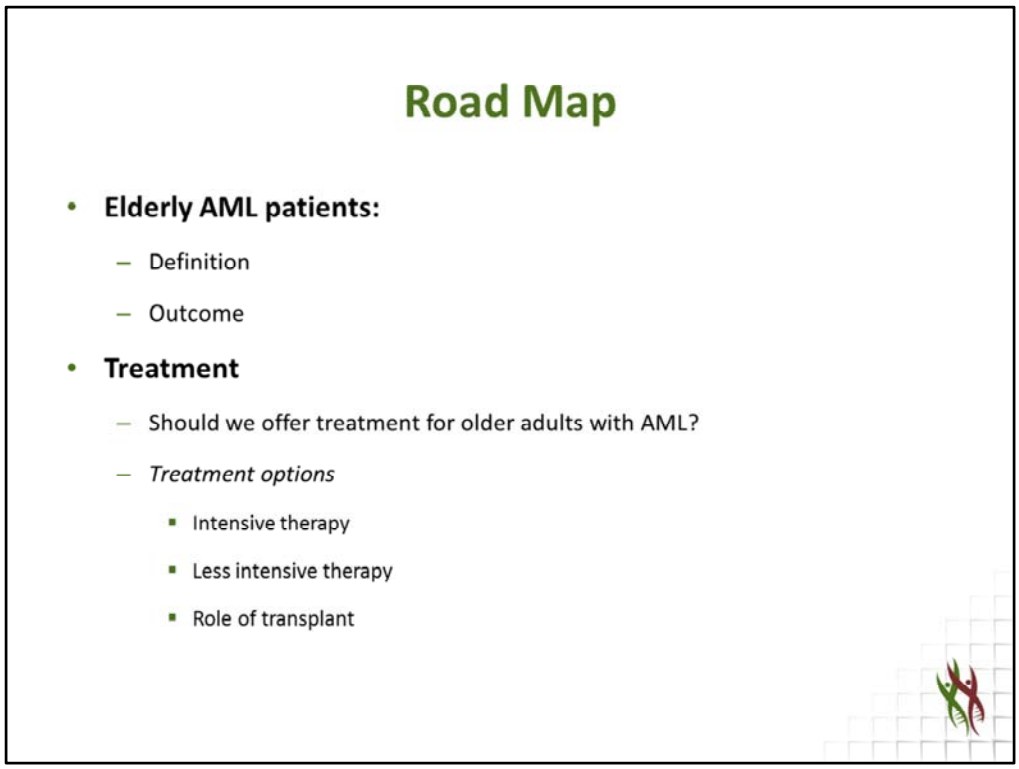
Tailoring Therapy to Older Patients with Acute Myeloid Leukemia

Welcome to *Managing AML*, I am Dr. Aziz Nazha. In today's presentation I will be discussing strategies in tailoring therapies in older patients with acute myeloid leukemia. I will be covering the unique therapeutic challenges that older patients with AML pose in clinical practice today, and discuss with you how to determine the optimal therapeutic approach based on individual patient needs and the current treatment paradigm. Let's begin.



This slide summarized the roadmap of this presentation. We first define who we think they are, older adults with acute myeloid leukemia, what is the definition of older adults with acute myeloid leukemia. Then we will discuss what is their outcome and why their outcome is different than younger adults with acute myeloid leukemia, and then we will focus on the treatment strategies for this patient population by answering a few questions. One of them will be, “Should we offer treatment for older adults with acute myeloid leukemia?” That is a really commonly asked question when we encounter patients, older patients, with AML. Then, what are the treatment strategies that we can provide these patients with in terms of intensive therapy approach, less intensive therapy approach, and what is the role of transplant in this patient population?

