Slide 1: BREAKTHROUGHS AND PROGRESS: ACUTE MYELOID LEUKEMIA (AML)

Operator:

Greetings and welcome to Breakthroughs and Progress: Acute Myeloid Leukemia (AML). It is now my pleasure to introduce your moderator, Lizette Figueroa-Rivera. Thank you, Lizette, please begin.

Slide 2: WELCOMING REMARKS

Lizette Figueroa-Rivera:

Hello, everyone. On behalf of The Leukemia & Lymphoma Society (LLS), I'd like to welcome all of you. Everyone with a blood cancer deserves a longer, better life. That's why The Leukemia & Lymphoma Society is on a mission to cure blood cancer and improve the quality of life of all patients and their families. How? We fund life-saving blood cancer research around the world, provide free information and support services for patients and their families, and are the voice for those seeking access to quality, affordable, coordinated care.

LLS has a bold goal. By 2040, LLS will enable people with blood cancer to gain more than 1 million years of life. This means more birthdays, more graduations, more cherished moments, and memories with family and friends. Doctors diagnose over 20,000 Americans with acute myeloid leukemia, AML, each year, making it one of the most common types of leukemia and one of the most aggressive.

In 2016, The Leukemia & Lymphoma Society launched the Beat AML Master Clinical Trial, the first collaborative precision medicine clinical trial in a blood cancer. The trial uses advanced technology to examine the genetic makeup of each patient's cancer and then matches patients to the most promising targeted treatment. Our understanding of the molecular basis for AML has dramatically improved over the past 10 years, and progress will continue in 2025 and beyond with a wide range of research ongoing in each area. Please continue to inform us of what you need during this time, and please let us continue to be there for you.

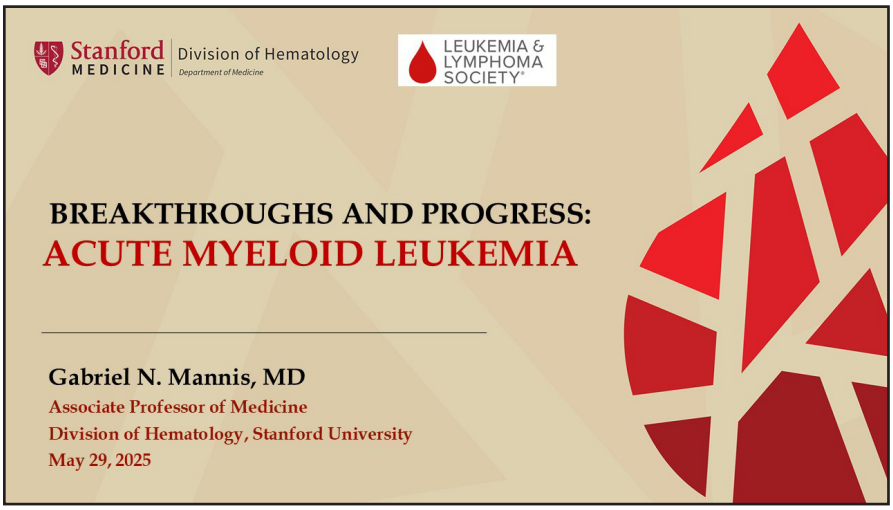
Support for this program is provided by Astellas Pharma US, Inc. and Genentech, a member of the Roche Group.

It's now my pleasure to introduce Dr. Gabriel Mannis, associate professor in the Division of Hematology at the Stanford Cancer Institute in Stanford, CA. Dr. Mannis, I'm privileged to turn the program over to you.

Slide 3: FACULTY

Dr. Gabriel Mannis:

Wonderful. Thank you, Lizette. It's really a thrill for me to be here. In my 10-plus years treating patients with AML, there have been countless patients of mine who have benefited from the services of LLS. Whenever LLS asks me to participate in anything they're doing, I jump at the chance to give back. Thank you all for being here.

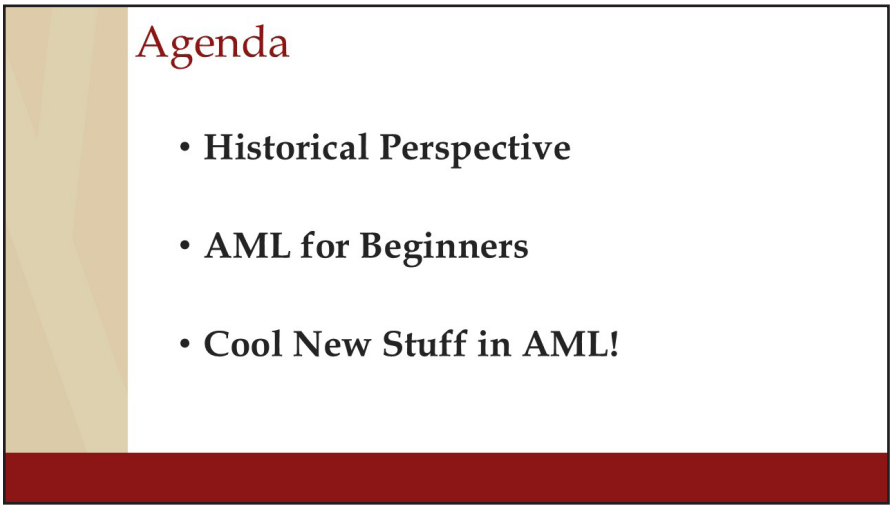


Slide 4: BREAKTHROUGHS AND PROGRESS: ACUTE MYELOID LEUKEMIA

I hope that this is informative or at least entertaining for all of you. Again, my name's Gabe Mannis. I'm here at Stanford and I focus almost exclusively on advancing patient care for patients with AML.

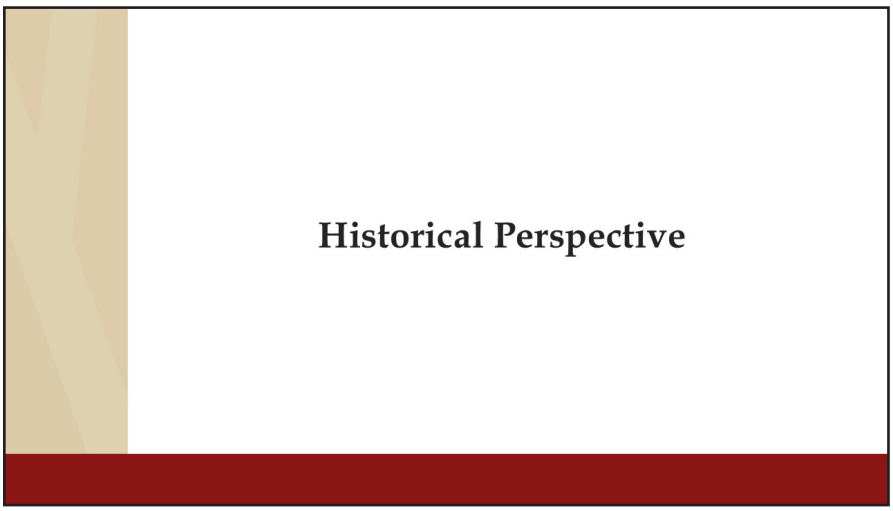
Slide 5: Disclosures

Here are my disclosures. I do sit on scientific advisory committees for several companies and receive research funding to run clinical trials to develop new drugs, but I promise this presentation will be free of any bias.



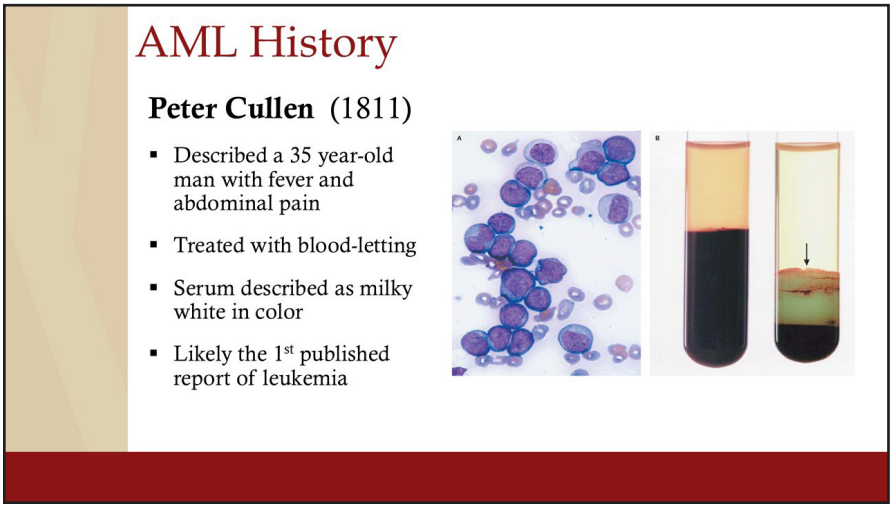
Slide 6: Agenda

Here is a brief agenda. I know that there are people listening to this who are at all stages of dealing with their AML. Some have been very recently diagnosed, maybe haven't even begun treatment yet, whereas some may have been dealing with AML for several years now. While I'll start with a brief historical perspective, I'll spend the first half of the talk going over a review of AML for people that are just getting familiar with it. Then, the last half is for the AML veterans, exciting new stuff that's happening in the field.



Slide 7: Historical Perspective

With that, I'll start with a brief historical perspective.



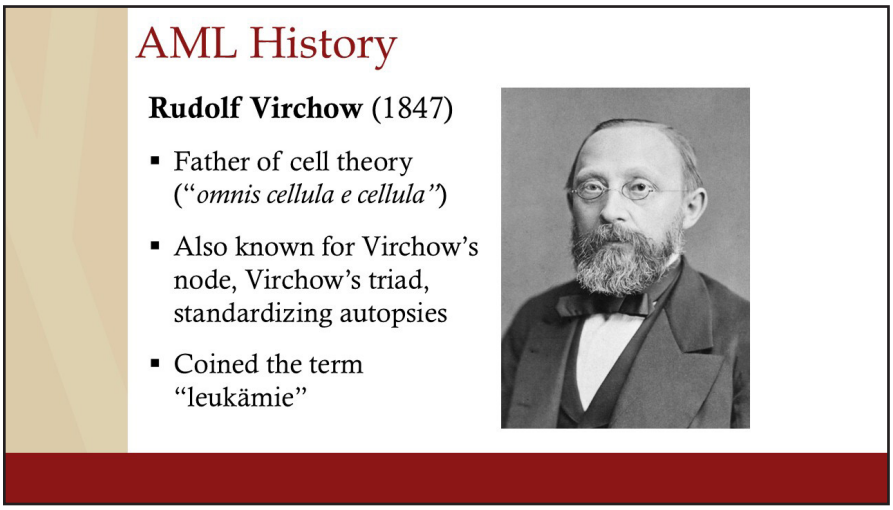
Slide 8: AML History – Peter Cullen (1811)

Probably the first described case of AML in history was back in the 1800s. Peter Cullen described a 35-year-old man with fever and abdominal pain. As most conditions were treated back in that time, this patient was treated with bloodletting.

As they took the blood out, the liquid that came out was described as milky white in color, very much like a Pepto-Bismol®-like color. We think this was likely the first published report of leukemia. Thinking about that, on the left here you see what leukemia cells look like. They're these big cells. The nucleus, or the dark purple part, is much bigger than it should be. Those are what blasts look like, for those of you who are familiar with that term.

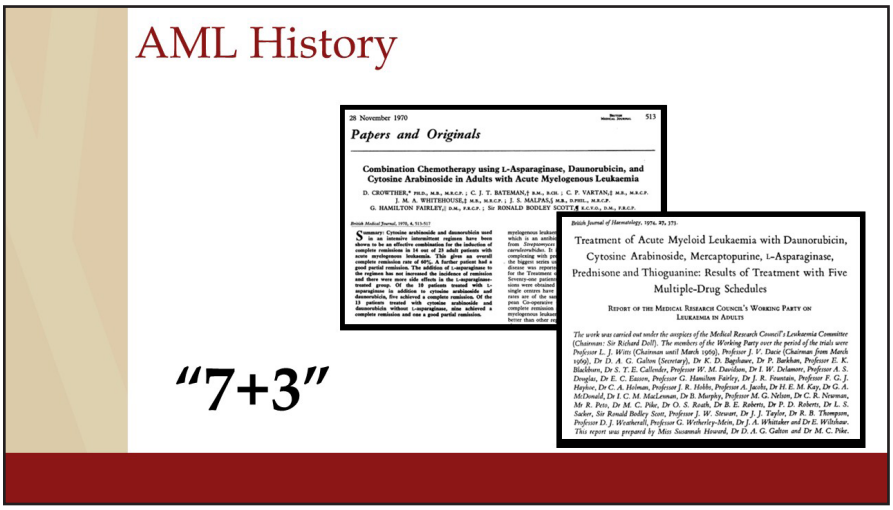
When you look at these test tubes (the left-hand test tube), when you spin down blood in a centrifuge, the left is what it should look like, where you see the red blood cells is this dark part and there's this thin layer. You may not even be able to see it between the dark part and the clear liquid above. There's a thin layer of white blood cells.

Whereas in a patient with leukemia who has a really high white blood cell count, when you spin down the blood, there's this big layer of white blood cells. That's what causes the blood to turn pinkish when the white blood cell count is very high.



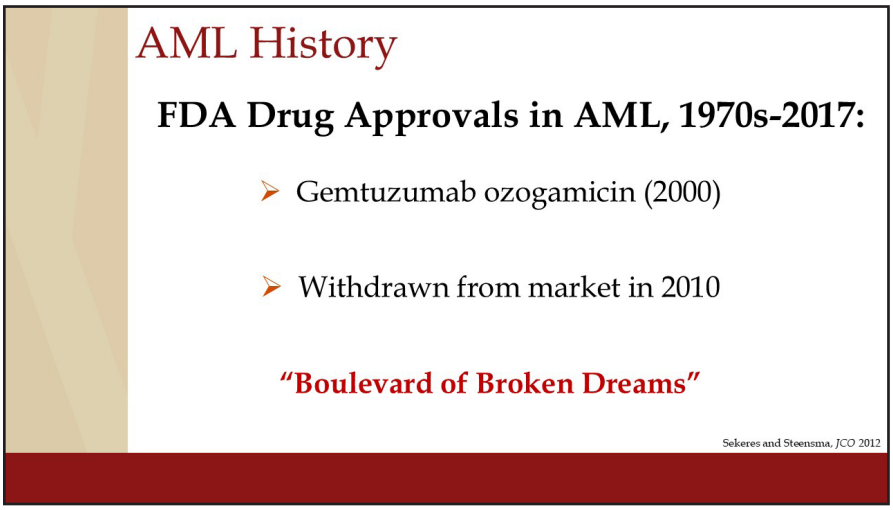
Slide 9: AML History – Rudolf Virchow (1847)

Rudolf Virchow, who's very famous in the medical field, much more famous for other things like cell theory, which says that every cell comes from another cell, but also his name has been attributed to all sorts of different things, he was probably the first person to coin the term in 1847.



