TRANSLATING HEMATOLOGIC ONCOLOGY DISCOVERIES INTO PRACTICE

New Podcast Alert: The HemOnc Pulse **p. 2**

Survival Outcomes Poor After CAR-T Failure in Aggressive BCL **p. 12**

bct
BLOOD CANCERS TODAY

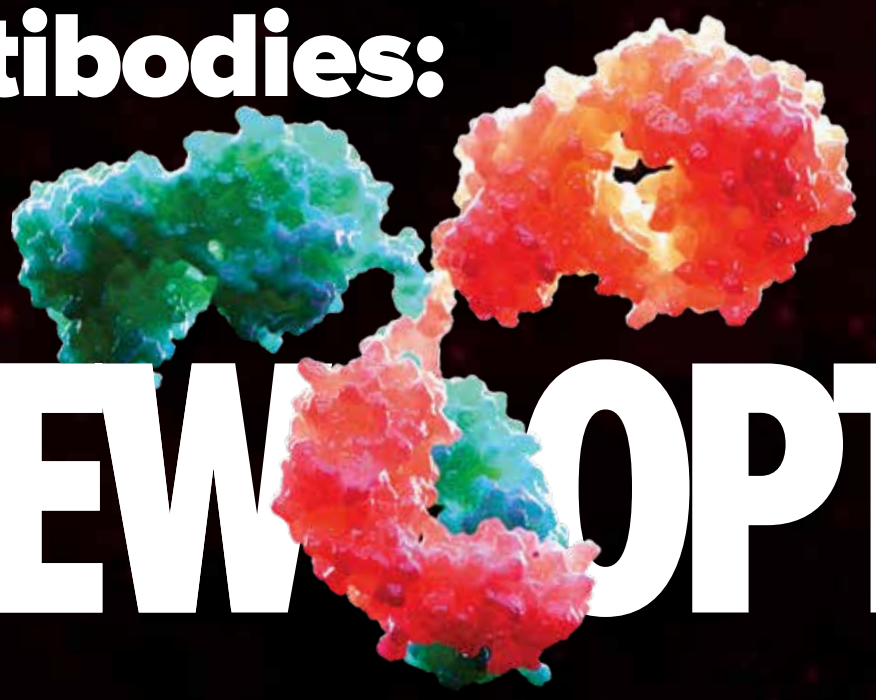
January 2023

bloodcancerstoday.com

Elranatamab Receives Breakthrough Therapy Designation **p. 15**

Meeting News From ASH 2022 **p. 16**

Bispecific Antibodies: NEW OPTIONS



With more bispecific antibodies in development for hematologic malignancies, physicians must determine how best to incorporate them into practice once they reach market

With expert opinions from:
Michael Dickinson, MD; Jing-Zhou Hou, MD, PhD; and more

MAIL TO:

GUEST EDITOR CHADI NABHAN, MD, MBA, FACP:
Taking the 'Pulse' of the New Year

An official publication of
soho
society of hematologic oncology

MashupMedia

Reimagining Publishing for Healthcare Professionals

Mashup Media proudly produces *Blood Cancers Today*,

an official publication of SOHO, a digital and print property that translates hematologic oncology advances into practice.

bct BLOOD CANCERS TODAY | soho society of hematologic oncology

Mashup Media is a multimedia publishing company

passionate about providing healthcare professionals a platform to further publicize their work. Driven by data and analytics, we produce cutting-edge products that deliver content from trusted sources and industry thought leadership.

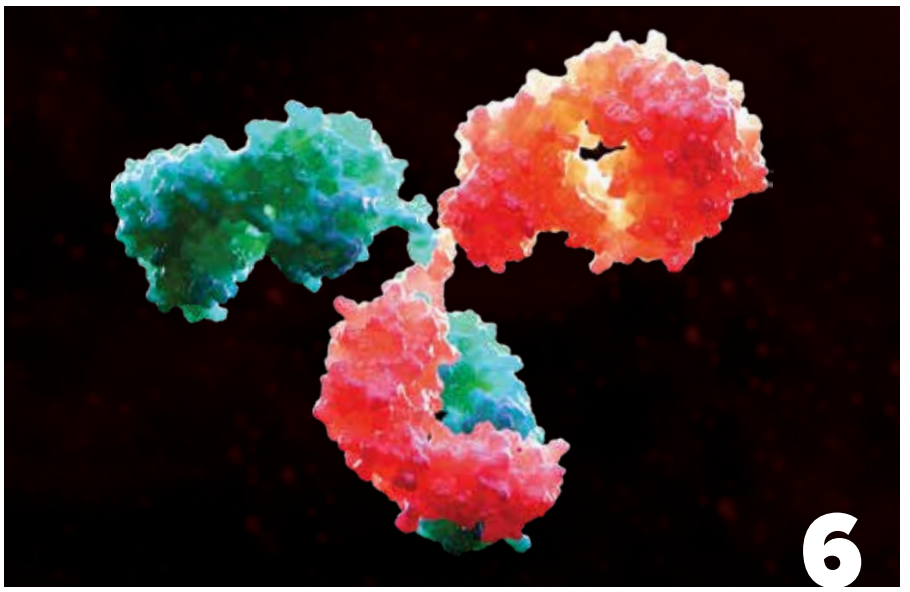
Our Brands

bct BLOOD CANCERS TODAY · CancerNursing TODAY · docwirenews · GUOncologyNow · mashup MD · Urban Health Today

Interested in learning more about our platforms?
Please visit **www.mashupmediallc.com**

MashupMedia
Reimaging Publishing for Healthcare Professionals

CONTENTS



Bispecific Antibodies: New Options

There are a multitude of bispecific antibodies under investigation right now in hematologic malignancies, with various tumor-specific targets, routes of administration, and treatment durations. Which drugs will make it to market first and how these drugs will be incorporated into treatment sequencing remains to be seen.

News

Jennifer R. Brown, MD, PhD

Anthony Mato, MD, MSCE

POINT | COUNTERPOINT

Should Small-Molecule Treatments for CLL Be Combined or Sequenced?

Jennifer R. Brown, MD, PhD, and Anthony Mato, MD, MSCE, debate whether combination small molecules are better than sequencing small molecules in CLL treatment. **9**

GET TO KNOW

Jonathon Cohen, MD, MS

Dr. Cohen discusses how he came to focus on lymphoma, as well as current research, pressing questions, and potentially paradigm-shifting data in the field of MCL. **4**

ONLINE EXCLUSIVE

The HemOnc Pulse

Visit ***bloodcancerstoday.com*** to hear every episode of the newly launched podcast The HemOnc Pulse, brought to you by *Blood Cancers Today* and the Society of Hematologic Oncology.

In the inaugural episode, host Chadi Nabhan, MD, MBA, FACP, talks with Hagop Kantarjian, MD, and Elias Jabbour, MD, about high-impact studies, novel treatment strategies, and controversial standard-of-care approaches for AML and ALL that were presented at the 2022 ASH Annual Meeting and Exposition.

Also, sign up to receive our weekly eNewsletters to have the latest headlines delivered to your inbox.

bct BLOOD CANCERS TODAY

Volume 2 | Number 1 | January 2023

Subscription inquiries should be sent to: KTrias@MashupMD.com
All correspondence for the Society of Hematologic Oncology should be sent to: Society of Hematologic Oncology, c/o JWC Covenant, Inc., P.O. Box 132919, The Woodlands, TX 77393.

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.

Blood Cancers Today is published monthly by Mashup Media, 670 Madison Avenue, 2nd Floor, Manalapan, NJ 07726. Periodicals postage paid at Freehold, NJ, and additional mailing offices. POSTMASTER: Send address changes to Mashup Media, 670 Madison Avenue, 2nd Floor, Manalapan, NJ 07726. ©2023

Guest Editor's Message

Taking the 'Pulse' of the New Year

Chadi Nabhan, MD, MBA, FACP
The HemOnc Pulse Podcast Host

Guess what? It's 2023 already. It's hard to believe that close to three years ago, the world almost entirely shut down and we were left to our own devices to interact with each other. But, as we start 2023, the world appears to have returned to normalcy. We see smiles versus masks everywhere, and in-person meetings are back in full swing.

We have just returned from attending the American Society of Hematology (ASH) Annual Meeting and Exposition in the beautiful city of New Orleans. It is a meeting I have not missed since 1999 (and no, I am not telling you how old I was then!). This year's ASH meeting was no different—an excellent meeting full of science, ideas, collaborations, friends, and yes, a brand-new podcast.

The team at *Blood Cancers Today* and I have partnered to bring you the best and latest in the world of hematologic oncology. To keep your fingers on the pulse of hematology, you'll want to listen to The HemOnc Pulse.

You may have already listened to the first episode of the podcast, and as we all ring in the new year together, more episodes will come your way. The focus of this podcast will be clinical advances, meeting updates, debates, controversies, policy, and all things hematologic oncology from A to Z.

As a hematologist and a medical oncologist, I understand the complexity of the field, and I look forward to providing clarity through discussions and debates with leading researchers. As they say, what makes a successful podcast are the guests and content. I promise both to exceed your expectations. You'll hear from phenomenal thought leaders in the field of hematologic oncology—the movers and shakers in the field. Our goal is to keep you updated and engaged by leveraging this format. In the end, could you think of anything better to listen to when you're driving?

It's impossible to end a column in January without suggesting some New Year's resolutions. My 2023 resolutions are simply to read 15 books and to stop making resolutions I can't keep. I also have decided that I no longer will aspire to compete in the Olympics.

I hope to see you again on these pages, and let's talk on the air while we all listen to The HemOnc Pulse.

All the best to you all and on to a happy, healthy, and prosperous 2023!

Chadi Nabhan, MD, MBA, FACP, *is a hematologist and medical oncologist and the award-winning podcast host of "Outspoken Oncology" and "Healthcare Unfiltered." He also serves on the editorial board for* JAMA Oncology.

Calendar

February 18–20
Clinical Hematology & Oncology: 2023
Hyatt Regency La Jolla at Aventine
San Diego, California

February 23–26
The 27th Annual International Congress on Hematologic Malignancies: Focus on Leukemias, Lymphomas, and Myeloma
Eden Roc Miami Beach Hotel
Miami Beach, Florida

March 2–3
American Society of Hematology Summit on Immunotherapies for Hematologic Diseases
Omni Shoreham Hotel
Washington, DC

March 31–April 2
National Comprehensive Cancer Network 2023 Annual Conference
Orlando World Center Marriott
Orlando, Florida

April 14–19
American Association for Cancer Research Annual Meeting 2023
Orange County Convention Center
Orlando, Florida

April 27–29
International Summit on Hematology and Blood Disorders
Hilton Garden Inn
Lake Buena Vista/Orlando
Orlando, Florida

May 3–6
The 17th International Congress on Myelodysplastic Syndrome
Marseille Chanot Convention Center
Marseille, France

May 10–13
The American Society of Pediatric Hematology/Oncology Conference
Fort Worth Convention Center
Fort Worth, Texas

May 12–14
The Turkish Society of Hematology's 9th International Congress on Leukemia, Lymphoma, Myeloma
Virtual event
Turkey

June 2–6
The American Society of Clinical Oncology Annual Meeting
McCormick Place Convention Center
Chicago, Illinois

MARK YOUR CALENDARS
SEPTEMBER 6–9
2023 SOHO Annual Meeting
George R. Brown Convention Center
Houston, Texas

June 8–11
European Hematology Association Hybrid Congress
Messe Frankfurt
Frankfurt, Germany

June 13–17
17th International Conference on Malignant Lymphoma
Palazzo dei Congressi
Lugano, Switzerland

July 27–29
32nd Annual Mayo Clinic Hematology/Oncology Reviews 2023
The Ritz-Carlton Amelia Island
Amelia Island, Florida

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

Jonathon Cohen, MD, MS

Jonathon Cohen, MD, MS, Associate Professor in the Department of Hematology and Medical Oncology at the Emory University School of Medicine, discusses how he came to focus on lymphoma, as well as current research, pressing questions, and potentially paradigm-shifting data in the field of mantle cell lymphoma (MCL).

Where did you grow up and how did you first become interested in medicine?
I lived in Florida for most of my childhood. Then we moved around a little bit. I spent some time in southwest Virginia and went to high school in Jacksonville, Florida.

I was always interested in medicine from a young age. I think I was just interested in the science. As I got to college, I started some of the pre-med classes, and it just went from there. I had some experiences in the clinic. I wouldn't say I had an "aha" moment. It just always felt like the right thing. As I learned more about the field, I became that much more interested.

What led to your specialization in hematologic oncology, and lymphoma in particular?
I was always somewhat interested in oncology. I had family members who dealt with cancer.

My first real experience in the field was with my father-in-law, who's now a retired oncologist. When my wife and I were dating in college, I would go to visit her family over the holidays, and he would sometimes take me to work with him so I could see what his day-to-day life was like.

One thing I really liked about oncology is that you get to manage all different aspects of a patient's health care. In addition to managing the cancer, there's a good amount of psychology involved. We also evaluate a lot of infections, pulmonary issues, cardiac issues, etc. You get to use the breadth of your internal medicine knowledge.

My journey to the field of lymphoma was a matter of being in the right place at the right time, with the right mentor. I did my fellowship at Ohio State University. As first-year fellows, we were assigned to a clinic, and I was assigned to Dr. Kristie Blum's clinic. She was our fellowship director but also led the lymphoma program. I immediately found that was where I wanted to be. I enjoyed the science of it. I enjoyed taking care of patients—a wide range from young to old. Dr. Blum got me involved with clinical research and lymphoma.

Can you tell us about some of the research and clinical trials you're currently working on?
I spend most of my time on two different aspects of research. One is developing and carrying out clinical trials. The other is what we call outcomes research, or real-world evidence, where we're keeping track of how patients are being treated, what their outcomes are, and what some of the factors are that may impact those outcomes.

From the clinical trials standpoint, my primary focus is on a fairly rare subtype of lymphoma, MCL. I have developed studies on frontline treatments, as well as studies of patients in whom the diseases recur.

In the outcomes work, I'm a part of two large consortia in the United States that are evaluating newly diagnosed—as well as relapsed—patients with lymphoma. We are trying to learn more about the disease through those endeavors as well.

> **"Mentorship is important in any field, but I think in malignant hematology especially, it's critical."**

In your outcomes research, is there anything you found that is surprising or unexpected? Or anything that confirmed something that you saw on an experiential level in the clinic?
There are a couple projects we've been involved with that have done both of those things.

The first is that most of us recognize that being physically active and exercising is important just for our general health. We've done some projects now in collaboration with other centers that have suggested that being physically active likely leads to patients with lymphoma living longer. That has become a big part of what I discuss with patients, the importance of being active and maintaining that activity level.

Another finding has been surprising to me. The lymphoma community is relatively small, so my sense was that there are some agreed-upon treatment parameters. But what we found with some of these projects is just how varied the treatment is from center to center and from region to region. It doesn't necessarily mean that the treatment is bad or wrong, it's just different. This is becoming more apparent as we put together these larger-scale projects.