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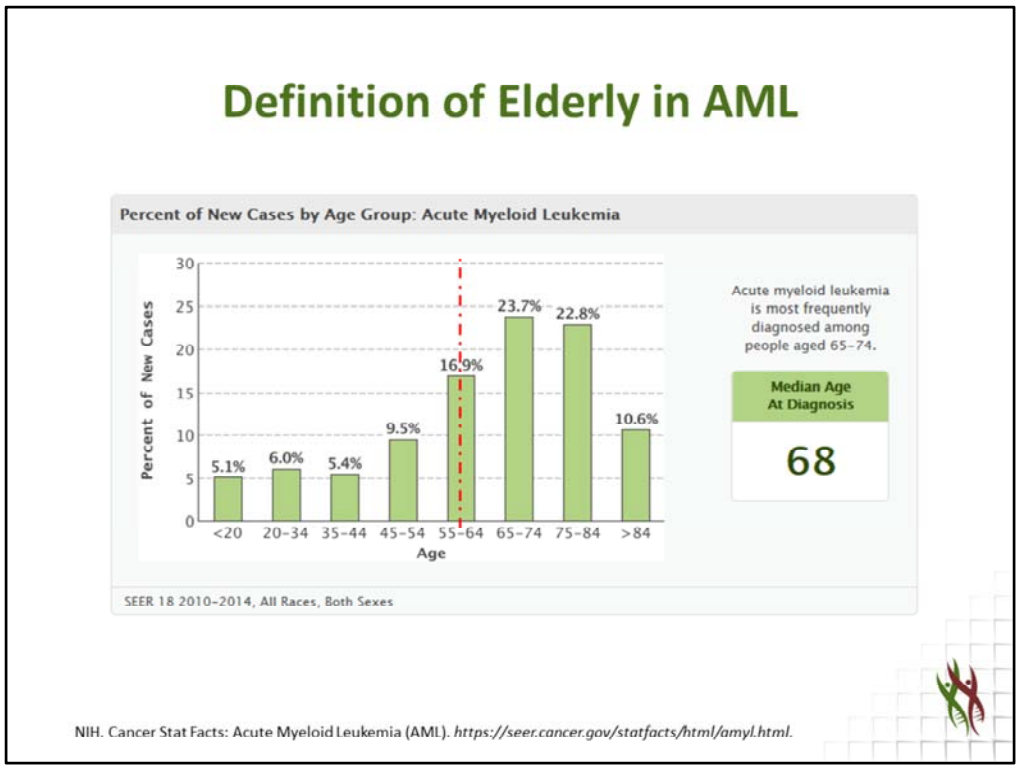

Acute myeloid leukemia is mostly diagnosed in people around the age of 65-74. This slide summarized SEER data between 2010 and 2014, and you can see the median age of diagnosis of AML is 68. AML is a disease of elderly patients, but for the definition of older adults with AML, we sometimes put a line in the sand and divide it into 60 years old and older, these are the definition of AML. Although you can see and sometimes in some clinical trials the age of 65 is used as the cutoff.

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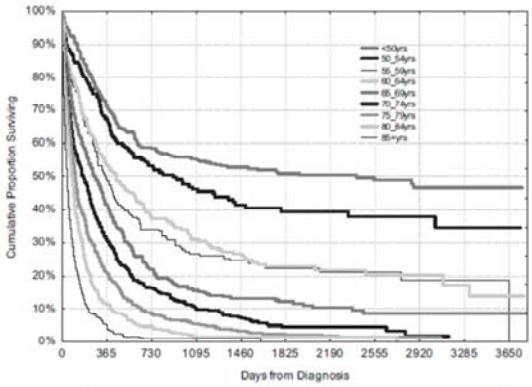
Outcome of Older Adults with AML



	All	
Age, y	n	OS
16-55	554	1119
56-65	437	359
66-75	738	184
76-89	968	80
Total	2697	196

Juliusson G, et al. *Blood*. 2009;113:4179-4187.

Now, why this is important is because the outcome of older adults with AML typically is different than the younger patients with AML. This is a large study from the Acute Adult Leukemia Registry from Sweden where they looked at the outcome of 2,697 patients with AML. You can see here that the outcome of patients younger than 50 years of age is much better than patients who were 65 or older, especially the outcome for 80 years old is much worse compared to 50 years old. We can see here the median overall survival for patients with age 16-55 is about 1,119 days, which is about 37 months, compared to the median overall survival for patients 66-75, which is about 184 days, it's about 6 months. For patients 76-89 it's about 80 days, which is about 2-3 months. You can see a significant difference in survival of this patient population compared to younger adults with AML.

