Advances in Acute Myeloid Leukemia

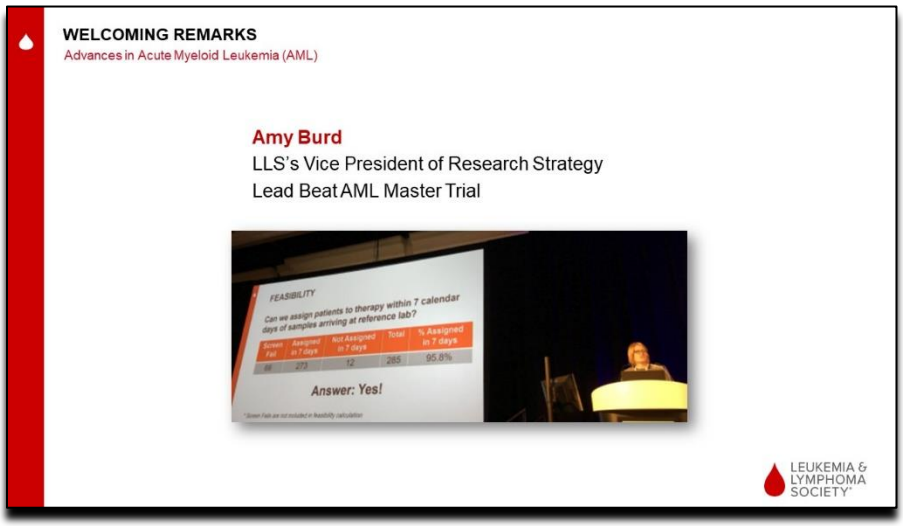
Operator
Greetings. And welcome to Advances in Acute Myeloid Leukemia, a live telephone and web education program. It is now my pleasure to introduce your moderator, Lizette Figueroa-Rivera. Thank you. You may begin.

Welcoming Remarks

Lizette Figueroa-Rivera
Hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. We have over 800 people participating from across the United States as well as other countries, including Argentina, Canada, Finland, India, Ireland, New Zealand, Peru, St. Kitts and Nevis, the United Kingdom, and Venezuela.

Special thanks to Dr. Uma Borate for sharing her time and expertise with us today.

Before we begin, I'd like to introduce Amy Burd, LLS's Vice President of Research Strategy and Lead on our Beat AML® Master Trial. Amy, please go ahead.



Welcoming Remarks

Amy Burd
Hello. I'm Amy Burd, LLS's Vice President of Research Strategy and lead on the Beat AML Master Trial. The Leukemia & Lymphoma Society is a champion for AML patients, caregivers, survivors, and families. Our vision centers on driving new breakthroughs and cures, helping all AML patients access the care they need to survive and thrive.

LLS is playing a significant role in the progress of diagnosing and treating AML, a fast-moving leukemia that starts in the bone marrow and requires rapid treatment. We've learned that AML is actually a multitude of subtypes with different molecular drivers. And the one-size-fits-all approach over the past 40 years using the same chemotherapy combination for everyone doesn't work for many.

LLS is innovating with our Beat AML master clinical trial launched in 2016. We set out to revolutionize how we treat patients with AML with a precision medicine trial using genomic technology to detect mutations causing newly diagnosed patients' cancer, so we can match them to a novel targeted treatment better suited for their disease. It's the first cancer clinical trial led by a nonprofit organization.

We work closely with the US Food and Drug Administration to design the master protocol for this trial, and they are very excited by our model.

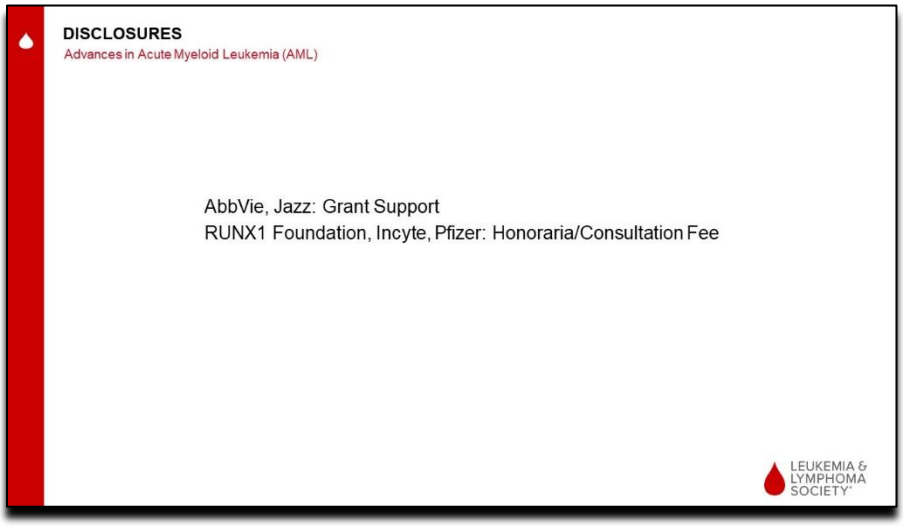
Most clinical trials in AML test only one agent at a time, but Beat AML is designed to speed up the process of finding better treatments for AML patients, testing multiple targeted therapies simultaneously. This gives patients the opportunity to get matched to a treatment best suited for their subtype of the disease.

Further, this trial is only open to newly diagnosed, untreated patients. Most AML clinical trials are for patients who have already relapsed and failed to respond to previous treatment. The data suggests that this umbrella approach has the potential to improve both short-term and long-term outcomes in AML and sets the stage for a precision medicine approach in other blood cancers.

Dr. Uma Borate, who is presenting today, has been a champion in our Beat AML master clinical trial and has been at the forefront of the research and has benefited many AML patients, and we are lucky to have her speak to us today about AML.

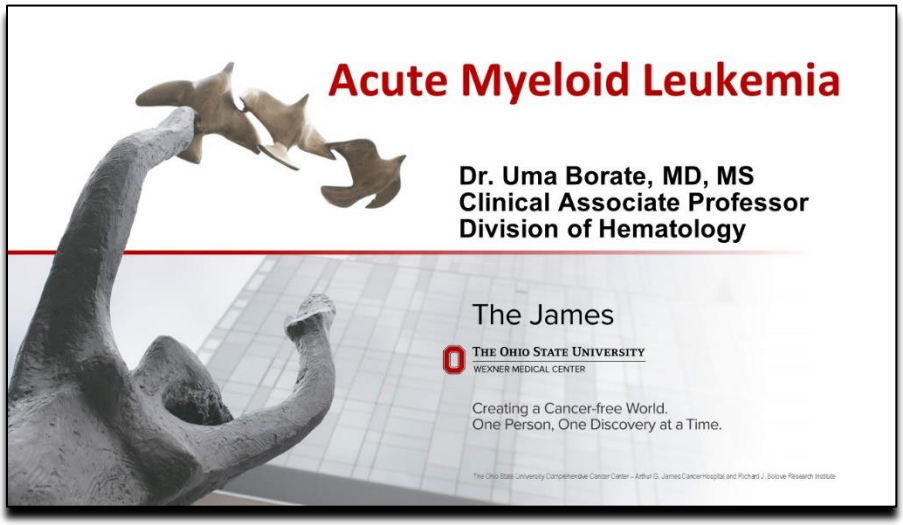
Lizette Figueroa-Rivera
Thank you, Amy, for your welcoming remarks and for your great strides with our Beat AML master clinical trial, which is bringing so much hope to AML patients and their loved ones.

For this program, we would like to acknowledge and thank Bristol Myers Squibb and Genentech, Inc., & Biogen for their support.



Disclosures

Following the presentation, we will take questions from the audience.

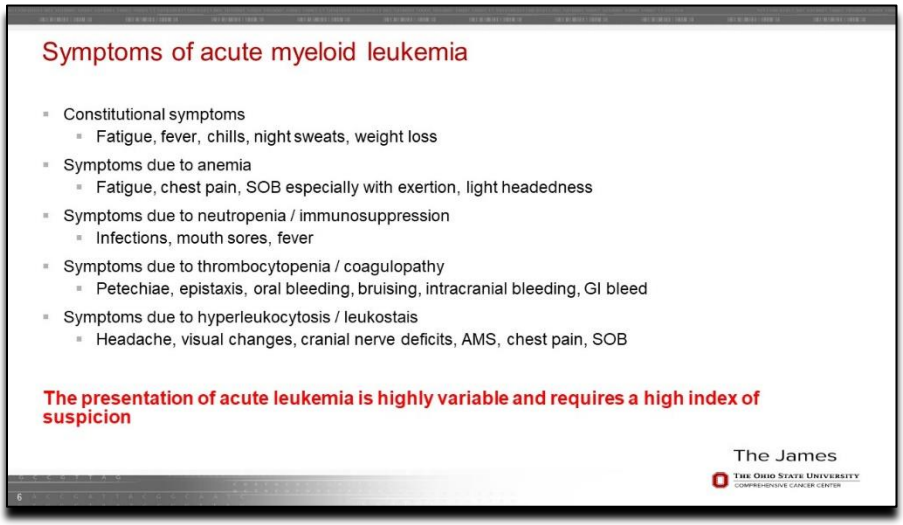


Acute Myeloid Leukemia

I am now pleased to introduced Dr. Uma Borate, Associate Professor at The Ohio State University, The James Comprehensive Cancer Center, in Columbus, Ohio. On behalf of The Leukemia & Lymphoma Society, thank you so much, doctor, for volunteering your time and expertise with us.

I'm now privileged to turn the program over to you.

Uma Borate
Thank you so much, Lizette. I really appreciate this opportunity by The Leukemia & Lymphoma Society to talk about acute myeloid leukemia.



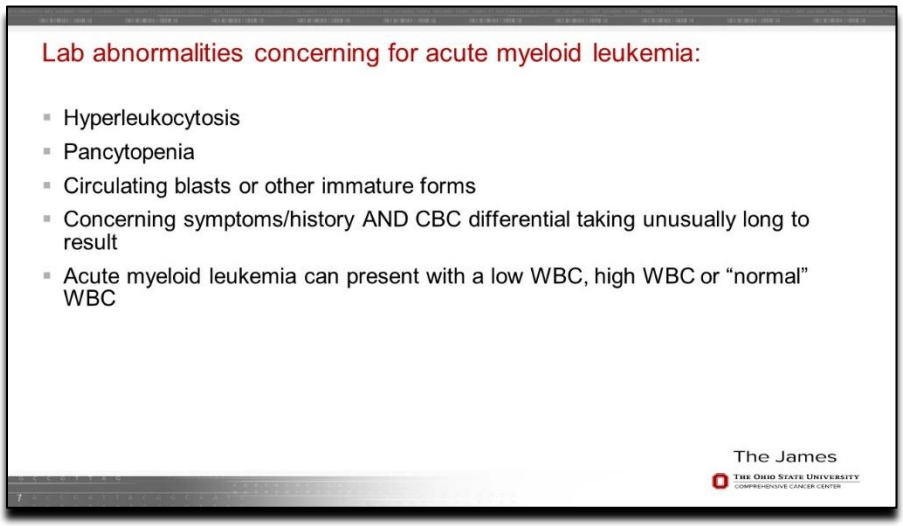
Symptoms of acute myeloid leukemia

As many of you on this program know, the symptoms of acute myeloid leukemia can be incredibly diverse and sometimes fairly vague. They can start with constitutional symptoms, like fatigue, fevers, chills, night sweats, and weight loss. You can have symptoms specifically from the anemia, including shortness of breath, dizziness, or light headedness, with exertion or otherwise.

You can present with symptoms of neutropenia or immunosuppression, including infections, mouth sores, as well as fevers. And last but not the least, you can have symptoms of bleeding because of low platelets or thrombocytopenia. And these can be minor bleeds or major bleeds, like intracranial hemorrhage, which is a bleed inside the brain, or a GI bleed.

