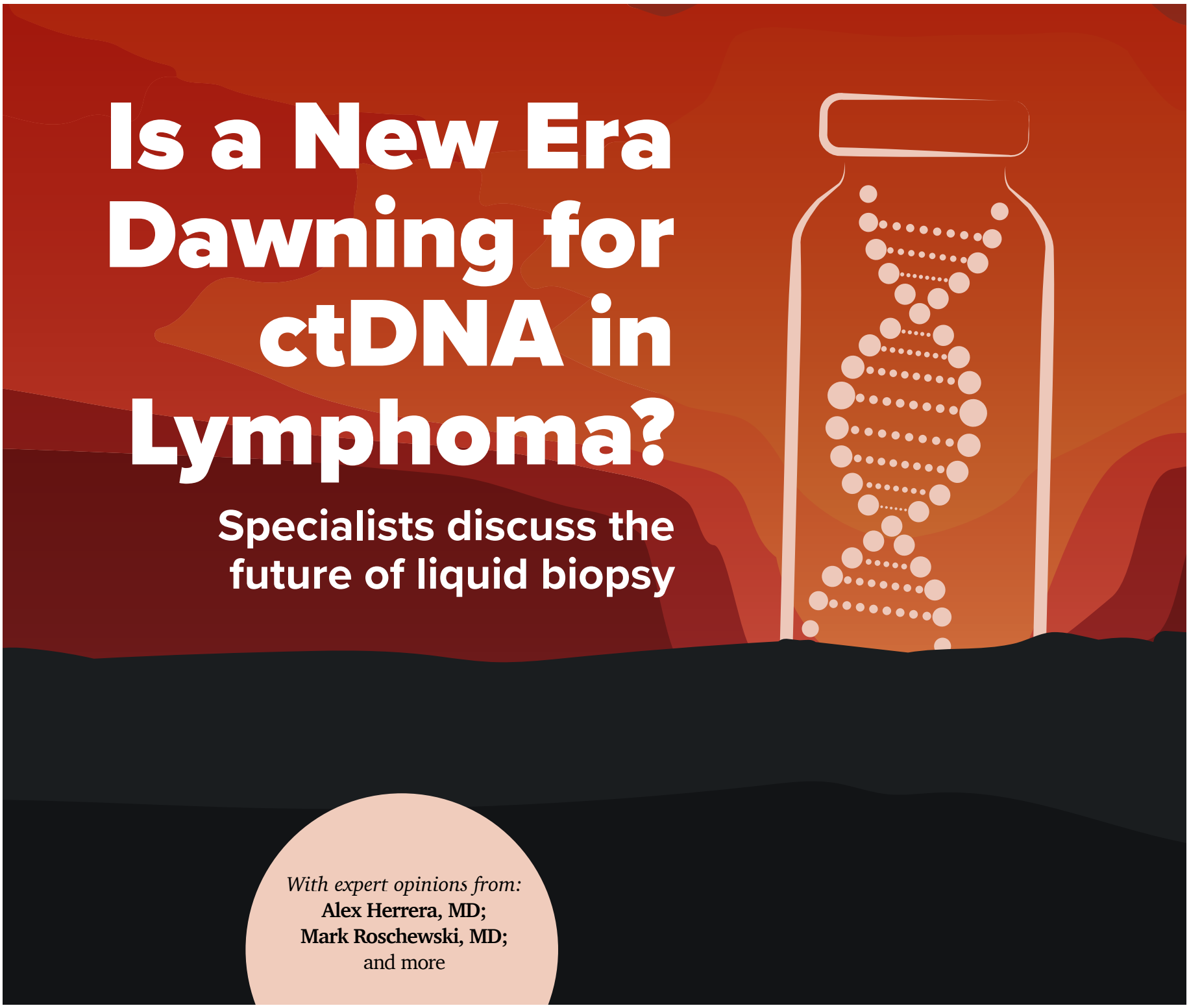
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Is a New Era Dawning for ctDNA in Lymphoma?

Specialists discuss the future of liquid biopsy

With expert opinions from:
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Mark Roschewski, MD;
and more

MAIL TO:



SOHO PRESIDENT DR. JENNIFER BROWN:

SOHO Annual Meeting Advances the Field of Hematologic Oncology Worldwide

An official publication of

soho society of hematologic oncology

DARZALEX | DARZALEX Faspro

In the treatment of newly diagnosed, transplant-ineligible multiple myeloma†:

ADVANCE THE FRONTLINE MOMENTUM WITH DARZALEX® + Rd

Help your patients live longer than Rd alone with DRd, an established frontline treatment proven to significantly extend overall survival



After 56 months: 32% reduction in the risk of death with DRd vs Rd alone in the MAIA trial (HR=0.68; 95% CI: 0.53, 0.86; *P*=0.0013; mOS not reached in either arm).[1]

*Median follow-up was 56 months in the DRd group (range: 53.0–60.1 months) and in the Rd group (range: 52.9–59.4 months).[1]

†Dara + lenalidomide + dexamethasone (D) followed by maintenance D; Rd alone followed by maintenance R.[1] ‡Dara + lenalidomide (R) + dexamethasone.[1]

IMPORTANT SAFETY INFORMATION

DARZALEX® AND DARZALEX FASPRO®: CONTRAINDICATIONS

DARZALEX® and DARZALEX FASPRO® are contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase (for DARZALEX FASPRO®), or any of the components of the formulations.

DARZALEX®: Infusion-Related Reactions

DARZALEX® can cause severe and/or serious infusion-related reactions including anaphylactic reactions. These reactions can be life-threatening and fatal outcomes have been reported. In clinical trials (monotherapy and combination; N=2644), infusion-related reactions occurred in 37% of patients with the Week 1 (16 mg/kg) infusion; 3% with the Week 2 infusion, and cumulatively 4% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion-related reaction at Week 2 or subsequent infusions. The median time to onset was 1.5 hours (range: 0 to 73 hours). Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX®. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, tachycardia, headache, laryngeal edema, pulmonary edema, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma.

Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting and nausea. Less common signs and symptoms were hearing allergic rhinitis, pyrexia, chest discomfort, pruritus, hypotension, and blurred vision.

When DARZALEX® dosing was interrupted in the setting of ASCT (CASSIOPEIA) for a median of 3.73 months (range: 2.8 to 4.9 months), upon re-initiation of DARZALEX®, the incidence of infusion-related reactions was 11% for the first infusion following ASCT. Infusion-related reactions occurring after initiation of DARZALEX® following ASCT were consistent in terms of symptoms and severity (Grade 3 or 4: <1%) with those reported in previous studies at Week 2 or subsequent infusions. In EQUULEUS, patients receiving combination treatment (n=97) were administered the first 16 mg/kg dose at Week 1 split over two days, ie, 8 mg/kg on Day 1 and Day 2, respectively. The incidence of any grade infusion-related reactions was 43%, with 36% of patients experiencing infusion-related reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions.

Pre-medicate patients with antihistamines, antipyretics, and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt DARZALEX® infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX® therapy if an anaphylactic reaction or life-threatening (Grade 4) reaction occurs and institute appropriate emergency care.

Please see Brief Summary of Full Prescribing Information for DARZALEX® and DARZALEX FASPRO® on adjacent pages.

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE ▶

MAIA Study Design: A phase 3 global, randomized, open-label study, comparing treatment with DARZALEX® (daratumumab) + Rd (n=368) to Rd (n=369) in adult patients with newly diagnosed transplant-ineligible multiple myeloma.

Treatment was continued until disease progression or unacceptable toxicity. The primary efficacy endpoint was progression-free survival (PFS) and OS was a secondary endpoint.[1]

Powerful efficacy to start the treatment journey[1,2]

At follow-up of 28 months, median progression-free survival (mPFS) was not reached with DARZALEX® + Rd vs 30.9 months (95% CI, 28.8 to not reached) with Rd alone[2]

- 70.6% of patients had not progressed with D-Rd vs 52.4% of patients in the Rd group (D-Rd: 95% CI, 65.0-75.6; Rd: 95% CI, 48.5-61.3)[1]

44% reduction in the risk of disease progression or death with D-Rd vs Rd alone (HR=0.56; 95% CI, 0.43-0.73; P<0.0001)

Efficacy results in long-term follow-up[3,4]

After 64 months of follow-up, the median PFS was 61.9 months (95% CI: 54.6, not evaluable) in the D-Rd arm and 34.4 months (95% CI: 28.4, 36.3) in the Rd arm

45% reduction in the risk of disease progression or death with DARZALEX® + Rd vs Rd alone (HR= 0.55; 95% CI, 0.45-0.67)

Secondary endpoint of overall survival (OS)[3,4]
After 56 months of follow-up:

- 66% of patients were still alive with D-Rd vs 53% with Rd alone (D-Rd: 95% CI, 60.8-71.3; Rd: 95% CI, 47.9-58.4)[3]
- Median OS was not reached for either arm

32% reduction in the risk of death in patients treated in the D-Rd arm vs Rd alone (HR=0.68; 95% CI: 0.53, 0.86; P= 0.0013)

Demonstrated safety profile (median treatment duration of 25.3 months)[1]

- The most common adverse reactions (≥ 20%) for D-Rd were diarrhea, constipation, nausea, upper respiratory tract infection, bronchitis, pneumonia, infusion-related reactions, peripheral edema, fatigue, asthenia, pyrexia, back pain, muscle spasms, dyspnea, cough, peripheral sensory neuropathy, and decreased appetite
- Serious adverse reactions with a 2% greater incidence in the D-Rd arm compared with the Rd arm were pneumonia (D-Rd 15% vs Rd 8%), bronchitis (D-Rd 4% vs Rd 2%), and dehydration (D-Rd 3% vs Rd <1%)

Safety results in long-term follow-up (median follow-up of 64.5 months)[4]

This information is not included in the current Prescribing Information and has not been evaluated by the FDA.

- Most frequent TEAEs for D-Rd ≥30% were diarrhea, neutropenia, fatigue, constipation, peripheral edema, anemia, back pain, asthenia, nausea, bronchitis, cough, dyspnea, insomnia, weight decreased, peripheral sensory neuropathy, pneumonia, and muscle spasms[4]
- Grade 3/4 infections were 40% for D-Rd vs 30% for R-d
- Grade 3/4 TEAEs occurring in ≥10% of patients/arm were neutropenia (54% for D-Rd vs 37% for R-d), pneumonia (20% vs 11%), anemia (17% vs 23%)[4]

Time-to-event analyses of adverse events are exploratory and observed. These analyses have not been adjusted for multiple comparisons and no conclusions should be drawn.

Cite as: Reference List for D-Rd in DARZALEX® (C) 4 Clinical Overview (R) 4 Nonclinical Overview (NR) PDR for U.S. Prescribing Drug Products. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2019/761036s014lbl.pdf. Accessed [Month Year]. Clinical Overview (R) 4 Nonclinical Overview (NR) TEAEs treatment-emergent adverse events.

[1] Dimopoulos MA, et al. *Lancet Oncol*. 2020;21(6):801-812.

[2] Facon T, et al. *N Engl J Med*. 2019;380(22):2104-2115.

[3] Facon T, et al. *Blood*. 2021;137(26):3616-3628.

[4] Safety analysis set. TEAEs are defined as any adverse event (AE) that occurs after start of the first study treatment through 30 days after the last study treatment, or the start of subsequent anti-myeloma therapy, whichever occurs earlier. Any AE that is considered related to any study component (any study related) regardless of the start relative to the start of subsequent anti-myeloma therapy, or any AE with an unknown relationship to study treatment considered drug related by the investigator.

See the rolled-out data.
Visit darzalexhcp.com

IMPORTANT SAFETY INFORMATION (CONTINUED)

For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion.

To reduce the risk of delayed infusion-related reactions, administer oral corticosteroids to all patients following DARZALEX® infusions. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease.

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusion with potential for increased intraocular pressure or glaucoma, have occurred with DARZALEX® infusion. If ocular symptoms occur, interrupt DARZALEX® infusion and seek immediate ophthalmologic evaluation prior to restarting DARZALEX®.

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj): Hypersensitivity and Other Administration Reactions

Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO®. Fatal reactions have been reported with daratumumab-containing products, including DARZALEX FASPRO®.

Systemic Reactions:
In a pooled safety population of 1916 patients with multiple myeloma (N=1703) or light chain (AL) amyloidosis (N=213) who received DARZALEX FASPRO® as monotherapy or in combination, 9% of patients experienced a systemic administration-related reaction (Grade 2: 3.3%, Grade 3: 1%). Systemic administration-related reactions occurred in 8% of patients with the first injection, 0.3% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.3 hours (range: 4 minutes to 3.5 days). Of the 140 systemic administration-related reactions that occurred in 77 patients, 121 (86%) occurred on the day of DARZALEX FASPRO® administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

Severe reactions included hypoxia, dyspnea, hypertension, tachycardia, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension, and blurred vision.

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen, and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO®.

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE

[redacted] and [redacted]: Mechanism of Action

[redacted] is a human IgG1κ monoclonal antibody that binds to CD38, a transmembrane glycoprotein highly expressed on the surface of multiple myeloma cells. Binding of [redacted] to CD38 induces tumor cell death through multiple immune-mediated mechanisms, including complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP). [redacted] also induces apoptosis of tumor cells directly through Fc receptor–mediated cross-linking.

In vitro studies have demonstrated that [redacted] is highly effective at killing multiple myeloma cells via these immune-mediated mechanisms. In addition, [redacted] has been shown to modulate the activity of certain immune cell populations, including regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), which may contribute to its overall antitumor activity.

[redacted]: Clinical Trials

The safety and efficacy of [redacted] were evaluated in [redacted], a multicenter, randomized, open-label, active-controlled trial conducted in patients with relapsed or refractory multiple myeloma who had received at least one prior line of therapy. The trial compared [redacted] in combination with [redacted] and dexamethasone ([redacted]) versus [redacted] and dexamethasone ([redacted]).

A total of [redacted] patients were randomized 1:1 to receive either [redacted] or [redacted]. Patients were stratified by number of prior lines of therapy (1 vs. 2–3) and by International Staging System (ISS) stage at study entry. The primary endpoint was progression-free survival (PFS) as assessed by an independent review committee (IRC) according to the International Myeloma Working Group (IMWG) criteria. Key secondary endpoints included overall response rate (ORR), very good partial response or better (≥VGPR), complete response or better (≥CR), time to response, duration of response, overall survival (OS), and safety.

The median PFS was not reached in the [redacted] arm and was [redacted] months in the [redacted] arm (hazard ratio [HR] = [redacted]; 95% CI: [redacted]; p < [redacted]), corresponding to a [redacted]% reduction in the risk of disease progression or death. The 12-month PFS rate was [redacted]% versus [redacted]%, respectively. The ORR was [redacted]% in the [redacted] arm and [redacted]% in the [redacted] arm (p < [redacted]). The ≥VGPR rate was [redacted]% versus [redacted]%, and the CR rate was [redacted]% versus [redacted]%.

Subgroup analyses consistently favored the [redacted] arm across all prespecified patient subsets, including age, sex, ISS stage, cytogenetic risk, number of prior lines of therapy, and prior exposure to [redacted]. The benefit was observed in patients with high-risk cytogenetic abnormalities, including del(17p) and t(4;14), although the magnitude of benefit was numerically smaller in this subgroup.

Minimal residual disease (MRD) negativity was assessed in patients who achieved a CR or better using next-generation flow cytometry (NGF) with a sensitivity of 10⁻⁵. MRD negativity was achieved by [redacted]% of patients in the [redacted] arm and [redacted]% in the [redacted] arm (p < [redacted]). Patients who achieved MRD negativity had significantly longer PFS than those who remained MRD positive, regardless of treatment arm.

Overall survival data were immature at the time of the primary analysis, with [redacted] deaths reported (n = [redacted]; [redacted]%). A trend toward improved OS was observed in the [redacted] arm (HR = [redacted]; 95% CI: [redacted]; p = [redacted]), but the difference did not reach statistical significance. Updated OS analyses are planned.

[redacted]: Indications and Usage

[redacted] is indicated for the treatment of adult patients with [redacted]:

- In combination with [redacted] and dexamethasone for newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients who are receiving [redacted] who have received at least one prior therapy
- In combination with [redacted] and dexamethasone for newly diagnosed patients who are ineligible for autologous stem cell transplant
- In combination with [redacted] and dexamethasone for newly diagnosed patients who are eligible for autologous stem cell transplant
- In combination with [redacted] and dexamethasone for patients who have received at least one prior therapy
- In combination with [redacted] and dexamethasone for patients who have received at least one prior therapy including [redacted] and an immunomodulatory agent
- As monotherapy for patients who have received at least three prior lines of therapy including [redacted] and an immunomodulatory agent and who have demonstrated disease progression on the last therapy

[redacted] is also indicated in combination with [redacted] and dexamethasone for the treatment of adult patients with multiple myeloma

- In combination with [redacted] and dexamethasone for patients who have received at least one prior therapy
- In combination with [redacted] and dexamethasone for newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients who are receiving [redacted] who have received at least one prior therapy
- In combination with [redacted] and dexamethasone for newly diagnosed patients who are ineligible for autologous stem cell transplant
- In combination with [redacted] and dexamethasone for newly diagnosed patients who are eligible for autologous stem cell transplant
- In combination with [redacted] and dexamethasone for patients who have received at least one prior therapy
- In combination with [redacted] and dexamethasone for patients who have received at least one prior therapy including [redacted] and an immunomodulatory agent
- As monotherapy for patients who have received at least three prior lines of therapy including [redacted] and an immunomodulatory agent and who demonstrated disease progression on the last therapy

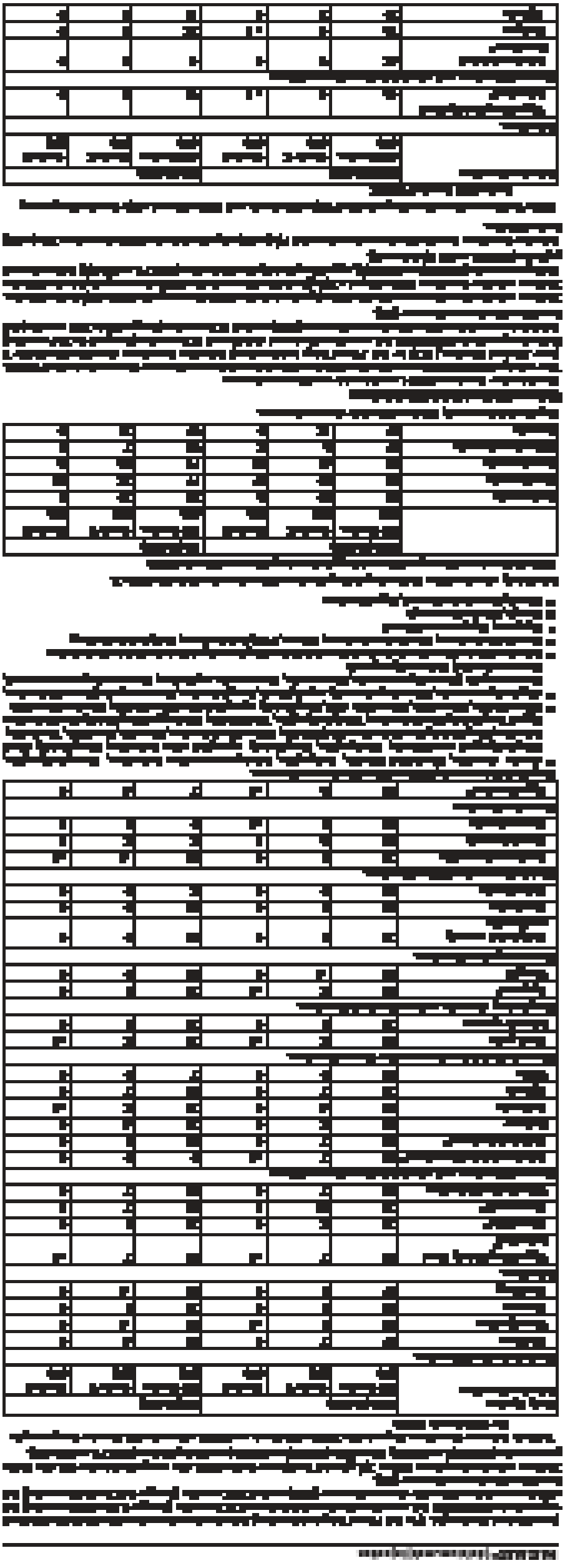
[redacted] is [redacted] and [redacted] mAb indicated for the treatment of [redacted] with [redacted]:

- In combination with [redacted] and dexamethasone for patients who have received at least one prior therapy
- In combination with [redacted] and dexamethasone for newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients who are receiving [redacted] who have received at least one prior therapy
- In combination with [redacted] and dexamethasone for newly diagnosed patients who are ineligible for autologous stem cell transplant
- In combination with [redacted] and dexamethasone for newly diagnosed patients who are eligible for autologous stem cell transplant
- In combination with [redacted] and dexamethasone for patients who have received at least one prior therapy
- In combination with [redacted] and dexamethasone for patients who have received at least one prior therapy including [redacted] and an immunomodulatory agent
- As monotherapy for patients who have received at least three prior lines of therapy including [redacted] and an immunomodulatory agent and who demonstrated disease progression on the last therapy

Please see full Prescribing Information for [redacted] and [redacted] at [redacted].