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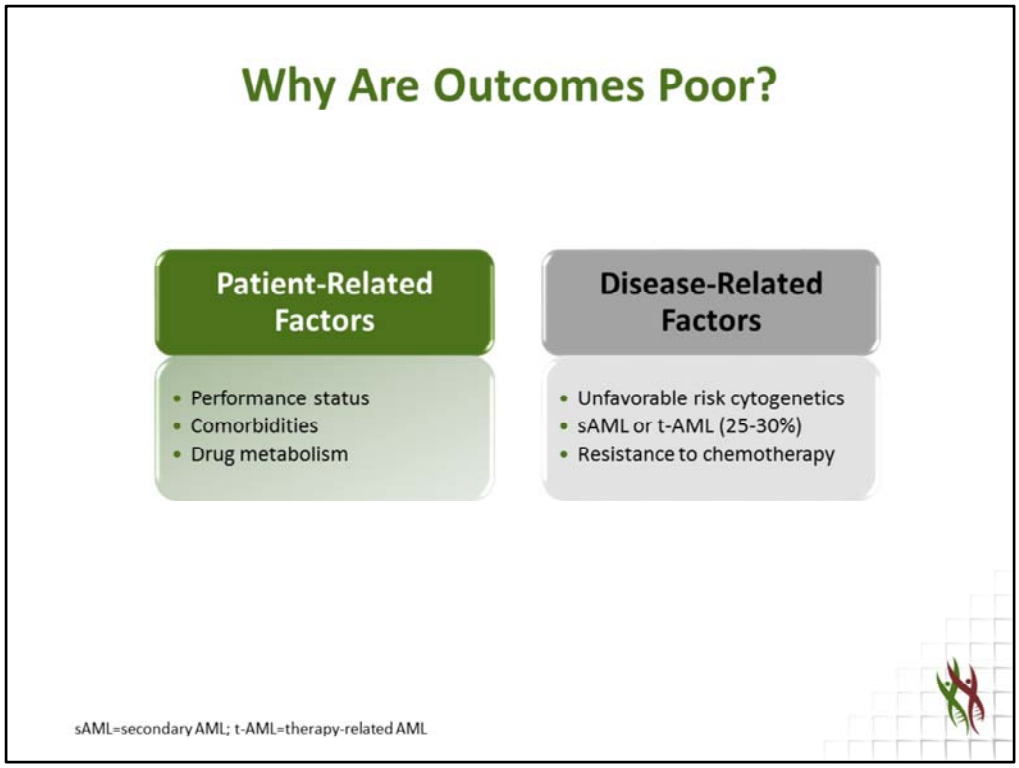

Of course the question is, "Why is the outcome of older folks is worse or poor in general and is worse compared to younger AML?" This can be divided into patient-related factors and disease-related factors. Older adults with AML tend to have worse performance status compared to younger adults. They tend to have multiple comorbidities given their age in terms of heart, lung, and other problems, and also most importantly the drug metabolism of this patient population is different than younger adults with AML**.** It is also noted that there are disease-related factors, the biology of the disease for older adults with AML is different than younger adults with AML. For example, this patient population had higher unfavorable risk cytogenetics, about a third of them tend to have secondary myeloid leukemia or therapy-related acute myeloid leukemia which tend to have worse outcome in general compared to de novo acute myeloid leukemia, and in general this patient population have resistance to standard chemotherapy to the active chemotherapy that we have when we treat AML. In other words, the biology of the disease in older adults with AML is different than the biology of the disease in younger adults, and thus does impact their outcome.

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Characteristics of the Disease

	Younger than 56 y	56-65 y	66-75 y	Older than 75 y
No. patients	368	246	274	80
Sex, male, no. (%)	193 (52)	139 (57)	154 (56)	44 (55)
Race, white, no. (%)	318 (86)	216 (88)	254 (93)*	73 (91)
Presentation, de novo, no. (%)	NA†	192 (78)	208 (76)	62 (78)
Performance status, no. (%)				
0	129 (35)	72 (29)	73 (27)	14 (18)
1	180 (49)	112 (46)	126 (46)	40 (50)
2	46 (13)	34 (14)	52 (19)	14 (18)
3	9 (2)	24 (10)	19 (7)	11 (14)
Unknown	4 (2)	4 (2)	4 (1)	1 (1)

	Younger than 56 y	56-65 y	66-75 y	Older than 75 y	P*
No. patients	323	183	199	54	
Cytogenetic risk group, no. (%)					< .001†
Favorable	51 (16)	10 (5)	10 (5)	2 (4)	
Intermediate	149 (46)	101 (55)	110 (55)	24 (44)	
Unfavorable	108 (33)	70 (38)	78 (39)	27 (50)	
Unknown	15 (5)	2 (1)	1 (1)	1 (2)	
Specific abnormalities, no. (%)					
−5 or 5q−	21 (7)	27 (15)	28 (14)	14 (26)	< .001
−7 or 7q−	28 (9)	35 (19)	36 (18)	12 (22)	< .001
17p	6 (2)	16 (9)	14 (7)	6 (11)	.001
t(8;21)	22 (7)	7 (4)	4 (2)	0 (0)	.019
inv(16)	31 (10)	4 (2)	7 (4)	4 (7)	.002

Appelbaum FR, et al. *Blood*. 2006;107:3481-3485.