We also have some very acute presentations with hyperleukocytosis when the white blood cell count is really high, which should include all of the above and make the patient very sick with headache, other neurological deficits, shortness of breath. Also present, like chest pain or an acute MI.

So, in summary, the presentation of acute myeloid leukemia is highly variable and requires a high index of suspicion. I wanted to mention this because as many of you on the call know, there are patients all over the world that can attribute the variety of symptoms to many other conditions, and it can take a while before they actually come to medical attention and have the right diagnosis.

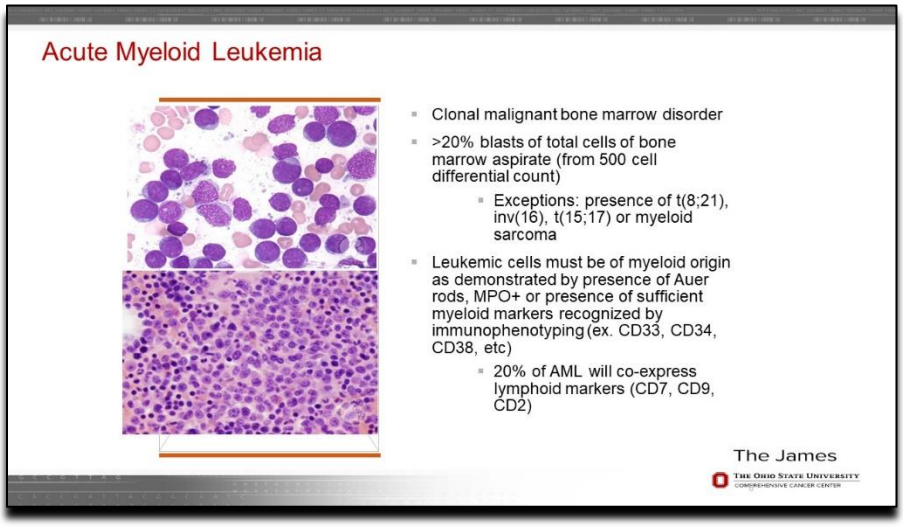


Lab abnormalities concerning for acute myeloid leukemia

So, what are the lab abnormalities that are concerning for acute myeloid leukemia when you do get to a doctor and get blood work done? So, the first lab abnormality that could raise a suspicion for AML is hyperleukocytosis, meaning a high white blood cell count. However, leukemia patients--AML patients can also present with what we call pancytopenia, meaning all their blood counts are low. So, this is the exact opposite of having a high white cell count.

Sometimes when blood work is done, in their blood work you can see what we call circulating blasts or leukemia cells and other immature forms. And another red flag is along with these concerning symptoms that I just mentioned, if the blood work is taking a long time to come back, I think that is something that we as physicians always wonder, “Well, there's something going on that we need to pay additional attention to.”

So, in summary, acute myeloid leukemia can present with a high white count, a low white count, or sometimes even a normal white blood cell count.



Acute Myeloid Leukemia

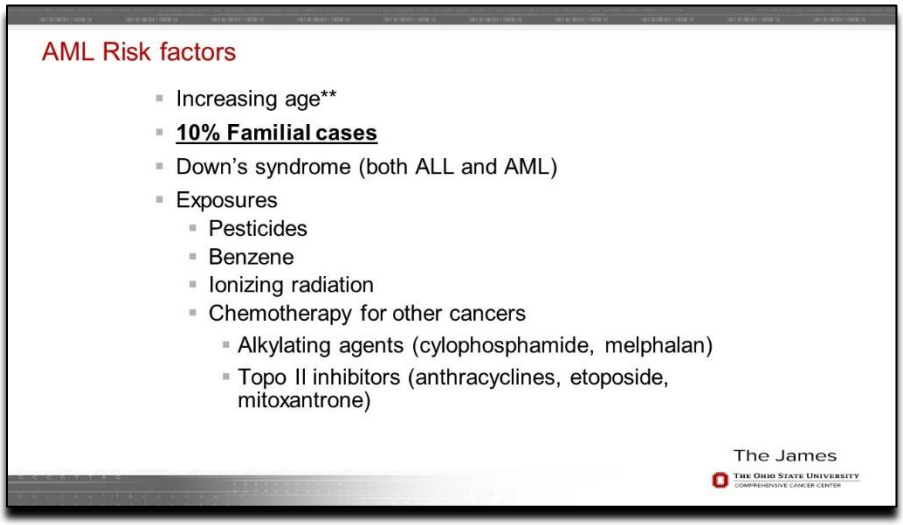
So when we diagnose a patient with AML, what are we really looking for under the microscope? So what you can see here on the slide is a picture of the bone marrow biopsy smears and biopsy sections of a patient with AML. And what we are looking to identify is a clonal malignant bone marrow disorder. And by clonal, we mean a number of cells that look exactly like each other.

In our bone marrow, we're supposed to have a wide variety of cells. They don't identically resemble each other. But in AML, when the leukemia takes over the bone marrow, a lot of these cells look very similar or clones of each other.

We see and we count that the number of blasts or leukemia cells is more than 20% of the bone marrow aspirate. That's the liquid portion that is taken during the bone marrow biopsy procedure. And this is counted for about 500 cells. And out of that, more than 20% have to have these malignant features or these clones. These are also called blasts.

The exceptions are certain types of AML with different chromosomal changes, like seen on the slide, where you could have less than 20% of these malignant cells and still have a diagnosis of AML.

And last but not the least, we run some pretty sophisticated analyses. We call them flow cytometry, where we look at the different markers on these blasts and we confirm that these are actually myeloid blasts. And you can see the different markers as presented on the slide.



AML Risk Factors

So, when we see all of these things in a patient with suspected acute leukemia, we then can confirm the diagnosis of AML.

When I see a patient in clinic, the first question I get asked after I talk about this diagnosis is, "Why did I get this?" And I know for many of you on this webcast and call, this is a question that still continues to bother patients and family members: Why does one get AML? And we know now that there are multiple reasons why this can happen.

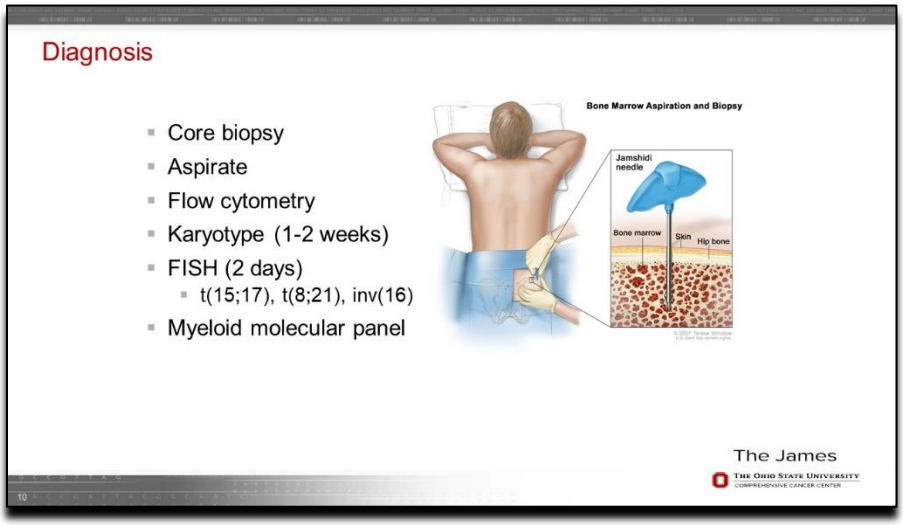
The most I think obvious cause for many cancers, including AML, is increasing age. And while I know there are several patients on this call and otherwise that get AML at a relatively young age, AML is definitely more common the older we get, with most patients diagnosed over the age of 60.

The other thing that I wanted to point out, which was not really known. In fact, when I did my fellowship, a lot of times we would tell patients, "Oh, this leukemia is not inherited. It's not something you can pass down to your children." We now know that about 10% of AML cases are actually familial, where you may have a grandparent, a parent, an aunt, an uncle who has had some type of blood cancer that has a myeloid origin or sometimes even a lymphoid malignancy. So this is something that you really need to remember and talk to your doctor about.

There are other genetic conditions, including Down syndrome and others, that can predispose people to ALL or AML. And last but not the least, we have now increasing data about environmental exposures. So, for example, prolonged exposure to benzene, radiation, pesticides. There is definitely an association between developing leukemias with these type of exposures.

Last but not the least, another common factor in AML patients is receiving chemotherapy for other cancers. So, for example, if a patient has had breast cancer or lung cancer before, received chemotherapy for the same, there is definitely an increased risk of developing AML between 2 to 10 years after treatment for the prior cancer.

So this is a short summary of some of the common reasons why people can develop AML. I will end by saying for a lot of patients, like all of you on the call, it's not entirely clear what the contribution of maybe genetics, maybe environment, maybe all of the above is. And there is a lot of research that is still ongoing with this regard.



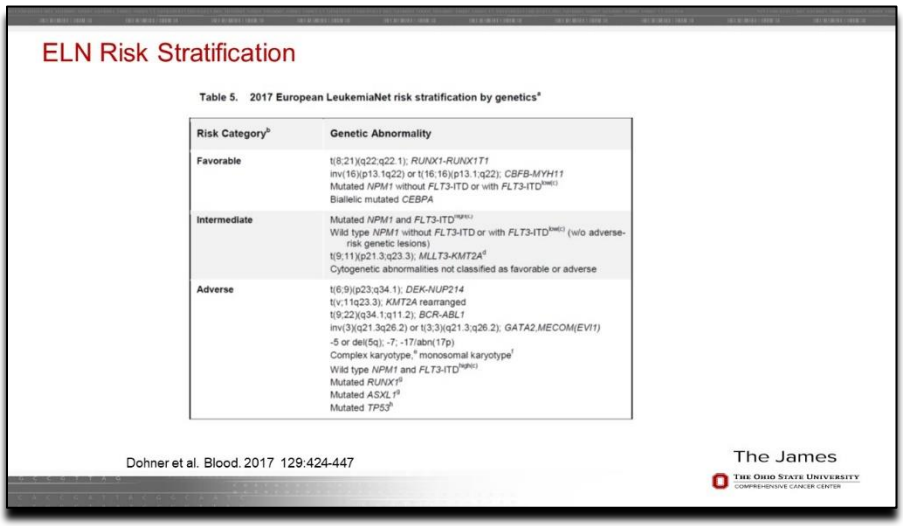
Diagnosis

So, what do we do to diagnose this disease? And as I already mentioned, the first step is typically what we call a bone marrow biopsy. And I know this may not exactly bring back fond memories for many of you on this call. This is not a procedure that I think anybody looks forward to.

This is a typical position that the patient is in. You can see the needle. And you can see that the idea is to insert the needle all the way into the bone marrow space so that we can get enough of the liquid bone marrow as well as a piece off the bone marrow with the bone around it to do all the different testing that we do to receive an accurate diagnosis and prognostic information for AML.

And the different tests are listed here. I already spoke about flow cytometry. Karyotype is looking under the microscope to see all the different chromosomes that make up the AML cells. We also do a test called fluorescence in situ hybridization, or FISH, and that tells us a lot about the different chromosomal abnormalities that potentially led to AML.

And last but not the least, nowadays, as Dr. Amy Burd mentioned in her introduction, we do a myeloid molecular mutational panel, which tells us the number of genes that might be mutated in different AML patients and how we can use that information for both prognostic reasons but also to direct different treatments.