Slide 10: AML History – 7+3

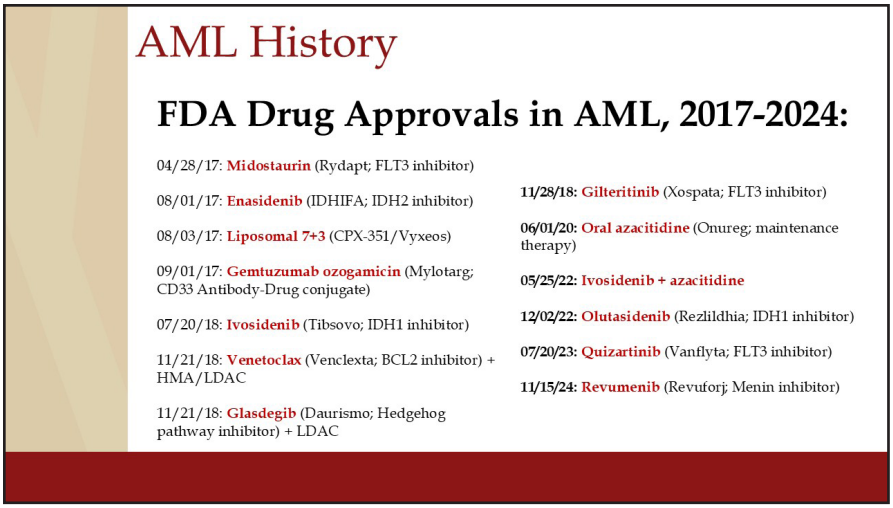
Again, looking at the history, really the first effective treatment for leukemia dates back to the 1970s. Here are some of the original papers that describe essentially what has become and what has endured as one of our standard treatments, which is this 7+3, which is 7 days of a chemotherapy called cytarabine and 3 days of a type of chemotherapy, an anthracycline, typically either doxorubicin or idarubicin. These were the first papers that really showed that was effective in AML.



Slide 11: AML History – FDA Drug Approvals in AML, 1970s-2017

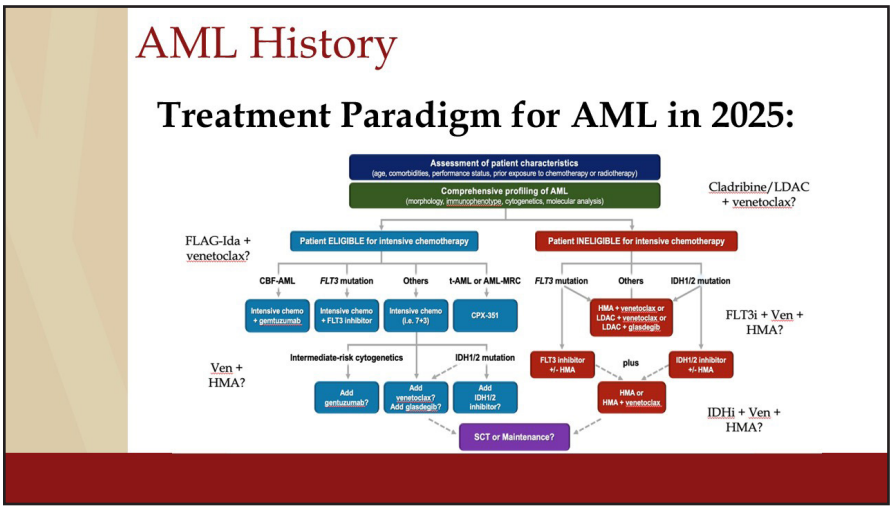
From the 1970s up until 2017, sadly there was only 1 drug approved in AML and that was this drug, gemtuzumab ozogamicin. This later was taken off of the market because of concerns about safety. When it was initially approved, it was approved at a high dose given differently than the way we give it now.

AML historically was one of the most difficult spaces to get drugs approved and find new things to treat patients. It was dubbed by many as the Boulevard of Broken Dreams. When I was in my training as a fellow, this is one of the things that drew me to the field, is that it seemed like all of these other cancer fields were making so much progress and yet in AML, we had been left behind.



Slide 12: AML History – FDA Drug Approvals in AML, 2017-2024

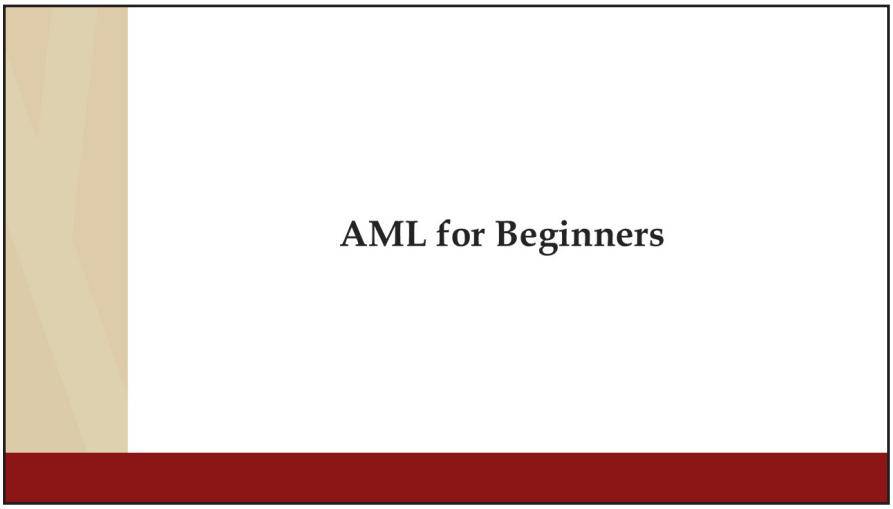
I started practicing right around this time and between 2017 and 2024, we have now had 13 new drugs or drug combinations approved, most recently in November of 2024.



Slide 13: AML History – Treatment Paradigm for AML in 2025

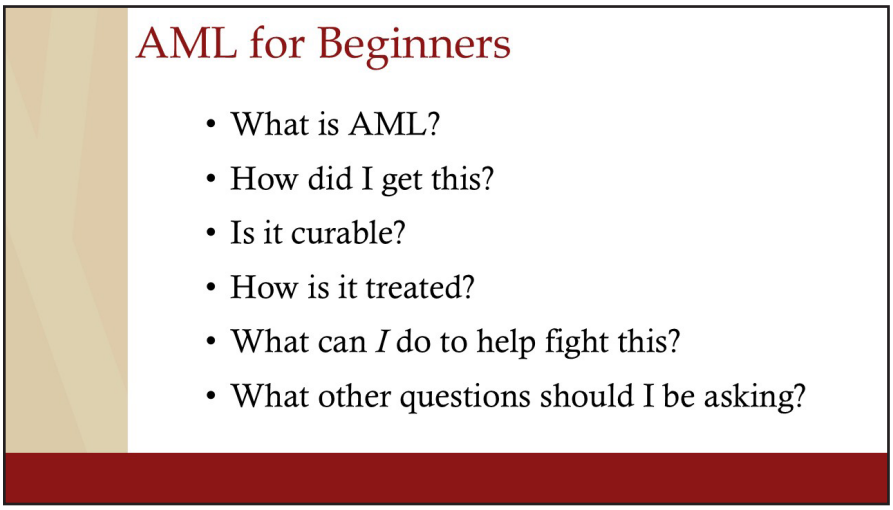
Really, we've gone from having to think about just 7+3 or just a drug like azacitidine to really a dizzying array of possibilities for treatment. Things have really become much more fun for me in practice, but more importantly, outcomes have become much better for patients, both in terms of how effective these treatments are and how safe they are.

It's never a good time to get AML, but there's never been a better time, I suppose, than now.



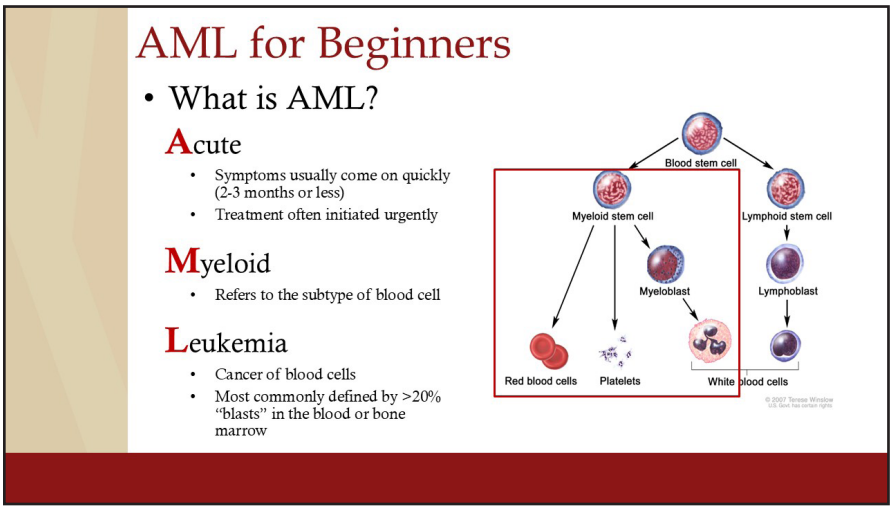
Slide 14: AML for Beginners

With that as a background, I will launch into the basics of AML. I expect for many of you, this will be a review. I think many of my patients are logged on, so hopefully they know all this stuff. Hopefully, I have taught them this through our visits and through the time in the hospital.



Slide 15: AML for Beginners

The things I will try to cover: What is AML? How did I get this? Is it curable? How is it treated? What can I do to help fight this? and, What other questions should I be asking? These are the most common things that we tend to cover in our initial meetings.



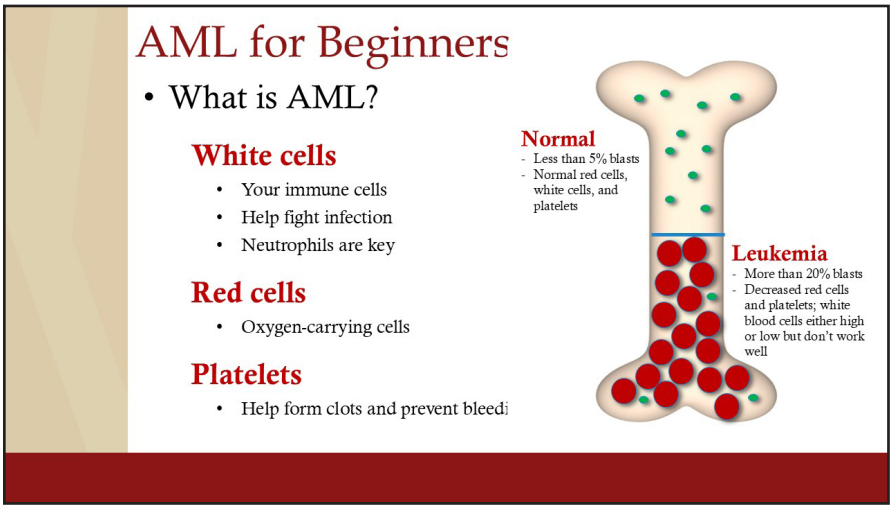
Slide 16: What is AML?

What is AML? The A stands for acute. Acute means the symptoms usually come on quickly, most people are feeling fine and then over 2 or 3 months they start to feel unwell. Oftentimes, they go from 2 months ago feeling perfectly fine to being in the hospital starting chemotherapy immediately.

The M stands for myeloid. Myeloid refers to the subtype of the blood cell that has cancer. Just a basic biology lesson, in the bone marrow there's a blood stem cell and the first important division that happens in those stem cells can either make a myeloid stem cell or a lymphoid stem cell.

If you go down the lymphoid pathway, you get your lymphocytes, and when people have a lymphoma or multiple myeloma, those are cancers on the lymphoid side. AML happens on the myeloid side. In my opinion, the myeloid side is the much more important side because from the myeloid side you get your red blood cells, you get your platelets, and you get your neutrophils. Those are probably the 3 most important types of blood cells.

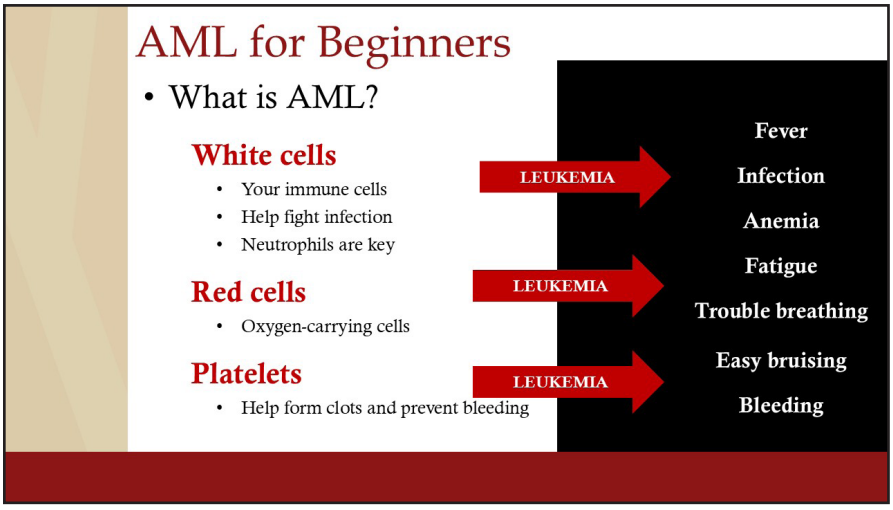
Leukemia, of course, just means it's a cancer of blood cells, specifically a cancer of the white blood cells. We typically, classically refer to leukemia as greater than 20% blasts or leukemia cells, either in the blood or the bone marrow.



