

OncPathways

- 4** Increasing Treatment Pathways Pave the Way for Heartening Future Throughout Hematologic Malignancies
- 6** Targeted Therapies Plus Chemotherapy Provide Path Around Acquired Resistance in AML

Oncology Treatment Pathways[®]

Diagnostic Testing & Personalized Medicine

Precision Genomics Moves Toward Increased Granularity in Molecular Sequencing

Caroline Seymour

PRECISION MEDICINE INVOLVES

more than molecularly sequencing a tumor and matching it with a targeted therapy, according to Kelvin P. Lee, MD, who argued that bulk sequencing may become an antiquated approach when single-cell RNA sequencing technology becomes available because it can provide a clearer picture of the complexity and heterogeneity of tumors.

“Once we move away from bulk sequencing, which essentially says, ‘This whole tumor is all the same’ and get down to a much finer specificity that [enables us to identify] tumor cells that have this mutation and look like this vs tumor cells that have that mutation and look like that, we will get more and more sophisticated in how we treat



Kelvin P. Lee, MD

patients. The more heterogeneous the tumor--and they become more heterogeneous as they are later in treatment--the harder they are to treat, and the less helpful our current precision genomics technology is in that setting,” Lee said in an interview with *OncLive*[®] following an Institutional Perspectives in Cancer webinar on Precision Medicine.

In the interview, Lee, director of the Indiana University (IU) Simon Comprehensive Cancer Center, the H.H. Gregg Professor of Oncology, professor, Department of Medicine, Division of Hematology/Oncology, associate dean for cancer research, IU School of Medicine, discussed the nuances of an effective molecular tumor board, explained the practical application of precision oncology genomics, and highlighted the pathways that have the potential to change the treatment landscape for precision oncology.

OncLive[®]: How is precision medicine practiced at Indiana University?

Lee: The take-home message is that every tumor should be sequenced. If you don’t do it now, you may not be able to do it later. The information can be useful in designing a treatment plan, but it also helps us understand that cancer. The more information we have on lung cancers from patients, the better we can design new therapies and move that field forward. If a patient has a tumor specimen that you can send to precision genomics, send it because maybe we don’t have an answer today, but maybe in 2 weeks we will have an answer, and that becomes important for that patient.

At IU there is a precision medicine team, and our patients are referred to them. That precision medicine team sets up the testing and the [molecular] sequencing and

then does tumor boards, where they go through the results, they talk about what abnormalities and what mutations were found and then they go through what [mutations] are potentially actionable and how we want to utilize [treatment for] those [alterations]. The nice thing about tumor boards is that all the experts are in the room, and now that we have extended [ours] to be virtual, not only can we do precision medicine downtown at University Hospital, but now we have clinics that are in our suburban and metropolitan regions. We're moving those facilities out farther, so we can do precision medicine, hopefully, out in the community. Hopefully, with the expansion, primary care physicians and community oncologists can also utilize this [opportunity to] get the referrals and then sit in virtual tumor boards and get answers for their patients.

Your colleague, Bryan P. Schneider, MD, of IU Melvin and Bren Simon Comprehensive Cancer Center, presented on tailored to fit treatments. What goes into offering patients individualized treatment, and how do you see these approaches evolving?

The key piece is not only doing the [molecular] sequencing and understanding what the mutations are, but also what you're doing with that information. For many of the mutations, the therapeutic that might be applicable to that patient or that mutation are in clinical trials. An effective precision medicine program has to not only have the expertise as to what these mutations are, what these established targets or established therapeutics are that we might be able to use, but also has to have an ongoing real-time knowledge of all the clinical trials that are available and in the literature.

Not only are there new compounds that a patient might be eligible for in a clinical trial, but there are also drugs that have been used for other things that are being repurposed for targeting mutations that we had not previously expected those drugs to be able to do. The precision medicine team must be aware of the literature, not only published literature but abstracts and journal or meeting work that says, "Maybe you can use this malaria drug to target this mutation," which may be something that had not been previously understood. That is, overall, a key piece of what makes precision medicine so effective and so important, but so difficult to do. It's not just sequencing stuff, and then saying, "There it is" and then figuring out how to manage that [patient].