ELN Risk Stratification

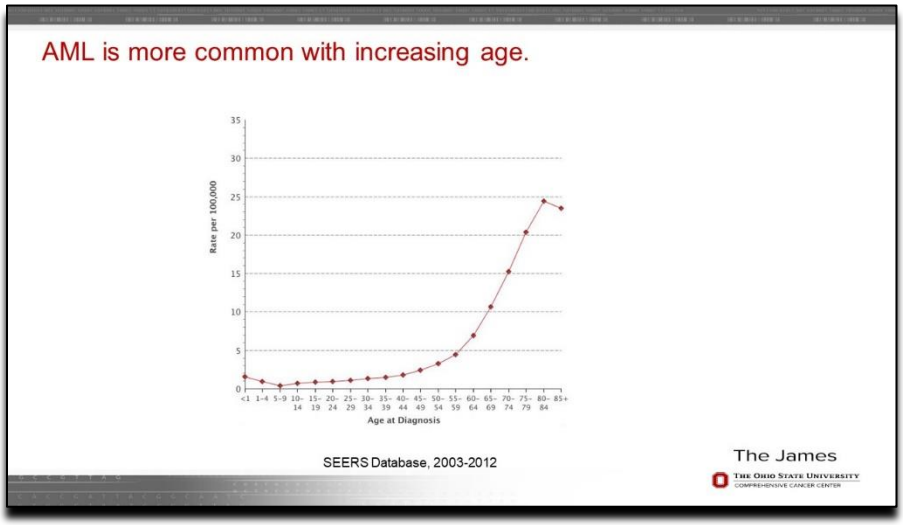
And so, once we get that information we usually sit down with the patient, and we talk about this slide that you can see in front of you. So, the first thing that we use all this information for is to risk-stratify an AML patient. And what does that mean?

By that, I mean we usually categorize the specific type of AML that a patient is diagnosed with into these three different risk categories. You have your favorable risk AML, and I'll talk about what that means in a minute. And you can see the variety of chromosomal abnormalities and mutations that can place a patient in the favorable risk category.

So, of note, t(8;21) inv (16), if you have an NPM1 mutation without a *FLT3* mutation or another mutation called *CEBP*-alpha will result in a favorable risk categorization.

For other abnormalities or, if you have a completely normal chromosomal analysis, the patient actually is placed in the intermediate risk category, along with some of the other abnormalities that you can see over there. And then last but not the least, there is an adverse risk category with a number of different mutations, as you can see listed there, including one that we call complex karyotype, meaning there are three or more different chromosomal abnormalities seen in the leukemia blasts.

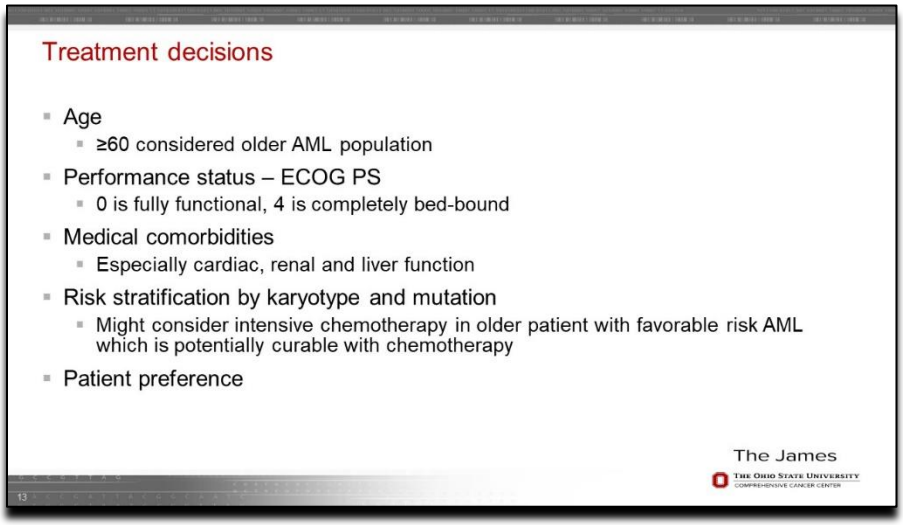
And I'll talk about in a minute why we do this and how that impacts our treatment decision and a patient's prognosis.



AML is more common with increasing age

So coming back to what I mentioned before: AML is more common with increasing age. And as you can see again, not to discount the fact that AML obviously can happen in younger patients, you can see that there is right from the age of zero, we know that AML can happen in infants as well. But you can see the curve is fairly flat with a pretty uniform incidence all the way up to age 50, and then you suddenly see the curve kind of go up. This hockey stick curve, as we call it, where the incidence sharply starts to go up and then sort of plateaus after age 85.

And I think this is very reflective of the majority of AML patients that we see. Again, obviously, we see younger patients with AML as well and we'll talk a little bit about that in a minute.



Treatment decisions

So the next question after we've had the discussion about why somebody may have developed AML: What prognostic category do they fall in, is well, how are you going to treat my disease? And how do you decide what treatment to give me?

So there are a number of things. And the AML team taken into consideration while discussing treatment options. So, the first one—and I don't want to keep hammering this—is age. And I know again this sounds very ageist, but 60 or older is considered sort of older AML. And I'll talk a little bit about why that is and why age 60 was chosen and why that may not really be the paradigm moving forward.

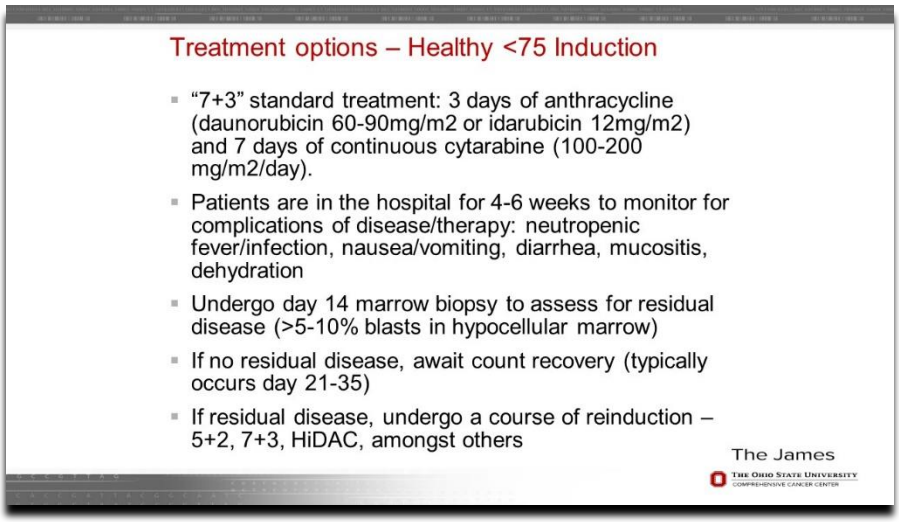
The next thing we look at is what we call performance status. And by performance status, we really try to assess how functional is a patient when they have received this diagnosis of AML. So, for example, if you have an AML patient that is still doing all what we call activities of daily living: driving, going to the grocery store, maybe they were working a few days before they got sick. That could be the ECOG performance status, as we call it, of zero, meaning full-functioning normal activity. As opposed to somebody who is really very sick because of their disease and has come to the emergency room or to the hospital essentially not even able to get out of bed.

We also look at all the different medical comorbidities. This is a word that's been used a lot with the COVID pandemic, but these are really important. For example, cardiac disease, history of myocardial infarction, heart attacks, heart disease, kidney disease, liver disease, diabetes. These are things that we really have to take into consideration before we decide on what treatment is appropriate.

And then last but not the least, as I talked about, we really have to have the information we need to risk-stratify into those three different groups: the favorable, intermediate, and high risk. Because, as I'll talk about in a minute, this has implications as to what we call treatment that has curative potential versus treatment that may have to be tailored to the risk category that the patient is in.

And then last but not the least—but not at all the least—I want to emphasize this and highlight it and underline it: patient preference is a big part of this decision making. There are patients that have very different goals and have different preferences. Some absolutely do not want to be in the hospital for extended periods of time and would prefer outpatient therapy. Others don't really have a strong preference in that regard.

There are considerations with caregiver support, travel, transport, financial considerations. So, a lot of those patient preferences are always considered when treatment decisions are made. And if not, they should be considered when these treatment decisions are made.



Treatment options – Healthy <75 Induction

So let's move forward and talk a little bit about sort of treatment options, including the more traditional ones and then some of the newer treatment options that we have. So, as Dr. Burd again mentioned in her introduction, for 40-plus years we had this one-size-fits-all approach, where pretty much any AML patient that was considered "healthy" or younger. And by younger now, we've sort of moved our scale to maybe 70—even 75 sometimes—that patients would be offered what we call induction therapy.

And that was a very original name for this induction therapy. It was called 7+3, and the reason was you got two drugs, you got 3 days of anthracycline drug, either daunorubicin (Cerubidine®) or idarubicin (Idamycin®, Idamycin PFS®), and then you got 7 days of another drug called cytarabine (Cytosar-U®), which was given to you by continuous infusion. And these are the typical doses that we use for the 7+3 standard chemotherapy.

And this was very--and still continues to be--very intensive treatment. And I mentioned patient preference, but for this treatment in most centers in the United States or otherwise, patients are typically in the hospital for 4 to 6 weeks. And the reason for this is we know that this type of chemotherapy is going to completely sort of destroy—and intentionally so—the leukemia cells in the bone marrow, but then also the normal cells that might help to make neutrophils and platelets and all the cells that you need. And because of that, we know that patients are going to have complications, such as neutropenic fevers or infections.

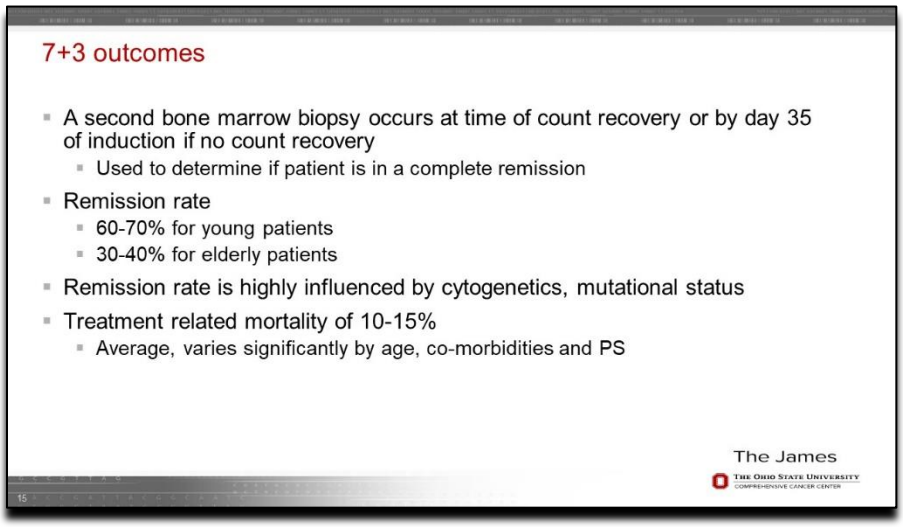
Once we kill off a lot of the healthy cells and the leukemia cells, there's a lot of risk for what we call mucositis, meaning mouth sores, diarrhea, nausea. Your entire gut is very vulnerable to bacteria, which we all have. Obviously, if you're not eating well, you're at the risk of dehydration. And then, at that time patients need a lot of what we call supportive care with transfusions, both red blood cell as well as platelet transfusions. Almost everybody is on some type of IV antibiotic to protect against infection.

And so, many of you on this call know, this is a very intensive sort of hospitalization. And the goal of keeping patients in the hospital is to support them through this time when they're very vulnerable. And once the effects of the chemotherapy wear off, we want to see the healthy bone marrow regenerate and make normal blood cells. And that typically happens at the end of this time.