Slide 17: What is AML?

I talked about the 3 most important types of cells. The white blood cells are your immune cells, they help fight infection. Of the white blood cells, the most important type of white blood cell is the neutrophil. Those are the cells that help protect you against life-threatening bacterial and fungal infections. The red blood cells carry your oxygen, and the platelets help you form blood clots and prevent bleeding.

In my cartoon bone here, on the top, you have what a normal bone marrow would look like with less than 5% blasts and normal red blood cell, white cell, and platelet numbers.

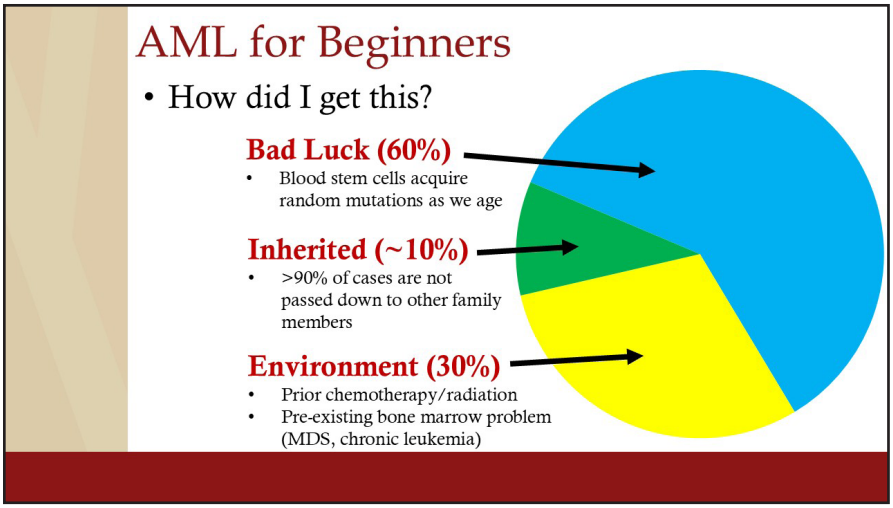


Slide 18: What is AML?

With leukemia, these cancerous cells fill up the bone marrow and essentially crowd out the healthy stuff. You get to more than 20% blasts in the bone marrow and as these leukemia cells grow, what happens with most patients is that their red blood cells go down, their platelets go down, and their white blood cells either go down, which is actually more common, or they start to spill out into the blood, and people can present with really high white blood cell counts.

When that happens, when the white cells don't work, people often get fevers or infections. That's one of the most common

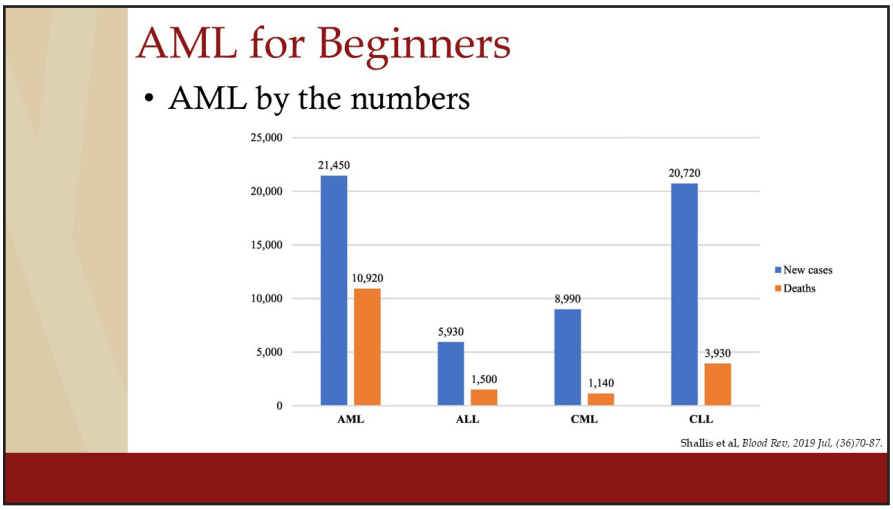
ways people are diagnosed with AML. Maybe the second or tied for first most common is when people have low red blood cells. This is anemia. They develop fatigue, maybe shortness of breath when they're climbing upstairs. Then, when the platelets are low, this results in easy bruising and bleeding.



Slide 19: How did I get this?

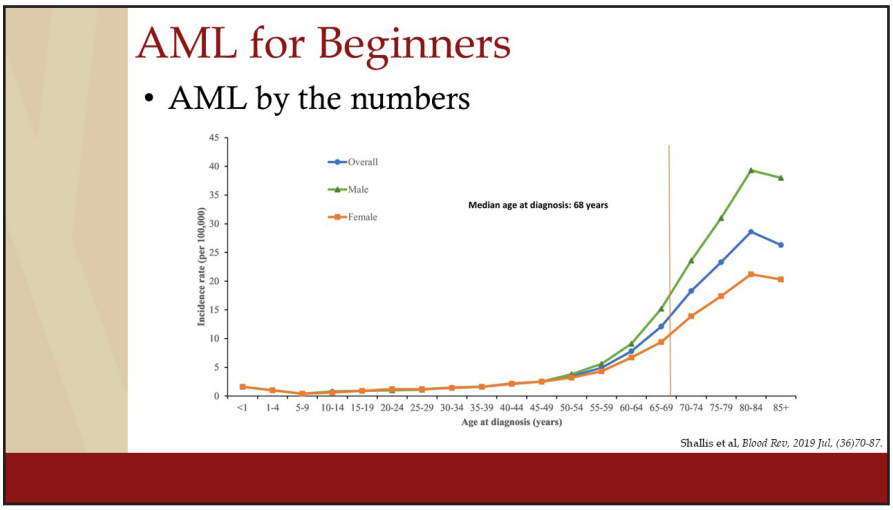
How does AML happen? How do people get it? Well, the reality is that we say 60% of the time we think it's just bad luck. The longer you live, the more opportunity there is for mistakes to happen when your cells are dividing, so the older you get, the more mutations you acquire in your bone marrow. If you get just the right mutations and just the right genes, that can trigger this cancerous process.

About a third of patients, we can point a finger at what probably caused their leukemia, and these are things like prior chemotherapy or radiation for other cancers, or if they have a pre-existing bone marrow problem, most commonly something called MDS or myelodysplastic syndrome. Over time, this can evolve into acute leukemia. Then, just in the last 5 to 10 years, we've learned that actually there are some forms of AML that are passed down in family. This is relatively rare, but generally a few have a first-degree relative who also has leukemia, or if you have a family member who had a cancer at a young age, those may be some warning signs that the AML could actually be something that is genetic instead of acquired.



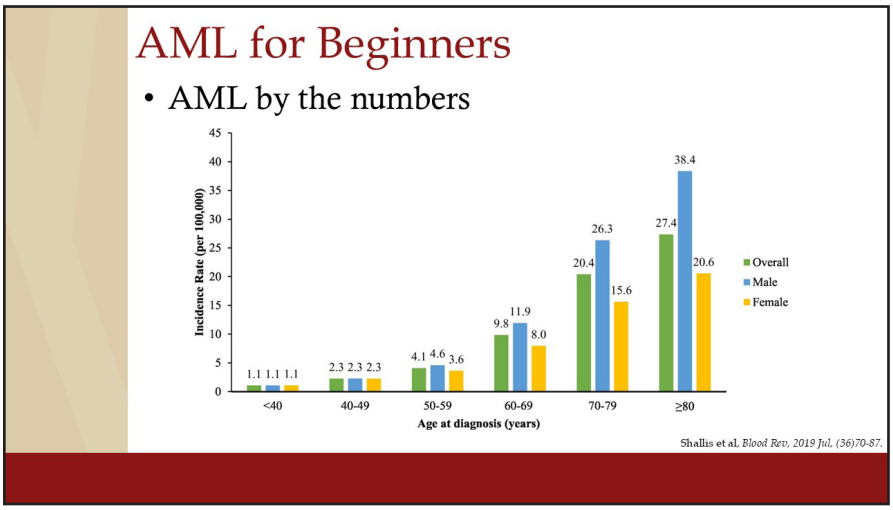
Slide 20: AML by the numbers

By the numbers, as Lizette mentioned at the beginning, AML is really neck and neck with CLL (chronic lymphocytic leukemia) as the most common leukemia in adults. It's by far the most common acute leukemia in adults. ALL or acute lymphoblastic leukemia, is much more common in children.



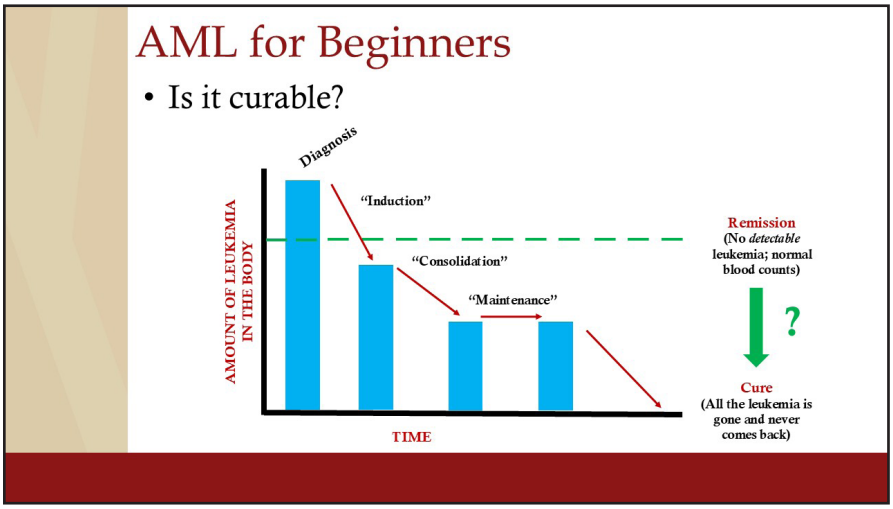
Slide 21: AML by the numbers

It is, as I said, a disease typically of older people. The median age at diagnosis is right around 70, but there are people who get AML as children and then as young adults. As you get older, it tends to be more common in men.



Slide 22: AML by the numbers

On this next slide, I just wanted to point out that if you focus on the green bars, when you add up the percentage of people who get this diagnosis over the age of 60, it ends up being more than half of people. In general, more than half of people are over the age of 65 at the time of diagnosis, which really limits the kinds of treatments that we can use because as you get older, giving intensive chemotherapy becomes much more difficult.



Slide 23: Is it curable?

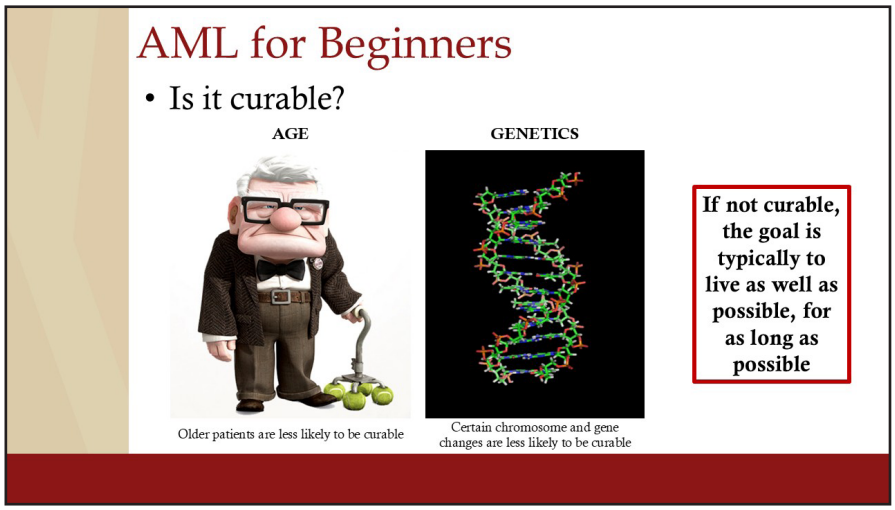
Is it curable? Well, the short answer is yes for some people. This is a graph I like to show my patients, which looks at the amount of leukemia in the body over time. When people are diagnosed, we say hopefully this is the most amount of leukemia you'll ever have in your body. The goal with the first treatment, whatever that is, is to knock down the amount of leukemia from here down to here.

There's this imaginary line that I call the remission line, which means no detectable leukemia. When we do a bone marrow biopsy, we don't see any leukemia. The blood counts are normal, but it doesn't mean the leukemia's gone, it's just a matter of how good the tests are that we have to detect every last leukemia cell. We continue to treat the leukemia even once it's in remission because we know it's just hiding beneath the surface.

We often call the first treatment induction, and then subsequent rounds, we call consolidation. We may refer to them as maintenance, depending on the goal of treatment, but for some patients the goal is cure, meaning there's no

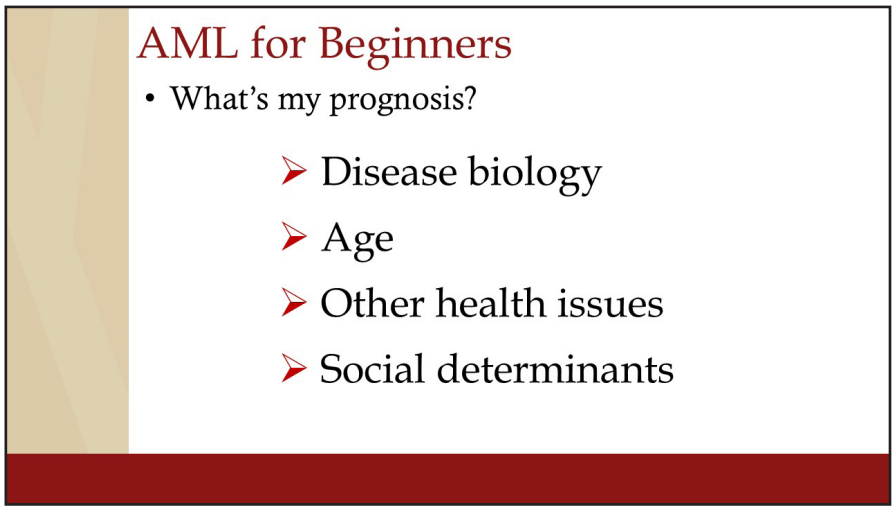
leukemia left in the body and the leukemia never comes back. Unfortunately, we don't have a test for this, so we can't do a test to say, "Yes, you're cured."