[redacted] is a [redacted] mAb that binds to [redacted], a [redacted] glycoprotein highly expressed on the surface of [redacted] cells, including [redacted] cells, [redacted] cells, and [redacted] cells. [redacted] is also expressed on [redacted] cells, [redacted] cells, and [redacted] cells, but at lower levels. The [redacted] mAb is an [redacted] that binds to a [redacted] epitope on the [redacted] domain of [redacted]. The [redacted] mAb is a [redacted] that binds to a [redacted] epitope on the [redacted] domain of [redacted].

[redacted] and [redacted]: Mechanism of Action



[redacted]

[redacted]	[redacted]			[redacted]		
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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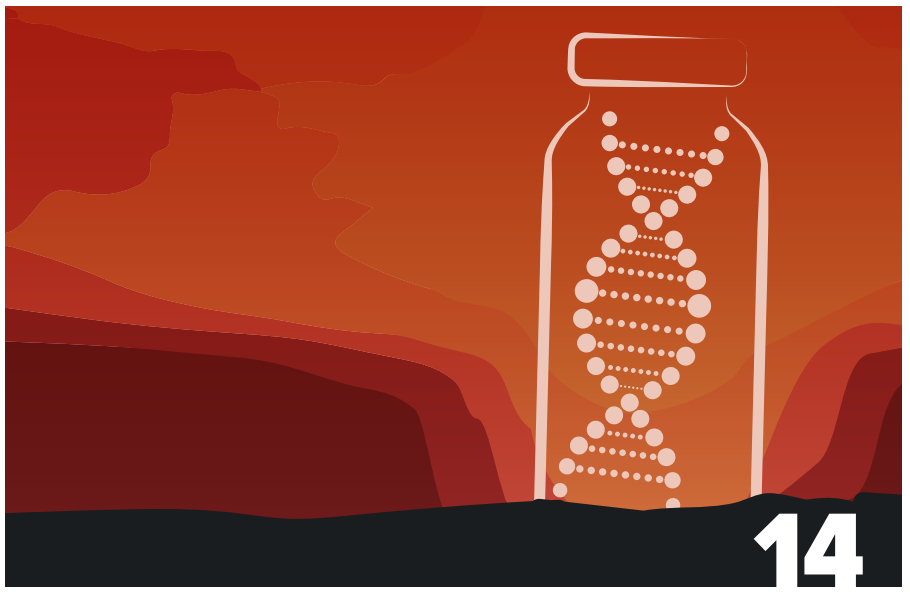
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- [redacted]

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ONLINE FIRST

Visit **bloodcancerstoday.com** to listen to all the latest episodes of The HemOnc Pulse with host **Chadi Nabhan, MD, MBA, FACP.**

Read more from a recent episode with *Blood Cancers Today* Editor-in-Chief **Sagar Lonial, MD, FACP,** on page **36**.

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About the Society of Hematologic Oncology
The Society of Hematologic Oncology was established as a nonprofit corporation in 2012 with aims to promote worldwide research, education, prevention, clinical studies, and optimal patient care in all aspects of hematologic malignancies and related disorders. The Society's global network supports and is supported by members from more than 110 countries, who are leading the vital efforts to further treatments for those afflicted by these diseases.

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SOHO Annual Meeting Advances the Field of Hematologic Oncology Worldwide



Jennifer Brown, MD, PhD
Dana-Farber Cancer Institute

The Society of Hematologic Oncology (SOHO) Annual Meeting is a unique opportunity to hear updates on all hematologic malignancies in a concise format. Over the years, I have had the privilege of participating as a speaker, and I believe attending the event is a must for clinicians who want to learn about the latest advances in hematologic oncology.

I have always found the sessions to be informative and engaging, as they are carefully crafted to encourage thought-provoking discussions and a fresh approach. It is truly remarkable to hear what fellow experts have to say, not just in my specific area of disease but across various disease domains.

The appeal of the SOHO meeting lies in its collaborative environment and ability to provide succinct updates on all hematologic malignancies in just a few days.

There are several reasons I encourage clinicians to attend the meeting. For one, it offers a stage where we can engage in vigorous debates and arguments about the best treatment options. The sessions present cutting-edge science and results from trials, bridging the gap between research and real-world applications. This information is particularly valuable for clinicians who strive to apply the latest findings in their practice. Additionally, the smaller sessions provide ample opportunities for questions and answers, allowing us to connect with experts and delve deeper into specific topics.

This year, I had the honor of selecting personalized medicine as the theme of the 11th annual meeting. This topic has been a long-standing interest of mine, particularly in relation to genomics in chronic lymphocytic leukemia (CLL) and its application in the clinic. What makes CLL unique is that most of the relevant pathways for targeted therapies are active in all patients, regardless of specific mutations. This trait defied our initial assumptions and sets CLL apart from other diseases, such as acute myeloid leukemia, which has targeted inhibitors against specific mutations.

I would also like to highlight SOHO's global outreach efforts. The Society has made it a priority to expand internationally by providing funding for individuals to attend the annual meeting and encouraging local hematologists to play an active role in planning satellite meetings as part of the SOHO Ambassador Program. This approach has been well-received by international clinicians, empowering them to organize their own meetings and contribute to the field's collective knowledge.

SOHO's commendable dedication to global learning aligns with our collective efforts as clinicians and researchers to improve worldwide access to therapies and knowledge. Through its education program, SOHO advocates for enhanced insight and global access to new therapies. While these treatments are more readily available in the United States, their availability around the world is not as widespread. The goal is to bridge this gap, ensuring that patients worldwide can benefit from these medical advancements.

In closing, I urge all clinicians to mark their calendars for the annual meeting, as it represents an invaluable opportunity to expand our knowledge, engage in stimulating discussions, and collectively strive for advancements in the field of hematologic oncology.

Scan the QR Code to register for the Eleventh SOHO Annual Meeting.

Jennifer Brown, MD, PhD, *is the Director of the Chronic Lymphocytic Leukemia Center at the Dana-Farber Cancer Institute and the Worthington and Margaret Collette Professor of Medicine in the Field of Hematologic Oncology at Harvard Medical School. She is also President of the Society of Hematologic Oncology.*

2023 Midyear Highlights

The *Blood Cancers Today* Editorial Board reflects on the latest news in the field so far in 2023

BCT Editorial Board Rounds Up the News

Rapid Progress and Notable Successes in Cell Therapy



Sagar Lonial, MD, FACP
Editor-in-Chief
Winship Cancer Institute
at Emory University
School of Medicine

For me, the highlights thus far this year surround the rapid progress and success of cell therapy. On KarMMa-3 and CARTITUDE-4, we saw that chimeric antigen receptor (CAR) T-cell therapies are better than standard treatments, and that is a big step forward for the field.

We have also seen the impact of bispecific antibodies across myeloma and lymphoma, which is very exciting, as these therapies are off the shelf and have rapid activity. However, understanding dosing and scheduling will be critical in the future.

Practice-Changing Trials Plus Key Leukemia News (and Beyond)



Elias Jabbour, MD
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Significant advancements have been made in the field of blood cancer research so far in 2023, and some of those findings have already been published. It's exciting to report that a few key trials have the potential to be practice changing.

In myelodysplastic syndromes (MDS), two randomized trials have yielded insightful results. Notably, the COMMANDS trial examined the frontline application of luspatercept in low-risk MDS patients who had not undergone prior treatment with erythropoiesis-stimulating agents (ESAs). The study, which was published in *The Lancet* in June 2023, established this therapy to be superior to ESAs, and it now has the potential to be the new standard of care. We are awaiting its approval from the US Food and Drug Administration (FDA) for this indication.

Furthermore, the IMerge trial investigated the efficacy of imetelstat in low-risk MDS cases following ESA failure, achieving its primary endpoint and paving the way for anticipated approval in this subgroup of patients. Encouragingly, imetelstat has demonstrated promising activity across various MDS subsets.

Looking ahead, we're eagerly awaiting outcomes from the VERONA trial, a study that aims to uncover the role of venetoclax in MDS treatment. The findings from this trial hold the potential to further enhance our understanding of MDS treatment and improve treatment outcomes.

In myelofibrosis, trials are ongoing with JAK2 inhibitors in combination with agents such as MDM2 inhibitors or other agents. We know as well that imetelstat is being assessed in myelofibrosis, and we're awaiting the results of the trial.

In acute lymphocytic leukemia (ALL), we've seen the results of the ECOG-ACRIN E1910 trial, which assessed the role of blinatumomab as an upfront treatment for patients who are measurable residual disease (MRD)-negative. These results confirm findings from MD Anderson demonstrating that blinatumomab improves survival in MRD-negative patients. This is excellent news.

Another significant trial, PhALLCON, evaluated ponatinib as a frontline therapy for Philadelphia chromosome-positive (Ph+) ALL through a randomized study. Notably, the trial met its primary endpoint, demonstrating the superiority of ponatinib over imatinib therapy. Consequently, the drug is currently awaiting FDA approval.

Ponatinib More Effective Than Imatinib in Newly Diagnosed Ph+ ALL

Additionally, the launch of a randomized trial targeting older patients with ALL is anticipated to have practice-changing results, and the exploration of subcutaneous blinatumomab shows promise in expanding treatment options.

Finally, during the 2023 ASCO® Annual Meeting and the 2023 European Hematology Association (EHA) Congress, the FELIX trial demonstrated the promising activity of obe-cel, a "fast off-rate" CAR T-cell therapy, in adult patients with relapsed or refractory B-cell ALL.

Moving on to acute myeloid leukemia (AML), we have seen interesting data on the use of quizartinib, not only in *FLT3*-ITD-positive patients, as demonstrated in the QuANTUM-First trial—a randomized study showing improved survival with quizartinib—but also in patients without *FLT3*-ITD. For example, a promising study conducted in Spain showed improvements in patient outcomes.

Furthermore, in the United Kingdom, data indicated that adding gemtuzumab ozogamicin to induction chemotherapy yielded improved outcomes in patients with *NPM1*-positive disease.

The most exciting drugs in AML and ALL are the menin inhibitors. These therapies have promising activity, and several of them are being tested right now. Hopefully, they will be added to the armamentarium of acute leukemia therapy in the future.

In chronic lymphocytic leukemia (CLL), the new Bruton's tyrosine kinase (BTK) inhibitor pirtobrutinib was approved and is now being combined with BCL-2 or CD20 antibodies, showcasing potential activity in frontline CLL treatment. This progress is especially encouraging, as it suggests the possibility of shorter therapy durations while maintaining disease control over the long term, ultimately aiming for a potential cure.

Finally, in chronic myeloid leukemia (CML), we have new drugs—including new BCR-ABL1 inhibitors—under exploration in phase I and II trials. In addition, results showing ponatinib being very active in third-line therapy were published this year in the *American Journal of Hematology*. The availability of real-world data is increasing, providing valuable insights into the effectiveness of drugs like asciminib and ponatinib. Also, asciminib is being further investigated in the frontline setting, demonstrating the continuous progress being made in the field of CML therapeutics.

I look forward to the maturation of these data as we head into the second half of 2023 and beyond. There has been much exciting news in the treatment of leukemia, and the future is very promising for our patients.

2023 Midyear Highlights

Multiple FDA Approvals in Lymphoma



Kami Maddocks, MD
Associate Editor
The Ohio State University

Thus far, 2023 has brought us exciting data that will impact future practice in lymphoma and exciting FDA approvals for the treatment of different lymphomas. S1826, the SWOG phase III clinical trial that evaluated nivolumab, the PD-1 checkpoint inhibitor, in combination with doxorubicin, vinblastine, and dacarbazine (AVD) chemotherapy versus brentuximab vedotin (BV), the CD30 antibody-drug conjugate, in combination with AVD chemotherapy in newly diagnosed adolescents and adults with advanced-stage Hodgkin lymphoma, showed a significant improvement in one-year progression-free survival (PFS) with nivolumab-AVD (94% vs 86%). These exciting results came just a year after the frontline combination of BV-AVD was shown to have an overall survival (OS) benefit compared with that of standard doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) chemotherapy.

The ZUMA-7 trial results were presented and published and showed an OS benefit of axicabtagene ciloleucel versus standard of care in the second-line treatment of patients with refractory or early relapsed large B-cell lymphoma (LBCL), providing a potentially curative therapy in a population of patients with historically poor outcomes.

ZUMA-7: Is It a Whole New Ball Game in LBCL?

Approvals for the novel CD20 × CD3 bispecific antibodies epcoritamab and glofitamab for patients with relapsed or refractory LBCL came in May and June 2023. The therapies provide additional options for patients with these aggressive lymphomas, including patients who are not eligible for or don't have access to CAR-T therapies and patients who don't respond or relapse after CAR-T products.

Pirtobrutinib, a noncovalent, reversible BTK inhibitor, received approval for patients with relapsed or refractory mantle cell lymphoma who progress after a covalent BTK inhibitor. This therapy provides an exciting new option for these patients, including those who are not candidates for CAR-T therapy, need a bridge to CAR-T therapy after progressing on a covalent BTK inhibitor, or even progress after CAR-T therapy. The ongoing BRUIN CLL-321 study is evaluating pirtobrutinib versus a covalent BTK inhibitor and has the potential to further impact the treatment landscape.

I'm looking forward to what the rest of 2023 will bring for lymphoma treatment!

Setting the Stage for the Future of CAR-T, Immunotherapy in Multiple Myeloma



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On the heels of the 2023 ASCO® Annual Meeting and the 2023 EHA Congress, we continue to see tremendous progress in the treatment of relapsed and refractory multiple myeloma. At both meetings, investigators presented preliminary results from the phase III CARTITUDE-4 trial, which randomized patients with early relapsed myeloma who had received one to three prior lines of therapy to receive either ciltacabtagene autoleucel or a standard three-drug combination. The results showed marked improvement for utilizing CAR-T therapy, with higher rates of overall response, complete response, and MRD negativity. Longer follow-up is needed to estimate median PFS and OS, but these results are quite encouraging.

We also saw initial results from the first trial combining two bispecific T-cell redirection antibodies, teclistamab (BCMA-CD3) and talquetamab (GPRC5D-CD3). This was a phase I trial in patients with heavily pretreated relapsed or refractory myeloma, showing an overall response rate of 96% at the recommended phase II dose. These results rival those from CAR T-cell therapy in the late relapse setting and demonstrate the potency of immunotherapy.

The future of myeloma is to move these therapies into the early-line setting, including as part of initial therapy, and to further investigate combinations with bispecific antibodies and eventually combinations that utilize both CAR T cells and bispecific antibodies.

MyeloMATCH Initiative Now on the Horizon



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Associate Editor
Fred Hutchinson Cancer Center

After three-plus years of hard work by a large, dedicated (and at times perhaps functionally delusional) group of colleagues, the National Cancer Institute precision medicine initiative in AML—also known as MyeloMATCH—has a start-up date on the horizon.

This unique partnership of government, academia, and industry will bring trials for newly diagnosed AML cases to the whole cooperative group network, providing rapid diagnostic tests (cytogenetics, flow cytometry, and gene sequencing) to direct patients to specific trials based on genetic risks and the availability of targeted agents. This has been an exercise in persistence, patience, frustration, and (hopefully soon) elation.

ZUMA-7 Establishes New Standard of Care in Certain Settings



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Long-term results from ZUMA-7 have confirmed an OS benefit for second-line CAR T-cell therapy over salvage therapy followed by autologous hematopoietic stem cell transplantation for transplant-eligible patients with primary refractory or early relapsing LBCL.[1] This establishes CAR T-cell therapy as the new standard of care in this setting. It also makes CAR T-cell therapy a desirable option in the second-line setting for transplant-ineligible patients rather than reserving it for third-line therapy. The introduction of CAR T-cell therapy and the availability of numerous novel agents, including bispecific antibodies, has led to a recent overhaul of the management algorithm for LBCL.

Reference

1. Westin JR, Oluwole OO, Kersten MJ, et al. Survival with axicabtagene ciloleucel in large B-cell lymphoma. *N Engl J Med.* 2023;389(2):148-157. doi:10.1056/nejmoa2301665

Guillermo Garcia-Manero, MD

Dr. Garcia-Manero, the 2023 Society of Hematologic Oncology (SOHO) President-Elect, reflects on his role within the Society, what sets the SOHO Annual Meeting apart, and what he hopes to accomplish during his tenure as president.

What is your role within SOHO, and how has SOHO evolved over the years?

I've been involved with SOHO as long as I've been on the faculty in the Department of Leukemia at the University of Texas MD Anderson Cancer Center. I'm not someone who plans or thinks, "In five years, I want to be the president of SOHO." Often, opportunities happen unexpectedly, so when I was nominated for the position, I said, "Yes, absolutely, I would love to do this." I'm honored that I was selected.

Over time, my journey as an academic physician and the development of SOHO—particularly the Annual Meeting—have evolved organically. I've seen SOHO meetings grow from smaller gatherings that covered a single disease state to the current, comprehensive SOHO Annual Meeting. In the beginning, meetings focused on acute myeloid leukemia (AML). Then we asked ourselves, "Why are we only discussing leukemia?" That's when we began expanding to incorporate myelodysplastic syndromes (MDS) and eventually other hematologic malignancies.



As Chief of the Section of Myelodysplastic Syndromes and Chronic Myelomonocytic Leukemia at the MD Anderson Cancer Center, I've been involved with the SOHO Education Committee for many years, which has allowed me to contribute significantly to the Society. In collaboration with the committee, I've organized the MDS sessions for the annual meeting, helping to select the agenda and speakers. This ongoing involvement has created a strong connection and sense of responsibility for me as the lead of the MDS portion of the meeting.

What other significant changes have you observed in SOHO since its inception?

We've always had a strong focus on education, and that will never change, but a transition seems to be taking place this year. I see a shift from an annual meeting that is exclusively educational to one where a significant amount of new data is presented. I see this shift happening especially in AML and MDS (the areas I review) in regard to clinical trials. From my perspective, this shift is incredibly important.

