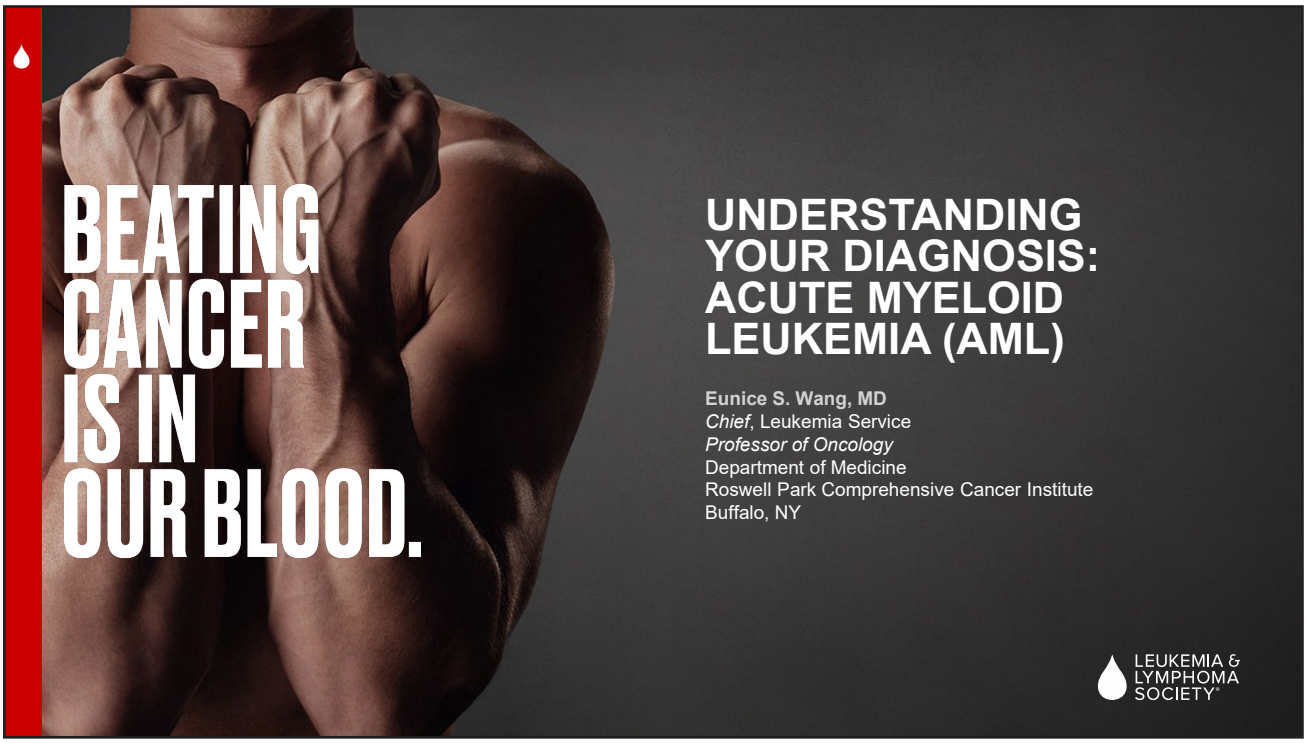


Slide 1: Beating Cancer is in Our Blood

Lizette Figueroa-Rivera:

Hello, everyone. On behalf of The Leukemia & Lymphoma Society, I'd like to welcome all of you. Special thanks to Dr. Eunice Wang for volunteering her time and expertise with us today.

As the world's largest voluntary health agency dedicated to fighting blood cancers, The Leukemia & Lymphoma Society is leading the offensive to dramatically improve outcome for patients with acute myeloid leukemia or AML.

LLS began funding AML research at our inception, over 70 years ago, and approximately 26% of our annual research budget goes to AML research. In the past years we've invested nearly $100 million in AML research, with a focus on understanding the underlying causes of the disease to develop better therapies and save more lives.

There have been few advances in treatment for AML in 40 years and LLS aims to change that through a precision medicine approach. And our presenter Dr. Wang will discuss the advances in AML treatment that have occurred within the past couple of years.

Now through our Beat AML initiative, our AML Master Trial is a groundbreaking collaborative clinical trial simultaneously testing several targeted therapies for newly diagnosed patients with AML. LLS is fostering collaboration among researchers at multiple institutions, regulators, pharmaceutical and biotechnology companies, primary healthcare physicians and patients to develop effective, individualized therapies to treat patients with AML. And according to Dr. Louis DeGennaro, our LLS President and CEO, our Beat AML Master Trial demonstrates our ability to convene the medical and research communities to think and act boldly in the quest for new and better treatments for blood cancer patients, and our aim to accelerate the rate at which precisely targeted breakthrough therapies reach the patients who urgently need them.

And you can find more information about our continued dedication to AML patients on our website.

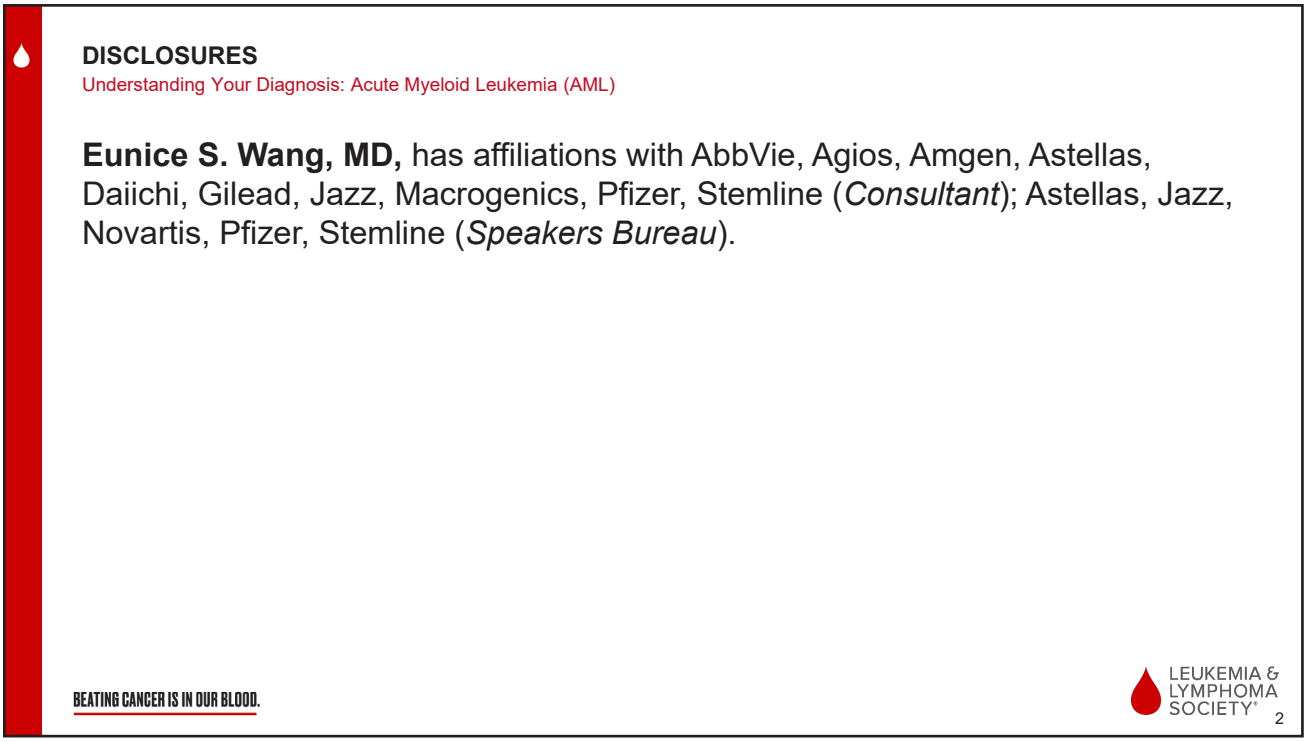
And for this program we'd like to thank and acknowledge Agios, Bristol-Myers Squibb, Daiichi Sankyo, Genentech & Biogen, and Jazz Pharmaceuticals for support of this program.

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

I am now pleased to introduce Dr. Eunice Wang from the Roswell Park Comprehensive Cancer Institute in Buffalo, New York. Dr. Wang, I'm privileged to turn the program over to you.

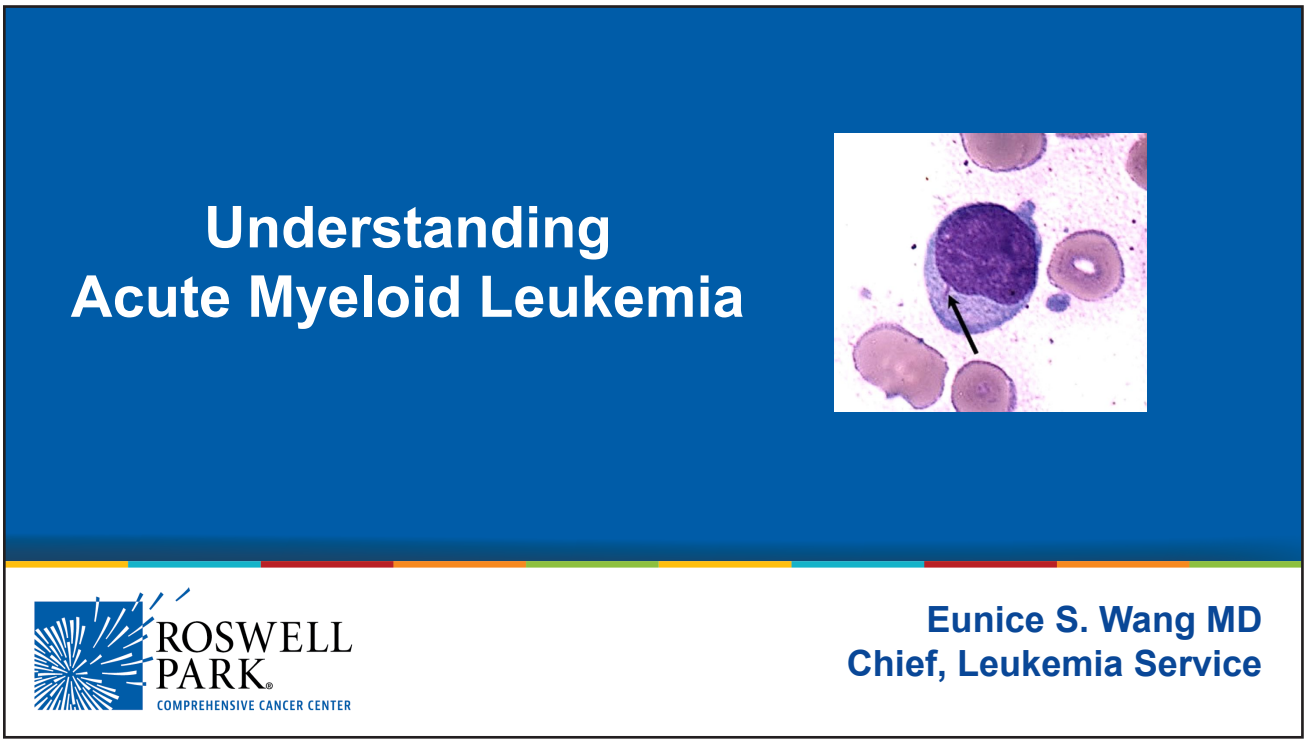
Dr. Eunice Wang:

Thank you very much. I'm extremely grateful to LLS and all the sponsors for providing the funds and the opportunity for me to speak here today.



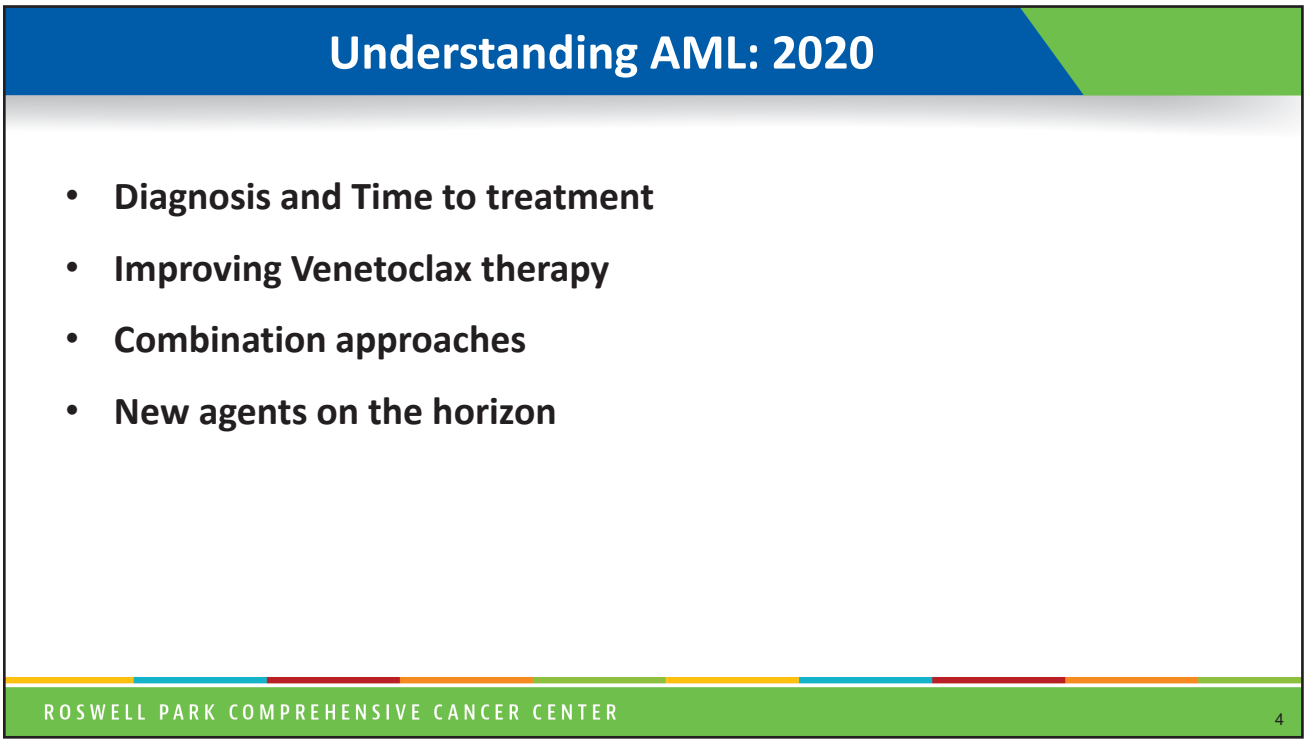
Slide 2: Disclosures

Shown here are some of my disclosures.



Slide 3: Understanding Acute Myeloid Leukemia

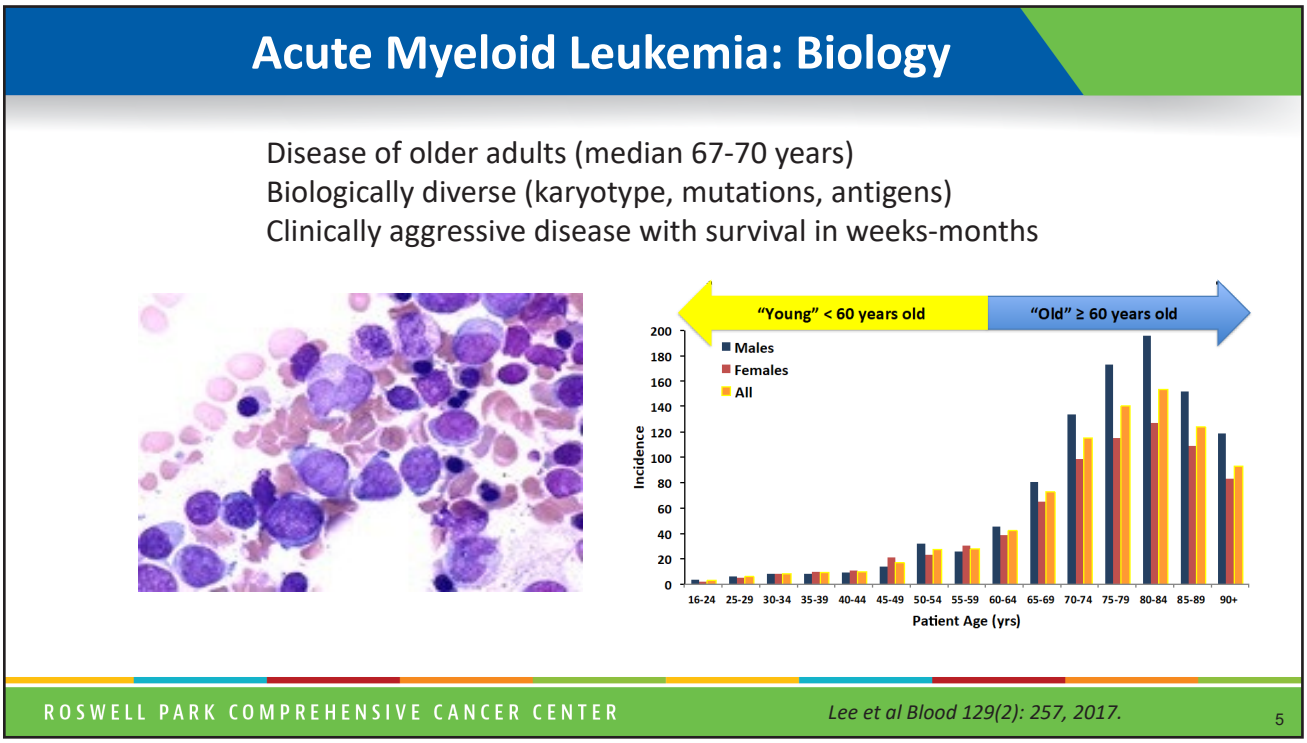
Understanding Acute Myeloid Leukemia. What do we know about acute myeloid leukemia? What is the origin of acute myeloid leukemia? How do we treat acute myeloid leukemia?



Slide 4: Understanding AML: 2020

So, what I'd like to focus on today is some developments on the forefront of AML diagnosis, prognosis and treatment. Here's a summary of some of the topics that I'll be overseeing today. I'm going to be talking about how do we make a diagnosis of AML. When should we start treatment, what are the things that we need to be looking at when we're making an AML diagnosis in the current era? As was mentioned previously, precision medicine and individualizing treatment for AML has gone to the forefront of how we view and deal with AML in 2020. We have a number of novel agents, many of them targeted against specific mutations, which have been developed specifically over the last couple of years and offered many hopes and opportunities for prolonged survival for AML patients, when previously there was no option for these individual patients. These include older patients or those with comorbidities, and for all AML patients the advent of novel therapy promises to extend life span for all individuals with AML.