Next-generation sequencing is now allowing us to get at whole genomes, instead of just testing for *BRCA* mutations or [other single-gene mutations]. We are identifying other mutations, and now instead of having to re-sequence somebody's tumor, we have all that data that's there. If something pops up that later becomes this polymorphism or this mutation that is important in this cancer, we have that data; we can go back and look at those aspects. What it allows us to do is really what I would consider the next generation of precision medicine: to understand how mutations work together.

For immunotherapy, [tumor] mutational burden has been a key driver of whether checkpoint inhibitors are important. Now as we understand more of what a person's cancer has, in terms of mutations, our informatics, our artificial intelligence, and our machine learning technology is poised to take that data and say, "if you have these 2 mutations: Are

they compensating for each other, and do you have to target both?" Now, if a patient has 1 mutation, they get this 1 drug, but biology is much more complicated. There are mutations that may work in concert with each other that may develop other additional vulnerabilities that we didn't anticipate because one mutation is causing the cell to do something and another mutation is stressing the cells, so maybe there is a target that's not either one of those 2 mutations but that is in the pathways that those mutations are driving that can be gone after. The exciting thing for me is understanding that. I'm an immunologist, so understanding the complexity of cells, because immune systems see lots of things simultaneously, is really what we are looking forward to.

Christopher A. Fausel, PharmD, MHA, BCOP, of IU Melvin and Bren Simon Comprehensive Cancer Center, discussed the elements of the molecular tumor board at IU. What are some of the considerations that are made during a tumor board?

It's a very active process; patients are identified at the beginning of the week, and then the team asks: What are the mutations? What are the [alterations] that are actionable? Then they begin to sort through what treatment options are available and what the adverse effects [AEs] are. PharmDs have to ask: What are the AEs, particularly for experimental agents? What are the interactions with other drugs? How do we get these things and what literature supports the use of this agent? Then, are there odd things that we have to understand? Are there subsets of patients who have particularly bad responses that had been reported in the literature? All that gets pulled together.

Our tumor board is later in the week where all that information is presented: the patient case is presented, the genomic description or the description of the genetic changes are reviewed, and then the treatment options are also reviewed if they're available, and the strength of each [drug] in terms of the data that says that this drug would be particularly good in this patient, or this drug would not be something that we'd be looking for in this patient. A lot of what makes tumor boards effective is that research. It's not just, I have a piece of paper says I can give this drug and then you are done. It really is a lot of thoughtful research that goes into understanding the options that a patient might have.

Dr Fausel's presentation covered several case studies and treatment plans for patients. How can these examples better inform future treatment decisions?

The case study showed what the right process is to analyze the data you get to reach a meaningful action plan. As the technology goes forward, and as our ability to detect things gets more sophisticated, as we start to move toward single-cell sequencing, for example, RNA sequencing, when we start to look at the epigenome, we will have substantially more data than we have now. Then we'll start looking at what the patient's immune system looks like when we start [molecularly] sequencing that. The amount of data that will be collected and the kinds of data that will be collected will grow exponentially.

The key piece of molecular tumor boards and the key piece of precision medicine is: How do you analyze that data? The analytical pipeline is going to be the same, the structure is going to be the same. How do you act? How do you take

that data in? How do you analyze it, and then how do you use that analysis to come to specific treatment recommendations for that patient? That framework, that pipeline is going to be the same regardless of what the data coming in is. The key thing that was important in that whole process of going through these case studies is to recognize what the steps were that were taken from the very beginning, from the actual case itself where the patient comes in with their history. How were those data put together and analyzed? How was that used to make decisions for the treatment plan for that patient? It's the structure of the analytical process that was the most important aspect of going through those case studies.

Could you speak to the importance of early genomic testing vs delayed genomic testing?