I also think the hybrid meeting format we adopted has allowed individuals from other countries who may have faced travel challenges in the past to attend the meeting. SOHO has consistently captured the interest of international participants, and now the meeting is more accessible to them than ever.

Can you speak about the value of the SOHO Annual Meeting and your goals for it?

There are multiple reasons people attend events like the SOHO Annual Meeting. First, there's the educational component, an area where I believe SOHO excels. Second, there's the research aspect, which we're really starting to focus on. Finally, there are the networking and collaboration opportunities with meeting sponsors and investigators, which also happen at the American Society of Hematology (ASH) and American Society of Clinical Oncology (ASCO) annual meetings. These three components are vital, and I aim to prioritize and enhance each of them during my time as president.

Regarding the educational component, I believe we're already in a strong position, so my focus will be maintaining the quality of our educational program.

As president, I want sponsors, companies, and clinical trial organizers to know our meeting is an ideal venue for meaningful interactions given that it strikes the perfect balance in terms of size. I think leaders in the field are generally enthusiastic about attending, and I believe we can further enhance the research aspect of the annual meeting and develop ongoing research activities.

Do you have any final thoughts you'd like to share?

The SOHO Annual Meeting stands out as one of the most comprehensive gatherings in the world for those who are interested in malignant hematology. What sets our meeting apart from other conferences like ASH or ASCO is its smaller size and exclusive focus on malignant hematology, which holds immense significance for the hematology-oncology community. Our concentrated focus on leukemia, lymphoma, myeloma, and transplant offers attendees an incredible opportunity to access the latest research in three or four days.

The small size of the SOHO Annual Meeting also provides clinicians with the chance to explore advancements outside of their specific areas of expertise. I frequently gain valuable insights and ideas when I sit in on a presentation by a colleague who is in a different subspeciality than my own. This collaborative environment supports the exchange of knowledge and mutual enrichment as we gather, listen, and learn from each other.

Guillermo Garcia-Manero, MD, *is Chief of the Section of Myelodysplastic Syndromes and Chronic Myelomonocytic Leukemia at the University of Texas MD Anderson Cancer Center.*

Get to Know

Learn more about the leaders, innovators, and educators in hematologic oncology



John DiPersio, MD, PhD

Dr. DiPersio, the Virginia E. and Sam J. Golman Professor in Medicine and Director of the Center for Gene and Cellular Immunotherapy at the Washington University School of Medicine in St. Louis, discusses the key events that shaped his career, his lab's most transformative research, and the future of transplant. This interview has been edited for print. For the full interview visit *bloodcancerstoday.com*.

Where did you grow up and when did you know you wanted to be a physician-scientist?
I was born in the north end of Boston. I lived in Belmont and Brighton. Then I moved to Scituate, a town south of Boston, where I grew up through high school. I went to a large Catholic high school in Braintree, Massachusetts.

I was interested in science, mostly physics and astronomy. My dad was a pilot who worked for the US Air Force. When I was in high school, I wanted to go into aeronautical space engineering, but I lost my left eye playing hockey, so my flight career was terminated. I couldn't become a pilot or an astronaut.

I went to Williams College, and I decided to regroup. I majored in biology with a minor in chemistry and did some research projects. I was interested in medical school and pursuing a career as a physician-scientist.

What led you to specialize in hematologic oncology and hematopoietic stem cell transplantation (HSCT)?
I did a research project and thesis in college with **Bill DeWitt, PhD,** who studied red blood cell production in the frog.

When I went to medical school, I did an MD-PhD. My doctoral advisor was a hematologist, and we were trying to identify a protein that stimulated white blood cell production. My project was to purify and characterize the first white blood cell growth factor. We made a lot of progress. Although I didn't identify it when I was a graduate student, it turned out to be a cytokine called GM-CSF. It was later cloned by a pharmaceutical company.

When I finished my residency in medicine at the University of Texas (UT), I was interested in a hematology-oncology fellowship and went to the University of California, Los Angeles (ULCA). I joined a lab that focused on hematopoietic growth factors, stem cell biology, and the genes involved in progression to acute leukemia. I continued working to identify growth factors, and we finally succeeded.

After my postdoc at UCLA, I got a job there as an attending in hematology-oncology. Then I went to the University of Rochester as the first director of its Bone Marrow Transplant Program.

I was recruited to Washington University in 1994 as the Head of the Transplant Division. A year or two after I arrived, I was appointed Chief of the Division of Oncology, which included bone marrow transplant and solid tumor oncology. We had only six or seven faculty at that point. Now we have 150 faculty. We started with about 16 employees. Now we have 1,600 employees.

"The final frontier will be addressing relapse after transplant by using targeted therapies, immunotherapies, and a safer transplant platform for gene therapy."

Was there a particular mentor or group of mentors who shaped your career path?
Dr. DeWitt got me involved with blood cell production research when I was in college. **Marshall Lichtman, MD,** was my major mentor in medical school. He became the President of the American Society of Hematology and the Dean of the University of Rochester. He's a great colleague and friend.

Don Seldin, MD, who was the Chairman of Medicine at UT Southwestern at Parkland Hospital, always reminded me that academic medicine was what I wanted to do. He was supportive of me pursuing a career as an academic physician-scientist.

When I got to UCLA, **Judy Gasson, PhD,** was my mentor, and I worked in her lab. She became the Cancer Center Director at UCLA. I was also under the mentorship of **David Golde, MD,** who was the Head of the Hematology Division at that time.

When I started as a junior faculty member at the Washington University School of Medicine in St. Louis, my great colleagues and mentors included **Tim Ley, MD,** who was a well-known expert in the field of acute leukemia; **Stan Korsmeyer, MD;** and **John Atkinson, MD,** Chairman of Medicine. They were great supporters. Even though they were my colleagues, they were my mentors as well.

What are some of your current research projects?
My lab is broken up into multiple areas. One area works on the genetics and genomics of acute leukemia. It's a collaborative effort with Dr. Ley and his colleagues to understand mutations associated with acute leukemia and how to overcome resistance for patients who receive treatment and transplant for acute myeloid leukemia (AML). That work has been translated into several novel immunotherapies for AML, including chimeric antigen receptor T-cell therapies and bispecific therapies that we either helped develop or are developing on our own.

We also work on improving transplant therapies and identifying ways to more efficiently mobilize stem cells. In that regard, we've been leaders in the world. We were involved with the approval of the first small-molecule mobilizing agents, and we were involved with a CXCR4 inhibitor that hopefully will be approved soon by the US Food and Drug Administration (FDA). We've also developed our own completely novel approach, and we are in the process of licensing it. We've been a major player in that area.

Along with mobilization, we're interested in how stem cells interact with the hematopoietic niche and how they traffic outside of the bone marrow, as well as understanding the factors and tethers that pull stem cells into bone marrow.

Another area of interest is developing transplant conditioning regimens that don't involve chemotherapy or radiation. We've developed antibody-based conditioning regimens for stem cell transplant that are effective across histocompatibility barriers in a mouse. We're trying to carry those forward into the human setting. This work has broad implications for patients with malignancies, as well as patients with nonmalignant diseases like thalassemia or sickle cell anemia. It would be a huge step forward. We've made a lot of progress and we're excited about that.

We also study graft-versus-host disease (GVHD). We identified Janus kinase inhibitors as a way to prevent GVHD. Ruxolitinib was the first drug the

FDA ever approved to treat acute GVHD.

Additionally, we're interested in enhancing treatment for patients who relapse after transplant. We've focused on immunotherapy targeting for AML, T-cell acute lymphoblastic leukemia, and multiple myeloma.

I was also involved with co-founding two companies, Magenta in Boston and Wugen in St. Louis.

How have you seen HSCT evolve throughout your career?

It's evolved in a few major ways. It has become better and safer, so we can transplant older patients with less toxicity and better outcomes. We've also found ways to improve conditioning regimens and GVHD treatment.

We are excited about measures to prevent GVHD while maintaining good graft-versus-leukemia effect. That has changed the playing field a bit. By manipulating the cells, reducing the number of conventional T cells, increasing the number of regulatory T cells, and manipulating the grafts, the GVHD complications have decreased and the engraftment rates have improved.

I think the next big phase will be antibody-based conditioning regimens that don't involve chemotherapy or radiation. That will make it easier for patients with malignant or nonmalignant disease to receive a transplant.

We haven't fixed everything yet. People still relapse. The final frontier will be addressing relapse after transplant by using targeted therapies, immunotherapies, and a safer transplant platform for gene therapy. If you had the perfect model for gene therapy, you would not give chemotherapy or radiation therapy before you infuse genetically modified stem cells. You would give an antibody. But that option has not been possible traditionally. However, I think we are finally seeing it come to fruition.

We can also use these antibodies to work across histocompatibility barriers. I could do an allogeneic transplant with just antibodies and no chemotherapy or radiation therapy. Just a year ago, that was unheard of.

Those approaches can be used to transplant genetically modified cells, which can be used to cure sickle cell anemia, thalassemia, and genetically inherited diseases. However, that has been difficult due to the need for transplant conditioning and all its associated risks. If we figure out how to reduce the risk of the conditioning, then everything would be better.

What would you tell someone who is just starting out in the field of hematologic oncology?

It's a rapidly evolving field. There's lots to do. We now have a lot of great tools to look across the entire genome in an unbiased way.

In the past, I'd have an idea and test that idea. We would only discover things we were looking for. Now, we can do big screens to look at mutations or epigenetic changes and see if there's any common thread. You can do these big experiments now that you could never do before. Instead of testing a single hypothesis, you can do hypothesis-generating experiments. It's exciting.

We think we know what's going on, but we have no idea what's going on. The smarter we are, the dumber we are. We have just scratched the surface. There's so much more to learn, and the tools we have to interrogate areas of basic and translational science now are fantastic. That's the advantage that kids today have. We have amazing tools to look at these biologic processes. The acquisition of new knowledge will increase exponentially over time.

What are your favorite hobbies and activities outside of work?

I love art, mostly modern art. I doodle and paint for fun. I sell something occasionally. I also love music, in particular jazz. I've been listening to jazz my whole life. I have around 3,000 jazz albums and CDs. I love jazz. My family hates it, but I love it.

I've played hockey my whole life. I played in high school, and I played National Collegiate Athletic Association hockey in college. I'm a hockey nut. I have season tickets to the Blues, even though they're doing terribly this year. I also love golf and being outdoors.



Dr. DiPersio chats with Chadi Nabhan, MD, MBA, FACP, host of The HemOnc Pulse at the SOHO booth during the 2022 American Society of Hematology Annual Meeting and Exposition.

What brings you joy in life?

I have a great family. I got married late in life. I have a wife who's an academic hematologist and oncologist working in pediatrics.

I have twins, a boy and a girl, aged 12. They're good kids. When you're an older parent, you're just happy that they're alive every day, and they seem to be happy. I think as a younger parent, you're worried that they're not writing poems and doing multivariate calculus by the time they're four years old. For me, if they're happy and normal kids, and they're kind to other people, that's all I care about.

I have lots of friends and colleagues. I started with just a few people, and now there's a massive army of characters involved with the cancer center. I am proud and happy to have contributed in a small way to our success as a Division of Oncology and a National Cancer Institute Comprehensive Cancer Center even though my exceptionally talented colleagues did all of the heavy lifting. It's been a great experience for me here. I have great friends, great supporters, and terrific colleagues. That's the best part of life.

John DiPersio, MD, PhD, *is the Virginia E. and Sam J. Golman Professor in Medicine and Director of the Center for Gene and Cellular Immunotherapy at the Washington University School of Medicine in St. Louis.*

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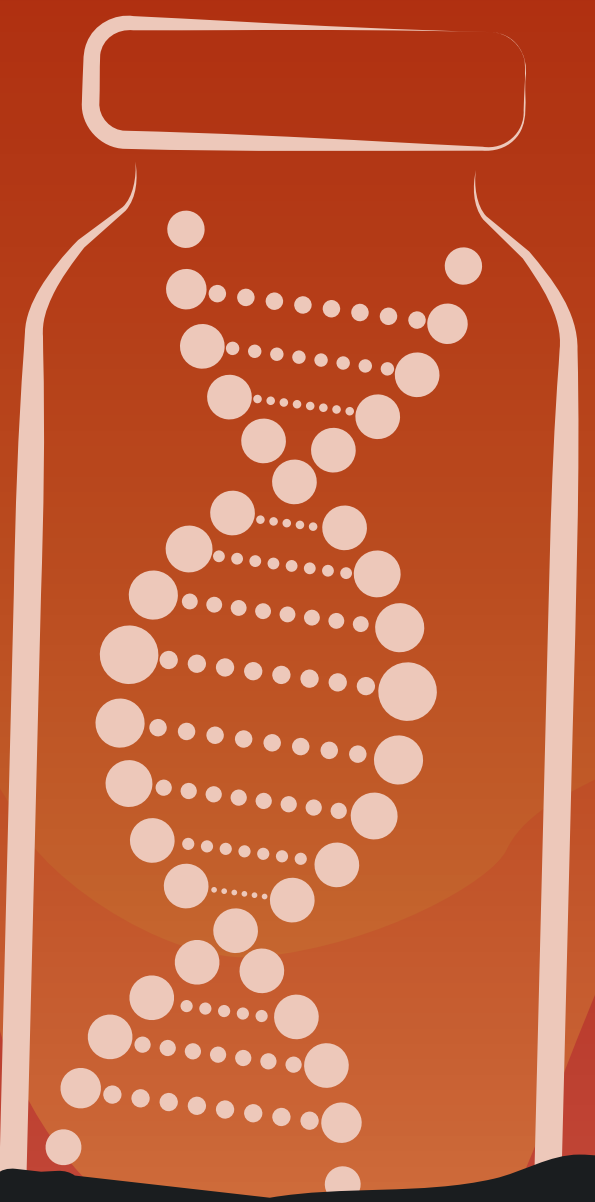
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In Focus

Blood Cancers Today *takes an in-depth look at hot topics in hematologic oncology*

Is a New Era Dawning for ctDNA in Lymphoma?

Specialists discuss the future of liquid biopsy



A new era of liquid biopsies for lymphoma may be on the horizon. Critical advances in understanding and detecting circulating tumor DNA (ctDNA) and cell-free DNA (cfDNA) in lymphoma could usher in a future with less invasive but more informative biopsies.

While ctDNA testing has yet to be used routinely in a clinical setting, hematologic oncologists are evaluating it in multiple contexts across lymphoma subtypes. There are numerous potential applications of ctDNA under study, from diagnostic genotyping to monitoring the disease burden over time, predicting treatment outcomes, adapting therapy, and evaluating post-treatment outcomes.[1-3]

"I think ctDNA is a really exciting, noninvasive, real-time biomarker tool that's become a very active area of research in lymphoma," said **Swetha Kambhampati, MD,** an Assistant Professor in the Division of Lymphoma at the City of Hope in Duarte, California.

A common overarching goal that unites the many potential applications of ctDNA is gaining information about a patient's disease that can be used to tailor therapy.

"You can detect tumor-associated mutations in the blood pretty reliably and get a decent genotype of a patient's tumor, and that can inform you about the patient's biology," said **Alex Herrera, MD,** an Associate Professor in the Division of Lymphoma at the City of Hope. "As we develop more targeted therapies, that can be instructive and help us think about personalizing therapy."

The idea of using ctDNA as a biomarker in oncology dates back multiple decades. A 2001 review article[4] stated that "circulating nucleic acids might eventually be used for the development of noninvasive diagnostic, prognostic, and follow-up tests for cancer."

However, researchers have gained a greater understanding of its biology in lymphoma in recent years, which has helped paint a larger and more detailed picture of its potential applications.

For one, it's become clear that "virtually all cases of lymphoma," including early-stage disease, have measurable levels of ctDNA in the peripheral blood and that genotypic profiles in ctDNA "strongly correlate with profiles in tumor tissue," according to a 2022 review article written by lead author by **Mark Roschewski, MD,** a Senior Clinician and the Clinical Director of the Lymphoid Malignancies Branch of the Center for Cancer Research at the National Cancer Institute in Bethesda, Maryland.[3]

"We first started studying the role of ctDNA in aggressive B-cell lymphomas in 2014 and things have evolved quickly," Dr. Roschewski told *Blood Cancers Today*.

Since that time, the field has "learned fundamental principles related to the potential utility of ctDNA at baseline, during therapy, at the end of therapy, and after therapy," Dr. Roschewski said. He believes these principles are "unlikely to change," and they "appear to be true across other lymphoma subtypes as well."

As clinicians and researchers learn more about the biology of ctDNA in lymphoma, the field is also witnessing parallel progress in another area.

"A second major advance is that the technology continues to improve, and the analytical sensitivity of the new assays is much improved," Dr. Roschewski said. "This allows additional questions to be asked and they are the focus of clinical trials now."

Using ctDNA to Ask Questions

While a mutation profile "can never replace the gold standard of pathological tissue-based diagnosis," liquid biopsies may have a "huge advantage over tissue biopsies because they allow serial testing and are considered a 'real-time' snapshot of disease burden," **Sarah Huet, PharmD, PhD,** and **Gilles Salles, MD, PhD,** both from the Université Claude Bernard Lyon 1, wrote in a 2020 publication.[1]

The ability to capture serial samples in a noninvasive fashion has created new avenues for research, allowing investigators to capture dynamic changes in ctDNA before, during, and after treatment. While many studies have conducted retrospective analyses of ctDNA, the pivotal phase III POLARIX trial prospectively evaluated ctDNA in patients with diffuse large B-cell lymphoma (DLBCL).[5]

"I am now a believer in the value of liquid biopsy and its future."

—Margarita Sánchez-Beato, PhD

The trial, which resulted in the approval of pola-R-CHP in the frontline setting for patients with DLBCL,[6] evaluated ctDNA in paired baseline and on-treatment plasma samples from patients with DLBCL who were receiving pola-R-CHP or R-CHOP.

The investigators, led by Dr. Herrera, measured patients' plasma ctDNA levels at baseline and during the first day of the second cycle of treatment. They used the Roche Avenio Non-Hodgkin Lymphoma Cancer Personalized Profiling by Deep Sequencing (CAPP-Seq) assay to measure ctDNA.

The study showed that patients with baseline ctDNA levels above the median had shorter progression-free survival (PFS) and overall survival (OS) than those with baseline ctDNA levels below the median.

"More importantly, we showed that changes in on-treatment ctDNA—[through] dynamic assessment of ctDNA—were associated with outcomes," Dr. Herrera said. "That was prognostic."

For example, patients who showed larger reductions in ctDNA levels after one treatment cycle had longer PFS and OS than those who had smaller reductions in ctDNA levels.[5]

"Patients who achieved a significant decline in their ctDNA had better outcomes, whereas patients who did not have a twofold log drop—which was our threshold—had poor outcomes," Dr. Herrera said.

However, he emphasized an important caveat to those results.

"The reality is—even though the findings were significant, and they were a decent discriminator of who was likely to do well or not well with the therapy—there were still a majority of patients who didn't achieve a twofold log drop [and] actually appeared to do fine," Dr. Herrera said. "They were still cured due to therapy."

An abstract Dr. Herrera and colleagues presented at the 2023 ASCO® Annual Meeting built upon those findings, showing that achieving ctDNA negativity at day one of cycle five and at the end of treatment were also prognostic for longer OS and PFS.[7]

While more questions remain, the POLARIX trial can inform the design of future studies that prospectively evaluate ctDNA.

"Even though this was a promising validation of something that we've studied for many years and primarily done in a retrospective way, I still think there's room to improve," Dr. Herrera said.

Beyond DLBCL, ctDNA is also under study in other subtypes of lymphoma.

