Slide 1: EXPLORING NEW APPROACHES IN AML TREATMENT

Greetings and welcome to ***Exploring New Approaches in AML Treatment*** telephone and web education program. It is my pleasure to introduce your moderator Lizette Figueroa-Rivera.

Slide 2: INTRODUCTION

Hello, everyone. On behalf of The Leukemia & Lymphoma Society, I'd like to welcome all of you.

Special thanks to Dr. Joseph Jurcic for volunteering his time and expertise with us today, especially during these busy times.

Advancements in genomics and precision medicine are fueling a renaissance in acute myeloid leukemia (AML) research. Today we know that AML is not a single disease, but rather a group of more than 10 subtypes and other rare mutations. Once an elusive enemy, researchers are now able to identify and target the specific subtypes, and 9 new therapies, all advanced with LLS support, have been added to our arsenal in the past few years, following approval from the U.S. Food and Drug Administration, the FDA.

Still much work remains. One quarter of LLS's annual research funding is dedicated to AML. And, LLS is leading the charge against AML through the Beat AML Master Clinical Trial, a collaborative clinical trial that aims to change the paradigm of treatment through a precision medicine approach. And, to learn more about LLS's research initiatives in AML, and our Master Clinical Trial, please visit www.LLS.org. We strive to see even more advancements and treatments for AML in the upcoming years.

For this program we would like to acknowledge and thank Agios Pharmaceuticals, Bristol-Myers Squibb, Genentech and Biogen, and Jazz Pharmaceuticals for support of this program.

I am now pleased to introduce Dr. Joseph Jurcic, Professor of Medicine at Columbia University Irving Medical Center, Director of Hematologic Malignancies, and Attending Physician at New York-Presbyterian Hospital, New York City, NY.

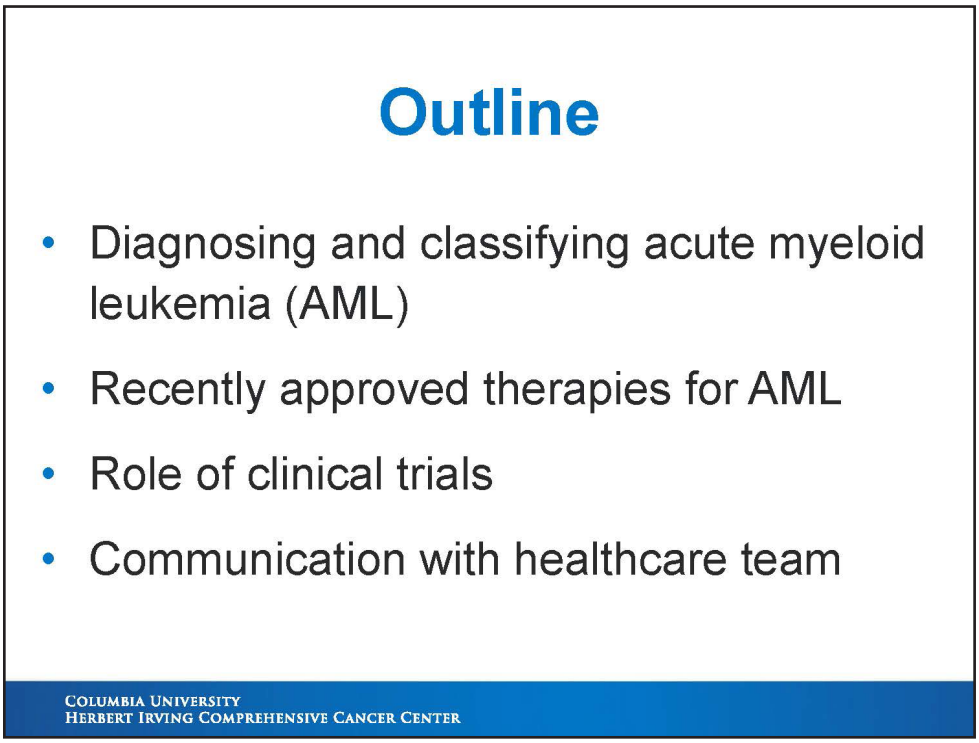
Dr. Jurcic, I'm privileged to turn the program over to you.

Slide 3: EXPLORING NEW APPROACHES IN AML TREATMENT

Thank you so much for having me today, and you're completely correct, this is a very exciting time in AML therapy with multiple new therapies that have been approved and more on the horizon.

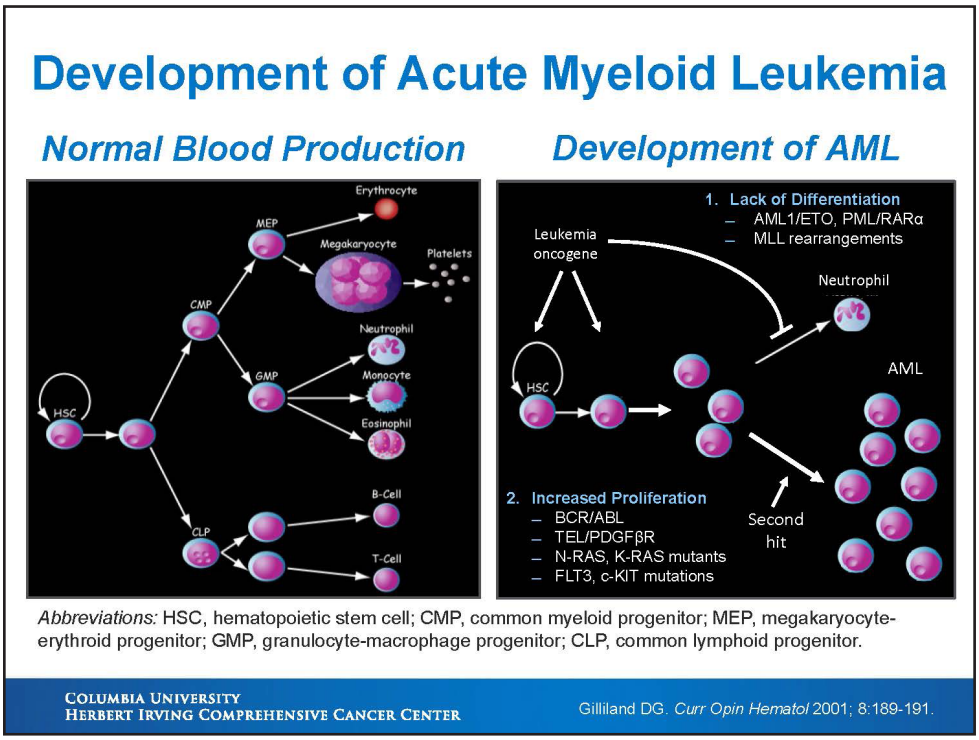
Slide 4: DISCLOSURES

So here are my disclosures. I receive research funding from a number of pharmaceutical companies and serve as an advisor and consultant to several companies as well.



Slide 5: OUTLINE

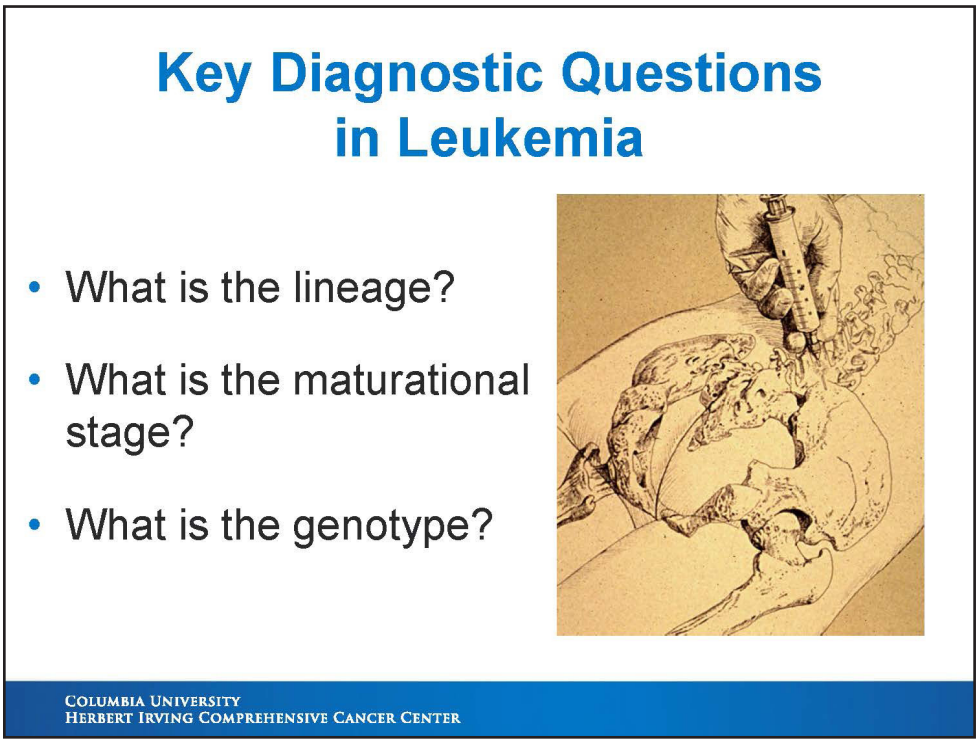
So, today we're going to be talking about the diagnosis and classification of acute myeloid leukemia. And, this is particularly important because so many new tools are available to understand this disease and actually help direct therapy. And, that will lead directly into the second topic which are the recently approved drugs for acute myeloid leukemia. We'll also talk about the role of clinical trials and advancements in new therapies over time. And finally, discuss communication with the healthcare team and give hopefully some useful advice as you navigate this complex disease.



Slide 6: DEVELOPMENT OF ACUTE MYELOID LEUKEMIA

So, to understand how acute myeloid leukemia develops you really need to understand something about normal blood cell production. And so, on the left hand panel we see a schema of normal blood production. There's a hematopoietic stem cell that's capable of self-renewal, and the stem cell can differentiate into 2 main lines of blood cells. There's the common myeloid progenitor that gives rise to red blood cells and to platelets and neutrophils and other related white blood cells. And then, there's the lymphoid pathway that gives rise to B cells and T cells.

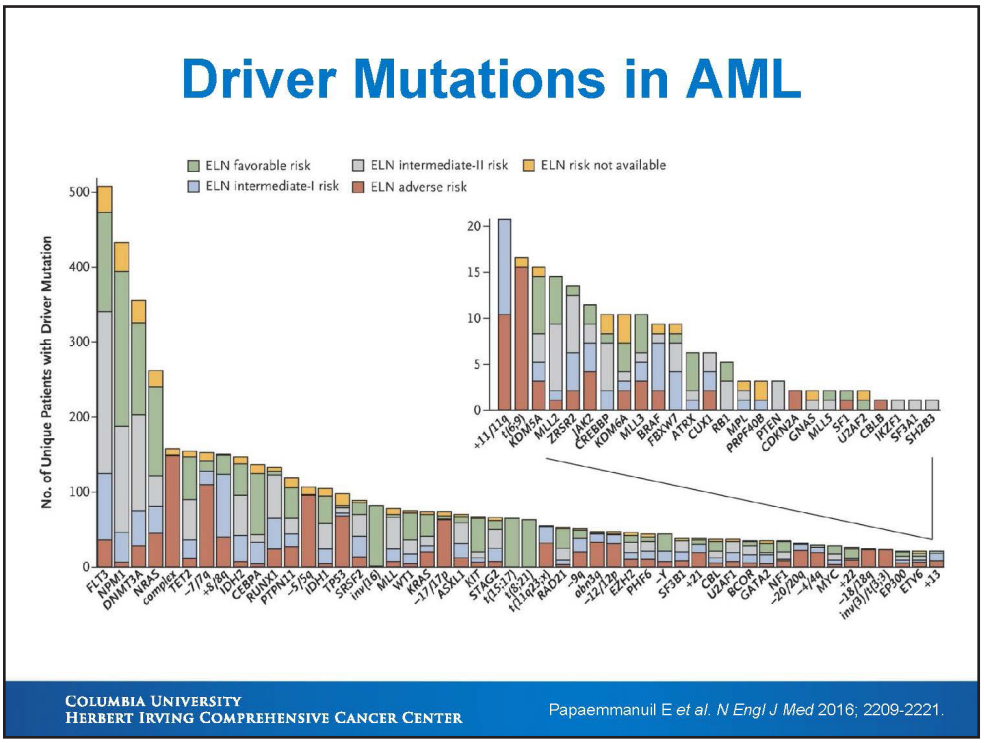
In acute myeloid leukemia there're really 2 hallmarks of the disease. There's a lack of differentiation. So, the cells get stuck at an early stage and are incapable of maturing into normal neutrophils, quote, infection-fighting cells. And then, there's increased proliferation. So, these early cells then just begin to grow out of control and overtake the bone marrow, leading to ineffective blood cell production. And, this is what's responsible for the impaired immune system, for the anemia, and for the low platelets, putting people at risk for bleeding complications.



Slide 7: KEY DIAGNOSTIC QUESTIONS IN LEUKEMIA

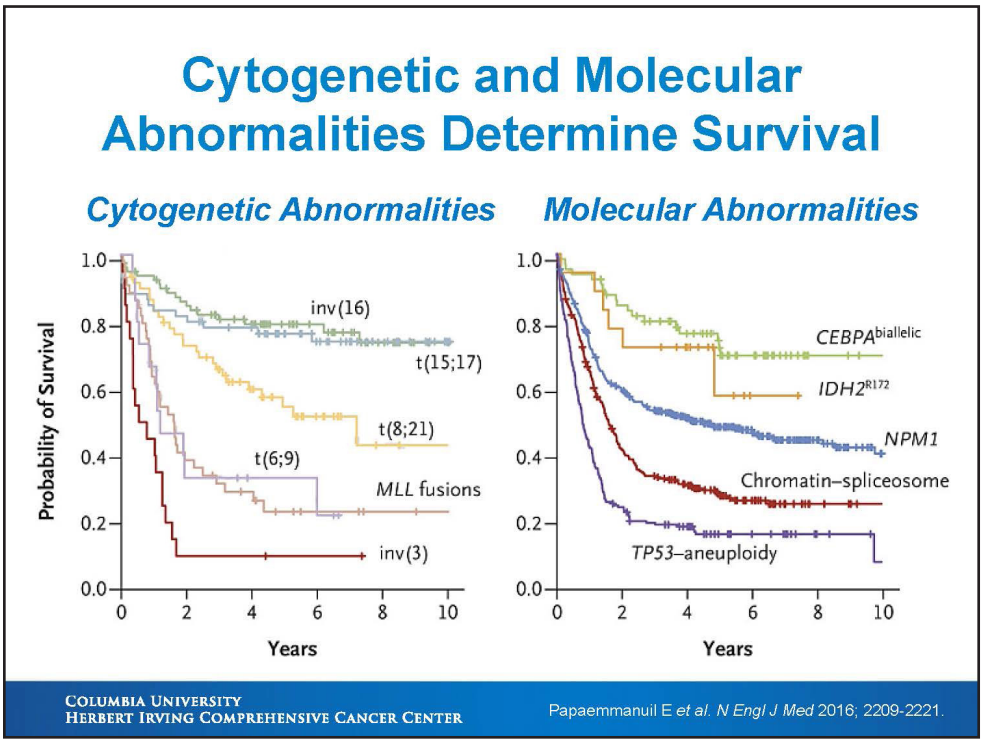
So how do we diagnose acute myeloid leukemia? Well, we can analyze the blood, but the gold standard is still a bone marrow aspiration and biopsy. And, we do this to determine the lineage. So, are we dealing with myeloid cells, with T cells, with B cells, are we dealing with early myeloid cells, so-called blasts, or more mature cells like promyelocytes or monocytes, abnormal red blood cells, abnormal platelets? These are all key diagnostic questions.