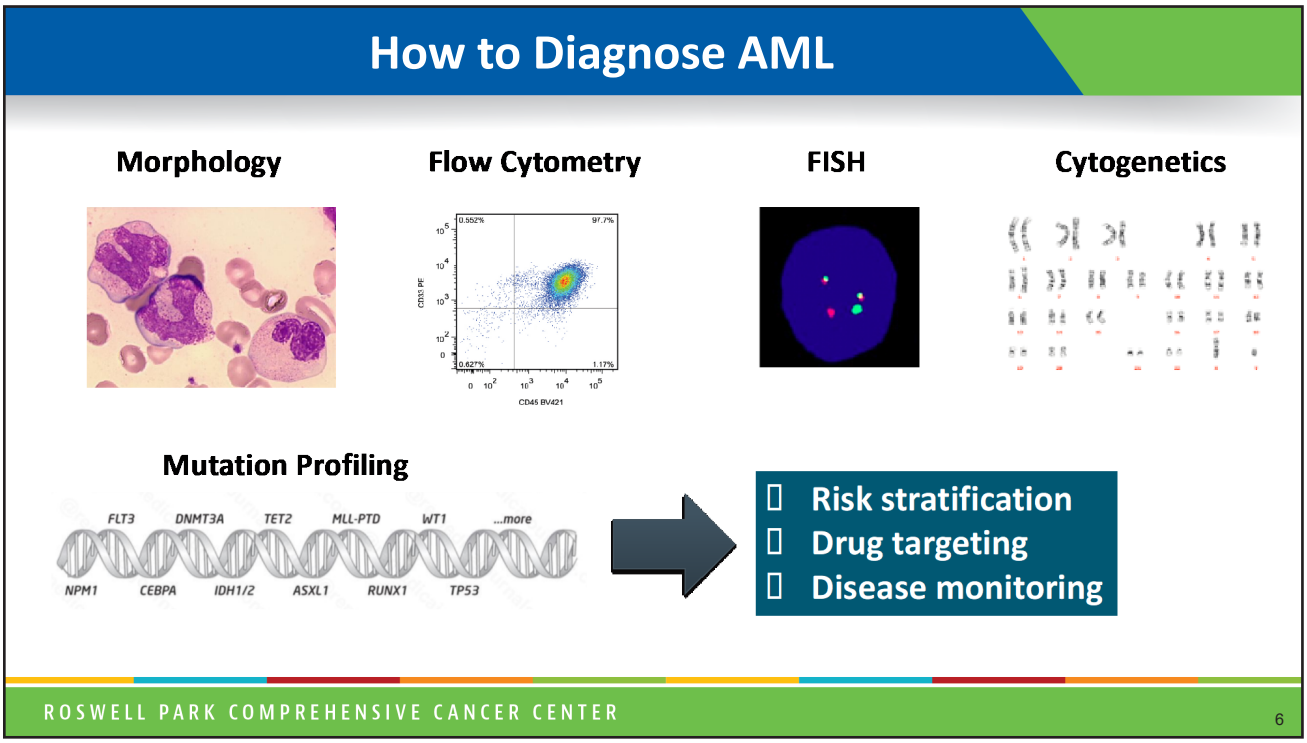
I'll be talking about some updates and new data presented at the recent hematology meeting in December, 2019, novel combination approaches, novel agents that are being developed, and newer agents that are on the horizon that may be options in clinical trials for patients now and in the near future.



Slide 5: Acute Myeloid Leukemia: Biology

Acute myeloid leukemia. What is acute myeloid leukemia? Acute myeloid leukemia is an aggressive blood cancer, occurring largely in older adults. Many studies have demonstrated that the average age of presentation of acute myeloid leukemia is in individuals in their 60s and 70s. And we often see patients with this disease that are older than 67 or 70 years old. We see individuals 60, 70, 80s or even 90s. And as our population ages, the incidence of acute myeloid leukemia is also increasing.

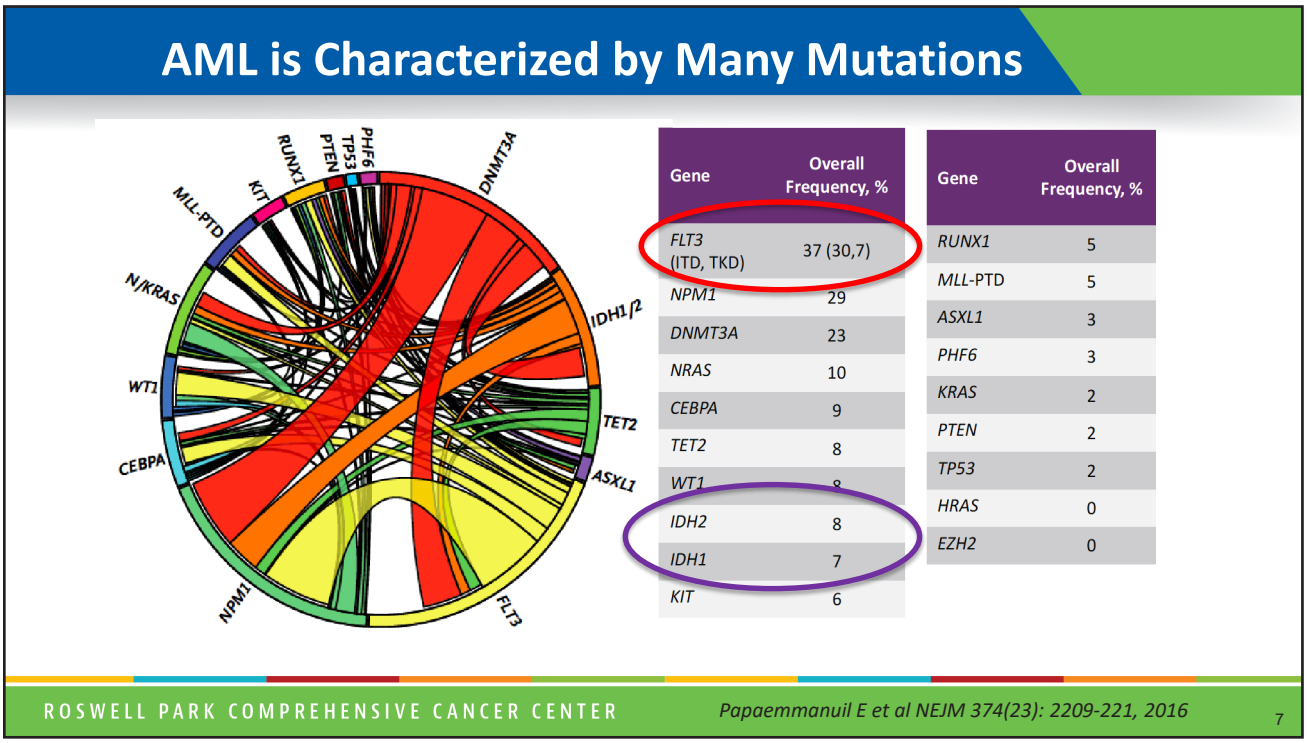
Now despite the fact that this is a very aggressive blood cancer with growth and increased white blood cells and increased tumor cells in the blood, occurring in a matter of days, this is an incredibly biological diverse disease. What do we mean by that? We mean that it's not just the same disease. When they have done characterization of AML in 400 individuals, they found 400 different types of AML in these individuals. These acute leukemia cells, acute blood cancer cells mutate, there's many of them, they diverge, they evolve, so it's an incredibly biologically complex disease and that has in part been why it's been so difficult until now to really target and treat this disease. Many individuals present with symptoms that have occurred not over months to years, but really over a matter of weeks. Most individuals will have normal blood counts as recently as a couple months prior to their diagnosis of AML, but some may develop symptoms related to compromised blood cells. They develop low blood counts, anemia, they develop infections that they're not able to clear, they develop bleeding complications from low platelet counts. Many of these individual patients have other comorbidities, which can complicate things.



Slide 6: How to Diagnose AML

Now how do we diagnose AML? In the current era it is not enough to just take a look at the blood cells and say these are acute leukemia cells. In fact, it is essential now that patients that have acute leukemia have an entire comprehensive work-up. What does that mean? That means that not only must we look at the morphology or how the cells look. You can see here in this slide a picture of about two or three cells that are acute leukemia cells. We also do testing to look at the tumor markers and proteins that are expressed by the leukemia cells. We do DNA testing to look for chromosomal abnormalities or deficiencies in the DNA. And we do mutation profiling where we can look at hundreds, even thousands of genes that are expressed in individual cancer cells and see how many of them are mutated.

Why is this important? It is important because the information from each of these tests is important for stratifying the prognosis of these patients, and for targeting patients with specific mutations. It is also important in some cases to characterize the disease so we can monitor whether the disease is still present in individual patients.



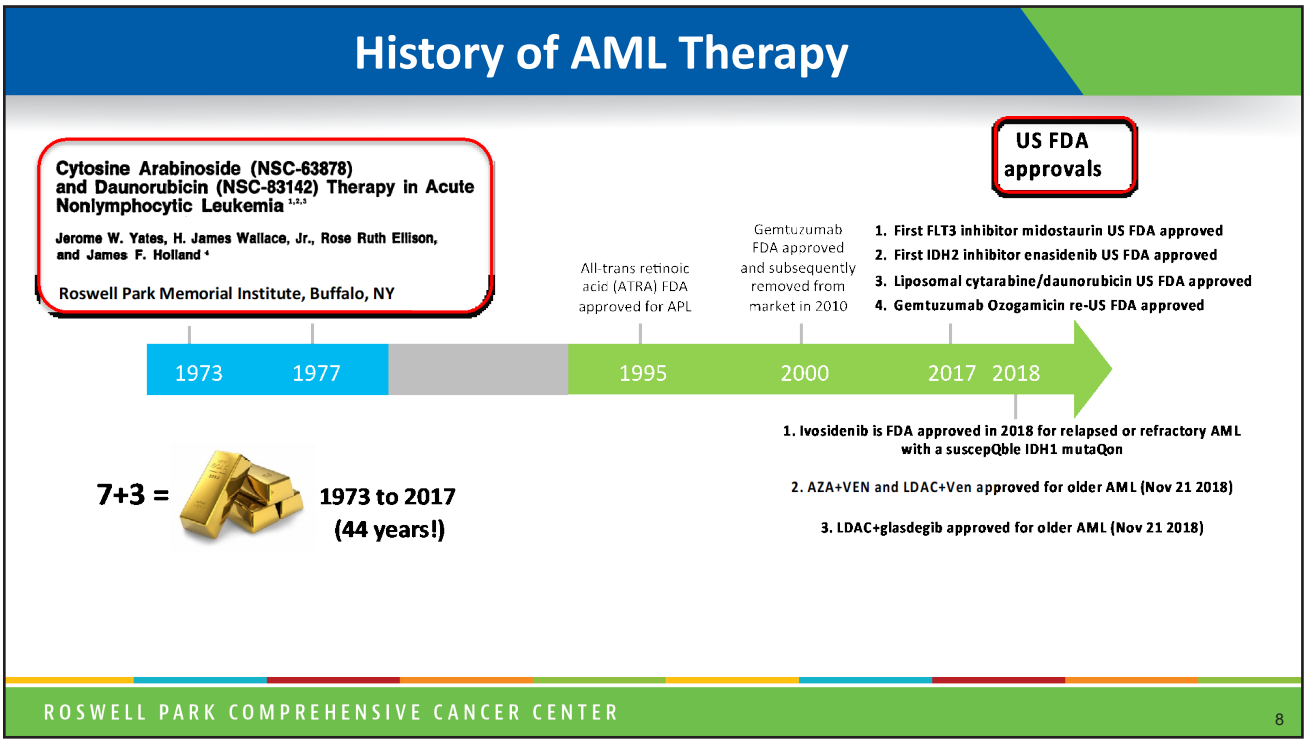
Gene	Overall Frequency, %
FLT3 (ITD, TKD)	37 (30,7)
NPM1	29
DNMT3A	23
NRAS	10
CEBPA	9
TET2	8
WT1	8
IDH2	8
IDH1	7
KIT	6

Gene	Overall Frequency, %
RUNX1	5
MLL-PTD	5
ASXL1	3
PHF6	3
KRAS	2
PTEN	2
TP53	2
HRAS	0
EZH2	0

Slide 7: AML is Characterized by Many Mutations

This picture here highlights many of the gene mutations that are found in AML cancer cells. You can see here that the most common gene mutation, FLT3 or Flit 3, is only found in a third of patients, 37% of patients. All other abnormalities occur in less than 30% of patients and many of these gene mutations occur in less than 10%. You can see that IDH1 and IDH2 mutations only occur in about 7 to 8%.

What does this mean? This means that there's not one dominant gene mutation that defines acute myeloid leukemia. Acute myeloid leukemia is defined by multiple mutations, many of patients may have mutations in more than one gene. For example, patients can have mutations in FLT3 as well as IDH1 or IDH2, and other genes, including NPM1, which further complicates things and is illustrated in this ribbon graph. The ribbons that are connecting are genes that are mutated in the same individual cell in a patient.

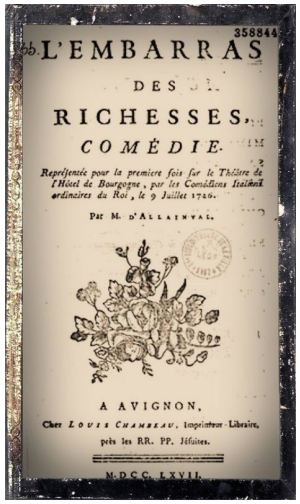


Slide 8: History of AML Therapy

How can we use this information? How have we treated AML? Well, as mentioned in the introduction, in the 1970s a chemotherapy regimen was developed right here actually at Roswell Park Cancer Center in Buffalo, New York. It consisted of seven days of a chemo drug called cytarabine and three days of a second chemo drug called daunorubicin. This regimen, which was termed 7+3, is an intensive chemotherapy regimen given on the inpatient setting, which requires patients to be hospitalized for four to six weeks. The intent of the 7+3 regimen is to eliminate or destroy all of the leukemia cells in the blood, but in the same time it destroys all of the cancer cells as well as the normal cells. So, patients need to be hospitalized because they need transfusions of red cells and platelets and they need antibiotics to treat the fact that they're severely immuno-deficient.

Now this incredibly high dose, toxic chemotherapy regimen has been the standard of care up until 2017, for over 44 years. And you can see here that since 2017 there have been a number of different drugs which have been approved. In total there have been eight new drugs approved for AML therapy in the last two years.

AML Therapy: Many New Drugs



Attributed to John Ozell's translation of a French play (1738); Translated in 1725 as The Plague of Riches

Definition: Generally used to describe an abundance of something, (typically positive) with the idea that there are so many of these good things that it's difficult to pick just one.

8 Drugs approved for AML in last 2 years
Midostaurin, Enasidenib, CPX-351, Gemtuzumab
Ivosidenib, Gilteritinib, Glasdegib, Venetoclax

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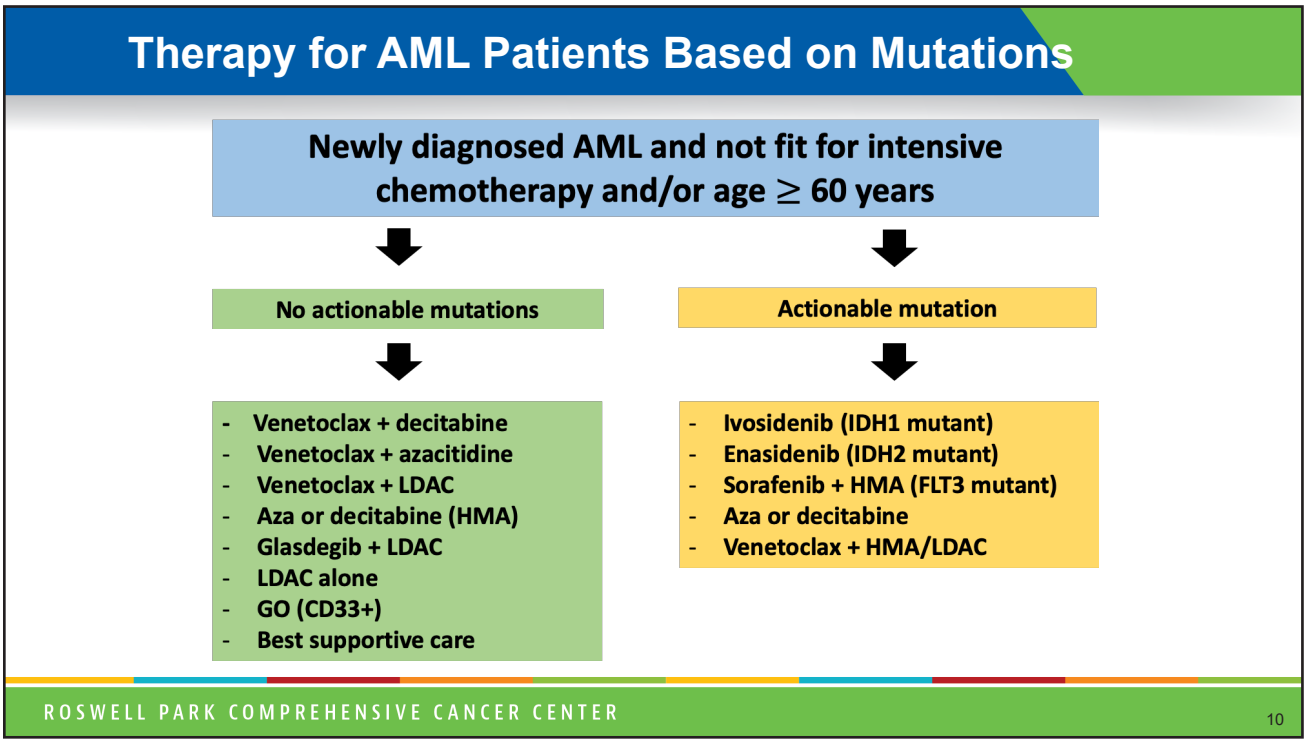
Slide 9: AML Therapy: Many New Drugs

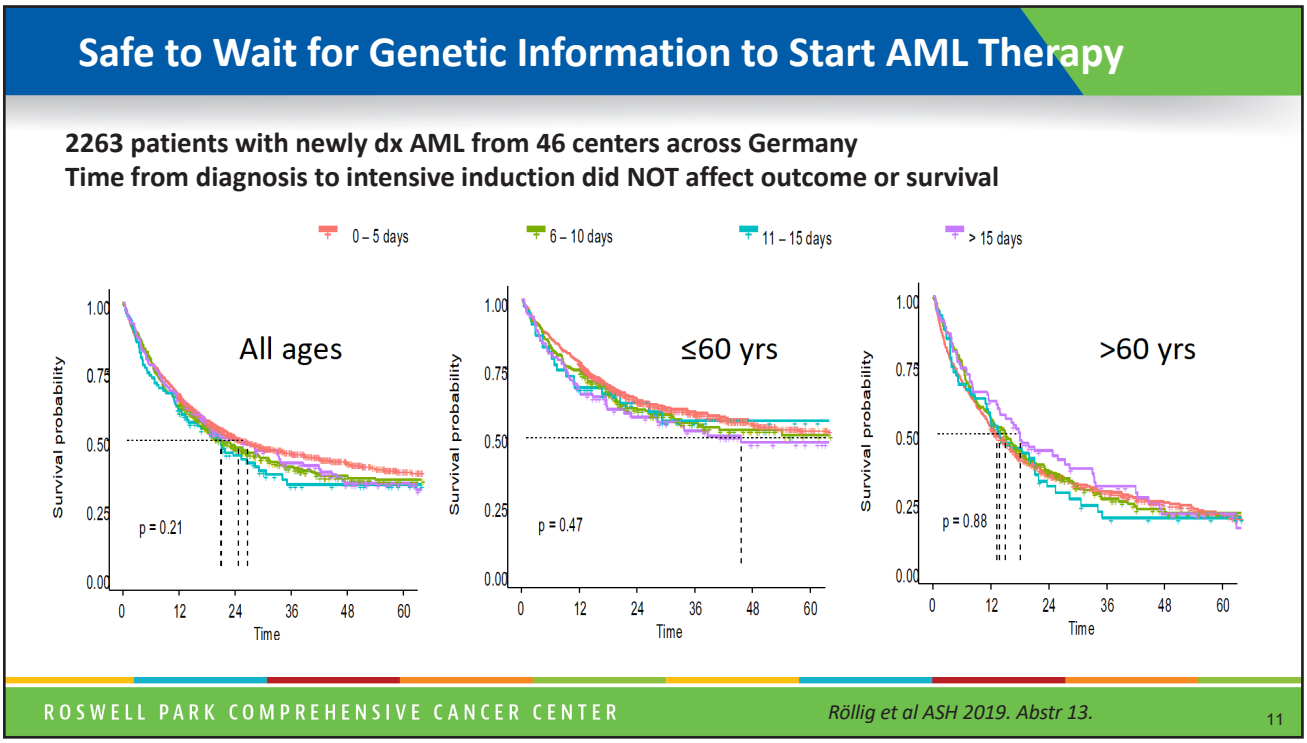
And this almost gives us what is termed here an embarrassment of riches, an abundance of options which are now available. But now it is important for now that we have an abundance of options, is to figure out how best to use these options and figure out which patients are most likely to benefit from these new therapies.