Oftentimes, it's just the test of time that if you make it a certain number of years without the leukemia coming back, we will say, "You are likely cured, probably cured." Some people may say you're cured, but it's not something we can really ever say for certain. We certainly do cure many patients with AML.



Slide 24: Is it curable?

What impacts how curable it is? Well unfortunately, patients who are older tend to be less likely to be curable. There are certain genetic changes in the leukemia cells that make the leukemia less likely to be curable. For many patients whose leukemia we don't think is curable, the goal is to get the leukemia under control, keep it under control, and keep people feeling well for as long as possible.



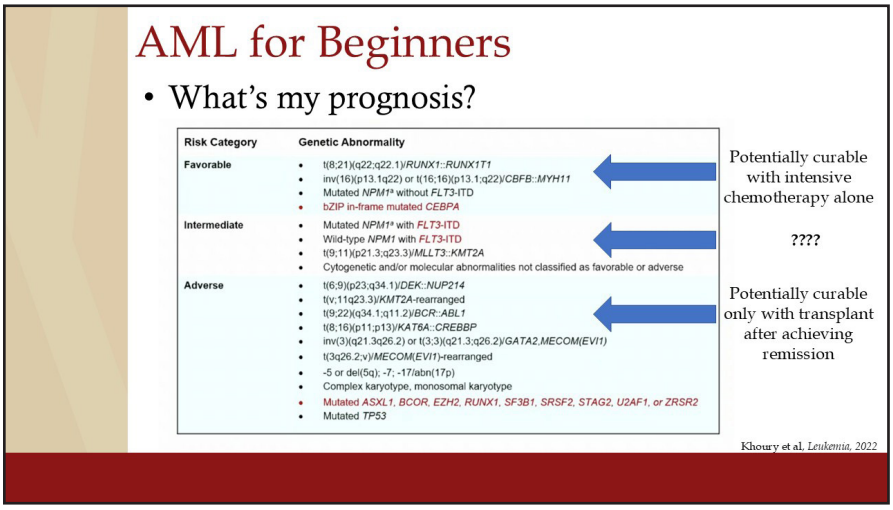
Slide 25: What's my prognosis?

The prognosis question is one, of course, I think every patient asks or if they don't ask, it's on their minds. There are several factors that go into it.

Maybe the most important are the characteristics of the leukemia cells themselves. So, looking at the chromosomes

and the gene mutations, the age is important, and it, in part goes along with the disease biology that, as you get older, you're more likely to have some of the higher risk gene mutations and chromosome changes.

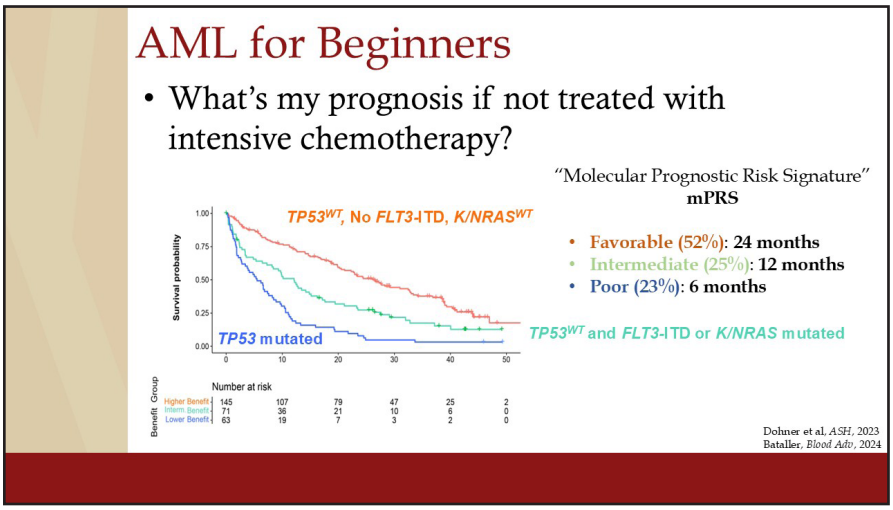
It's important to factor in your other health issues because that will impact how feasible it is to give the treatment, whether a bone marrow transplant may be possible, and then sadly, we know that there are social determinants that impact things in terms of socioeconomic status, race. Unfortunately, these things still contribute to how well some patients may do.



Slide 26: What's my prognosis?

For patients under the age of 60, who are able to receive intensive chemotherapy, historically we've divided patients into good, intermediate, and bad. Again, these are based on chromosome and gene changes. The main implication of this is that if you have one of the 4 good risk things, we think that we can cure a good percentage of patients with chemotherapy alone and avoid all of the risks and impositions of a bone marrow transplant.

If you have one of the bad risk things, we really think those patients benefit from a transplant once their leukemia is in remission. We generally will work on getting the patient into remission, and at the same time, trying to get them set up for a transplant. Most patients, 60% or so under the age of 60, will fall into the intermediate-risk category. Right now, there are places that recommend a transplant. There are places that don't, but this is certainly an area of study in the field to try and pick out which patients we can avoid bone marrow transplants in.

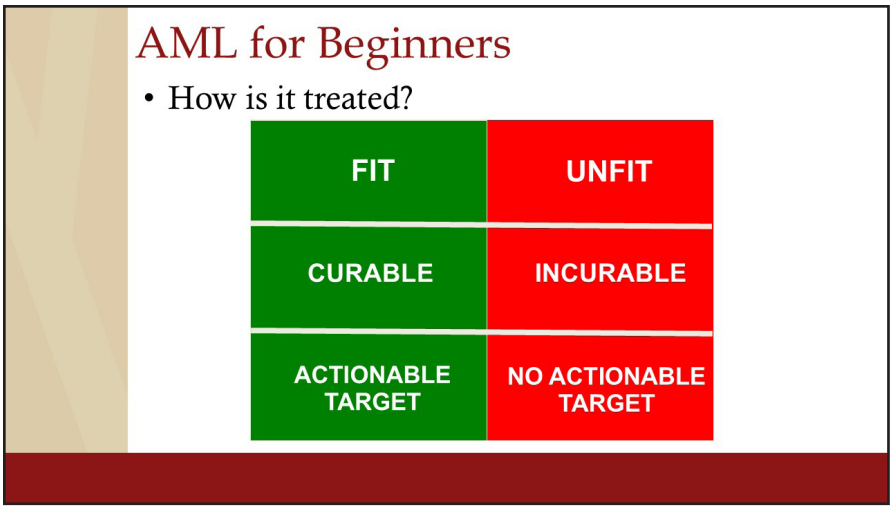


Slide 27: What's my prognosis if not treated with intensive chemotherapy?

Many patients now are receiving the combination of venetoclax (VENCLEXTA®) plus either azacitidine (VIDAZA) or decitabine (DACOGEN®), which we'll talk about. Very recently, there has been an improved prognostic scoring system for these patients.

The system I just showed you with that complicated table doesn't really apply to patients who are getting venetoclax-based treatment. We've pared it down to a 3 or 4-gene signature. Based on those 3 or 4 genes, we can generally predict how long patients can stay on treatment in remission. These are medians, so it means that half the patients will live longer, half shorter. Every patient is different.

There are a lot of other features that impact these numbers. This is just to give people a ballpark sense. If you have a TP53 mutation, these patients do the worst. This is still one of the biggest unmet needs in our field. It's figuring out how best to treat these patients. If you have this FLT3 or one of these RAS mutations, you're in the intermediate group. Fortunately, most patients are in the good-risk group and we think can survive a median of 2 years on venetoclax-based therapy.

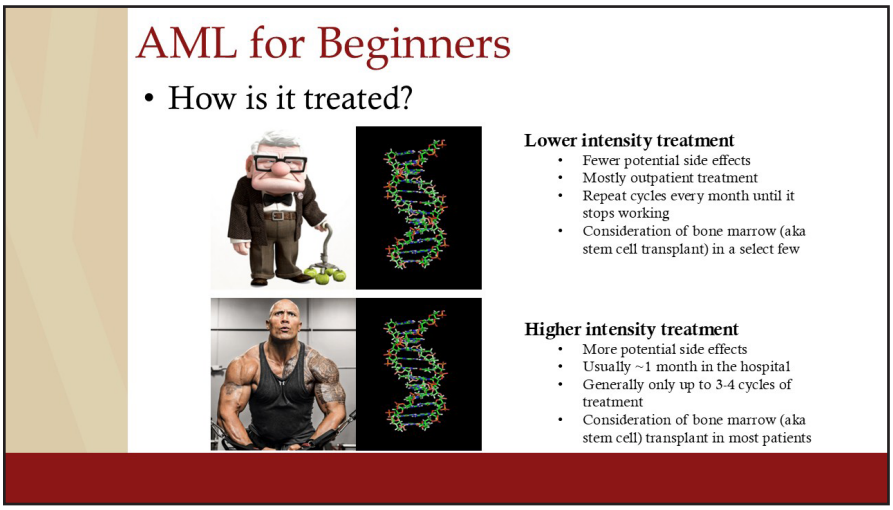


Slide 28: How is it treated?

Whenever I meet a patient, whether it's in the hospital or in the clinic, I think about 3 basic things. Number one, is the patient fit or unfit? That could be a whole talk in itself, but it has to do with both the age, the health problems, the

disease biology.

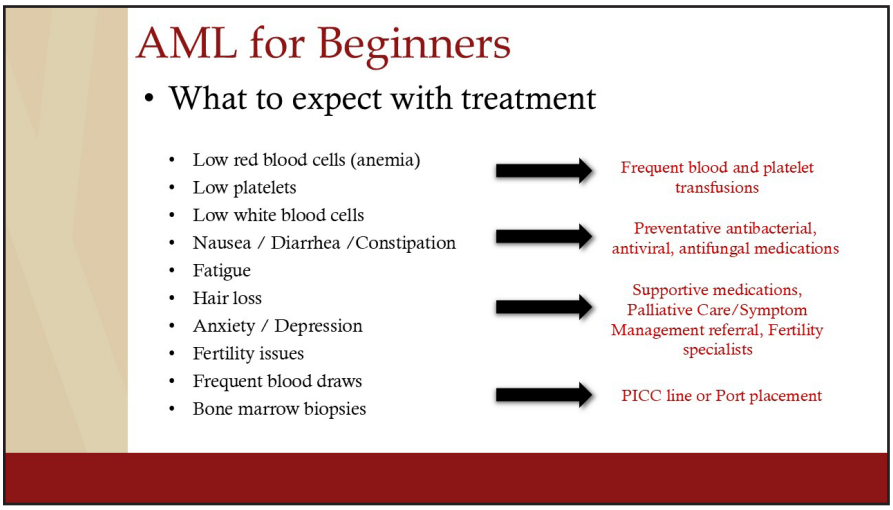
Maybe most important is the goal of treatment to cure the leukemia or is the goal to just prolong life, improve quality of life? That's a really important distinction to make when choosing initial therapy. Then the last thing there was, is there something that we can target with one of the drugs that we have available or are we using treatment that would be suitable for all kinds of leukemia?



Slide 29: How is it treated?

In general, and this is very general, when we think about fit and unfit, there's a lower intensity treatment, generally fewer side effects, usually mostly outpatient. It's continuous cycles of treatment, month after month. For select patients, they may be eligible for a transplant when they're in remission. For most patients receiving lower intensity treatment, at least as of 2025 (this may change in 2026), but for most patients receiving lower intensity treatment, bone marrow transplant is usually not part of the conversation.

For those patients who are fit, historically going back to the 1970s, the treatment has been in the hospital, traditional chemotherapy, lots of side effects, but it's generally time limited. Three to 4 cycles of chemotherapy and then stop or move on to bone marrow transplant as soon as the transplant is ready.



Slide 30: What to expect with treatment

What to expect: Low blood counts, gastrointestinal side effects, fatigue, hair loss. Certainly, mental health issues are important to think about. For young patients of reproductive age, fertility issues, and then blood draws and bone marrow biopsies. Patients end up getting frequent transfusions. We start them on preventative medications so that they don't get infections. We often try and integrate a lot of support. Palliative care, which are doctors that specialize in symptom management, are a key part of AML treatment here at Stanford. We have fertility specialists and then we often will place what's called a PICC line or a port to help facilitate blood draws.

Slide 31: What can I do on my own to maximize my chances of success during treatment?

The last part of the beginner talk is, "What can I do to maximize my chances of success?" I always encourage patients to stay active, even if it's just taking a short walk every day. It's important to maintain your strength going through this treatment because it is hard and it's a long process.

Slide 32: What can I do on my own to maximize my chances of success during treatment?

Maintaining your muscle mass, maintaining your nutrition as much as possible.

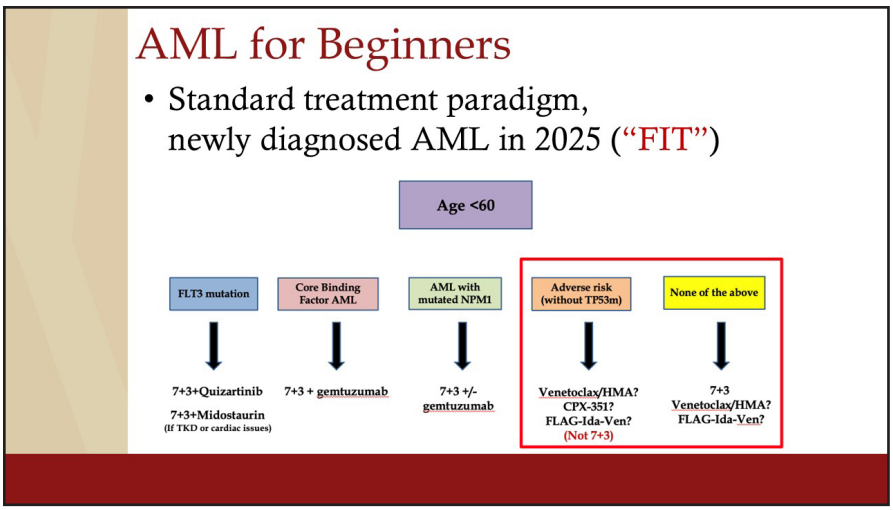
Slide 33: What can I do on my own to maximize my chances of success during treatment?

And then, with the caveat that I am married to a psychotherapist, so I'm biased, but I think working on the mental aspect is really important. Staying positive, staying focused, taking stock of what your priorities are, what's important to you, these things are really important to help get you through the treatment.