I'll give you an example. Historically, it has been "assumed" that hematopoietic stem cell transplant is an important part of treatment for MCL. It has become clear from several projects that a minority of patients actually receive a transplant. There's a number of reasons why that could be. It could be because some people don't feel like transplant is that important. Maybe those patients live far away from a transplant center.

You see at national meetings that people will start off a talk on MCL saying, "The standard of care is to get chemotherapy followed by a transplant." But then when you actually look at what's happening, that's not always the case.

What are *your* thoughts on the role of transplant in MCL?
My thoughts on that are evolving. Until recently, I felt it was probably important, or appropriate, for patients who are young and fit.

There's a large study that was presented at the 2022 American Society of Hematology (ASH) Annual Meeting and Exhibition that brings that into question, especially for those who receive a newer therapy called ibrutinib. It may be that those patients can receive ibrutinib and don't necessarily need a transplant. My guess would be that in the next six to 12 months, if not sooner, there's going to be a shift in how that is approached in patients for whom the Bruton's tyrosine kinase (BTK) inhibitor is indicative and appropriate.

I think there's going to be a transition period where it's going to be complicated. Then, hopefully, we'll settle on some sort of agreed-upon approach.

What do you see as the major challenges and unmet needs in the field of MCL?
There are a few issues. The first is, many patients with relapsed disease who receive a BTK inhibitor do well; however, when they ultimately progress, we know that for those patients, chimeric antigen receptor (CAR) T-cell therapy is active. But CAR-T isn't always available or, for whatever reason, may

not always be feasible.

For those patients, we don't really have great options. Those are patients who need clinical trials. But as a standard approach, we don't have a lot of great approaches.

In those patients who progress after CAR-T, we really struggle. In the handful of patients I've encountered who have had that experience, it has been very challenging to get their disease back under control. That is an area where we are falling short and need to improve therapies.

Although there has been a lot of interest and research done, we still don't do that well at risk stratifying patients up front and tailoring therapy appropriately.

A young patient who is eligible for it will still receive pretty intensive chemotherapy, and then you can talk about transplant. But there may be some patients who have a very indolent or slow-growing process who may not need therapy at all or might be able to get by with less-intensive therapy.

There is a lot we still haven't hashed out. Even though those patients tend to do well, we're probably overtreating at least some of them.

What do you think are some of the most pressing questions in MCL that still need to be addressed?

One of the biggest questions is going to be, "What, if anything, is the role for transplant?" Are there patients for whom transplant is still preferred? Are there patients where it hinders their overall disease course? Even with new studies coming out, that is still going to be an area of interest in my mind.

The other piece is that we still don't really know which is the most appropriate frontline therapy. Every center has their own treatment, some of which are based on studies, some of which are adapted from studies. I think we still don't really know how to treat patients with MCL.

Fortunately, the survival is much better than it has been in the past. There still is a ton of variability among oncologists—even oncologists who specialize in lymphoma—as far as how to treat it.

Is there a certain clinical trial going on right now that you feel could answer those questions? If not, is there a certain clinical trial design you feel would help answer those questions?

The US Intergroup has two studies that may help contribute somewhat to both of those issues.

First is the EA4151 trial, in which patients—regardless of their induction regimen—undergo minimal residual disease (MRD) assessment. Those who are MRD-negative are randomized to receive a transplant or not receive a transplant.

This research will help us, to some extent, identify populations that still may benefit from transplants versus those that may not.

Then there's sort of a companion trial, EA4181, that is looking at a couple of different frontline regimens to try to determine how important, for example, cytarabine is. How important is it that patients get a BTK inhibitor?

Those two studies, combined with the TRIANGLE study presented at ASH, hopefully will help us sort through some of those issues. Obviously, there will be more questions and new therapies we want to investigate. But I'm hopeful these studies will help us at least continue to move toward an answer.

What do you hope to see happen in the field? What do you think can happen in the next five to 10 years?

It would be great to be better at identifying which patients need which therapy. It may be, for example, that some patients really need cytarabine, a BTK inhibitor, and transplant. Whereas others may need none of those or just one of those.

Being able to better tailor therapy would be great. It will help patients, and it will help us make sure that we're doing things properly.

The other thing we haven't talked as much about is that there is a population that, despite all those interventions, still experiences early relapse. Those patients, unfortunately, tend to have a shorter survival.

I've been very interested in a number of ongoing studies looking at moving CAR-T, for example, earlier on in the course of therapy, especially for high-risk patients, and integrating bispecific antibodies for some of the high-risk patients.

There are some newer therapies that are either here or emerging that may positively impact outcomes for patients with high-risk disease. I'd love to get to a place where even high-risk patients are able to get their disease under control and enjoy a prolonged survival.

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

The key is to try to latch on to a mentor who is both clinically strong and interested in helping you get involved with research. That is critical. It's a small community, but all of oncology is becoming more complicated, especially malignant hematology. It really is exploding with the number of new therapies and classifications. Having somebody who you can rely on, who is going to help you gain that clinical expertise, and who is going to look out for research opportunities is important. Mentorship is important in any field, but I think in malignant hematology especially, it's critical.

The other piece is recognizing that there's a lot we still don't understand and that it's okay to ask questions. I send out questions to some of my colleagues regularly—even though I've been doing this now for a while—because it seems like every month you see something you've never encountered before. The key is to surround yourself with a good support team.

It's important to recognize that it's an ever-evolving field and understand that the right thing to do in November 2022 may not be the right thing to do in March 2023. Things change pretty rapidly.

What are some of your favorite hobbies and activities outside of work?

I have three kids who are all school age, so a lot of our time outside of work is going to sporting events and school activities. As a family, we really enjoy travel. My wife and I have had the opportunity to do a bit of exploring. We love the beach, so we've been to a number of beaches here in the Southeast, and we've also been to Europe a couple times.

We also are pretty big sports fans. We like to go to Braves games here in Atlanta. My two older kids are particularly into it.

My wife and I also enjoy trying new restaurants. She's a more adventurous eater than I am, but we still try to check out new things when we can.

As you can imagine, the work can sometimes be very intense; then other times, fortunately, there's a bit of time to relax or take a break. When we do have those free evenings or afternoons, we try to take advantage of it.

Is there a skill you have or something that people might be surprised to learn about you?

I can't really claim it as an active skill, but one thing people may not know is that I participated in the National Spelling Bee as a teenager. I placed 21st in the country, which was exciting. I still am a decent speller, but I certainly don't retain those nationally ranked spelling skills.

As an adult, I developed a talent for baking. In the last couple years during COVID-19, I started doing some baking, and that has been enjoyable. Probably my favorite thing I've made is an apple pie from scratch. And croissants—with the croissants, it's a two-day process, but it's incredibly satisfying when those come out good.

Any other thoughts you'd like to share?

The key thing that has helped me be successful is that there generally is a lot of cooperation and collaboration within our hematologic malignancy community. I would encourage anybody who is pursuing a clinical career in malignant hematology to avail themselves of the many people who are out there and are happy to help them in their career, whether they're at the same center or another.

There are a number of folks I've called upon over the years to provide help with clinical cases or research projects.

It's hard and complicated work. There are a lot of complex issues. It's important to identify that you're not going to always know exactly what to do and that there are others who may have had that experience and are happy to provide support.

Jonathon Cohen, MD, MS, *is an Associate Professor in the Department of Hematology and Medical Oncology at the Emory University School of Medicine.*

Bispecific Antibodies: New Options

With more bispecific antibodies in development for hematologic malignancies, physicians must determine how best to incorporate them into practice once they reach market | *By Leah Lawrence*

Monoclonal antibodies like rituximab helped to revolutionize the treatment of hematologic malignancies, but the recent advancements in the use of T-cell engager therapy and bispecific antibodies have revealed several clinical therapeutic advantages that experts hope will further improve outcomes and decrease adverse events.

"Most of us are excited and interested in bispecific antibodies because we are seeing groundbreaking updates from clinical trials [of these drugs]," said **Bhagirathbhai Dholaria, MBBS,** an Assistant Professor of Medicine in the Department of Medicine at Vanderbilt University Medical Center.

Bispecific antibodies differ from monoclonal antibodies by having two binding specificities against two different antigens in one antibody molecule. The most common bispecific antibodies in development act as a sort of bridge between cancer cells and T cells, Dr. Dholaria explained. For example, some bispecific antibodies being researched in multiple myeloma (MM) engage the tumor-specific B-cell maturation antigen (BCMA) and the CD3 antigen on T cells.

There are a multitude of bispecific antibodies under investigation right now in hematologic malignancies, with various tumor-specific targets, routes of administration, and treatment durations. Which drugs will make it to market first and how these drugs will be incorporated into treatment sequencing remains to be seen.

New Options

The first bispecific antibody to gain approval in a hematologic malignancy was the bispecific T-cell engager (BiTE™) blinatumomab, a molecule directed against CD19 and CD3. In 2014, the U.S. Food and Drug Administration (FDA) granted blinatumomab accelerated approval for Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) in adults and children. The drug gained regular approval with an expanded label for all patients with relapsed or refractory B-cell precursor ALL in 2017.[1]

The TOWER trial confirmed the clinical benefit of blinatumomab compared with standard of care in patients with relapsed or refractory B-cell precursor ALL. Overall survival (OS) was significantly prolonged in patients treated with blinatumomab (hazard ratio, 0.71; 95% CI, 0.55-0.93; P=.012). Median OS was 7.7 months with blinatumomab compared with 4.0 months with standard of care.[2]

"This provided the proof of principle that a bispecific antibody could lead to durable remission," said **Michael Dickinson, MD,** Lead of the Aggressive Lymphoma Disease Group within Clinical Haematology at Peter MacCallum Cancer Centre and Royal Melbourne Hospital in Australia. "This was an intravenous formulation given with continuous infusion. It is a small molecule with a short half-life."

In leukemia, blinatumomab is an important tool for inducing remission, often as a bridge to transplant in ALL, Dr. Dickinson said. In lymphoma, blinatumomab has been less successful.

"We know blinatumomab works and can shrink tumors, but the rate of complete remission was not high enough to justify the complexity of infusion," Dr. Dickinson said. "We haven't seen blinatumomab move forward in common lymphomas, but it did show that a complete remission could be achieved with this mechanism."

The newest bispecific antibody to gain regulatory approval in hematologic malignancies is teclistamab-cqyv, a bispecific BCMA-directed CD3 T-cell engager.[3] Teclistamab was approved in October 2022 for adult patients with relapsed or refractory MM who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

The approval of teclistamab was based on the single-arm, open-label MajesTEC-1 trial that included an efficacy population of 110 patients. The overall response rate (ORR) with teclistamab was 61.8%, with an estimated duration of response of 90.6% at six months and 66.5% at nine months.[4]

"This drug is highly potent, with treatment responses in phase I showing an ORR of over 70% in these highly refractory patients," said Dr. Dholaria. "The drug is also a subcutaneous formulation that is relatively easy to administer compared with blinatumomab. Patients go to the doctor's office once a week and get a shot."

Currently, teclistamab is given as long as the patient is responding.

"Right now, we don't know if someone on teclistamab can stop therapy safely," Dr. Dholaria said. "The answer might be that we can. Anecdotally, I have had a handful of patients who have stopped the drugs due to side effects [and] are still in remission."

Teclistamab is not alone as a fifth-line therapy for MM. Even with the antibody-drug conjugate belantamab mafodotin now pulled from the market, patients still have two FDA-approved chimeric antigen receptor (CAR) T-cell therapies: idecabtagene vicleucel and ciltacabtagene autoleucel.

"Hopefully, we will not see these agents working against each other, but working together for patients," Dr. Dholaria said. "If I have a patient who qualifies for both, which would I prefer? It is too early to know. A comparative study has not been done."

The currently available CAR T-cell therapies for MM have a four- to six-week manufacturing window, and patients cannot always wait that long. In that case, the "off-the-shelf" bispecific antibody may be a more appropriate drug, Dr. Dholaria said.

"However, the beauty of CAR T-cell therapy is that

it is a one-time treatment," he said. "If a patient responds, they can have a durable remission from that single infusion. That is a huge benefit compared with teclistamab, which is an ongoing therapy."

Overflowing Pipeline

In addition to these therapies on the market, there are multiple bispecific antibodies that are close to or pending regulatory approval.

The FDA has granted elranatamab, another BCMA-, CD3-targeted bispecific antibody, breakthrough therapy designation for relapsed or refractory MM.[5] This designation was based on six-month follow-up data from a cohort of the single-arm, open-label MagnetisMM-3 trial. Data from an interim analysis were presented at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting. With a median follow-up of 3.71 months, initial efficacy results showed an objective response rate of 60.6%, with a manageable safety profile.[6]

"In terms of response, this seems very close to what we see with teclistamab, with a comparable risk of cytokine release syndrome (CRS) and infections," Dr. Dholaria said.

Abstracts from the 64th American Society of Hematology (ASH) Annual Meeting and Exposition include studies of elranatamab in combination with daratumumab and in patients naïve to BCMA-directed therapies.

In the lymphoma realm, there are several bispecific antibodies that appear to be promising, not the least of which is mosunetuzumab, a CD20×CD3-directed bispecific antibody that has already gained regulatory approval from the European Medicines Agency for adult patients with follicular lymphoma (FL).[7] The FDA has granted mosunetuzumab priority review.

Mosunetuzumab is given intravenously with a step-up dosing strategy for a fixed course.

"It has been effective in inducing durable remissions in FL," Dr. Dickinson said. "The striking thing is that it seems to be very well tolerated, with low CRS and low neurotoxicity, which means it can be delivered in an outpatient setting."

Data from a phase II study of 90 patients with grade I-IIIa FL showed that intravenous mosunetuzumab was associated with a complete response (CR) rate of 60.0%, which was significantly higher than that of a historical control CR rate of 14% ($P<.0001$).[8] CRS was predominantly grade 1 and primarily confined to the first cycle.

Another frontrunner in lymphoma is glofitamab, according to **Amitkumar Mehta, MD,** Associate Professor and Director of the Lymphoma Program at the University of Alabama, Birmingham. Glofitamab is a bivalent, CD20×CD3-targeting bispecific antibody under investigation for the treatment of aggressive lymphomas.

"Glofitamab is a little different than the other bispecifics because it has a 2:1 ratio of engaging CD20 to CD3," Dr. Mehta explained. "All of the others have a 1:1 ratio. Glofitamab also has an intravenous administration."

Dr. Dickinson and colleagues presented data from a phase II trial of glofitamab at the 2022 ASCO Annual Meeting that demonstrated that fixed-duration glofitamab induced a response in 51.6% of patients, with 39.4% achieving a CR.[9]

"In diffuse large B-cell lymphoma (DLBCL), even more than FL, CR is probably the most important endpoint," Dr. Dickinson said. "We are trying to achieve deep and rapid remission that will translate into durable remission."