Slide 10: Therapy for AML Patients Based on Mutations

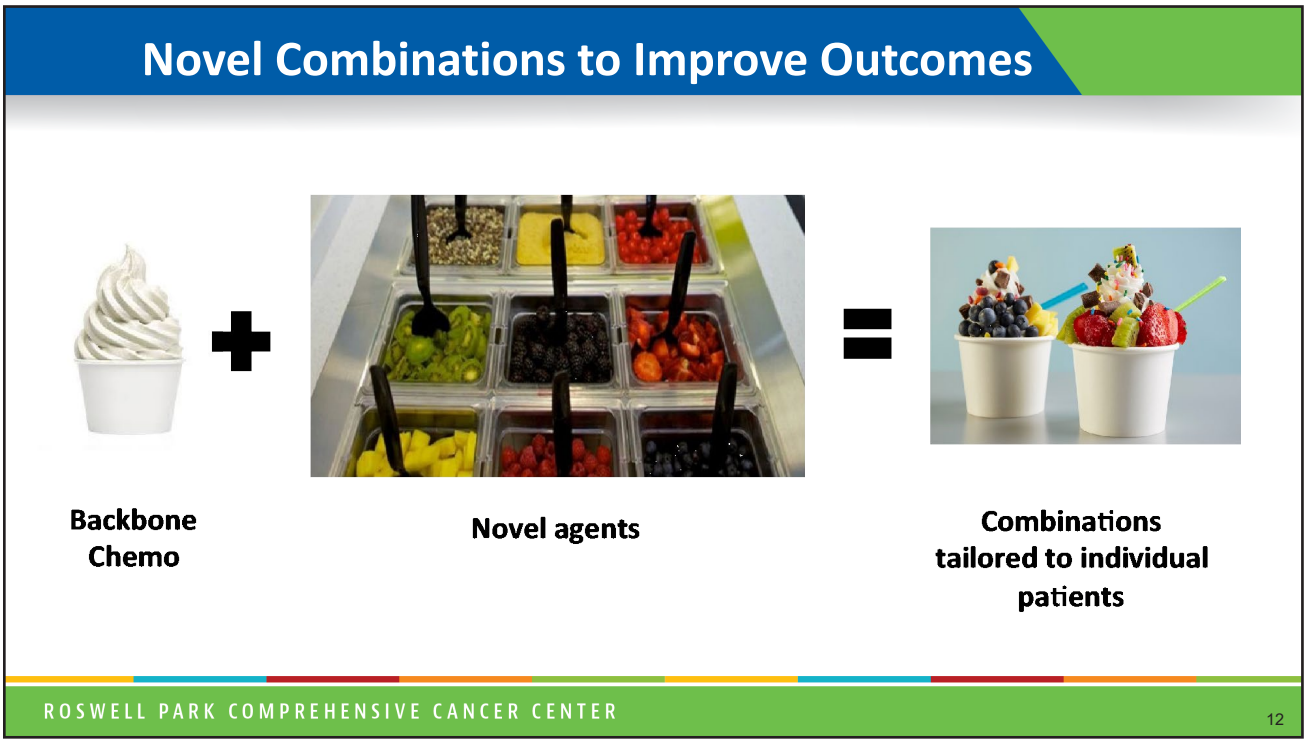
And older individuals, those that are above the age of 60 years old, who are not fit for chemotherapy, we have made the most progress in treating AML. And these individuals are not people who typically will be able to tolerate the high dose chemotherapy that is offered by 7+3, and they have other conditions like heart failure, diabetes, high blood pressure, stroke, etcetera, that can present problems and increase complications when giving a high dose chemotherapy regimen. For these individual patients you can see here that we are now offering therapy based on the presence or absence of what we call actionable mutations. What are actionable mutations? Those are the three mutations I mentioned previously, IDH1, IDH2 and FLT3. If you have one of those mutations, we now have targeted agents to treat your disease. And if you don't have them, we have other chemotherapy regimens which are specifically tailored to be tolerated in these older individuals.

Now some people will ask, well, doesn't it take a long time to get all of that mutational information back? I mean it's not instantaneous. And that is true because we need to extract the DNA and RNA from the cancer cells and then we have to run tests for each one of those mutations. So, it could take at best three to five days or even longer, seven to ten days, or even a couple weeks sometimes at some centers to get that information back.



Slide 11: Safe to Wait for Genetic Information to Start AML Therapy

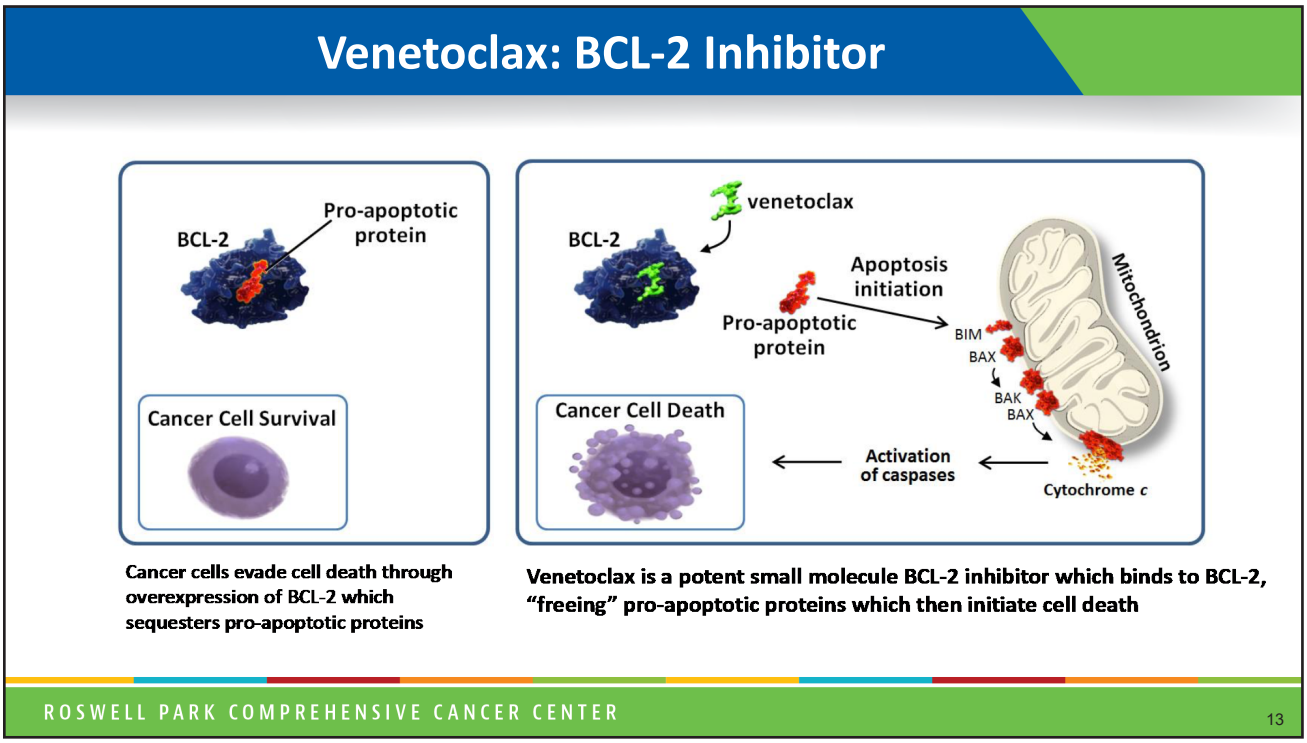
So, one question that has been raised by clinicians that treat acute myeloid leukemia is, is it safe to wait to get this mutational information back? We'd like to get the mutational information back because we'd like to offer some of these targeted therapies, but we don't want patients' aggressive acute leukemia to progress. So in this figure here, you can see data that was presented at that hematology meeting in December 2019, and here, and this data is important because it demonstrates that it's safe to wait for the genetic and the molecular information to come back from newly diagnosed AML patients in order to start therapy. In this particular study 2,263 patients, who were newly diagnosed with AML, from 46 different cancer centers across Germany were treated with intensive 7+3 chemotherapy, and they measured the time in which it took from diagnosis to initiation of the chemotherapy. And they looked across all age groups, younger patients, older patients, and you can see here that each of these lines, these colored lines on these graphs, represents the amount of time it took from diagnosis to when they started chemo. The pink is zero to 5 days, the green is 6 to 10 days, the turquoise 11 to 15, and the purple is greater than 15 days. And you can see here on these curves, are the survival curves of all of the patients. And you can see overall these are all overlapping. And this suggests that there really was no difference in how well these patients did, based on when they started chemotherapy. So, this data in most patients is indicated that it is safe to wait a few days for that cancer diagnosis to be confirmed. And this is important for patients to recognize because in that period of time when you're told that you have acute leukemia, the urgency is to start treatment or the feeling that you have is you have to start treatment. But to wait a few days to get that information can be very useful.



Slide 12: Novel Combinations to Improve Outcomes

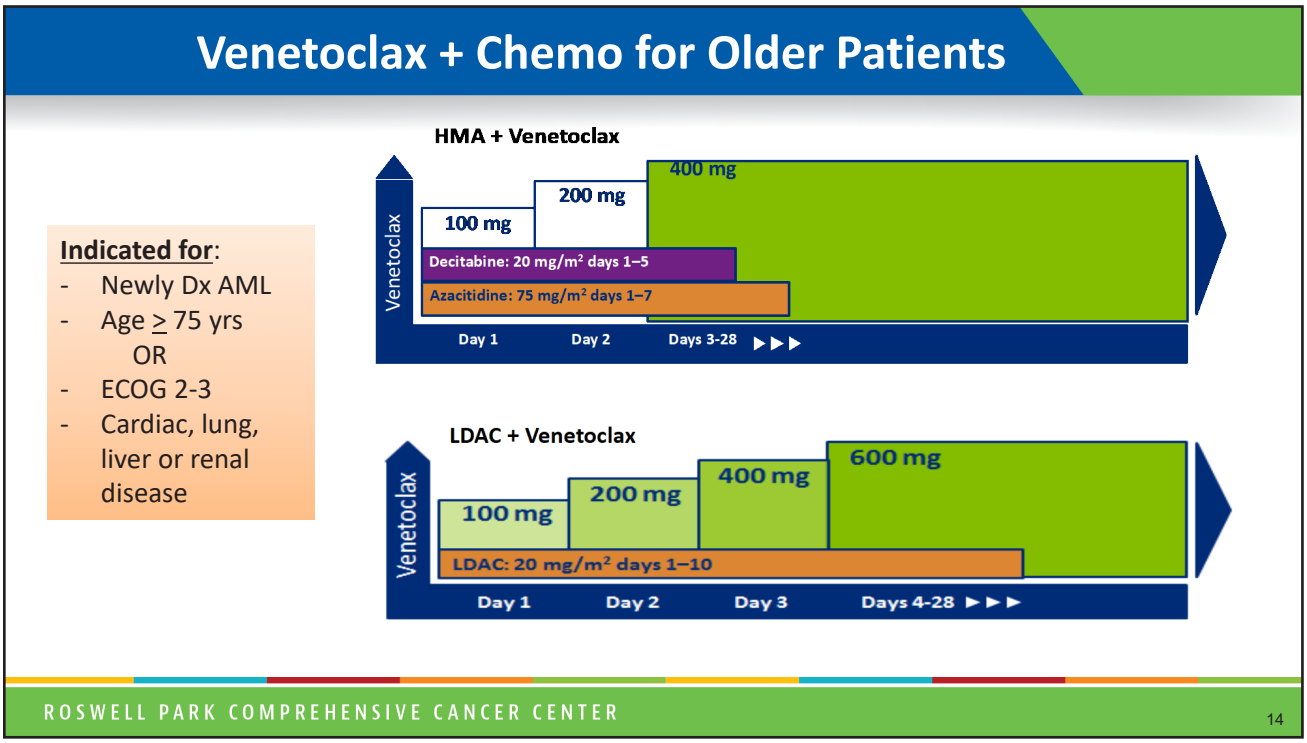
What are we doing nowadays with some of our novel regimens? Well, I'm going to talk a little bit about some of the novel drugs. And I'm going to talk about how to improve on the results of these novel drugs. And one way we can improve is by combinations to give potentially a chemotherapy drug and combine it with a targeted drug.

Now my kids when they were little used to love to go to the frozen yogurt bar and they used to go and they would all get vanilla yogurt, and they would all put different types of toppings. And so, the four of us, my husband and myself and my kids, would all have different toppings. And this is sort of a way to view what we're doing right now with individual AML patients. We are giving a potential chemotherapy drug and then we're tailoring it based on the mutations or lack of mutations, to individualize this therapy, as we individualize each frozen yogurt concoction for each patient.



Slide 13: Venetoclax: BCL-2 Inhibitor

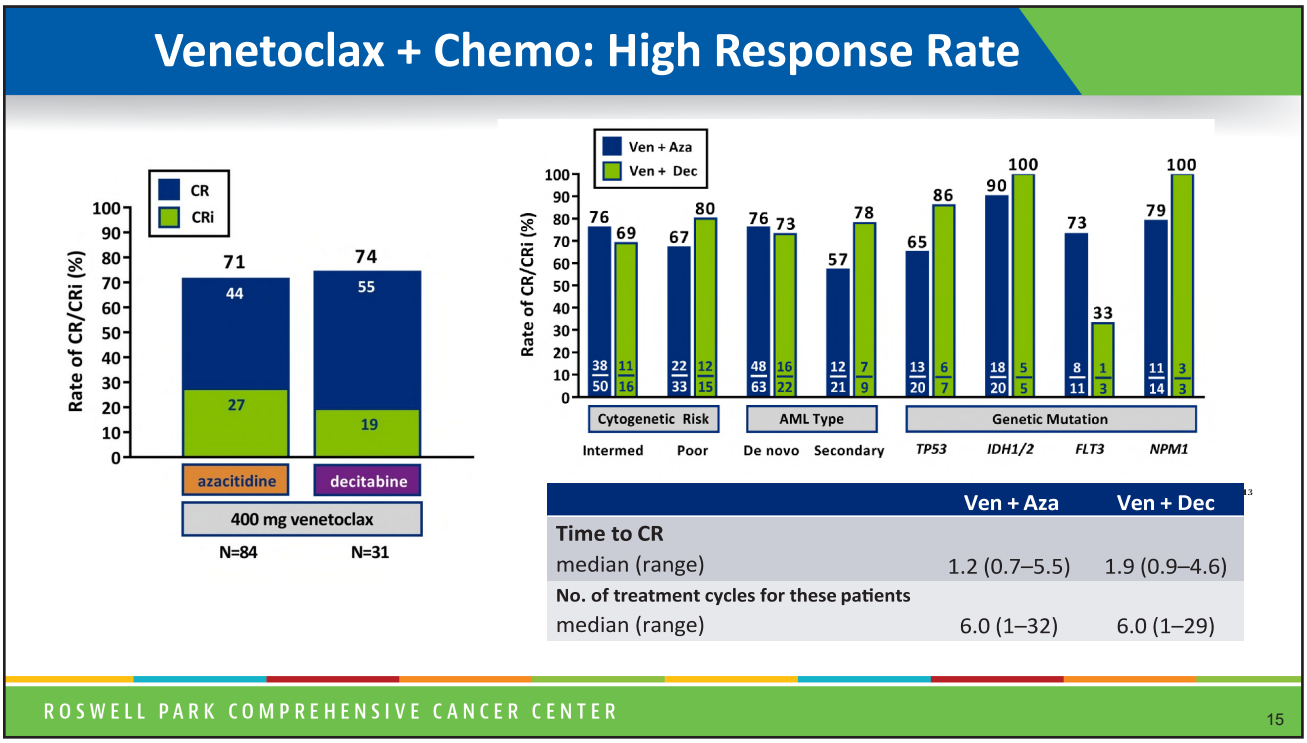
One of the most exciting drugs to enter into treatment for AML is this drug, venetoclax. Venetoclax is an oral, it's a pill that was used to treat patients with chronic lymphocytic leukemia, which is another type of blood cancer. And so, we know that this drug is safe. We know from our data in chronic leukemia patients that this is something we can give to individuals with other blood cancers, which is effective. This particular drug is an inhibitor of a process called BCL-2 or apoptosis. Basically, what happens is the leukemia cells are resistant to undergoing cell death. So, when you treat them with chemotherapy they up-regulate these processes that prevent them from dying when chemotherapy is applied. When you block the BCL-2, which is up-regulated in these cells, you then render those cells sensitive to chemotherapy and then now with the addition of the venetoclax drug, the chemotherapy can now work to kill the cancer cells.



Slide 14: Venetoclax + Chemo for Older Patients

There is data that has been published and is now widely known, that when you give chemotherapy, low dose chemotherapy for acute leukemia patients, the response rate can be quite low. But, when you give the chemotherapy in combination with this oral BCL-2 inhibitor venetoclax, all of a sudden you are getting doubling of response rates. In addition, the chemotherapy that you can give for these patients can be very, very low dose chemotherapy. So, the regimens that have been designed that incorporate this venetoclax drug are specifically designed for those older individuals, those patients either 75 years and above or those older patients with medical problems, that prevent them from getting the standard 7+3 intensive chemotherapy. So, this is perhaps the first chemotherapy drug which has specifically been approved for patients 75 years and above only, which is remarkable.