In the middle of treatment, that's usually what we call day 14, because it's right at that 2-week mark between beginning of treatment and the 4-week mark—we usually do another bone marrow biopsy to make sure that the chemotherapy has worked and all the leukemia is dead. And if there is residual leukemia, then we talk about whether we need to do some more treatment at that 2-week mark as well.

So if there's no residual leukemia we typically await count recovery. And as I said before, this starts happening at the end of the 3 weeks, the beginning of the 4-week mark. And so, on average, between day 21 and day 35 the day count starts. Day 1 is the day a patient starts their chemotherapy. This is when usually normal healthy cells start to grow back, and we start saying the patient is now recovering. And we try to make sure that this is the time when we prepare the patient to hopefully get out of the hospital and go home.

So what happens once we do that day 14 marrow and you actually see disease? And usually, if you see more than 5% to 10% of leukemia cells still in the bone marrow, this typically means that we will need more treatment. We call this reinduction. And there's a variety of different things that different centers do to get rid of the disease at that time.



7+3 outcomes

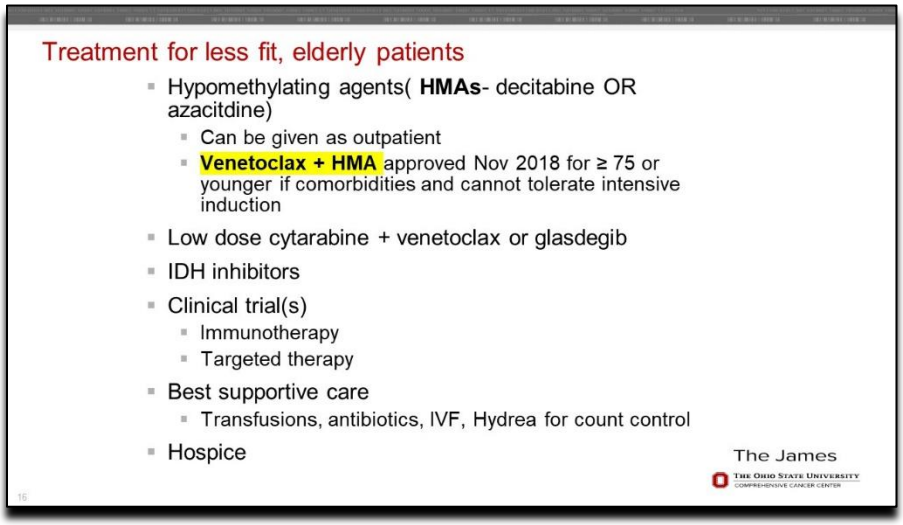
So what happens after a patient receives what we call 7+3? So, as I mentioned before we do a second bone marrow biopsy at the time of recovery, usually by day 35. And this is a bone marrow biopsy that actually determines if a patient is in complete remission.

So, I know there's a lot of questions about, “Well, when am I in remission?” And if at the end of intensive chemotherapy, after counts have recovered around day 28 to day 35, you have a bone marrow biopsy. And there's no leukemia that can be found, then your doctor will typically at that time say you are in complete remission.

Typically for this your blood counts also have to have recovered to a normal level. And there are different kinds of remission, and that's a little bit of a more nuanced conversation, but this is the average assessment of whether you're in remission or not. And if you look at everybody with AML that gets this treatment, the remission rate—and this is typically what we tell our patients—is about 60% to 70% of our younger patients. And again, the definition is less than 60, and 30% to 40% for our older patients.

And again, it's not so much an age thing but really this remission rate is influenced by our cytogenetics, by the different mutations that the AML has. And we know in general the older the patient the more likely they are to have what we call high risk or unfavorable risk AML with a lot more mutations that may not respond to this type of therapy.

The treatment-related mortality can be anywhere from ... and I think 10% to 15% is sort of older data. It can be anywhere as low as 1% to 15%. And this is average. It varies significantly again, like I said, by age, by comorbidities. And as I described, by what is the performance status of the patient before they started chemotherapy? How fit were they before they got sick with AML?



Treatment for less fit, elderly patients

So let's talk a little bit about treatment for less fit older patients. And I again want to stress: just because somebody is older does not mean they're automatically less fit. This definition really applies to older patients with multiple comorbidities who are already frail to begin with. And before 2018, the standard treatment - used to be called less intensive treatment - was with two drugs. They're called hypomethylating agents: decitabine (Dacogen®) or azacitidine (Vidaza®, Onureg®). It was usually given as an outpatient.

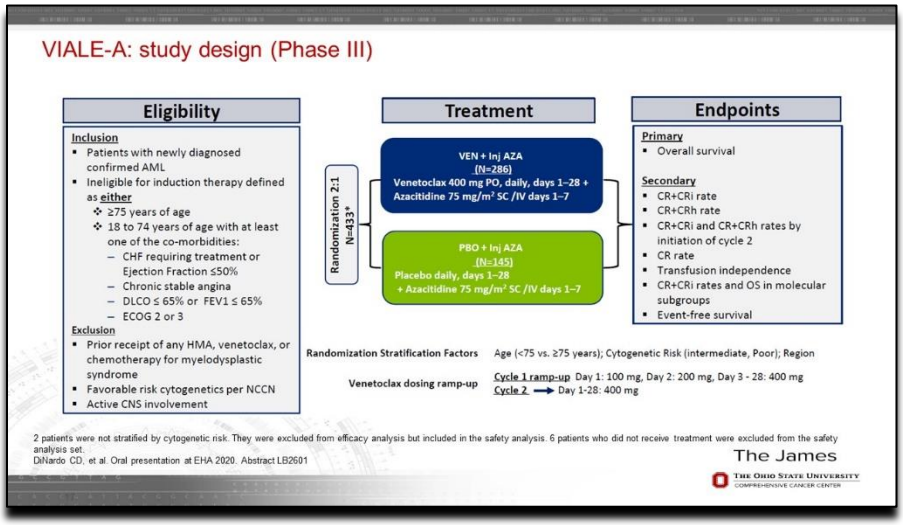
However, in November 2018 we really now have what we call a new standard of care treatment for this scenario. And that is using these hypomethylating agents but adding a drug called venetoclax (Venclexta®) in combination for patients. And I'll talk a little bit about how that came about.

And the way this works is between the hypomethylating agents therapy and venetoclax, we attack the leukemia blasts in two different ways in order to kill them more efficiently and for normal healthy cells to grow back.

There are many other combinations as well with other chemotherapies at a low dose. For example, cytarabine and venetoclax. We now do a lot of what we call targeted therapies in what we call newly diagnosed or upfront setting instead of waiting until the patient relapses. And then absolutely not last or least, our clinical trials, as Dr. Burd mentioned again in her introduction, especially with the Beat AML master trial, we are now moving those for newly diagnosed patients and not waiting until the leukemia relapses or comes back.

So we focus this talk on treatments, treatments, and treatments, but I do want to emphasize there is a proportion of patients who are so sick that no treatments can really be helpful or may not even be appropriate when somebody is really sick. Patient preference also goes into this. And for that, we definitely support patients with best supportive care, transfusions, antibiotics, other medicines to control their counts.

And last but not the least, we also discuss very openly if the patient does not want treatment, is very sick, and is at the end of life with this disease, then hospice can also be an appropriate option that we do discuss even before we initiate treatment. Again, this is very much driven obviously by the patient's condition, but also by patient preference.

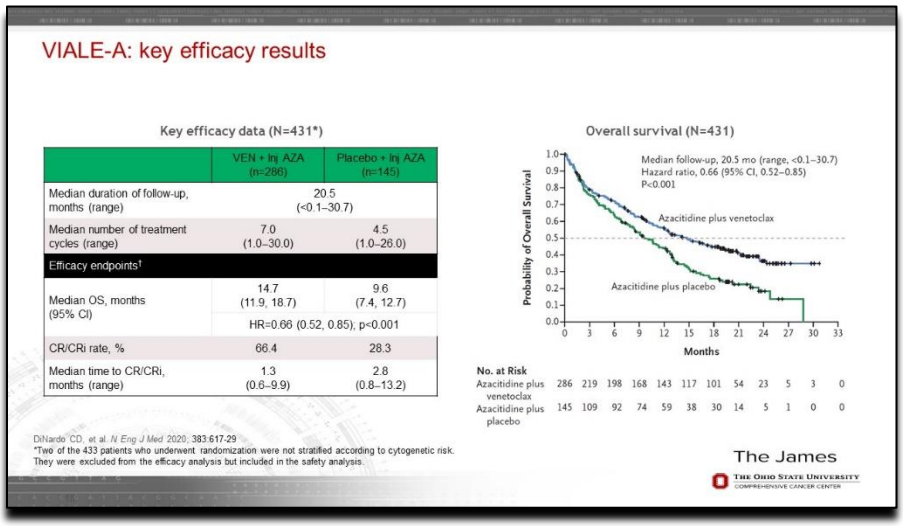


VIALE-A: study design (Phase III)

So let's talk a little bit about this new treatment from 2018 and more recently has now become an option for patients that is not intensive induction therapy that has to be done in the hospital.

So this was a study. It was a very large phase 3 randomized study called VIALE-A, where patients either had to be greater than 75 years of age or could be younger, age 18 to 74, but had other medical conditions—for example, heart failure, kidney disease, just were not doing well, other conditions—that did not allow them to be what we call fit enough to receive the intensive induction therapy that I described in the hospital.

And these patients were then what we call randomized, meaning half the patients randomly got this combination treatment with venetoclax the pill and injectable azacitidine or they got just the azacitidine, which was standard of care at that time, with the placebo pill.

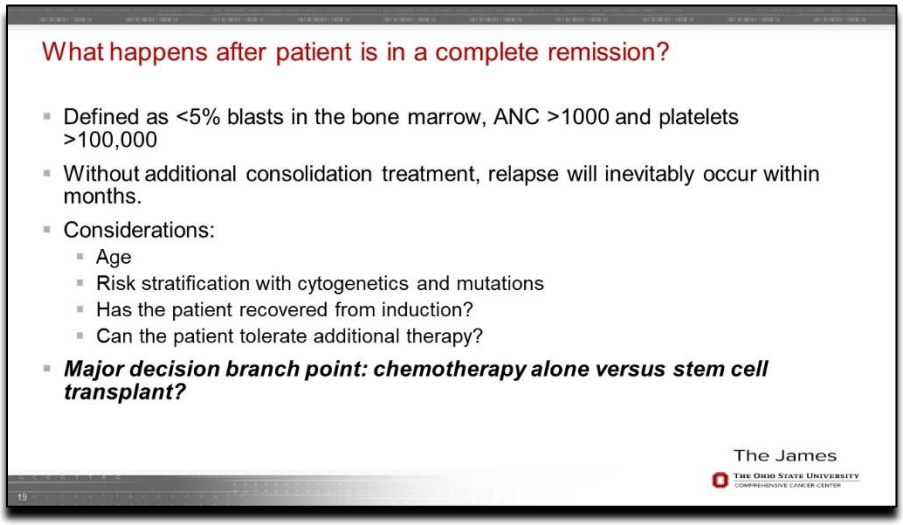


VIALE-A: key efficacy results

And what we saw with this treatment was patients that got the combination actually did significantly better than patients that got just the chemotherapy with placebo pill. And how much better, we saw that--you can see these sort of two curves – separate - and we saw that the survival increased from 9.6 months to 14.7 months.

Again, to emphasize to people that are on this call, these are median survivals, meaning half the patients did better than this and half the patients did worse than this. This does not mean that everybody on the study lived for this long.

And the other thing that was notable in this combination is the remission rate—that's the CR/CRi rate that you can see on the slide—almost tripled, from 28.3% to 66.4%. And so, this clearly showed us that this was a very effective therapy for patients that could not tolerate this intensive induction therapy in the hospital. And this became the new standard of care that now we've been using very well for the past almost 4 years.



What happens after patient is in a complete remission?