Trailing a bit behind the others is epcoritamab, according to Dr. Mehta. Epcoritamab is an immunoglobulin G (IgG) 1 CD20×CD3 bispecific antibody that was recently accepted for priority review by the FDA for relapsed/refractory LBCL in patients with two or more prior lines of therapy.[10]

Regulatory approval would be based on results from the LBCL cohort (157 patients) of a multicenter, phase I/II trial. Patients received step-up dosing to a 4-mg intravenous dose of epcoritamab administered in 28-day cycles. The ORR was 63%, with a CR rate of 39%.[11] Patients naïve to CAR T-cell therapy had an ORR of 69%, with a 42% CR rate; those with prior CAR T-cell therapy had rates of 54% and 34%, respectively.

Epcoritamab is also given on an indefinite basis.

Odronextamab, an IgG4-based CD20×CD3 bispecific antibody has also produced promising results for CD20-positive B-cell malignancies. Data from a single-arm, phase I study of 145 patients with a median of three prior therapies showed an objective response rate of 51%.[12] Odronextamab has had some delays, as it was placed on a partial clinical hold in late 2020 in order to reduce rates of severe CRS during step-up dosing; the hold has since been lifted.

There are also several bispecific antibodies being investigated for the treatment of other forms of lymphoma, including glofitamab for mantle cell lymphoma (MCL), as well as mosunetuzumab for chronic lymphocytic leukemia (CLL). Results of a first-in-human phase I study of NVG-111, a ROR1×CD3 bispecific antibody, in patients with relapsed or refractory CLL or MCL were presented at the 2022 ASCO Annual Meeting. Although results were only available for a small number of patients, the early data showed promising efficacy with a manageable safety profile.[13]

Drawbacks

Bispecific antibodies or T-cell-engaging therapies have advantages compared with existing therapies, like being more readily available, but they are still associated with certain adverse events.

"Because they are a T-cell-based therapy, they do share some similar toxicities seen with CAR T-cell therapy," said **Jing-Zhou Hou, MD, PhD,** a medical oncologist, hematologist, and clinical investigator at the University of Pittsburgh Medical Center Hillman Cancer Center in Pennsylvania. "The two major side effects of concern are CRS and immune effector cell-associated neurotoxicity (ICANS)."

For example, teclistamab was given regulatory approval with a Boxed Warning for life-threatening or fatal CRS and neurologic toxicity, including ICANS. In the MajesTEC-1 trial, CRS occurred in 72% of patients, neurologic toxicity in 57%, and ICANS in 6%. However, grade 3 CRS only occurred in 0.6% of patients and grade 3/4 neurotoxicity in 2.4%.[4]

"The new thing about this drug compared with other myeloma therapies is the significantly high proportion of patients experiencing CRS, especially during the first one or two doses," Dr. Dholaria said. "Patients are admitted to the hospital for 48 hours at a time during step-up dosing for monitoring for fever. Fortunately, CRS does not appear to be high in severity like with CAR T-cell therapy."

Teclistamab is generally well tolerated after these initial doses, and the risk for CRS is minimal, indicating that the rest of treatment can be given in an outpatient setting, Dr. Dholaria said.

Similar adverse events were seen with the other bispecific antibodies as well.

"Across all of these studies, there has been the use of step-up dosing, which has been shown to be effective," Dr. Dickinson said. "You give the first dose at a lower dose to get a lower overall rate of CRS. Across all of these agents, the second dose then had a lower rate of CRS compared with the first dose."

The idea, Dr. Dickinson said, is to get the patient through that initial CRS with a low dose, and then step the patient up to the most effective dose. Different agents have had slightly different step-up strategies, with some still establishing the best step-up dose to balance CRS risk with treatment efficacy.

In addition to the possibility of adverse events, another potential drawback to these drugs is cost.

"These drugs are ridiculously expensive," Dr. Dholaria said. "Teclistamab is currently quoted at $40,000 a month. This is an ongoing expense to the health care system infrastructure that all of us will have to pay for eventually, and as these drugs get incorporated into earlier lines of therapy, we will be treating a lot more patients with them."

Dr. Dholaria noted that CAR T-cell therapy is also expensive but is a one-time treatment. In addition, if a patient achieves remission after CAR T-cell therapy, there is no subsequent treatment needed.

"The cumulative financial toxicity over time for bispecific antibodies is going to come close to a one-time CAR-T infusion, and that is something to consider not only on the patient level but as the treating physician as well," Dr. Dholaria said. "Cost needs to be looked at, especially when they may be used in combination with other drugs that are equally as expensive."

Future Use

It is important to consider the possible cost of bispecific antibodies in combination with other therapies because these off-the-shelf drugs lend themselves to combination, according to Dr. Dickinson.

"Sponsors are aggressively developing bispecifics in combination with other drugs," Dr. Dickinson said. "We know there are a number of trials looking at patients in first or subsequent relapse using conventional platinum-containing chemotherapy combinations or in combination with R-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy, with promising early safety data."

For example, data presented at the 2022 ASH Annual Meeting and Exposition looked at teclistamab in combination with daratumumab and lenalidomide (MajesTEC-2).[14] There were also multiple abstracts looking at bispecific antibodies with different targets. Dr. Hou presented data from

a phase I study of TNB-486, a CD19×CD3 bispecific antibody for patients with relapsed or refractory B-cell non-Hodgkin lymphoma.[15] Early data showed an ORR of 81.2%, with a CR rate of 68.7% at doses 2.4 mg and higher. For patients with relapsed/refractory FL, the ORR is 87.5%, and all responders achieved a complete metabolic response. Responses were also seen among patients with previous CAR T-cell therapy.

"This drug was engineered with a prolonged half-life," Dr. Hou explained. "The half-life is about nine to 11 days, which would allow for biweekly or even monthly dosing."

Bispecific antibodies are also expected to be incorporated into earlier lines of therapy. For example, another phase I study presented at the 2022 ASH Annual Meeting and Exposition compared lenalidomide with or without teclistamab as a maintenance therapy after transplantation in patients with newly diagnosed MM.[16]

As availability of bispecific antibodies grows, there is also the expectation that access to these drugs will expand into community cancer centers. Unlike CAR T-cell therapy, which is administered at specialized treatment centers, bispecific antibodies are expected to be used in an outpatient setting.

"I think these drugs can be safely used in a community oncology center, but there will need to be a degree of understanding about toxicities so that when severe toxicities occur, there is a reliable response," Dr. Dickinson said.

Dr. Hou agreed, adding that it is possible that since CRS and neurotoxicity are most likely to occur in the first or second cycle that these drugs may be initially administered in the hospital until practitioners learn how to best minimize risk.

The Association of Community Cancer Centers (ACCC) conducted a survey in 2020 on bispecific antibodies with 129 community providers responding. Some of the common challenges to use of blinatumomab (the only available bispecific antibody at the time) included transitioning patients from the inpatient to outpatient setting (41%), managing patients in remote areas (28%), managing side effects (27%), assisting patients with treatment-related costs (24%), and lacking in-house expertise with the drug class (22%).[17]

Subsequently, the ACCC and the Society for Immunotherapy of Cancer developed an educational initiative on best practices in expanding access to bispecific antibodies and adverse event management.

"The toxicities with these drugs are no worse than those we see from CHOP chemotherapy, which is routinely given as a frontline regimen," Dr. Dickinson said. "While CRS and fever after an infusion are different from toxicities from conventional agents, once people get their head around them, they will realize that they are less severe and as manageable."

Experts eagerly await future trial results and decisions from the FDA on regulatory approval of some of these agents, all of which point to expanded use throughout the cancer care community.

"These are highly active agents in a number of treatment setting that do not require the complexity that CAR T-cell treatment might require and exposes the patient to a mechanism of cancer cell killing that is not the traditional cytotoxic method," said Dr. Dickinson.

Moving forward, Dr. Hou said he envisions ongoing availability of both new and improved CAR T-cell therapy options and bispecific antibodies.

"If a patient fails CAR T-cell therapy, they can get a bispecific antibody and vice versa," Dr. Hou said. "These two treatments should complement each other, give patients more options, and give physicians more weapons to fight these deadly diseases."

Leah Lawrence is a freelance health writer and editor based in Delaware.

References

1. U.S. Food & Drug Administration. FDA grants regular approval to blinatumomab and expands indication to include Philadelphia chromosome-positive B cell. July 12, 2017. Accessed December 6, 2022. www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-regular-approval-blinatumomab-and-expands-indication-include-philadelphia-chromosome

2. Kantarjian H, Stein A, Gokbuget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. *N Engl J Med.* 2017;376(9):836-847.

3. U.S. Food & Drug Administration. FDA approves teclistamab-cqyv for relapsed or refractory multiple myeloma. October 25, 2022. Accessed December 6, 2022. www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-teclistamab-cqyv-relapsed-or-refractory-multiple-myeloma

4. Moreau P, Garfall AL, van de Donk NWCJ, et al. Teclistamab in relapsed or refractory multiple myeloma. *N Engl J Med.* 2022;387:495-505.

5. Pfizer press release. Pfizer's elranatamab granted FDA breakthrough therapy designation for relapsed or refractory multiple myeloma. November 3, 2022. Accessed December 8, 2022. www.pfizer.com/news/press-release/press-release-detail/pfizers-elranatamab-granted-fda-breakthrough-therapy

6. Lesokhin AM, Arnulf B, Niesvizky R, et al. Initial safety results for MagnetisMM-3: A phase 2 trial of elranatamab, a B-cell maturation antigen (BCMA)-CD3 bispecific antibody, in patients (pts) with relapsed/refractory (R/R) multiple myeloma (MM). *J Clin Oncol.* 2022. doi:10.1200/JCO.2022.40.16_suppl.8006

7. Roche press release. European Commission approves Roche's first-in-class bispecific antibody Lunsumio for people with relapsed or refractory follicular lymphoma. June 8, 2022. Accessed December 7, 2022. www.globenewswire.com/news-release/2022/06/08/2458330/0/en/European-Commission-approves-Roche-s-first-in-class-bispecific-antibody-Lunsumio-for-people-with-relapsed-or-refractory-follicular-lymphoma.html

8. Budde LE, Sehn LH, Matasar M, et al. Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study. *Lancet Oncol.* 2022;23(8):1055-1065.

9. Dickinson M, Carlo-Stella C, Morschhauser F, et al. Glofitamab in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and ≥ 2 prior therapies: pivotal phase II expansion results. *J Clin Oncol.* 2022. doi:10.1200/JCO.2022.40.16_suppl.7500

10. AbbVie press release. U.S. FDA accepts for priority review the Biologics License Application for epcoritamab (DuoBody®-CD3xCD20) for the treatment of relapsed/refractory large B-cell lymphoma. November 21, 2022. Accessed December 7, 2022. https://news.abbvie.com/news/press-releases/us-fda-accepts-for-priority-review-biologics-license-application-for-epcoritamab-duobody-cd3xcd20-for-treatment-relapsedrefractory-large-b-cell-lymphoma.htm

11. AbbVie press release. AbbVie announces late-breaking results from phase 2 trial of investigational epcoritamab (DuoBody®-CD3xCD20) in patients with relapsed/refractory large B-cell lymphoma (LBCL) at the European Hematology Association (EHA) Annual Congress. June 11, 2022. Accessed December 7, 2022. https://news.abbvie.com/news/press-releases/abbvie-announces-late-breaking-results-from-phase-2-trial-investigational-epcoritamab-duobody-cd3xcd20-in-patients-with-relapsedrefractory-large-b-cell-lymphoma-lbcl-at-european-hematology-association-eha-annual-congress.htm

12. Bannerji R, Arnason JE, Advani RH, et al. Odronextamab, a human CD20×CD3 bispecific antibody in patients with CD20-positive B-cell malignancies (ELM-1): results from the relapsed or refractory non-Hodgkin lymphoma cohort in a single-arm, multicentre, phase 1 trial. *Lancet Haematol.* 2022;9(5):e327-e339.

13. Jasani P, Townsend W, Asher S, et al. First-in-human phase I study of a ROR1-targeting bispecific T-cell engager (NVG-111) shows evidence of efficacy in patients with relapsed/refractory CLL and MCL. *J Clin Oncol.* 2022. doi:10.1200/JCO.2022.40.16_suppl.7535

14. Searle E, Quach H, Wong SW, et al. Teclistamab in combination with subcutaneous daratumumab and lenalidomide in patients with multiple myeloma: results from one cohort of MajesTEC-2, a phase1b, multicohort study. Abstract #160. Presented at the 64th ASH Annual Meeting and Exposition; December 10-13, 2022; New Orleans, Louisiana.

15. Hou J-Z, Jacobs R, Cho S-G, et al. Interim results of the phase 1 study of Tnb-486, a novel CD19xCD3 T-cell engager, in patients with relapsed/refractory (R/R) B-NHL. Abstract #612. Presented at the 64th ASH Annual Meeting and Exposition; December 10-13, 2022; New Orleans, Louisiana.

16. Zamagni E, Boccadoro M, Spencer A, et al. MajesTEC-4 (EMN30): a phase 3 trial of teclistamab + lenalidomide versus lenalidomide alone as maintenance therapy following autologous stem cell transplantation in patients with newly diagnosed multiple myeloma. Abstract #3242. Presented at the 64th ASH Annual Meeting and Exposition; December 10-13, 2022; New Orleans, Louisiana.

17. Association of Community Cancer Centers. Using bispecific antibodies in community practice: challenges and opportunities. Accessed on December 6, 2022. www.accc-cancer.org/docs/projects/bispecific-antibodies/using-bispecific-antibodies-in-community-practice.pdf?sfvrsn=f5b5ac13_0

Should Small-Molecule Treatments for CLL Be Combined or Sequenced?

Jennifer R. Brown, MD, PhD, President of the Society of Hematologic Oncology, Director of the Chronic Lymphocytic Leukemia (CLL) Center at the Dana-Farber Cancer Institute, and Worthington and Margaret Collette Professor of Medicine in the Field of Hematologic Oncology at Harvard Medical School, and **Anthony Mato, MD, MSCE,** Director of the CLL Program at the Memorial Sloan Kettering Cancer Center, debate whether combination small molecules are better than sequencing small molecules in CLL treatment.

Combination Small Molecules Are Better Than Sequencing

By Dr. Brown


Jennifer R. Brown, MD, PhD

Why combinations? In general, we know that single-agent therapy selects for resistance. From a purely mathematical standpoint, if you have one drug, it's much easier to have some cells present that are resistant to that single drug, while if you have two drugs that are non-cross resistant with different mechanisms of resistance, it becomes orders of magnitude harder to have cells that become resistant to both drugs. I would argue the fact that responses with single-agent therapy are shorter in patients with a *TP53* aberration or complex karyotype also supports this. Furthermore, we know that combinations allow patients to achieve deep remission, often with undetectable minimal residual disease (MRD), which is a first step toward cure and is also associated with improved overall survival (OS) in some cases. It also allows discontinuation of therapy, which mitigates several problems, not only the selection pressure I just mentioned for resistance mutations, but also cumulative adverse events—which we know can be quite severe, particularly with ibrutinib—loss of adherence, and cost. I would also note that most therapeutic advances in cancer have often relied on combinations of highly effective therapies.