And you can see here that you can combine the venetoclax either with what we call hypomethylating therapy or with low dose chemotherapy.

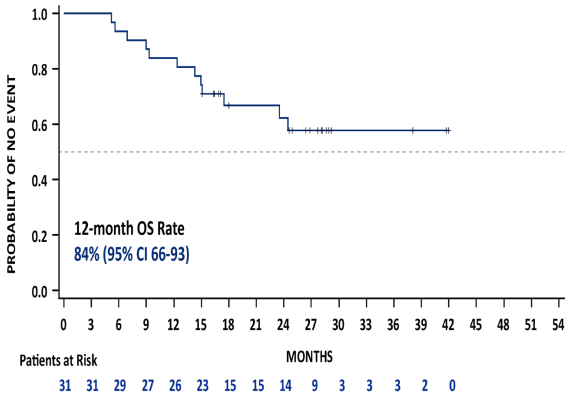


Slide 15: Venetoclax + Chemo: High Response Rate

What are the response rates? Well, when we combine the venetoclax with chemotherapy, either azacitidine, decitabine, we're seeing about 60 to 70% of patients benefit from treatment. We're seeing the time in which it takes for them to respond to be one to two months. And you can see across the board that different types of AML and AML with different mutations all respond to this combination of venetoclax plus chemotherapy.

Venetoclax-based Therapy Followed by Transplant

- 31 of 304 patients (10%) treated with venetoclax + chemo underwent transplant
-
- **Over two thirds (68%,** 21 of 31) patients were alive 12 months after transplant
- **55%** (17/31) of all patients undergoing transplant have remission of ≥12 months after transplant
- **71%** (12/17) of those patients remained in remission for ≥ 2 years



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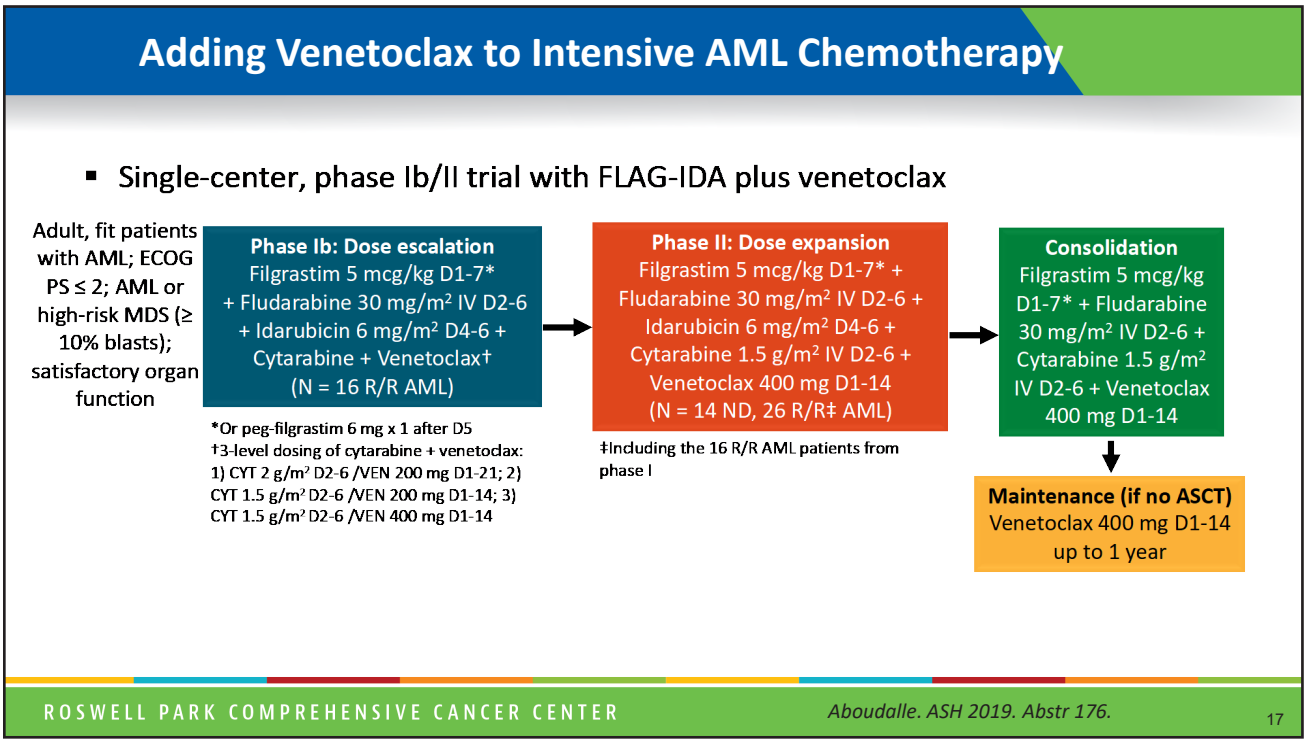
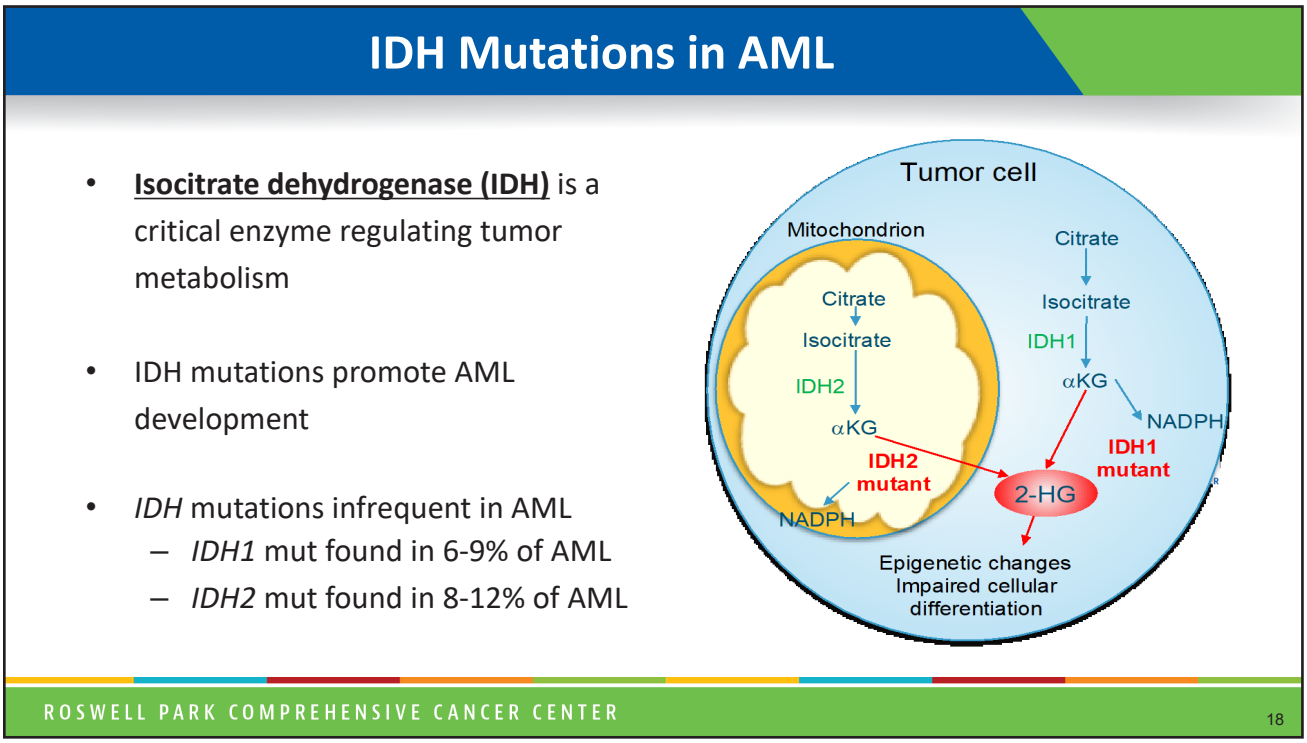
Slide 16: Venetoclax-based Therapy Followed by Transplant

One of the most interesting data presented at the hematology meeting was to say a certain percentage of patients that have acute myeloid leukemia, even though they receive chemotherapy, cannot be cured with chemotherapy alone and will require a bone marrow transplant to completely eliminate the AML cells from their body. So, in the past we have thought that older individuals who were older than 75 or who had medical problems were not eligible to undergo bone marrow transplant because they were not eligible to get intensive chemotherapy. So, in this data presented at the hematology meeting they looked at 30 patients who did not get intensive chemotherapy, they actually got venetoclax plus low dose chemotherapy. And these patients achieved a response with low dose chemotherapy and were subsequently able to go forward and get a bone marrow transplant, even though they had never received any high dose intensive chemotherapy. Now this very early study was very small numbers of patients, showed that patients that got venetoclax-based chemotherapy could successfully go on to transplant. And over two-thirds of patients were alive 12 months after transplantation. And about 71% of these patients were alive over two years. Now again, these are very small numbers of patients and very selected patients, but certainly it offers a way forward.



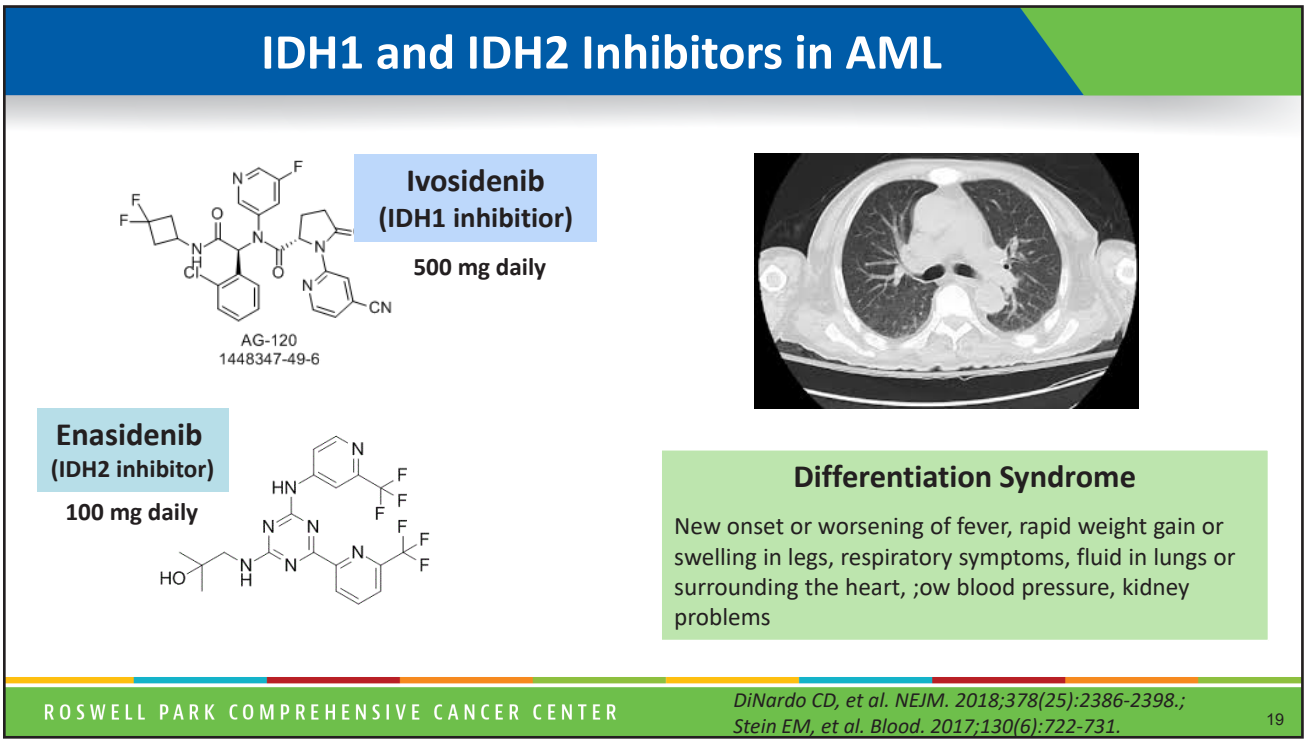
Slide 17: Adding Venetoclax to Intensive AML Chemotherapy

The other thing that we could do is we could say, well, if venetoclax works so well in combination with low dose chemotherapy, maybe we should combine venetoclax with high dose chemotherapy. What if we add venetoclax to 7+3 and can we further improve the outcomes of intensive chemotherapy for those patients? And there was some early data combining chemotherapy, high dose chemotherapy venetoclax, that showed very high response rates of 80 to 90%.



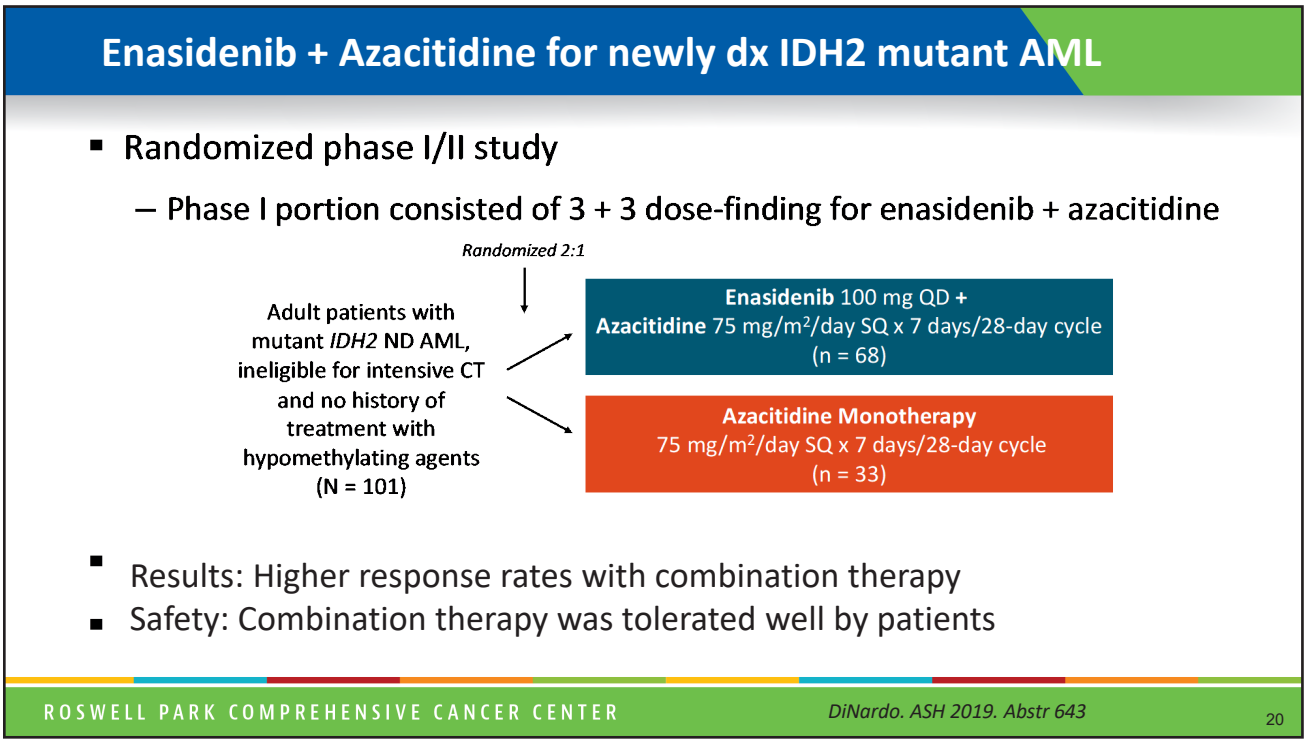
Slide 18: IDH Mutations in AML

Now what are some of the targeted therapies we talked about? We did talk about IDH mutations and these are found in probably 10 or 15% of patients. These IDH mutations are not very common, but what they do is they interfere with the metabolism of the cell and allow the blood cell to get stuck in an early immature form and then overgrow and become leukemia cells.



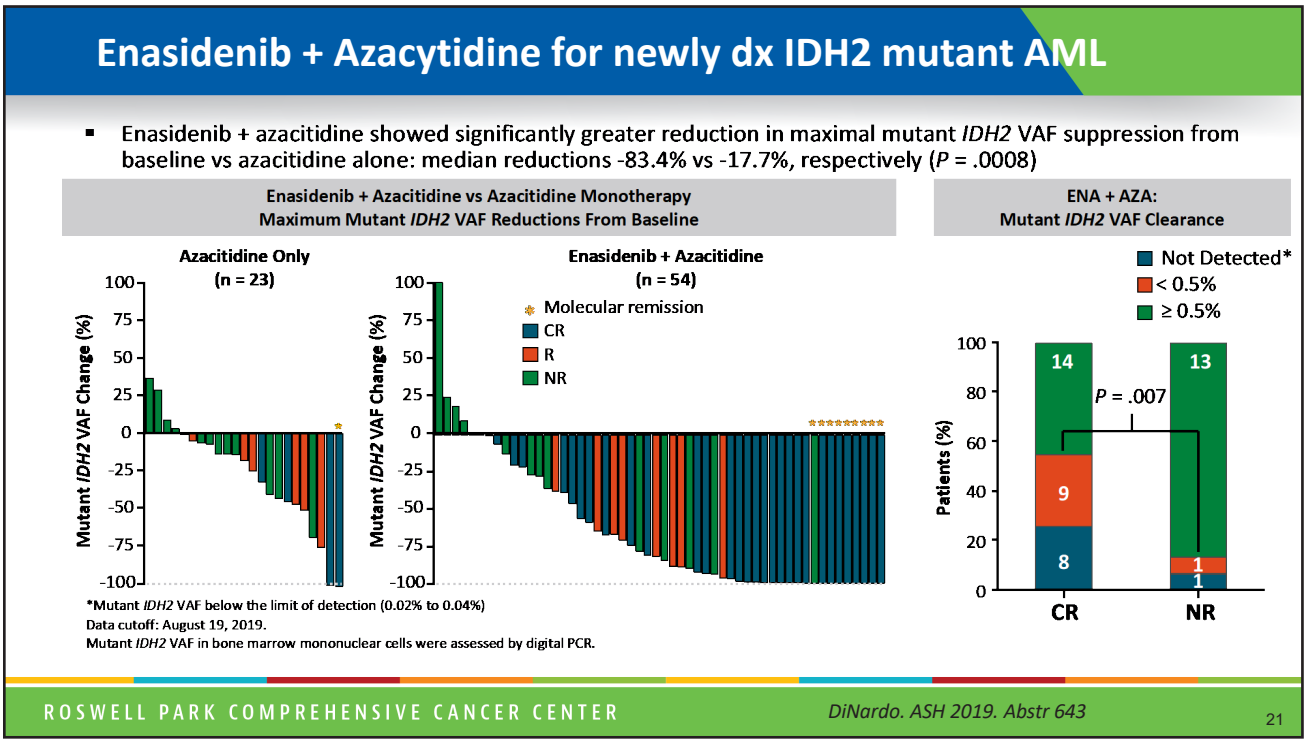
Slide 19: IDH1 and IDH2 Inhibitors in AML

So, we have developed over the last couple years, knowing the biology of how these IDH mutations are affecting the metabolism and the growth of these cells, specific pills, two inhibitors, ivosidenib and enasidenib. These are both pills that you take 500 or 100 milligrams once daily pills. And taking these pills as single drugs in patients that have leukemia with these specific mutations has led to overall response rates in almost half of individuals. Now we do get an unusual side effect with this pill therapy. This pill therapy requires long-term administration. It could take a few months to really have the disease really go under control, and you can develop what looks like almost like a pneumonia or fever, infection, and respiratory problems called differentiation syndrome. And patients will often be mistaken in having what they consider to be pneumonia, but in reality, they are having a side effect of the IDH treatment. So that is something that if you develop a high white cell count and fever, infections, weight gain, trouble breathing, that's something that we need to keep an eye out for.