This also has been demonstrated in multiple studies, this study is based on 698 patients treated on five large SWOG trials. You can see when the investigators compared the performance status of patients younger than 56 years old compared to patients 66-75 years old and even older than 75 years, you see a quarter to a third of those older adults with AML have a performance status 2-3. It should be noted also that these are patients who made it to clinical trials, typically we are selective in clinical trials in real life probably a higher percentage is observed. You can also see that about a third of the patients younger than 56 years old have unfavorable risk cytogenetics compared to about 50% of patients 75 years and older, and this also in turn can contribute to their worse outcome.

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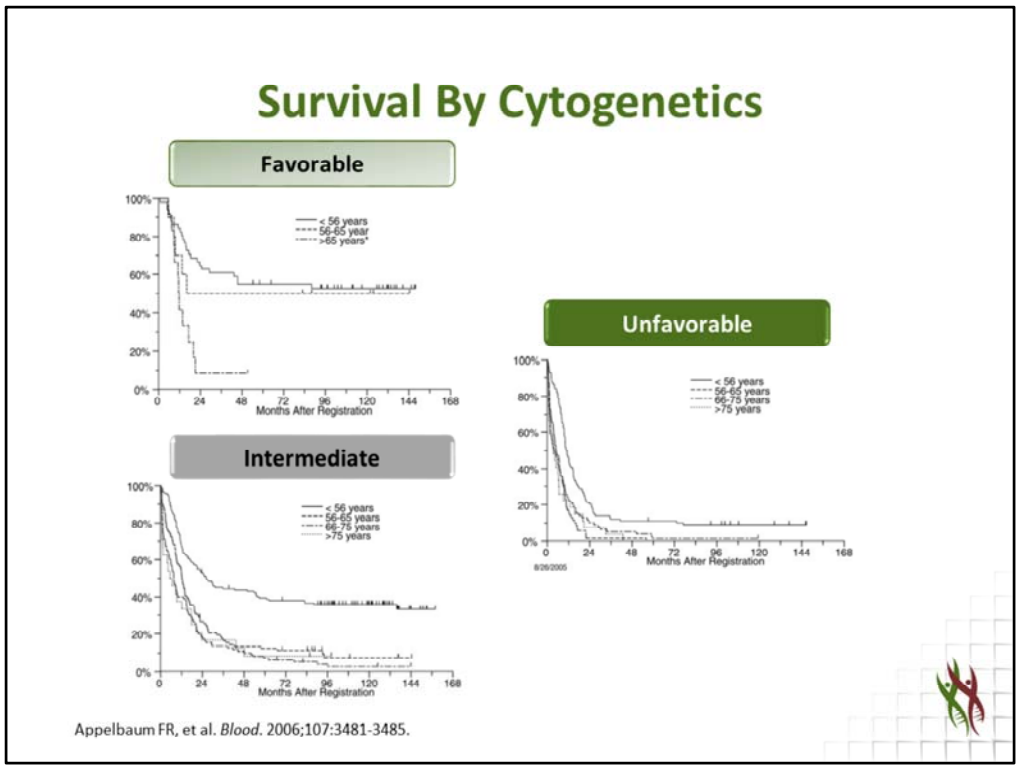

When you also dissect the older adult population based on the cytogenetics, that's when we divide AML to favorable, intermediate and unfavorable risk cytogenetics, you can see in each group or each subgroup, the older folks do worse compared to the younger adults, even in patients with favorable risks. Patients with favorable risk acute myeloid leukemia and older than 65 have much worse survival compared to patients less than 56 years old. Similarly, in patients with the intermediate risk group, you can see here patients 65 years old and older have much worse survival even though in patients with unfavorable risk cytogenetics typically they have worse overall survival in general, you can see older adults with AML have worse survival compared to younger patients 56 years old or younger.