Just to review some of the single-agent data and some of the issues with it: We have the Ohio State University long-term experience with ibrutinib where we have early Richter transformation that plateaus, but we see continuous CLL progression over time on therapy, rising to quite a high level, with risk factors including complex karyotype, (del)17p, and younger age. If we look also at the ALLIANCE trial, we see that increased karyotypic abnormality is associated with worse outcomes in the ibrutinib groups as well as patients with unmutated immunoglobulin heavy chain variant (IGHV). Furthermore, Dr. Mato has published that 17p deletion leads to worse OS with ibrutinib in a real-world setting. Dr. Inhye Ahn has also published a model in which 17p deletion is implicated in significantly worse outcomes with single-agent ibrutinib.

What about venetoclax? In the long-term follow-up data from the phase II study of continuous venetoclax in patients with (del)17p, you can see a very similar pattern, early Richter transformation and then continuous progression. Furthermore, with the CLL14 trial, we again see the higher-risk patients are relapsing earlier, reflecting this steady development of resistance in the higher-risk groups first, but that we'll see later in all patients. The median progression-free survival (PFS) is approximately 48 months for the *TP53*-aberrant patients, and a little over five years for the patients with unmutated IGHV. In data from the Mayo Clinic looking retrospectively at patients who were previously exposed to ibrutinib and venetoclax, then given combination therapy, you can see these patients have a very poor outcome with a combination of ibrutinib plus venetoclax. They had a 14-month median time to next therapy and only a two-year OS. That's the outcome of our sequential single-agent approach over time.

How can we do better? Combinations lead to deep remissions, which is, again, a first step toward a cure. But even if it's not a cure, depth of remission is associated with later and later relapse. In a large study from the United Kingdom looking at all-comer CLL patients, regardless of therapy or line of therapy, undetectable MRD was associated with better PFS and OS. In fact, outcomes were better when undetectable MRD was achieved after first-line therapy. Of course, we saw this with the chemoimmunotherapy data, that undetectable MRD was associated with prolonged PFS and a very long-term favorable outcome in patients with mutated IGHV. We now have data with venetoclax, similarly from CLL14, where depth of remission is associated with PFS, and in fact, undetectable MRD is associated with improved OS now in this study.

You may say, how can this be true of Bruton's tyrosine kinase (BTK) inhibitors? We know that if you stay on the drug, it doesn't matter if you have persistent disease. There are some emerging datasets suggesting that depth of remission may matter also, even with BTK inhibitors. Data from the MD Anderson Cancer Center show that achieving complete remission with ibrutinib was associated with better PFS compared with partial remission. In a five-year follow-up of the phase II MD Anderson study of ibrutinib plus or minus rituximab in high-risk patients, depth of remission was associated with a much better PFS compared with those with only partial remission.

We also have follow-up data from the HELIOS study, which combined ibrutinib with bendamustine plus rituximab. Ibrutinib was given continuously. Undetectable MRD correlates with outcomes in the bendamustine plus rituximab arm. But in the ibrutinib plus bendamustine and rituximab arm, even though patients are on continuous ibrutinib, we're still seeing decreases in PFS in patients with MRD at 1% or higher. These data suggest that perhaps depth of remission can improve PFS, potentially eventually OS, even with BTK inhibitors.

How do we achieve that? We know that combination with venetoclax or a B-cell lymphoma (BCL)-2 inhibitor is highly effective in vitro, certainly in combination with a BTK inhibitor, and clinically. In the phase II CLARITY study, patients had a median of one prior chemoimmunotherapy regimen and a median age in the mid-60s. They were given ibrutinib plus venetoclax for two years initially, then potentially extending to three years. There was a steady improvement in undetectable MRD up to the two-year time point in both blood and marrow. The rapidity with which disease was depleted was strongly associated with undetectable MRD and outcome. What's particularly remarkable about this study is the three-year PFS in the relapsed setting of 96%, which is really a very good number. As I mentioned, these are patients with one prior chemoimmunotherapy regimen and they're somewhat similar to the patients treated in the ASCEND trial, also with a median patient age in the mid-60s and one prior regimen. If you look at the three-year PFS in the acalabrutinib arm from the ASCEND trial, it's 63%.

This is an unholy cross-trial comparison, but at the moment we don't yet have any direct randomized trials, and this single-agent PFS is substantially lower than what we saw for the combination in CLARITY. The HOVON trial, also in relapsed patients, combined ibrutinib with venetoclax. MRD-positive patients continued on ibrutinib. Those who had undetectable MRD were randomized between ibrutinib or observation. At one year, 37% of patients had undetectable MRD. The study met its primary endpoint, which had a similar PFS in the observation and ibrutinib arms in patients with undetectable MRD.

What about frontline? MD Anderson data with ibrutinib plus venetoclax in high-risk patients showed a 93% three-year PFS rate, with no difference based on IGHV or (del)17p status. In the CAPTIVATE trial, the MRD arm first received three cycles of ibrutinib lead-in, then 12 cycles of ibrutinib plus venetoclax. Patients with undetectable confirmed MRD were randomized between ibrutinib and placebo. Those in whom MRD was not confirmed were randomized between ibrutinib or ibrutinib plus venetoclax. In patients with confirmed undetectable MRD, there was a two-year disease-free survival rate of 95% with placebo and 100% with ibrutinib. That was an excellent outcome. In the patients who did not have confirmed undetectable MRD and who were randomized to continue ibrutinib plus venetoclax,

after the first year of therapy, there was a further improvement in the rate of undetectable MRD in bone marrow of over 30%.

What about the fixed-duration arm of CAPTIVATE? The median patient time on study is 38 months. These are patients with high-risk markers, although they are young and fit. They received three months of ibrutinib lead-in and 12 cycles of combination ibrutinib plus venetoclax. Undetectable MRD rates are about 60%. The estimated three-year PFS in this study is 88% and similar for (del)17p, *TP53* aberrant, or unmutated IGHV patients. This is an extremely high PFS.

What about GLOW in older patients? These data are interesting, because they suggest that PFS is still well maintained, even for the patients who are MRD-positive. It has been suggested that something about the combination therapy may be altering the biology of the cells in terms of the rate of regrowth or recurrence, similar to what has been described in the CLL14 trial in the venetoclax arm.

What about combinations? I'm also a fan of not forgetting the CD20 antibodies. The Ohio State University study combining ibrutinib, venetoclax, and obinutuzumab was the only one of the triple-drug trials that has PFS data of at least three years: 95% in the treatment-naïve cohort and 95% in the relapsed/refractory cohort. This is very impressive PFS data. It was a 14-month fixed-duration regimen that patients discontinued after that period. In terms of the next-generation BTK inhibitors, we have looked at acalabrutinib, venetoclax, and obinutuzumab where we find very high rates (77%) of undetectable MRD in bone marrow. It is still very immature for PFS. With zanubrutinib plus obinutuzumab and venetoclax, almost 90% of patients achieved undetectable MRD in blood and marrow and were able to stop therapy after a median of 10 months.

I would argue that combination small molecules are the future. They achieve deep remissions leading to previously unprecedented two- to three-year PFS, even in the relapsed setting. Outcomes are similar in patients with high-risk markers. There's a suggestion that PFS may be better sustained off therapy even in patients without undetectable MRD in the GLOW trial. The combinations certainly result in less toxicity and cost.

What about resistance and retreatment? Data here are limited. In the MURANO trial—which is assessing single-agent venetoclax and subsequent retreatment—patients at the end of their first round of venetoclax plus rituximab had undetectable MRD. Then on retreatment, less than half of these patients achieved undetectable MRD. This was associated with an increase in their clonal fraction of 17p deletion and increased genomic complexity, which argues that we are still seeing clonal evolution after even this time-limited venetoclax regimen.

In terms of retreatment with combinations, data are extremely limited. We have limited data from the HOVON trial where they were able to reinduce undetectable MRD in seven patients with ibrutinib plus venetoclax. We have the CAPTIVATE retreatment data, in which patients have been retreated with single-agent ibrutinib with response. In terms of acquisition of mutations in these patients relapsing, in CLL14, we do see a little bit of clonal evolution with *TP53* and *BIRC3*, high-risk mutations, in one patient each on the venetoclax plus obinutuzumab arm. This was better than in patients who received obinutuzumab plus chlorambucil, though. Thus far in CAPTIVATE, after ibrutinib plus venetoclax, we are not seeing clonal evolution mutations in the 13 patients.

Combination small molecules are highly effective in achieving deep remission with undetectable MRD, which is associated with improved OS in multiple studies, including a venetoclax-based study. Tolerability is much improved with second-generation BTK inhibitors. We can discontinue therapy for extended periods, avoiding toxicity, cost, and development of resistance. The early data show few resistance mutations at relapse, suggesting the possibility of retreatment.

I do have a provocative and somewhat speculative question: What is wrong with sequential single agents? We obviously need randomized data comparing combinations with single agents, and we will get these data with the German CLL study group's CLL17 trial. In the relapsed setting, in a cross-trial comparison, initial PFS with a single agent appeared shorter compared with combination therapy. In the data we have, we know PFS to subsequent lines of therapy is shorter. If you use venetoclax after a patient has progressed on a BTK inhibitor, the median PFS is two years. If you use venetoclax like in the MURANO trial, it's five years. If you look at patients who have received both a BTK inhibitor and venetoclax—treated now with pirtobrutinib, for example—the median PFS is 18 months in patients who have received both previously, versus not reached, with 74% of patients still on drug, if they're only pretreated with a BTK inhibitor. If we look at ibrutinib plus venetoclax, we saw the frontline three-year PFS is 80% to 88% in the treatment-naïve group, but if we look at patients receiving the combination after both sequential ibrutinib or venetoclax, the median for this combination was only 14 months.

Data for retreatment after combinations are extraordinarily immature, but both the rationale and the early data suggest that we may be able to do better than these outcomes thus far.

Sequencing Small Molecules Is the Way to Go

By Dr. Mato

Anthony Mato, MD, MSCE

I don't think anyone woke up one day and said, "Let's do a triplet." Those were developed. For example, the fludarabine, cyclophosphamide, and rituximab regimen was done in the setting of understanding the activity of monotherapy as compared with doublets and triplets. Then maybe quadruplets were tested, and they said, "Nah, a little bit too toxic. Let's go back to triplets." Oncologists who are advocating for combinations in the modern era have completely forgotten the lessons of the past. I'll ask the question, "Is the whole greater than the sum of the parts?" as my argument for why we should stick with monotherapy until somebody does the appropriate study to convince me we should be doing a combination.

I would argue combining agents in the modern era has not been well studied in CLL despite the many studies Dr. Brown offered. There are a few prospective studies comparing novel agents with relevant controls. Contribution of effect is rarely assessed, and I think we should demand that. Follow-up is lacking when subjects are censored on clinical trials. There is absolutely very little data on retreatment. When you talk about sequencing of novel agents, they're mostly from retrospective trials, and in the setting of combinations, which aren't even approved in the United States, we have no real-world data on this particular topic. I would say we have to demand certain things to move forward in the era of combinations.

Certainly, we need data for time-limited approaches, and that exists. But what else is needed? We need decisions based on MRD status and depth of remission. We need combinations that don't include venetoclax as the backbone. Certainly, we're going to run out of combinations very quickly if it's venetoclax, venetoclax, venetoclax, plus something else. We need sequencing data upon progression. Dr. Brown already admitted that was a major weakness from the data noted. We really need to understand the mechanisms of resistance for novel-novel combinations, not, "This is a BTK inhibitor, this is venetoclax, and so combined, we have no idea." We need studies to assess the contribution of effect. It's not okay to say, "I want to prescribe ibrutinib plus venetoclax or ibrutinib plus venetoclax plus obinutuzumab," without really understanding if a doublet is better than a triplet or if a doublet is better than a monotherapy.

We need clinically relevant monotherapy controls, and then we need to understand comparisons of combinations to decide what's most appropriate. I would argue, in terms of standard of care or for controls for clinical trials, that the gold standards have to be monotherapy with a BTK inhibitor or venetoclax with obinutuzumab. I'll consider that a monotherapy as well since no one ever assessed for contribution of effect for obinutuzumab. The major phase III trials that support the use of continuous BTK inhibitors in the frontline setting—SEQUOIA, ELEVATE-TN, ECOG 1912, FLAIR, ALLIANCE, ILLUMINATE, and RESONATE-3—are the controls to beat, if we want to make the argument that we should use a combination. I won't go through these trials in detail, but for ibrutinib, there are five positive clinical trials, some of which have an OS benefit. In the impressive ELEVATE-TN trial of acalabrutinib, not only do we have a positive result, but we also assessed for contribution of effect.

Then, zanubrutinib is compared with bendamustine plus rituximab. I'll start by highlighting the longest-term follow-up data we have for a BTK inhibitor in the frontline setting, which is from ibrutinib in the RESONATE-2 trial. The comparison is against chlorambucil. The eight-year, and even now nine-year, follow-up data are

quite impressive for ibrutinib monotherapy. More than 60% of patients are still progression-free when we have the longest-term follow-up for this molecule. The sustained PFS benefit with ibrutinib versus chlorambucil was also similar in mutated versus unmutated IGHV patients.

Why aren't novel agents the controls in future novel agent combination studies? We continue to rely on controls that provide very limited knowledge. While we have a PFS benefit for BTK inhibitors and venetoclax, we won't be able to highlight a combination trial that demonstrates a benefit against any clinically relevant monotherapy or combination with venetoclax control.

One could say, "Maybe ibrutinib is too toxic." I'm not saying that, but I am saying that there are certain adverse events that are associated with continuous therapies. Atrial fibrillation rates range between 6% and 17%, and hypertension rates range between 14% and 34%. Even if you want to say that ibrutinib monotherapy may not be the go-forward or the standard of care now—which I still argue—there's a point to be made for using that molecule.

We can think about next-generation drugs. The acalabrutinib long-term follow-up data in the frontline setting show in 99 patients quite excellent PFS. At 48 months, it's 95.7% for patients overall; it's 82% for patients with a *TP53* aberration and 91% for patients with a complex karyotype. In the ELEVATE-TN trial, we finally get an assessment of contribution of effect. We have a comparison of acalabrutinib plus obinutuzumab versus acalabrutinib, and we have a significant advantage in PFS for acalabrutinib plus obinutuzumab versus acalabrutinib monotherapy. There is maybe an OS advantage, and I would argue that is a combination that has been tested appropriately.