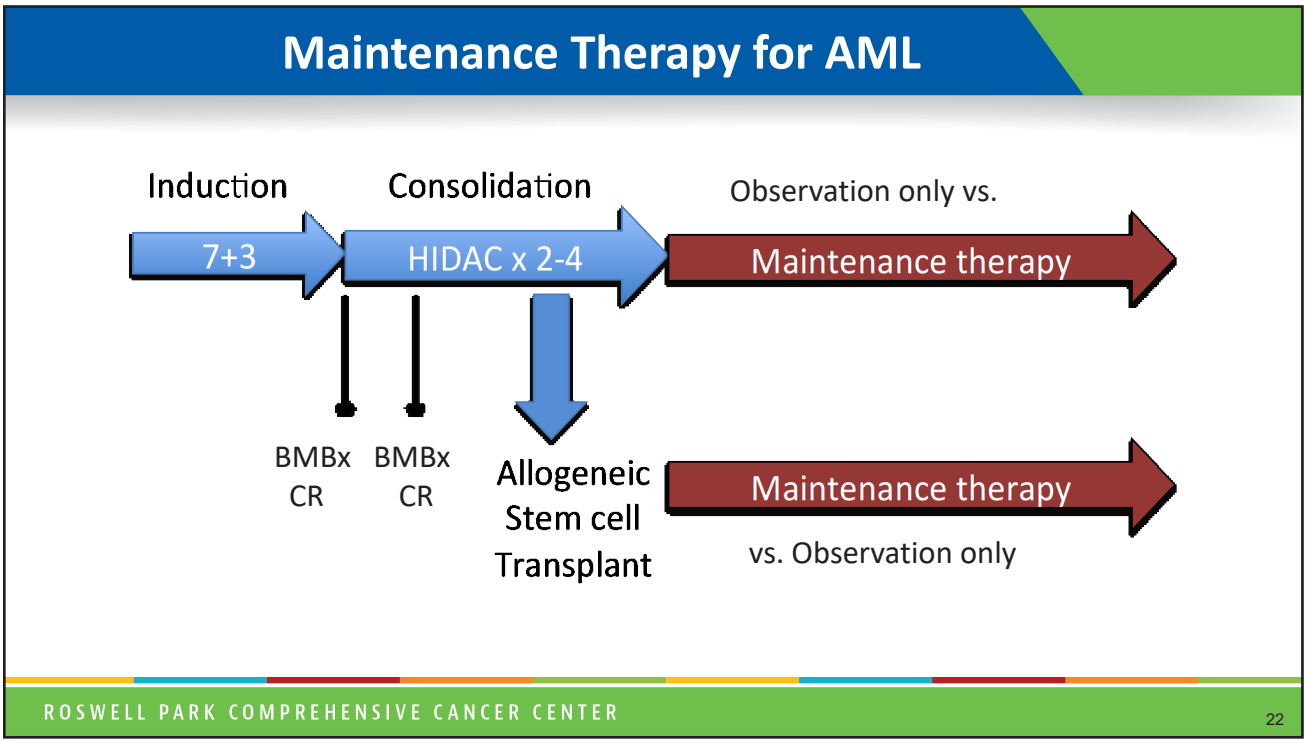
Slide 20: Enasidenib + Azacitidine for Newly Dx IDH2 Mutant AML

How are we improving on IDH therapy? Well, we are combining IDH inhibitors. In this particular case we combined the IDH2 inhibitor enasidenib with low dose chemotherapy, azacitidine, for newly diagnosed patients who have IDH mutation in their leukemia cells.



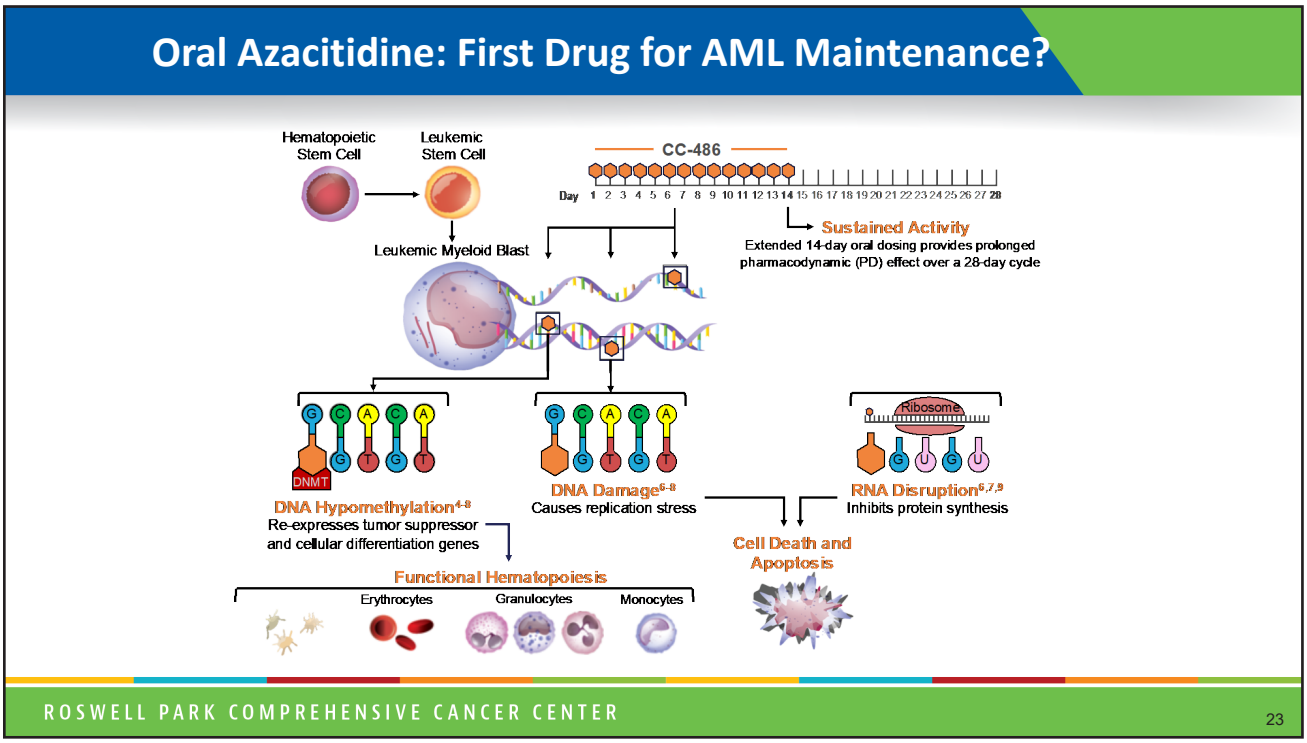
Slide 21: Enasidenib + Azacitidine for Newly Dx IDH2 Mutant AML

As you can see here, that when you added the IDH2 inhibitor enasidenib to azacitidine the amount of decrease of the bone marrow blasts and amount of mutated bone marrow cells that contain the mutation went down dramatically. If you look at what these curves show, anything below that horizontal line is decrease percentage of mutant AML cells in those patients. And you can see that when we add the IDH2 inhibitor to the low dose chemotherapy, we're really improving the efficacy and the response rate in those patients. So again, combination therapy, moving forward.



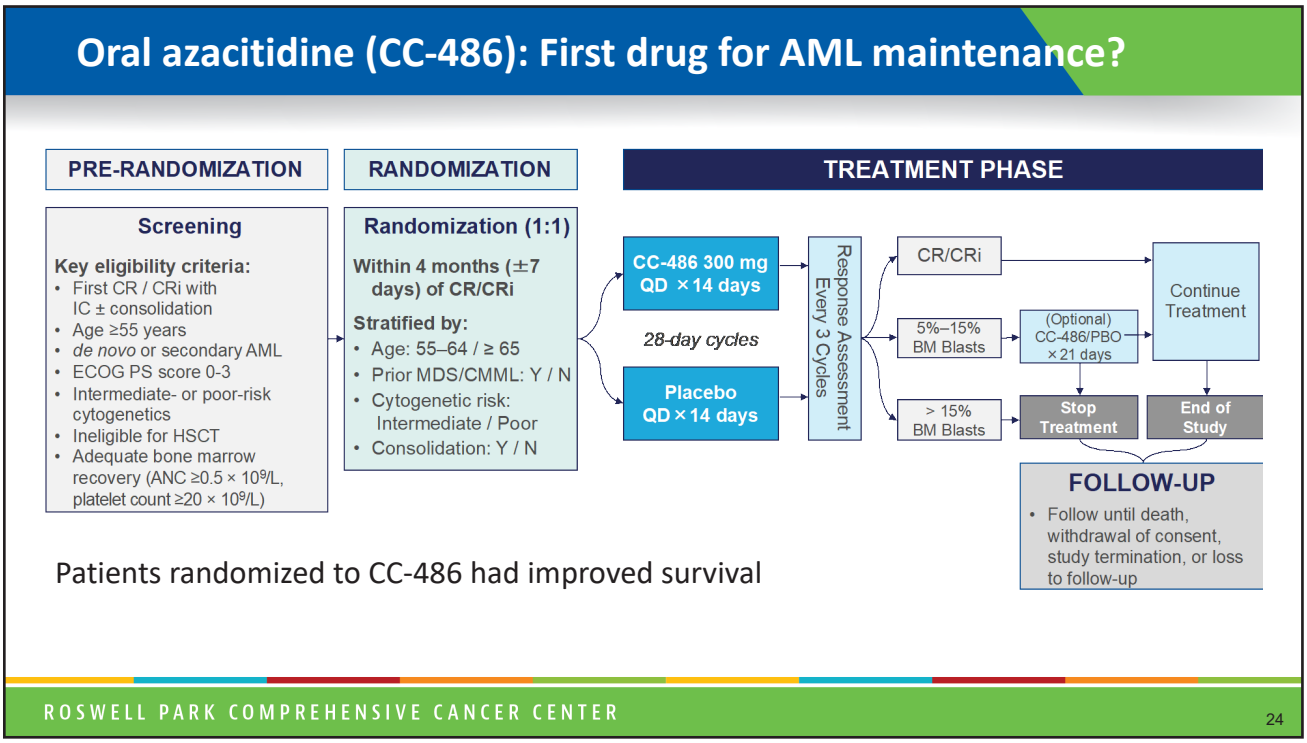
Slide 22: Maintenance Therapy for AML

One of the most exciting things that we saw, however, was the use of another pill to really further improve outcomes for another subset of leukemia patients. Now typically we talked about how patients can get intensive chemotherapy, how to get induction or intensive chemotherapy with 7+3, and then often go on to get either a bone marrow transplant or to get additional cycles of chemotherapy. Now if you're not eligible to get a bone marrow transplant, you get a few extra cycles of chemotherapy and then we stop. And patients are always concerned at that point and they say, well, is my disease cured after the intensive chemotherapy, after six or nine months? And we'll say to them we don't know, we're just going to watch and wait. And for many individuals watching and waiting and having the fear that the leukemia is going to come back can be extremely nerve-racking. So, we have tried over many years to develop what we call maintenance therapy, where we try to give something after intensive chemotherapy to prevent the disease from coming back rather than just observing it.



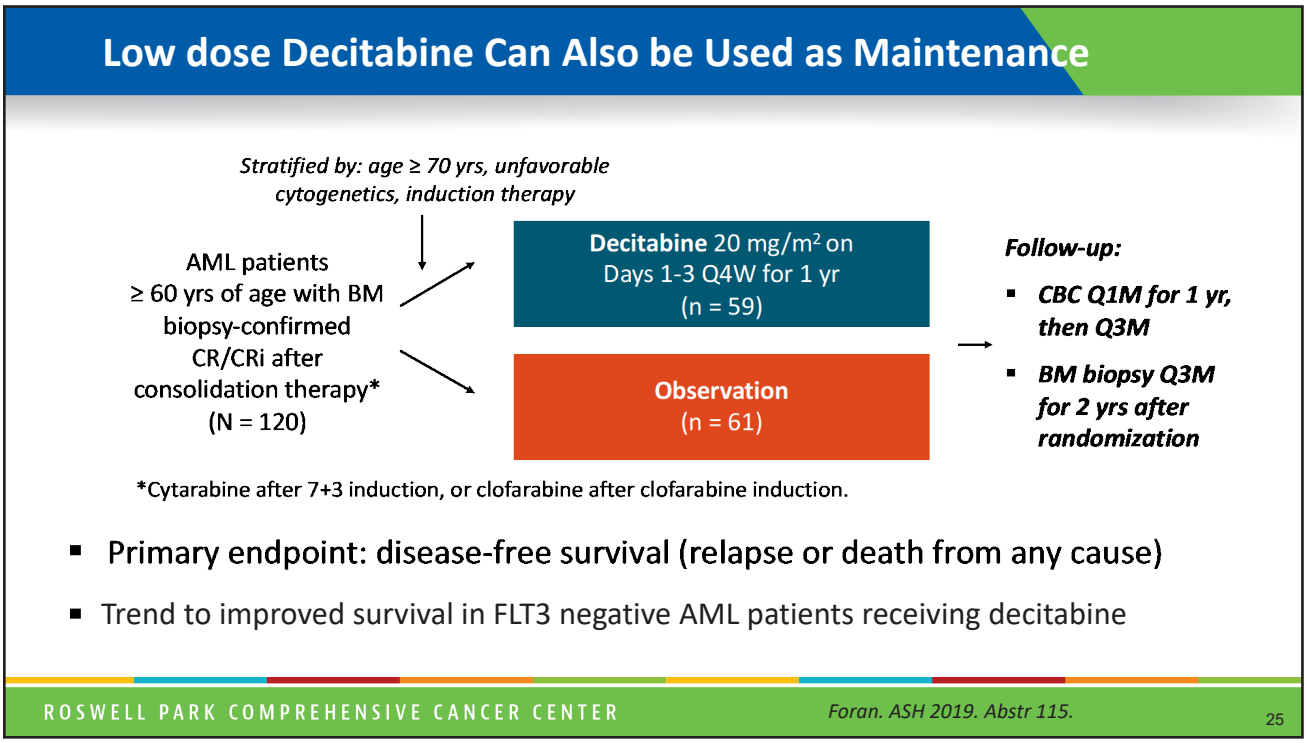
Slide 23: Oral Azacitidine: First Drug for AML Maintenance?

And we now have a new pill, this is the azacitidine chemotherapy that we talked about before. This azacitidine is typically given as either an IV or as shots. And we now have a pill version of the same drug, oral azacitidine.



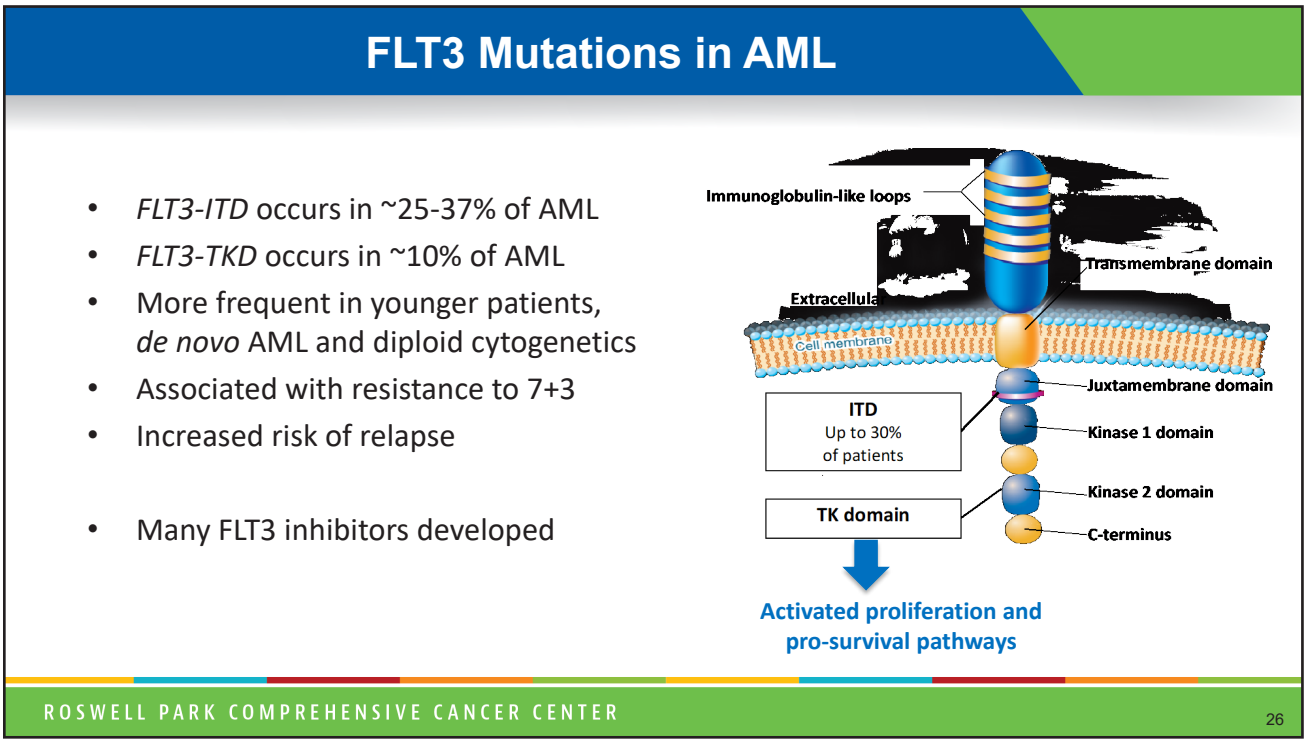
Slide 24: Oral Azacitidine (CC-486): First Drug for AML Maintenance?

And this drug, when we give this particular oral azacitidine to older patients, after intensive chemotherapy, as opposed to just watching them by themselves, adding this particular drug for 14 days a month, so two weeks of pills, two weeks no pills, two weeks pills, two weeks no pills, for a year of therapy as opposed to just watching them, the addition of this chemotherapy pill 50% of the time was significantly effective in prolonging survival of these patients and prolonging the time or delaying the time in which the cancer might be recurred. So that I think is something that we're looking forward to.