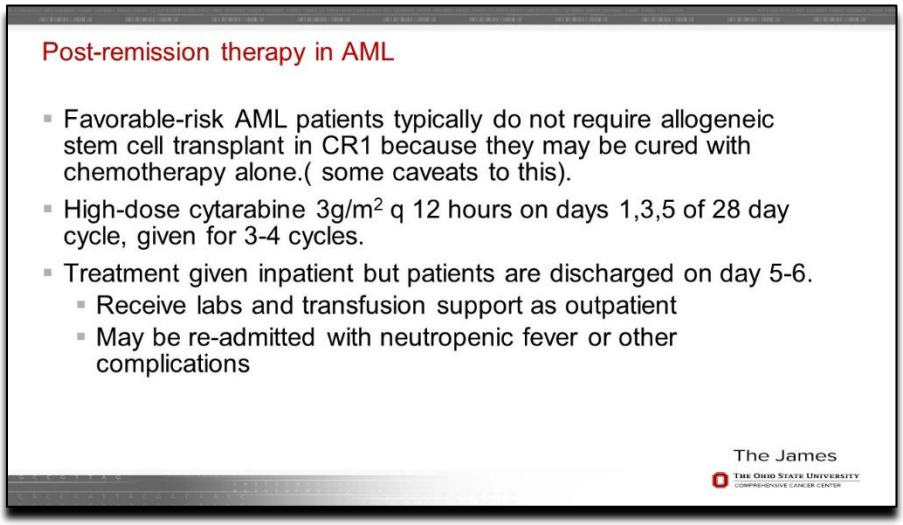
So, now that we discussed the treatment with the patient, either the patient has received intensive induction or azacitidine and venetoclax and—good news—the patient is now in remission. What happens then?

And just to again re-emphasize this is how we define remission when we have a bone marrow biopsy. We really want the leukemia to be gone. The blasts have to be less than 5%. The neutrophil count is over 1,000 and platelets are over 100,000.

But we know that without additional treatment, unfortunately relapse will inevitably occur within months. And so, then we again have the discussion based on age, based on where that ELN risk stratification has happened: whether it's favorable or high risk or in-between.

How did the patient do with induction? Did they get really sick? Did they have multiple complications? Can the patient or does the patient want additional therapy?

And at this point, you have a major decision to make. Based on all of these factors, is chemotherapy alone going to be enough to offer the best chance of continued remission or cure? Or at this point, is proceeding to a stem cell transplant the best option for a long-term remission or cure?



Post-remission therapy in AML

So, what are the decisions that really make this possible?

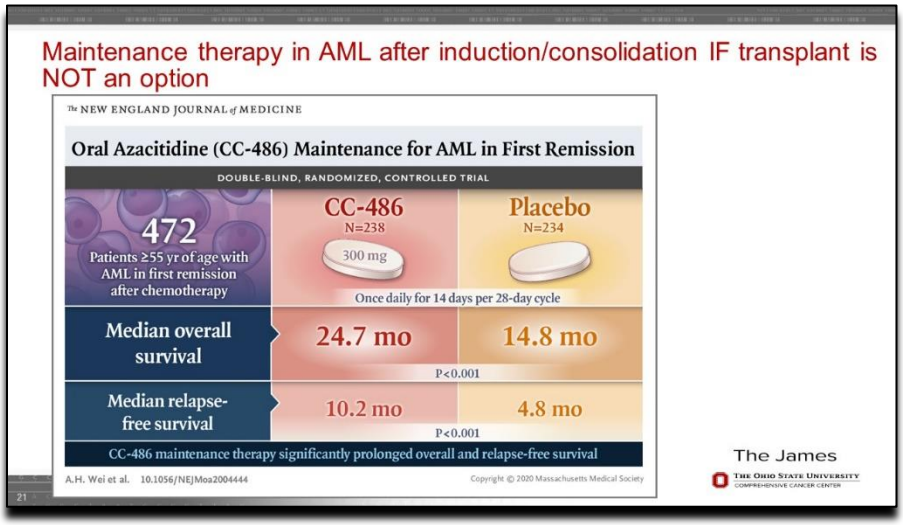
Uma Borate
So, once remission is reached and once we have this discussion, the first thing that I wanted to mention is favorable risk AML patients based on that ELN risk stratification typically do not require an allogeneic—allogeneic meaning from a donor—stem cell transplant in CR1. CR1 stands for complete remission one, meaning complete remission after just one type of therapy because we know that they may be cured with chemotherapy alone.

There are definitely some caveats to this. So, for example, if the patient is favorable risk but they have other mutations which make us concerned that they could relapse sooner, then we do talk about stem cell transplant even in this scenario.

But typically at this point, consolidation chemotherapy may be enough to cure a patient and stem cell transplant is not always recommended. And the type of chemotherapy is again using cytarabine, a drug that we already used previously. But now it's at a different dose and a different schedule. It's typically given for three or four cycles. Each cycle is about a month.

And then when this treatment is given, patients are still usually treated as an inpatient, but most of us now are moving to the option of giving this even as an outpatient. Patients are usually treated for 5 to 6 days. And then while they're recovering from this treatment, you still need regular labs, regular transfusion support.

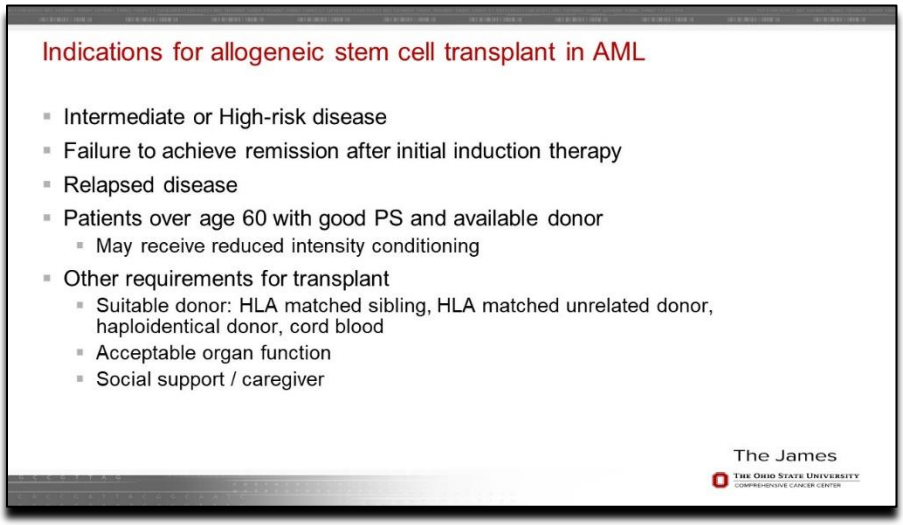
And a very important point that I emphasize to patients is there's still the possibility that even with this treatment, you can develop neutropenic fevers. And if that happens, you have to get readmitted to the hospital for workup and antibiotic therapy.



Maintenance therapy in AML after induction/consolidation IF transplant is NOT an option

So, in general, once you have gone through induction, you have gone through consolidation. And if transplant is not something that you are moving towards, either because of the type of AML you have or maybe this is not an option for a variety of reasons, then there is now the option of maintenance therapy in AML using an oral azacitidine formulation called CC-486 (Onureg®). And this is what we call a recommendation for maintenance for AML in first remission. And this was a trial that again showed the benefit of this approach.

This is a pill that was given to patients versus placebo. It's given once for 14 days in a row every 28-day cycle. So, patient starts it once daily, they take it for 14 days, then they have 14-days' break, and the whole cycle is 28 days. And the median overall survival in patients that were in this study actually significantly went up compared to 14.8 months. For patients that got the drug, it went up to 24.7 months in this study. And you can see down there that even the relapse-free survival, meaning the time without relapse, almost doubled in this study. So this is now also an option that you can talk about with your doctor if transplant is not something that you're proceeding with after you've completed your AML treatment.



Indications for allogeneic stem cell transplant in AML

So, let's talk a little bit about transplant and what that means in terms of why a transplant conversation happens with a diagnosis of AML. So, the first thing I wanted to point out, as we discussed before, if you have intermediate or high-risk disease, your percentage of remission with intensive induction

therapy is usually less than 50%. With high-risk disease, it's probably closer to 30%, 35%. And that's not really good odds for somebody who is fighting AML.

And so, we know that the more aggressive approach to add to this remission so that you can cure a patient and assure them or at least do whatever you can to stack the odds in your favor to have a long-term remission or cure is an allogeneic stem cell transplant. So typically, if you have intermediate- or high-risk disease, this is something that will be discussed with you almost immediately at diagnosis but definitely after the first complete remission has been achieved, because this is the most aggressive sort of proven strategy for long-term remission or cure.

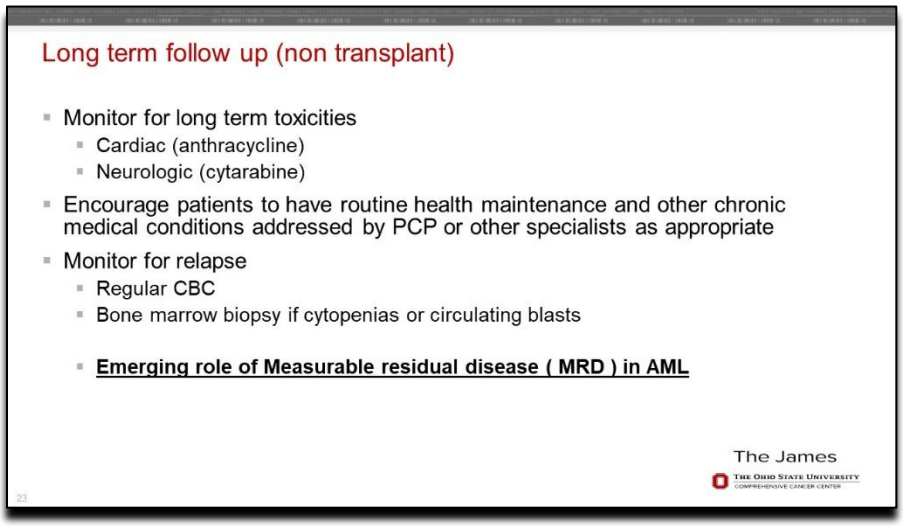
If there is inability or failure of the treatment to achieve remission after initial induction therapy, the treatment is just not effective enough, then we know that this is a high-risk disease and can relapse. And so therefore, transplant is something that is discussed as again a very aggressive strategy to make sure that we can offer patients the best chance of remission.

We also talked about if the disease relapses after all the treatment is done, then we know chemotherapy is just not enough to keep somebody in remission. And transplant is part of the strategy for long-term remission or cure.

And then last but not the least, we know that older patients generally have sometimes intermediate or high-risk disease and have a higher risk of relapse. And so, if they do have an available donor, they're doing well, we definitely recommend transplant in a lot of cases. Just a caveat that the intensity of the conditioning regimen—and that's the regimen people get before they get transplant—is typically reduced to avoid again what we call comorbidities that may come with age.

So other requirements for transplant as many of you may know, you have to find an appropriate donor. We have multiple options now, including what we call haploidentical donors. So not perfect matches. There's cord blood. Acceptable organ function. You have to have healthy heart, lungs, kidneys to survive the transplant in good condition.

And then last but not the least—and this can be a big consideration for people—is having adequate social support or a caregiver that can help them throughout this process and after.