And then, we want to understand as much as we can about the origins of the leukemia. So, we want to look at the genotype, what are the chromosome changes that have occurred in this particular person's disease, what are the genetic abnormalities? This is really important in determining prognosis and also can help lead to a therapeutic pathway for this particular individual. So, when we talk about personalized medicine, this is a prime example. And, we in AML have been doing this now for over a decade.



Slide 8: DRIVER MUTATIONS IN AML

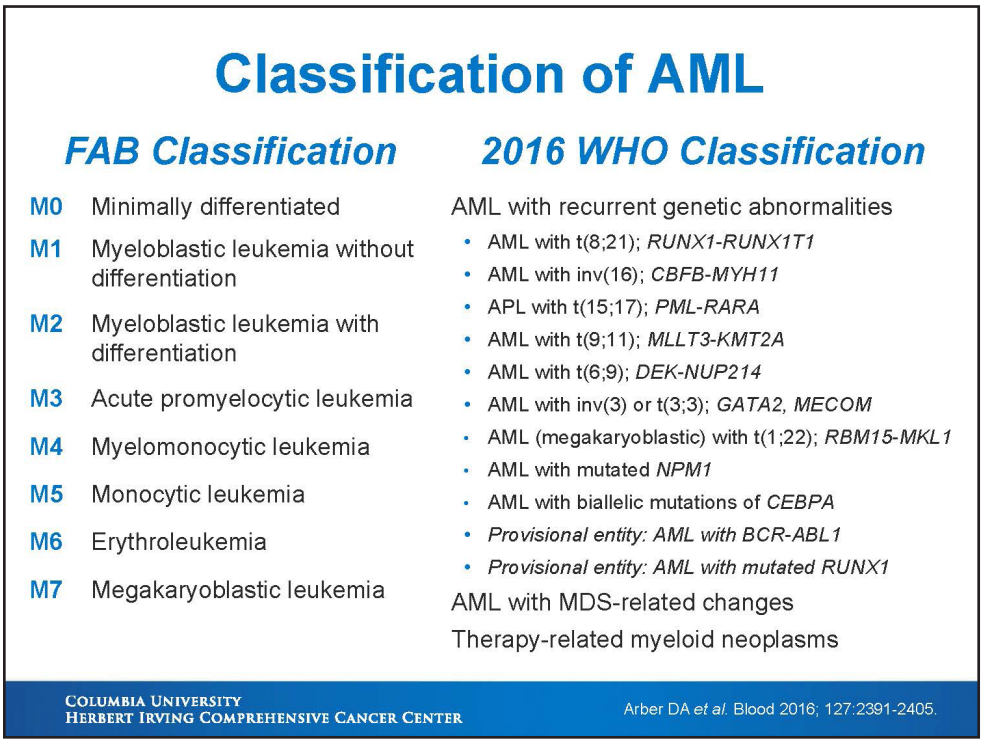
You can see here in this slide some of the driver mutations that can occur in acute myeloid leukemia. And, there's obviously a large number, but some of the more common are the FLT3 abnormalities, which we're going to discuss a bit later, this serves as an important target for therapies, as well as NPM1, DNMT3A. We also have targeted therapies for IDH1 and IDH2, which we'll be discussing. Others at this point serve as prognostic markers like RUNX1 and so forth.



Slide 9: CYTOGENETIC AND MOLECULAR ABNORMALITIES DETERMINE SURVIVAL

So taken together, these chromosome abnormalities and molecular abnormalities can help define prognosis. And so, we look at certain patients with inversion 16, or 15;17 translocation, which is the abnormality in a subtype of AML called acute promyelocytic leukemia, and these patients have an overall better outlook, compared to those who have unfavorable chromosome abnormalities like inversion 3.

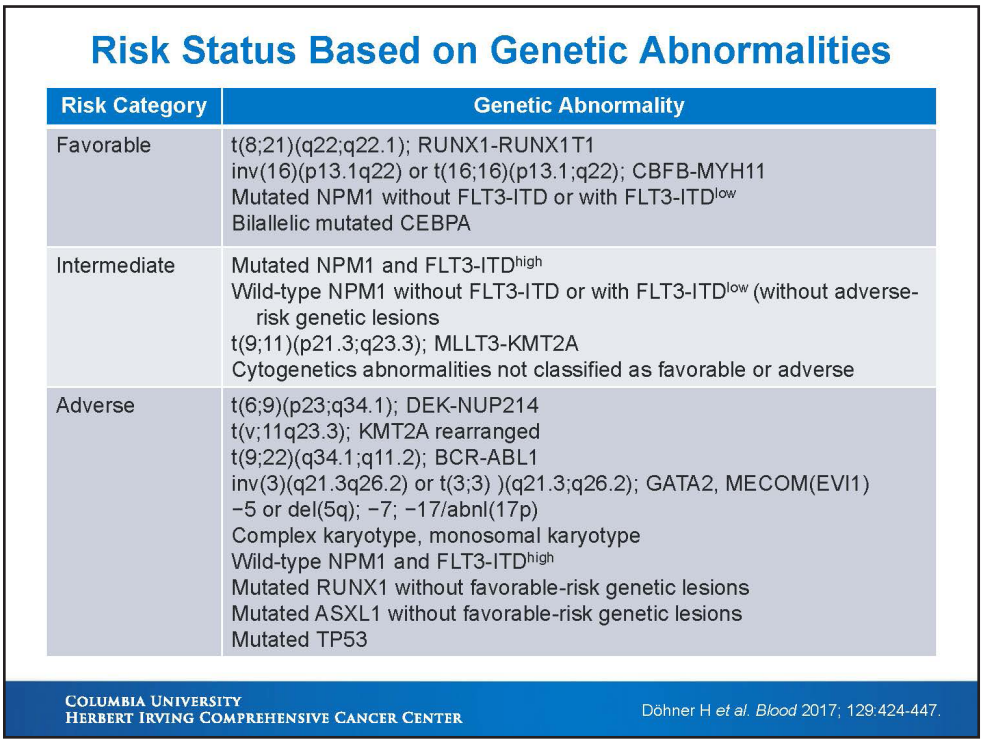
Similarly, certain molecular abnormalities are associated with a more favorable prognosis, like IDH2 mutation, NPM1 mutation, whereas others like TP53 abnormalities are associated with a worse prognosis.



Slide 10: CLASSIFICATION OF AML

In fact, this sort of data has really allowed us to rethink how we classify acute myeloid leukemia. Back in 1976, a group of pathologists who were French, American, and British, came up with the so-called FAB Classification System. And, in this system the various subtypes of AML were named solely on the basis of how these cells looked under the microscope, were these immature blast cells, were these more mature monocytes, promyelocytes, etc.

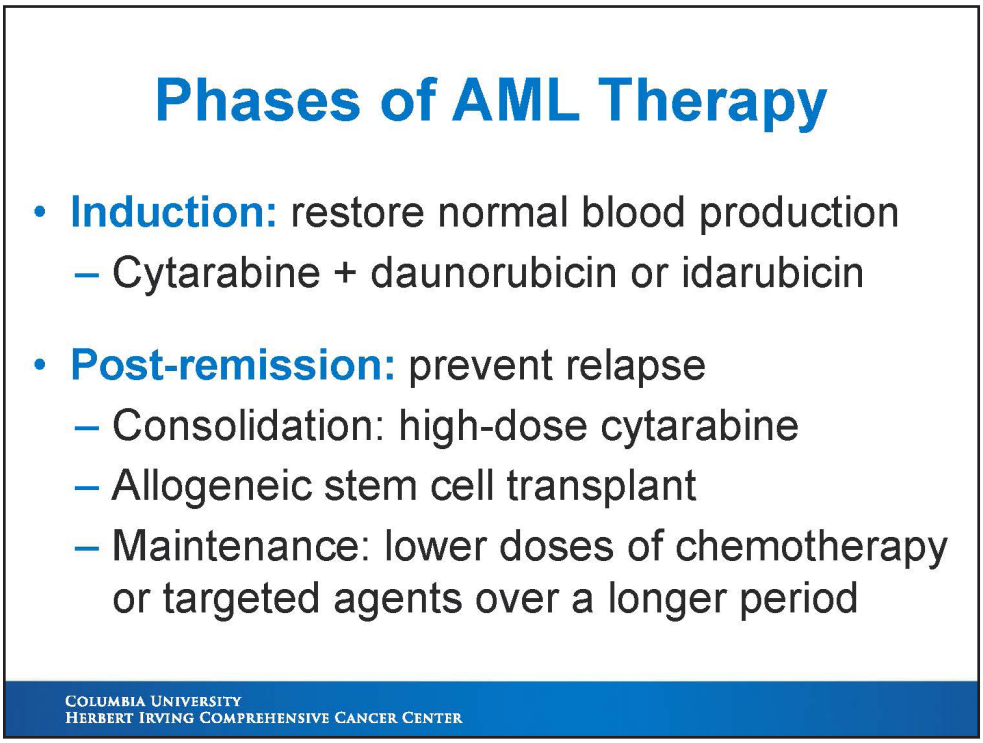
Well, all of this really changed in 2008 with the World Health Organization Classification System, and then that system was updated in 2016. And so, now each subtype of AML is named according to the unique abnormalities that occur in that disease. For instance, 8;21 translocation has become its own type, etc. Right down the list. And so, we can see that now we're thinking of the disease not so much as how it looks under the microscope, but what are the genetic and chromosome abnormalities that occur in that particular person's disease, that can drive that disease and bide our therapies.



Slide 11: RISK STATUS BASED ON GENETIC ABNORMALITIES

And so, it gets even more complicated when we think about risk stratification, because we use all of this information to determine the risk categories into favorable, intermediate risk, or adverse risk categories.

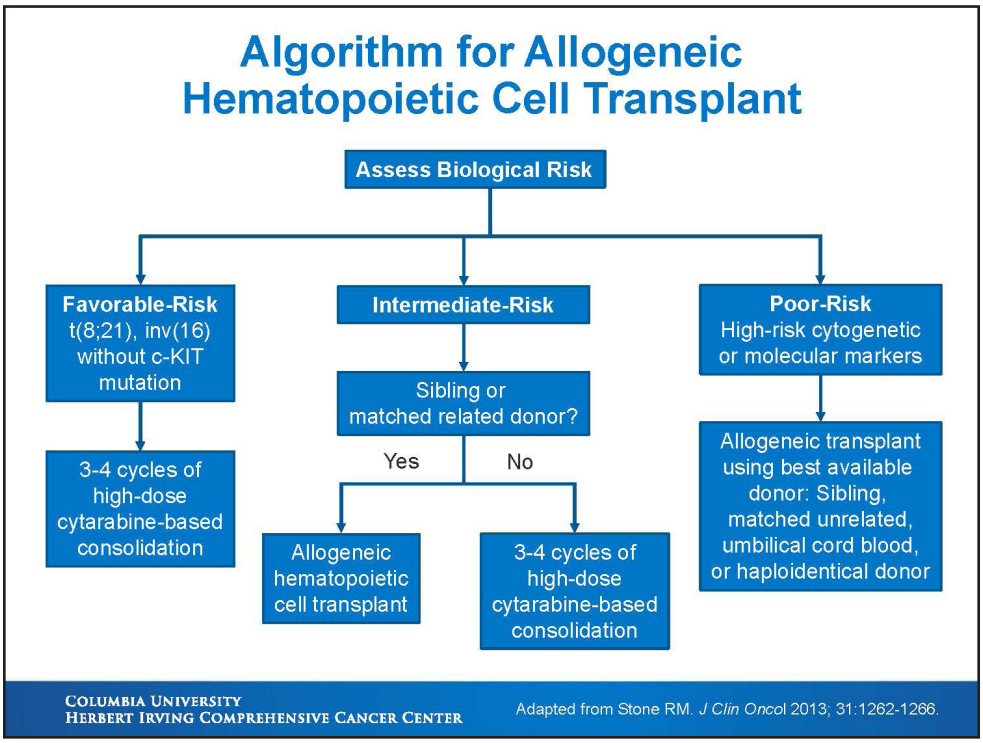
And, this changes every few years. This is the current one that we are using now, again, don't expect anybody to memorize all of this, but it's very important that your physician perform these tests so that we can accurately risk-stratify your disease, because this is going to really help define what path you're going to take as you go through the process.



Slide 12: PHASES OF AML THERAPY

And so, for younger patients, generally we think of the disease as having 2 phases of therapy. The first is induction treatment. And, the purpose of induction therapy is to restore normal blood cell production. This is usually done with 2 medications, cytarabine, typically given over 7 days, and 3 days of either daunorubicin or idarubicin.