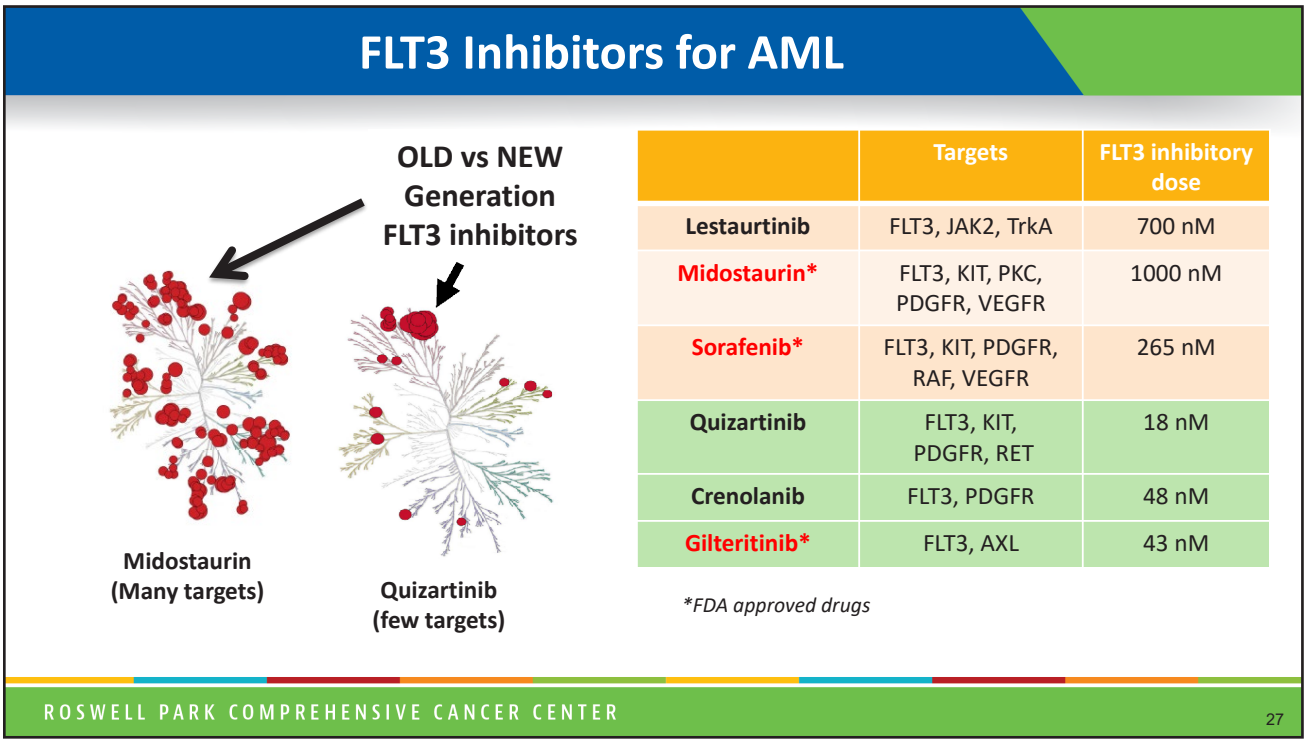
Slide 25: Low-Dose Decitabine Can Also be Used as Maintenance

Does it have to be oral azacitidine, could we use other drugs in this setting? There is a related drug, decitabine, which we give IV, typically is given for five days, and there is other data presented by other clinicians at the meeting showing that you can give decitabine as well as oral azacitidine in the same setting with potential benefit. So, giving one of these drugs, oral azacitidine or decitabine in patients after they finish chemotherapy, who are not going on to transplant, does appear to potentially be of benefit.



Slide 26: FLT3 Mutations in AML

We mentioned before FLT3 mutations. FLT3 mutations occur in about 25 to 37% of patients with AML. There's two types of mutations which can occur, either ITD mutations or tyrosine kinase domain mutations. Regardless, if you have a FLT3 mutation in your AML cell, there now are a number of drugs which are FDA approved. And you can see here the list of all of the drugs which have been found to be potent inhibitors of the FLT3 mutation in leukemia cells.

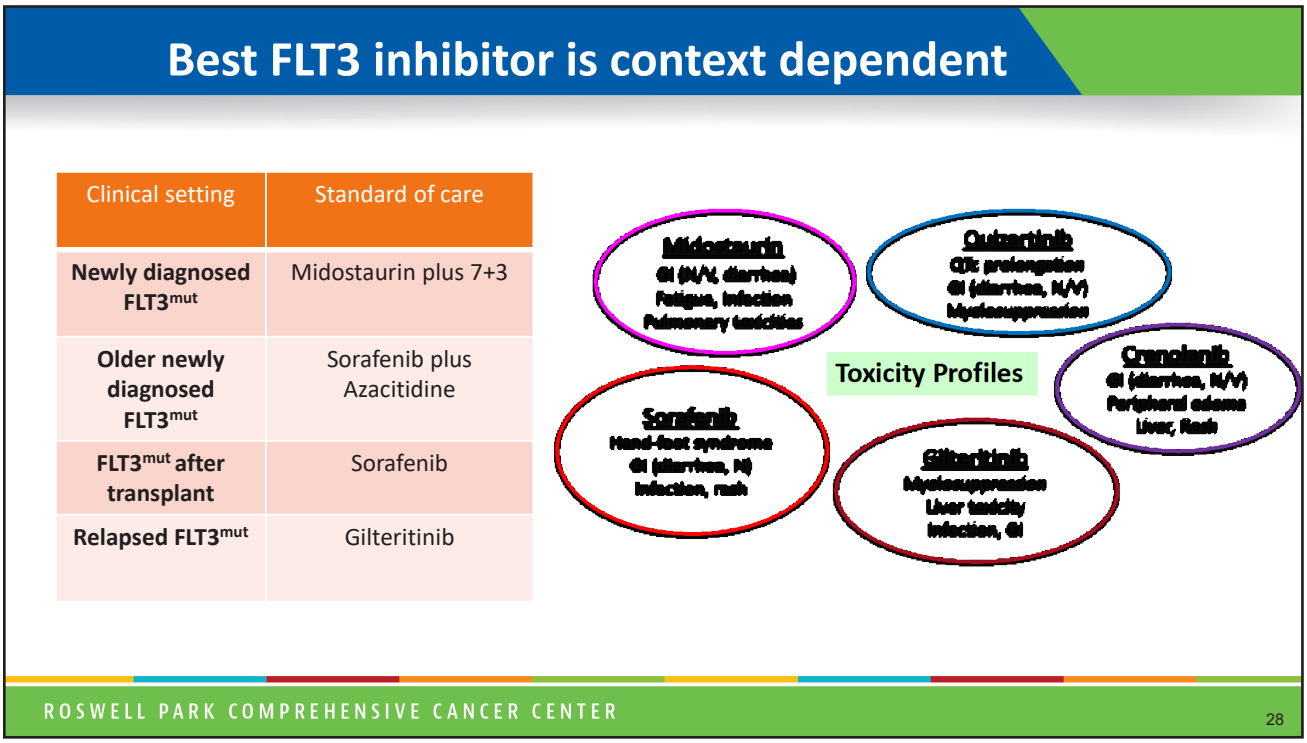


	Targets	FLT3 inhibitory dose
Lestaurtinib	FLT3, JAK2, TrkA	700 nM
Midostaurin*	FLT3, KIT, PKC, PDGFR, VEGFR	1000 nM
Sorafenib*	FLT3, KIT, PDGFR, RAF, VEGFR	265 nM
Quizartinib	FLT3, KIT, PDGFR, RET	18 nM
Crenolanib	FLT3, PDGFR	48 nM
Gilteritinib*	FLT3, AXL	43 nM

**FDA approved drugs*

Slide 27: FLT3 Inhibitors for AML

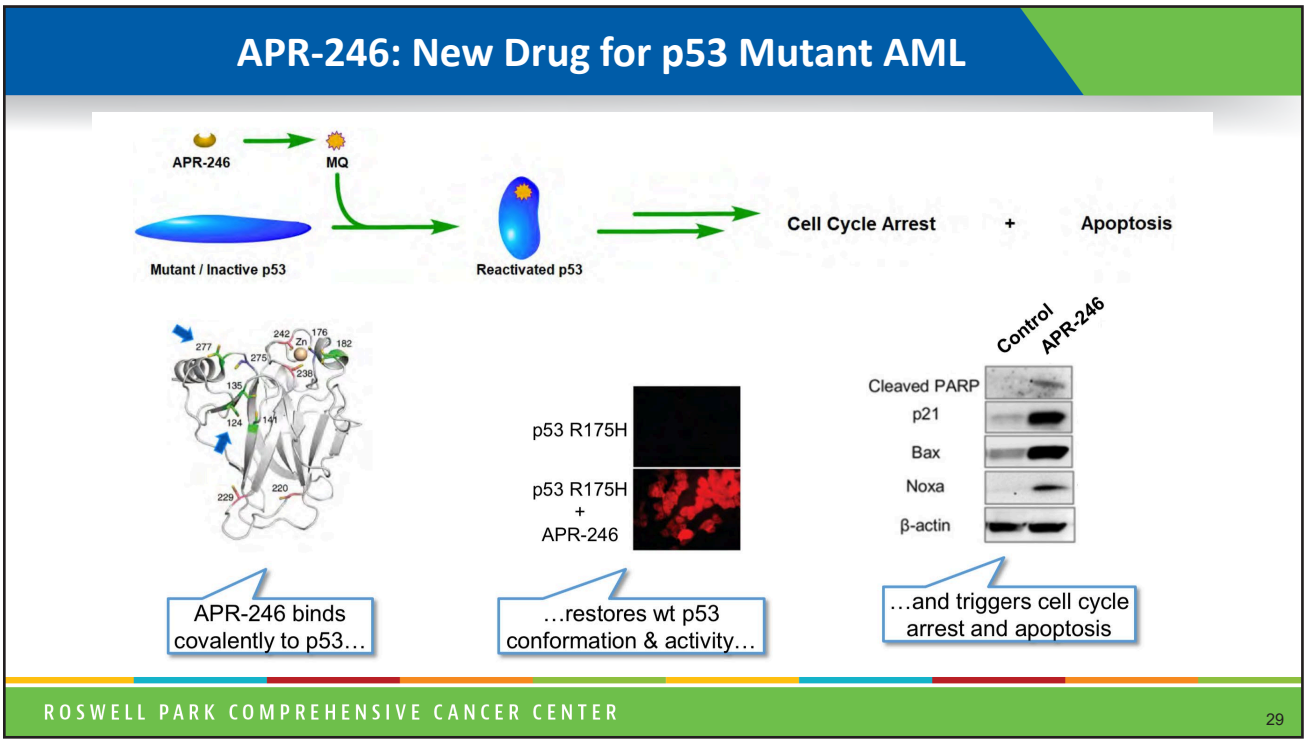
The three drugs here, midostaurin, sorafenib and gilteritinib are all FDA approved. Midostaurin is being used in combination with chemotherapy for patients with newly diagnosed FLT3 mutant AML. Gilteritinib is being used as a single oral pill for patients who have relapse and refractory acute leukemia with FLT3 mutations.



Slide 28: Best FLT3 Inhibitor is Context Dependent

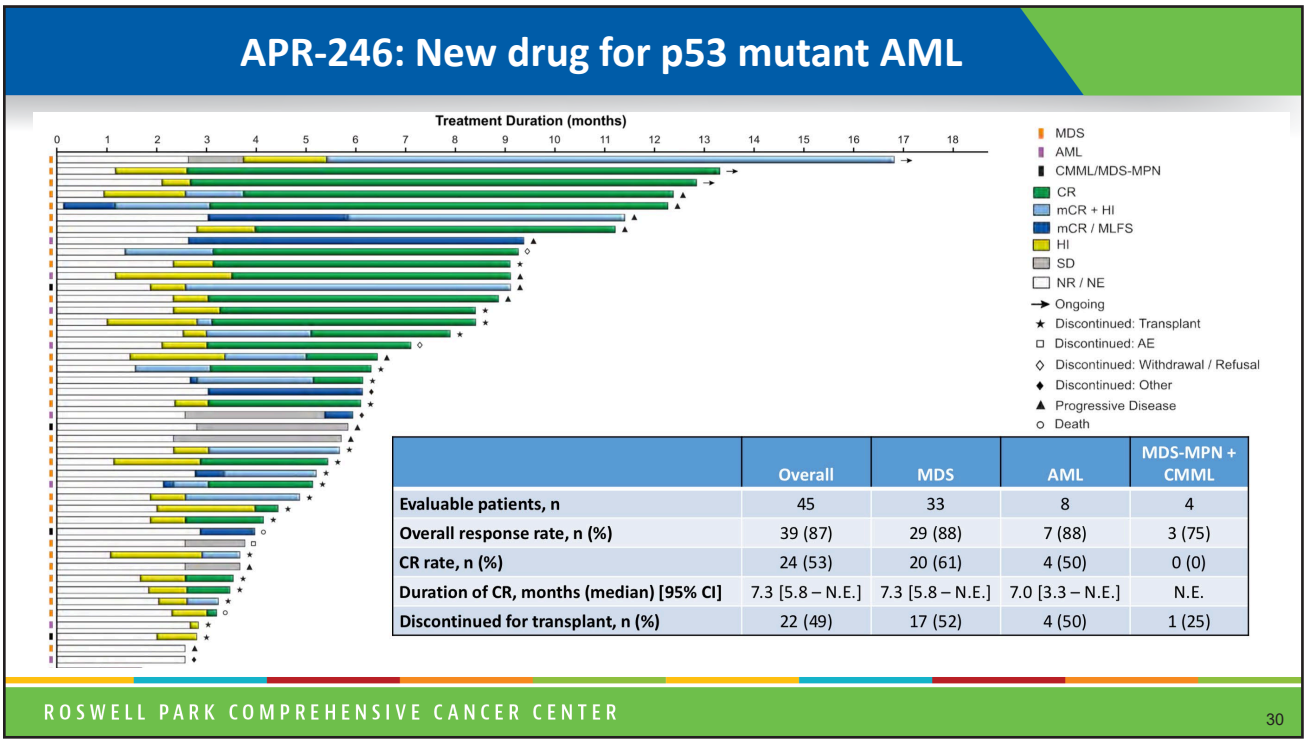
Why do we need to have all of these different FLT3 mutations, FLT3 drugs? Well, we, just like when you have high blood pressure, a lot of times the first pill that you take you might not tolerate. You might have side effects, you might have diarrhea, nausea, vomiting. So, the abundance or the number of these FLT3 inhibitors has allowed us to pick and choose the best inhibitor for the best patients, based on clinical side effects as well as their particular situation that they find themselves in.

What are we looking for, for the future? There is a lot of energy, a lot of enthusiasm, a lot of optimism in the field of AML therapy. To have 44 years of no progress and then to have eight drugs approved in two years is just astonishing. And in fact there're probably going to be additional drugs that we hope are going to be approved in the near future.



Slide 29: APR-246: New Drug for p53 Mutant AML

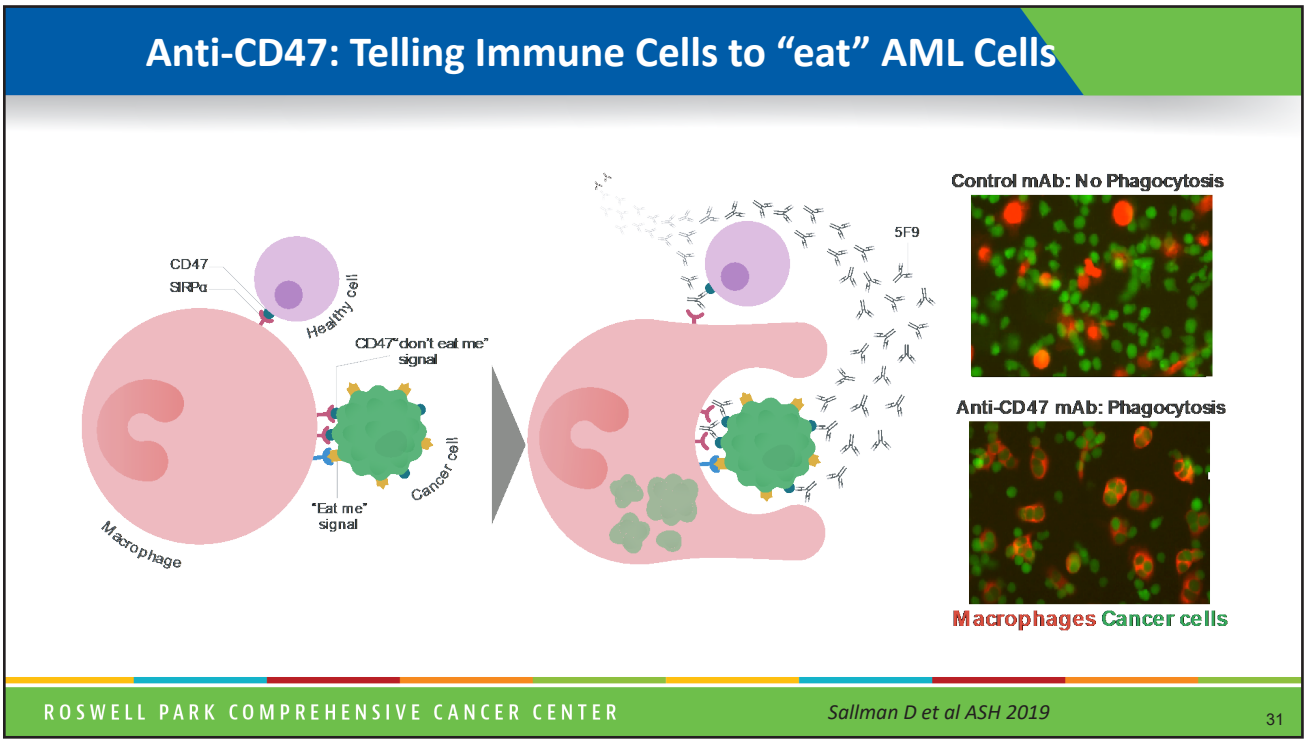
I just wanted to highlight a couple, what I think are the most exciting drugs. There's not that much data on these drugs. The first drug is this drug APR-246 and this particular drug targets a mutation called P53. P53 is a gene that works to prevent or suppress cancer development, both solid cancers as well as leukemias. When this drug is mutated and it's knocked off and it's no longer turned on, then the cancer cells can progress. What this drug does is it binds to the P53, which has been knocked down, and it restores the function of the P53, and that results in suppression of leukemia growth.