Long term follow up (non transplant)

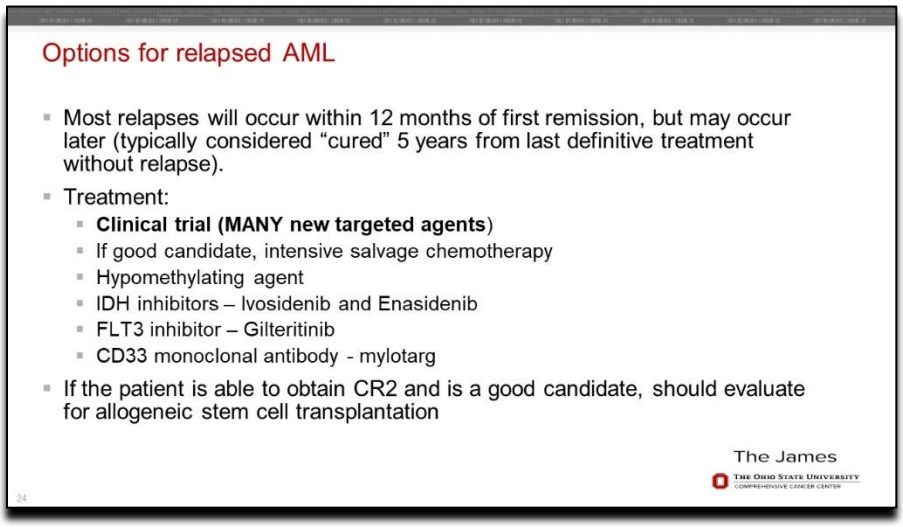
So, what does long-term follow-up look like once all of this done? Hopefully everything has gone well. The disease is under control. But we cannot forget that all of these treatments have long-term toxicities.

So, for example, cardiac toxicity from the anthracycline I talked about, neurological toxicities from cytarabine. These are things that your primary care doctor or your oncologist has to monitor for. And we always tell patients, “This is great, you survived AML. But you have the rest of your life to live.”

So we have to encourage everyone to pay attention to other chronic conditions and screen for other cancers, because we know that this is something that could affect in general just your quality of life and length of life.

We usually monitor for relapse with regular CBCs (complete blood counts). And if we see any sign that something is not quite what it should be, we usually do another bone marrow biopsy.

I won't get into this at this talk, but there is a huge move in the AML research community to study what we call measurable residual disease, or MRD, at various points in AML treatment. So, we're not content with just looking at it under the microscope and saying, “Oh, there’s no more leukemia blasts.” We want to go as deep as possible to look at is there a leukemia cell hiding within 100,000 cells or whether maybe even within a million cells, which we cannot see with the naked eye. And there's a lot of research now going on looking at measurable residual disease in AML.

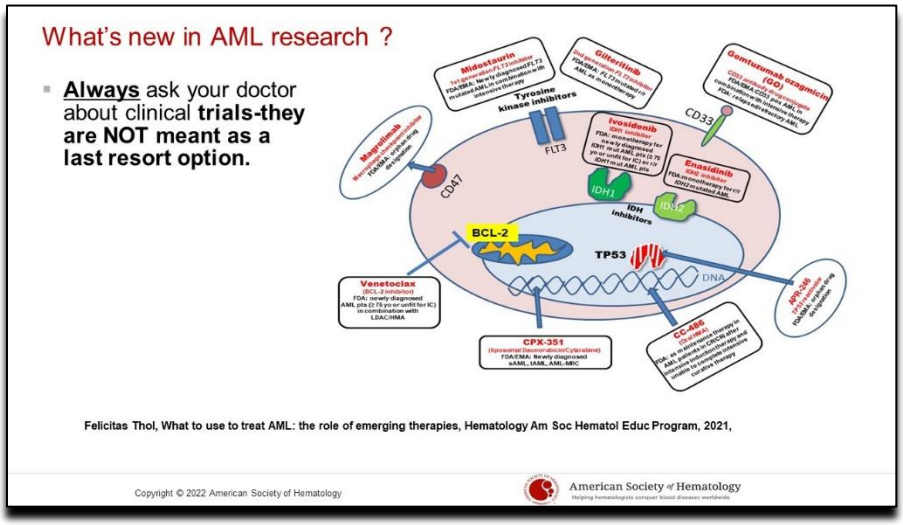


Options for relapsed AML

So I won't go again into detail and options for relapsed disease, but this is a question that a lot of leukemia patients ask: “How will I know if I'm cured?” And I usually tell patients most relapses will occur within the first year or two years of treatment. Very rarely they can happen after 5 years when you usually tell people that they may be cured. And there are multiple treatment options, including clinical trials for many, many targeted agents, that are ongoing.

So if this is something you're dealing with, please know that there are many options right now to target relapsed AML as well.

And if you get into what we call a second remission and you’re doing well, transplant is always a consideration and something that again could be done to guarantee, to a certain extent - and again, guarantee's not really a word we use with any cancer unfortunately - but at least give you the best shot of a long-term remission or cure.

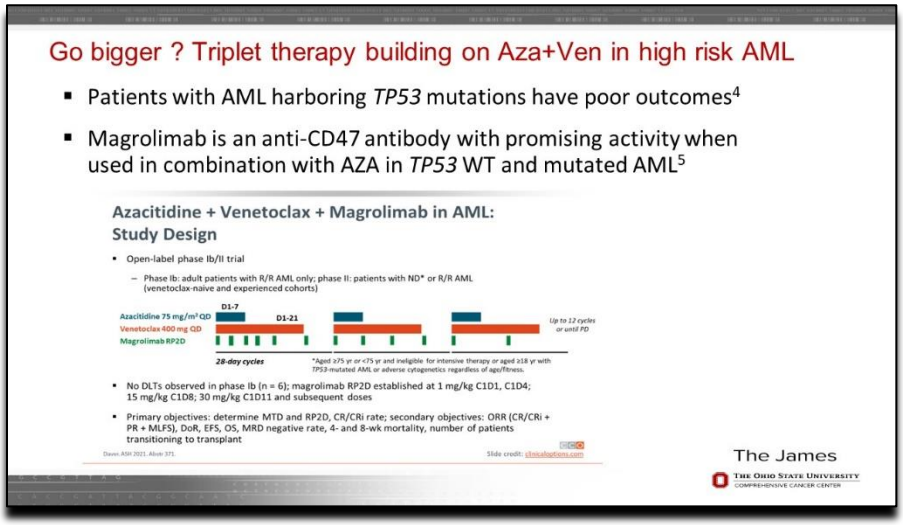


What's new in AML research?

So what's new in AML research? And I put this slide out just to show all the different ways that we're targeting the leukemia blasts. So you can see there's *FLT3* here. So we're looking at *FLT3* inhibitors. As you know, *FLT3* is a mutation that can be targeted using different drugs, like midostaurin (Rydapt®), gilteritinib (Xospata®). Or targeting CD33 using a drug called gemtuzumab ozogamicin (Mylotarg™).

We're targeting different types of chemotherapy. You have venetoclax here. And then you also have magrolimab, which we'll talk about in a minute. It's an antibody that targets CD47. And this is an immune molecule that's present on leukemia cells but also on many immune cells. And it can alert your immune system to help it identify and destroy the leukemia cells that are present in the blood and bone marrow.

So, always ask your doctor about clinical trials. They're not meant as a last-resort option, as Dr. Burd mentioned in her introduction.

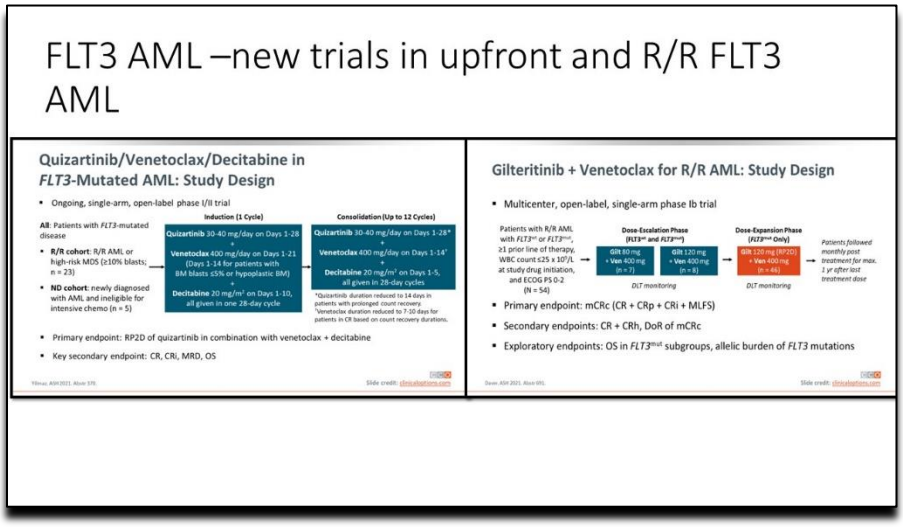


Go bigger? Triplet therapy building on Aza+Ven in high risk AML

So, the things that we're working on is, do we go bigger? Do we build what we call triplet therapy on top of the azacitidine and venetoclax combination that I just mentioned? Do we then add things like magrolimab, which is a CD47 antibody I just described? We already know that it has very promising activity against what we call a *TP53* mutation, which places patients in this adverse risk and doesn't really respond well to our chemotherapies and other treatments. So if we add magrolimab to this

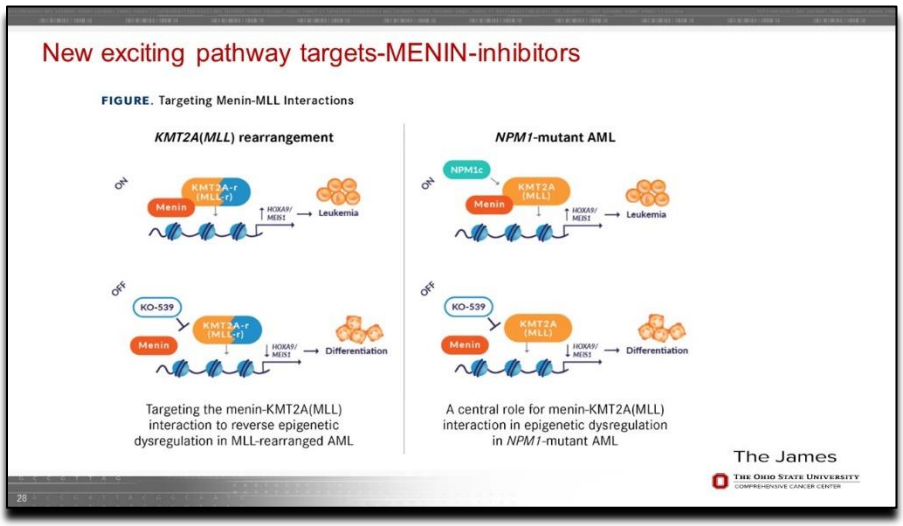
combination, can we achieve more remissions—more long-term remissions—and better outcomes? So this is something that is being looked at.

I do want to mention that currently, all studies looking at magrolimab are on what we call FDA clinical hold because they're analyzing certain events that have taken place in these studies to make sure that they're not an added risk to patients. But once that is analyzed and if this is considered safe, these. studies will move forward. But right now, these studies are not enrolling patients on magrolimab trials, So just something that I wanted to mention that has happened a little bit more recently.