After a patient will go into remission, then we need to give additional therapy to prevent relapse, this is so-called post-remission therapy. When somebody comes in with newly diagnosed acute myeloid leukemia, they have about 10 to the 12th leukemia cells in their body, so that's 10 with 12 zeroes after it. And, we need to kill about 99.9% of those cells to get that person into a remission, to have their bone marrow looking normal and their blood counts restored to normal. But, that still leaves 10 to the 9th, 10 with 9 zeroes after it, disease, that many leukemia cells in their body. And so, we need to destroy those cells to give the highest chance of a cure afterwards. And so, we do this with post-remission therapy that can either consist of consolidation therapy, often with higher doses of chemotherapy, or allogeneic stem cell transplant. Now, more commonly what we're seeing is maintenance therapy integrated into AML treatment programs with lower doses of chemotherapy or with targeted agents given over a longer period of time.



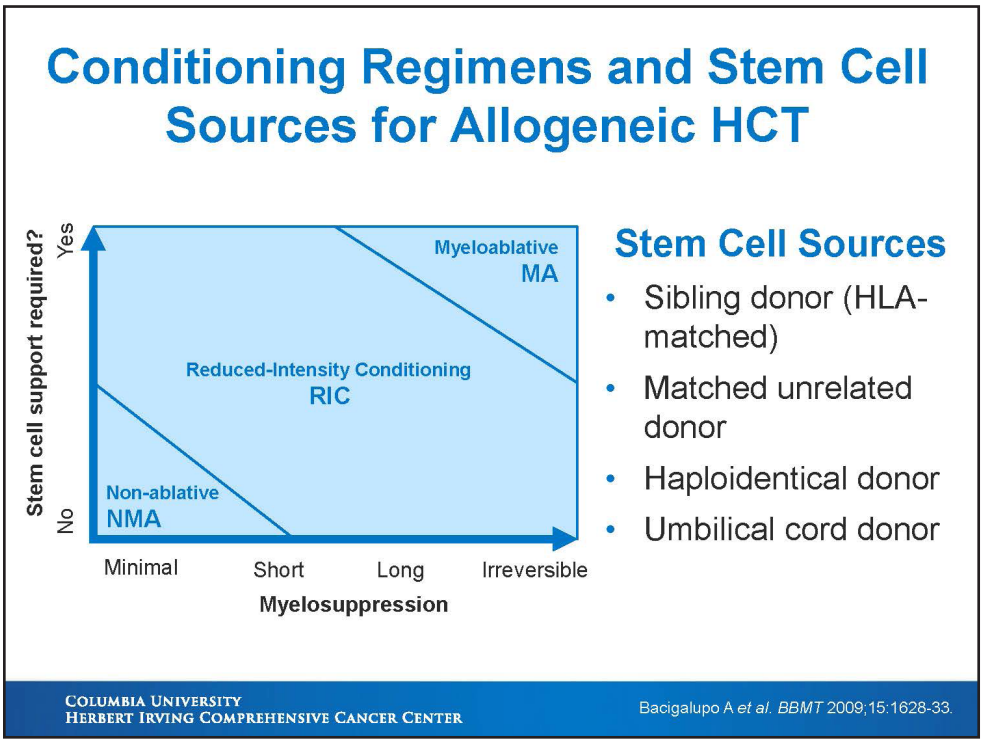
Slide 13: : ALGORITHM FOR ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT

And so, how do we put this altogether? Well, when I'm evaluating a patient with newly diagnosed leukemia, I gather all of the cytogenetic and molecular abnormality, I look at their comorbid conditions, other medical problems they have, their age, and we assess their risk. And, for favorable risk patients who have good risk cytogenetics, those patients have a good chance of cure with chemotherapy alone. And so, we would recommend consolidation treatment with high-dose cytarabine-based therapies.

For patients with poor risk disease, we know that the chance of a cure with chemotherapy alone is 10% or so. And so, we want to do everything we can to get that person to a potentially curative allogeneic stem cell transplant, which includes sibling donor, transplants, matched unrelated donor transplants, mismatched transplants, alternative donor transplants with haploidentical donors, in other words half-matched donors, or umbilical cord blood.

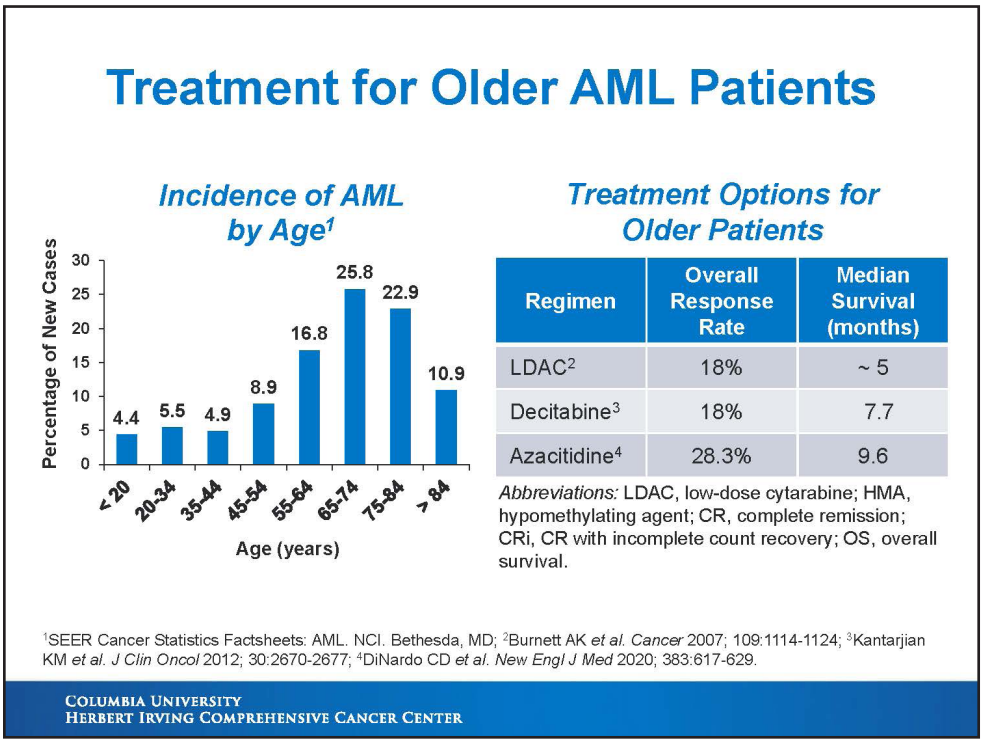
And so, patients with intermediate risk disease, we know that some can be cured without transplant and if the transplant we think is too high a risk we would recommend consolidation therapies. Otherwise, if we have a good-matched donor and don't have too many medical problems, besides the leukemia, we can take them to allogeneic transplant and offer a chance of cure for those patients.

So, the good news is that over time we've seen advances in stem cell transplantation, so now this therapeutic modality is available to more and more patients. We can give reduced intensity treatment before the transplant, which opens this up to older individuals who can't tolerate the very intensive so-called myeloablative therapies that used to be given before transplants.



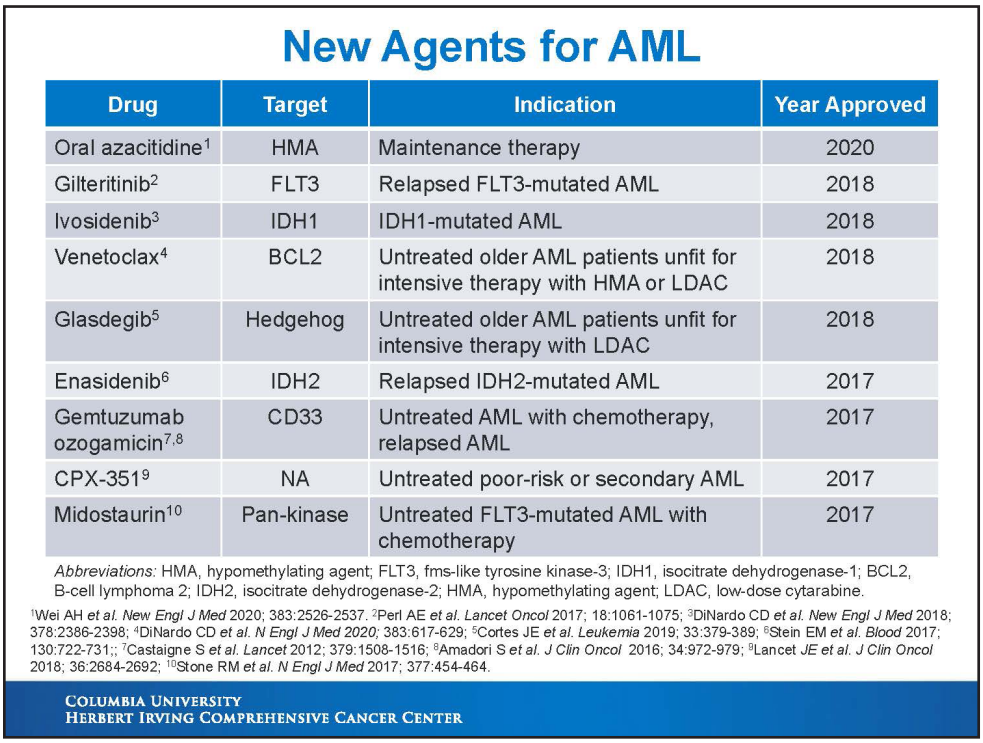
Slide 14: CONDITIONING REGIMENS AND STEM CELL SOURCES FOR ALLOGENEIC HCT

We also have alternative stem cell sources that I mentioned earlier, so that we can use half-matched transplants. Parents can donate to children and siblings can donate to each other. So, this has been a major advance in the field, allowing more patients to undergo allogeneic transplant as part of their treatment strategy for AML.



Slide 15: TREATMENT FOR OLDER AML PATIENTS

So, everything that I've told you applies to younger patients with AML, but the fact of the matter is, this is a disease of, generally speaking, older individuals. The median age at diagnosis is typically 68 years. Many of these individuals can't tolerate the intensive treatments that I've just spoken about. And so, there's been a lot of research over the past few decades looking at less intensive therapies for older individuals. Low-dose cytarabine has been used, so-called Low-DAC, as well as hypomethylating agents, decitabine and azacitidine. And, these single agents can produce responses in somewhere around 20% to 30% of patients, but as single drugs, still the median overall survival of these individuals is less than a year. So clearly, advances have needed to be made and I'm going to show you some promising data that perhaps moves the bar forward for this difficult-to-treat population.



New Agents for AML

Drug	Target	Indication	Year Approved
Oral azacitidine[1]	HMA	Maintenance therapy	2020
Gilteritinib[2]	FLT3	Relapsed FLT3-mutated AML	2018
Ivosidenib[3]	IDH1	IDH1-mutated AML	2018
Venetoclax[4]	BCL2	Untreated older AML patients unfit for intensive therapy with HMA or LDAC	2018
Glasdegib[5]	Hedgehog	Untreated older AML patients unfit for intensive therapy with LDAC	2018
Enasidenib[6]	IDH2	Relapsed IDH2-mutated AML	2017
Gemtuzumab ozogamicin[7,8]	CD33	Untreated AML with chemotherapy, relapsed AML	2017
CPX-351[9]	NA	Untreated poor-risk or secondary AML	2017
Midostaurin[10]	Pan-kinase	Untreated FLT3-mutated AML with chemotherapy	2017

Abbreviations: HMA, hypomethylating agent; FLT3, fms-like tyrosine kinase-3; IDH1, isocitrate dehydrogenase-1; BCL2, B-cell lymphoma 2; IDH2, isocitrate dehydrogenase-2; HMA, hypomethylating agent; LDAC, low-dose cytarabine.

[1]Wei AH *et al. New Engl J Med* 2020; 383:2526-2537. [2]Perl AE *et al. Lancet Oncol* 2017; 18:1061-1075; [3]DiNardo CD *et al. New Engl J Med* 2018; 378:2386-2398; [4]DiNardo CD *et al. N Engl J Med 2020;* 383:617-629; [5]Cortes JE *et al. Leukemia* 2019; 33:379-389; [6]Stein EM *et al. Blood* 2017; 130:722-731;; [7]Castaigne S *et al. Lancet* 2012; 379:1508-1516; [8]Amadori S *et al. J Clin Oncol* 2016; 34:972-979; [9]Lancet *JE et al. J Clin Oncol* 2018; 36:2684-2692; [10]Stone RM *et al. N Engl J Med* 2017; 377:454-464.