	Overall	MDS	AML	MDS-MPN + CMML
Evaluable patients, n	45	33	8	4
Overall response rate, n (%)	39 (87)	29 (88)	7 (88)	3 (75)
CR rate, n (%)	24 (53)	20 (61)	4 (50)	0 (0)
Duration of CR, months (median) [95% CI]	7.3 [5.8 – N.E.]	7.3 [5.8 – N.E.]	7.0 [3.3 – N.E.]	N.E.
Discontinued for transplant, n (%)	22 (49)	17 (52)	4 (50)	1 (25)

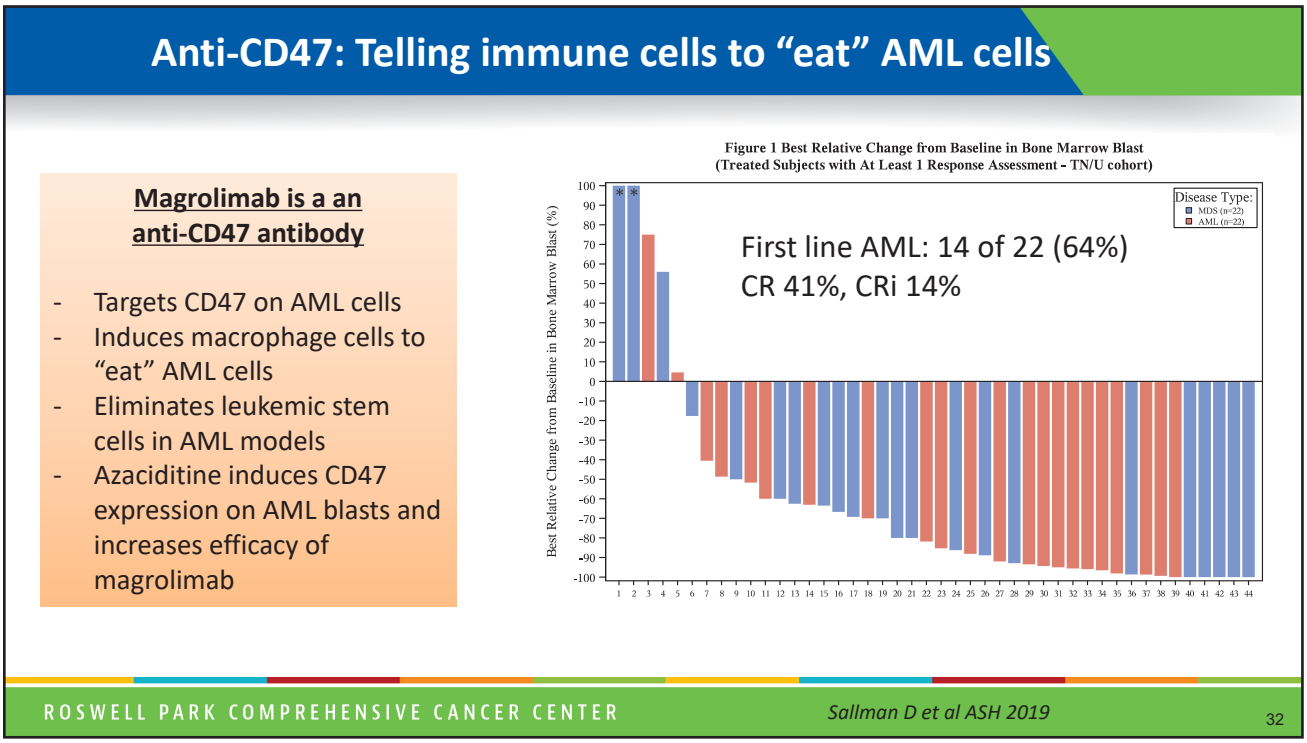
Slide 30: APR-246: New Drug for p53 Mutant AML

So when we combine this P53 mutant inhibitor with chemotherapy single agent, you can see that for patients that have P53 mutant acute myeloid leukemia, many of them in this particular trial were living all the way up to a year or more, based on this graph, which shows the duration of their treatment. And you can see that response rates in patients receiving this particular P53-targeted drug, were 80 to 90%.



Slide 31: Anti-CD47: Telling Immune Cells to "eat" AML Cells

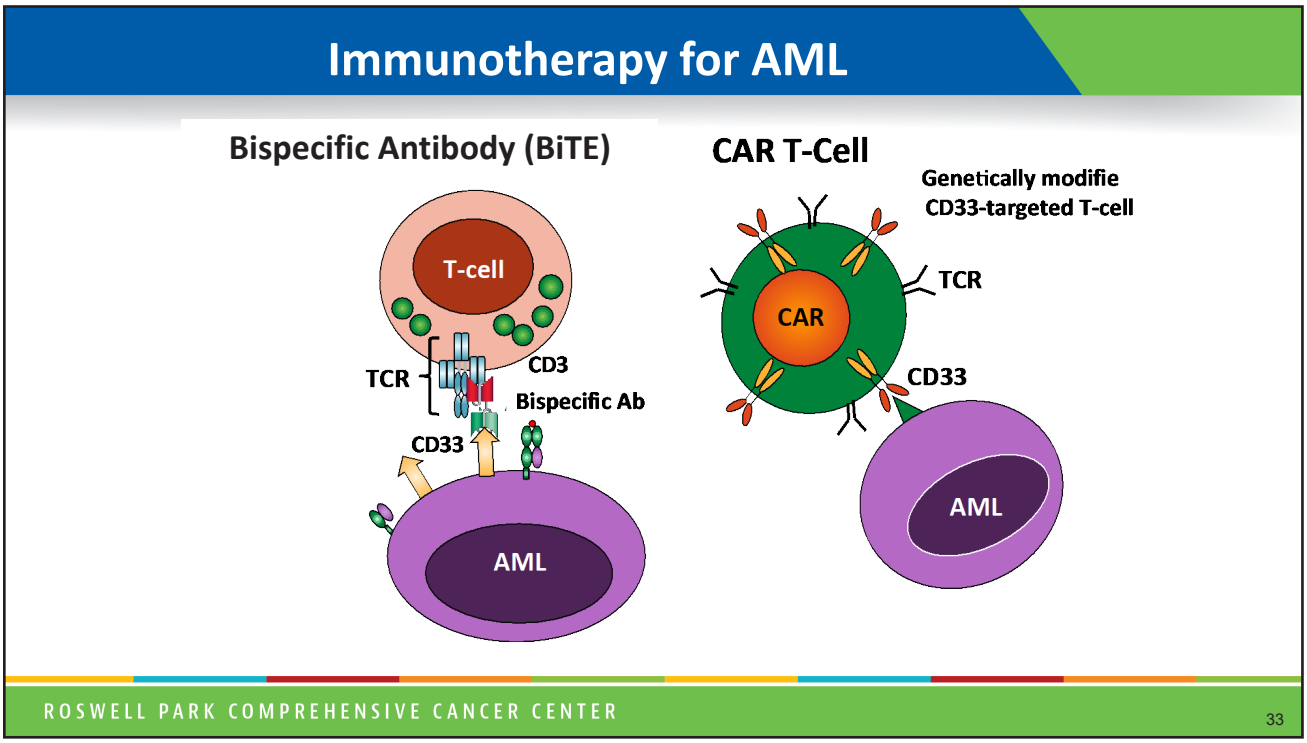
What about immunotherapy? We know immunotherapy works well for solid tumors. There are a couple of immunotherapies that are being developed for acute myeloid chemotherapy. This is one of the most intriguing ones, where there is an immune cell called a macrophage, which binds to leukemia and other cancer cells and basically eats them and carries them off. This is a way that they clear cancer cells as well as infections from the body. But these macrophage cells, when they encounter a cell that expresses a, a marker called CD47, that's a marker to them, telling them not to eat that particular cell.



Slide 32: Anti-CD47: Telling Immune Cells to "eat" AML Cells

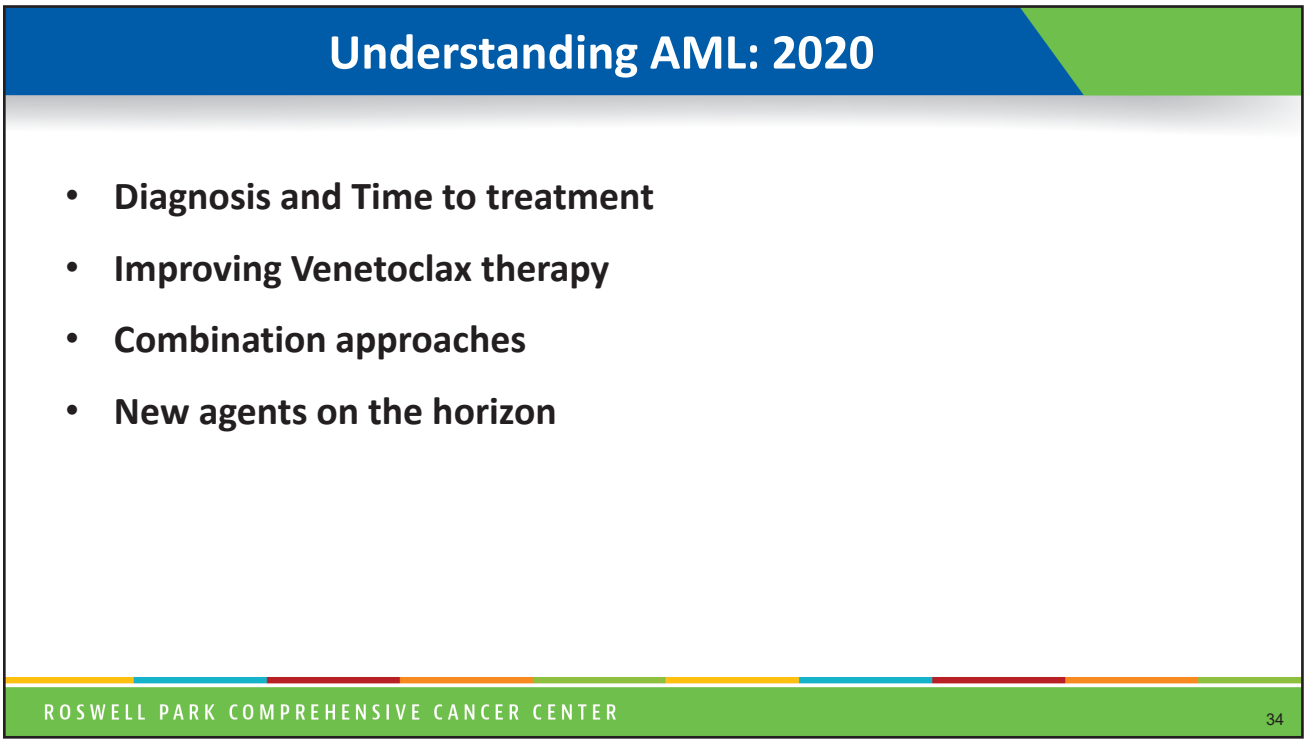
So, leukemia cells will express the CD47 and these immune cells will not engulf them or eat them because they don't recognize them as being cancer cells. So, if you use an antibody drug and you block that marker, all of a sudden, these macrophage cells can go in, engulf and eat, actually engulf the cancer, the leukemia cells, and carry them off. And early studies have shown that when you use this approach in combination with low dose chemotherapy, again, you can get very, very high response rates.

The last thing I want to mention is, and you can see here, that response rates for this type of, do not eat me antibody, can be as high as 60 or 70%.



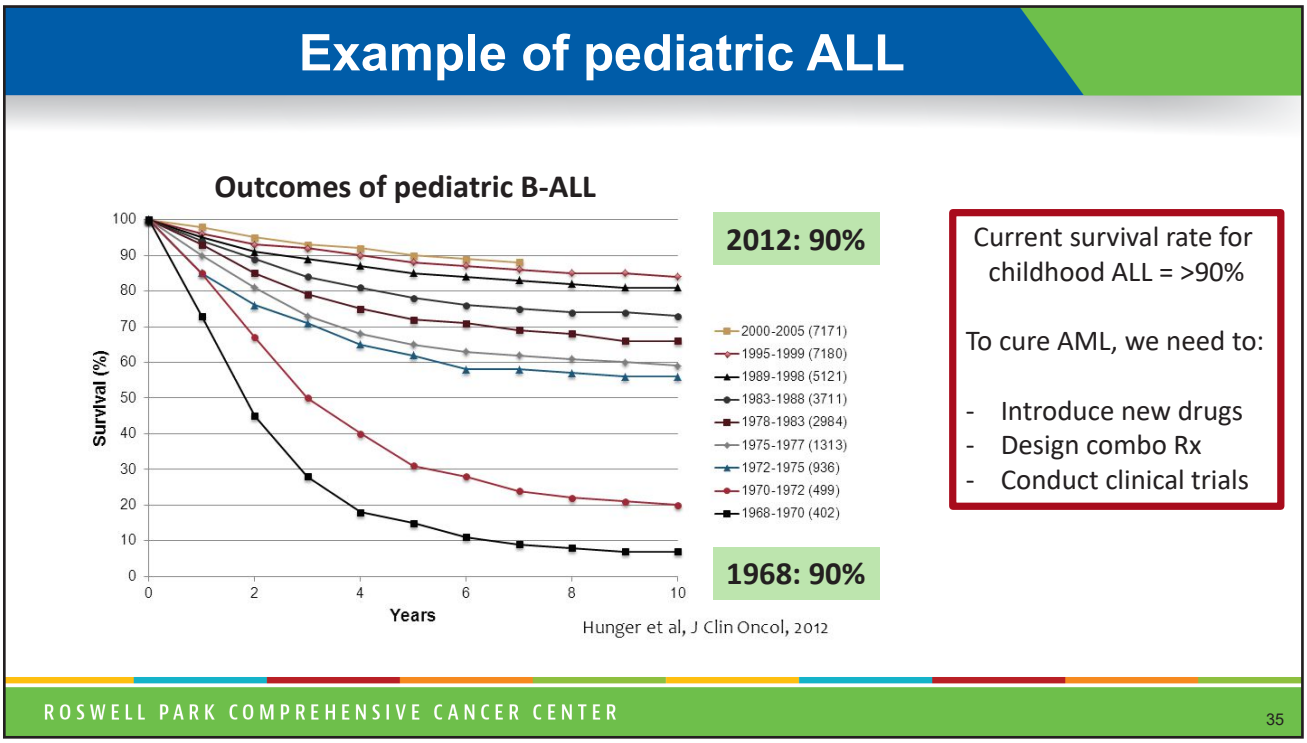
Slide 33: Immunotherapy for AML

The last thing I'd like to mention would be other types of immunotherapy. There are antibodies which are binding and activating immune cells and having them recognize the cancer cells by binding both the immune cells and the cancer cells. And there are genetically modified immune cells, where we can take T-cells or immune cells from individuals, we can harvest them out of their blood, we can genetically modify them in the lab and re-target them and re-infuse them into the body to target AML cells. Both of these approaches are very encouraging and have generated responses, particularly in patients who have failed multiple lines of therapy or prior allogeneic stem cell transplantation.



Slide 34: Understanding AML: 2020

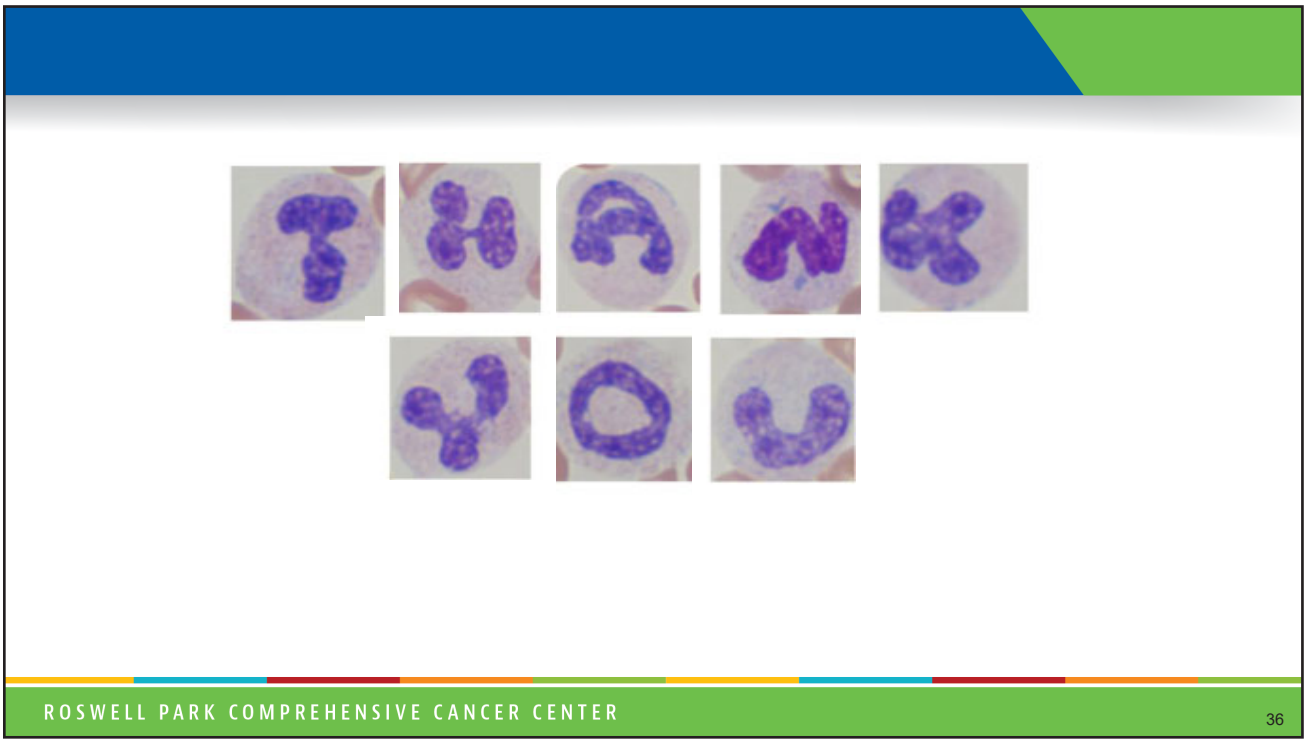
So, I know I've covered a lot in the last 30 minutes. We've talked a little bit about how to make a diagnosis of AML, what to do to make a diagnosis, when to start therapy. We've talked about venetoclax-based therapy and combination targeted approaches. And lastly, talking about some of the newer agents and the immunotherapies which have been on the horizon.