The data suggests that with early genomic testing, when you apply it to precision medicine to identify therapeutics, the anti-cancer effect, or the ability to impact a person's cancer is greater on early diagnosis than late diagnosis. There probably are a variety of biologies that are implicated by that. When a tumor has been exposed to lots of things, it probably not only has its initial mutations, but probably has a lot of adaptations that have happened because of chemotherapy that has been given that we don't necessarily pick up; it may not be a genomic abnormality, but it may be overexpression of a particular gene that confers resistance. As those tumors become more resistant to therapy, the initial driver mutations may become less important as things go forward.

It speaks to biology also, because in the beginning, probably, in tumors that have not been treated or not been heavily pretreated at the time

of diagnosis, they're probably less genetically complicated, so maybe they have just one mutation. Maybe all of them have that one mutation, you treat them with a drug, and they all die. As tumors go along, they become much more heterogeneous, so instead of one population of cancer cells, now you have 75 different populations or tribes, for example, that are living, and some of them are sensitive, some of them are different. Some of them have different mutations, and precision genomics is moving towards being able to understand complex tumors, such that some of the cells have one mutation and some of them have a completely different set of mutations. We don't pick that up right now, simply because we don't have the single-cell RNA sequencing technology yet, although that's coming.

What would you like to emphasize about the future of precision genomics?

We are beginning to see precision medicine in the context of immunotherapy. In that sense, the change in framework is it's not the cancer alone that's important because not only do you have to sequence the cancer, and understand it's genetic makeup, you also have to sequence the immune system—the normal part of the patient that is essentially the effector part. Instead of giving chemotherapy, where you're saying, "I have a drug, I know everything about that drug, and all I need to do is figure out what's going on in the cancer," if I can find that this drug will hit this piece of the cancer, then let's put those two together.

For immunotherapy, you have the cancer, which is doing stuff and it's dynamic, and it's activating the immune system and suppressing the immune system. We have to understand that, and some of the suppression that it does is

not because it is suppressing the immune system, it's making the normal tissue around it suppress the immune system.

People say that cancer is a non-healing wound, so essentially, for wound healing, you don't want your immune system to fire up and start destroying all the tissue around a healing wound. Otherwise, you'll never heal. The normal body has perfectly good mechanisms to shut off your immune response and cancers take advantage of that, but that phenomenon is not in the cancer. It's in the surrounding tissue. You have to look in the surrounding tissue to see what's going on there.

Then, you have to look at the immune system because the immune system is the thing that's going to kill the cancer cell, and people have different immune systems. It's very clear that there are lots of genetic variabilities in that. Maybe that genotype within somebody's immune system is not good at getting activated by this immunotherapy. Maybe we should try something different. It's another level of complexity that precision medicine has a tremendous role in, but it becomes that much more complicated because now you're not just looking at the cancer, we're now looking at the cancer, the cancer's effect on its surrounding microenvironment, and the immune system's ability to target that cancer and perhaps live in that environment that surrounds the tumor. It's an additional level of analysis and complexity. That's coming though. With the expansion of immunotherapy that will be a much bigger piece of what we do in terms of therapy. Those kinds of analyses and guidance by precision medicine will be a key component of how we deploy immunotherapy in patients with cancer. ■

Increasing Treatment Pathways Pave the Way for Heartening Future Throughout Hematologic Malignancies

Caroline Seymour

ONE THEME THROUGHOUT HEMATOLOGIC MALIGNANCIES

is the abundance of therapies available to patients, whether that's



Stephen Oh, MD

JAK inhibitors in myelofibrosis, cellular therapies in diffuse large B-cell lymphoma (DLBCL), or targeted agents in chronic lymphocytic leukemia (CLL), explained Stephen Oh, MD, PhD, who added that the availability of these agents allows for increased personalization.