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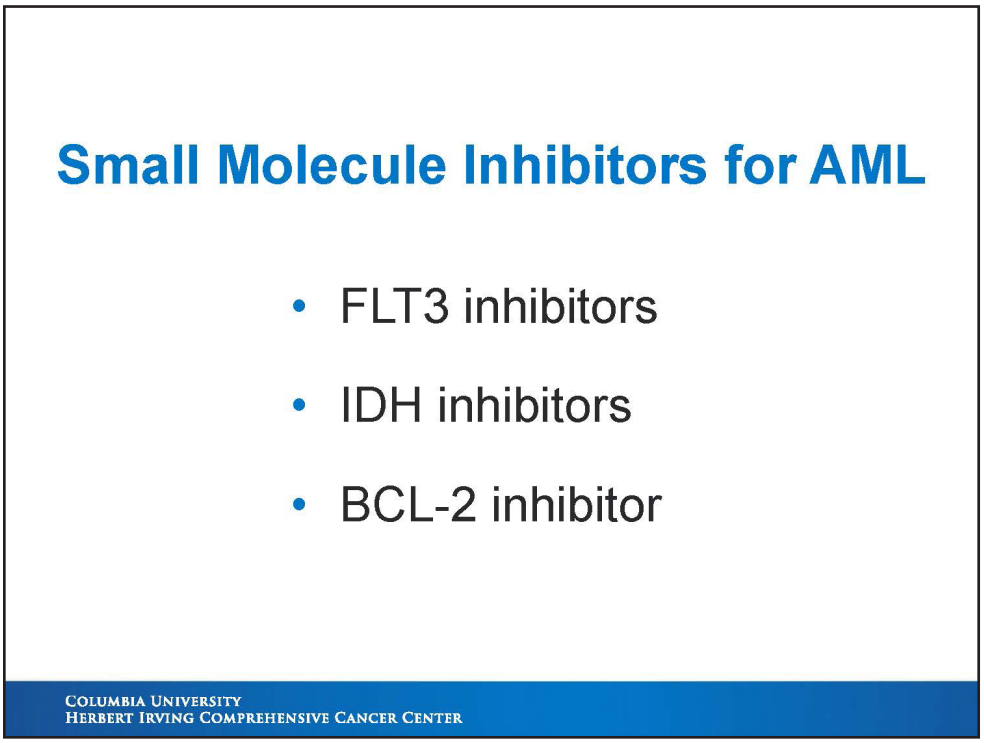
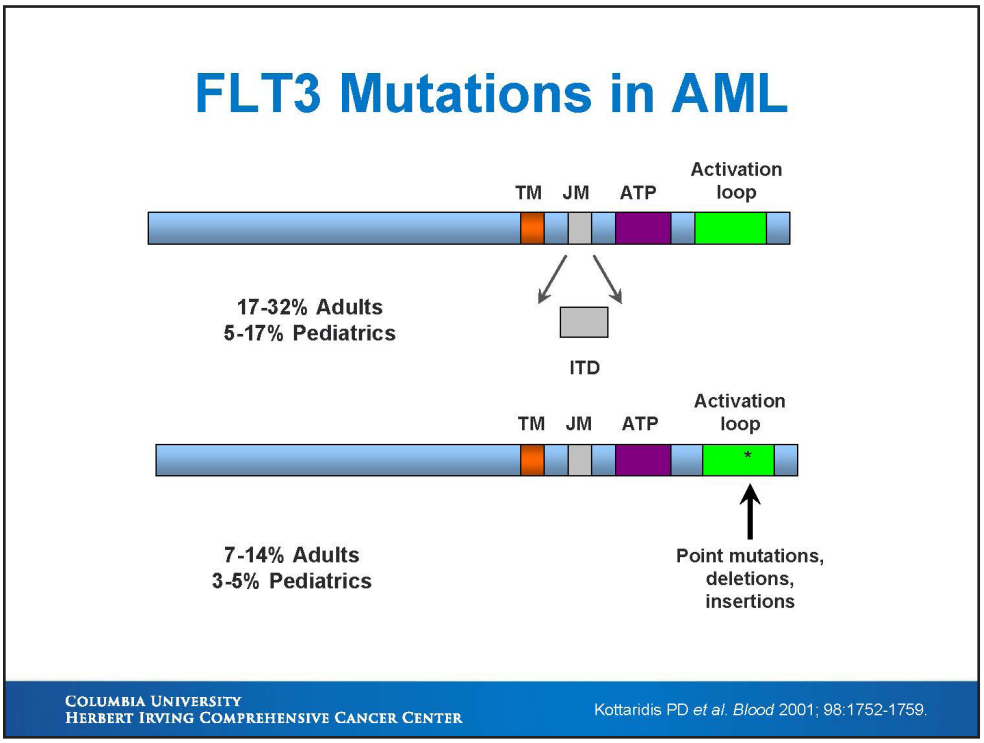
Slide 16: NEW AGENTS FOR AML

Over the past 4 years there have been 9 new drugs approved for acute myeloid leukemia. I've listed them here and we'll talk about most of them individually. But as you can see, many of them are targeted agents, targeting specific pathways, and so that's why full genetic profiling is really necessary to offer the optimal treatment for patients in the modern era. It's no longer a one size fits all 7 plus 3 chemotherapy paradigm any longer.



Slide 17: SMALL MOLECULE INHIBITORS FOR AML

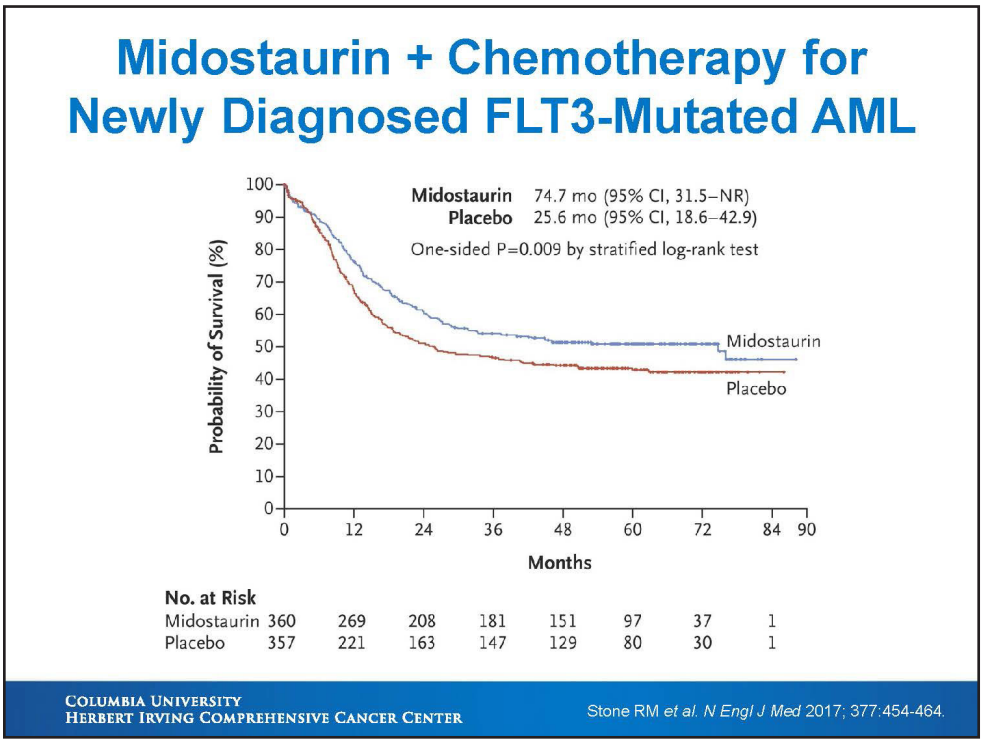
So, first I'm going to touch on the so-called small molecule inhibitors and will speak about the FLT3 inhibitors, as well as the IDH inhibitors and the BCL-2 inhibitor venetoclax.



Slide 18: FLT3 MUTATIONS IN AML

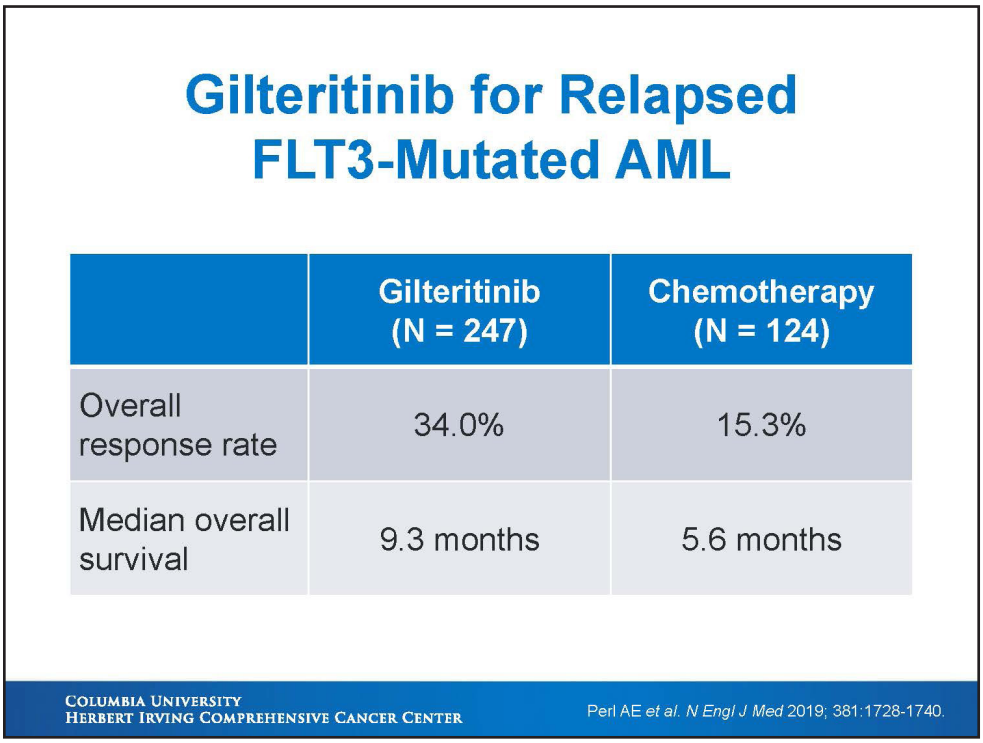
So, FLT3 mutations are commonly seen in AML, it's about 30% of patients that will have a so-called FLT3 internal tandem duplication or ITD mutation. So, this particular form of AML responds well to chemotherapy, however, the remission durations are actually quite short. And so, this has been a challenging group to treat.

There's another subgroup of patients with FLT3 mutations who have a so-called activation loop mutation, is probably not the driving mutation in this particular disease, however, it can still serve as an important therapeutic target.



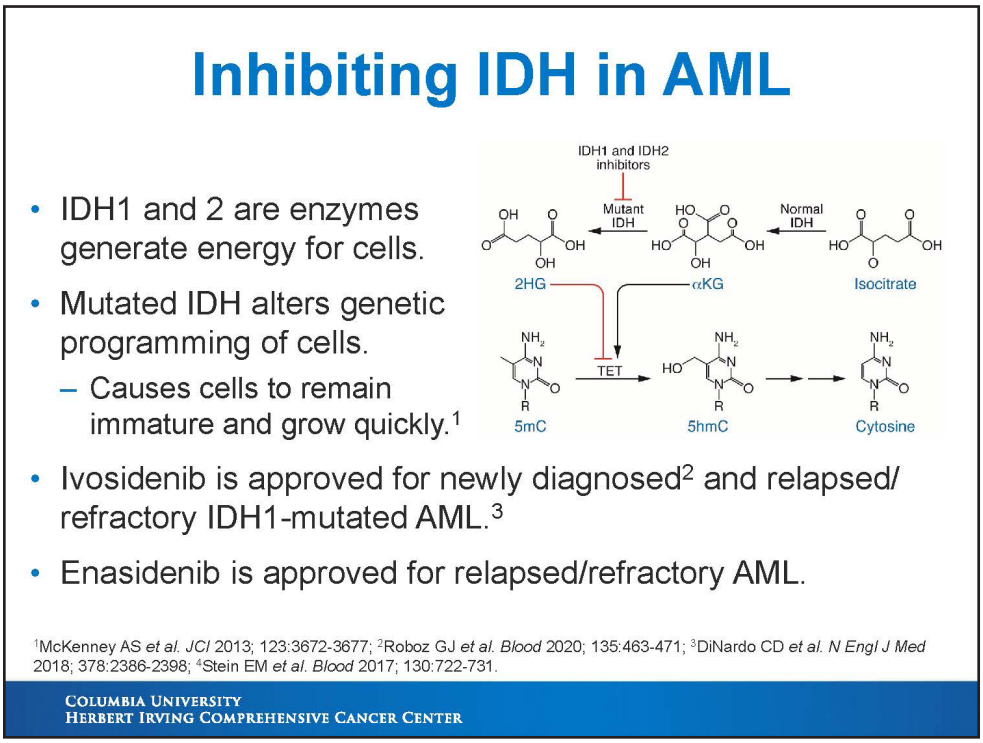
Slide 19: MIDOSTAURIN + CHEMOTHERAPY FOR NEWLY DIAGNOSED FLT3-MUTATED AML

So, midostaurin is a pan-kinase inhibitor that inhibits the FLT3 internal tandem duplication, as well as point mutations. And, this is one of the very first studies to look at combining a targeted agent with chemotherapy and indeed what was seen is patients who received midostaurin with 7 plus 3, cytarabine and daunorubicin chemotherapy, fared better and had a longer survival than those patients who received only traditional chemotherapy.



Slide 20: GILTERITINIB FOR RELAPSED FLT3-MUTATED AML

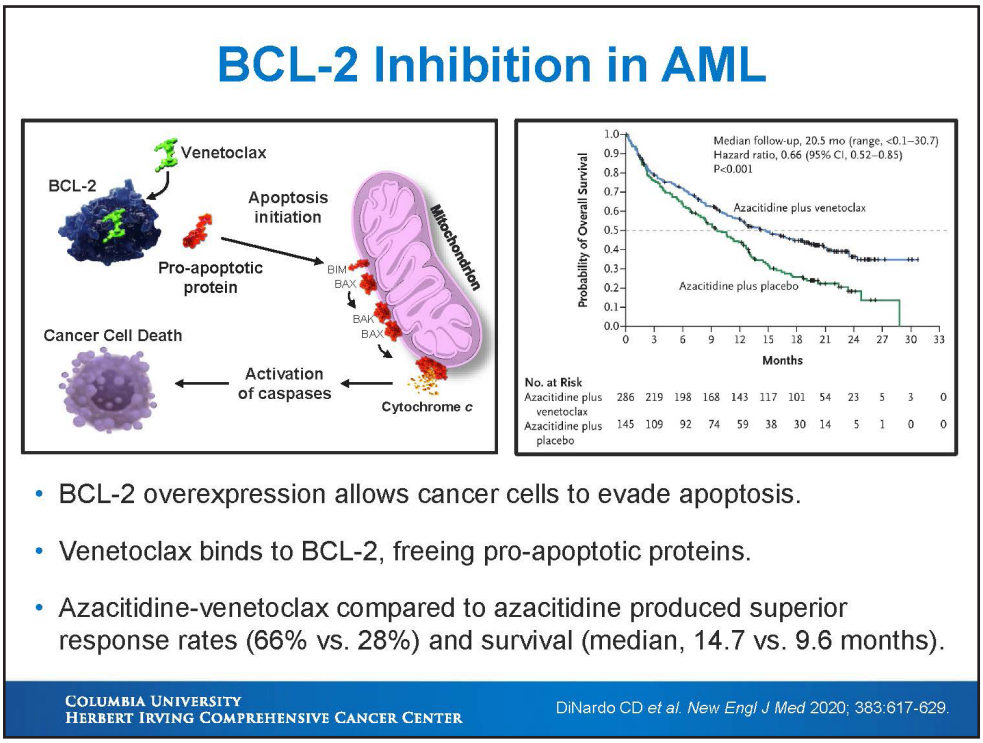
So, this finding has really led to the development of other FLT3 inhibitors. And, gilteritinib is currently FDA approved for the treatment of relapsed FLT3 mutated AML. In a randomized study comparing single-agent gilteritinib, an oral agent, versus traditional chemotherapy, can see an almost greater than doubling of the response rate, 34% versus 15% in favor of gilteritinib. This has also resulted in a significant improvement in survival of these patients. And now, based upon this promising data, gilteritinib has been combined with chemotherapy, for the up-front treatment of AML in FLT3 mutated patients. And, looks very promising in randomized trials comparing gilteritinib with midostaurin in combination with chemotherapy underway. There's also another FLT3 inhibitor currently in development, called crenolanib, also being studied in exactly the same setting in combination with chemotherapy.