For example, research by Dr. Roschewski and colleagues has shown that early changes in ctDNA are associated with outcomes in patients with treatment-naïve mantle cell lymphoma (MCL).[8,9]

In a recent study, they analyzed ctDNA dynamics in patients with previously untreated MCL who received induction therapy with bortezomib and DA-EPOCH-R for six cycles.[9] They randomly assigned patients who responded to therapy to receive bortezomib maintenance or undergo observation.

The researchers collected serum samples before treatment, after an initial bortezomib treatment window, after cycles one and two, at the end of induction, and at each follow-up visit. They used next-generation sequencing (NGS) to identify and quantify ctDNA in the serum samples.

Patients who did not have detectable ctDNA after two cycles of induction had significantly longer PFS and OS compared with those who had detectable ctDNA. These results suggest that "interim ctDNA negativity strongly correlates with improved survival and supports the investigation of response-adapted strategies," the study's authors concluded.[9]

The findings, combined with other emerging data on ctDNA in MCL, have big-picture implications that can inform the design of future studies.

"These concepts can be applied to clinical trials now where these biomarkers can identify patients who are responding to therapy compared [with] those with more resistant disease," Dr. Roschewski said.

While the body of research on ctDNA in aggressive lymphomas has been expanding, there's still much to be done in other subtypes.

"We do need more data and a validated strategy in other types of lymphomas, particularly for indolent lymphomas and Hodgkin [lymphoma]," Dr. Kambhampati said.

In follicular lymphoma, which is the most common indolent non-Hodgkin lymphoma, this work is underway.

In Focus

A recent prospective pilot study evaluated if ctDNA could predict response to therapy and disease progression within 24 months of diagnosis in patients with follicular lymphoma.[10] This prospective pilot study represents the "first analysis of both basal and dynamic changes in ctDNA levels that employ longitudinal cfDNA genotyping" in a multicenter cohort of patients with follicular lymphoma.[10]

It was key to "establish the best moment and the best conditions" in the pilot study to collect the samples, said **Margarita Sánchez-Beato, PhD,** who was the senior author of the study. Dr. Sánchez-Beato is the Head of the Lymphoma Research Group in the Medical Oncology Department and Scientific Coordinator of the Technical Support Units at the Instituto Investigación Sanitaria Puerta de Hierro-Segovia de Arana in Spain.

To determine the optimal timing and conditions, Dr. Sánchez-Beato and colleagues prospectively collected basal pretreatment, on-treatment, end-of-treatment, and follow-up plasma samples from patients with follicular lymphoma who received chemotherapy plus rituximab. They performed targeted deep sequencing on cfDNA and tumor genomic DNA from diagnostic biopsy samples.

Nearly three-quarters (73%) of alterations detected in the diagnostic tissue samples were detected in basal cfDNA.[10] Furthermore, the study showed that basal ctDNA levels are "associated with the risk of early progression and response to treatment" in follicular lymphoma and that cfDNA "monitoring and genotyping during treatment and follow-up predict response to treatment and early progression."[10]

follow-up evaluations in DLBCL and classical Hodgkin lymphoma, according to an article by **Pierre Decazes, MD, PhD,** of the Henri Becquerel Cancer Centre and the University of Rouen, and colleauges.[11]

Furthermore, PET imaging results have been used to adapt therapy in patients with classical Hodgkin lymphoma[12] and DLBCL.[13]

However, a retrospective analysis of patients with DLBCL who received EPOCH with or without rituximab suggests "ctDNA identifies patients at risk of recurrence prior to imaging."[14] The study used a quantitative high-throughput method that combined amplification of immunoglobulin gene segments with NGS to detect ctDNA in serial samples of serum obtained during treatment and follow-up.

"Compared [with] imaging tests, these assays appear to have a major advantage regarding analytic sensitivity," Dr. Roschewski said.

Beyond greater sensitivity, there are practical advantages to reducing the "scan burden" on patients, clinicians, and health care systems, he said.

Dr. Herrera agreed that scanning patients less would be preferable.

"I'd love to scan patients less frequently or not at all," Dr. Herrera said.

However, there is evidence that suggests imaging and ctDNA assessments can be complementary tools.

For example, a recent prospective study of patients with newly diagnosed large B-cell lymphoma (LBCL) receiving R-CHOP or similar regimens showed that combining information on the ctDNA load with data on the total metabolic tumor volume from FDG-PET/CT "improved the risk stratification" of patients with aggressive LBCL, "even with a short follow-up."[15]

> **"Compared [with] imaging tests, these assays appear to have a major advantage regarding analytic sensitivity."** *—Mark Roschewski, MD*

Gaining these prognostic insights early is critical, Dr. Sánchez-Beato said, as they could allow clinicians to make informed decisions about adapting therapy.

"You have this information at the beginning," she said. "You can decide."

Dr. Sánchez-Beato also pointed back to another practical benefit of using a liquid biopsy: the ability to collect serial samples.

"If it was a bone marrow biopsy, it would be impossible, but it is viable to take samples of the peripheral blood at different timepoints," she said.

Does Imaging Have a Complementary Role?

Imaging tests are another noninvasive way to collect information about disease burden at multiple timepoints in patients with lymphoma.

For example, ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) scans are a "standard at baseline to describe the extension of the disease" and during

While more research remains to be done on imaging and ctDNA assessments in lymphoma, they may eventually augment one another as noninvasive methods to assess changes in disease burden over time.

"There is a growing trend toward a PET/ctDNA combination to monitor [measurable] residual disease (MRD) in patients … new parameters will become more and more accessible as tumors are increasingly segmented automatically and could help to determine whether ctDNA should replace or be additional data to PET/CT," Dr. Decazes and colleagues wrote.[11]

The Path to an 'Optimal' ctDNA Assay

As clinicians and researchers elucidate the biology and prognostic value of ctDNA in lymphoma, they see a growing need for further advances in ctDNA assays.

"In an ideal world, we would have [an even more] sensitive assay to really help us identify who are the highest-risk patients," Dr. Herrera said. "Because even here [in the POLARIX trial], it was hard to identify a group of patients who really did poorly enough that you would really want to change their therapy."

However, designing a ctDNA assay that is both highly sensitive and accurate necessitates overcoming technical and biological challenges.

"Because you have different mutations and markers that may be important in different lymphoma subtypes … it's hard to do one all-encompassing ctDNA technique," Dr. Kambhampati said.

An "optimal" ctDNA assay must be able to "efficiently utilize all available cfDNA" while maintaining a low background error profile that allows it to detect low-level signals and be able to "identify the relevant mutations" across lymphoma subtypes, according to Dr. Roschewski and colleagues.[3]

Polymerase chain reaction (PCR)- or NGS-based approaches are currently used in ctDNA assays, but those approaches fall across a spectrum in terms of sensitivity and potential limitations. For example, digital PCR has a sensitivity of around 1:10,000 but is limited by the amount of available DNA, while CAPP-Seq, an NGS-based approach, has a sensitivity of around 2.5:100,000 but is limited by its error profile.[3]

Other assays include NGS-based immunoglobulin gene sequencing, Lymphopanel, and whole-genome sequencing. Another approach for "improving the limit of detection" for ctDNA is phased variant enrichment and detection by sequencing (PhasED-Seq).[3]

Targeted sequencing approaches such as CAPP-Seq and PhasED-Seq also have another potential advantage. They can "move beyond simple disease detection and perform mutational profiling and molecular genotyping," Dr. Roschewski and colleagues wrote.[3]

Despite the wide array of ctDNA assays and approaches available, there is more to be done before they enter routine clinical use.

"The most progress in clinical application of ctDNA techniques has been made in DLBCL so far, but we know we need more progress in the other tumor subtypes," Dr. Kambhampati said.

Plus, with numerous assays and techniques available, there is a need for greater consistency across the board, Dr. Roschewski emphasized.

"The field currently lacks proper standardization of the way these tests are collected, processed, and analyzed," Dr. Roschewski said. "That creates a gap where different studies are using techniques that may not be equal to other techniques or processes."

The Journey to the Clinic

Beyond improving assays to measure ctDNA, there are several other steps to be taken along the journey to its wider implementation and clinical use.

"In the future, one hopes to have more harmonization of the standards for collection, processing, and analysis," Dr. Roschewski said. "Further, these tests are not widely available for clinical use. In part, this is because there is not [a] defined clinical utility but also because [these tests] require central processing and the turnaround time for clinicians is not yet feasible."

When it comes to adapting therapy based on ctDNA, Dr. Herrera agreed that speed is a critical consideration.

"The obvious and inherent challenge is time," he said. "If you're going to adapt therapy based on a ctDNA test, there is a certain requisite amount of time that it takes to run the sample, determine whether there's ctDNA present and how much ctDNA there is, and then feed that back to the treating physician or the investigator to make a determination about the treatment."

a higher level of confidence about the trajectory of the disease and the appropriateness of the current course of treatment.

"If we come up with a validated, reproducible, and accurate method of measuring disease in a noninvasive manner through liquid biopsy, I think this would be incredible from a patient perspective," Dr. Kambhampati said.

"I think ctDNA is a really exciting, noninvasive tool that's become one of the cutting-edge technologies to look at in lymphoma." *—Swetha Kambhampati, MD*

Another important step along the path to routine clinical use will be ensuring quality and consistency in sample collection and storage.

"Using proper cell-stabilizing tubes can really improve the results, and then having protocols for storage and shipment that are harmonized across centers will further improve the validity of results," Dr. Roschewski said.

The quality and quantity of the sample is especially important when testing lymphomas that have a lower tumor burden, Dr. Sánchez-Beato said.

"This is one of the critical points, to have samples of the highest quality to perform this assay in a standardized way," she said. "The amount of peripheral blood to collect is also critical, especially in the case of indolent lymphomas."

With the array of biological, technological, and logistical challenges, will it be possible for ctDNA to move into the realm of routine clinical practice?

"We have examples of other diseases, such as leukemias and multiple myeloma, where MRD assessment is a standard part of what they do and how they assess the disease to make therapy decisions," Dr. Herrera said. "I think it's possible [for ctDNA], but there are logistical hurdles to overcome."

The field will need to validate assays, standardize practices, and design specific studies to move forward.

"We would require trials that assess ctDNA-guided therapy," Dr. Herrera said. "If those trials result in an improvement in outcomes for patients, then it's worth all the infrastructure and all the logistical challenges."

If the use of ctDNA and cfDNA does eventually reach the clinic, it could have significant implications for patients and health care professionals alike. For example, if ctDNA could be used to identify the baseline tumor volume and genotype, it could reduce the need for scans or invasive biopsies.

"Patients obviously may still need imaging and other response assessments, but it would be an amazing tool to complement what we already have, and potentially even replace some of the invasive techniques," Dr. Kambhampati said.

It could also allow patients and clinicians to have

While questions and challenges surrounding ctDNA testing remain, she is optimistic about its applications.

"I think it's truly remarkable progress that's been made in the field," Dr. Kambhampati said. "While a lot more remains to be done, I think we have a better understanding of using ctDNA for tumor quantification, risk stratification, and prognostication so that we can better individualize our treatments for our patients."

Dr. Sánchez-Beato agreed, emphasizing that her experience studying liquid biopsy in follicular lymphoma has shifted her views on its potential.

"I must say that at the beginning, I was quite skeptical about the value of liquid biopsy," she said. "But when we began to work with [these] data, [they were] surprising … I am now a believer in the value of liquid biopsy and its future."

Cecilia Brown is an Associate Editor for Blood Cancers Today.

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SOHO Ambassador Program Strengthens Global HemOnc Community



The Raouché in Beirut, Lebanon.

From Houston, Texas, to Beirut, Lebanon, the Society of Hematologic Oncology (SOHO) global community continues to grow thanks in large part to the efforts of its Ambassador Program.

Established in 2012, the program's mission is to foster the worldwide exchange of knowledge and collaboration among thousands of hematologist oncologists, regardless of geography.

The Ambassador Program works by having select individuals, recognized as experts in their respective countries, represent the Society in their given regions. This is often achieved by facilitating informal discussions among local experts or through one of the many official SOHO satellite meetings, which are held in person (and often as hybrid events) within the ambassador's region.

For the global hematology-oncology community, the program has the added benefit of actively reducing barriers to access and knowledge.

"If you can't go to SOHO, SOHO is coming to you," said **Elias Jabbour, MD,** a Professor in the Department of Leukemia at the University of Texas MD Anderson Cancer Center. "The idea is we bring the information to the people."

Ambassador Program by the Numbers

Since the program's inception, 126 ambassadors in 63 countries have joined the initiative, according to **Hagop Kantarjian, MD,** co-founder of SOHO and the Society's Ambassador Program.

"[SOHO] advocates our mission by uniting members [from] around the world to discuss and unify the most advanced management and treatment approaches for patients with hematologic malignancies," Dr. Kantarjian said. "The SOHO Ambassador Program is one of our core initiatives to accomplish this mission."

The ambassadors play a vital role in cross-collaboration within the greater SOHO regional networks and actively facilitate the exchange of information and communication between the Society and local experts in the field of hematologic oncology.

"The program stands as a great initiative," said **Phillip Scheinberg, MD,** ambassador of the SOHO Brazil chapter, which hosted one of the first regional SOHO events in 2018. "Because of it, SOHO has rapidly become a known society in Brazil, and the quality of the regional meeting has earned a good reputation."

Dr. Scheinberg, who is the Head of the Division of Hematology at Hospital A Beneficência Portuguesa in São Paulo, Brazil, explained how the regional meetings instilled a sense of community within the larger SOHO network.

"It approximated people from different parts of the world, not only toward the annual meeting in Houston, but it also instilled a sense of ownership in each region," Dr. Scheinberg said. "It enabled us to work in our own countries in order to make SOHO a success."

Giving Back

In 2023, SOHO Israel held its first regional meeting, and shortly after the annual event in Houston this September, the new Middle East/North Africa (MENA) chapter will hold its inaugural meeting, marking a milestone for the region, which had relied on unofficial gatherings until now.

Dr. Jabbour, who is originally from Lebanon, and **Amer Zeidan, MBBS, MHS,** a native of Jordan, serve as ambassadors to the region. The two will co-chair the program with **Ahmad Ibrahim, MD,** of the Middle East Hospital in Bsalim, Lebanon, who is also an ambassador, and **Rami Komrokji, MD,** Head of the Leukemia and MDS Section at Moffitt Cancer Center.

Both Drs. Jabbour and Zeidan stated that one of their motivations in organizing a local chapter is to give back to their communities.

"I think part of giving back is to help mentor these rising stars so they can fulfill their dreams, whether they choose to come to the United States or remain in their home regions," Dr. Jabbour said. "By engaging in top-notch research that benefits their community, they can advance their careers and academic pursuits."

The goal is to establish collaborative channels for medical research and education, aiming to help build capacity in their home regions, Dr. Zeidan explained.

"We, along with many of our colleagues who have relocated to the United States, often receive inquiries about patient care and guidance for managing cases in our home countries," Dr. Zeidan, who is an Associate Professor of Medicine at Yale University, said. "We share a strong desire to enhance knowledge and foster collaboration in medical education, research, and related activities to benefit the people in our countries and regions of origin."

SOHO MENA will have the distinct challenge of customizing each local event according to the specific needs of the region.

"The presentations will be tailored based on the country," Dr. Zeidan said. "What can be done in the United States may not be appropriate in these regions because of regulations or lack of drugs or resources. For example, we will have cases and meet-the-expert sessions according to the country."

The goal is to alternate future meetings between Lebanon and Jordan, eventually expanding into other countries within the region on a rotating basis, Dr. Zeidan said, adding that he was inspired by a meeting organized by SOHO Brazil, where there was an emphasis on global reach.

"Hopefully it will not end with the meeting," Dr. Zeidan said. "The meeting will be just a starting point for additional collaborations. Beyond the scientific talks, in-person networking is invaluable for progress in research."

Where Are You Going?

Unlike larger conferences, SOHO meetings in general are more intimate and allow participants to focus and absorb the content in a way that is not possible at the annual American Society of Clinical Oncology (ASCO) or American Society of Hematology (ASH) meetings.

"You can't go to all of the sessions, and you just become very conflicted," Dr. Scheinberg said, in reference to the large trade shows. "Here we have one room. We cover acute lymphocytic leukemia in the morning. We cover multiple myeloma in two or three hours. We have world-class speakers in one room. You're not there fighting over your time with anybody else or any of their presentations."

Each regional meeting has its own character, and by Dr. Scheinberg's own admission, SOHO Brazil "tries to keep things light and informal." This tone becomes evident when skimming through the chapter's annual meeting program, where titles reflect a breezy creativity (for example, a session on chronic lymphocytic leukemia was titled, "Mirror, Mirror on the Wall, Who Is the Most Beautiful BTK Inhibitor of Them All").

"I came to the United States and Dr. Kantarjian mentored me. I am where I am today because of that, and it's the same for Amer Zeidan and his mentorship. There are people in these regions we can do the same for." *—Elias Jabbour, MD*

Dr. Scheinberg admits that he spends an inordinate amount of time crafting clever titles but said SOHO Brazil attendees go crazy for the program. He explained that the informality of the meeting brings a lot of value to people.

"That differs from other events, such as pharmaceutical events where everything has to be approved down to the individual slide," he said. "The model, objectives, and format are all inspiring, dynamic, comprehensive, interactive, and fresh. It is also very different from what we have seen from other societies."

Across the Atlantic in France, **Mauricette Michallet, MD,** one of the ambassadors for SOHO France, explained they try to keep the program distinct from the meeting in Houston, while maintaining the basic structure.

"We see the program in the United States, and we try to be innovative," she said. "We include the latest news on all the [hematologic] malignancies and account for what happened at [the] ASH [Annual Meeting] and the European Hematology Association [Congress]."

Dr. Michallet, who is a Professor at the Léon Bérard Cancer Centre in Lyon, France, joined the Ambassador Program after regularly attending the SOHO Annual Meeting for many years, she said. At one point, she and a fellow clinician organized a local meeting in France. Unfortunately, those plans were upended by COVID-19, forcing the team to cancel the 2020 meeting, which would have been the first one in the country.

"We organized two years later in 2022, which was the first SOHO meeting in France," Dr. Michallet explained. "That meeting was a success," she said, estimating there were between 120 and 180 registrants per day.

The chapter is currently organizing the 2023 SOHO France meeting, which is scheduled for September.



Physicians from Brazil attend the SOHO Annual Meeting in Houston in large part due to the SOHO Ambassador Program. Image courtesy of Dr. Phillip Scheinberg.

Field Dispatch



Dr. Zeidan speaking during SOHO Brazil. Image courtesy of Dr. Zeidan.

"We already have the program, and it includes participation from French, European, and American people," she said.

SOHO France also works in tandem with SOHO Italy, Dr. Michallet noted, adding that the two organizations share significant developments and research in hematologic oncology within their respective countries.

"We have a good collaboration with Italy and with Claudio Cerchione, who was invited to the SOHO meeting in France in 2022," she said. "I think it's important to [have] collaboration between countries in Europe [that are holding] SOHO meetings."

As for SOHO Italy, now in its fifth year, **Claudio Cerchione, MD,** the region's ambassador, echoed Dr. Michallet's sentiments.

"The idea of SOHO Italy is to be a local part of SOHO and to connect worldwide experts in the idea of spreading their expertise in our country," Dr. Cerchione said. "I think that we are doing something different in Italy. Before, all the education was [based] in Italy, in Italian, and now we are also sharing international content. I think this is becoming [a] really important point of education, [as is] the possibility of [working] together."