Slide 34: What else should I be asking?

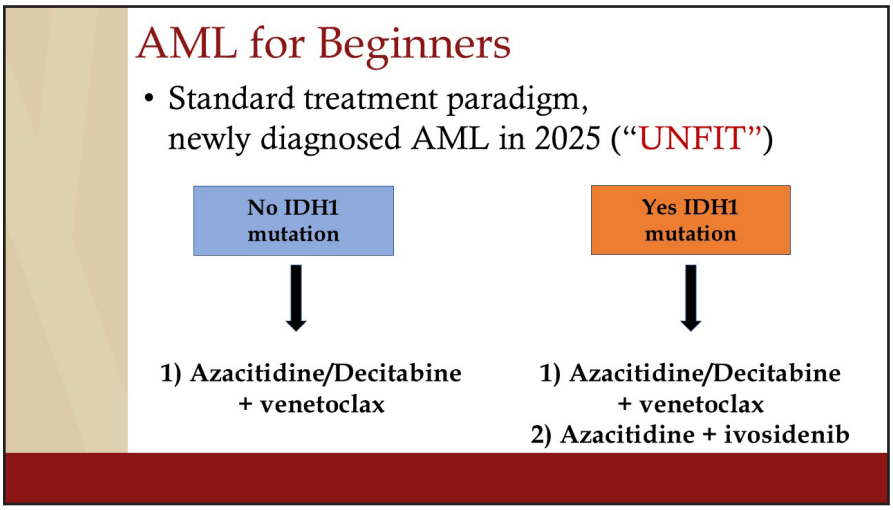
Other things to ask, especially early on in the treatment or if things aren't going well, or if the leukemia comes back at some point, what are the possibilities? What other treatments are out there? Do I have backup options if this current treatment doesn't work? I think a lot of patients are afraid to ask their doctor for a second opinion. I will say, certainly at academic institutions, we encourage that.

I often learn from my colleagues. I think, for doctors who don't see a lot of AML, they often are very grateful to have someone who specializes in AML help them out. I would not be afraid to ask for a second opinion at a place where there's a lot of AML expertise. Then of course, are there clinical trials available that I might be eligible for?



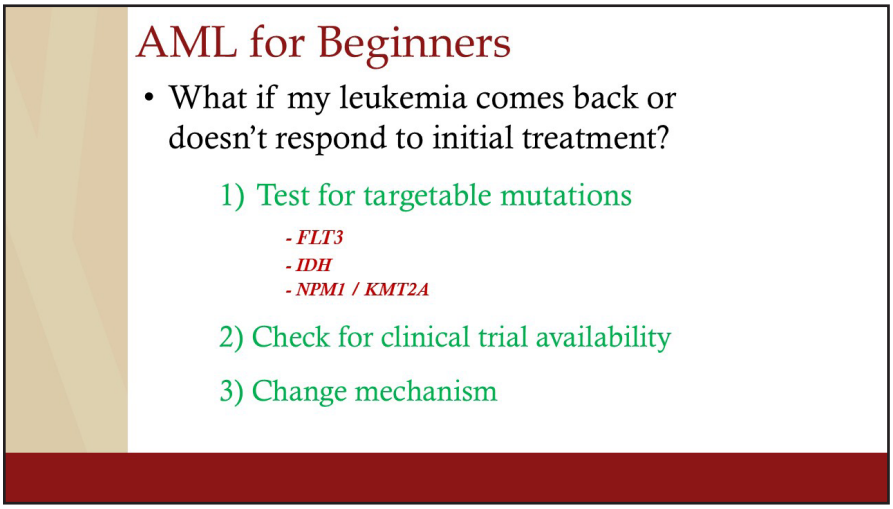
Slide 35: Standard treatment paradigm, newly diagnosed AML in 2025 ("FIT")

This I don't want to focus on but this is what I consider my algorithm for patients under the age of 60 who are fit for intensive chemotherapy in 2025. This changes almost every year. Don't hold me to this, but I just wanted to include this, so you had this as a reference.



Slide 36: Standard treatment paradigm, newly diagnosed AML in 2025 ("UNFIT")

The paradigm is much simpler these days for patients over the age of 75 or for those who can't receive intensive chemotherapy for any reason. Essentially, it's the combination of venetoclax plus either azacitidine or decitabine. For those patients that happen to have an IDH1 mutation, there's also the option of combining an IDH1 inhibitor, ivosidenib with azacitidine.



Slide 37: What if my leukemia comes back or doesn't respond to initial treatment?

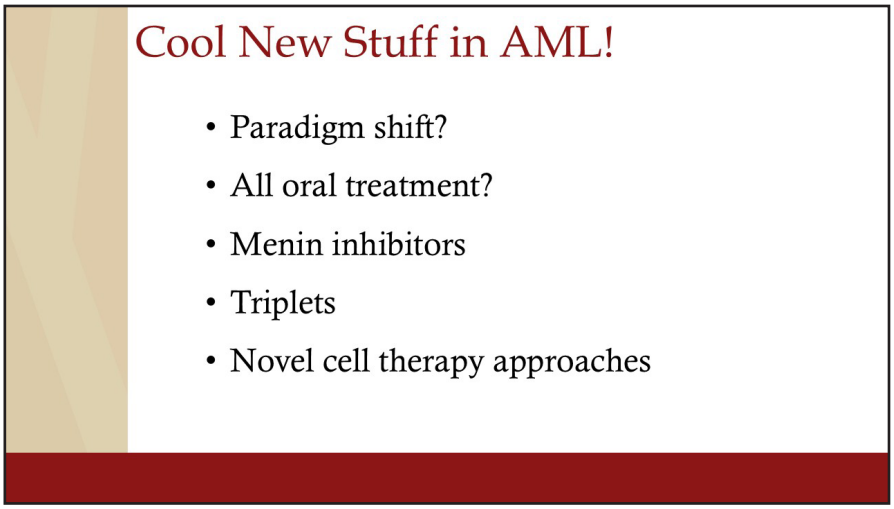
What if leukemia relapses at some point, or it doesn't respond to initial treatment? Importantly, and I think a lot of doctors that don't see a lot of AML may miss this, but it's important to retest for mutations that may be targetable, whether or not you had them initially. Those include FLT3, IDH, and more recently NPM1 or KMT2A. Clinical trials are always preferred in this setting.

Then, if none of those are available, thinking about changing the way that you're treating the leukemia. If you initially got traditional chemotherapy, my preference and what I usually do is to switch to the newer venetoclax, more targeted treatment, and vice versa. If you get venetoclax and azacitidine first, maybe try more traditional chemotherapy, trying to find something that the leukemia is not resistant to.

Obviously, this is very nuanced. I think any time leukemia relapses or does not respond to initial treatment, this is a scenario in which it's really important to seek out a second opinion and make sure that someone from a specialized center is helping to guide the care.

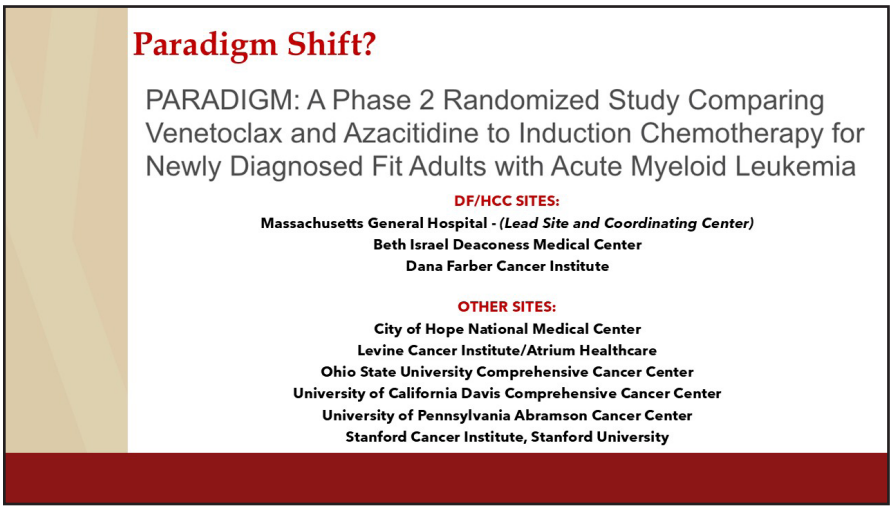
Slide 38: Cool New Stuff in AML!

I want to leave plenty of time for questions in the last 10 minutes, so I just want to talk about what I think are the coolest new things immediately on the horizon in AML.



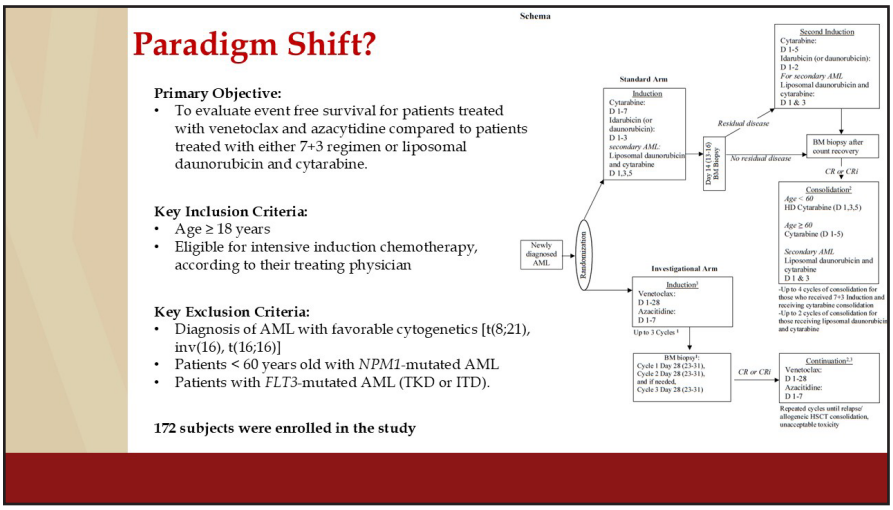
Slide 39: Cool New Stuff in AML!

There's a lot out there, so I had to pick just the top 3 or 4. We'll talk about a potential paradigm shift that I hinted at, getting rid of intravenous chemotherapy for AML, this new class of drugs called menin inhibitors, triplets, and then people always are interested in cell therapy approaches, so I'll spend a minute on that.



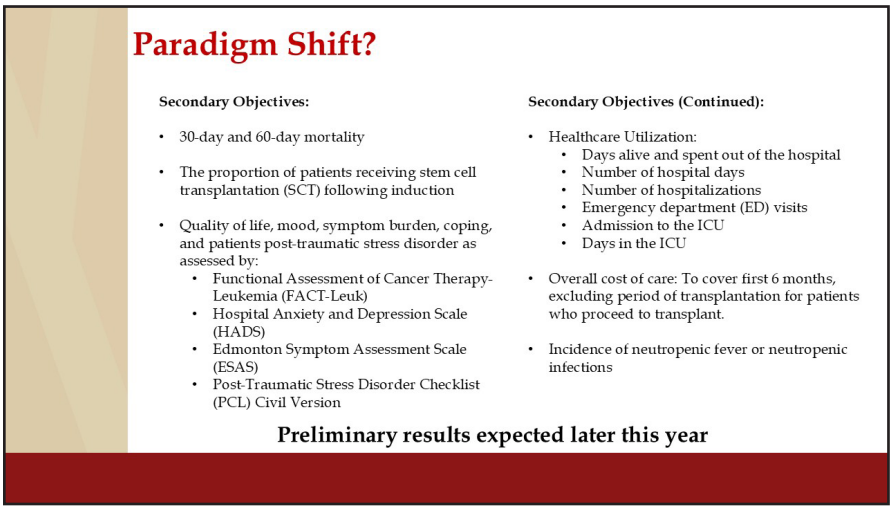
Slide 40: Paradigm Shift?

One of the most important studies in AML of late that was just completed, we participated here at Stanford, was a study looking into young fit adults, people who are eligible to get 7+3 type chemotherapy. Do they do better with 7+3 or what if we treated them with the same treatment we're giving to patients who are 75 and older?



Slide 41: Paradigm Shift?

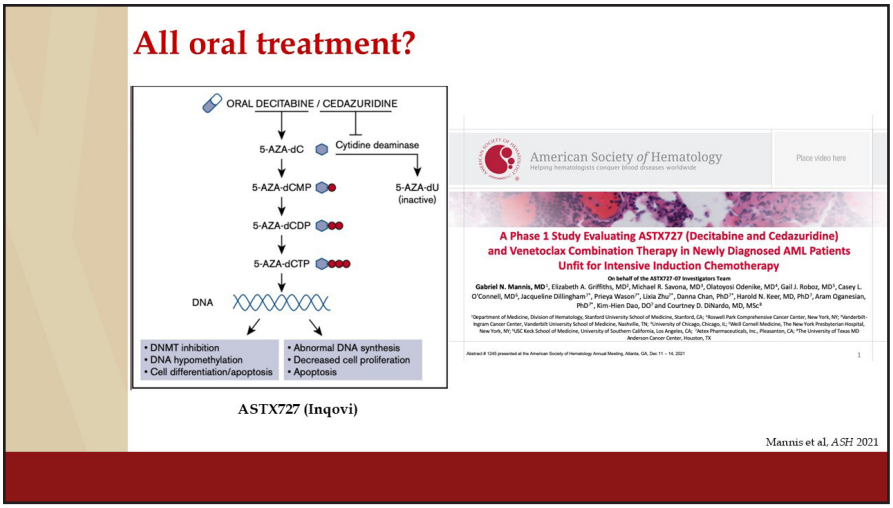
Essentially, this is a randomized study, so half the patients get 7+3, half the patients get venetoclax and azacitidine. You had to be eligible for intensive chemotherapy. If you had one of the favorable risk leukemias, you were not eligible for this study because we know that we can cure many of those people with intensive chemotherapy, so we didn't want to randomize them to the lower intensity treatment.



Slide 42: Paradigm Shift?

172 patients were enrolled in this study. This study completed accrual earlier this year. Not only are they looking at response rates and survival, but importantly, I think they're looking at a lot of patient-reported outcomes, like side effects, mental health, time in the hospital, cost of care, infectious rates. I expect that the results will be released by the end of this year.