"We are going to see use of all these agents to some extent, and it's going to be an evolving situation in terms of for whom these specific agents would be the best choice. Whether we're talking about myelofibrosis, CLL, DLBCL, or GVHD [graft-vs-host-disease], all these fields are evolving rapidly. It's important to keep up on latest developments because things are always changing," Oh said in an interview with *OncLive*® following an Institutional Perspectives in Cancer webinar on hematologic malignancies.

In the interview, Oh, associate professor, Department of Medicine, Division of Hematology, Department of Pathology and Immunology, Washington University School of Medicine in St. Louis, hematologist, Siteman Cancer Center, discussed current and emerging agents in myelofibrosis, advances in the treatment of patients with relapsed/refractory DLBCL, updates

in acute and chronic GVHD, and CLL management.

***OncLive*®: In your presentation on myelofibrosis, you focused on some of the newer-generation JAK inhibitors. How do these agents distinguish themselves from ruxolitinib (Jakafi) and fedratinib (Inrebic)?**

Oh: Currently, we have 2 FDA-approved oral therapies for myelofibrosis: the JAK inhibitors ruxolitinib and fedratinib.* Those drugs are commonly used for the treatment of patients with myelofibrosis, and the benefits of those drugs largely relate to improvement in symptoms, a reduction in symptomatic splenomegaly, and things like that. We are anticipating that 2 additional JAK inhibitors are going to be approved and become commercially available soon and those are pacritinib [Vonjo] and momelotinib, each of which have distinct properties in addition to providing similar aspects of spleen and symptom response as the other JAK inhibitors.

Pacritinib seems to cause little thrombocytopenia, so it may have a niche in those patients with myelofibrosis who have very low platelet counts. Momelotinib is unique in terms of ameliorating anemia, which is distinct compared with the other JAK inhibitors and likely relates, at least in part, to the drug targeting not just JAK 1/2 but also ACVR1, which is involved in the production of hepcidin. With that mechanism, the drug does provide anemia benefits and, for that reason, could

be a particularly useful option for patients with myelofibrosis who have severe anemia.

Where might these newer agents play a role in treatment among current staples like ruxolitinib?

Currently, ruxolitinib is the most widely used oral therapy for patients with myelofibrosis. As we go forward, it is going to continue to be frequently used, particularly as initial treatment for patients who have significant symptoms and large spleens and symptoms related to that, etc. Over time [we will see] subgroups of patients for whom choosing a different agent, either initially or as a second-line or beyond agent makes [more] sense [than ruxolitinib]. For patients whose primary problem is anemia, perhaps momelotinib would be a good choice. For those patients with severe thrombocytopenia, pacritinib would be a good choice.

In terms of development therapeutics, which agents are the most exciting to you?

It really is, overall, quite an exciting time in terms of developmental therapeutics for patients with myelofibrosis. There is approximately 9 ongoing phase 3 studies with novel agents for patients with myelofibrosis. We anticipate that at least some of those agents will be approved soon. Some of the specific agents that I would highlight include pelabresib, which is a BET inhibitor from Constellation.

That drug appears to provide some degree of symptom and spleen benefits, but also some degree of anemia benefits. This drug is being studied alone and in combination with ruxolitinib, and if it were to become commercially available, the one question would be: Can we pair it with a different JAK inhibitor besides ruxolitinib? There are so

many different scenarios for which that drug could be used, but it's looking very promising. We'll see whether the ongoing phase 3 study leads to approval soon.

Other agents to be excited about include navitoclax, which is a BCL-XL/BCL-2 inhibitor, which is also currently in phase 3 studies. That agent also could potentially be paired with ruxolitinib or another JAK inhibitor or be used as monotherapy. There has been some hint from early data that it might, again, provide some degree of spleen and symptom benefit, but perhaps other measures of disease efficacy and perhaps some degree of molecular response. Those are things that we'll be continuing to look out for.

We also have other agents such as pascalisib, which is a PI3 kinase inhibitor and imetelstat, which is now in phase 3 testing. The list goes on and on, and beyond that, of course, there are agents in early-phase studies, which are looking intriguing.