Dr. Cerchione, who is a hematologist at the Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori IRCCS in Meldola, Italy, estimated 1,000 people will register for SOHO Italy's fifth annual meeting, which will be a hybrid event (the in-person program will be held in Rome October 3-6, 2023). He was effusive in his thanks to the clinicians at MD Anderson, many of whom sit on SOHO Italy's Scientific Board, including Dr. Jabbour, for their support and guidance and said SOHO Italy is becoming more than just a conference, with its novel projects and notable growth.

"Today, we are increasing our activities, so the annual conference became four days long," Dr. Cerchione said. "We are connecting with major institutions [from around] the world. We want to be something more than a conference—we want SOHO Italy [to be] a live scientific society," he said.

Free Is Free

An added benefit of the regional SOHO meetings is that they are free, which is quite a bargain in an era where the cost of a conference registration alone can run $1,000 or more. There is no catch to that free price tag—participants just need to sign up for a SOHO membership, which is also free for life and provides a deep discount to the SOHO Annual Meeting in Houston.

"SOHO membership is free," Dr. Scheinberg said. "Once you're a SOHO member, you can register for the SOHO Brazil event for free. It's very easy. It has been a successful model in Brazil, where we have averaged between 1,000 and 1,500 attendees in the medical and multidisciplinary sessions over the years."

The affordability of these local meetings, offered through membership at no cost, ensures accessibility for those who may not have been able to afford to attend otherwise.

"Some colleagues work in small institutions that have no funding," Dr. Cerchione said. "Our idea is to give this education free to everyone."

These regional events are important, as only a minority of people have the privilege to travel to the ASCO or ASH annual meetings, or to go to Houston for SOHO, Dr. Jabbour said.

> **"Our idea is to give this education free to everyone."**
>
> *—Claudio Cerchione, MD*

"Rather than limiting the attendance to a select few physicians at these conferences, we can take a proactive approach by expanding our reach to an entire region and beyond," he said, adding that "I'm fortunate. I came [to the United States] and [Dr. Kantarjian] mentored me. I am where I am today because of that, and [it's the] same for Amer [Zeidan] and his mentorship. There are people in these regions we can do the same for."

Leah Sherwood is Managing Editor of Blood Cancers Today.



SOHO Italy 2022. Image courtesy of SOHO.

Regulatory Actions

Recent therapy approvals, updates, and clinical trial results in the field of hematologic oncology

FDA Approves Glofitamab for Relapsed or Refractory DLBCL

The US Food and Drug Administration (FDA) approved glofitamab for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified or large B-cell lymphoma after two or more lines of systemic therapy.

The accelerated approval was based on results from the phase I/II NP30179 trial that assessed glofitamab as a fixed course for 8.5 months in 132 patients with relapsed or refractory DLBCL. Nearly one-third (30%) of patients had relapsed after prior chimeric antigen receptor T-cell therapy.

The overall response rate (ORR) with glofitamab treatment was 56% (n=74), with 43% achieving a complete response (n=57). Responses lasted for at least nine months in 68.5% of patients, and the median duration of response was 1.5 years.

The most common adverse events were cytokine release syndrome (70%), musculoskeletal pain (21%), fatigue (20%), and rash (20%).

Glofitamab is the first FDA-approved bispecific antibody for the treatment of relapsed or refractory DLBCL that is given for a defined period.

Source: Genentech, June 2023

FDA Puts Clinical Hold on CART-ddBCMA

The FDA has put a clinical hold on the investigational new drug CART-ddBCMA for the treatment of patients with relapsed or refractory multiple myeloma (MM).

The clinical hold was received on June 16 following the recent death of a patient. Arcellx, the manufacturer of CART-ddBCMA, said in a press statement that the company believes that "limitations on bridging therapy are a contributing factor." Arcellx reported that it is working with the FDA to amend the protocol to expand options for patients that are consistent with current clinical practice. The company also reported that the FDA provided clearance to Arcellx to continue to dose patients who have undergone lymphodepletion.

CART-ddBCMA is under evaluation in the phase II iMMagine-1 study, a pivotal, open-label, multicenter, clinical trial. The primary objective of the study is to evaluate the ORR over a 24-month period. In addition to safety, secondary endpoints include depth of disease response, duration of response, and overall survival over a 24-month period.

Source: PR Newswire, June 2023

Blinatumomab Receives Full FDA Approval for MRD-Positive B-Cell Precursor ALL

The FDA has approved the supplemental Biologics License Application for blinatumomab as a therapy for adults and children with CD19-positive B-cell precursor acute lymphoblastic leukemia (B-cell ALL) who are in their first or second complete remission (CR) with measurable residual disease (MRD) of at least 0.1%, according to a news release from Amgen.

This approval converts the accelerated approval of blinatumomab—a bispecific T-cell engager that targets CD19 surface antigens on B cells—to full approval. The approval is based on additional data from two studies that were submitted.

"In a phase II study, roughly 80% of adult patients treated with blinatumomab experienced a complete MRD response," principal investigator **Elias Jabbour, MD,** of the University of Texas MD Anderson Cancer Center, said in the news release. "The FDA's decision to grant a full approval for blinatumomab further validates the use of this therapy to treat adults and children with B-cell precursor ALL with MRD present following a remission, which is a strong predictor of relapse in this patient population."

The FDA previously granted breakthrough therapy and priority review designations to blinatumomab. In addition to its approval for patients with CD19-positive B-cell ALL who are in their first or second CR with MRD of at least 0.1%, blinatumomab is also approved in the United States for the treatment of relapsed or refractory CD19-positive B-cell ALL in adults and children.

Source: Amgen, June 2023

NDA Submitted to FDA for Imetelstat

A New Drug Application (NDA) for the telomerase inhibitor imetelstat has been submitted to the FDA. Imetelstat is used in the treatment of transfusion-dependent anemia in adult patients with low- to intermediate-1-risk myelodysplastic syndromes who have failed to respond or have lost response to or are ineligible for erythropoiesis-stimulating agents.

The NDA submission is based on results from the IMerge phase III trial, in which the primary endpoint of eight-week transfusion independence was significantly higher with imetelstat versus placebo ($P<.001$). Mean hemoglobin levels in imetelstat-treated patients increased significantly ($P<.001$) over time compared with placebo patients, Geron, the manufacturer of the drug, reported in a press release.

Geron is expected to submit a Marketing Authorization Application in the European Union in the second half of 2023.

Source: Business Wire, June 2023

FDA Receives Supplemental BLA for Ciltacabtagene Autoleucel

The FDA has received a supplemental Biologics License Application (BLA) for ciltacabtagene autoleucel that seeks to expand its label to include the treatment of adults with relapsed and lenalidomide-refractory MM who have received at least one prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent.

The supplemental BLA submission is supported by data from the CARTITUDE-4 trial, an international, randomized, open-label, phase III study evaluating the efficacy and safety of ciltacabtagene autoleucel. The study compared ciltacabtagene autoleucel with standard-of-care regimens in adults with relapsed and lenalidomide-refractory MM who received one to three prior lines of therapy.

Source: PR Newswire, June 2023

Positive Opinion Issued for JZP458

The European Medicines Agency Committee for Medicinal Products for Human Use issued a positive opinion recommending Marketing Authorization to JZP458 for its use as a component of a multiagent chemotherapeutic regimen for the treatment of ALL and lymphoblastic lymphoma in adult and pediatric patients (one month and older) who developed hypersensitivity or silent inactivation to *Escherichia coli*-derived asparaginase.

JZP458 is a recombinant *Erwinia* asparaginase or crisantaspase that uses a *Pseudomonas fluorescens* expression platform, according to Jazz Pharmaceuticals, the manufacturer of JZP458.

Source: Jazz Pharmaceuticals, July 2

SWITCH TREATMENT AT THE CRITICAL MOMENT

Consider ICLUSIG for your appropriate patients

ICLUSIG®

CML | **Ph+ ALL**

ICLUSIG IS THE ONLY 3RD-GENERATION TKI IN CML AND PH+ ALL AND SHOWS ACTIVITY AGAINST ALL KNOWN SINGLE POINT MUTATIONS, INCLUDING T315I[1-3]

INDICATIONS AND USAGE

ICLUSIG is a kinase inhibitor indicated for the treatment of adult patients with:

- Chronic phase (CP) chronic myeloid leukemia (CML) with resistance or intolerance to at least two prior kinase inhibitors
- Accelerated phase (AP) or blast phase (BP) CML or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom no other kinase inhibitors are indicated.
- T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Ph+ ALL

Limitations of Use: ICLUSIG is not indicated and is not recommended for the treatment of patients with newly diagnosed CP-CML.

IMPORTANT SAFETY INFORMATION

WARNING: ARTERIAL OCCLUSIVE EVENTS, VENOUS THROMBOEMBOLIC EVENTS, HEART FAILURE, and HEPATOTOXICITY

See full prescribing information for complete boxed warning.

- Arterial occlusive events (AOEs), including fatalities, have occurred in ICLUSIG-treated patients. AOEs included fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. Monitor for evidence of AOEs. Interrupt or discontinue ICLUSIG based on severity. Consider benefit-risk to guide a decision to restart ICLUSIG.
- Venous thromboembolic events (VTEs) have occurred in ICLUSIG-treated patients. Monitor for evidence of VTEs. Interrupt or discontinue ICLUSIG based on severity.
- Heart failure, including fatalities, occurred in ICLUSIG-treated patients. Monitor for heart failure and manage patients as clinically indicated. Interrupt or discontinue ICLUSIG for new or worsening heart failure.
- Hepatotoxicity, liver failure and death have occurred in ICLUSIG-treated patients. Monitor liver function tests. Interrupt or discontinue ICLUSIG based on severity.

Please see accompanying Brief Summary of full Prescribing Information on the following pages, and Important Safety Information, including Boxed Warning, throughout.

ICLUSIG DELIVERED CLINICALLY MEANINGFUL RESPONSES IN RESISTANT OR INTOLERANT CP-CML AND PH+ ALL[1]

CP-CML[1,a]



55% achieved MCyR by 12 months (n=148/267) (95% CI: 49, 62)

40% achieved MMR at any time (n=105/267) (95% CI: 35, 47)

Estimated 5-year survival in CP-CML[1]

73% overall survival (95% CI: 66, 79)

63% progression-free survival (95% CI: 45, 80)

Ph+ ALL[1]



41% achieved MaHR by 6 months[2] (n=13/32; 95% CI: 24, 59)[b]

Median time to MaHR 0.7 months (range: 0.4-5.0)

Cytogenetic responses at any time[1,c]

38% CCyR (n=12/32)

47% MCyR (n=15/32)

SAFETY PROFILE[1]:

Serious adverse reactions occurred in **69%** of patients who received ICLUSIG. Serious adverse reactions in >2% of patients included ABLs (20%), pneumonia (10%), cardiac arrhythmias (8%), pancreatitis/lipase elevation (7%), abdominal pain (5%), cardiac failure (5%), hemorrhage (5%), sepsis (5%), VTEs (5%), fluid retention and edema (4.5%), pyrexia (4.5%), secondary malignancies (3%), anemia (3.2%), hypertension (3.0%), thrombocytopenia (3.0%), febrile neutropenia (2.8%), cellulitis (2.7%), and arthralgia (2.2%). Fatal adverse reactions occurred in 8% of patients who received ICLUSIG; the most frequent fatal adverse reactions were ABLs (2%), sepsis (1.6%), and hemorrhage (1.2%).

Permanent discontinuation of ICLUSIG due to an adverse reaction occurred in 21% of CP-CML, 12% of AP-CML, 15% of BP-CML, and 9% of Ph+ ALL patients. The most frequent adverse reactions that led to treatment discontinuation were thrombocytopenia (4.5%) and ABLs (4%).

Dose interruption of ICLUSIG for more than 3 days due to an adverse reaction occurred in 71% of patients and dose reduction of ICLUSIG due to an adverse reaction occurred in 63% of patients. Adverse reactions which required a dosage interruption or dose reduction in >5% of patients included thrombocytopenia (21%), pancreatitis/lipase elevation (17%), abdominal pain (14%), rash and related conditions (14%), neutropenia (14%), hepatic dysfunction (12%), ABLs (10%), arthralgia (8%), anemia (7%), ALT increased (6%), and AST increased (5%).

The most common (≥20%) non-hematologic adverse reactions were rash and related conditions, arthralgia, abdominal pain, fatigue, constipation, headache, dry skin, fluid retention and edema, hepatic dysfunction, hypertension, pyrexia, nausea, hemorrhage, pancreatitis/lipase elevation, ABLs, diarrhea, vomiting, and myalgia.

Learn more at ICLUSIG.com/HCP

PACE TRIAL DESIGN[1,2]: PACE was a single-arm, phase 2 trial in adult patients with CML or Ph+ ALL who were resistant or intolerant to dasatinib or nilotinib, or who had the BCR-ABL1 T315I mutation regardless of prior TKI use (N=449; n=270 CP-CML; n=62 Ph+ ALL). The primary efficacy endpoint for CP-CML was MCyR at 12 months. The primary efficacy endpoint for Ph+ ALL was MaHR by 6 months.

Starting dose for ponatinib was 45 mg once daily. Dose reductions to 30 mg or 15 mg once daily were applied to manage adverse events, per protocol, or implemented proactively in 2013: 15 mg once daily for CP-CML patients with MCyR, and 30 mg once daily for patients with CP-CML without MCyR, patients with AP-CML, and patients with BP-CML.

[a] The primary endpoint for Ph+ ALL of MaHR by 6 months combined complete hematologic response (CHR) and no evidence of leukemia.
[b] CHR: WBC per institutional ULN, WBC ≤ ULN, platelet ≥100,000/mm³, no blasts or promyelocytes in peripheral blood, bone marrow blasts ≤5%, <5% myelocytes plus metamyelocytes in peripheral blood, basophils <20% in peripheral blood, no extramedullary involvement (including hepatosplenomegaly or splenomegaly).

ANC=absolute neutrophil count; AP-CML=accelerated phase chronic myeloid leukemia; BCR-ABL1=BCR-ABL1 tyrosine kinase inhibitor; CCyR=complete cytogenetic response; CHR=complete hematologic response; MaHR=major hematological response; MCyR=major cytogenetic response; Ph+ ALL=Philadelphia chromosome positive acute lymphoblastic leukemia; TKI=tyrosine kinase inhibitor; ULN=upper limit of normal for the lab; WBC=white blood cell.

ICLUSIG
(ponatinib) tablets
15 mg / 30 mg / 45 mg / 1 mg

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Arterial Occlusive Events (AOEs): AOEs, including fatalities, have occurred in patients who received ICLUSIG in OPTIC and PACE. These included cardiovascular, cerebrovascular, and peripheral vascular events. The incidence of AOEs in OPTIC (45 mg—45 mg) was 14% of 84 patients; 6% experienced Grade 3 or 4. In PACE, the incidence of AOEs was 28% of 449 patients; 14% experienced Grade 3 or 4. Fatal AOEs occurred in 2.1% of patients in OPTIC, and in 2% of patients in PACE. Some patients in PACE experienced recurrent or multiple vascular occlusion. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. The most common risk factors observed with these events in PACE were history of hypertension, hypercholesterolemia, and non-ischemic cardiac disease. In OPTIC and PACE, AOEs were more frequent with increasing age.

In OPTIC, patients with uncontrolled hypertension or diabetes and patients with clinically significant, uncontrolled, or active cardiovascular disease were excluded. In PACE, patients with uncontrolled hypertension or diabetes and patients with clinically significant or active cardiovascular disease within the 3 months prior to the first dose of ICLUSIG were excluded. Consider whether the benefits of ICLUSIG are expected to exceed the risks.

Monitor for evidence of AOEs. Interrupt, then resume at the same or decreased dose or discontinue ICLUSIG based on recurrence/severity. Consider benefit-risk to guide a decision to restart ICLUSIG.

Venous Thromboembolic Events (VTEs): Serious or severe VTEs have occurred in patients who received ICLUSIG. In PACE, VTEs occurred in 8% of 449 patients including serious or severe (Grade 3 or 4) VTEs in 5.6% of patients. VTEs included deep venous thrombosis, pulmonary embolism, superficial thrombophlebitis, retinal vein occlusion, and retinal vein thrombosis with vision loss. The incidence was higher in patients with Ph+ ALL (19% of 32 patients) and BP-CML (10% of 62 patients). One of 84 patients in OPTIC experienced a VTE (Grade 1 retinal vein occlusion). Monitor for evidence of VTEs. Interrupt, then resume at the same or decreased dose or discontinue ICLUSIG based on recurrence/severity.

Heart Failure: Fatal, serious or severe heart failure events have occurred in patients who received ICLUSIG. In PACE, heart failure occurred in 9% of 449 patients; 7% experienced serious or severe (Grade 3 or higher). Heart failure occurred in 13% of 84 patients in OPTIC; 13% experienced serious or severe (Grade 3 or 4). In PACE, the most frequently reported heart failure events (≥2%) were congestive cardiac failure (3.1%), decreased ejection fraction (2.9%), and cardiac failure (2%). In OPTIC, the most frequently reported heart failure events (1 patient each) were left ventricular hypertrophy (1.2%) and BNP increased (1.2%). Monitor patients for signs or symptoms consistent with heart failure and manage heart failure as clinically indicated. Interrupt, then resume at reduced dose or discontinue ICLUSIG for new or worsening heart failure.

Hepatotoxicity: ICLUSIG can cause hepatotoxicity, including liver failure and death. Fulminant hepatic failure leading to death occurred in 3 patients, with hepatic failure occurring within 1 week of starting ICLUSIG in one of these patients. These fatal cases occurred in patients with BP-CML or Ph+ ALL. Hepatotoxicity occurred in 28% of 84 patients in OPTIC and 35% of 449 patients in PACE. Grade 3 or 4 hepatotoxicity occurred in OPTIC (8% of 84 patients) and PACE (12% of 449 patients). The most frequent hepatotoxic events were elevations of ALT, AST, GGT, bilirubin, and alkaline phosphatase. Monitor liver function tests at baseline, then at least monthly or as clinically indicated. Interrupt, then resume at a reduced dose or discontinue ICLUSIG based on recurrence/severity.

Hypertension: Serious or severe hypertension, including hypertensive crisis, has occurred in patients who received ICLUSIG. Patients may require urgent clinical intervention for hypertension associated with confusion, headache, chest pain, or shortness of breath. Monitor blood pressure at baseline and as clinically indicated and manage hypertension as clinically indicated. Interrupt, dose reduce, or stop ICLUSIG if hypertension is not medically controlled. For significant worsening, labile or treatment-resistant hypertension, interrupt ICLUSIG and consider evaluating for renal artery stenosis.

Pancreatitis: Serious or severe pancreatitis has occurred in patients who received ICLUSIG. Elevations of lipase and amylase also occurred. In the majority of cases that led to dose modification or treatment discontinuation, pancreatitis resolved within 2 weeks. Monitor serum lipase every 2 weeks for the first 2 months and then monthly thereafter or as clinically indicated. Consider additional serum lipase monitoring in patients with a history of pancreatitis or alcohol abuse. Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG based on severity. Evaluate for pancreatitis when lipase elevation is accompanied by abdominal symptoms.

Increased Toxicity in Newly Diagnosed Chronic Phase CML: In a prospective randomized clinical trial in the first line treatment of newly diagnosed patients with CP-CML, single agent ICLUSIG 45 mg once daily increased the risk of serious adverse reactions 2-fold compared to single agent imatinib 400 mg once daily. The median exposure to treatment was less than 6 months. The trial was halted for safety. Arterial and venous thrombosis and occlusions occurred at least twice as frequently in the ICLUSIG arm compared to the imatinib arm. Compared to imatinib-treated patients, ICLUSIG-treated patients also had a greater incidence of myelosuppression, pancreatitis, hepatotoxicity, cardiac failure, hypertension, and skin and subcutaneous tissue disorders. ICLUSIG is not indicated and is not recommended for the treatment of patients with newly diagnosed CP-CML.