The combinations noted by Dr. Brown have not had an appropriate assessment for contribution of effect. We have maybe a snippet of data suggesting lower adverse event rates associated with the next-generation BTK inhibitor acalabrutinib. I think the case is made for BTK inhibitors as a monotherapy. That is an excellent choice for treatment-naïve CLL. The next-generation BTK inhibitors seem potentially equally active and better tolerated. We now have evolving data for acalabrutinib plus obinutuzumab as a standard of care. That is a combination that has been appropriately developed. Dr. Brown also mentioned poor-risk disease, and we always like to say, "With (del)17p, we need to have combinations in order to overcome the poor-risk features associated with CLL." But how do the BTK inhibitors perform in that situation?

I'll highlight the longest-term follow-up data we have for ibrutinib in (del)17p disease, which are excellent data. The PFS and OS estimates at four years were 79% and 88%. Dr. Matt Davids did a summary of the acalabrutinib experience, and there was a quite high overall response rate, with a 48-month PFS of 89%. In the largest prospective study of a BTK inhibitor in the frontline setting in (del)17p for zanubrutinib, at 24 months, the PFS is excellent at 88.9%. I don't think the ibrutinib plus venetoclax data or any of the triplet data look any worse or any better than this. The data Dr. Brown noted suggested that maybe there's still room to go, and yes, I agree with that. But have the combinations demonstrated a benefit?

The gold standards for future comparison and standard of care should be BTK inhibitor-based therapy and venetoclax plus obinutuzumab. In the CLL14 study, the five-year PFS for venetoclax plus obinutuzumab is 62.6%, and even for (del)17p, it's 49%. So, if the gold standards for future comparison—and standard of care—are BTK inhibitors and venetoclax plus obinutuzumab, are there adequate data to support current doublet combinations in clinical practice today? I argue no.

There's an argument people make that you need a combination to overcome the poor-risk features of CLL. I don't think that is held up, even with this snippet of data we have from CAPTIVATE, which shows patients with (del)17p are falling off the curve compared with all the other patients. In the data for GLOW, if we're making the argument that ibrutinib plus venetoclax is a standard of care moving forward, then we need to compare it with either ibrutinib or venetoclax or venetoclax plus obinutuzumab. Certainly, ibrutinib has already beat the combination of obinutuzumab plus chlorambucil, as has venetoclax-based therapy. So why wouldn't the combination of ibrutinib plus venetoclax beat a control that is essentially a straw man?

There is certainly a price to be paid for putting targeted therapies together in terms of what the adverse event profile looks like. Data from the Ohio State University that look at the combination of ibrutinib, venetoclax, and obinutuzumab are quite impressive in terms of PFS and OS, but I can't tell you ibrutinib, venetoclax, and obinutuzumab is better than ibrutinib plus venetoclax, and I can't tell you ibrutinib plus venetoclax is better than ibrutinib. However, we've already decided in the Eastern Cooperative Oncology Group and ALLIANCE studies that the triplet is already the experimental arm to move forward in the future, even though I haven't even made the case for the doublet yet.

Finally, I'll highlight important lessons of CLL13. First, there's an important assessment of contribution of effect rituximab versus obinutuzumab. There's an important assessment of doublet versus triplet, and there are relevant comparisons and endpoints. I'll argue that the MRD data are very similar between venetoclax plus obinutuzumab and the triplet, which is venetoclax plus obinutuzumab and ibrutinib. There are no data for ibrutinib plus venetoclax because it wasn't included. I'll also argue that when you think about the PFS for this trial, they're very similar between venetoclax plus obinutuzumab and the triplet. We haven't made a strong case from the perspective of MRD with the limited follow-up. We haven't made a case from the perspective of PFS, but I can make the case that toxicities are higher with a triplet compared with a doublet.

The rates of febrile neutropenia are 7.8% for venetoclax, ibrutinib, obinutuzumab versus 3.1% for venetoclax and obinutuzumab. So, what do we need to move forward? We have the data for time-limited approaches. We need data on MRD-driven decision-making. We need combinations that don't include venetoclax. We need sequencing data upon progression. We need to understand mechanisms of resistance and contribution of effect. We need to have clinically relevant monotherapy controls to make the case and comparison of combinations.

What about relapsed/refractory disease? I made the case for what I would do in the frontline if I start with ibrutinib monotherapy or acalabrutinib, but what do I do next? I think there is adequate therapy to manage patients in the relapsed/refractory setting if they've started with one targeted therapy. An example of data from Dr. Kerry Rogers shows PFS looks quite good when sequencing from ibrutinib to acalabrutinib. This is in the setting of intolerance, of course. There were very limited adverse events.

You can think of a sequence where you can go from BTK inhibitor to BTK inhibitor in the setting of intolerance. In the data for venetoclax 24-month median PFS—Dr. Brown already pointed this out—I think it's unfair to make a comparison between this study and the MURANO trial. Certainly, MURANO was a BTK inhibitor-naïve population; however, patients are much less heavily pretreated in MURANO. I would argue it's probably somewhere in between where the median PFS for venetoclax plus rituximab lands in a patient population that previously received a BTK inhibitor.

Even the National Comprehensive Cancer Network guidelines include venetoclax retreatment, so it must be okay. You can think about going from venetoclax—if you're BTK inhibitor-naïve—to a BTK inhibitor. You can go to ibrutinib. The median PFS is 32 months, and the response rate is 84%. These aren't just data we generated; these data were also generated in Australia and are nearly identical with a median PFS of 34 months. You could say, "You accumulate this resistance along the way if you start with a BTK inhibitor and then you go to venetoclax or vice versa in these double-exposed or double-refractory patients." However, there are drugs like the non-covalent BTK inhibitors, like pirtobrutinib, that have been developed. Even in the double-exposed patient population, there is a median PFS after five prior lines of therapy of 18 months.

The conundrum that remains is, should we use all our best agents together or save some of the ammunition for the future? This is just my own math, probably not completely accurate, but I think it makes the point: If you start with ibrutinib monotherapy as first-line therapy, I would guess the medium PFS conservatively is going to be about 100 months; it hasn't been reached yet to my knowledge. In the second-line setting, you could think about venetoclax monotherapy PFS being about 24 months, or even longer with venetoclax plus rituximab. I'm going to discount the MURANO data and say it's not 53 months, it's 40 months. In third-line treatment, you might get 18 to 20 months with pirtobrutinib. Ibrutinib plus venetoclax has to have a median PFS of 130 or 140 months in order to just meet the data that we would estimate from sequencing monotherapies across three lines of therapy.

There's almost no data on retreatment or mechanisms of resistance. Without long-term data, we should not dangle the word cure for patients with any novel agent combination. Certainly, if a cure is not there, if a contribution of effect is not there, and if sequencing data is not there, then just saying there is a high rate of undetectable MRD alone is not enough for me.

I'll end with this quote, "More is not always better. Sometimes it's just more."

Survival Outcomes Poor After CAR-T Failure in Aggressive BCL

Take-aways:

- Nearly half of patients with relapsed/refractory aggressive B-cell lymphoma who received an anti-CD19 CAR-T therapy relapsed.
- Survival outcomes were poor in patients who had progressive/relapsed disease after receiving CAR-T.
- Relapse within the first 30 days, which occurred in 22% of patients who relapsed, was associated with the worst survival outcomes.

Survival outcomes are typically poor in patients with relapsed/refractory aggressive B-cell lymphoma (BCL) who relapse after treatment with anti-CD19 chimeric antigen receptor (CAR) T cells, according to a multicenter analysis.

While anti-CD19 CAR T cells "represent a major advance in the treatment" of patients with relapsed/refractory aggressive BCL, "a significant number of patients experience failure," which "remains a major issue, representing an unmet medical need," according to the study's first author, **Roberta Di Blasi, MD, PhD,** of the Hôpital Saint Louis in Paris, France.

For example, multiple clinical trials assessing CAR-T treatments—including the JUILET, ZUMA-1, and TRANSCEND trials—show at least half of patients relapse six months after receiving the therapy. Furthermore, a multicenter French study based on data from the DESCAR-T registry—which collects real-world data on patients who receive commercial CAR-T treatments for up to 15 years after the infusion—indicated more than half of patients experienced treatment failure six months after receiving CAR-T.

Dr. Di Blasi and colleagues conducted the multicenter analysis using the DESCAR-T registry to assess outcomes of patients who progress or relapse after CAR-T, identify prognostic markers, and evaluate potential treatment options for patients who have CAR-T treatment failure.

Study Design and Methods

Researchers studied patients from the DESCAR-T registry, which included those who were eligible to receive CAR-T for a hematologic malignancy covered by the French health care system.

They identified 680 patients with relapsed/refractory aggressive BCL who were registered in DESCAR-T as of August 2018. Most patients (80.1%) received an infusion of a commercially available CAR T-cell product by the time of the analysis in April 2021. The patients received axicabtagene ciloleucel (n=350) or tisagenlecleucel (n=200) and were evaluated at post-infusion days 30, 90, 180, 270, and 360. Patients also received evaluations 18, 24, and 36 months after treatment.

The study's primary endpoint was overall survival (OS), with secondary endpoints including progression-free survival (PFS), baseline patient characteristics, treatment proposed at failure, response to salvage treatment, and prognostic factors associated with PFS and OS.

The researchers analyzed outcomes according to the time of patient relapse. They defined very-early relapse as occurring between the date of CAR-T infusion and day 30, early relapse as occurring between days 31 and 90, and late relapse as occurring after day 90.

Results

More than half of patients (56%) were considered non-progressive after a median follow-up of 7.9 months. Complete remission occurred in 58% of patients who were non-progressive at that time point, while 11% had partial remission, and 1% had stable disease.

The remaining patients had progressive/relapsed disease after treatment and comprised the population analyzed in the study. The 238 patients with progressive/relapsed disease included 136 who progressed/relapsed at a median follow-up of nine months after receiving axicabtagene ciloleucel and 102 who progressed/relapsed at a median of 7.8 months after receiving tisagenlecleucel.

Nearly 75% of patients who progressed/relapsed presented with diffuse large BCL prior to lymphodepletion, while 66% had progressive disease at the time of infusion. More than half of patients (57.1%) who progressed/relapsed received more than three lines of therapy before CAR-T, while 38.9% of patients had elevated lactate dehydrogenase (LDH) levels.

The median time to treatment failure after infusion was 2.7 months, while the median PFS was 2.8 months (95% CI, 2.4-3.1) from the time of relapse/progression after CAR T-cell infusion. The median OS from the time of relapse/progression after infusion was "consistently poor" at 5.2 months (95% CI, 4.1-6.6), according to Dr. Di Blasi and colleagues.

Nearly half of patients (42.9%) with progressive/relapsed disease had an early relapse, 22.7% had a very-early relapse, and 34.5% had a late relapse (see **TABLE 1**). Patients with earlier relapses had reduced PFS and OS compared with patients with later relapses (see **TABLE 2**).

While 47.9% of patients were alive at six months, only 18.9% of patients who had very-early relapse/progression were alive at that time point.

Several factors were associated with reduced survival. High LDH at infusion (hazard ratio [HR], 3.42; 95% CI, 1.93-6.05; $P<.001$) and abnormal levels of ferritin at time of infusion (HR, 1.02; 95% CI, 1.00-1.03; $P=.01$) were both significantly associated with worsened PFS outcomes in a multivariate analysis. Elevated LDH (HR, 2.1; 95% CI, 1.16-3.78; $P=.01$), elevated C-reactive protein (HR, 1.11; 95% CI, 1.04-1.19; $P=.003$), and very-early disease progression (HR, 2.93; 95% CI, 1.56-5.5; $P=.0009$) were all significantly associated with worsened OS outcomes in a multivariate analysis.

Most patients (64.7%) with progressive/relapsed disease following CAR-T received an additional line of treatment. The most common salvage treatment was lenalidomide (38.3% of patients; see **TABLE 3**). There was no significant difference in median OS among patients receiving different salvage treatments, nor any significant difference in median PFS.

Limitations and Conclusions

The study's limitations included a short follow-up period and the potential for missing registry data on patients at the time of relapse.

However, the study's relatively large sample size allowed researchers to draw conclusions about patterns of treatment outcomes in this population of patients who received commercially available CAR-T treatments in France.

TABLE 1. Time of Relapse in Patients with Aggressive B-Cell Lymphoma After Failure of Anti-CD19 CAR T-Cell Therapy

Time of relapse	Percentage of patients
Very-early relapse	22.7%
Early relapse	42.9%
Late relapse	34.5%

TABLE 2. Survival Outcomes After CAR-T Failure in Patients with Aggressive B-Cell Lymphoma

Survival outcomes	Very-early relapse	Early relapse	Late relapse
Median PFS	1.7 months	2.6 months	4.2 months
Median OS	1.9 months	6.1 months	9.6 months

TABLE 3. Salvage Therapies After CAR-T Failure in Patients with Aggressive B-Cell Lymphoma

Salvage therapy type	Percentage of patients receiving it
Lenalidomide	38.3%
Targeted treatments	21.4%
Immunochemotherapy regimens	20.1%
Radiotherapy	11.0%
Bispecific antibodies	7.1%

"In conclusion, this DESCAR-T registry study confirms that the outcome of patients at the time of failure after CAR T-cell treatment remains extremely poor, and that this outcome is worse in the event of failure within the first month," Dr. Di Blasi and colleagues wrote. "Alternative therapeutic strategies (immunotherapy by bispecific antibodies, lenalidomide) may improve PFS rates in these patients. Patients with [relapsed/refractory] aggressive BCL failing after anti-CD19 CAR T-cell treatment constitute an unmet medical need, and further innovative strategies are needed to improve the outcome of such patients."

Reference

Di Blasi R, Le Gouill S, Bachy E, et al. Outcomes of patients with aggressive B-cell lymphoma after failure of anti-CD19 CAR T-cell therapy: a DESCAR-T analysis. *Blood*. 2022. doi:10.1182/blood.2022016945

Lenalidomide Plus Rituximab Is a 'Chemo-Free Alternative' in Follicular Lymphoma

Take-aways:

- Lenalidomide plus rituximab led to a similar ORR, PFS, and CR rate compared with rituximab plus chemotherapy in patients with previously untreated advanced-stage follicular lymphoma.
- Patients in the two treatment groups had similar rates of progression and relapse.
- The doublet treatment and rituximab plus chemotherapy showed comparable safety and efficacy after six years of follow-up.

Lenalidomide plus rituximab is "an acceptable chemotherapy-free alternative" to rituximab plus chemotherapy in patients with previously untreated advanced-stage follicular lymphoma (FL), according to long-term results from the phase III RELEVANCE trial.

While immunochemotherapy has "remained the frontline gold standard for patients with FL needing systemic therapy," **Franck Morschhauser, MD, PhD,** of University of Lille's Centre Hospitalier Universitaire de Lille in France, and colleagues conducted the RELEVANCE trial because FL can be "immune-responsive to non-chemotherapy regimens."