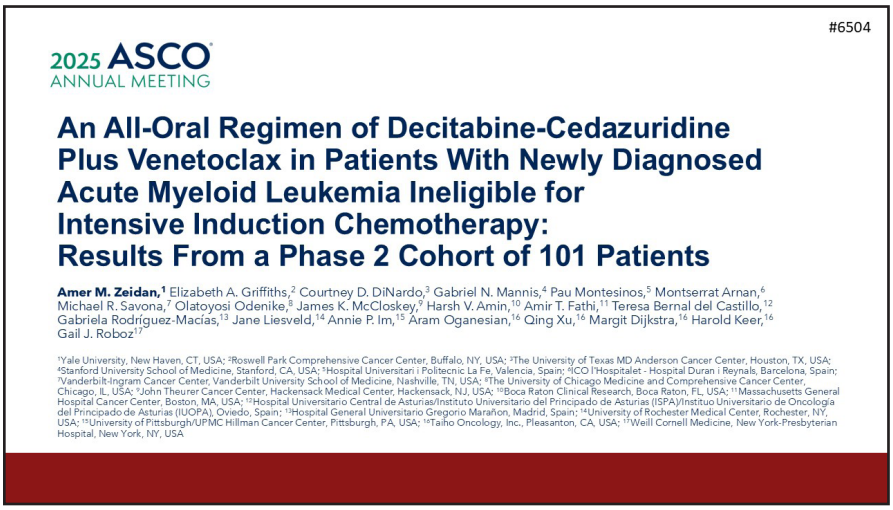
If it shows that there's no difference between the traditional intensive chemotherapy from the 1970s and the more modern chemotherapy that's just been approved in the last 10 years, we could see a huge shift in how we are treating newly diagnosed patients with AML.



Slide 43: All oral treatment?

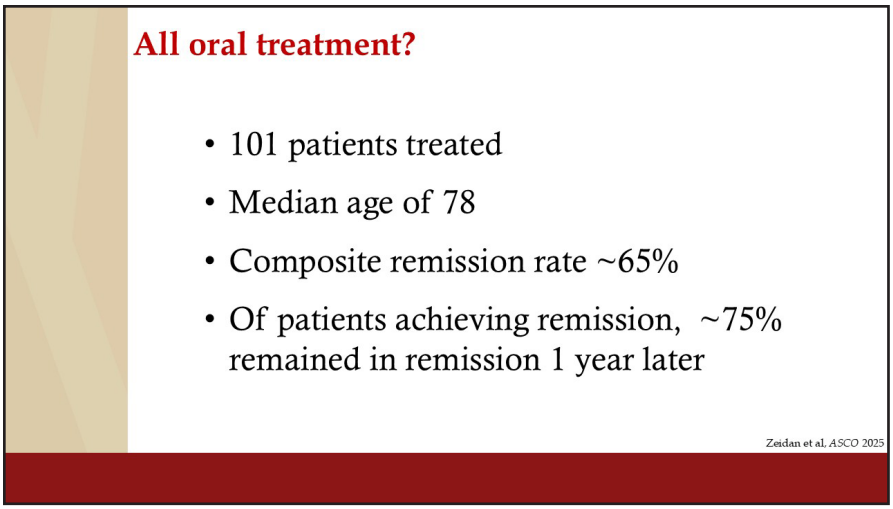
For those patients who are getting azacitidine or decitabine and venetoclax, they know that one of the hassles of this treatment is that month after month they're going into the infusion center 5 days in a row, 7 days in a row, and they do this month after month, potentially for years.

In the last couple of years, an oral formulation of these drugs was developed. It combines decitabine with a drug that helps it be absorbed through the oral route.



Slide 44: An All-Oral Regimen of Decitabine-Cedazuridine Plus Venetoclax in Patients With Newly Diagnosed Acute Myeloid Leukemia Ineligible for Intensive Induction Chemotherapy: Results From a Phase 2 Cohort of 101 Patients

I presented the initial study a couple of years ago and this study has now completed the Phase II portion. This is the only slide I can show you from this presentation because this is being presented on Monday at the big oncology meeting in Chicago, so the slides are still embargoed. I'll get in trouble if I show you the slides, but I can show you the results.

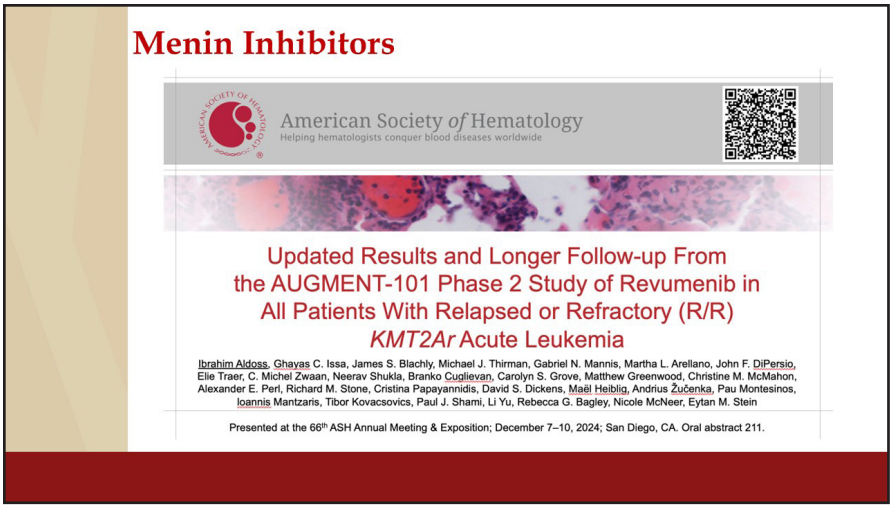


Slide 45: All oral treatment?

101 patients were treated. Median age was 78 and two-thirds of patients went into remission, which is essentially identical to the results with the IV, the intravenous formulation, suggesting that we could treat most patients. Again, more than half of patients are older patients getting this kind of treatment and potentially in the near future, we could treat them with 2 different pills and avoid all these visits to the infusion centers to get their IV treatment.

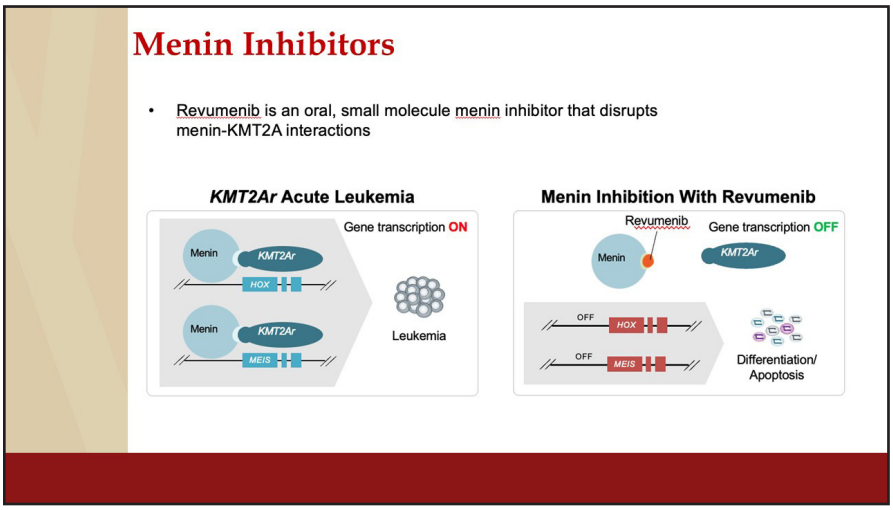
Slide 46: Menin Inhibitors

By far, the most noteworthy, exciting thing in the AML field over the last year or 2 has been the development of a brand new class of drugs called menin inhibitors. The first menin inhibitor was approved in November of 2024.



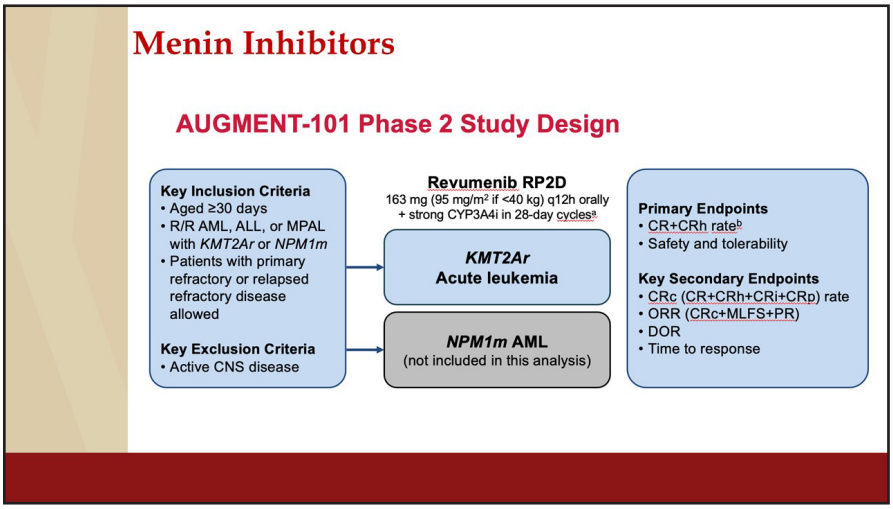
Slide 47: Menin Inhibitors

This drug, revumenib, which was approved to treat relapsed or refractory leukemias with this KMT2A translocation. This was just presented in December.



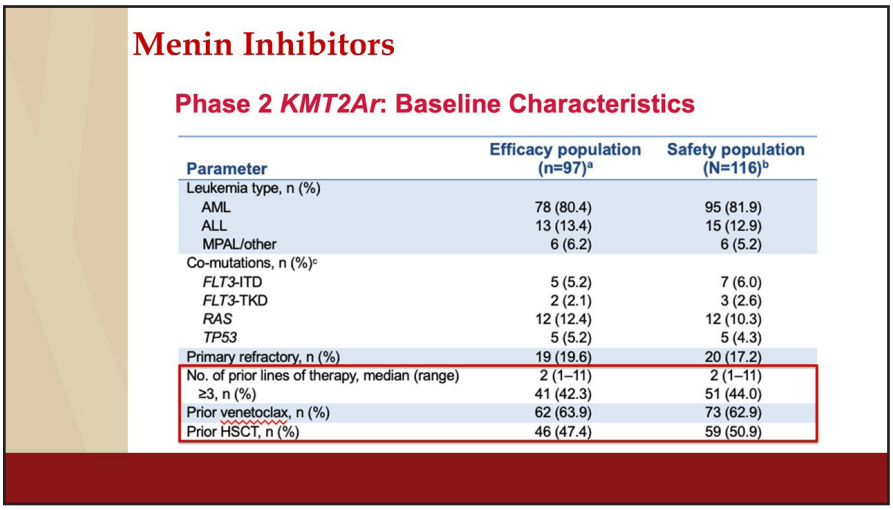
Slide 48: Menin Inhibitors

Revumenib works in a really neat way. Instead of most chemotherapy that directly kills leukemia cells, what these menin inhibitors do is they block this interaction between this protein menin and this KMT2A. When KMT2A and menin can't form this compound, it turns off gene expression. By turning off these 2 genes, it allows the cells to differentiate, really turn into normal, healthy cells.



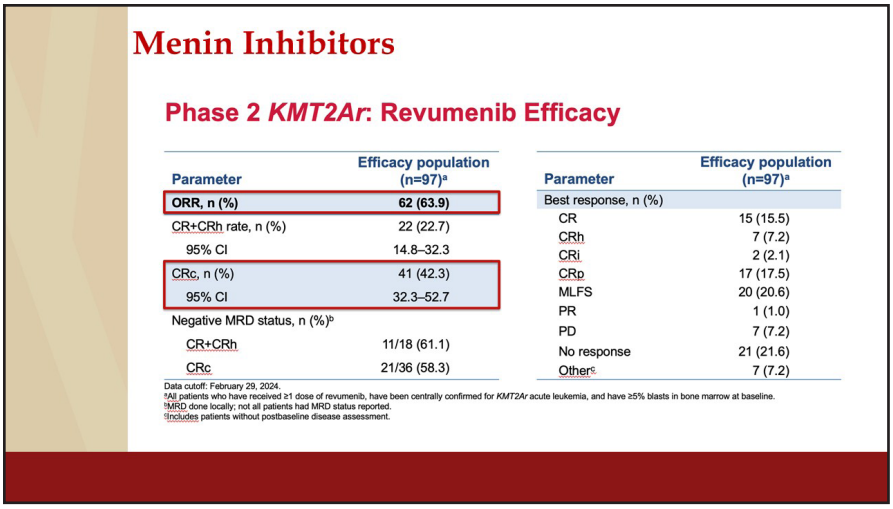
Slide 49: Menin Inhibitors – AUGMENT-101 Phase 2 Study Design

This was the study design. I show this just because there were 2 different cohorts: a cohort for this KMT2A leukemia, which is much less common, but also a cohort for NPM1 leukemia, which is one of the most common types of AML in adults.



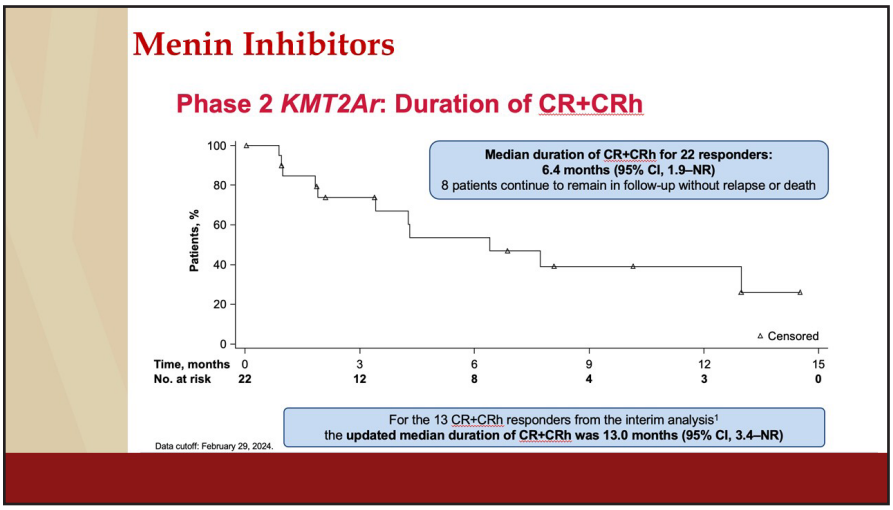
Slide 50: Menin Inhibitors – Phase 2 *KMT2Ar*: Baseline Characteristics

This was just the KMT2A portion, but patients had gotten a lot of therapies, two-thirds had prior venetoclax, and half of patients had already had a prior bone marrow transplant.