Slide 35: Example of Pediatric ALL

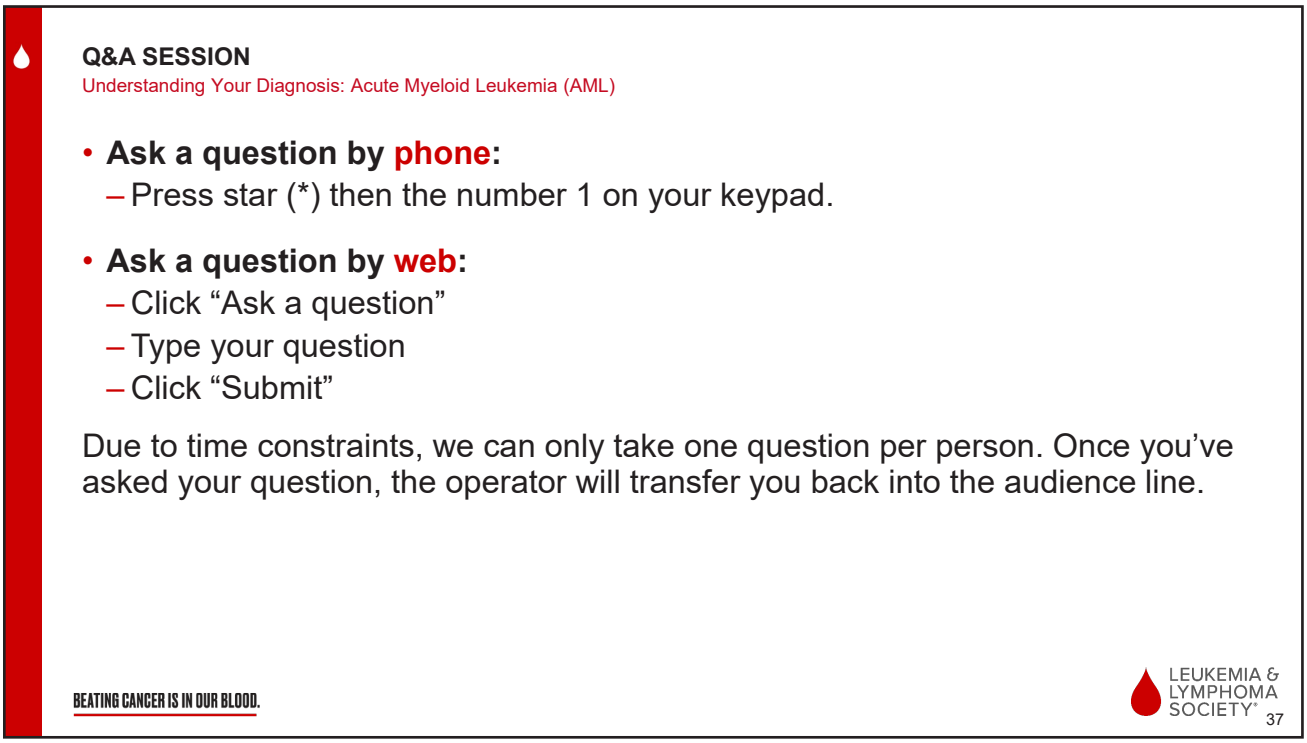
Now I'd like to just close with an example from another disease, acute lymphocytic leukemia in children used to be a universally fatal disease. So, in the 1960s and 70s, 90% of patients died, 90% of children with acute lymphocytic leukemia would die of their disease. In the 2000, in the 2020 era, 90% of pediatric patients with ALL are going to survive. So, we've gone from a survival rate of less than 10% to a survival rate of over 90%. And this is showing you how the survival of pediatric ALL patients has improved decade by decade over time to where we are now over 90% survival.

How have we done this? We have done this by introducing new drugs, new combinations and conducting clinical trials. Almost every single pediatric ALL patient in this country participates in a clinical trial and that is how we are going to advance the field. And I think that's what I look forward to happening for acute myeloid leukemia.



Slide 36: Thank You

So, I'd like to thank everybody for taking the time out to listen to me today. And I'd be happy to take some questions. Thank you very, very much.



Slide 37: Q&A Session

Ms. Figueroa-Rivera:

And thank you so much for your presentation, Dr. Wang. I’m very glad to hear about the new advances in treatment for AML.

It is now time for the question and answer portion of our program.

Ms. Figueroa-Rivera:

And we’ll take the first question from our web audience. Doctor, Nicole asks can AML patients over the age of 75 on monthly Vidaza® injection therapy be cured by Vidaza alone?

Dr. Wang:

So that’s a great question. I have used Vidaza for older patients with AML for several years, and although I’ve had a handful of patients survive months to years, even as far as three, four, five years, I have never cured anybody with Vidaza. And I think that although those drugs are very useful and they offer a way to prolong survival in older patients, I do not feel that they are able to completely eradicate the disease. I think that is why many individuals, including myself, are not using single agent Vidaza anymore, but are looking for some of these novel combinations. For example, the CD47 plus azacitidine or venetoclax plus azacitidine as an alternative approach to see whether we could potentially prolong survival when we haven’t seen the same response with azacitidine alone.

Ms. Figueroa-Rivera:

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

Operator:

Thank you, Lizette. We’ll hear from Joe in Wisconsin. Please go ahead, your line is open.

Joe:

Yes, thank you very much. I just wanted to ask about the anti-CD47. Is that specific to a particular mutant type or would that be applicable in a FLT3 situation? Thank you.

Dr. Wang:

So, thanks, Joe, that's an excellent question. The CD47 drug appears to be mutation nonspecific. So, you can have FLT3, you can have IDH1, IDH2, you can even have P53. In fact, the data with P53 mutant disease is very promising. That particular agent does not rely upon a specific mutation and therefore that can be broadly applicable to many types of AML with many different mutations.

Ms. Figueroa-Rivera:

Thank you. And, Doctor, putting the two together for over a 75-year-old patient as well as FLT3, Jillian is asking if gilteritinib is better than salvage therapy for a 75-year-old person with the FLT3 and are there any new options better than gilteritinib?

Dr. Wang:

So, for an individual with relapsed and refractory AML characterized by FLT3 mutation, gilteritinib has been shown in a randomized clinical trial to be superior to salvage chemotherapy. High dose chemotherapy, low dose chemotherapy, it didn't matter what intensity of chemotherapy, gilteritinib out-performed chemotherapy in that setting. It was probably the first time that we've had a targeted pill taken daily perform better than high dose chemotherapy. And that shows the power of precision medicine therapy in the new era.

Is there anything better than gilteritinib? At this time I think that the novel other FLT3 inhibitors in development for FLT3 mutant disease, a couple of them are called quizartinib and crenolanib they're being studied in various settings and they offer alternatives. And there are newer FLT3 inhibitors as well, being developed in early stage trials. And there are many combinations being developed combining gilteritinib with other drugs such as azacitidine or venetoclax, to see whether we can further enhance the efficacy with a combination.

Ms. Figueroa-Rivera:

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

Operator:

Next, we'll hear from James in Pennsylvania. Please go ahead, your line is open.

James:

Thank you so much. I have a problem within a problem. I have broad spectrum antibiotics Cipro® and Levaquin® are decimating my tendons and severe pain. I was just wondering if there's an out. I called my Hershey Med doctor and he just switched me from one fluoroquinolone to the other. So, I feel like I'm going to be a wizened old man soon if I don't get out of the fluoroquinolones.

Dr. Wang:

Sure. So many patients with AML have very low blood counts, particularly their neutrophil count, and many of these individuals will develop recurrent, potentially life-threatening bacterial infections unless they're on what we call prophylactic or preventative antibiotics to try to prevent these types of infections. Although Levaquin and ciprofloxacin are the most common antibiotics used in that setting, we have also used other drugs. We've used Augmentin® or amoxicillin or potentially cephalosporins, which are broad spectrum. So those might be alternative ones to pursue if the Levaquin and the ciprofloxacin are not faring well for you in particular. It is very important that patients that have a low neutrophil count get

not only antibiotic preventative therapy, but typically also preventative antiviral medicines to prevent herpes infections, and antifungal medicines.

James:

Yes, I get those.

Dr. Wang:

Great.

James:

Thank you.

Ms. Figueroa-Rivera:

Thank you. The next question, Doctor, is from Wiley. Wiley's asking is there research about pregnancies post-AML treatment?

Dr. Wang:

That's an excellent question. In my practice, generally patients who are getting chemotherapy and on active chemotherapy are not really eligible to get pregnant because many of the chemotherapy drugs are targeting rapidly growing cells and that would include leukemia cells as well as a growing child or fetus. However, many patients that have achieved complete remission, even those that have achieved it with chemotherapy or with an allogeneic stem cell transplant, if they are in complete remission and their disease has been quiescent or not present for a few years, if they have restoration of normal menstruation we have had patients who have received prior therapy for AML go on to have successful pregnancies. That is something that I think I would defer to the local physician or the local oncologist as well as your local gynecologist to assess whether if you are in that particular situation, whether that might be possible for an individual patient.

Ms. Figueroa-Rivera:

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

Operator:

Yes, thank you, Lizette. We'll hear from Amanda in Tennessee. Please go ahead, your line is open.

Amanda:

I know you talked about Venclexta® and decitabine earlier. My husband's 70 with health issues, but, you know, COPD and so forth, COPD, chronic pain, I mean his doctor said he can maybe go into remission. He is 70, you know, but I'm just wondering if there's, he's not a candidate for a bone marrow transplant and not quite, there were no genetic mutations in his first bone marrow biopsy. He's having one again tomorrow. I guess that's just to see how well the AML's progressed. But I guess my question is, I mean, do you get, do you know people that go into remission that are his age on Venclexta and decitabine?

Dr. Wang:

Yeah, so definitely, if your husband is 71 years old and has comorbidities, those are precisely the patients for which Venclexta or venetoclax plus decitabine or other low dose chemotherapy was designed to treat. So yes, we have had

patients go into remission with venetoclax-based therapy. We've had patients remain in remission for longer periods of time. The data suggests that patients could achieve remission and last up to a year or two or potentially longer if they achieve a remission. So, I do think the answer to that question is yes. It's not 100%, but I think that certainly it sounds like, and I would defer to your local oncologist, the data suggests that there is a possibility for individuals like your husband to receive that treatment with benefits.

Ms. Figueroa-Rivera:

Thank you. And we'll take the next question from the web. Cary's asking about myelodysplastic syndromes or MDS and if a patient had MDS prior to their AML diagnosis, how does that affect the treatment plan?

Dr. Wang:

Yes, that's an excellent question. Many of our patients will have what we call pre-leukemia or myelodysplastic syndrome prior to development of AML. In general, we find that these patients may be more difficult to treat than patients that have had no prior diagnoses. Some of the treatments that we give to patients with AML, such as azacitidine or decitabine, are also used to treat patients with MDS. So, if patients have MDS and have already received those agents, it may be more difficult to offer those agents again with any benefit because they're most likely, almost certainly, resistant to them again. There's also data from many years of research with 7+3 that those individual patients that have what we call secondary or MDS arising out of prior, AML arising out of prior MDS, don't do as well long-term, even with intensive chemotherapy. Currently, the recommendations are that if you have a prior MDS that that be taken into consideration when making choices for your AML therapy. Those choices in many cases for younger individuals may require or may include stem cell or bone marrow transplant because of the amount of prior damage in the bone marrow replacing the bone marrow in many individuals may be the best long-term therapeutic option.

Ms. Figueroa-Rivera:

Thank you. And Gregory is asking are there things to do to prevent recurrence?

Dr. Wang:

Yes. So recurrence, it depends, if you have a targeted, targetable mutation, if you have an IDH1 or IDH2 or a FLT3 mutation, there are many studies that are now looking at whether continuing some of those inhibitors long-term could prevent recurrence. Obviously, one of the most exciting data from the hematology meeting last year, was the use of oral azacitidine or decitabine to prevent recurrence in patients after intensive chemotherapy. So, we are looking to see whether we can use low dose chemotherapy or targeted inhibitors to prevent recurrence. Is there a vaccine or anything like that? At this time no. We would love to have a leukemia vaccine that we could prevent people from developing recurrence. Right now, most of the research has been looking at extending the use of the targeted or non-targeted agents or using low dose therapy for longer to try to delay or prevent recurrence.

Ms. Figueroa-Rivera:

Thank you. And Susan is asking if there are any CAR-T cell therapy options available for AML.

Dr. Wang:

Yes, there are. So, there are a number of groups that are looking at CAR-T cell therapy. The problem with CAR-T cell therapy for AML as opposed to other blood cancers like lymphoma or myeloma or ALL, is that the AML cells are incredibly diverse. So, in order to develop a CAR-T cell you have to reprogram the T-cell to target the leukemia cells, but not all AML cells express the same surface marker, so it's difficult to find something to target with a CAR-T cell.

There are CAR-T cells in development that are targeting many different markers on AML cells. Most of them, however, are in very early testing, but we already are seeing some responses with CAR-T cells in patients that are refractory to other therapies. So, there are a number of small CAR-T cell therapies ongoing.

Ms. Figueroa-Rivera:

Thank you. And, Doctor, can you just explain for some people in the audience what CAR-T cell therapy is?

Dr. Wang:

CAR-T cell therapy is a CAR, stands for chimeric antigen receptor T-cells. So, your leukemia cells express markers on their surface, tumor markers. And what happens is when you develop AML, your body's immune system or your T-cells have failed to recognize and destroy the cancer cells. For some reason they don't recognize that the AML cells are cancerous, and they don't target and remove them.

What we do in CAR-T cell therapy is we take the T-cells and we genetically modify them to express receptors or CARs that will bind to the leukemia cell markers. And so, we take the T-cells that don't express and don't recognize those markers, we genetically modify them with these receptors, these CARs, we take those cells, we reinfuse them into patients. Those are the patient's own T-cells. So, the patient doesn't reject them because they're their own cells. Those T-cells now are able to in the patient's body recognize the, now recognize the AML cells and then they do what they do best, which is to destroy the cancer cells.

Ms. Figueroa-Rivera:

Thank you so much. And Joyce is asking does AML most often use stem cell transplants or bone marrow transplants? She's not clear if bone marrow is only used for small groups now, since stem cell is better.

Dr. Wang:

Stem cells are the mother cells that live in the bone marrow, that produce all of the other cells. So, the stem cells produce red cells, white cells and platelets. In the past when we were doing transplants, we would harvest the stem cells from inside the bone marrow, and so those types of transplants were called bone marrow transplants. What we now have the possibility to do is we don't have to harvest the stem cells directly from the bone marrow, like we don't have to do 20 bone marrow biopsies. We can give patients growth factors and we can have them, the stem cells, push out of the bone marrow into the peripheral blood, and then we can collect the stem cells from the peripheral blood.

Many patients nowadays would prefer to have peripheral stem cell transplants because it's a little easier to collect the cells from the donor point of view. They don't have to undergo multiple bone marrow biopsies. In some select cases where we're not able to get enough stem cells from the blood, then we do, in that small subset of cells, do need to go back and do multiple bone marrow biopsies to harvest the stem cells for the transplant.

That's a good question.

Ms. Figueroa-Rivera:

Thank you. And thank you for clarifying. Barbara's asking what is the chance of developing another blood cancer post-bone marrow transplant?

Dr. Wang:

Well, post-bone marrow transplant for AML, the greatest risk is recurrence of the original leukemia. In terms of developing a second bone marrow or second blood cancer, some patients after bone marrow transplant will develop lymphomas, which are diseases of the lymph nodes, after bone marrow transplant. Although those are relatively rare. But I think after a bone marrow transplant the greatest risk to the patient is either graft-versus-host disease or recurrence of the original AML.

Ms. Figueroa-Rivera:

Thank you. And Darlene is asking is it ever appropriate to say AML is cured versus in remission? And if so, what deciding factors are involved?

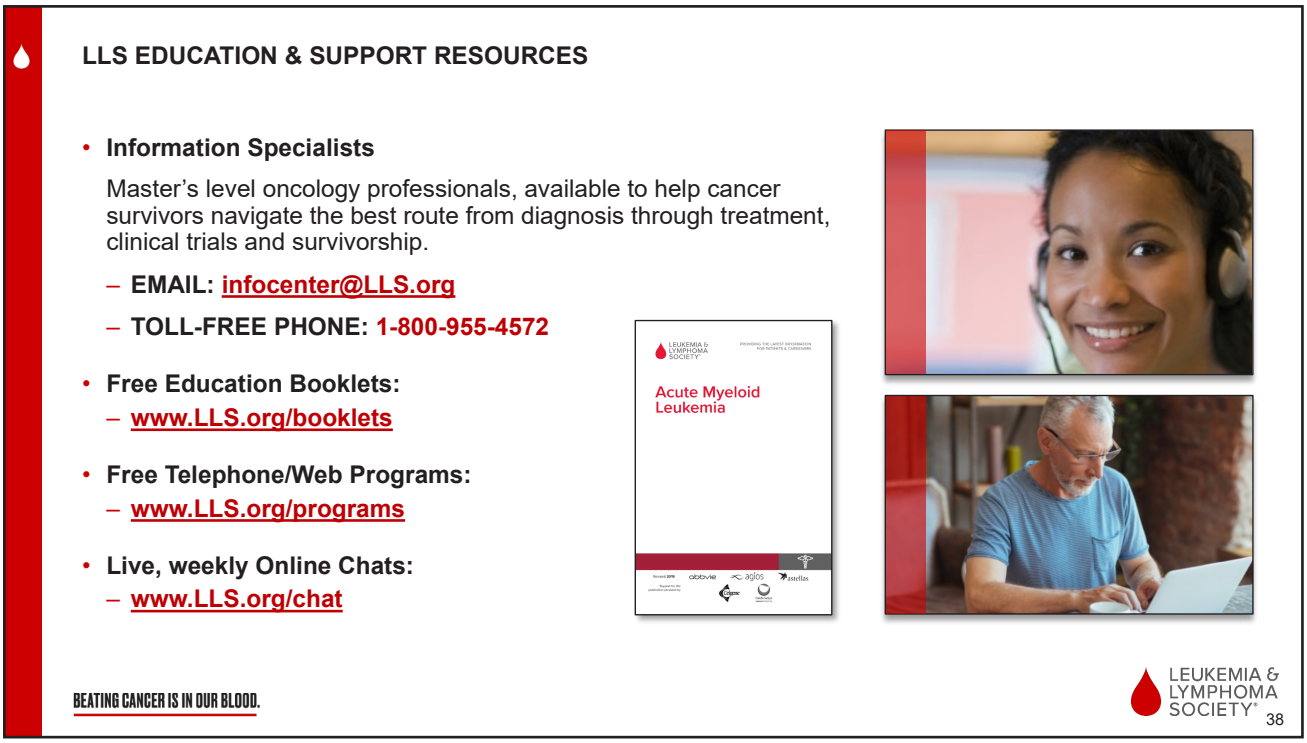
Dr. Wang:

So, in the old days we used to say that if patients were – remained in remission for five years or longer, that statistically their chances of having the disease come back were very, very low. So, some people would use that landmark, five-year survival and remission as being cured. Now we now know that there are patients that can have disease that comes back even after five years. So, I don't know that all of us feel comfortable. However, I think as the general landmark, five years tends to be the one where we say the chances are more likely that you're cured than that you're not.

Ms. Figueroa-Rivera:

Well, thank you for your question, Darlene, which is our final question today. And thank you so much, Dr. Wang, for your continued dedication to 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.



Slide 38: LLS Education & Support Resources

If we weren't 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 reach us by email at infocenter@LLS.org. Now Information Specialists are available to answer your questions about treatment, including clinical trials, and answer other questions you may have about support, including financial assistance for treatment.

Slide 39: LLS Education & Support Resources

Again, we'd like to acknowledge and thank Agios, Bristol-Myers Squibb, Daiichi Sankyo, Genentech & Biogen, and Jazz Pharmaceuticals for support of this program.

Slide 40: Thank You

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

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