***FLT3* AML –new trials in upfront and R/R FLT3 AML**

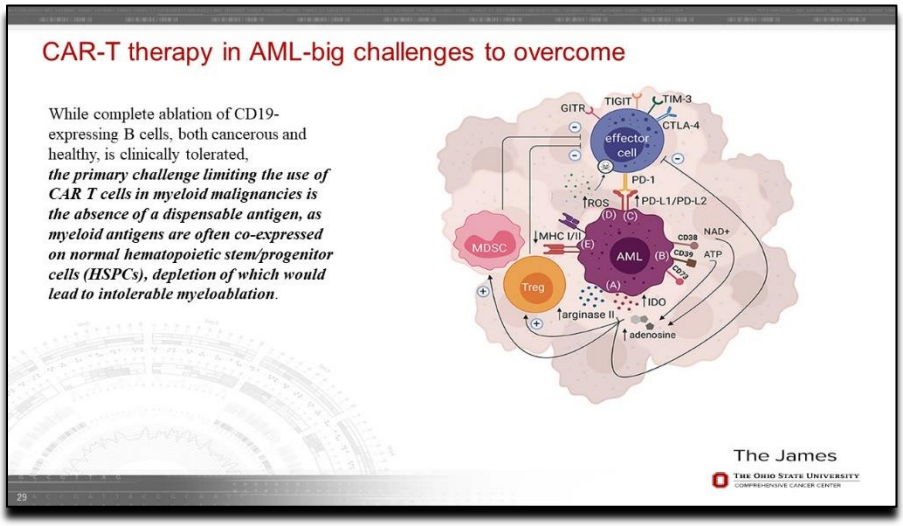
The other combination, so for example, for *FLT3* AML, we're looking at different combinations, adding *FLT3* inhibitors both in newly diagnosed patients or in relapsed/refractory patients, again to maximize response and make patients candidates for long-term remissions and stem cell transplant.



New exciting pathway targets-MENIN-inhibitors

And then this, I think, is something that I'm personally very excited about. It's a new pathway. We call these drugs menin inhibitors. And this is a pathway that exists in leukemia cells that can be targeted with these new drugs, specifically in leukemias that have *MLL* gene rearrangements and *NPM1* gene rearrangements, both of which can be seen either in the favorable risk, intermediate risk, or in the high-risk patients.

This is an oral medication that's showing a lot of promise in early phase trials in patients who may have gone through many therapies and still not achieved remission.



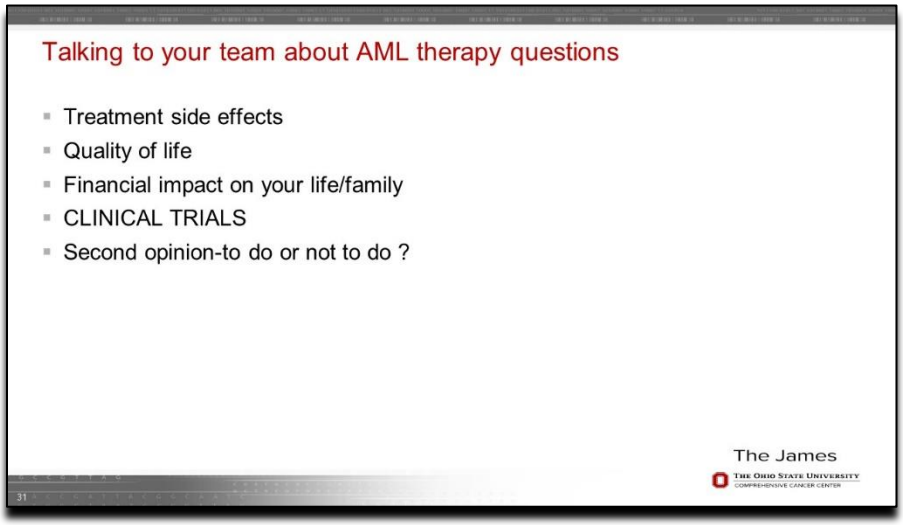
CAR-T therapy in AML-big challenges to overcome

Another question that I know many of you may have: “What about CAR-T therapy?” We've heard about the success of CAR-T in ALL, which is lymphoblastic leukemia. And I will say the biggest challenge we have is the lymphoblastic leukemia CAR-T cells were directed against CD19, which in both cancerous conditions and in healthy conditions, if you destroy all your B cells without CD19, your body can still tolerate it. We can give you immune therapy to protect against infections, but we haven't really identified that magic target in AML, because most often the targets on AML blasts are also present on normal hematopoietic stem cells that you need and I need for normal platelets and neutrophils.

And so, we haven't really figured out how to kill just leukemia cells using CAR-T therapy, but I 'm really hopeful that we'll get there in the future.

Talking to your AML treatment team about what matters to you

So I wanted to finish this talk about telling you to please talk to your AML treatment team about what matters to you. When in doubt, ask the questions that you may be afraid to ask. But I always think it's better to ask things, because there's a lot of information that is out there that we would like to share with you but also guide you to the right sources.

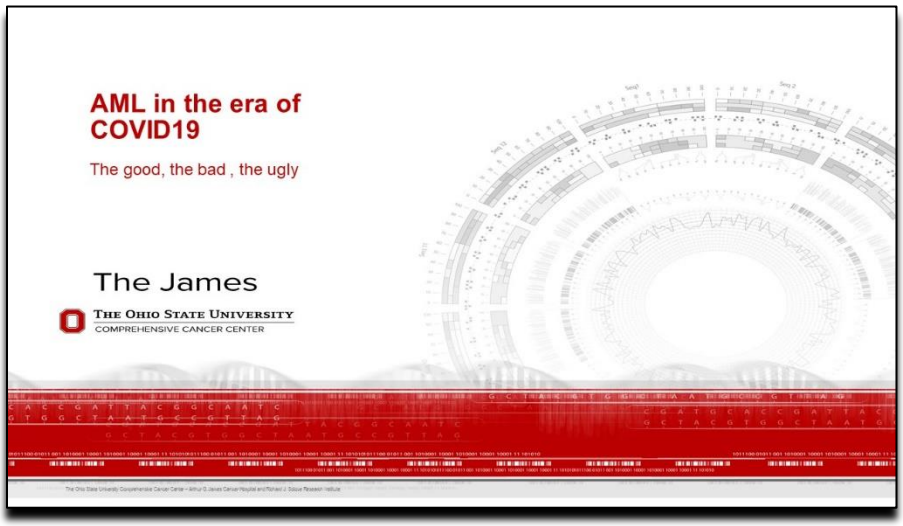


Talking to your team about AML therapy questions

And these are the things that I tell our patients to please ask about, because sometimes as physicians we forget that these are things that you may not know about or may not tell you everything that might be important to you.

What are the treatment side effects? How is my quality of life going to be? What will be the financial impact on my family, my life?

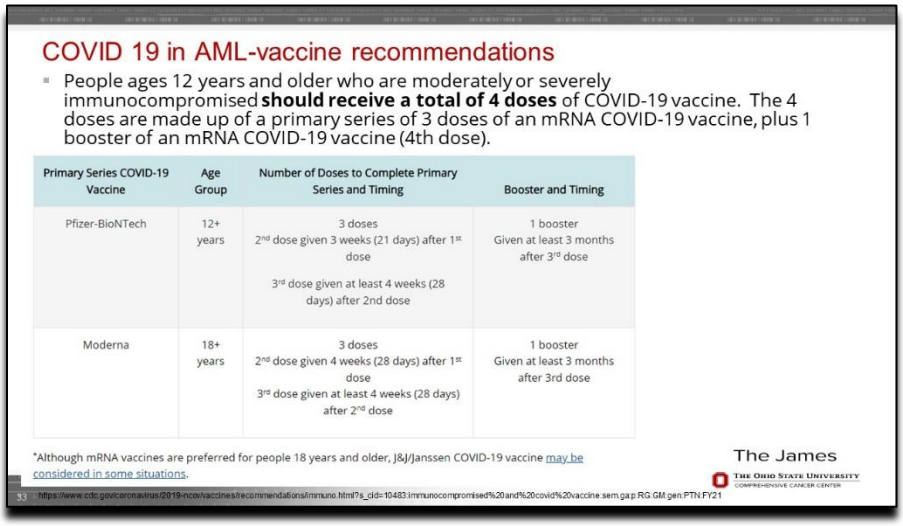
What clinical trials do you have right now? And is it something that I would be eligible for? And last but not the least, should I get a second opinion? Is this something that I should do now or should I do later? What would you recommend? And I again want to encourage people to ask their doctors these questions because I think these are important when you're going through therapy at any phase in therapy.



AML in the era of COVID19

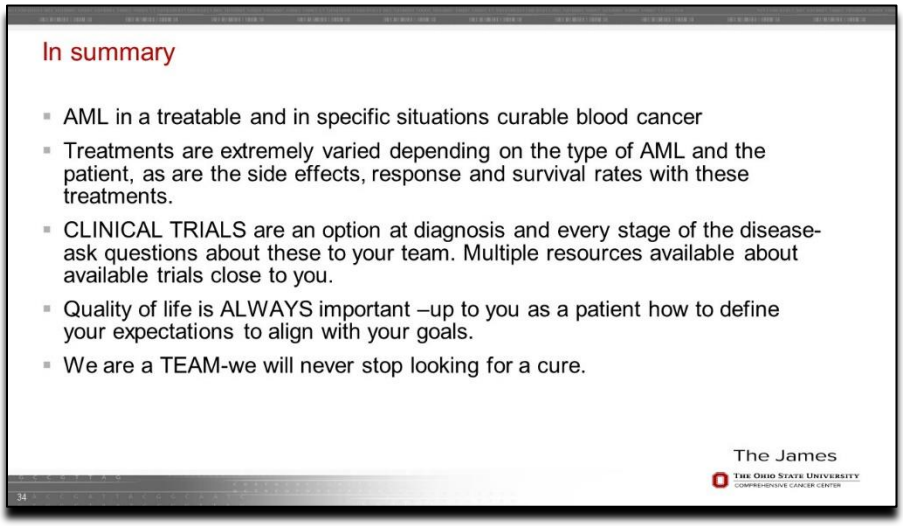
So in terms of COVID-19 - is something that our leukemia patients have had to deal with for 2 years. I think this is in general caused a lot of distress and disruption for all of us but especially in the healthcare field, especially while treating leukemia.

In an unusual twist, I do think some good came out of it when we were allowed to do virtual visits. So it was really nice to be able to take care of patients without having to have them travel 2, 3, 4 hours to see me.



COVID 19 in AML-vaccine recommendations

But I did want to mention that this is the current recommendation for COVID-19 in AML. These are the vaccine recommendations by the CDC. For patients that are 12 or older, we typically recommend four total doses. And you can see the schedule here for Pfizer-BioNTech and Moderna and when you should receive the third and then the fourth booster. So this is something that you may want to talk to your doctor about if you are in this space.



In summary

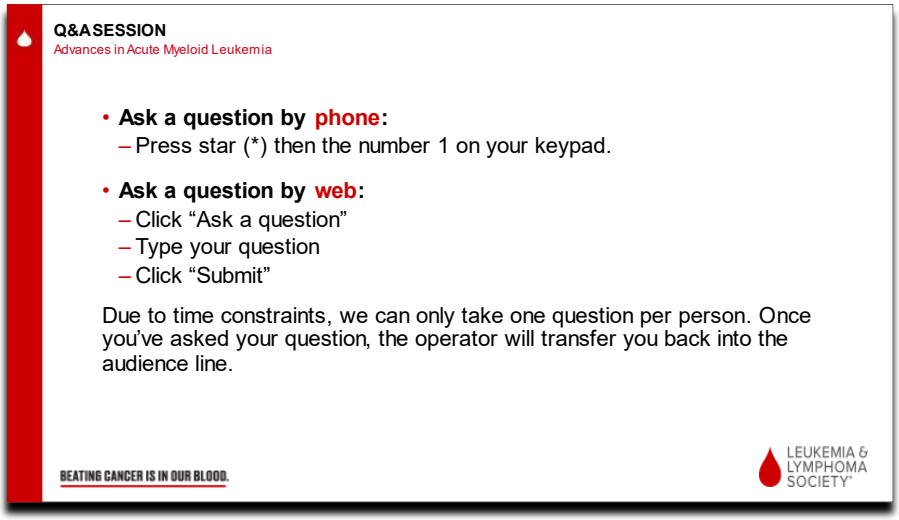
So, in summary, I did want to emphasize AML is a treatable disease in specific situations. It's definitely a curable blood cancer. The treatments are extremely varied. Again, like I said it depends on the type of AML. It depends on the patient. And so are the side effects.