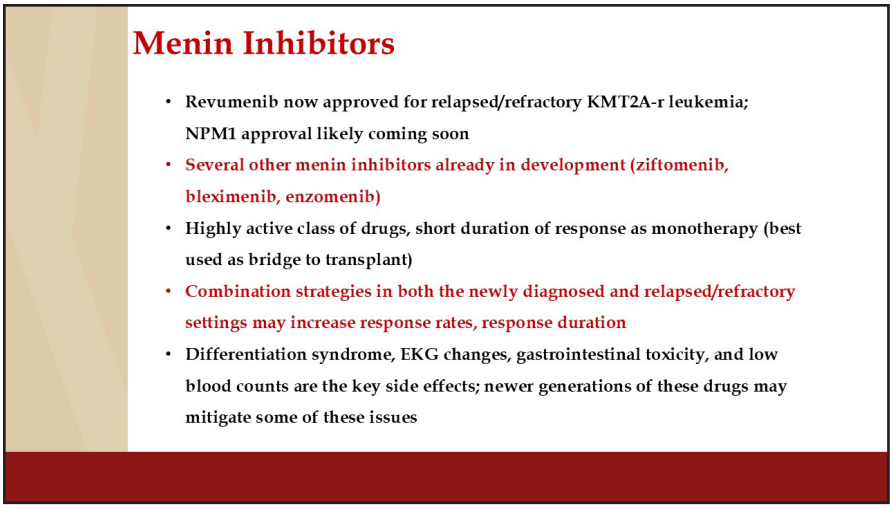
Slide 51: Menin Inhibitors – Phase 2 *KMT2Ar*: Revumenib Efficacy

This is a bad group of patients, really difficult to treat, and in this study over 60% of patients responded to just this pill, with over 40% of patients going into remission.



Slide 52: Menin Inhibitors – Phase 2 *KMT2Ar*: Duration of CR+CRh

Really promising, really exciting. This led to the approval. Unfortunately, with just the pill alone, although we're seeing 60% of patients respond, the responses are generally short-lived.



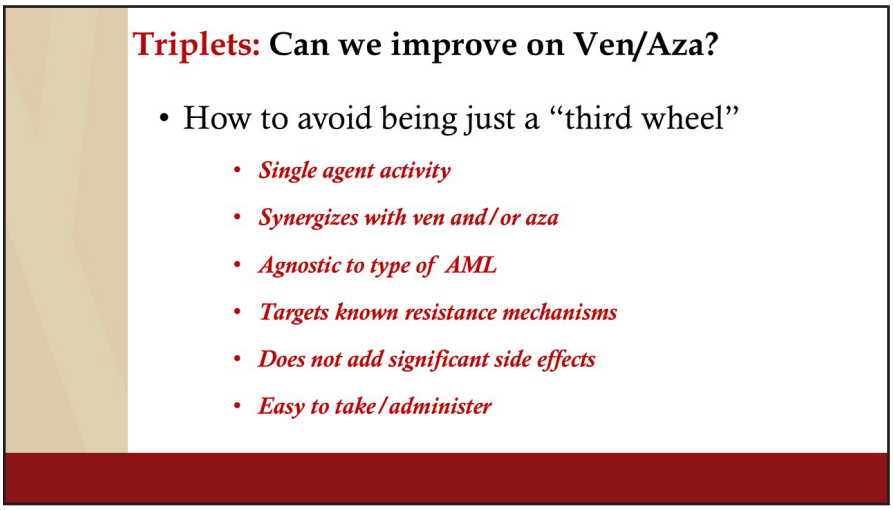
Slide 53: Menin Inhibitors

This drug, revumenib, is now approved for KMT2A. The approval has been submitted for patients with NPM1, so that will likely happen this year. There are other menin inhibitors that are far along in their developments and also will likely be approved. These drugs are very active, but the response rates aren't that long. When you use it just as a pill by itself, it's best used as a way to get to a transplant.

We're now combining these drugs with other drugs to see if we can prolong that duration of response and get more patients into response. They're also being studied not just in relapse-refractory patients, but in the newly diagnosed setting. There are some key side effects to know about, and we've learned a lot about these drugs over the last couple of years. Some of the newer drugs that are in development that have not yet been approved, may get around some of these issues that we've seen with the first generation, so a lot more to come in terms of the menin inhibitors.

Slide 54: Triplets

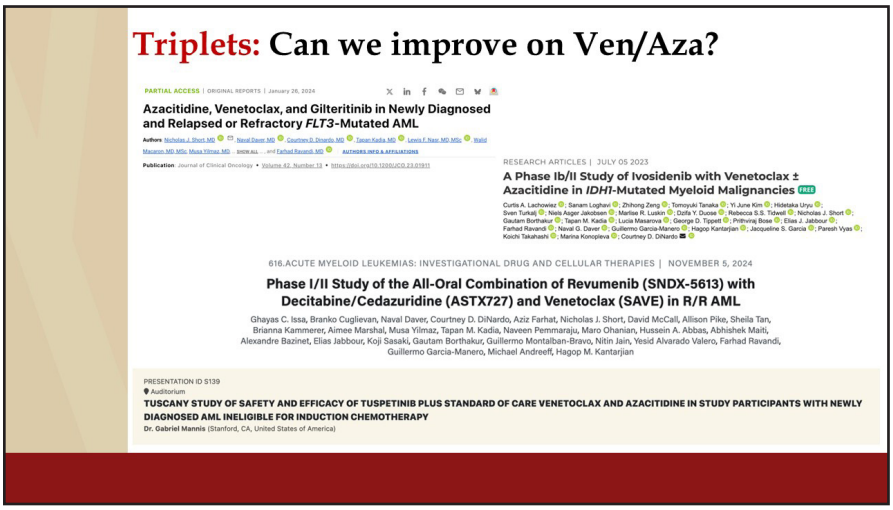
The next big area of investigation in AML is looking at triplets. When I say triplet, I mean adding to the backbone of venetoclax plus azacitidine or venetoclax plus decitabine, so adding a third drug to see if we can improve the outcomes for patients.



Slide 55: Triplets: Can we improve on Ven/Aza?

There are lots of these studies underway, as I'll show you, but the really important thing is that for a third drug to really add something to this backbone, we want to make sure that the third drug is active on its own, that hopefully it synergizes with the other 2 drugs. Ideally, we could use this across different AML types, not just specific types of AML.

Importantly, we don't want it to add a lot of side effects because people that are on venetoclax and azacitidine know that there are side effects that come with it, low blood counts in particular, so adding a third drug, we want to make sure that it doesn't make things worse. We hope that it makes things better.

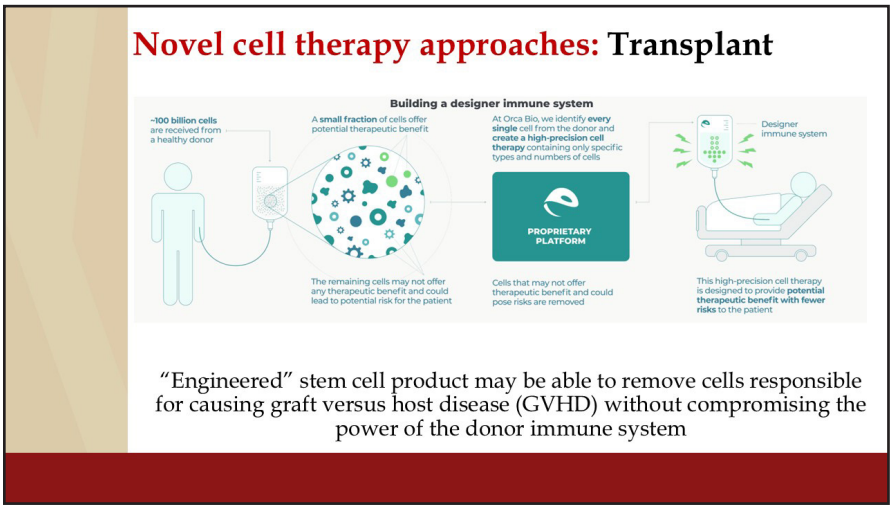


Slide 56: Triplets: Triplets: Can we improve on Ven/Aza?

Gilteritinib, which targets the FLT3 or FLT3 mutation, is one that's being looked at as a triplet.

There are triplets involving the IDH inhibitors, both IDH1 and IDH, with the menin inhibitors looking at the menin inhibitor plus venetoclax and the oral decitabine.

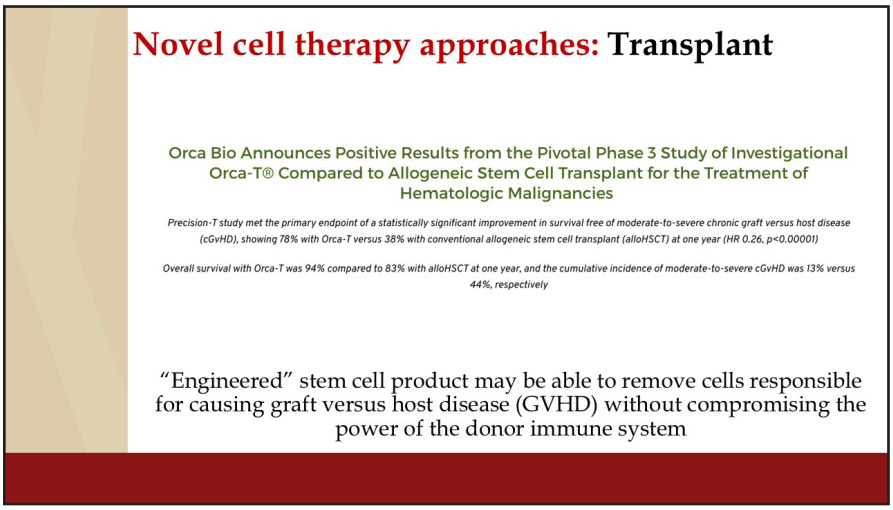
This is a study I'll be presenting in Milan in 2 weeks at the European Hematology Association meeting, looking at this new drug, tuspetinib, which seems really exciting, not a lot of side effects, applies to all kinds of AML. We're really excited about this triplet.



Slide 57: Novel cell therapy approaches: Transplant

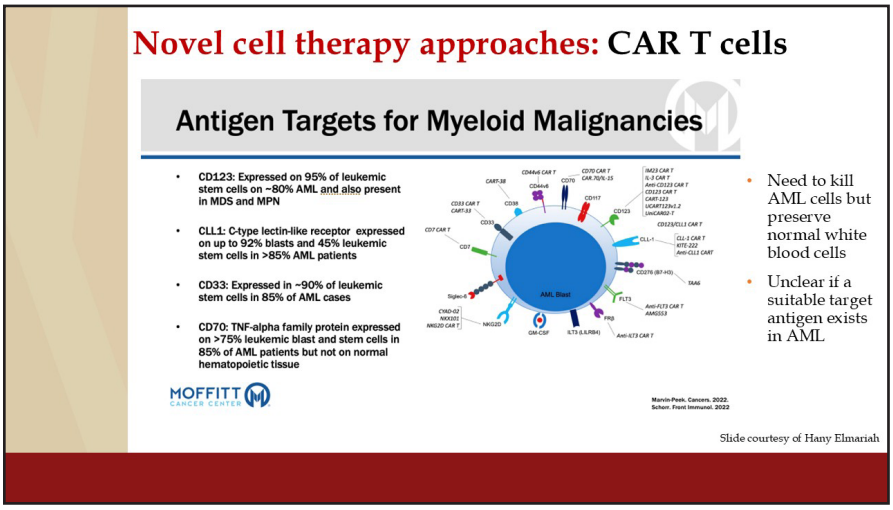
I think lastly, cell therapy approaches. I want to talk one about transplants and one about CAR T cells. One of the most exciting things in the transplants field is this Orca-T transplant, this company Orca Bio. Essentially, what they're doing instead of just transplanting all of a donor's cells, they're collecting the donor cells and then picking out which cells they want and which cells they don't want.

In particular, they're trying to keep the cells in that are helpful for killing leukemia, taking the cells out that are responsible for graft-versus-host disease, which is one of the main complications of a bone marrow transplant.



Slide 58: Novel cell therapy approaches: Transplant

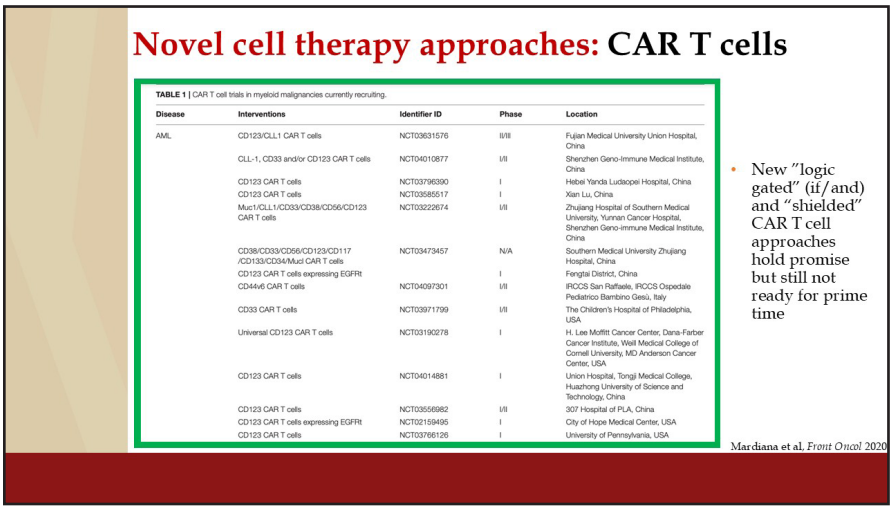
This was just resulted or at least there was a press release that their Phase III trial, which compared this engineered transplant to a standard transplant, was much more effective in limiting graft-versus-host disease. 70% of patients who received this Orca-T transplant for graft-versus-host disease-free versus 38% with a conventional transplant, and not just that, but at one year 94% of patients with the Orca-T transplant were alive compared to 83% of patients with a standard transplant. This could be a new frontier in transplant technology, which I think is really exciting.