Slide 21: INHIBITING IDH IN AML

So, there are 2 enzymes, IDH1 and IDH2, which generate energy for cells to divide and function normally. So, mutations can occur in both of these genes that alter the genetic programming of these cells, and allow these cells to stay at their immature state and grow more quickly. There're now 2 drugs licensed for these IDH mutations. Ivosidenib is specific for IDH1, and it has been approved for newly diagnosed older individuals who are intolerant of standard chemotherapy, but also for patients who have either relapsed following treatment or are refractory to our standard treatments.

Enasidenib is a drug that targets IDH2 and is approved for relapsed and refractory AML with the IDH2 mutation.



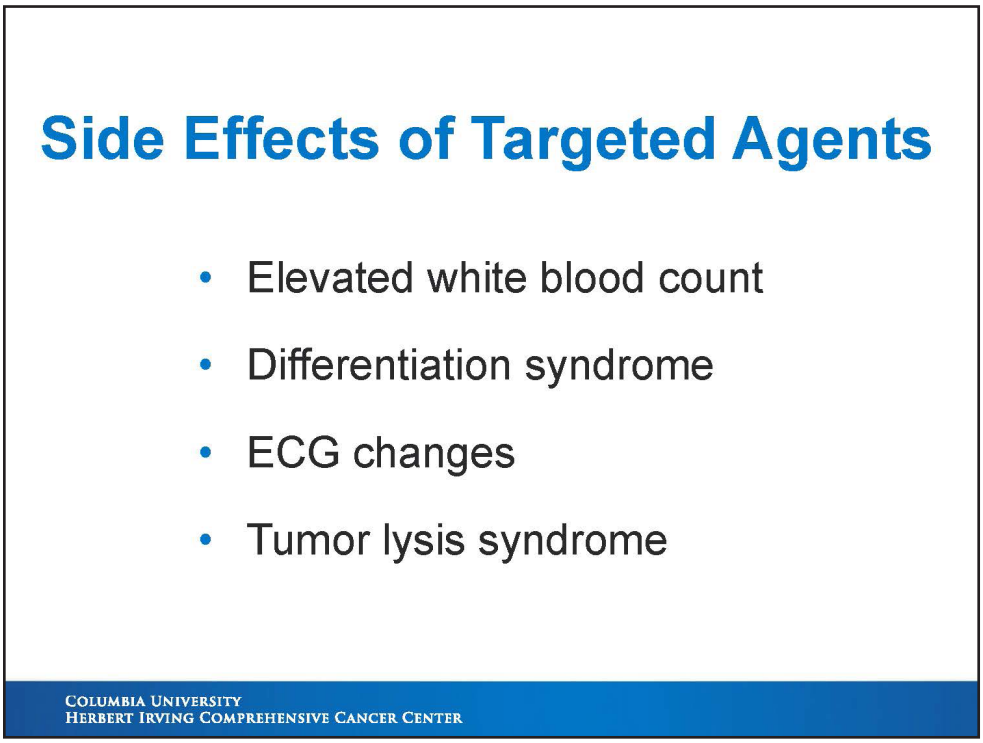
Slide 22: BCL-2 INHIBITION IN AML

And then, we have BCL-2 inhibition. So, BCL-2 is a protein that's over-expressed on many different types of cancer cells, and allows cells to evade what is known as apoptosis. In other words, a programmed cell death. Like all of our cells, every cell in our body has a natural life cycle, it's born, it lives its life, and then it dies off.

So, what venetoclax does is bind to this protein BCL-2, and it frees other proteins, pro-apoptotic proteins, that allow the cells to undergo this natural apoptotic death.

Azacitidine, as I mentioned, is one of the hypomethylating agents that's been studied in acute myeloid leukemia and shows some activity. But, you can see that in a randomized study where patients were assigned to receive either azacitidine or azacitidine with venetoclax, the combination produced superior response rates, 66% response rate versus 28% with azacitidine alone, and prolonged the survival of these older individuals who were unable to take traditional chemotherapy, who had an almost 15-month overall survival compared to around 10% with just azacitidine.

And so, while this treatment is not curative, it certainly has moved the needle forward and represents an important option for patients who are unable to tolerate standard chemotherapy. And of course, based on this data, venetoclax and other BCL-2 inhibitors are being looked at in combination with other chemotherapeutic agents, which will hopefully improve things for even more patients going forward.



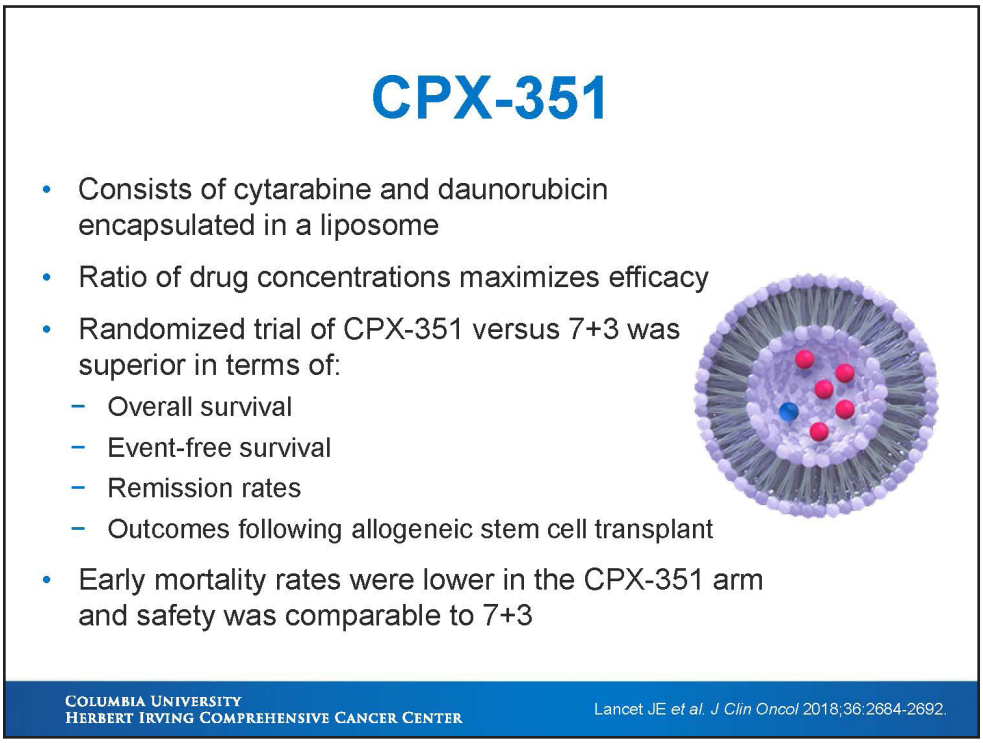
Slide 23: SIDE EFFECTS OF TARGETED AGENTS

So, these targeted agents do have side effects. There is no drug without potential adverse effects. So, many of these drugs will actually cause differentiation. So, as this happens, the cells will mature into more normal cells from their leukemic blast state and the white count can become elevated as well. So many times, we'll need to manage this with a medicine called hydroxyurea to bring down the white count, keep it from going too high. And oftentimes, we can see as this process is occurring, differentiation syndrome. This is generally marked by shortness of breath, cough, weight gain, and swelling. And what happens is, as these cells are differentiating, they can set up inflammatory states, particularly in the lungs as they're most often affected, and cause this kind of shortness of breath and fluid retention. So, you can actually get fluid around the lungs, fluid around the heart as well. And so, as this occurs, we will often treat with a medication called dexamethasone, a corticosteroid, which calms down these effects of the differentiation syndrome and allows treatment to continue. So, this is something to be on the lookout for when you're on these medications and report these sorts of side effects immediately to your physician, so the proper interventions can be made early before any untoward effects do occur.

Some of these drugs will also cause EKG changes, in particular they can affect something called a QTC. And, if this becomes prolonged it can lead to cardiac arrhythmias, so it's important to monitor the EKGs periodically throughout the treatment on these drugs, and also close attention should be paid to electrolytes, particularly potassium and magnesium.

In the case of venetoclax, it has been associated with marked tumor lysis syndrome. This was first noted not in AML, but in another form of leukemia, chronic lymphocytic leukemia. It seems to be less pronounced in acute myeloid leukemia, but something that needs to be watched for. So occasionally, we can see a dramatic response to the drug with the sudden killing of all sorts of leukemia cells, releasing their contents into the bloodstream, causing abnormalities of various electrolytes like potassium, phosphorus, and so forth.

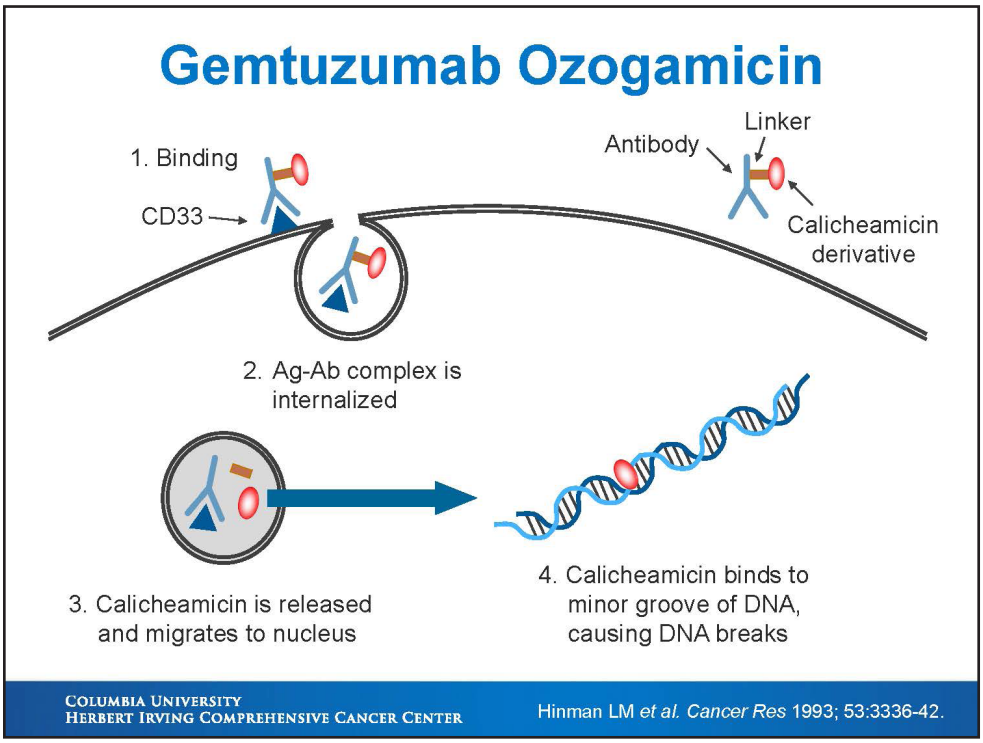
This can also result in kidney damage. And so, it's important to maintain proper hydration throughout treatment and careful monitoring of the electrolytes, particularly while you're first starting out on these treatments.



Slide 24: CPX-351

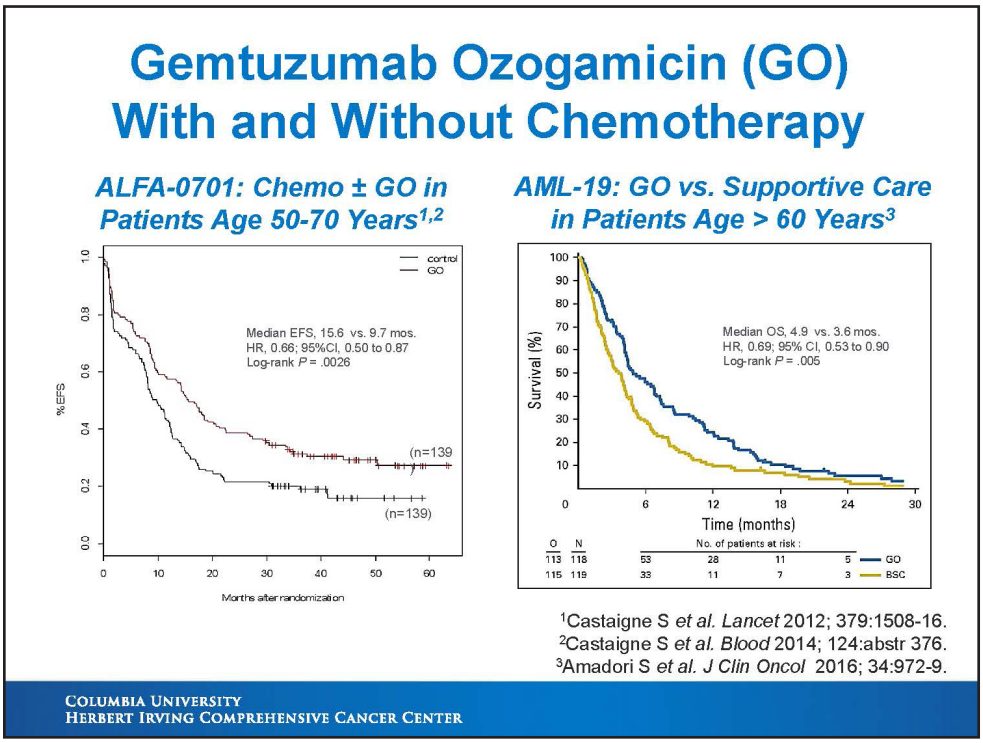
So now, I'll turn to a sort of different class of medications. I mentioned cytarabine and daunorubicin have really been the gold standard of care for treatment in AML for decades. But, sometimes we can begin to use these drugs more effectively and CPX-351 is an example of this. The drug itself consists of cytarabine and daunorubicin, encapsulated in a liposome, essentially a fat globule. And, what this does is maximize the concentrations of these drugs toward efficacy.

And, there's been a randomized study of CPX-351 compared to standard 7 plus 3 chemotherapy, daunorubicin and cytarabine, in older patients with high-risk leukemia and secondary leukemia often evolving from myelodysplastic syndrome related to prior treatments. And, what was shown was that CPX provided a greater overall survival, greater event-free survival, higher remission rates, particularly in those patients who underwent an allogeneic stem cell transplant following their therapy. So, we really think that this becomes a new standard of care for that select group of individuals who are older and can't tolerate intensive chemotherapy with these high-risk abnormalities.