For example, combining the immunomodulator lenalidomide with rituximab, an anti-CD20 monoclonal antibody, showed "promising activity with high response rates" in patients with previously untreated FL in previous phase II trials, according to Dr. Morschhauser and colleagues.

Earlier results from the RELEVANCE trial showed lenalidomide plus rituximab "provided similar efficacy" to rituximab plus chemotherapy, but the researchers conducted the six-year follow-up analysis because long-term data on the toxicity and efficacy of the doublet treatment are "highly needed," they wrote.

Study Design and Methods

The RELEVANCE investigators randomly assigned patients 1:1 to receive lenalidomide plus rituximab (n=513) or rituximab plus chemotherapy followed by rituximab maintenance (n=517). For patients receiving rituximab plus chemotherapy, the investigators chose among chemotherapy regimens of cyclophosphamide, doxorubicin, vincristine, and prednisone (n=28); bendamustine (n=117); or cyclophosphamide, vincristine, and prednisone (n=372).

Nearly all patients receiving lenalidomide plus rituximab (99%) received at least one dose of the study drug, with 69% completing the full 120 weeks of treatment. The same was true for patients receiving rituximab plus chemotherapy, as 97% received at least one dose of the study drug, and 71% completed the full course of treatment.

Most patients receiving rituximab plus lenalidomide (81.7%) and most patients receiving rituximab plus chemotherapy (77.4%) entered clinical follow-up.

The study's co-primary endpoints were the confirmed/unconfirmed complete response (CR) rate at 120 weeks and PFS as assessed by an Independent Review Committee per 1999 International Working Group criteria. The researchers also conducted post hoc exploratory analyses on survival from a risk-defining event according to progression of disease within two years of first-line therapy.

Results

The overall response rate (ORR) was similar between treatment groups: 61% in patients receiving the doublet and 65% in those receiving rituximab plus chemotherapy. Confirmed/unconfirmed CR rates were also similar between groups: 48% in patients receiving the doublet and 53% in those receiving rituximab plus chemotherapy (P=.10). See **TABLE 4** for a summary of responses.

PFS was also similar between groups (hazard ratio, 1.03; 95% CI, 0.84-1.27; P=.78), with a six-year PFS rate of 60% (95% CI, 55-64) in patients receiving the doublet and 59% (95% CI, 54-64) in patients receiving rituximab plus chemotherapy. The median PFS was not reached in either group after a median follow-up of 72 months and 354 PFS events.

"Subgroup analyses of PFS were consistent with the first interim analysis," Dr. Morschhauser and colleagues wrote. "The efficacy of [lenalidomide plus rituximab] continued to be independent of conventional prognostic factors, including disease stage, Follicular Lymphoma International Prognostic Index score, bulky disease, and age."

The researchers estimated the six-year OS rate was 89% in both treatment groups. The median OS was not reached in either group.

"Similarly, event-free survival and time to next anti-lymphoma treatment did not differ significantly between the groups," Dr. Morchhauser and colleagues wrote. "Exploratory analysis on the three different [rituximab plus] chemotherapy groups showed no statistical difference in PFS, by [Independent Review Committee] and investigator, nor OS."

The rate of relapse or progression within the first two years of first-line therapy was 13% in patients receiving the doublet and 11% in those receiving rituximab plus chemotherapy.

TABLE 4. Treatment Responses to Lenalidomide Plus Rituximab Versus Rituximab Plus Chemotherapy in Patients with Previously Untreated Advanced-Stage Follicular Lymphoma

Treatment responses	Lenalidomide plus rituximab	Rituximab plus chemotherapy
ORR	61%	65%
Six-year PFS rate	60%	59%
Confirmed/unconfirmed complete response rate	48%	53%
Two-year relapse/progression rate	13%	11%

In the Literature

Progression of disease within two years of first-line therapy was associated with a significantly lower five-year survival rate of 59.5% (95% CI, 49.9-67.8) compared with the reference group's five-year survival rate of 95.2% (95% CI, 93.3-96.6; $P<.0001$). However, the five-year survival rate was similar between treatment groups among patients who had disease progression, with a rate of 59% in patients receiving the doublet and 60% in those receiving rituximab plus chemotherapy.

Around a fifth of patients in each group received additional treatment after relapse. Among patients who relapsed and received additional treatment, the ORR was 61% in those who initially received the doublet treatment and 59% in those who initially received rituximab plus chemotherapy.

The confirmed/unconfirmed CR rates in patients who received additional treatment after relapse were similar between groups. The rate was 37% in patients receiving the doublet and was 45% in those receiving rituximab plus chemotherapy. There was no significant difference in survival after progression between the treatment groups.

A small fraction of patients in each treatment group had histologic transformation over a 72-month follow-up period, with a 4.4% six-year cumulative incidence of transformation in patients receiving the doublet and 3.3% in those receiving rituximab plus chemotherapy.

Secondary primary malignancies were reported in 7% of patients receiving the doublet and 10% of patients receiving rituximab plus chemotherapy in the initial analysis, increasing to 11% and 13%, respectively, in the most recent analysis.

There were slight increases in patients reporting at least one grade 5 treatment-emergent adverse event between the initial analysis and the most recent analysis, growing from six to nine patients in the group receiving the doublet and remaining stable at six patients in the group receiving rituximab plus chemotherapy.

Around one-third of patients in both the doublet and rituximab plus chemotherapy groups prematurely discontinued treatment, with progressive disease (12.5% vs 13.7%) and toxicity (8.5% vs 3.1%) being the most common reasons. Approximately one-fifth of patients in each treatment group prematurely discontinued study participation, with the most common reasons being death (54% vs 49%) and withdrawal of consent (27% vs 40%).

Deaths nearly doubled between the initial analysis and the most recent analysis, increasing from 66 to 114 deaths. Deaths occurred in 12% of patients who received the doublet and in 11% of those receiving rituximab plus chemotherapy, with eight total deaths occurring on treatment. Lymphoma caused 29 deaths in the group receiving the doublet and 17 deaths in the group receiving rituximab plus chemotherapy. Death from other causes was more common in patients receiving rituximab plus chemotherapy, occurring in 13 patients compared with six patients in the doublet group. Death from cardiac disorders occurred in four patients receiving the rituximab plus chemotherapy treatment and in no patients receiving the doublet.

"The overall safety profile in both groups was consistent with the first interim analysis, and no new safety signals were detected," the researchers wrote.

Conclusions and Future Directions

Patients in both treatment groups "maintained very favorable outcomes" and had "excellent" six-year OS rates of 89%, according to the researchers.

Overall, the long-term results from the study showed lenalidomide plus rituximab "provides an acceptable, long-term, chemotherapy-free alternative to [rituximab plus] chemotherapy on the basis of immunomodulation in patients with advanced untreated FL in need of treatment," Dr. Morschhauser and colleagues concluded.

The research was supported by Celgene, a Bristol Myers Squibb Company, and the Lymphoma Academic Research Organization.

Reference

Morschhauser F, Nastoupil L, Feugier P, et al. Six-year results from RELEVANCE: lenalidomide plus rituximab (R2) versus rituximab-chemotherapy followed by rituximab maintenance in untreated advanced follicular lymphoma. *J Clin Oncol*. 2022;40(28):3239-3245.

Regulatory Actions

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

FDA Approves Brentuximab Vedotin for High-Risk Pediatric Lymphoma

The U.S. Food and Drug Administration (FDA) has approved brentuximab vedotin for the treatment of pediatric patients aged two years and older with previously untreated high-risk classical Hodgkin lymphoma, in combination with standard-of-care, dose-intensive chemotherapy AVE-PC (doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide).

The approval is based on data from a phase III study conducted by the Children's Oncology Group and funded by the National Cancer Institute that showed patients receiving brentuximab vedotin in combination with standard-of-care, dose-intensive chemotherapy AVE-PC had superior event-free survival compared with patients who received standard-of-care chemotherapy with ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide). Patients had a 59% reduction in the risk of disease progression or relapse, second cancer, or death (hazard ratio, 0.41; 95% CI, 0.25-0.67; P=.0002).

This FDA approval marks a new indication for the drug, which is already approved for adult patients with certain lymphomas.

Source: Business Wire, November 2022

Subcutaneous Epcoritamab for LBCL Granted Priority Review

The FDA has approved a priority review for the Biologics License Application (BLA) for subcutaneous epcoritamab, an investigational bispecific antibody, for the treatment of patients with relapsed or refractory large B-cell lymphoma (LBCL) after two or more lines of systemic therapy.

The BLA submission is based on safety and preliminary efficacy data from the LBCL cohort of the open-label, multicenter, phase II EPCORE NHL-1 clinical trial evaluating epcoritamab in patients with relapsed, progressive, or refractory CD20-positive mature B-cell non-Hodgkin lymphoma (NHL).

The FDA has set a target action date of May 21, 2023, according to the manufacturer of the drug.

Source: Business Wire, November 2022

Elranatamab Receives Breakthrough Therapy Designation

The investigational cancer immunotherapy drug elranatamab was granted Breakthrough Therapy Designation by the FDA for relapsed or refractory multiple myeloma (MM).

Elranatamab is a B-cell maturation antigen CD3-targeted bispecific antibody. The decision is based on updated data from the phase II MagnetisMM-3 study that showed an overall response rate of 61% and a manageable safety profile after a median follow-up of 6.8 months.

Elranatamab has also been granted Orphan Drug Designation by the FDA and the European Medicines Agency (EMA) for the treatment of MM. The FDA and EMA have granted elranatamab Fast Track Designation and the PRIME scheme, respectively, for the treatment of patients with relapsed or refractory MM. The Medicines and Healthcare products Regulatory Agency (MHRA) in the U.K. has also granted elranatamab the Innovative Medicine Designation and the Innovation Passport for the treatment of MM.

Source: Business Wire, November 2022

U.K. Regulator Grants 'Innovation Passport' to ALETA-001 for NHL, ALL

The MHRA in the U.K. has granted an Innovation Passport under the Innovative Licensing and Access Pathway for ALETA-001 for the treatment of patients with NHL and acute lymphoblastic leukemia (ALL) who have failed to respond to or relapsed after CD19 chimeric antigen receptor (CAR) T-cell therapy.

CAR T-cell therapy engager ALETA-001 is an off-the-shelf preclinical biologic program developed to treat and prevent cell therapy relapse of existing CD19-targeted CAR T-cell therapies.

ALETA-001 is expected to enter clinical development this year, with Cancer Research U.K.'s Centre for Drug Development sponsoring and conducting a phase I/IIa clinical trial.

Source: Business Wire, November 2022

BTK Inhibitor Approved in Singapore for Relapsed/Refractory MCL

The Bruton's tyrosine kinase (BTK) inhibitor orelabrutinib has been approved by the Health Sciences Authority of Singapore for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).

In June 2021, orelabrutinib was granted Breakthrough Therapy Designation for the treatment of relapsed or refractory MCL by the FDA. In December 2020, orelabrutinib received approval from the China National Medical Products Administration in two indications: relapsed or refractory chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma and relapsed or refractory MCL. At the end of 2021, orelabrutinib was included in the National Reimbursement Drug List in China.

Source: Business Wire, November 2022

Zanubrutinib Gains European Commission Approval for CLL

The European Commission (EC) has approved the BTK inhibitor zanubrutinib for the treatment of adult patients with treatment-naïve or relapsed/refractory CLL.

The EC approval is based on positive results from two phase III clinical trials: the SEQUOIA trial, which compared zanubrutinib with bendamustine plus rituximab in treatment-naïve CLL, and the ALPINE study, which compared zanubrutinib with ibrutinib in patients with relapsed or refractory CLL.

In these trials, zanubrutinib demonstrated superior efficacy versus either bendamustine plus rituximab or ibrutinib in first-line or relapsed/refractory CLL, respectively.

Zanubrutinib is currently approved in the European Union for the treatment of adult patients with Waldenström's macroglobulinemia who have received at least one prior therapy or as the first-line treatment for patients unsuitable for chemoimmunotherapy. In September 2022, the Committee for Medicinal Products for Human Use of the EMA issued a positive opinion recommending approval of zanubrutinib for the treatment of adult patients with marginal zone lymphoma who have received at least one prior anti-CD20-based therapy.

Source: Business Wire, November 2022

Highlights from the **2022 ASH ANNUAL MEETING AND EXPOSITION**

Phase III ALPINE Data Suggest Zanubrutinib Is Superior to Ibrutinib in CLL/SLL

Zanubrutinib may be "more efficacious and better tolerated" than ibrutinib as a treatment for patients with relapsed/refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), according to a final analysis of the phase III ALPINE study.

Jennifer Brown, MD, PhD, of the Dana-Farber Cancer Institute, and colleagues conducted the study and presented its results at the 2022 American Society of Hematology (ASH) Annual Meeting and Exposition.

The study included 652 patients with relapsed/refractory CLL or SLL who received at least one prior line of therapy and had measurable disease. The researchers randomized patients 1:1 to receive zanubrutinib (n=327) or ibrutinib (n=325) until disease progression or unacceptable toxicity occurred. Both treatment arms included similar proportions of patients aged 65 years and older, male patients, those with unmutated immunoglobulin heavy chain gene (IGHV), patients with del(17p), and those who had a *TP53* mutation without del(17p). Patients in both treatment arms had a median of one prior line of therapy.

Patients who received zanubrutinib had superior progression-free survival (PFS) compared with those who received ibrutinib in the intention-to-treat population at a median follow-up of 29.6 months (hazard ratio [HR], 0.65; 95% CI, 0.49-0.86; two-sided P=.0024), when assessed by an independent review committee. The median PFS was 35 months in patients who received ibrutinib, while it was not reached in patients who received zanubrutinib.

Patients treated with zanubrutinib had a higher overall response rate (ORR) as assessed by an independent review committee, with an ORR of 86.2% compared with 75.7% in the group that received ibrutinib (nominal two-sided P=.0007).

In patients with del(17p)/*TP53* mutation, those who received zanubrutinib had a longer PFS than those who received ibrutinib, per assessment by an independent review committee.

"PFS, regardless of [independent review committee] or [investigator] assessment, consistently favored zanubrutinib across other major predefined subgroups, including IGHV status," Dr. Brown and colleagues wrote.

More patients who received ibrutinib (41.2%) discontinued treatment than those who received zanubrutinib (26.3%). Adverse events led to treatment discontinuation in 16.2% of patients receiving zanubrutinib and 22.8% receiving ibrutinib, while progressive disease led to treatment discontinuation in 7.3% and 12.9%, respectively.

Cardiac disorders led to treatment discontinuation in 4.3% of patients receiving ibrutinib and 0.3% of those receiving zanubrutinib. Patients who received ibrutinib had a higher rate of atrial fibrillation/flutter (13.3%) than those receiving ibrutinib (5.2%). No patients who received zanubrutinib had grade 5 adverse events due to cardiac disorders, while 1.9% of those who received ibrutinib did.

Patients treated with ibrutinib had higher rates of grade ≥3 adverse events, serious adverse events, dose interruptions, and dose reductions than patients who received zanubrutinib.