Neuropathy: Peripheral and cranial neuropathy occurred in patients in OPTIC and PACE. Some of these events in PACE were Grade 3 or 4. Monitor patients for symptoms of neuropathy such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness. Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG based on recurrence/severity.

Ocular Toxicity: Serious or severe ocular toxicity leading to blindness or blurred vision have occurred in ICLUSIG-treated patients. The most frequent ocular toxicities occurring in OPTIC and PACE were dry eye, blurred vision, and eye pain. Retinal toxicities included age-related macular degeneration, macular edema, retinal vein occlusion, retinal hemorrhage, and vitreous floaters. Conduct comprehensive eye exams at baseline and periodically during treatment.

Hemorrhage: Fatal and serious hemorrhage events have occurred in patients who received ICLUSIG. Fatal hemorrhages occurred in PACE and serious hemorrhages occurred in OPTIC and PACE. In PACE, the incidence of serious bleeding events was higher in patients with BP-CML, BP-CML, and Ph+ ALL. Gastrointestinal hemorrhage and subdural hematoma were the most frequently reported serious hemorrhages. Events often occurred in patients with Grade 4 thrombocytopenia. Monitor for hemorrhage and manage patients as clinically indicated. Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG based on recurrence/severity.

Fluid Retention: Fatal and serious fluid retention events have occurred in patients who received ICLUSIG. In PACE, one instance of brain edema was fatal and serious events included pleural effusion, pericardial effusion, and angioedema. Monitor for fluid retention and manage patients as clinically indicated. Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG based on recurrence/severity.

IMPORTANT SAFETY INFORMATION (cont'd)

Cardiac Arrhythmias: Cardiac arrhythmias, including ventricular and atrial arrhythmias, occurred in patients in OPTIC and PACE. For some patients, events were serious or severe (Grade 3 or 4) and led to hospitalization. Monitor for signs and symptoms suggestive of slow heart rate (fainting, dizziness) or rapid heart rate (chest pain, palpitations or dizziness) and manage patients as clinically indicated. Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG based on recurrence/severity.

Myelosuppression: Grade 3 or 4 events of neutropenia, thrombocytopenia, and anemia occurred in patients in OPTIC and PACE. The incidence of myelosuppression was greater in patients with AP-CML, BP-CML, and Ph+ ALL than in patients with CP-CML. Obtain complete blood counts every 2 weeks for the first 3 months and then monthly or as clinically indicated. If ANC less than 1×10^9/L or platelets less than 50×10^9/L, interrupt ICLUSIG until ANC at least 1.5×10^9/L and platelets at least 75×10^9/L, then resume at same or reduced dose.

Tumor Lysis Syndrome (TLS): Serious TLS was reported in ICLUSIG-treated patients in OPTIC and PACE. Ensure adequate hydration and treat high uric acid levels prior to initiating ICLUSIG.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS (also known as Posterior Reversible Encephalopathy Syndrome) has been reported in patients who received ICLUSIG. Patients may present with neurological signs and symptoms, visual disturbances, and hypertension. Diagnosis is made with supportive findings on magnetic resonance imaging (MRI) of the brain. Interrupt ICLUSIG until resolution. The safety of resumption of ICLUSIG in patients upon resolution of RPLS is unknown.

Impaired Wound Healing and Gastrointestinal Perforations: Impaired wound healing occurred in patients receiving ICLUSIG. Withhold ICLUSIG for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of ICLUSIG after resolution of wound healing complications has not been established. Gastrointestinal perforation or fistula occurred in patients receiving ICLUSIG. Permanently discontinue in patients with gastrointestinal perforation.

Embryo-Fetal Toxicity: Based on its mechanism of action and findings from animal studies, ICLUSIG can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with ICLUSIG and for 3 weeks after the last dose.

ADVERSE REACTIONS

The most common (≥20%) adverse reactions are rash and related conditions, arthralgia, abdominal pain, headache, constipation, dry skin, hypertension, fatigue, fluid retention and edema, pyrexia, nausea, pancreatitis/lipase elevation, hemorrhage, anemia, hepatic dysfunction and ACSEs. The most common Grade 3 or 4 laboratory abnormalities (≥20%) are platelet count decreased, neutrophil cell count decreased, and white blood cell decreased.

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-844-817-6466 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Strong CYP3A Inhibitors: Avoid coadministration or reduce ICLUSIG dose if coadministration cannot be avoided.

Strong CYP3A Inducers: Avoid coadministration.

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed during treatment with ICLUSIG and for 5 days following last dose.

Females and Males of Reproductive Potential: Verify pregnancy status of females of reproductive potential prior to initiating ICLUSIG. Ponatinib may impair fertility in females, and it is not known if these effects are reversible.

Pre-existing Hepatic Impairment: Reduce the starting dose of ICLUSIG to 30 mg orally once daily for patients with pre-existing hepatic impairment as these patients are more likely to experience adverse reactions compared to patients with normal hepatic function.

Please see accompanying Brief Summary of full Prescribing Information on the following pages, and Important Safety Information, including Boxed Warning, throughout.



References: 1. ICLUSIG (ponatinib) [prescribing information]. Cambridge, MA: Takeda Pharmaceuticals U.S.A., Inc.; 09/2022. 2. Data on file. Cambridge, MA: Takeda Pharmaceuticals U.S.A., Inc.; 2022. 3. Cortes JE, Schroder SB, Chen TC, et al. Poster presented at: The American Society of Hematology Annual Meeting; December 7-10, 2013; New Orleans, LA. 4. Gilde CE, Zabriskie MS, Stevens GLS, et al. Cancer Cell. 2018;34(4):531-543. 5. Deininger MW, Hodgson JG, Shah NP, et al. Blood. 2016;127(5):703-712. 6. Jabbour E, Kantarjian H, Cortes J. Clin Lymphoma Myeloma Leuk. 2015;15(6):323-334. 7. Zabriskie MS, Gilde CE, Tantravahi SK, et al. Cancer Cell. 2018;34(2):328-342. 8. O'Hare T, Shakespeare WC, Zhu X, et al. Cancer Cell. 2009;16(5):401-412. 9. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. Blood. 2018;132(4):393-404. 10. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. N Engl J Med. 2013;369(19):1783-1796.

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ICLUSIG (ponatinib) tablets

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	CP-CHOP (N = 277)		EP-CHOP (N = 111)		R-CHOP (N = 142)		PTCL-ALL (N = 32)	
	All CTCAE Grade n (%)	CTCAE Grade 3 or 4 n (%)	All CTCAE Grade n (%)	CTCAE Grade 3 or 4 n (%)	All CTCAE Grade n (%)	CTCAE Grade 3 or 4 n (%)	All CTCAE Grade n (%)	CTCAE Grade 3 or 4 n (%)
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[redacted]

Highlights From the **2023 ASCO® Annual Meeting**

POLARIX Trial Analysis Compares Pola-R-CHP, R-CHOP in Older Adults

Pola-R-CHP and R-CHOP "demonstrated similar safety profiles" in older adults with previously untreated diffuse large B-cell lymphoma (DLBCL), but the "risk-benefit profile favored" pola-R-CHP, according to results from the POLARIX trial.

The phase III study showed a significant improvement in progression-free survival (PFS) with pola-R-CHP over R-CHOP in patients aged 18 to 80 years who had previously untreated DLBCL. The two regimens showed "similar" safety profiles, according to the authors of the study, which was led by **Bei Hu, MD,** of the Levine Cancer Institute.

However, combination regimens "may be associated with higher rates of toxicity" in patients with previously untreated DLBCL, the researchers wrote. Due to this concern, they compared the efficacy and safety of pola-R-CHP and R-CHOP in patients who were at least 70 years old when they enrolled in the POLARIX trial.

Patients with previously untreated DLBCL were randomized 1:1 to receive six cycles of pola-R-CHP or R-CHOP, plus two cycles of rituximab. Researchers analyzed 284 patients for efficacy (pola-R-CHP, n=141; R-CHOP, n=143) and 280 patients for safety (pola-R-CHP, n=137; R-CHOP, n=143). The median patient age was 74 years (range, 70-80 years), and most patients (69.7%) had an International Prognostic Index score of three to five.

In the group receiving pola-R-CHP, 88.3% of patients received all six doses of polatuzumab vedotin. In the group receiving R-CHOP, 91.6% of patients received all six doses of vincristine.

With a median follow-up of 24.2 months by the data cutoff, the risk of progression, relapse, or death was lower with pola-R-CHP than R-CHOP (hazard ratio, 0.64; 95% CI, 0.41-0.99). See **TABLE 1** for data on PFS, overall survival (OS), and disease-free survival (DFS).

Death by any cause occurred in 14.2% of patients who received pola-R-CHP and in 19.6% of those who received R-CHOP. The "safety profiles were generally comparable" for pola-R-CHP and R-CHOP, according to the study's authors. See **TABLE 2** for data on adverse events (AEs).

"Pola-R-CHP and R-CHOP demonstrated similar safety profiles in [patients] aged ≥70 years with previously untreated DLBCL," the researchers concluded. "The risk-benefit profile favored pola-R-CHP versus R-CHOP."

Reference

Hu B, Reagan PM, Sehn LH, et al. Subgroup analysis of elderly patients (pts) with diffuse large B-cell lymphoma (DLBCL) in the phase 3 POLARIX study. Abstract #7518. Presented at the 2023 ASCO® Annual Meeting; June 2-6, 2023; Chicago, Illinois.

TABLE 1. Outcomes of Both Treatments

Outcome measure	Pola-R-CHP	R-CHOP
Two-year PFS rate	77.1%	67.0%
Two-year OS rate	86.2%	82.0%
Two-year DFS rate	80.6%	73.4%

TABLE 2. AEs of Both Treatments

AE type	Pola-R-CHP	R-CHOP
Patients with grade 3-5 AEs	73.7%	69.9%
Patients with grade 5 AEs	5.0%	4.9%
Patients with serious AEs	59.0%	38.5%
Peripheral neuropathy, any grade	72.0%	46.9%
Grade 3-4 neutropenia	42.0%	35.0%
Grade 3-4 infection	22.0%	12.6%

Lisocabtagene Maraleucel Shows 'Durable' CRs in TRANSCEND CLL 004 Trial

Lisocabtagene maraleucel demonstrated "durable" complete responses (CRs) and a "manageable safety profile" in patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), according to the primary analysis of the phase I/II TRANSCEND CLL 004 study.

The study, led by **Tanya Siddiqi, MD,** of the City of Hope National Medical Center, included patients who received at least two prior lines of therapy, including a Bruton's tyrosine kinase (BTK) inhibitor (n=117).

Patients who progress on a BTK inhibitor and experience treatment failure with venetoclax-based regimens do not often achieve a CR with current treatment regimens, according to the study's authors.

"For people living with relapsed or refractory CLL or SLL after treatment with BTK [inhibitor]- and [B-cell leukemia/lymphoma 2 inhibitor]-based regimens, there is no standard-of-care treatment. Achieving deep and lasting remission in this situation is challenging, as most patients experience disease progression despite continuous treatment," Dr. Siddiqi said in a news release.

"The durable complete responses observed with [lisocabtagene maraleucel] in the TRANSCEND CLL 004 trial are remarkable and represent a major step in bringing a personalized, T-cell-based treatment approach delivered as a one-time infusion into clinical practice for a complex and historically incurable disease."

The study's primary endpoint was the rate of CR and CR with incomplete marrow recovery (CRi) in a prespecified subset of patients. The prespecified subset included efficacy-evaluable patients who received a dose of 100×10^6 chimeric antigen receptor (CAR) T cells and had disease progression on a BTK inhibitor, as well as venetoclax treatment failure (n=49). Key secondary endpoints were the overall response rate (ORR) and the rate of undetectable measurable residual disease (MRD) in blood.

The study met its primary endpoint, as the CR rate was 18.4% in the prespecified subset of patients for the analysis (95% CI, 8.8-32.0; one-sided P=.0006). Among patients who achieved a CR, no disease progression or deaths were reported. The median duration of CR was not reached at a median follow-up of 21.1 months.

The ORR was 42.9%, with a median duration of response of 35.3 months at a median follow-up of 19.7 months.

In the 117 patients who were evaluable for safety, any grade of cytokine release syndrome (CRS) occurred in 84.6% of patients, with no grade 4 or 5 CRS reported. Neurological events occurred in 45.3% of patients, with no grade 5 neurological events reported. The researchers reported grade 3 or higher infections in 17.9% of patients, hypogammaglobulinemia in 15.4%, and prolonged cytopenia in 53.8%. One death related to lisocabtagene maraleucel was due to hemophagocytic lymphohistiocytosis.

The CAR-T therapy "demonstrated durable CR/CRi, high [undetectable] MRD rates, and a manageable safety profile" in patients with heavily pretreated, high-risk relapsed or refractory CLL/SLL and "high unmet need," Dr. Siddiqi and colleagues concluded.

Reference

Siddiqi T, Maloney DG, Kenderian S, et al. Lisocabtagene maraleucel (liso-cel) in R/R chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): primary analysis of TRANSCEND CLL 004. Abstract #7501. Presented at the 2023 ASCO® Annual Meeting; June 2-6, 2023; Chicago, Illinois.

Dose Reduction May Enable Long-term Use of Ibrutinib in B-Cell Malignancies

In a pooled analysis of 10 clinical trials, researchers reported that dose reduction of ibrutinib may be an effective strategy to mitigate the risk of cardiac AEs from recurring or worsening in patients with B-cell malignancies.

The study, led by **Deborah Marie Stephens, MD,** of the Huntsman Cancer Institute at the University of Utah, evaluated 222 patients with grade 1 to 4 cardiac AEs. Data were pooled for patients treated with ibrutinib from 10 studies, including CLL (n=781), mantle cell lymphoma (n=250), marginal zone lymphoma (n=63), and Waldenström macroglobulinemia (n=169).

The occurrence of both initial and recurrent cardiac AEs was identified by preferred terms within the cardiac disorders system organ class. Recurrence was defined as an AE of the same or worse grade, and the measurement period extended up to 30 days after the last dose of ibrutinib or the start of the next-line therapy, whichever came earlier.

Of the evaluable patients, 22 (10%) had ibrutinib dose reduction to 420 mg (n=3), 280 mg (n=10), or 140 mg (n=9) after a cardiac AE (**TABLE 3**).

The recurrence of cardiac AEs was observed in 14% of patients with dose reductions, while it occurred in 18% of patients without dose reductions. When specifically considering serious cardiac AEs, the recurrence rate was 5% in patients with dose reductions compared with 10% in patients without dose reductions. There were zero deaths due to cardiac AE recurrence. **TABLE 4** shows PFS in both treatment arms.

"Dose reduction for cardiac AEs may enable [patients] to continue to benefit from long-term ibrutinib and mitigate the risk of cardiac AE recurrence or worsening," the authors concluded.

Reference

Stephens DM, Brown JR, Ma S, et al. Ibrutinib dose modifications for management of cardiac adverse events in patients with B-cell malignancies: pooled analysis of 10 clinical trials. Abstract #7538. Presented at the 2023 ASCO® Annual Meeting; June 2-6, 2023; Chicago, Illinois.

TABLE 3. Patient Characteristics with Dose Reduction Versus Without

Patient characterisitcs	With dose reduction (n=22)	Without dose reduction (n=200)
Age (≥75 years)	45%	29%
Heavily pretreated (≥1 prior therapy)	45%	73%
Ibrutinib discontinuation rate	23%	48%

TABLE 4. Comparison of PFS in Both Groups

PFS	With dose reduction	Without dose reduction
PFS (overall, n=22)	Median PFS: NR	24-mo PFS: 91%
PFS (420-mg dose, n=18)	Median PFS: NR	24-mo PFS: 94%

NR = not reached

Cilta-cel LEGEND-2 Data Show Impressive OS in Relapsed or Refractory MM

Patients with relapsed or refractory multiple myeloma (MM) treated with LCAR-B38M—known in the United States as ciltacabtagene autolecuce (cilta-cel)—had a median OS approaching five years, according to data from the LEGEND-2 study.

Previously presented results from the study showed encouraging efficacy and manageable safety in the 74 treated patients. This current study reports results from patients with at least five years' follow-up, the longest for any BCMA-targeted CAR T-cell therapy study.

In LEGEND-2, patients underwent lymphodepletion with cyclophosphamide 300 mg/m^2 (n=66) or 250 mg/m^2 plus fludarabine 25 mg/m^2 (n=8) prior to receiving LCAR-B38M in a single (n=9) or three split (n=65) infusions.

As of November 2022, the median follow-up was 65.4 months and 74 patients had received LCAR-B38M.

The ORR was 87.8% with 73% of patients achieving complete response. The measurable residual disease-negative complete response rate was 67.6%, with a median duration of response of 23 months. The median PFS was the same as previously reported.

Median OS was 55.8 months, with almost half (44.6%) of patients alive and 17.6% still disease free.

The researchers identified factors associated with disease progression. Patients without progressive disease were more likely to have baseline Eastern Cooperative Oncology Group performance status of 0, immunoglobulin G type MM, International Staging System stage I MM, numerically shorter time from diagnosis, fewer prior lines of therapy, no light chain MM, and no extramedullary disease.

Cilta-cel gained FDA approval for relapsed/refractory MM in February 2022 based on the initial results of CARTITUDE-1.

Reference

J-Q Mi, W-H Zhao, L-J Chen, et al. Long-term remission and survival in patients with relapsed or refractory multiple myeloma after treatment of LCAR-B38M CAR-T: at least 5-year follow-up in LEGEND-2. Abstract #8010. Presented at the 2023 American Society of Clinical Oncology Annual Meeting; June 2-6, 2023; Chicago, Illinois.



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Highlights From the **2023 European Hematology Association (EHA) Congress**

Anemia Is Prevalent, Linked with 'Substantial' Health Care Burden in Myelofibrosis

More than three-quarters of patients with myelofibrosis (MF) had anemia, and those with anemia experienced "substantial" health care resource utilization burden, according to a recent study.

John Mascarenhas, MD, of the Tisch Cancer Institute at Mount Sinai, and colleagues presented the study's results during the 2023 EHA Congress.

They conducted the study to address the "limited data on real-world clinical management of anemia" and the "associated health care resource utilization" in patients with myelofibrosis.

Dr. Mascarenhas and colleagues used the IQVIA PharMetrics Plus database to identify pharmacy, hospital, and medical claims data for adults with *International Classification of Diseases, Ninth Revision (ICD-9)* and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* codes for MF from 2009 to 2022.

To be eligible for inclusion, patients were required to have an *ICD-9* or *ICD-10* code for anemia within three months before the first MF code until the end of the study period. The study's investigators considered the date of the first code for anemia as the first index date. All eligible patients had at least 12 months of continuous enrollment with medical and pharmacy benefits after treatment.

Dr. Mascarenhas and colleagues identified 11,371 patients with MF and found that 76.8% had concurrent anemia. After they applied eligibility criteria, they evaluated 1,148 patients who had MF with concurrent anemia. The median patient age at index was 62 years. Just under one-third (31.2%) of patients received red blood cell transfusions, with a mean of 7.8 transfusions.

Less than half (40.5%) of patients received systemic therapies for MF. Hydroxyurea was the most common therapy, with 17.6% of those patients receiving it. Ruxolitinib, received by 17% of those patients, was the second most common therapy.

In the 40.5% of patients who received supportive care therapies, erythropoiesis-stimulating agents, received by 16%, were the most commonly used.