Slide 25: GEMTUZUMAB OZOGAMICIN

Another new agent that is not so new, has an interesting past, is gemtuzumab ozogamicin. And, this belongs to a general class of agents that are known as antibody drug conjugates. So, the drug itself consists of an antibody that binds to a protein that is seen on the surface of acute myeloid leukemia cells of CD33. In addition to the antibody, it's linked to a chemotherapeutic agent known as calicheamicin. So, you can think of this drug as targeted chemotherapy. The drug is delivered by an antibody directly to the leukemia cell. After it is bound to the surface of the leukemia cell, it's brought into the cell, in something called a liposome, or a lysosome rather, and then the calicheamicin is released and can damage DNA and kill the drug in that fashion.



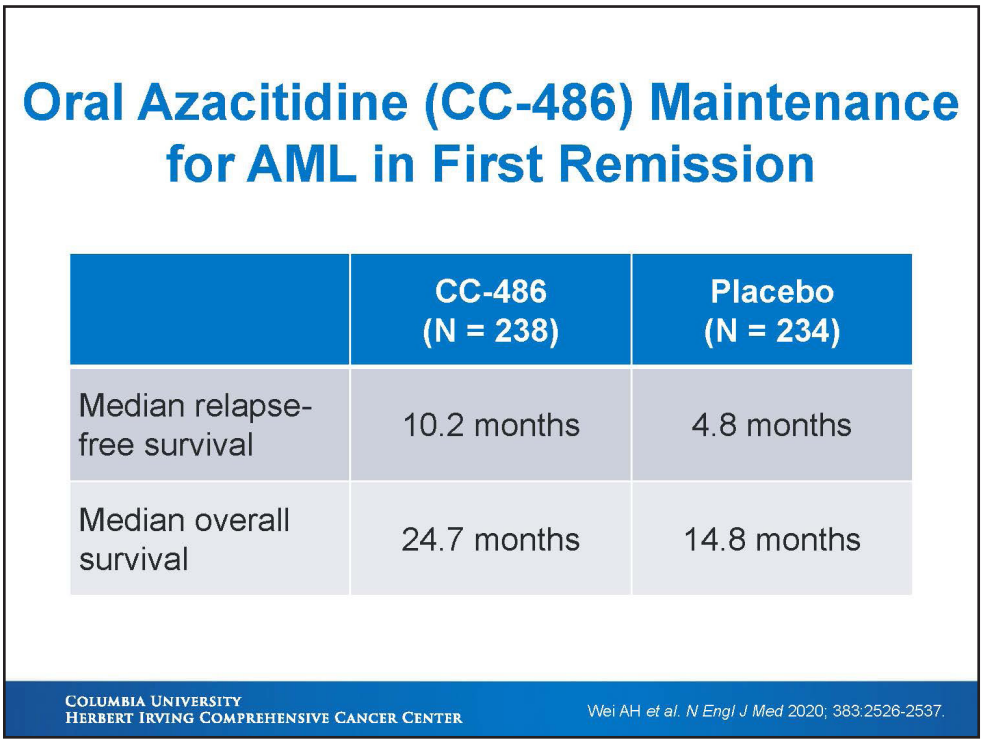
Slide 26: GEMTUZUMAB OZOGAMICIN (GO) WITH AND WITHOUT CHEMOTHERAPY

So, the drug has a bit of a checkered past. It was initially licensed for patients who were older and had relapsed acute myeloid leukemia. Then it was actually removed from the market. There was a randomized study looking at 7 plus 3 chemotherapy with or without gemtuzumab ozogamicin. And, in that study there was a higher peri-induction mortality, and so the drug was removed from the market for safety concerns. However, there were a number of other studies that continued to be conducted, both in Europe and the United States, and what was clear was that for patients with favorable risk or intermediate risk group, there did seem to be a survival advantage and the risks of the drug seemed to be less than the potential benefits from receiving it. And so, there've now been studies that have actually led to the relicensing, reapproval of the agent by the FDA.

One was conducted in patients aged 50 to 70, looking at the drug again using a different dosing scheme than the original study, in combination with chemotherapy. And, here the drug was found to be safe and there was an improved event-free survival for these patients.

Other studies have looked at the agent in the setting of relapsed and refractory AML, as well as up-front AML, and it has shown benefit. And so, the drug is now reapproved by the FDA and available for use.

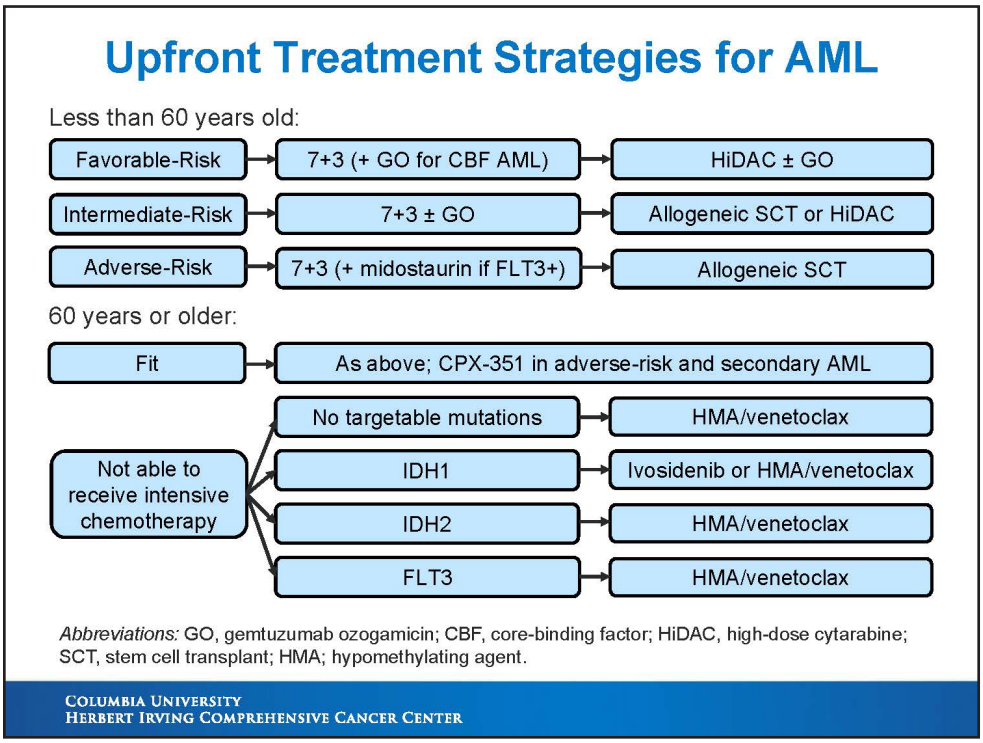
Generally speaking, I tend to use this drug in patients with more favorable risk disease. That does seem to be where the benefit of the agent is greatest.



Slide 27: ORAL AZACITIDINE (CC-486) MAINTENANCE FOR AML IN FIRST REMISSION

Then, another new chemotherapeutic agent that has recently been licensed is an oral form of azacitidine. So as you recall, azacitidine was one of the mainstays of treatment in combination with venetoclax for older individuals with AML.

Well, it's also available in an oral formulation known as CC-486. And, this has been studied in individuals who underwent intensive chemotherapy, but did not undergo transplant, and instead received some consolidation therapy, and then went on to maintenance therapy with this oral agent. And, what was found was that there was an improvement in relapse-free survival and overall survival, compared to those patients who were taking a placebo. And so, now we have a maintenance therapy approved for AML that is capable of prolonging patients' lives.



Slide 28: UPFRONT TREATMENT STRATEGIES FOR AML

So putting all of this information together, this slide summarizes our current treatment strategies for acute myeloid leukemia. You can see for patients who are younger, less than 60 years of age, for favorable-risk disease, we use traditional chemotherapy, 7 and 3, we use gemtuzumab ozogamicin for core-binding factor leukemias, namely those with 8;21 inversion 16, and those patients will go on to receive high-dose cytarabine-based consolidation.

For intermediate-risk and adverse-risk patients, we will also give them 7 plus 3 chemotherapy, but generally try to move towards allogeneic transplant if this is at all feasible. And of course, for those patients with FLT3 mutated disease, we'll give them midostaurin.

For patients who are 60 years and older, who are fit, we can give them the liposomal formulation of cytarabine and daunorubicin, CPX-351, if they have adverse-risk cytogenetics or secondary myeloid leukemia, and then ultimately we will try to take those patients to transplant as well, as this will offer the best chance of long-term survival.

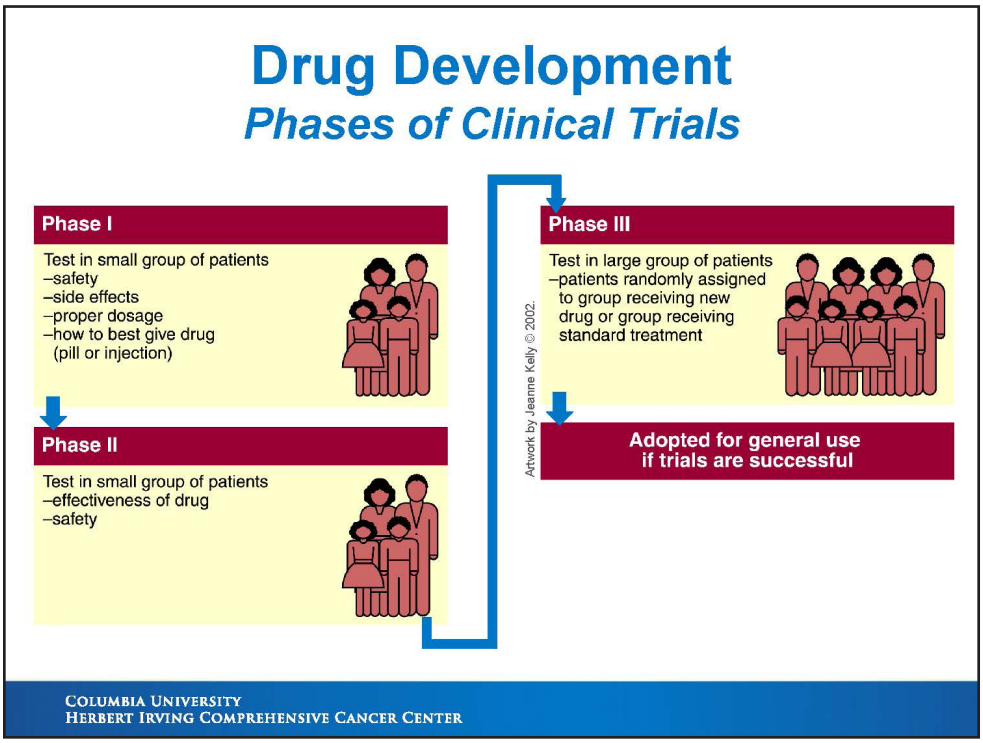
For those patients that can't receive an intensive chemotherapy regimen, we have hypomethylating agents like azacitidine or decitabine with venetoclax as our first-line therapy. For patients with IDH1 and IDH2 mutations, we have ivosidenib and enasidenib as options, as well as, azacitidine and venetoclax. And, for those patients with FLT3 abnormalities initially, we would recommend azacitidine and venetoclax, recognizing that gilteritinib remains an option if this patient goes on to relapse.

Slide 29: ROLE OF CLINICAL TRIALS IN AML

So, how do we make progress in AML? Well, we've seen a lot of it with these new drugs, and it's all done through clinical trials. So, these clinical trials allow us to determine if these new treatments are safe, if they're effective, and if they can work better than our current therapies.

They also help us to find new ways to prevent and detect cancer, and help us improve the quality of life for people either during and after treatment.

So, taking part in a clinical trial, you can add to our knowledge about leukemia and also help improve care for patients in the future.

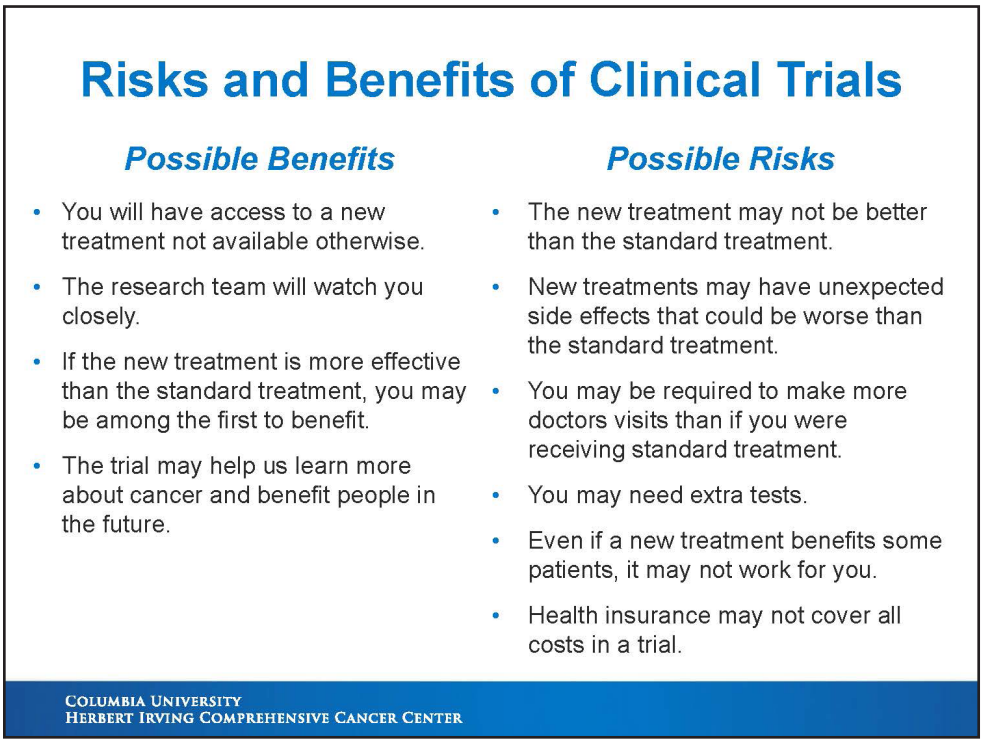


Slide 30: DRUG DEVELOPMENT: *PHASES OF CLINICAL TRIALS*

When we talk about drug development, typically there are 3 phases of clinical trials. Phase I, we test the drug in small groups of patients and the primary endpoint there really is safety. What sort of dose can we give that shows some degree of efficacy, but side effects are tolerable.