Broadly speaking, as the field moves forward, and as we are seeing some promising developments with some of these novel agents, we're looking at the fundamental question of whether we can or should focus on measures of efficacy that are beyond or distinct from symptom and spleen benefits. This is where this notion of what constitutes disease-modifying therapy has come into play and become the subject of vigorous debate in the field. By whatever definition one might use as far as disease-modifying therapy, [we then have to determine] which agents seem to have the capacity, potentially, to provide that. Historically, most of the studies have utilized spleen reduction or symptom benefit as the primary end points. Now we're considering whether we can look at things like overall survival or

other measures that might reflect disease-modifying activity as end points in these studies.

Turning to the presentation that Iskra Pusic, MD, of Siteman Cancer Center, gave on updates in acute and chronic GVHD, what stood out to you about the progress that has been in this setting?

It's clear from Dr Pusic's presentation, that there has been tremendous progress in the development of new agents to treat patients with acute and chronic GVHD, and that pertains to agents that are commercially available, as well as those that are currently under investigation, which is exciting. It has also become clear from some of the research that has been conducted at Washington University how that has evolved from bench to bedside in terms of, for instance, the application of JAK inhibitors in that setting. It has been an exciting development to see progress along those lines.

Moving on to the presentation Neha Mehta-Shah, MD, MSCI, of Siteman Cancer Center, gave on advances in the management of relapsed/refractory DLBCL, what has become clear about the treatment paradigm?

Relapsed/refractory DLBCL is a situation, again, where there has been tremendous progress over the past several years to the point that there's a plethora of potential options or pathways to consider for patients in this category. Treating physicians have a bit of a conundrum as to whether to pursue cellular therapies or transplant or other novel agents and in what sequence makes sense for individual patients. It's nothing but a good thing that now there are so many different types of options and specific therapies.

Brad S. Kahl, MD, of Siteman Cancer Center, closed out the night by speaking about CLL management. What distinguishes the treatment paradigm from that of other hematologic malignancies?

What I took from Dr Kahl's presentation is that in the CLL field, once again, I'm very heartened to see that there has been quite a bit of progress in terms of new agents

in this field. For some patients, it is now a realistic option that traditional chemotherapy perhaps could be avoided in the appropriate setting. It's also become quite clear that with more experience with the different targeted agents, now second-generation and even third-generation agents, which are coming to the forefront, in terms of efficacy and adverse effect profile, [physi-

cians know] which agents might be preferentially used. ■

***Editor's Note:** This interview took place prior to the February 28, 2022, FDA approval of pacritinib for the treatment of adult patients with intermediate- or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis with a platelet count below $50 \times 10^9/L$.

Targeted Therapies Plus Chemotherapy Provide Path Around Acquired Resistance in AML

Kyle Doherty

TARGETED THERAPIES, specifically those agents directed at mutated proteins and aberrant protein-to-protein interactions, have been shown to improve survival among patients with relapsed or refractory acute myeloid leukemia (AML). However, developed resistance to targeted therapies has proved to be a problem, according to a presentation by Eytan M. Stein, MD, during the *26th Annual International Conference on Hematologic Malignancies*®.¹



Eytan M. Stein, MD

"The challenge of single-agent inhibitors is [developed] resistance," Stein, director of the Program for Drug Development in Leukemia, Memorial Sloan Kettering Cancer Center in New York, New York, said. "We can overcome the resistance by moving agents upfront in combination with broadly active standard of care agents, [such as] chemotherapy."

Addressing RAS Pathway Mutations *FLT3*

Approximately 30% of patients with AML display mutations in the FMS-like tyrosine kinase 3 receptor (*FLT3*). Among these patients, 23% have *FLT3*-internal tandem duplications (*FLT3*-ITD) and 7% have *FLT3*-tyrosine kinase domain mutations (*FLT3*-TKD).² Several agents have been investigated in the space, however a lack of prolonged efficacy remains a challenge for their integration into clinical practice.