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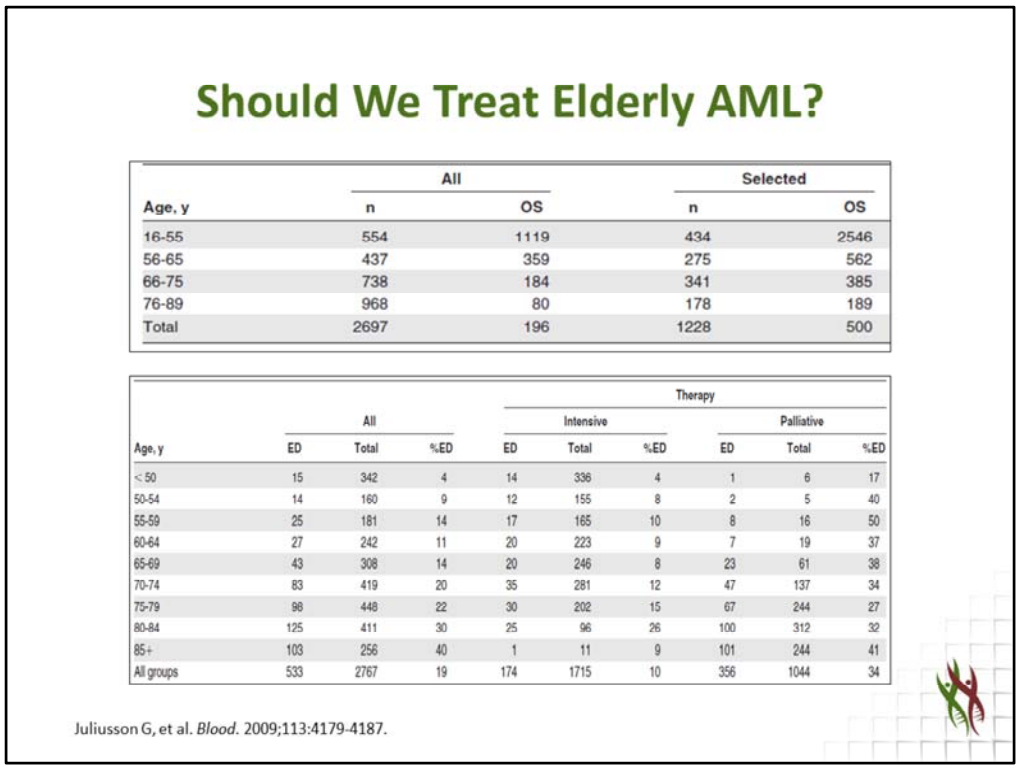

The first question when we encounter an older adult with acute myeloid leukemia comes to mind, should we offer treatment to this patient? That is the first common question, should we treat an 80 or 85 year old? Should we offer treatment in the first place or not? And the answer is yes, and that is based on multiple studies. This again, this study took about 2,600 patients from the Swedish registry. You can see here the median overall survival, as we discussed in a previous slide, for patients age of 76-89 is much lower than compared to patients 65 to age of 55, but the survival actually improved when these patients, the same patient population, offer treatment. You can see improvement in overall survival of patients who received intensive treatment in patients 66-75 years of age, and even in patients of 76-89 of age, that you can see a few months difference in survival. So, yes, treatment for older adults with AML can prolong survival. Another important question is that most of the physicians fear is that the induction mortality or the early death that is related to the disease is higher in older adults with AML, and that may sometimes prevent them from providing therapy to that. It turns out, actually, that if you offer older adults treatment, they have less early death compared if you don't offer them treatment and this is shown here in the slide. If you take all patients, you see younger patients have about 4% induction mortality or early death mortality, this is defined as death within 30 days of therapy**,** typically intensive chemotherapy, whereas 40% of patients 85 years and older have early death or mortality. However, when the investigators of this study looked at the patients and divide them into patients who received intensive chemotherapy versus the patients who received palliative treatments, just supportive care, you can see that older adults who received intensive chemotherapy had less early death compared to patients who received palliative care. In other words, early death should not persuade a decision in choosing therapy for older adults with AML, and therapy, whether intensive or non-intensive, can prolong survival for patients with AML. In conclusion, all patients with AML should be at least offered therapy regardless of their age.