Deaths occurred in 14.7% of patients who received zanubrutinib and 18.5% who received ibrutinib (overall survival [OS] HR, 0.76; 95% CI, 0.51-1.11).

"As ALPINE is the first study to demonstrate PFS superiority in a head-to-head comparison of [Bruton's tyrosine kinase] inhibitors, zanubrutinib has now proven superiority to ibrutinib in both ORR and PFS in [patients] with [relapsed/refractory] CLL/SLL. Efficacy benefits with zanubrutinib were observed across all major subgroups, including high-risk [patients]," Dr. Brown and colleagues concluded. "Zanubrutinib had a favorable safety profile compared with ibrutinib, with a lower rate of treatment discontinuation and fewer cardiac disorder events, including fewer cardiac events leading to death."

Reference

Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib demonstrates superior progression-free survival (PFS) compared with ibrutinib for treatment of relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma (R/R CLL/SLL): results from final analysis of ALPINE randomized phase 3 study. Abstract #LBA-6. Presented at the 64th ASH Annual Meeting and Exposition; December 10-13, 2022; New Orleans, Louisiana.

Iberdomide Plus Dexamethasone Has 'Encouraging' Efficacy in Relapsed/Refractory Myeloma

Iberdomide plus dexamethasone had "encouraging efficacy and safety" in patients with triple-class-exposed relapsed/refractory multiple myeloma (MM) who previously received anti-B-cell maturation agent (BCMA) therapy, according to a recent study.

Sagar Lonial, MD, of the Winship Cancer Institute at Emory University, and colleagues conducted the dose-expansion phase of the study evaluating iberdomide plus dexamethasone in 28 patients with heavily pretreated relapsed/refractory MM. They presented the study at the 2022 ASH Annual Meeting and Exposition.

All patients received prior anti-BCMA therapy, as well as at least one immunomodulatory agent, proteasome inhibitor, and anti-CD38 monoclonal antibody. The patients received a median of seven prior regimens. All patients had documented progressive disease on or within 60 days of their last line of therapy. The median patient age was 65 years, with a median time of 7.8 years since initial diagnosis.

The patients received oral iberdomide 1.6 mg on days one through 21 of each 28-day cycle, with weekly dexamethasone 40 mg or 20 mg for patients 75 years of age or older. The study's primary objectives were to determine preliminary efficacy and safety. The median follow-up was 8.1 months, with a median number of 3.5 cycles received and 21.1% of patients continuing treatment. In the 68.4% of patients who discontinued treatment, progressive disease was the primary reason

for discontinuation.

The ORR was 36.8%, with 5.3% of patients having complete responses (CRs), 13.2% having very good partial responses, and 18.4% having partial responses. The median response duration was 7.5 months, while the median PFS was 2.4 months. The clinical benefit rate was 39.5%.

Immunophenotyping "showed comparable immunodeficiency" between patients who previously received anti-BCMA agents, as well as those who were triple-class-exposed and those without prior anti-BCMA exposure; however, this "was more pronounced following [T-cell engager]-based therapies," according to the study's authors.

"Importantly, [iberdomide plus dexamethasone] remained immune-stimulatory in this population, increasing T-[cell] and [natural killer]-cell proliferation and T-cell activation," Dr. Lonial and colleagues wrote.

Grade 3 or 4 treatment-emergent adverse events occurred in 78.9% of patients. The most frequent event was neutropenia, occurring in 50% of patients. Anemia occurred in 28.9% of patients, leukopenia in 23.7%, and thrombocytopenia in 21.1%.

Nearly a quarter (23.7%) of patients developed grade 3 or 4 infections. None of the patients discontinued iberdomide due to treatment-emergent adverse events. The study's authors reported that two patients died, but the deaths were due to sepsis and disease progression and "were not considered related to study treatment."

"[Iberdomide plus dexamethasone] showed encouraging efficacy and safety in [patients] with triple-class-exposed [relapsed/refractory MM] and prior anti-BCMA therapy," Dr. Lonial and colleagues concluded, noting that the study's "findings support further development of [iberdomide] in [relapsed/refractory MM], including in anti-BCMA-exposed [patients]."

Reference

Lonial S, Abdallah AO, Anwer F et al. Iberdomide (IBER) in combination with dexamethasone (DEX) in relapsed/refractory multiple myeloma (RRMM): results from the anti-B-cell maturation antigen (BCMA)-exposed cohort of the CC-220-MM-001 trial. Abstract #1918. Presented at the 64th ASH Annual Meeting and Exposition; December 10-13, 2022; New Orleans, Louisiana.

TRIANGLE Trial Results Support First-Line Ibrutinib Use in MCL

High-dose cytarabine-containing immunochemotherapy followed by autologous hematopoietic stem cell transplantation (AHSCT) "failed to show superiority" over an ibrutinib-containing treatment without AHSCT in patients with mantle cell lymphoma (MCL), according to results from the phase III TRIANGLE trial.

Martin Dreyling, MD, of the LMU University Hospital Munich in Germany, and colleagues conducted the study and presented its results at the 2022 ASH Annual Meeting and Exposition.

The European MCL Network initiated the randomized, open-label, three-arm TRIANGLE trial to assess the addition of ibrutinib to high-dose cytarabine-containing immunochemotherapy followed by AHSCT and rituximab maintenance, which is the current standard of care for younger patients with MCL. They compared this regimen with the previous standard treatment of high-dose cytarabine-containing immunochemotherapy followed by AHSCT, as well as an ibrutinib-containing treatment without AHSCT.

The trial included 870 patients aged up to 65 years with previously untreated advanced stage II-IV MCL. The median patient age was 57 years old, and all patients were "suitable" candidates for high-dose cytarabine and AHSCT, according to the trial's investigators. Most (76%) of the patients were male, while 87% had stage IV MCL.

The investigators randomized patients 1:1:1 to the three trial treatment arms, with 288 patients receiving immunochemotherapy plus AHSCT, 292 receiving ibrutinib and immunochemotherapy followed by AHSCT and rituximab maintenance, and 290 receiving an ibrutinib-containing treatment without AHSCT.

Patients receiving immunochemotherapy plus AHSCT underwent three cycles of high-dose cytarabine-containing immunochemotherapy without ibrutinib. Patients receiving ibrutinib and immunochemotherapy followed by AHSCT and rituximab maintenance, or an ibrutinib-containing treatment without AHSCT, underwent three immunochemotherapy cycles with ibrutinib added and two years of maintenance therapy. The trial's investigators planned AHSCT for all responding patients who were randomized to receive it.

The ORR was 94% in patients receiving immunochemotherapy followed by AHSCT. The CR rate was 36% in the 272 evaluable patients in that treatment arm. The ORR was 98% and the CR rate was 45% in the 559 evaluable patients in the two ibrutinib-containing treatment arms.

High-dose cytarabine-containing immunochemotherapy followed by AHSCT "failed to show superiority over" an ibrutinib-containing treatment without AHSCT at a median follow-up of 31 months, according to Dr. Dreyling and colleagues. The three-year failure-free survival (FFS) rate in patients receiving AHSCT without ibrutinib was 72%, while it was 86% in patients receiving an ibrutinib-containing treatment without AHSCT (HR, 1.77; P=.9979).

The three-year FFS rate was 88% in patients who received ibrutinib in addition to immunochemotherapy followed by AHSCT and rituximab maintenance, while it was 72% in patients receiving immunochemotherapy plus AHSCT (HR, 0.52; P=.0008).

The three-year OS rate was 86% in patients who received immunochemotherapy plus AHSCT, while it was 91% in those who received ibrutinib plus immunochemotherapy and AHSCT and was 92% in patients receiving ibrutinib-containing treatment and no AHSCT.

The researchers reported "no substantial differences" in the occurrence of grade 3-5 adverse events during induction with chemoimmunotherapy versus ibrutinib plus chemoimmunotherapy, with similar rates of neutropenia (47% vs 49%), leukopenia (15% vs 15%), febrile neutropenia (9% vs 12%), infections and infestations (9% vs 12%), and cardiac disorders (2% vs 3%).

The two AHSCT-containing arms "did not substantially differ" in grade 3-5 adverse events, but "in contrast, during maintenance, there were substantially more" grade 3-5 adverse events in patients receiving ibrutinib plus AHSCT than patients receiving AHSCT or ibrutinib, according to Dr. Dreyling and colleagues.

"The addition of ibrutinib during induction and as maintenance with or without [AHSCT] showed strong efficacy with acceptable toxicity," Dr. Dreyling and colleagues concluded. "It has been clearly demonstrated that the current standard high-dose regimen is not superior to the new ibrutinib-containing regimen without [AHSCT]. More follow-up is needed to clarify the role of [AHSCT] in the context of ibrutinib-containing treatment."

Reference

Dreyling M, Doorduijn JK, Gine E, et al. Efficacy and safety of ibrutinib combined with standard first-line treatment or as substitute for autologous stem cell transplantation in younger patients with mantle cell lymphoma: results from the randomized Triangle trial by the European MCL Network. Abstract #1. Presented at the 64th ASH Annual Meeting and Exposition; December 10-13, 2022; New Orleans, Louisiana.

This article discusses the current state of the art in the mechanisms of resistance to BCL2 inhibitor therapy in chronic lymphocytic leukemia. The following material is reproduced from "SOHO State of the Art Updates and Next Questions: Mechanisms of Resistance to BCL2 Inhibitor Therapy in Chronic Lymphocytic Leukemia and Potential Future Therapeutic Directions," published in the July 23, 2022, issue of Clinical Lymphoma, Myeloma & Leukemia. *The article was written by Rory Bennett, MBChB, FRACP, FRCPA; Ella Thompson; and Constantine Tam, MD.*

Present-Day BCL2 Inhibitor Therapy and Future Therapeutic Directions

Chronic lymphocytic leukemia (CLL) constitutively overexpresses the B-cell lymphoma 2 (BCL2) protein and related family proteins, resulting in dysregulation of normal intrinsic apoptosis and ultimately in inhibition of cell death. Therapeutic use of BCL2 inhibitors (eg, venetoclax) in CLL, as both continuous monotherapy or in a fixed-duration combination, has resulted in clinical benefit with significant rates of complete responses (CRs), including those without detectable minimal residual disease (MRD).

This review seeks to describe both the disease factors that influence primary venetoclax sensitivity and resistance and those resistance mechanisms that may be acquired secondary to BCL2 inhibitor therapy in CLL and proposes future applications of BCL2 inhibitor therapy in CLL and potential means by which BCL2 inhibitor-resistance may be abrogated.

Therapeutic BCL2 Inhibition

BCL2 is now an established therapeutic target in the treatment of CLL. The selective BCL2 inhibitor venetoclax demonstrated considerable overall response rates (ORRs) and CR rates in early-phase monotherapy clinical trials treating lymphoid malignancies, including CLL, and importantly including a small number of MRD-negative remissions. When venetoclax is administered in combination with anti-CD20 monoclonal antibodies or a Bruton's tyrosine kinase (BTK) inhibitor, the rates of undetectable MRD CRs observed in CLL appear to be augmented. Fixed-duration venetoclax combination therapy is now an emerging standard of care in the treatment of both frontline and relapsed/refractory CLL.

However, differential baseline sensitivity to venetoclax therapy between lymphoid neoplasms and among CLL patients has been repeatedly observed. In addition, most patients who are continuously exposed to venetoclax following an initial response will eventually develop secondary resistance.

The balance and interactions between BCL2 family member proteins determine whether apoptosis may occur. Intrinsic cellular apoptosis may be induced in normal circumstances by the antagonistic binding of BH3-only proteins to anti-apoptotic BCL2 at the BH3-binding groove, which releases the restraints on BAX/BAK. When *BCL2* is overexpressed in CLL, the consequent sequestration of pro-apoptotic proteins tips the balance of BCL2 family proteins toward cell survival.

Intrinsic Sensitivity/Resistance to Venetoclax

Baseline venetoclax sensitivity or resistance is influenced by the expression of *BCL2* relative to other BCL2 family member proteins, microenvironmental factors such as nodal T-cell stimulation, and tumoral heterogeneity.

Perhaps the most fundamental factor conferring tumoral sensitivity to *BCL2* inhibition is the degree of constitutional *BCL2* expression and dependence upon the protein for survival. In general, malignancies of mature B lymphocytes exhibit upregulated *BCL2* and also dependence upon the protein. However, upregulation of *BCL2* alone does not universally correlate with marked sensitivity to BCL inhibitor therapy. There are likely other mechanisms at play, including dysregulation of other BCL2 family proteins such as BCL-W.

Stimulation by microenvironmental agonists, including those via T-cell stimulation, likely contribute to upregulated nuclear factor kappa B (NF-kB) signaling with secondary baseline increase in antiapoptotic BCL2 family proteins such as BCL-XL and MCL1. Those cells with higher baseline levels of BCL-XL cells due to CD40 signaling are less sensitive to venetoclax, even when combined with anti-CD20. The observation that those patients with higher volumes of residual nodal disease post-venetoclax therapy appear to have shorter progression-free survival (PFS) may attest to the importance of the microenvironment in determining venetoclax resistance.

Secondary Resistance: CLL-Type Progression

With selection pressure applied by continuous venetoclax exposure, secondary resistance mechanisms develop in oligoclonal fashion. Those mechanisms include acquisition of *BCL2* variants, dynamic aberrations of alternative BCL2 family proteins, and mutations affecting both BAX and other BH3 proteins.

The discovery of mutations within *BCL2* is considered to be a major advance in understanding the mechanisms of secondary venetoclax resistance. The first-in-human venetoclax-induced *BCL2* variant discovered was Gly101Val. The discovery followed targeted amplicon next-generation sequencing of the entire *BCL2* gene from paired pre- and post-venetoclax patients' samples from early-phase venetoclax clinical trials.

The survival of CLL cells appears to correlate with upregulation of BCL2 family proteins, particularly MCL1 and BCL-XL. Baseline differential dependence upon particular BCL2 family proteins has been well described between lymphoid malignancies. The balance and interactions among BCL2 family proteins is additionally affected by continuous venetoclax exposure and underpins an important feature of drug resistance.

BCL-XL is likely more heavily implicated in venetoclax resistance than *MCL1*. Direct co-inhibition of BCL-XL and BCL2 by combination BH-3 mimetics in venetoclax-resistant CLL cell lines is seen to abrogate venetoclax resistance more effectively than co-inhibition of *BCL2* and *MCL1*. In addition, in the presence of *BCL2* inhibition, BCL-XL appears to bind BIM preferentially to MCL1. These findings are collectively suggestive of a functional hierarchy among BCL2 family proteins under venetoclax therapeutic pressure.

Future Therapeutic Strategies to Optimize *BCL2* Inhibition

It is probable that the duration of venetoclax selection pressure to a heterogeneous CLL tumor environment is an important determinant of emergence of *BCL2* resistance mutations. In contrast to continuous venetoclax therapy, combinations with anti-CD20 monoclonal antibodies have not been seen to select for *BCL2* resistance mutations.