The responses and survival rates again very different. As Dr. Burd said in her introduction, it could be like 10 different diseases all rolled in one.

Clinical trials are always an option at every stage of your disease, right from diagnosis to relapse to otherwise. Please ask your team about them. And there are multiple resources available that I'm sure LLS will talk a little bit more about.

And this is something that I always say: quality of life is always important. But it's up to you as the patient how you define that, what your expectations are. Are they aligned with your goals? And to communicate that to us because I can tell you, I've had very different conversations with patients about what they think is important for their quality of life.

And then last but not the least, we are a team. I'm grateful to The Leukemia & Lymphoma Society and all of you on the call. We together are never going to stop looking for a cure. So I really appreciate all the support. Thank you.



Q&A Session

Lizette Figueroa-Rivera
And thank you so much, Dr. Borate, for your very informational presentation. It is now time for the question-and-answer portion of our program. And for everyone's benefit, can you please keep your questions general in nature without too many personal details?

Lizette Figueroa-Rivera
Thank you. And we'll take our first question from the web audience. Doctor, Phil is asking about MDS, myelodysplastic syndrome: "Is it considered a kind of AML but at a lower spectrum?"

And also, Kathleen is a caregiver to her mom who has MDS and is asking, "Is a bone marrow biopsy required to know if MDS has progressed to AML?"

Uma Borate
So I'll take Phil's question first. MDS is--can be considered sometimes as what we call a precursor to acute myeloid leukemia. So it's a very arbitrary division, Phil. The process is not that dissimilar in that both MDS and AML have the same type of molecular or different mutations. They have the same type of chromosomal abnormalities.

But typically in MDS, the number of these blast cells are less than 20% and the treatments are definitely different. Once the blast cells go above 20%, the patient is considered now to have acute myeloid leukemia, or AML.

So, sometimes we call this a precursor to AML. Sometimes it's called pre-leukemia. I don't think any of them are really accurate because there are MDS patients that will never progress to acute myeloid

leukemia and do fine with other treatments. And then there are some that are so much on the borderline that they will progress very quickly to acute myeloid leukemia despite treatments.

So, that's question one.

And then the second question in terms of how do you assess progression of MDS. I think there can be clues without a bone marrow biopsy that the MDS may be progressing. So, for example, if you start needing more transfusions or your loved one starts needing more transfusions, that's concerning.

But you're right that the most definitive way to diagnose MDS progression is with a bone marrow biopsy.

Lizette Figueroa-Rivera
Thank you. And we'll take the next question from the telephone audience, please.

Operator
This question comes from Elaine calling from California. Please go ahead.

Elaine
But my sister's done about six rounds of chemo. She tried an immunotherapy and she's got AML, and she's been in treatment about 10 months. And they were talking about doing another drug because the immunotherapy, she had to be pulled off the clinical drug. It was not working. But they're talking about navitoclax along with venetoclax and another drug. She's being treated at City of Hope. And I'm curious about other clinical trials and this particular drug or if City of Hope, with all the clinical trials, is a good place. Should we be reaching out to another, if that makes sense?

Uma Borate
Yes. So, I will say City of Hope is a fantastic institution, and they typically have a very, very large number of clinical trials. So, I think if that's something that's being discussed with your sister, I do think that's a really good place to be at.

Unfortunately, I can't answer specifics not knowing all the different details about her treatment. But I think again these are great questions. If you accompany her to her visit or are part of that discussion with the team and ask specifics about why was this treatment chosen, why this trial—I think those are really good questions to ask her team.

Elaine
Well, can I ask other question? Can I just ask another part? They had--with regular chemo on five rounds, they got her down to 5% and it's now gone back up because they had to--in-between the clinical trials.

When and at what percentage may AML progress to major organs? Is there a percentage if she's at 50% versus like when and how?

Uma Borate
That's a great question. There's unfortunately not a cutoff where you're like, “Oh, 50% means now it's going to the heart or the lungs or the kidneys or that it's overwhelming the body.” I've had patients that have very high levels of leukemia in the bone marrow that don't otherwise have what we call organ issues or dysfunction.

It's so dependent on that particular specific case and where the patient is in that treatment journey, how weak they are, what other medical conditions they have. But there's not one level at which it's considered too advanced.

Lizette Figueroa-Rivera
Thank you. And our next question comes from Mary. Mary asks, “What degree of isolation is necessary to avoid infection with a suppressed immune system?”

Uma Borate
That's a great question, Mary. We get that a lot. Obviously, patients want to do everything they can to protect themselves and as do caregivers.

Typically, our answer is we want to balance living life with the risk of being too isolated. So, with COVID—but even without COVID—we usually say the biggest risk that you have is all the different bacteria that are on your skin, in your body, and in your mouth. That's not something you can do a lot about.

But what you can control is not being in environments where there's a lot of people or crowds where you can be exposed to different things, like coughing and sneezing and so on. And obviously, now with COVID sort of on the wane, there's a lot of situations where masks are not in use.

So we just tell people while they're going about their daily lives to be careful. Maybe go to restaurants when it's not busy. Maybe you go to grocery stores again when it's not busy. And really try to stay away from people who are sick.

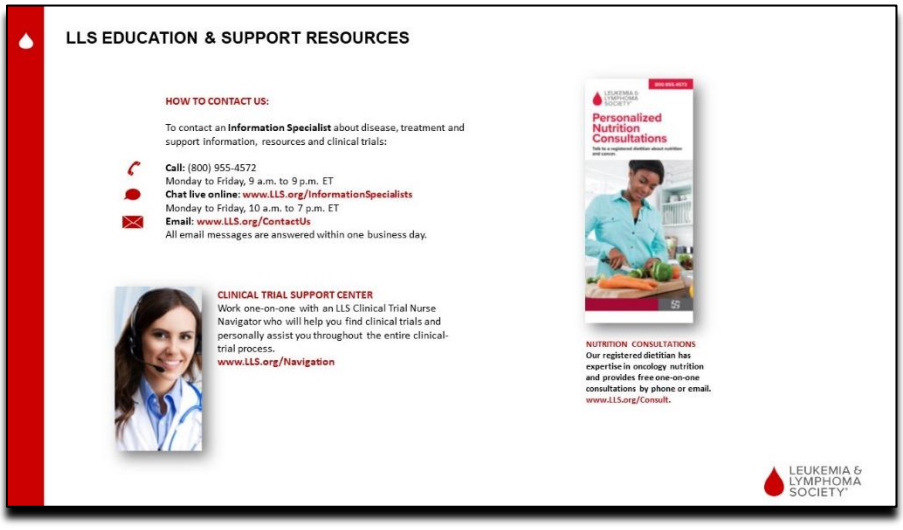
But other than that, there's not really evidence that a very high degree of isolation is going to be helpful, because like I said, the biggest risk of infection is from your own body and there's really not any way you can isolate from that.

Lizette Figueroa-Rivera
Thank you so much. And our last question today comes from Tony. Tony asks: “I’ve been in remission for 8 years. I will be 60 this year. Am I more at risk for relapse?”

Uma Borate
First of all: congratulations, Tony! That's amazing to hear that.

Not really in terms of because you're turning 60. I think the risk of relapse goes down significantly after 5 years. As we say, we tell patients for the most part you're cured after 5 years.

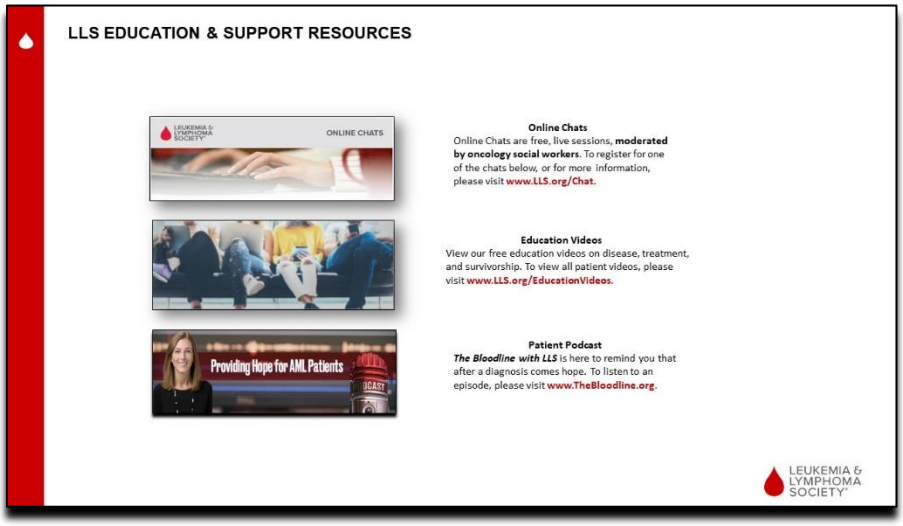
In general, the risk of relapse remains fairly consistent. Obviously, the longer you live, there's just a chance that anything can happen. But there isn't really this increased risk just because you're turning 60 or are going to be older than 60.



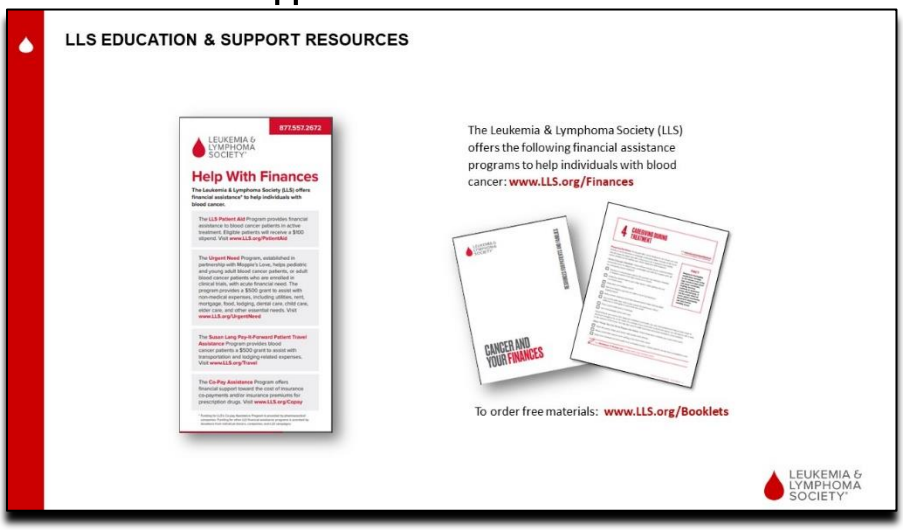
LLS Education & Support Resources

Lizette Figueroa-Rivera
Well, thank you so much, Tony, for your question, which was our final question today.

And a special "thank you" to Dr. Borate for sharing her experience with us and for her continued dedication to our blood cancer patients. If we were not able to get to your question today, you can contact an Information Specialist at The Leukemia & Lymphoma Society at 1-800-955-4572 from 9:00 AM to 9:00 PM Eastern time or go to LLS.org/InformationSpecialists to chat online. Or you can email us at LLS.org/ContactUs.



LLS Education & Support Resources



LLS Education & Support Resources

As Dr. Borate mentioned, a clinical trial may be a treatment option for you. LLS has a Clinical Trial Support Center where Clinical Trial Nurse Navigators will personally assist you throughout the entire clinical trial process. And you may reach out to them at www.LLS.org/Navigation.

Thank You

Again, we'd like to acknowledge and thank Bristol Myers Squibb and Genentech, Inc., and Biogen for their support.

Dr. Borate, thank you again for volunteering your time with us today. And on behalf of The Leukemia & Lymphoma Society, thank you all for joining us for this program. Please let us know what you need from us during this time. And you take care.