Investigators evaluated midostaurin, a multitargeted tyrosine kinase inhibitor, in patients with wild-type or *FLT3*-mutant relapsed or refractory AML or MDS in a phase 2B study (NCT00045942). Among the 95 patients enrolled in the study, 35 were *FLT3*-mutant and 57 had wild-type disease. Patients were treated with 50 mg or 100 mg of midostaurin twice daily.

Patients with *FLT3*-mutant disease experienced an overall response rate (ORR) of 71%, with all responses being blast responses. Patients

with wild-type disease had an ORR of 56%; 24 patients had a blast response. The study authors concluded that midostaurin displayed hematologic activity in both patients with *FLT3*-mutant and wild-type disease, but there were no clear differences in the blast responses when stratified by type of *FLT3* mutation or dose of study drug.

"Midostaurin is a relatively weak *FLT3*-inhibitor," Stein said. "[Investigators observed] some decrease in the level of blast, but nothing that was good enough to be a true complete remission [CR]. In the relapsed or refractory setting, midostaurin has very little, if any, significant clinical activity."

In the phase 3 QuANTUM-R trial (NCT02039726), the potent, selective type 2 *FLT3* inhibitor quizartinib was compared with salvage chemotherapy in patients with relapsed/refractory *FLT3*-ITD-positive AML. Patients were randomized 2:1 to receive either quizartinib (n = 245) or salvage chemotherapy (n = 122) and the primary end point of the study was overall survival (OS). At

a median follow-up of 23.5 months (range, 15.4-32.3), the median OS in the quizartinib group was 6.2 months (range, 5.3-7.2) compared with 4.7 months (range, 4.0-5.5) in the chemotherapy group (HR, 0.76; 95% CI, 0.58-0.98; $P = .02$).³

Stein noted that although a survival benefit was observed with single agent quizartinib, the FDA did not approve the drug, but it has been approved for use in Japan.

In a similar phase 3 study, ADMIRAL (NCT02421939), the FLT3-inhibitor gilteritinib (Xospata) was compared with salvage chemotherapy in patients with relapsed or refractory AML harboring a *FLT3*-ITD mutation. Patients were randomized 2:1 to received either gilteritinib ($n = 247$) or salvage chemotherapy ($n = 124$). The primary end points of the trial were OS and CR/CR with partial hematologic recovery (CRh) rate. Patients treated with gilteritinib experienced a median OS of 9.3 months vs 5.6 months in the salvage chemotherapy arm (HR, 0.665; 95% CI, 0.518-0.853; 2-sided $P = .0013$).⁴

“You will notice in both of these studies that there is a tail to the curve, where almost no patients end up surviving very long,” Stein said. “And if you just gave these patients FLT3-inhibitors and didn’t follow that up with an allogeneic stem cell transplant, I would argue that nearly all of these patients end up relapsing by a year after going on therapy, whether they go on quizartinib or gilteritinib.”

Stein explained that the 3 most common mutations among patients who relapsed on gilteritinib were *FLT3*-F691L, *NRAS*, and *KRAS*. The *FLT3*-F691L mutation is a “gate-keeper mutation” that can prevent the binding of gilteritinib, reducing efficacy and ultimately leading to resistance against the agent, Stein said. The RAS mutations then

become the driving mutations in disease growth via clonal evolution.⁵

IDH1/2

Another mutation type common in patients with AML are mutations of isocitrate dehydrogenase 1 (*IDH1*) and isocitrate dehydrogenase 2 (*IDH2*), which are observed in up to 25% of patients with AML. Patients with an *IDH1* or *IDH2* mutation experience an increase in intracellular beta hydroxyglutarate, freezing the cell in an undifferentiated state, Stein said. *IDH1* and *IDH2* are mutations of clinical interest because if effectively drugged and the intracellular beta hydroxyglutarate is decreased, cells will begin differentiating again and patients will go into a complete clinical remission, Stein explained.