More than one-third (39.2%) of all patients were hospitalized, spending a median of five days in the hospital. On average, patients had 68.9 all-cause total health care visits, 26.9 total pharmacy visits, and 43.9 total medical visits per patient per year. The corresponding mean number of MF-related event rates was 1.5, 12.8, and 1.7 per patient per year, respectively. The corresponding mean number of anemia-related event rates was 1.8, 13.9, and 1.6 per patient per year, respectively.

"Transfusions were frequently used as supportive care in these patients," Dr. Mascarenhas and colleagues concluded, noting that "patients with anemia incurred substantial [health care resource utilization] burden in routine clinical practice" and "more effective therapies are required to address the unmet need of anemia burden."

Reference

Mascarenhas J, Subbiah K, Jones S, et al. Real-world treatment patterns and healthcare resource utilization in myelofibrosis patients with anemia. Abstract #P1059. Presented at the 2023 European Hematology Association Congress. June 8-15, 2023; Frankfurt, Germany.

JAK2 Mutant Allele Burden Linked with Chronic Kidney Disease in MPN

Patients with chronic myeloproliferative neoplasms (MPNs) who present with a higher *JAK2* mutant allele burden have "higher occurrence" of chronic kidney disease and "unfavorable dynamics of kidney function over time," according to research presented at the 2023 EHA Congress.

The study, led by **Marko Lucijanić, MD, PhD,** of the Clinical Hospital Dubrava and the University of Zagreb, investigated the relationship because an "accumulating pool of evidence suggests MPN might be causally related" to chronic kidney disease, but it is "unknown at the moment whether higher *JAK2* mutant allele burden at the time of presentation might be associated with higher occurrence or worsening of kidney function over time."

The researchers retrospectively analyzed a cohort that included 230 patients with MPNs who had the *JAK2* V617F mutation. All patients received treatment between 2006 and 2022 at a single center in Zagreb, Croatia. The study included 98 patients with polycythemia vera (PV), 94 with essential thrombocytopenia (ET), 20 with primary myelofibrosis, and 18 with other *JAK2*-mutated MPNs. The median patient age was 67 years.

All patients in the study had available data on the *JAK2* V617F allele burden. The researchers determined the *JAK2* mutant allele burden using quantitative real-time polymerase chain reaction testing and compared it with baseline clinical data, including serum creatinine levels. In a subset of patients, they repeatedly assessed allele burden and serum creatinine over a six-month period and a 12-month period.

The median *JAK2* mutant allele burden was 26.3% at baseline. It significantly differed among MPN subsets, with a median of 47.5% in polycythemia vera, 21.6% in primary myelofibrosis, 21.6% in other MPNs, and 16.5% in ET ($P>.05$ for all analyses). However, 32.6% of patients who had a higher mutant allele burden had chronic kidney disease, nearly double that of those with a lower mutant allele burden (16.7%; $P=.012$).

Patients who had a lower baseline mutant allele burden showed significant improvement in kidney function at six and 12 months, but those with a higher baseline mutant allele burden did not show this improvement, according to the study's authors. Furthermore, age also impacted dynamics of kidney function over time ($P>.05$ for difference at both timepoints).

"MPN patients presenting with higher *JAK2* mutant allele burden have higher occurrence of [chronic kidney disease] and unfavorable dynamics of kidney function over time," Dr. Lucijanić and colleagues concluded. "These observations support the view that MPN disease biology might participate in deteriorated kidney function observed in a high number of MPN patients. Future studies are warranted."

Reference

Lucijanić M, Veic P, Aric I, et al. Higher JAK2 allele burden in patients with chronic myeloproliferative neoplasms is associated with higher prevalence of chronic kidney disease and unfavorable dynamics of kidney function over time. Abstract #PB2194. Presented at the 2023 European Hematology Association Congress. June 8-15, 2023; Frankfurt, Germany.

Phase III COMMANDS Trial Shows Promise of Luspatercept Across MDS Mutations

Luspatercept-aamt demonstrated "favorable outcomes" compared with epoetin alfa across common mutations in myelodysplastic syndromes (MDS), according to a news release on phase III COMMANDS trial data presented at the 2023 EHA Congress.

The open-label, randomized trial evaluated luspatercept-aamt versus epoetin alfa, an erythropoiesis-stimulating agent (ESA), for the treatment of anemia in adults with very low-, low-, or intermediate-risk MDS who require red blood cell (RBC) transfusions and are ESA-naïve. The study's primary endpoint was RBC transfusion independence for 12 weeks with a mean hemoglobin increase of ≥1.5 g/dL.

The 2023 EHA Congress presentation included safety and efficacy data consistent with the results presented at the 2023 ASCO® Annual Meeting by **Guillermo Garcia-Manero, MD,** of the University of Texas MD Anderson Cancer Center.

The data presented at the 2023 EHA Congress add to those results by showing patients who received luspatercept-aamt had a "higher probability of achieving clinical benefit, regardless of overall mutational burden," officials said in a news release. The investigators compared the treatments across patients with MDS who had mutations in genes, including *SF3B1, SF3B1a, ASXL1, TET2, DNMT3A, EZH2, IDH2,* and *U2AF1*. See **TABLE 5** for results across mutation and treatment types.

"Clinical experience has demonstrated that just one in three patients with low-risk myelodysplastic syndromes experience responses to erythroid-stimulating agents over six to 18 months, leaving a significant need for more effective options to address chronic anemia," **Matteo Giovanni Della Porta, MD,** study investigator and Head of the Leukemia Unit at Humanitas Cancer Center in Milan, Italy, said in the release. "In the COMMANDS study, the median duration of red blood cell transfusion independence was nearly one year longer with Reblozyl than with epoetin alfa and showed safety consistent with its known profile, demonstrating its potential as a first-line treatment in patients with transfusion-dependent, very low- to intermediate-risk MDS."

Reference

Bristol Myers Squibb to present first results at ASCO and EHA from phase 3 COMMANDS study of Reblozyl® (luspatercept-aamt) in first-line treatment of anemia in adults with lower-risk myelodysplastic syndromes (MDS). Business Wire. May 25, 2023. Accessed June 21, 2023. https://www.businesswire.com/news/home/20230524005878/en/Bristol-Myers-Squibb-to-Present-First-Results-at-ASCO-and-EHA-from-Phase-3-COMMANDS-Study-of-Reblozyl%C2%AE-luspatercept-aamt-in-First-Line-Treatment-of-Anemia-in-Adults-with-Lower-Risk-Myelodysplastic-Syndromes-MDS

TABLE 5. Treatment Responses by MDS Mutation Type

Mutation	Luspatercept-aamt	Epoetin alfa	Risk difference
ASXL 1	15/31	3/29	0.38 (0.17 to 0.59)
CBL	0/5	2/5	−0.40 (-0.85 to 0.05)
DNMT3A	19/28	11/25	0.24 (−0.02 to 0.50)
DTA.SF3B1.n	12/31	12/40	0.09 (−0.14 to 0.31)
EZH2	5/10	2/9	0.28 (−0.13 to 0.69)
IDH2	3/6	1/5	0.30 (−0.23 to 0.83)
RUNX1	1/4	0/9	0.25 (−0.17 to 0.67)
SF3B1	64/92	27/90	0.40 (0.26 to 0.53)
SF3B1.alpha	41/55	16/55	0.45 (0.29 to 0.62)
SF3B1.beta	1/4	0/8	0.25 (−0.18 to 0.68)
SRSF2	5/14	2/14	0.21 (−0.10 to 0.53)
TET2	30/48	16/53	0.32 (0.14 to 0.51)
U2AF1	6/16	4/19	0.16 (−0.14 to 0.46)

Gilteritinib Maintenance Shows Benefit in MRD-Positive AML

Gilteritinib "appears to have a clear benefit" for patients with *FLT3*-ITD acute myeloid leukemia (AML) who have measurable residual disease (MRD) before or after hematopoietic stem cell transplantation (HSCT), according to results from a phase III study.

The BMT-CTN1506 trial, also known as the MORPHO trial, was a randomized, placebo-controlled study that evaluated the use of gilteritinib as post-transplant maintenance. The primary objective of the study was to determine if gilteritinib maintenance improved relapse-free survival (RFS) over placebo for patients with *FLT3*-ITD AML who received allogeneic HSCT in their first remission. Secondary objectives included overall survival (OS), examining the effect of MRD status before and after transplant on RFS and OS, nonrelapse mortality rates, event-free survival, and graft versus-host disease (GVHD).

The study included 356 patients with *FLT3*-ITD AML who were in their first remission after no more than two cycles of induction therapy and had HSCT planned within 12 months. After patients received induction and consolidation therapy, they were registered and underwent HSCT. Following engraftment, which took place 30 to 90 days after HSCT, the researchers randomized patients to receive placebo or gilteritinib 120 mg daily for 24 months. They collected marrow aspirates for MRD before transplant, before randomization, and at three, six, 12, 18, and 24 months after randomization.

The RFS was higher for patients who received gilteritinib than in those who received placebo in an intention-to-treat analysis, but the difference was not significant (hazard ratio [HR], 0.679; 95% CI, 0.459, 1.005; two-sided P=.0518). The OS was similar between groups (HR, 0.846; 95% CI: 0.554, 1.293; two-sided P=.4394). The two-year RFS rate was 77.2% in patients receiving gilteritinib, while it was 69.9% in those receiving placebo.

Half (50.6%) of the patients had detectable MRD before transplant or before randomization. The researchers reported the "effect of gilteritinib was more pronounced" in patients who had detectable MRD (HR, 0.515, 95% CI, 0.316, 0.838; P=.0065) than in those without detectable MRD (HR, 1.213, 95% CI, 0.616, 2.387, P=.575).

Dose interruptions occurred in 80.3% of patients receiving gilteritinib and in 72.9% of patients receiving placebo. Around half (54.5%) of the patients receiving gilteritinib required dose reductions, while 25.4% of patients receiving placebo required dose reductions.

Treatment-emergent adverse events (AEs) were more common in patients receiving gilteritinib, as well as treatment-emergent AEs that led to withdrawal of treatment. Neutrophil decrease occurred in 42.1% of patients receiving gilteritinib, nearly triple the rate of 15.8% in patients receiving placebo. Chronic GVHD occurred in 52.2% of patients receiving gilteritinib and in 42.1% of patients receiving placebo.

"Gilteritinib appears to have a clear benefit for the 50% of [patients] with detectable MRD pre- or post-[HSCT], compared to those without detectable MRD. [Treatment-emergent] AEs associated with gilteritinib were primarily myelosuppression and increased incidence of chronic GVHD," Dr. Levis and colleagues concluded. "These data are among the first to support the effectiveness of MRD-based post-[HSCT] maintenance therapy."

Reference

Levis MJ, Hamadani M, Logan B, et al. BMT-CTN 1506 (MORPHO): a randomized trial of the FLT3 inhibitor gilteritinib as post-transplant maintenance for FLT3-ITD AML. Abstract #LB2711. Presented at the 2023 European Hematology Association Congress. June 8-15, 2023; Frankfurt, Germany

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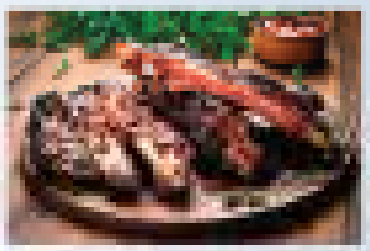
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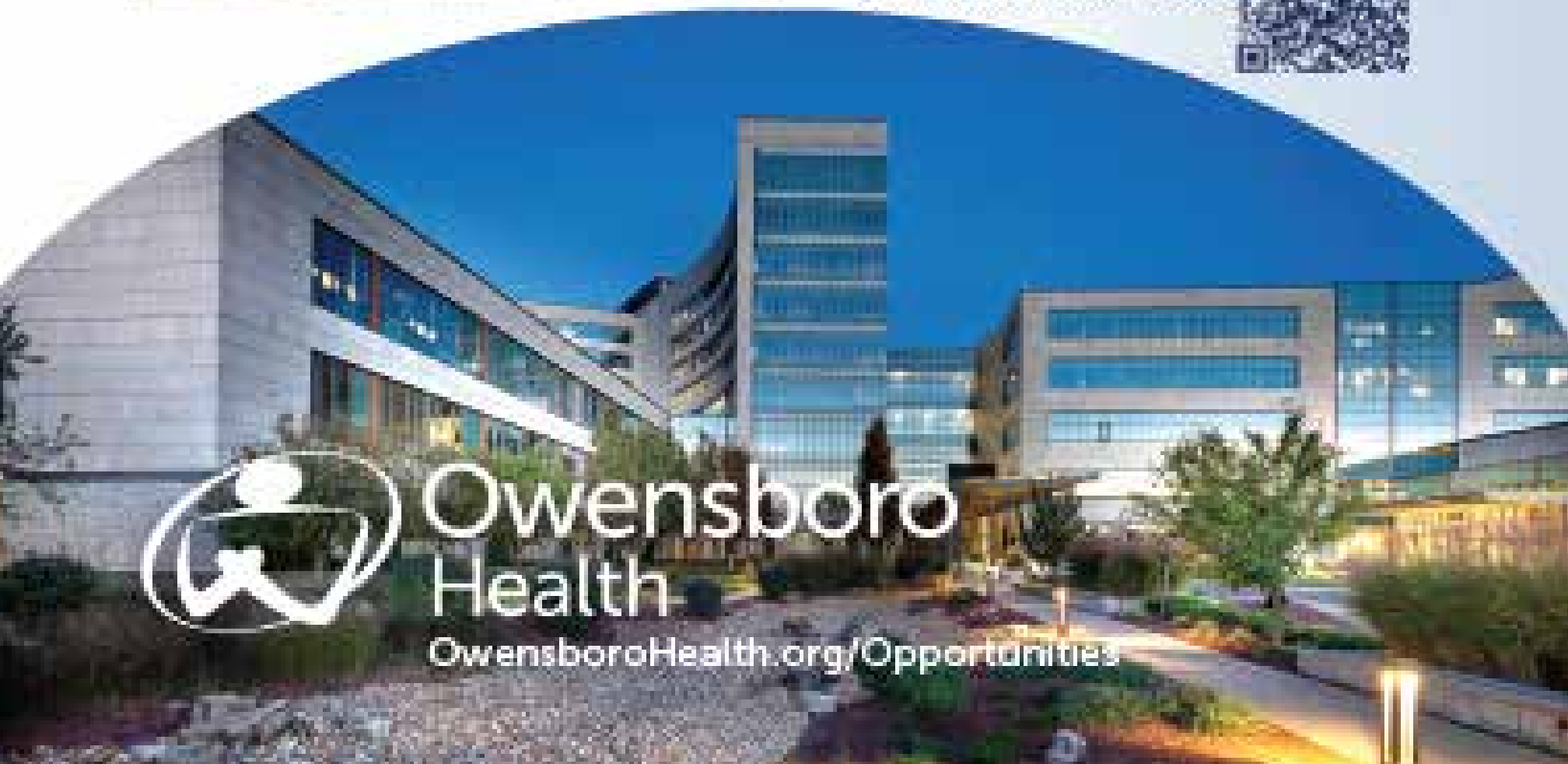








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Spotlight on The HemOnc Pulse

Chadi Nabhan, MD, MBA, FACP, a hematologist and medical oncologist and host of The HemOnc Pulse, a podcast brought to you by Blood Cancers Today *and the Society of Hematologic Oncology, covers the latest news in hematologic oncology with leaders in the field.*

What Makes This MRD Approach 'Premature' in Multiple Myeloma?

On a recent episode, *Blood Cancers Today* Editor-in-Chief **Sagar Lonial, MD, FACP,** discussed the latest updates in multiple myeloma (MM) and how he approaches treatment for patients with newly diagnosed MM. Dr. Lonial is Chair and a Professor in the Department of Hematology and Medical Oncology, the Anne and Bernard Gray Family Chair in Cancer, and Chief Medical Officer of Winship Cancer Institute at Emory University School of Medicine in Atlanta, Georgia.



Sagar Lonial, MD, FACP

The episode opened with a discussion about the role of risk stratification, key considerations when choosing an initial induction therapy, and the evolution of treatments for MM.

"The disease is one of the poster children for advances in science," Dr. Nabhan said.

Dr. Lonial emphasized the progress that has been made in recent years, outlining the data that inform the risk-adapted treatment approaches he uses for patients with MM. For example, the RVD-1000 series that evaluated lenalidomide, bortezomib, and dexamethasone in 1,000 patients with MM showed median progression-free survival (PFS) and overall survival outcomes that were "better than most others had seen," Dr. Lonial said.

"In about 20 years, we've more than tripled that [median survival] with the use of triplet therapy, aggressive consolidation, and then continuous lenalidomide maintenance," he said.

However, he emphasized that key questions remain, such as which proteasome inhibitor to use, and if a CD38-directed antibody should be added to treatment regimens for high-risk MM.

In terms of autologous hematopoietic stem cell transplantation (AHSCT), Dr. Nabhan asked Dr. Lonial for his opinion on potentially delaying AHSCT until the second line of therapy in certain patients with MM. Dr. Lonial said the idea of delaying AHSCT in patients who achieve a deep response to frontline therapy is "a little bit misplaced."

"If your goal is to give patients the longest duration of first remission, there is no question that an early [AHSCT] is the way to go," he said.

The episode also featured a discussion about measurable residual disease (MRD) considerations in practice, and if MRD status should be used to guide treatment decisions in MM.

Dr. Lonial emphasized that consistent sample timing and quality matter when evaluating MRD, saying that he "feels uncomfortable making clear claims about using MRD to make treatment decisions" based on "the idea that it doesn't matter when" the sample is collected. While measuring MRD at consistent timepoints is key, Dr. Lonial pointed out what he believes is a more critical detail.

"Sustained MRD negativity is probably more important than achieving MRD negativity," he said. "I don't think we should be prepared to make treatment decisions on a single value at an early timepoint. I realize that contradicts much of what is going on in the social media world … [but] I think looking at a six-month endpoint and saying, 'I can predict to 10 years what's going to happen,' is a little premature."

Dr. Nabhan asked if there were unified measurements and definitions of MRD in MM. The depth of sensitivity in MRD assays is a key detail to consider when interpreting results, Dr. Lonial said.

"In my quest to get the longest PFS upfront, as well as potentially get to a curative endpoint in some patients, I think 10^{-6} is the right endpoint," he said.