Once we determine the optimal dose to give the patients, we'll then take a group of people who have the same disease, that are similar in profile, and we will treat them all uniformly with our particular dose of a new medication. Here the goal is to see how well it works and to confirm the safety of the agent.

If this looks promising and we see a high number of people responding, better than what we might expect otherwise, then we'll take this to a Phase III study. And here, we'll test these agents in large groups of patients. Half will get the standard of care, which can be either a more traditional chemotherapy regimen or sometimes it's appropriate to use a placebo versus the new treatment. And, if that new treatment does prove to be better, then that drug will go before the FDA and likely be approved.



Slide 31: RISKS AND BENEFITS OF CLINICAL TRIALS

So, the possible benefits of being in a clinical trial are that you have access to new treatments that are otherwise not available. You'll be watched very closely. And so, we watch everybody with AML closely, obviously, but there's prescribed monitoring on clinical trials and so often we will be able to catch new problems sooner than we might otherwise.

If the new treatment is more effective than the standard care, you may be among the very first people to benefit. And, these trials really advance the therapy of cancer and can benefit people in the future.

The risk of being in a trial is that the new treatment might not be better than the standard of care. So in general, we're very careful of when we do these randomized trials, so that the new treatment is not going to be worse, but we can't guarantee that a new treatment is going to be better than the standard until that Phase III trial is completed.

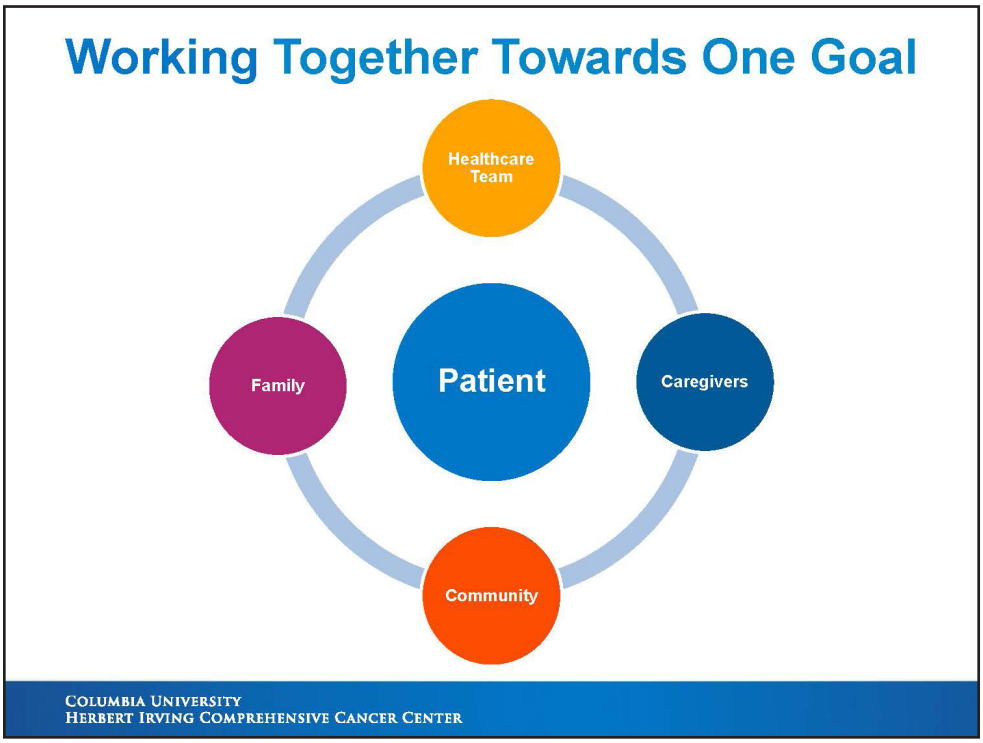
We also know that new treatments can sometimes have unexpected side effects that are worse than the standard of care. And, because the monitoring is so close, you may be required to make more visits to your physician. You also might need extra tests that would ordinarily not be performed. And, this can even include bone marrow aspirations and biopsies.

We know that even if a new treatment proves to be effective for a large group, it may not benefit you individually.

And finally, healthcare insurance may not approve all the costs associated with a clinical trial, and this is something that really should be looked into before agreeing to participate.

Slide 32: IT TAKES A VILLAGE TO TREAT AML

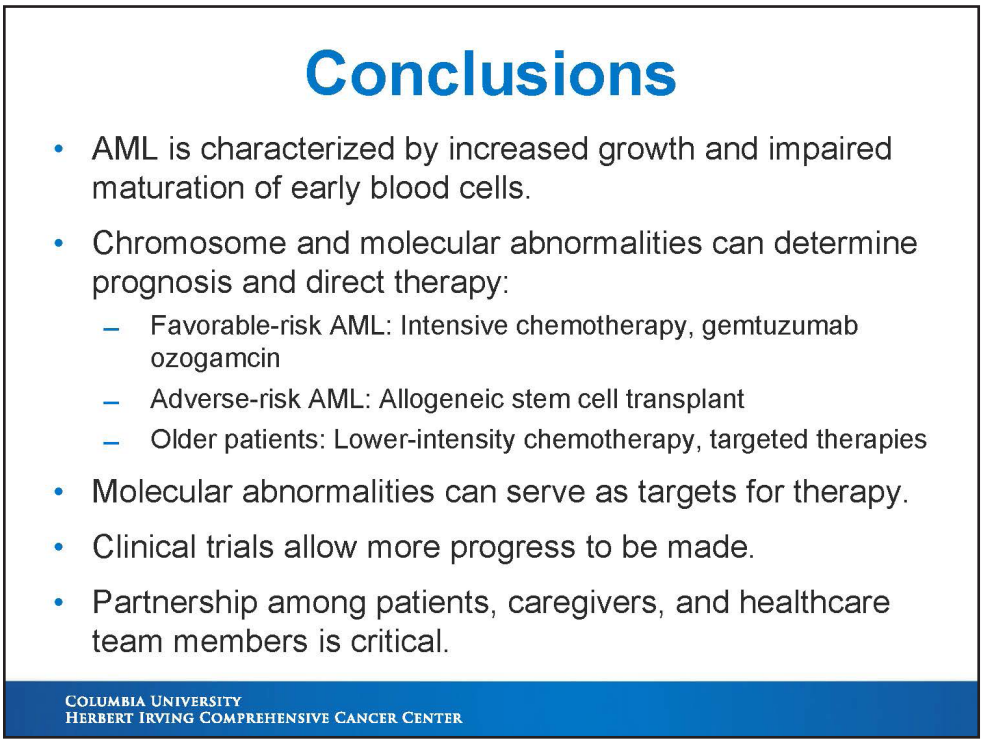
Well, as I'm sure many of you recognize, it's not just a doctor alone treating this disease, it really does take a village to treat acute myeloid leukemia. We have leukemia physicians, transplant physicians, consultants, infectious disease, radiation oncology, pathologists, radiologists, blood bank, nurses, social work, occupational and physical therapy, nutrition services, and pharmacy. Everybody working together to treat this very complex disease, and so you really need to think of your treatment team as a support system.



Slide 33: WORKING TOGETHER TOWARDS ONE GOAL

And in fact, the support system really even goes beyond just your healthcare team. It extends to your caregivers and your family and your community. And remember, all of these people working towards one goal and seeing that you have the best possible outcome for your acute leukemia.

And so, it's important to be able to speak with all members of your healthcare team, particularly your physicians because we're also your cheerleaders throughout this whole process.



Slide 34: CONCLUSIONS

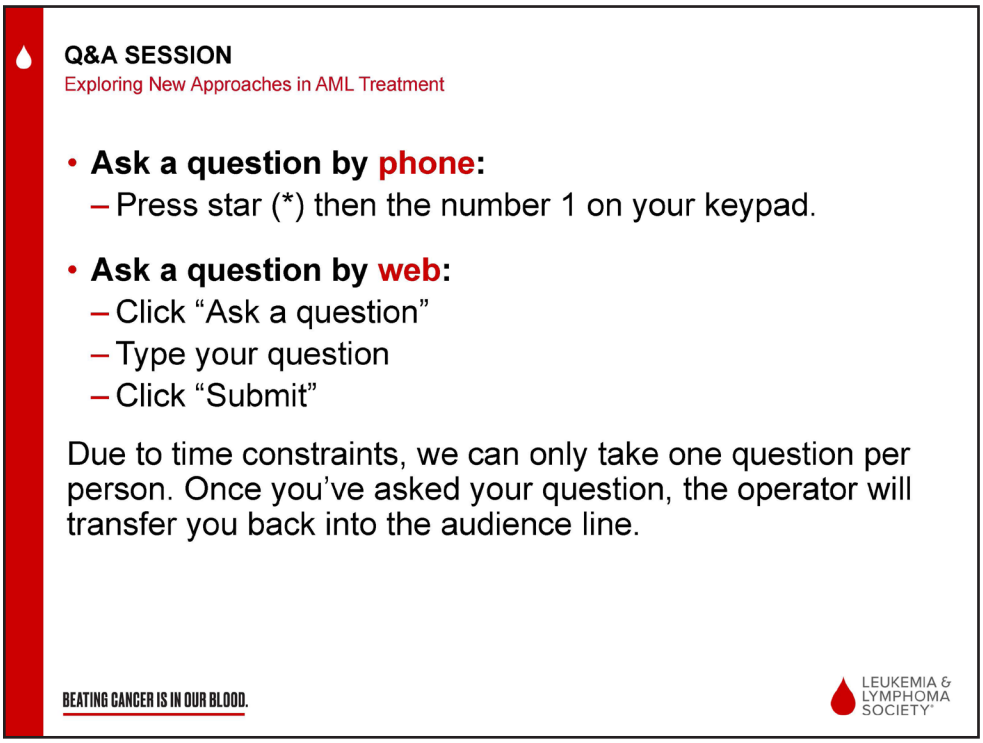
So, to wrap things up, we can see that AML is characterized by the increased growth and impaired maturation of these early blood cells. And, I've stressed the chromosome and molecular abnormalities that can occur in this disease because they will actually determine your prognosis and help direct therapy. For instance, for favorable risk AML, we'll give intensive chemotherapy, we'll add gemtuzumab ozogamicin. For adverse risk patients, we'll try to get people to an allogeneic stem cell transplant because this will offer the best chance of cure. And, for older individuals, we can see the addition of venetoclax to lower intensive therapies like azacitidine, has been a major advance. There is still room for improvement. And so, we need to build upon this and look at other targeted therapies with the azacitidine-venetoclax as a base to it.

We can see these molecular abnormalities can serve as targets for therapy, I've shown you this with gilteritinib, midostaurin, and the IDH inhibitors as well.

Clinical trials really will allow more progress to be made in the coming years.

And finally, partnership with patients, caregivers, and healthcare team members is critical for the success of treatment.

And so, with this I will be happy to take any questions. Thanks very much.



Slide 35: Q&A SESSION

Ms. Figueroa-Rivera:

Thank you so much, Dr. Jurcic. It’s time for our question-and-answer portion of our program.

And, we’ll take the first question from our web audience. Doctor, Amy is asking about vaccine therapy in trials for AML. What kind of progress is happening in this field of immunotherapy for people who do not choose or are not eligible for stem cell transplants?

Dr. Jurcic:

So, vaccine therapy is an interesting strategy to use the body’s immune system to further eliminate residual disease and prevent relapse. And so, you’re absolutely correct that the population that’s being looked at are those patients who can’t go on to a stem cell transplant.

And in fact, one of the more promising targets has been something called WT1, so vaccines have been made against this particular oncoprotein and are currently being studied in clinical trials. I think it’s a promising idea and again deserves further study. There have already been some preliminary studies looking quite good, but again, this is still a therapy that won’t be an accepted one until it’s proven to be better in a randomized Phase III study. And, that’s where we are right now with the vaccine therapies.

Ms. Figueroa-Rivera:

Thank you. Now, we’ll take the next question from our telephone audience, please.

Operator:

We have a question from Eleanor in New York. Eleanor, please state your question.

Eleanor:

Ivosidenib is a form of Tibsovo®. I am in 16 months, 18 months of successful remission now. What is the remission length of time, what do I expect, and how do I handle the side effects, which are not too bad, but they're getting to be a problem.

Dr. Jurcic:

So, the average remission duration is actually less than what you've experienced already. So, it's always difficult to predict the future for any one particular individual. The fact is, it seems like you're having a fantastic response to the drug, and I would urge people in general, if a medication is working to try to stay on that drug for as long as possible.

We do know that drugs like ivosidenib and enasidenib are not curative by themselves. And so, eventually relapse is expected to occur. The timing of that is always very difficult to predict.

But, I think you also need to remember there are other newer options that can be available, I've talked about some of the other novel agents just a while ago. And, clinical trials are always an option.

So, I'm not sure which particular side effects you're experiencing at the moment, so it's difficult for me to address that question in detail. But, I think you can work with your provider to sort of delineate these particular abnormalities, and perhaps there're some medications that can be given along with the ivosidenib that would mitigate some of these side effects and make the treatment easier to take. Because again, since it is working, you want to get all the potential mileage out of this as much as you possibly can before having to go on to a different treatment.

Ms. Figueroa-Rivera:

Thank you, Doctor. And, Ruth and Renee are asking about IDHIFA®. They're asking, how can a patient determine the efficacy of IDHIFA?

Dr. Jurcic:

So, IDHIFA is the same drug as enasidenib. I've tried to use generic names throughout my talk. So, this is the IDH2 inhibitor. And generally speaking, when we initially place people on this medication, it can take a little while to work. You might see a rise in the white count that we talked about, you might see signs of differentiation and have to go on hydroxyurea or dexamethasone, particularly in those few weeks to months of therapy. But, it can actually take up to 4 or even 6 months of treatment to see maximum benefit. Over that course of time, you would expect to see improvement in the peripheral blood counts, and of course the gold standard way of measuring the response is with a bone marrow aspiration and biopsy, which should be done to demonstrate that the blast count within the bone marrow is decreasing over time.

Ms. Figueroa-Rivera:

Thank you. And, Zerona and Amanda are both asking about familial history. Can AML be genetic? Should my young children be treated?