The *IDH1* inhibitor ivosidenib (Tibsovo) was examined as a single agent in patients with relapsed or refractory AML harboring an *IDH1* mutation in a phase 1 trial (NCT02074839). In the primary efficacy population ($n = 125$), the median OS was 9.0 months (95% CI, 7.1-10.0). Among patients who experienced a CR or CRh ($n = 38$), the median OS was 18.8 months (95% CI, 14.2-not estimable [NE]). Similar to patients treated with FLT3 inhibitors, a drop off in survival was seen around 12 to 16 months because of relapse, Stein noted.⁶

Enasidenib (Idhifa), an *IDH2* inhibitor, was also tested as a single agent in patients with *IDH2*-mutant AML in a phase 1/2 trial (NCT01915498). The efficacy results with enasidenib were very similar to those seen with ivosidenib, Stein noted. Specifically, the median OS was 8.8 months (95% CI, 7.8-9.9) among all treated patients ($n = 214$) and the median OS for patients who achieved a CR ($n = 42$) was 18.9 months (95% CI, 14.5-24).

The same drop in survival at the tail of the curve was observed.⁷

“The most common causes of relapse [among patients treated with *IDH* inhibitors] are RTK pathway mutations and [new] mutations in *IDH*,” Stein said. “One of the mutations in *IDH* can be a second site mutation that can prevent drug binding. The other mutations that we see in *IDH* are what we call isoform switching. Isoform switching is a mechanism of clonal evolution, when you have a patient with *IDH2*-mutant AML and you give them an *IDH2* inhibitor, there are some cases where *IDH1* mutation then pops up and takes over driving the disease.”

Stein went on to explain that the same mechanism of isoform switching can occur where *IDH1*-mutant disease can switch to *IDH2*-mutant disease. Any new targeted therapy will eventually experience problems with resistance, more than likely through second site mutations or clonal evolution, Stein said.

Tackling Resistance

To overcome problems with resistance, targeted therapies are being examined in combination with intensive chemotherapy. Midostaurin plus chemotherapy was evaluated in patients with AML harboring an *FLT3* mutation in a phase 3 trial (NCT00651261). The study design consisted of 1 to 2 cycles of induction chemotherapy (cytarabine plus daunorubicin) plus midostaurin or placebo. If patients achieved CR, consolidation high-dose cytarabine was administered in combination with midostaurin or placebo for 4 cycles. If CR persisted, patients received single-agent targeted therapy for 12 cycles.

Patients treated with the combination experienced a median OS of 74.7 months (95% CI, 31.5-not reached) compared with 25.6 months among patients who re-

Stein explained that the **3 most common mutations** among patients who **relapsed on gilteritinib** were **FLT3-F691L, NRAS, and KRAS**. The **FLT3-F691L mutation** is a **“gatekeeper mutation”** that can prevent the binding of gilteritinib, reducing efficacy and ultimately leading to **resistance** against the agent, Stein said. The **RAS mutations** then become the **driving mutations in disease growth** via clonal evolution.⁵

ceived placebo (HR, 0.78; 95% CI, 0.63-0.96; $P = .009$).⁸

Another phase 3 trial combining a targeted therapy with chemotherapy, QuANTUM-First (NCT02668653) displayed positive topline results. The trial met its primary end point for OS and the combination was found to be manageable in terms of safety.⁹

Similarly positive results have been observed when IDH inhibitors are combined with induction chemotherapy, followed by consolidation, and single-agent maintenance therapy. In a phase 1 study (NCT02632708), patients with *IDH1* mutations received ivosidenib 500 mg once daily and those with *IDH2* mutations received enasidenib 100 mg once daily. For those treated with ivosidenib, the median OS was not reached, and the 12-month survival probability was 78% when evaluated after induction on day 1. Among patients treated with enasidenib plus chemotherapy, the median OS was 25.3 months (95% CI, 25.5-NE) and the 12-month survival probability was 74%.¹⁰ Stein noted that the same design is now being done as a randomized phase 3 trial in Europe.