Slide 59: Novel cell therapy approaches: CAR T cells

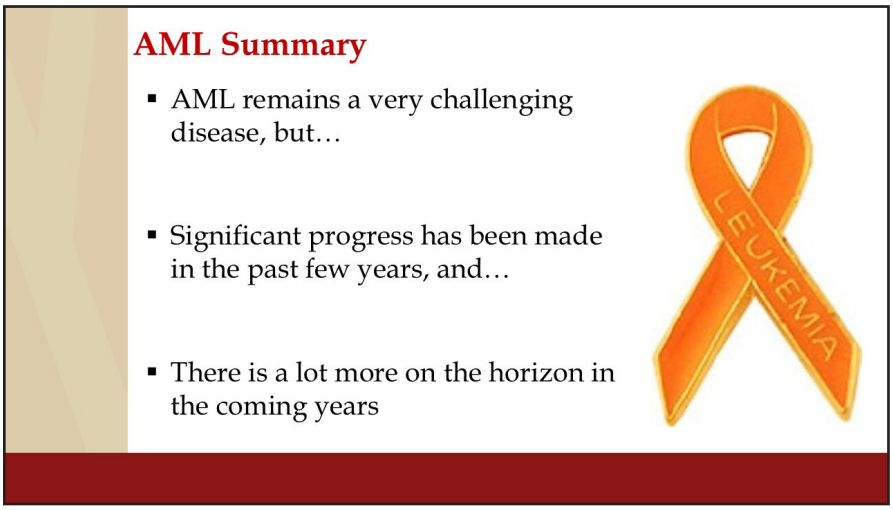
Lastly, I get asked all the time about CAR T cells. We've seen an explosion of CAR T cells for lymphoma, for myeloma, even for ALL. The way that a CAR T cell works is that you engineer a cell, you take a T-lymphocyte and engineer it to attack a specific protein on the surface of cells. The problem in AML is that there's not a protein that is on AML cells but is not also on really important cells.

In lymphoma, you can wipe out all your B lymphocytes because they're not that important, but the myeloid cells, your platelets, your neutrophils, your red blood cells, you can't get rid of all of those while you're getting rid of the AML.



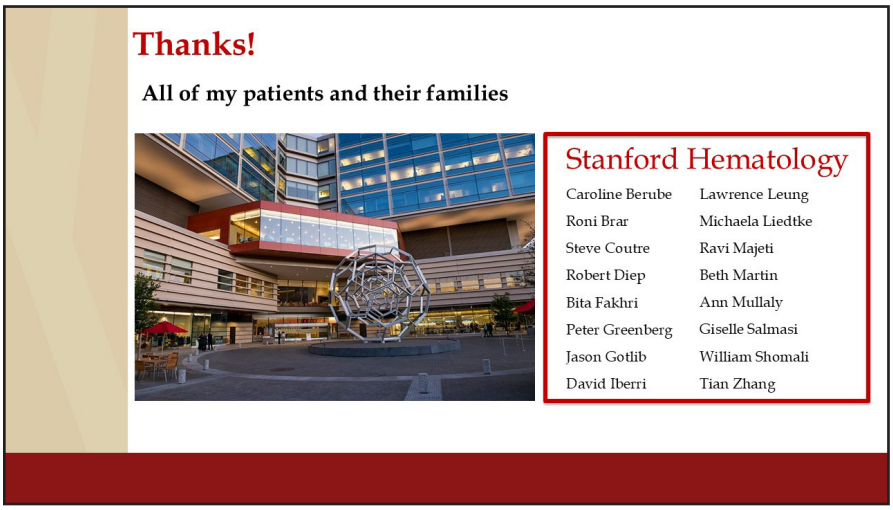
Slide 60: Novel cell therapy approaches: CAR T cells

We've identified some targets. There are certainly a lot of clinical trials happening. There are some new technologies that I think hold promise, but I think a CAR T cell in AML is still several years away. These are not ready for prime time. Certainly, I encourage participation in the clinical trials, but it is not yet part of the standard arsenal for AML patients.



Slide 61: AML Summary

I think I did well on time here. Just to summarize, AML still unfortunately in 2025, is a very challenging disease. That being said, we have made significant progress and that gives me hope, gives me optimism. It allows me to continue week after week, seeing a full clinic of AML patients. I think there's a lot more on the horizon in the coming years.



Slide 62: Thanks!

With that, I will conclude and just say thank you, in particular, to all of my patients and their families who have allowed me to participate in their care and to my colleagues here at Stanford. With that, I will wrap up and pass it back to the moderators to see about some questions.

Slide 63: ASK A QUESTION

Lizette:

Well, thank you so much for such great information, Dr. Mannis. There's been so much advancement in the treatments for AML, as well as some really exciting results that can really affect the landscape of treatment that will really affect patients' quality of life. Thank you so much. As you mentioned, it is time for our question-and-answer portion of our program.

The first question comes from Linda. Linda is asking: How do I combat AML relentless fatigue during immunotherapy sessions and in between?

Dr. Mannis:

That's a really good question. Fatigue certainly is one of the most common things we deal with, with AML and its

treatment. I think it's important to make sure that we understand what's driving the fatigue because it can be driven by a lot of different things. The AML itself can cause fatigue, the treatment can cause fatigue. There are other things that it's important not to miss as well, so common things being common.

If we can't explain the fatigue in terms of either blaming it on the leukemia or the treatment, thinking about things like checking thyroid levels, checking testosterone levels. If people are particularly anemic during treatment, meaning low hemoglobin levels, potentially giving them a little bit more blood to maintain a higher hemoglobin levels. There aren't great medications to boost energy, but there certainly are some out there for cancer-related fatigue.

Certainly, one of my recommendations for patients with AML, who have a lot of symptoms going through their treatment, is potentially ask their doctor for a referral to a palliative care specialist or a symptom management specialist. They often have more expertise and can spend more time, honestly, just addressing the symptoms themselves. Oftentimes, when you go in to see your leukemia doctor, I admit fault as well, is that we spend most of the time talking about the leukemia itself, the treatment, less time on some of the symptoms that go with it.

Having this extra layer of support with a palliative care specialist can often be very helpful. Thinking about: Is the leukemia under control? Are there other things that can be modified? Then I think making sure, as I said, nutrition is important, staying active is important. Both of those things can help with energy levels.

Lizette:

Let's take our next question from our telephone audience, please.

Operator:

We do have a question from Deanna. Go ahead, Deanna, your line is open.

Deanna:

I have also myotonic dystrophy with AML. My physiatrist recommended that I should get a transplant. I avoided the transplant option because of the fact that I have an underlying genetic issue of the myotonic dystrophy. What is your take on that?

Dr. Mannis:

I can't speak specifically to the myotonic dystrophy. Certainly, transplant in general is a difficult process or can be a difficult process even for completely healthy people. As the years have gone by, we've seen significant improvements in the transplant process. We are able to transplant people who are older and older and people who have underlying conditions. The way that we do that is typically to reduce the pre-transplant chemotherapy that's given to make it much gentler.

The consequence of that is that the more you decrease the intensity of the transplant, the higher the risk that the leukemia may come back later. Certainly, consultation with a transplant team is important. The transplant team will do a full assessment. It will be a very individualized thing. As part of the transplant work-up, typically, they will do lung function testing, heart function testing, a full battery of labs. It's hard to comment on one specific condition, but I will say that the transplant process has gotten better and better over time.

I still, as a leukemia specialist, my goal is to put the transplant people out of business. I would love to be able to cure all patients with AML without a bone marrow transplant, but for many patients, it is a necessary evil. Certainly, I would recommend meeting with a transplant team and having that evaluation to see if you are a reasonable candidate or not.

Lizette:

Our next question Doctor is from Craig: After chemo and stem cell transplant, what is the best way to treat the neuropathy and foot and ankle pains when extremely severe, combined with damaged varicose veins? Is there a normal timeline when it lessens?

Dr. Mannis:

Neuropathy, unfortunately is common. Fortunately, with most AML treatment, neuropathy is not a problem. After transplant in particular, neuropathy can be an issue. There are common medications that are given, things like gabapentin or cymbalta, which helps some people but not all.

There are some other things that we do in terms of supplementing vitamins, in particular B vitamins. I have some patients who swear that the only thing that has worked are things like yoga and stretching. For some people, the neuropathy will fade over time, although it often takes 6 to 12 months or maybe even longer for it to fade. Unfortunately, there are neuropathies that are more permanent.

When my patients have particularly difficult-to-treat neuropathy, I often will either refer to a neurologist or again to the palliative care team where they may have more up-to-date, latest and greatest, treatments for neuropathy. Certainly, any stubborn symptom like that is worth potentially getting a second set of eyes to take a look at it outside of the leukemia specialist.

Lizette:

We'll take the next question from the telephone audience, please.

Operator:

The next question comes from Jon. Jon your line is open.

Jon:

First of all, I want to thank you for the information. It gives us a much better understanding of it. My husband is on azacitidine and venetoclax. Is it normal, after taking venetoclax for about 7 to 14 days, to have a real drop in his neutrophils and white blood cells, even platelets at times? Then he doesn't take it for approximately, maybe it could be 6 weeks or whatever until he builds up again and starts the routine of infusions again. Is that a normal process? The other question I have is, does venetoclax cause diabetes?

Dr. Mannis:

The second part is the easiest. Venetoclax does not cause diabetes or at least it would be very, very unusual for it to cause diabetes. The first part of the question, it is very common and expected that within a week or 2 of starting venetoclax that the blood counts will go down. That's a classic venetoclax effect. It's often delayed, so it may start within a week of starting venetoclax, 2 weeks later, even 3 weeks later, we see the neutrophils go down.

One of the tricks of managing venetoclax, part of the art of this is that every patient responds a little bit differently. Some people may need 21 days of venetoclax per cycle, some may need 14, and some may need 7. It just depends on the individual. Once the leukemia is in remission, it's really important to continue adjusting the number of days of venetoclax that you're receiving month after month to try and get to a point where the blood counts may go down a little bit, but they shouldn't be going down to the point that the white blood cells are super low for a long time or that your needing transfusions.

It's the kind of thing that needs continuous management. No 2 people are really the same in how they react to the venetoclax.

Lizette:

Our next question is from Derek: With the new testing technologies and next generation sequencing for MRD, which is measurable residual disease, how is this changing maintenance therapy for patients?

Dr. Mannis:

This is a very germane topic. MRD, measurable residual disease, is where the field is going in terms of trying to decide

who needs a transplant, who doesn't need a transplant, who benefits from maintenance, maybe even someday giving us an answer of – is someone cured or not. In one of the early slides I showed you that imaginary remission line where we say remission is less than 5%, below that you are in remission.

Essentially, tests for MRD are tests that look below that line. We now have more and more sophisticated tests to look deeper and deeper below the surface. While it's not quite ready for prime time, we are starting to use some of these MRD tests to inform treatment decisions. Maybe the most important one, the most data-driven one, is patients with these FLT3 or FLT3 mutations.

Those patients oftentimes will be referred for bone marrow transplant. We have learned through a recent large clinical trial, that for patients who have detectable FLT3—so we don't see any leukemia in the bone marrow, but we can detect this gene mutation at very low levels, either when it's detectable right before or right after the transplant—those people will live longer and do better if they get maintenance therapy with a FLT3 inhibitor after transplant.

That's one of the examples where some of these newer tests that are more sensitive to pick up leukemia have informed how we are treating patients. I think it's just a matter of time before we get more and more data so that we can use these results to help prevent people from relapsing, hopefully prevent people from needing bone marrow transplants. This is a huge frontier and something we're working on actively here at Stanford to try and improve on some of these MRD tests. Great question.

Lizette:

Along the same lines regarding maintenance therapy, Marv is asking: Would you say the patients have a better chance to not relapse if they do maintenance therapy?

Dr. Mannis:

I think it very much depends on the scenario and I think it depends what is meant by maintenance. In my mind, maintenance typically means that there's still some leukemia there under the surface, and you want to keep somebody on treatment to help prevent that from growing back as long as possible. There are scenarios where we would give maintenance therapy.

For patients that we treat with curative intent, a patient that gets intensive chemotherapy 3 or 4 cycles of consolidation, I generally don't think there's a role for maintenance therapy because the goal of that treatment is to wipe out every last leukemia cell. There are situations where we're not sure or we are doubtful that we've gotten every last leukemia cell. In those situations, I would think about maintenance.

I think you also have to consider the downsides in terms of being long-term on any kind of chemotherapy and the side effects, the costs, and whether you're better off just treating the leukemia when it comes back and having a break from treatment or being on treatment continuously. There are a lot of factors that go into it. I would say there's no one-size-fits-all approach to maintenance therapy.

In general, I think people aren't doing a lot of maintenance outside of the setting where people are getting continuous cycle after cycle of chemotherapy. I wouldn't really call that maintenance. It depends how you use the word.

Lizette:

Thank you Marv for your question, which was our final question today. Special thank you to Dr. Mannis for volunteering your time today and your expertise with us.

Slide 64: LLS EDUCATION & SUPPORT RESOURCES

You can definitely contact the LLS Information Specialists at 1-800-955-4572. We are here from 9:00 AM to 9:00 PM Eastern TIME, or you can reach us by email at LLS.org/ContactUs.

We also do have a Clinical Trial Nurse Navigator in our Clinical Trial Support Center. They really are able to identify AML clinical trial options for you and your unique situation, and you can also contact them through LLS.org/Navigation.

Slide 65: LLS EDUCATION & SUPPORT RESOURCES

The Leukemia Lymphoma Society offers financial assistance to help individuals with blood cancer. For more information, you can visit us at LLS.org/Finances.

Slide 66: LLS EDUCATION & SUPPORT RESOURCES

We've also started a Medical Debt Case Management Program that provides one-to-one in-depth personalized support to empower patients to address their medical debt, and they may be reached at LLS.org/MedicalDebt or by calling 833-507-8036, and that's between 8:30 AM to 5:00 PM Eastern Time, Monday through Friday.

Slide 67: THANK YOU

Support for this program is provided by Astellas Pharma US Inc. and Genentech, a member of the Roche Group. Dr. Mannis, thank you again for volunteering your time with us today.
On behalf of The Leukemia and Lymphoma Society, thank you all for joining us. Bye and we wish you well.