Dr. Jurcic:

So generally speaking, AML is not inherited. There are a few cases that are, but by and large this is not something that is either inherited or is passed on. So that said, there are certain conditions that can predispose people to developing acute myeloid leukemia. Diseases like Fanconi's anemia, which is a disease of DNA repair, certain bone marrow failure states can do this, Li-Fraumeni syndrome, which is a whole collection of cancers that people can be predisposed to, caused by a mutation, and one of the major tumor suppressor genes, P53. These things can lead to leukemia. There're also some unique families that have shown certain mutations, mutations in RUNX1, mutations in CEBP-alpha. Again these abnormalities usually occur sporadically, are not inherited, but can occasionally occur in families.

We do think that if you have one of these mutations that is found in all of your cells, then it is worth consulting a genetic counselor. But by and large, if these are simply mutations that are acquired in life that are causing the leukemia, the disease is not inherited and there's no special screening required for close relatives.

Ms. Figueroa-Rivera:

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

Operator:

We'll go to Doreen in Michigan. Doreen, please go ahead with your question.

Doreen:

Yes, I was wondering about, holistic treatments, is there anything like a massage, acupuncture, reflexology, could that be included with these treatments or is that something that would harm the person who has leukemia? Also, there's a product called Propolis, it's derived from the beehive and I read about some certain cases of leukemia that are really being helped by this product. So, my main thing is nutritional therapy and holistic treatments, could they be of service to a person with AML or would that be a deterrent?

Dr. Jurcic:

So again, I think it depends upon the actual treatment that is being given. Many of these things that you have mentioned are terrific adjuncts to the standard therapies. For instance, reflexology, massage therapy, these things can make it easier to go through the process of receiving treatment and help with side effects and generally give someone a greater sense of well-being. So, I wholeheartedly support that sort of approach.

One has to be a little careful with acupuncture, only because we're introducing needles, patients' immune systems can be impaired, platelets can be low, there could be bleeding, but admittedly the needles in acupuncture are small. I found acupuncture to be most helpful in people in chronic pain syndromes. In general, that's not a big part of acute myeloid leukemia.

So, there are a lot of remedies that have been written about. I'm actually not familiar with the particular one that you have mentioned. I do think that some are safe to combine with standard chemotherapeutic agents. Others are not. Others can actually add to side effects and interfere with the way chemotherapy works. So, one has to be particularly careful when you start taking systemic holistic therapies such as this. And, I would be careful to have the discussion with your provider and look up any particular drug interactions that might occur.

Ms. Figueroa-Rivera:

Thank you for the question. And our next question, both Walter and Oscar are asking about age. Walter's 80 and Oscar is 84, in remission and really looking to see, because of their age, are they not candidates for bone marrow transplants? And, in remission, if remission fails, what would they do next?

Dr. Jurcic:

Sure. So again, this is a very common problem, particularly now that our therapies for older individuals have become more effective and more patients are getting into remission. So, we talked about azacitidine and venetoclax giving an average remission duration of about a year or so. What do you do next after that stops working? Well, in most centers, transplant can be done up until about age 75. Issues with transplant after this really become one of tolerability of the chemotherapy that's given prior to the transplant to suppress the immune system, as well as a higher chance of graft-versus-host disease. This is where the new white blood cells, the new immune cells that are now growing in your body after the transplant, can begin to recognize normal tissues in your body as, quote, foreign, and begin to attack them. So, this can result in skin rashes, GI complications, liver problems. And, it can be quite debilitating. And, we know that this risk is higher as one ages.

And so, transplant above the age of 75 really does become very difficult. Again, there are exceptions and sometimes we do transplants in people over the age of 75, but, in most centers that seems to be the rule of thumb these days.

Interesting because not so long ago, 15 or 20 years ago, we would say, well, we'll do it up to age 60 or 65. So, this bar has been pushed and hopefully as transplant technology continues to improve and risks of graft-versus-host disease are reduced over time, we will be able to offer this modality to older individuals.

So that said, it is important to plan your next step, because what we're really thinking about is a series of therapies over time that can produce remissions and hold that remission for a while, and then we change treatments and we move on to the next, and the next. And so, I think one of the clues that we can use, are what are the genetic abnormalities that can occur. And in fact, this can change over time. We know that when people relapse, you can sometimes relapse with a different strain, if you will, of the leukemia. A different clone has grown up as we've eliminated one particular strain of the leukemia with the treatment that person is currently on. And sometimes, the leukemia cells can acquire new genetic abnormalities and those abnormalities can serve as targets for therapy. And so, at the time of relapse it's important to recharacterize the disease from the start. Chromosome analysis, molecular analysis, to see what the therapeutic options might be.

In addition to the targeted agents, we can think about clinical trials. So, there're many new drugs that are being looked at and it changes on a month-to-month basis, if not more quickly. So, it's a bit difficult to answer that question for any one particular moment in time, but clinical trial options at the time of relapse really should be explored, in addition to a full chromosome and molecular analysis of the disease because it can change.

Ms. Figueroa-Rivera:

Sure, and Ronald is also asking has cord blood transplant been approved for older patients?

Dr. Jurcic:

So again, cord blood transplants can be done in older individuals. One of the potential advantages is that the quality of the match doesn't have to be quite as great, and the risk of graft-versus-host disease can be lower. So again, I think that you would need to talk to the transplant physicians at your particular center, but I think the same sort of age guidelines that I discussed earlier would also apply to alternative donor transplants like the half-matched transplant, so-called haploidentical transplant, as well as cord blood.

Ms. Figueroa-Rivera:

Thank you. And, we'll take the next question from our telephone audience, please.

Operator:

We have Nancy in Michigan. Nancy, please go ahead with your question.

Nancy:

Yes, Doctor. I'm just wondering, my daughter is 37, her job allowed her to travel really all over the world, including China and places like India. And, I'm just wondering, 3 years ago she was shot in that country western festival in Las Vegas, she had 2 bullets, 1 inch from her spine. And, I'm wondering if the shrapnel from those bullets or the travel overseas, I mean maybe something she ate or something caused this AML, because she has been in excellent health until these 2 things occurred.

Dr. Jurcic:

So, it's generally thought that the travel or a foreign body would not cause the disease. For the vast majority of people with AML, we simply do not know the root cause. We know certain exposures can do this, like chemicals of benzine, polyene, or radiation exposure can increase your risk of developing leukemia. Exposure to chemotherapy

that has cured one cancer can years later manifest as leukemia. So, this is known. But, even in those patients with these exposures, not all develop AML. So, it is really difficult to say what the true cause of this is. We know there are associations, but I can say with the things that you have actually mentioned, there are no known associations with foreign bodies or gunshot wounds or travel. I hope that helps.

Ms. Figueroa-Rivera:

Thank you. And, we do hope that your daughter is doing well.

Dr. Jurcic, our last question today. Michael asks what is the best way to address AML? How much time should be allowed before doing a transplant once it is clear that the chemo treatment has led to remission?

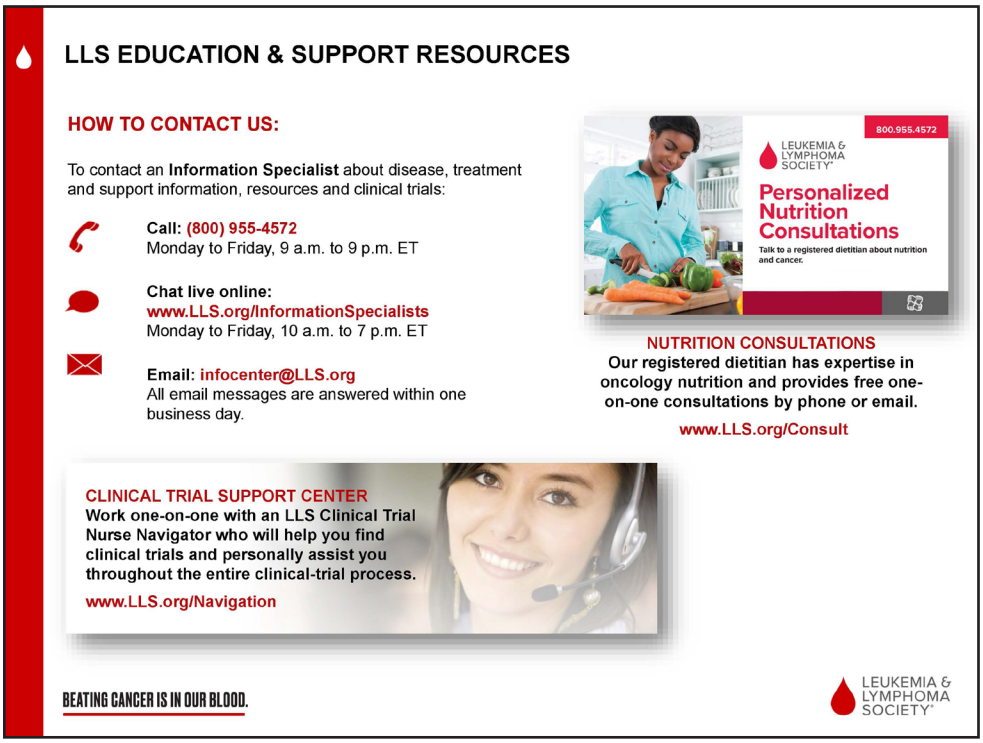
Dr. Jurcic:

So, that's a great question. And so, I'm going to break it down into 2 parts.

Well, there used to be a dogma that once AML was first diagnosed you had to treat it immediately. We now recognize that knowing that molecular characterization in patients is so important, and in fact understanding the disease and giving the appropriate therapy upfront can lead to better outcomes. And so, we do have a few weeks in most patients where we can wait before initiation of therapy. So, that characterization I think is key in determining the best therapy for a patient, which will lead to the best outcome.

Now, as far as the timing of the transplant, yes, transplants work best in patients who have the least amount of disease in their body possible. And so, we didn't have a lot of time to talk about this and the hour is coming to a close, but there's a whole area of study in acute myeloid leukemia looking at measurable residual disease. And, we know that transplants work best if you can get the disease down to these very low levels. And so, a person goes into remission rapidly with chemotherapy or whatever targeted therapy they're taking and there's no detectable residual disease, that's a good time for a transplant.

Many times we'll actually offer a post-remission therapy to try to eliminate that residual disease prior to the transplant. And so, it can vary but generally speaking I would say the soonest the transplant should be performed after the start of the AML therapy, would be about 2 months. But, it can vary. And of course, you don't want to wait too long because if you're leaving this minimal residual disease untreated, that disease can again begin to grow and reach a critical mass and cause relapse. So, the key is really timing this optimally and I would say somewhere between 2 and 4, maybe 6 months after therapy is the optimal time for the transplant.



Slide 36: LLS EDUCATION & SUPPORT RESOURCES

Thank you. And, thank you for all of your questions today. And, thank you so much Dr. Jurcic for your continued dedication to our patients.

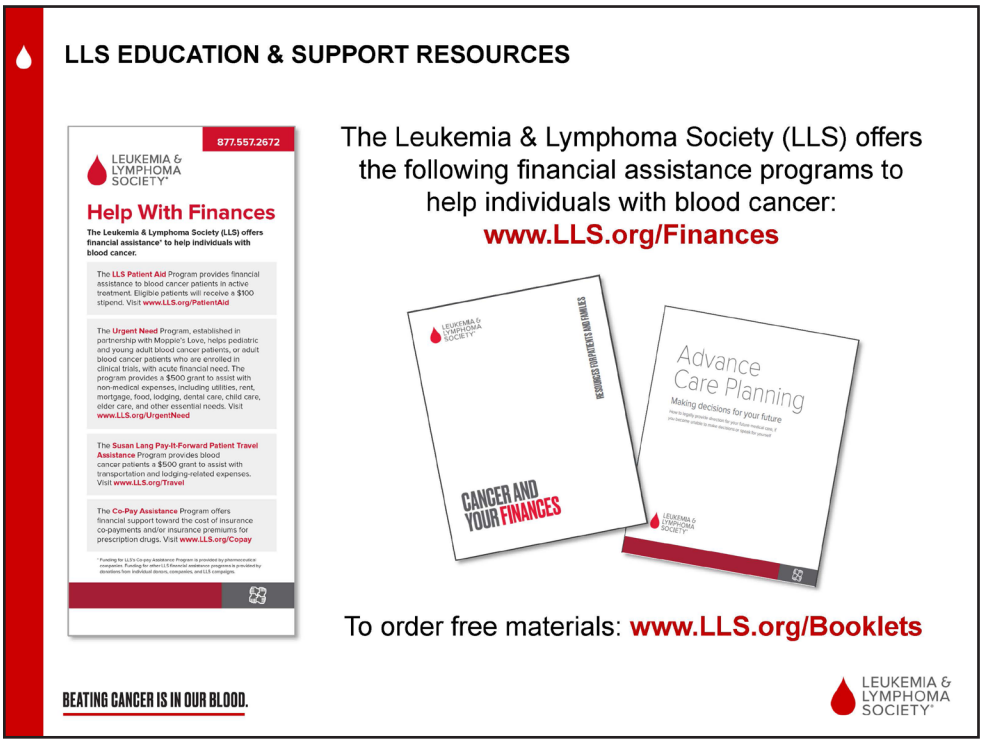
And, for those of you who participated in today's program, we hope the information presented today will assist you and your family in your next steps.

Now, if we were not able to get to your question today or you want more information, you may speak to an LLS Information Specialist at 1-800-955-4572 from 9 AM to 9 PM Eastern Time, or you can reach us by e-mail at infocenter@LLS.org.

Information Specialists are available to answer your questions about treatment, including clinical trials, and answer other questions that you might have about support, including financial assistance for treatment.

Slide 37: LLS EDUCATION & SUPPORT RESOURCES

We also have a Clinical Trial Support Center where Clinical Trial Nurse Navigators, who are registered nurses with expertise in blood cancers, can assist you in finding out if a clinical trial is right for you. They can be found at LLS.org/Navigation.



Slide 38: LLS EDUCATION & SUPPORT RESOURCES

As a reminder, you can download and print the slides, as well as listen to the audio of today's program from our website at LLS.org/Programs.

And again. we would like to acknowledge and thank Agios Pharmaceuticals, Bristol-Myers Squibb, Genentech and Biogen, and Jazz Pharmaceuticals for support of this program.

Slide 39: THANK YOU

Dr. Jurcic, thank you again for volunteering your time with us today. And, on behalf of The Leukemia & Lymphoma Society, thank you all for joining us. Goodbye and we wish you well.