In the phase 3 AGILE study (NCT02677922), ivosidenib was combined with azacitidine (Onureg) and evaluated in patients with AML harboring an *IDH1* mutation. Patients treated with the combination ($n = 100$) experienced a median OS of 24.0 months compared with 7.9 months among the 100 patients who received

placebo plus azacitidine (HR, 0.44; 95% CI, 0.27-0.73; $P = .0005$).¹¹

“[These results] argue that we should be combining some of these targeted agents, [such as] FLT3 inhibitors and IDH inhibitors, with intensive chemotherapy to eliminate the most common source of clonal evolution, which is *RAS*-mutant disease,” Stein said. “Maybe there will be other better targeted therapies for *KRAS*-mutant disease, [but] combining targeted therapies with more broadly active treatments like chemotherapy and hypomethylating agents is really the way to go.” ■

References

- Stein EM. Clinical benefits and challenges with targeted therapies in AML. Presented at: 26th Annual International Conference on Hematologic Malignancies®: Focus on Leukemias, Lymphomas, and Myeloma. February 24-27, 2022; Miami Beach, FL.
- Fischer T, Stone RM, DeAngelo DJ, et al. Phase IIB trial of oral midostaurin (PKC412), the FMS-like tyrosine kinase 3 receptor (FLT3) and multi-targeted kinase inhibitor, in patients with acute myeloid leukemia and high-risk myelodysplastic syndrome with either wild-type or mutated FLT3. *J Clin Oncol*. 2010;28(28):4339-4345. doi:10.1200/JCO.2010.28.9678
- Cortes JE, Khaled S, Marinelli G, et al. Quizartinib versus salvage chemotherapy in relapsed or refractory FLT3-ITD acute myeloid leukaemia (QuANTUM-R): a multicentre, randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2019;20(7):984-997. doi:10.1016/S1470-2045(19)30150-0
- Perl AE, Larson RA, Podoltsev NA, et al. Follow-up of patients with FLT3-mutated R/R AML in the phase 3 ADMIRAL trial. *J Clin Oncol*. 2021;39(suppl 15):7013. doi:10.1200/JCO.2021.39.15_suppl.7013
- Tarver TC, Hill JE, Rahmat L, et al. Gilteritinib is a clinically active FLT3 inhibitor with broad activity against FLT3 kinase domain mutations. *Blood Adv*. 2020;4(3):514-524. doi:10.1182/bloodadvances.2019000919
- DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in *IDH1*-mutated relapsed or refractory AML. *N Engl J Med*. 2018;378(25):2386-2398. doi:10.1056/NEJMoa1716984.
- Stein EM, DiNardo CD, Fathi AT, et al. Molecular remission and response patterns in patients with mutant-*IDH2* acute myeloid leukemia treated with enasidenib. *Blood*. 2019;133(7):676-687. doi:10.1182/blood-2018-08-869008
- Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *N Engl J Med*. 2017;377(5):454-464. doi:10.1056/NEJMoa1614359
- Quizartinib added to chemotherapy demonstrates superior overall survival compared to chemotherapy alone in adult patients with newly diagnosed FLT3-ITD positive AML. News release. Daiichi Sankyo Company Ltd. November 18, 2021. Accessed February 28, 2022. [bwnnews.pr/3kV7K6C](https://www.bwnnews.pr/3kV7K6C)
- Stein EM, DiNardo CD, Fathi AT, et al. Ivosidenib or enasidenib combined with intensive chemotherapy in patients with newly diagnosed AML: a phase 1 study. *Blood*. 2021;137(13):1792-1803. doi:10.1182/blood.2020007233
- Montesinos P, Recher C, Vives S, et al. AGILE: a global, randomized, double-blind, phase 3 study of ivosidenib + azacitidine versus placebo + azacitidine in patients with newly diagnosed acute myeloid leukemia with an *IDH1* mutation. *Blood*. 2021;138(suppl 1):697.