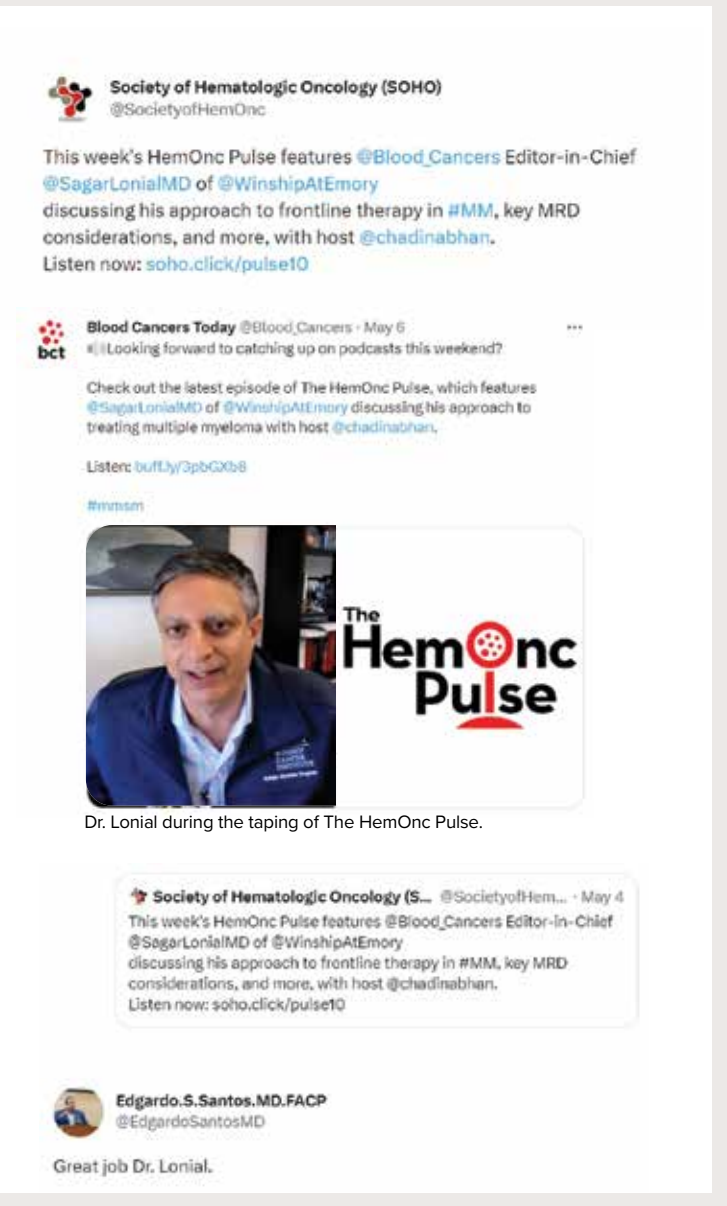
They also discussed smoldering MM and the importance of having a common definition of "high-risk" smoldering MM. The definition has varied throughout clinical trials, making it "challenging" to understand which patients benefit from early intervention, Dr. Lonial said. However, he noted the "current easiest definition" is to use the 20/2/20 criteria to stratify patients based on the number of risk factors.

Dr. Nabhan asked Dr. Lonial how he advises patients who have high-risk smoldering MM. Dr. Lonial said those conversations are informed by data and guided by a patient's personal mindset, needs, and goals.

"I usually talk to the patient at length," he said. "I tell them about the two randomized trials that show a pretty significant reduction in risk of progression … I guide them down what would be the appropriate approach based on where their mentality is."

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Dr. Lonial during the taping of The HemOnc Pulse.

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Knowledge Hubs

In each issue of Blood Cancers Today, *we will take a closer look at a particular topic in hematologic malignancies. This month, we feature the latest news on myeloproliferative neoplasms, multiple myeloma, and mantle cell lymphoma.*

MPN

Agent Orange Exposure Associated with MPNs in Veterans

Exposure to Agent Orange (AO) is associated with an increased risk of myeloproliferative neoplasms (MPNs), increased risk of arterial thrombosis (AT), and increased bleeding, according to research presented at the 2023 ASCO® Annual Meeting.

MPNs, including polycythemia vera, essential thrombocythemia (ET), and primary myelofibrosis (PMF), are acquired stem cell disorders. They arise from mutations and lead to thrombotic and bleeding complications. AO, a chemical herbicide used during the Vietnam War, has been associated with other cancers. Researchers led by **Andrew Chua Tiu, MD,** of the Georgetown Lombardi Comprehensive Cancer Center in Washington, DC, sought to understand links between the chemical and MPNs, as well as increased risks for bleeding, AT, and venous thromboembolism (VT) in patients with MPNs.

Why I chose this article:



John Mascarenhas, MD

"For the first time an association between this known carcinogen and risk of developing an MPN was determined. Furthermore, they found an increased risk of having an arterial thrombosis in patients with MPNs as well as those without MPNs. Bleeding was also more common in MPN patients with Agent Orange exposure. This is important, as the data support the coverage of care for veterans who develop MPNs or thrombo-hemorrhagic complications and indicate this exposure is a risk factor for clotting that may have management implications."

This case-control study searched the Veterans Affairs Informatics and Computing Infrastructure database, covering the period from January 1, 2006, to January 26, 2023. The researchers identified 95,768 patients with MPNs and any bleeding events, AT, or VT. They then identified age-matched controls in the database. The MPN group was mostly male (93.6%), White (76.0%), and aged 60 years or older (86.8%).

Analyses showed that patients with MPNs had increased risk of AT (29.5% vs 24.5%), VT (6.7% vs 3.8%), and concomitant AT and VT (8.1% vs 4.2%). Bleeding events were more common in patients with ET, PMF, and polycythemia vera versus controls. Gastrointestinal bleeding was the most common, followed by genitourinary or pulmonary bleeding. The researchers found a significant association between exposure to AO and the development of MPNs. Exposure was also associated with more AT in both groups, those with MPNs and those without.

"This is the largest database evaluating MPNs, thrombosis, and bleeding in veterans exposed to Agent Orange," the authors wrote, adding "further studies, including [analysis of] *JAK2* mutation, CHIPs, and cardiovascular risk factors, will be needed to evaluate contribution to thrombosis and bleeding risk."

Reference

Tiu AC, McKinnell Z, Liu S, et al. Association of Agent Orange and myeloproliferative neoplasms, thrombosis, and bleeding among veterans. Abstract #7011. Presented at the 2023 ASCO® Annual Meeting; June 2-6, 2023; Chicago, Illinois.

MYELOMA

Clonal Plasma Cells in Autograft Predict Inferior Post-AHSCT Survival in Multiple Myeloma

The presence and degree of clonal plasma cells in autografts for patients with multiple myeloma (MM) who are undergoing autologous hematopoietic stem cell transplantation (AHSCT) were "highly predictive of inferior" survival outcomes, according to a recent study.

Oren Pasvolsky, MD, of the University of Texas MD Anderson Cancer Center, the Rabin Medical Center, and Tel Aviv University, and colleagues conducted the study because most patients with MM who undergo AHSCT "eventually relapse, perhaps due to the presence of clonal plasma cells in the autograft."

They conducted a retrospective analysis to evaluate the impact of clonal plasma cells in the autograft in patients with high-risk chromosomal abnormalities who received AHSCT between 2008 and 2018.

Dr. Pasvolsky and colleagues used next-generation flow cytometry to determine if autografts contained clonal plasma cells. They found that 75 patients (18%) had clonal plasma cells present in the autograft and 341 (82%) did not.

Patients with clonal plasma cells in the autograft had a measurable residual disease (MRD)-negative complete remission (CR) rate of 11% after transplant. Patients without clonal plasma cells in the autograft had a significantly higher MRD-negative CR rate of 42% ($P<.001$).

The median progression-free survival (PFS) was 12.8 months in patients who had clonal plasma cells in the autograft, significantly shorter than the median PFS of 32.1 months in those who did not have them ($P<.001$). Patients with clonal plasma cells in the autograft had a median overall survival (OS), of 36.4 months, significantly shorter than the median OS of 81.2 months in patients who did not have them ($P<.001$).

Why I chose this article:



Rafael Fonseca, MD

"The authors show that the presence (and burden) of circulating plasma cells in the collected autograft is a major predictor of outcomes for myeloma. Whether this means that residual cells cause the relapse, or whether this is an indicator of more aggressive disease remains to be determined."

In the subset of patients who had an MRD-negative very good partial response or better before AHSCT, patients with clonal plasma cells in the autograft also had "inferior" PFS (hazard ratio [HR], 4.21; $P=.006$) and OS (HR, 7.04; $P=.002$) compared with those who did not have clonal plasma cells in the autograft.

Furthermore, the degree of clonal plasma cell positivity in the autograft was independently predictive of worse PFS (HR, 1.50; $P=.001$) and OS (HR, 1.37; $P=.001$) in a multivariate analysis.

"In conclusion, both the presence and degree of [clonal plasma cells] in the autograft were highly predictive of inferior PFS and OS," Dr. Pasvolsky and colleagues wrote.

Reference

Pasvolsky O, Milton DR, Rauf M, et al. Impact of clonal plasma cells in autografts on outcomes in high-risk multiple myeloma patients. *Blood Cancer J.* 2023;13(1):68. doi:10.1038/s41408-023-00842-6

Long-term Analysis of LYMA Trial Evaluates Rituximab Maintenance in MCL

Rituximab maintenance is a "safe standard of care" in young patients with mantle cell lymphoma (MCL), according to the first long-term analysis of the LYMA trial.

Clémentine Sarkozy, MD, PhD, of the Institut Curie Saint Cloud in France, and colleagues conducted the analysis and presented their results during the 2023 ASCO® Annual Meeting.

The phase III LYMA trial previously "demonstrated the efficacy" and safety of rituximab maintenance after frontline AHSCT in young patients with MCL, according to Dr. Sarkozy and colleagues.

The LYMA trial included 299 patients, 240 of whom were randomized to receive three years of rituximab maintenance therapy (n=120) or observation (n=120). The study's primary endpoint was the three-year event-free survival (EFS) rate.

At a median follow-up of seven years, the median EFS and PFS "were still statistically superior in favor" of rituximab maintenance over observation (EFS, not reached vs 5.8 years, respectively; PFS, not reached vs 6.1 years, respectively).

The estimated seven-year EFS rate was 76.7% in patients receiving rituximab maintenance and 46.0% in those undergoing observation. The seven-year estimated PFS rate was 78.5% in those receiving maintenance and 47.4% in those undergoing observation ($P<.0001$).

The estimated seven-year OS rate was 83.2% in those receiving rituximab maintenance and 72.2% in those undergoing observation. More than one-quarter (27.5%) of patients in the observation arm died, while 18.3% of those receiving maintenance died.

The causes of death "were not significantly distinct between" the groups, according to the study's authors. Lymphoma, which was the cause of death in 50% of patients in each group, was the "leading cause" of death, Dr. Sarkozy and colleagues wrote. Less than 10% of deaths were related to infections.

Ending maintenance was "not associated with an increase in the relapse incidence," according to the study's authors, as 81% of the progressions in the maintenance arm "occurred during the theoretical three years" of maintenance and only 19% occurred after the end of maintenance.

Furthermore, 60% of the progressions and relapses in the observation arm occurred during the "theoretical three years of maintenance," while 40% occurred after that three-year period.

There were no differences in salvage treatments received by patients receiving maintenance and those who were undergoing observation.

However, OS after relapse was "significantly impacted" by previous rituximab maintenance, according to the study's authors. The median OS after relapse was 1.1 years for the 21 patients in the maintenance arm who relapsed and 4.6 years for the 53 patients in the observation arm who relapsed.

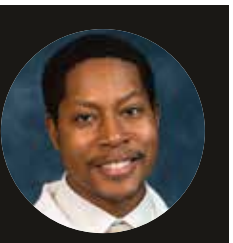
"Given the timing of relapses in [the rituximab maintenance] arm, this reflects the aggressiveness of early disease progression during [rituximab maintenance]," Dr. Sarkozy and colleagues wrote.

Based on these data, patients who relapsed during rituximab maintenance "have a particularly poor outcome and represent an unmet medical need," according to the study's authors.

However, the maintenance strategy improved certain outcomes over observation.

"The [benefit] in favor of [rituximab maintenance] in terms of EFS (the primary objective) and PFS remains after seven years of [follow-up], but not in OS," Dr. Sarkozy and colleagues concluded. "The end of [rituximab maintenance] was not associated with an increase in relapse rate. [Rituximab maintenance] was not associated with an increase in infectious-related mortality, making this strategy a safe standard of care with long-term [follow-up]."

Why I chose this article:



Tycel Phillips, MD

"This study shows that further follow-up has indicated that the OS benefit of rituximab maintenance is no longer present. As presented, it appears that those who relapsed on the rituximab maintenance arm had worse outcomes/survival as compared with those who relapsed on the observation arm, likely leading to the loss of significant benefit within the rituximab maintenance arm. There were no new safety signals, and OS was not adversely impacted by toxicity. The study still demonstrates that rituximab maintenance has a PFS benefit in this patient population."

Reference

Sarkozy C, Thieblemont C, Oberic L, et al. Very long-term follow-up of rituximab maintenance in young patients with mantle cell lymphoma included in the LYMA trial, a LYSA study. Abstract #7508. Presented at the 2023 ASCO® Annual Meeting; June 2-6, 2023; Chicago, Illinois.



Online Knowledge Hubs From *Blood Cancers Today*

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- Leukemia
- Lymphoma
- MPN
- MDS
- Myeloma
- Transplantation and Cellular Therapy

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Calendar

September 12–14
4th International Conference on Lymphocyte Engineering
Holiday Inn Munich – City Centre
Munich, Germany

September 22–23
National Comprehensive Cancer Network 2023 Annual Congress: Hematologic Malignancies
Hilton San Francisco Union Square
San Francisco, California

September 27–30
20th International Myeloma Society Annual Meeting and Exposition
Megaron Athens International Conference Centre
Athens, Greece

September 29–October 1
Association of VA Hematology/ Oncology 2023 Annual Meeting
Sheraton Grand Chicago Riverwalk
Chicago, Illinois

October 3–6
5th SOHO Italy Annual Conference
A. Roma Lifestyle Hotel
Rome, Italy

October 6–7
Acute and Chronic Leukemias: Practical Applications 2023 (Mayo Clinic Course)
Orlando World Center Marriott
Orlando, Florida

October 6–9
20th International Workshop on Chronic Lymphocytic Leukemia
Hynes Convention Center
Boston, Massachusetts

October 18–21
Lymphoma, Leukemia & Myeloma Congress
Sheraton New York Times Square Hotel
New York, New York

October 20–24
European Society of Medical Oncology Congress 2023
IFEMA Madrid
Madrid, Spain

November 1–5
Society for Immunotherapy of Cancer 38th Annual Meeting
San Diego Convention Center
San Diego, California

November 2–3
15th International Congress on Myeloproliferative Neoplasms
New York Marriott-Brooklyn Bridge
Brooklyn, New York

November 2–4
European Hematology Association-Specialized Working Group Scientific Meeting on MDS/MPN/AML
Budapest Novotel City and Congress Center
Budapest, Hungary

November 10–11
ASTCT/EBMT 6th International Conference on Relapse After Transplant and Cellular Therapy
Sheraton Universal Hotel
Los Angeles, California

December 9–12
65th American Society of Hematology Annual Meeting and Exposition
San Diego Convention Center
San Diego, California



MARK YOUR CALENDARS
SEPTEMBER 4–7, 2024
2024 SOHO Annual Meeting
George R. Brown Convention Center
Houston, Texas

The HemOnc Pulse



A podcast hosted by Dr. Chadi Nabhan

Keeping your finger on the pulse of hematologic oncology

You can find it here:
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HemOnc Happenings

Reporting on recent announcements, awards, and appointments in the hematology/oncology sphere

SOHO Announces Annual Award Recipients

The Society of Hematologic Oncology (SOHO) has announced it will honor **Hagop Kantarjian, MD,** and **Jorge Cortes, MD,** with awards during the 11th SOHO Annual Meeting in Houston, Texas.

Dr. Kantarjian, who is a Professor and Chair of the Department of Leukemia at the University of Texas MD Anderson Cancer Center, will receive the Emil Freireich Distinguished Pioneer Award. Dr. Cortes, who is Director of the Georgia Cancer Center in Augusta, will receive the Michael J. Keating Award.



Hagop Kantarjian, MD



Jorge Cortes, MD

The Freireich award, which is the Society's most distinguished award, "serves to honor those [who] have been pioneers in their work and made a notable impact worthy of high regard and recognition by their peers," according to SOHO.

Dr. Kantarjian is an active SOHO member, serving as Secretary on the SOHO Board of Directors and as Chair of its Steering Committee and Scientific Committee. He has served the Society since its inception.

Dr. Kantarjian, who has authored over 2,000 peer-reviewed publications, focuses on translational-clinical developmental therapeutics in leukemia. His research and collaborations were the basis for the US Food and Drug Administration approval of more than 20 drugs to treat leukemia, according to his biography from the MD Anderson Cancer Center.

The Keating award recognizes a SOHO member who has significantly contributed to the advancement of cancer treatment and research in the field of hematologic oncology. Dr. Cortes is an active member of the SOHO Education Committee and the SOHO Scientific Committee and has served the Society for a decade.

Previously, Dr. Cortes worked at the MD Anderson Cancer Center for 27 years, where he was a Professor of Medicine and an internist. Additionally, he had multiple roles in the Department of Leukemia and the Division of Cancer Medicine at MD Anderson.

Source: SOHO, June 2023



First Female Clinician Receives the Robert A. Kyle Lifetime Achievement Award



María-Victoria Mateos, MD, PhD

María-Victoria Mateos, MD, PhD, Head of the Myeloma and Clinical Trials Unit in the Hematology Department and a Professor of Medicine at the University of Salamanca, has received the Robert A. Kyle Lifetime Achievement Award from the International Myeloma Foundation (IMF).

The award honors individuals whose work has resulted in significant advances in myeloma research, treatment, and care. The award ceremony was held during the 14th Annual International Myeloma Working Group Summit in Frankfurt, Germany.

"It is a great honor for me to be the recipient of the Robert A. Kyle Lifetime Achievement Award, with the name of the father of myeloma," Dr. Mateos said in a news release. "Prof. Kyle has dedicated his life to myeloma research. He has educated many doctors in myeloma, but he's always been focused on patient-centered care. These are the three pillars that inspire me in my career every day, and I am committed to continuing this legacy for younger generations of doctors."

Dr. Mateos previously received the Brian G.M. Durie Outstanding Achievement Award in 2019 from the IMF and the Bart Barlogie Clinical Investigator Award in 2022 from the International Myeloma Society.

Source: IMF, June 2023

Blood Cancers Today Board Member Receives IMF Brian G.M. Durie Outstanding Achievement Award

Blood Cancers Today Associate Editor **Thomas Martin, MD,** of the University of California, San Francisco (UCSF) Helen Diller Family Comprehensive Cancer Center, has received the IMF Brian G.M. Durie Outstanding Achievement Award.

This award recognizes excellent achievements in multiple myeloma research. It is named after the IMF's Chairman of the Board and Chief Scientific Officer, **Brian G.M. Durie, MD,** who is a hematologist.

"I am sincerely humbled and flattered to be the recipient of the prestigious Brian G.M. Durie Outstanding Achievement Award," Dr. Martin said in a news release. "Dr. Durie has been an inspiration and a mentor, personally to me and to all of us in this field. His dedication to myeloma research and to the patients is unsurpassed, and it's such an honor to receive this award in his name."

Dr. Martin is a Professor of Clinical Medicine; Associate Chief of Adult Hematology, Blood Marrow Transplantation, and Cell Therapy; Co-Director of the Myeloma Program; and Clinical Research Director of Hematologic Malignancies at the UCSF Helen Diller Family Comprehensive Cancer Center. He has authored numerous articles in peer-reviewed literature.

Dr. Durie applauded Dr. Martin's exceptional achievements.

"As a myeloma researcher in the midst of a stellar career, it is wonderful to be able to celebrate Dr. Martin's many accomplishments. He is a researcher, a teacher, and a doctor loved by his many patients for his knowledgeable and compassionate care—he is a true model for all young researchers in the field."

Source: IMF, June 2023



At far right, Dr. Martin receives the Brian G.M. Durie award. Image courtesy of Dr. Martin.

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SUPERIOR EFFICACY IN CLL[1,2]

Superior PFS vs BR in 1L and superior PFS and ORR vs ibrutinib in 2L

ROBUST EFFICACY IN WM[1,3]

~4-year head-to-head data vs ibrutinib

CONSISTENT SAFETY[1-4]

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Explore the data at BRUKINSA.com

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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Infections

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Cytopenias

[redacted]

Second Primary Malignancies

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Embryo-Fetal Toxicity

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