Mechanistically, the venetoclax-killing effect may be enhanced in combination with a second agent and may allow for fixed-duration venetoclax exposure. Patients with detectable MRD at the end of fixed-duration therapy appear to have shorter PFS, independent of other response observed. Combination therapies appear to augment rates of CR and, importantly, rates of undetectable MRD over those seen with continuous venetoclax monotherapy in early clinical trials.

There is a strong theoretical rationale for therapeutic combinations in the setting of oligoclonal resistance mechanisms. BTK inhibitor therapy and anti-CD20 monoclonal antibodies demonstrate synergism with venetoclax due to a posited increase in CLL cellular *BCL2* dependence and downregulation of microenvironmental signaling. However, many questions remain regarding the optimal combinations and sequencing of targeted therapies in CLL.

A less understood area of growing interest is the potential utility of targeting the mechanisms of venetoclax resistance and even the microenvironment in which venetoclax-resistant clones may be selected for. Due to their roles in resistance previously described, potential targets under evaluation include MCL1, BCL-XL, and epigenetic modifiers, along with manipulation of NF-kB and PI3K/AKT/mTOR pathways.

In addition to these approaches seeking to abrogate resistance at treatment outset, a second yet untested approach could add an appropriate second agent as dominant resistant clones emerge under serial molecular evaluation.

soho

society of hematologic oncology

www.sohoonline.org

JOIN THE SOCIETY FOR FREE!

SOHO has no parallel general sessions so that delegates may attend all general and plenary sessions in sequential order. In addition, presentations are limited to the latest advances' allowing all topics to be covered in only 3.5 days. ***SOHO MEMBERSHIP IS FREE! SIGN UP AT SOHOONLINE.ORG.***

BENEFITS OF SOHO MEMBERSHIP

DISCOUNTED REGISTRATION RATES
Save 40% off the nonmember registration rate for the SOHO Annual Meeting

FREE ONLINE JOURNAL ACCESS
Free online access to the official society journal, *Clinical Lymphoma, Myeloma & Leukemia*

SPEAKERS' SLIDES
Member-only access to a full library of slides presented during the SOHO Annual Meeting

ANNUAL MEETING VIDEOS
Member-only access to a full library of videos captured during the SOHO Annual Meeting

HOUSING & REGISTRATION
Receive advance access to Members' Only Housing and Registration

TICKETED SESSIONS
Receive advance access to Ticketed Sessions such as MTP and other special events

ONLINE NETWORKING
Communicate with colleagues using the online membership directory and other networking tools

CME & CNE CERTIFICATION
Certification Credit through CME and CNE Accredited Learning Programs

SOHO'S MISSION IS TO EXPEDITE WORLDWIDE RESEARCH & EDUCATION THROUGH THE EXCHANGE OF SCIENTIFIC INFORMATION...

HISTORY OF THE SOCIETY OF HEMATOLOGIC ONCOLOGY

Over the course of the last decade, it has been recognized by hematologists and hematologist oncologists that the amount of research and interest in the field of hematologic oncology has increased to the point that the exchange of information could not be accomplished at the other major scientific societies. It was clear that this specialized group needed an opportunity to focus on these malignancies, and to have a meeting where outstanding leaders, innovators and budding young investigators, could interact to stimulate progress in this important field. In 2012, the decision was made to form a new society, the **Society of Hematologic Oncology** (SOHO), which would sponsor an annual meeting to bring together leading investigators and practitioners in the field.

Today, SOHO is a non-profit association committed to promoting worldwide research, education, prevention, clinical studies and optimal patient care in all aspects of hematologic malignancies and related disorders.

GLOBAL REACH

SOHO represents physicians and other health care professionals from all corners of the world. The SOHO global network supports and is supported by nearly 6,000 members from 122 countries, who are leading vital efforts to further treatments for patients with hematologic malignancies. The society is an organization that focuses on learning and educational excellence, and promotes diversity and inclusion.

Clinical Trial Updates

Blood Cancers Today *shares clinical trials currently enrolling patients*

Dose-Finding and Efficacy Study of Venetoclax, CC-486, and Obinutuzumab in Follicular Lymphoma

This study focuses on finding a safe and tolerable dose for a three-drug regimen that combines venetoclax, CC-486 (also known as oral azacitidine), and obinutuzumab to treat participants with cancer who have minimally pre-treated follicular lymphoma (FL) and have experienced disease progression despite previous therapies.

If a safe and tolerable dose can be found in the first phase of the study, a second phase will launch within an expansion cohort. Participants in the expansion cohort will receive the dose established in the first phase of the study to determine the efficacy of the regimen/established dose. Participants in the expansion cohort will also receive the same study drugs from the first phase of the study but in a different order/combination (first pairing the two oral drugs, CC-486 and venetoclax, then adding the third drug, obinutuzumab, to treatment).

The end goal of this research is to establish a new chemotherapy-sparing treatment option for patients with FL that is just as effective as current standard-of-care options.

Principal investigator: **Sonali Smith, MD**
Treatment agents: Venetoclax, CC-486 (oral azacitidine), obinutuzumab
NCT04722601

Assessment of Allogeneic HSCT in Medicare Beneficiaries with Multiple Myeloma

This is a prospective cohort study of approximately 544 patients receiving allogeneic hematopoietic stem cell transplantation (HSCT) for multiple myeloma at Center for International Blood and Marrow Transplant Research centers in the United States who are matched to historical controls treated with autologous HSCT (AHSCT) between 2010 and 2016.

The primary outcome measure is to compare the five-year overall survival (OS) between the allogeneic HSCT cohort and an age and disease risk-matched cohort of AHSCT patients.

Secondary outcome measures will assess the following with a time frame of five years post-transplant and will include:

- Progression-free survival (PFS)
- Relapse or progression
- Transplant-related mortality
- Incidence of acute graft-versus-host disease (GVHD)
- Incidence of chronic GVHD

Investigators: **Anita D'Souza, MD, MS,** and **Parameswaran Hari, MD, MS**
Treatment agent: Allogeneic HSCT
NCT03127761

Dose-Escalation Study of Minnelide in Relapsed or Refractory AML

This study seeks to determine the safety and recommended dosing of Minnelide in acute myeloid leukemia (AML). Phase I of the dose-escalation trial will establish the maximum tolerated dose (MTD) and recommended phase II dose of Minnelide as a single agent in patients with relapsed or refractory AML who are ineligible to receive intensive chemotherapy. The oral formulation of Minnelide will be used. Minnelide is a pro-drug of triptolide (a potent heat shock protein 70 inhibitor) with promising preclinical activity in AML.

Primary outcome measures include MTD of Minnelide (time frame, up to 28 days for each dosing cohort) and the number of participants who experience dose-limiting toxicities (time frame, up to 28 days for each dosing cohort).

Secondary outcome measures include complete response rate (time frame, up to 12 months); overall response rate (ORR; time frame, up to 12 months); relapse-free survival (time frame, up to 18 months); and OS (time frame, up to 12 months).

Principal investigator: **Kendra L. Sweet, MD**
Treatment agent: Minnelide
NCT03760523

Luspatercept with or without Hydroxyurea for the Treatment of MDS/MPNs with Ring Sideroblasts and Thrombocytosis or Unclassifiable with Ring Sideroblasts

This phase II trial is studying the effects of luspatercept with or without hydroxyurea in patients with myelodysplastic syndromes (MDS)/myeloproliferative neoplasms (MPNs) with ring sideroblasts and thrombocytosis or unclassifiable with ring sideroblasts.

The primary objective is to document the erythroid response rate assessed as per the 2015 International Working Group MDS/MPN response criteria.

Secondary outcome measures include documenting:

- Response duration, time to AML transformation, AML-free survival, and OS in patients with MDS/MPN with ring sideroblasts and thrombocytosis and MDS/MPN-unclassifiable with ring sideroblasts
- Safety of luspatercept (luspatercept-aamt) in patients with MDS/MPN with ring sideroblasts and thrombocytosis and MDS/MPN-unclassifiable with ring sideroblasts

Principal investigator: **Abhishek Mangaonkar, MD**
Treatment agents: Luspatercept, hydroxyurea
NCT05005182

Brentuximab Vedotin and Nivolumab for the Treatment of Relapsed Classical Hodgkin Lymphoma

This phase II trial is investigating how well brentuximab vedotin and nivolumab work in treating patients with relapsed classical Hodgkin lymphoma (HL). The combination of brentuximab vedotin and nivolumab may allow patients to defer HSCT, sparing the considerable cost and toxicity of transplantation.

The primary objective is to assess the durability of response to brentuximab vedotin plus nivolumab by 24-month PFS in participants with first relapse of classical HL who achieved early complete metabolic response (CMR).

The secondary objectives include:

- Estimate CMR and ORR after four cycles and at the end of brentuximab vedotin plus nivolumab therapy
- Estimate the PFS and OS for the entire cohort and for subgroups of patients defined by their response
- Estimate the PFS and OS separately for responders who did and did not receive radiotherapy
- Evaluate the toxicities of brentuximab vedotin plus nivolumab therapy

Principal investigator: **Alex Herrera, MD**
Treatment agents: Brentuximab vedotin, nivolumab
NCT04561206

HemOnc Happenings

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

Dr. Jabbour Receives Multiple Awards

Elias Jabbour, MD, Professor of Medicine in the Department of Leukemia at the University of Texas MD Anderson Cancer Center and Associate Editor of *Blood Cancers Today*, was honored with the King Hussein Lifetime Achievement Award for Cancer Research during the King Hussein Cancer Research Conference in Jordan in November 2022.

"The King Hussein Award recognizes the pillars and pioneers who have played critical roles in both advancing regional research and the fight against cancer at the international level through its Lifetime Achievement Award," the organizers said.

Elias Jabbour, MD

Dr. Jabbour also received the Presidential Lebanese Order of Merit Award in July 2022 and will be recognized with the Ben Qurrah Award from the National Arab American Medical Association.

The award ceremony honors "Arab-Americans who have made remarkable contributions in the field of medicine and who have succeeded in the worldwide advancement of science," according to the National Arab American Medical Association.

Sources: King Hussein Cancer Research website, National Arab American Medical Association website, and University of Texas MD Anderson Cancer Center website, November 2022

Dr. Eshhar Honored with SITC Richard V. Smalley Memorial Award

Zelig Eshhar, PhD, of the Weizmann Institute of Science and the Tel Aviv Sourasky Medical Center, was honored with the 2022 Richard V. Smalley Memorial Award during the 2022 Society for Immunotherapy of Cancer (SITC) Annual Meeting in November 2022.

Dr. Eshhar received the award for his pioneering work in chimeric antigen receptor (CAR) T-cell therapy. He has conducted research on CAR-T therapies for multiple myeloma and numerous other malignancies.

Zelig Eshhar, PhD

"The Richard Smalley Memorial Award is presented each year to a luminary in the field that has significantly contributed to the advances in cancer immunotherapy research," the organizers said. "The award serves to honor those that have been pioneers in their work and made a notable impact worthy of high regard and recognition of their peers. Named in memory of a former Society president and SITC charter member Richard Smalley, this is the society's most prestigious award."

Dr. Eshhar was also honored with a panel at the SITC annual meeting. The panel included **Carl June, MD**; **Crystal Mackall, MD**; **Steven Rosenberg, MD, PhD**; and **Michel Sadelain, MD, PhD**.

"I am deeply humbled to honor Dr. Zelig Eshhar, one of the earliest pioneers of CAR-T therapy, during the SITC Annual Meeting," Dr. Mackall said in a statement.

Source: SITC Annual Meeting, November 2022

Dr. Bhardwaj Honored with ESMO Award for Immuno-Oncology

The European Society for Medical Oncology (ESMO) recently announced **Nina Bhardwaj, MD, PhD,** of the Tisch Cancer Institute, has received the 2022 ESMO Award for Immuno-Oncology for "her outstanding contribution to cancer immunology research."

Dr. Bhardwaj is a Professor of Medicine in Hematology, Medical Oncology, and Urology. She is the Director of Immunotherapy, Medical Director of the Vaccine and Cell Therapy Laboratory, and Co-Director of the Cancer Immunology Program at the Tisch Cancer Institute. She is a faculty member of the Icahn Genomics Institute and holds the Ward Coleman Chair in Cancer Research.

Nina Bhardwaj, MD, PhD

"Dr. Bhardwaj has made seminal contributions to human dendritic cell biology, specifically with respect to their isolation, subset discovery, immunobiology, antigen presenting function, and use of vaccine adjuvants in humans," ESMO officials said in the announcement.

Dr. Bhardwaj was slated to deliver her award lecture during the ESMO Immuno-Oncology Congress in December 2022.

Source: ESMO press release, November 2022

Yale Researcher Receives Award for Myeloid Malignancy Work

Giulia Biancon, PhD, of the Yale Cancer Center recently received the 2022 Italian Scientists and Scholars in North America Foundation (ISSNAF) Young Investigator Paola Campese Award for her research on myeloid malignancies.

"ISSNAF confers the Young Investigator Awards every year to outstanding, early-career Italian researchers who work in the United States or Canada in recognition of their significant and innovative contributions to their field of study," according to a press release from the Yale School of Medicine. "Specifically, the Paola Campese Award for Research in Hematologic Malignancies was established by Stefania and Vito Campese in 2011 in memory of their young, talented, and generous daughter, Paola."

Organizers presented the award to Dr. Biancon during a ceremony in November 2022 at the Italian Embassy in Washington, DC.

Dr. Biancon's research is focused on "dissecting the role of splicing factor mutations in myeloid malignancies merging molecular and computational biology," according to the release.

Dr. Biancon is a postdoctoral associate in the lab of **Stephanie Halene, MD, PhD**. Dr. Halene is the Arthur H. and Isabel Bunker Associate Professor of Medicine in Hematology, Associate Professor of Pathology, and Chief of the Section of Hematology at the Yale School of Medicine.

Source: Yale School of Medicine release, November 2022

Dr. Hendricks-Ferguson Receives Distinguished Researcher Award From APHON

Verna Hendricks-Ferguson, PhD, the Irene Riddle Endowed Chair at the Trudy Busch Valentine School of Nursing, recently received the 2022 Distinguished Researcher Award from the Association of Pediatric Hematology Oncology Nurses (APHON).

Dr. Hendricks-Ferguson "has an impressive list of data-based published articles focused on pediatric oncology patients, and her publications have been frequently cited by other investigators," according to an announcement from Saint Louis University. "Her award letters of recommendation described the numerous organizations she has also participated in and her 'continued passion and commitment to contribute to the science of pediatric palliative care/end-of-life care for children with cancer and their parents.'"

The Distinguished Researcher Award is selected annually by the APHON Evidence-Based Practice/Research Committee and presented at its annual conference.

Source: Saint Louis University press release, September 2022