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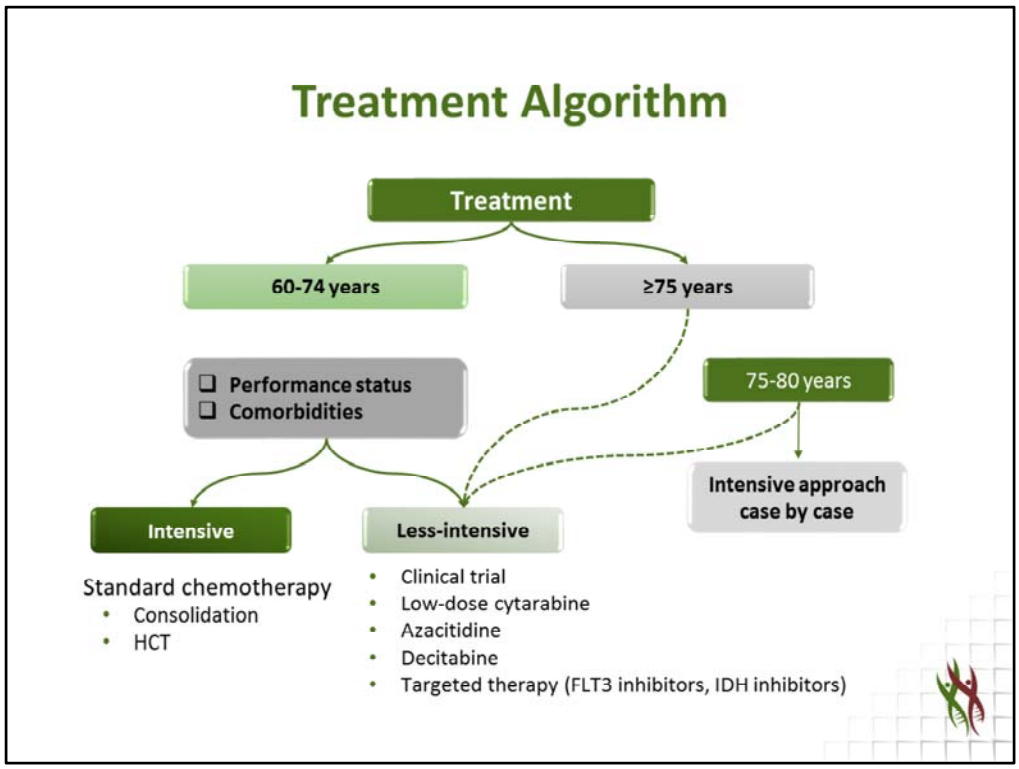

Of course, another important question is which type of therapy we should offer these patients. This slide summarizes treatment algorithm for older adults with AML, but honestly you can summarize it in one line. Any older adult patient with AML should be offered a clinical trial or should be referred to academic centers that have clinical trials to participate in. In the absence of a clinical trial, or the patient chooses not to participate in a clinical trial, then we can divide the treatment algorithm loosely based on age, and most investigators will divide the patient population into age 60-74 years and about 75 years old. Again, this is a line in the sand, it is not based on data. But if you have patients with newly diagnosed AML age 60-74 years old, we really have two options here. Can we offer the patient intensive chemotherapy or should we choose a less intensive approach? We make this decision first by acknowledging the goal of therapy and the patient's goal of therapy. This is very important, we have to tailor the therapy options in accordance with the goal of the patients from the treatment. Is the goal to be as aggressive as they can be with the treatment, or is the goal to get better quality of life with less intensive treatment? If the patient chooses to get aggressive treatment we then evaluate if the patient can receive intensive chemotherapy. Although there has been multiple models to define whether the patient can receive intensive chemotherapy or not, the application of these models in clinical practice remain challenging. Most of the time, we decide whether the patient can receive intensive chemotherapy or not based on their performance status and comorbidities. A patient with good performance status and less comorbidities may be offered intensive chemotherapy, and patients with worse performance status and multiple comorbidities that we do not think that they can tolerate the treatment with intensive chemotherapy can be offered a less intensive approach. There is the intensive approach, again standard chemotherapy followed by consolidation or transplant, and I will touch base on this in the next few slides. The less intensive approach, again, a clinical trial is always recommended for this patient population.

Outside of a clinical trial, low-dose cytarabine can be an option, azacitidine or decitabine can be an option, and in a subset of patients that they have molecularly targeted lesions we can offer FLT3 inhibitors, IDH inhibitors, and I will touch base on these treatment options in the next few slides. For patients above the age of 75, most experts in the field will say patients from 75-80 years of age can still be offered intensive chemotherapy on a case-by-case discussion. Again, you tailor the discussion with the patient goal of therapy, expectations of the treatment, and what's the goal of the patient of the therapy and what is the goal of the treatment in general. This patient population can be offered intensive chemotherapy, again, on a case-by-case discussion. Above the age of 80 we typically do not offer these folks chemotherapy, again, the preferred route is a clinical trial. If a clinical trial is not available the other options of less intensive approach here can be offered to the patient.

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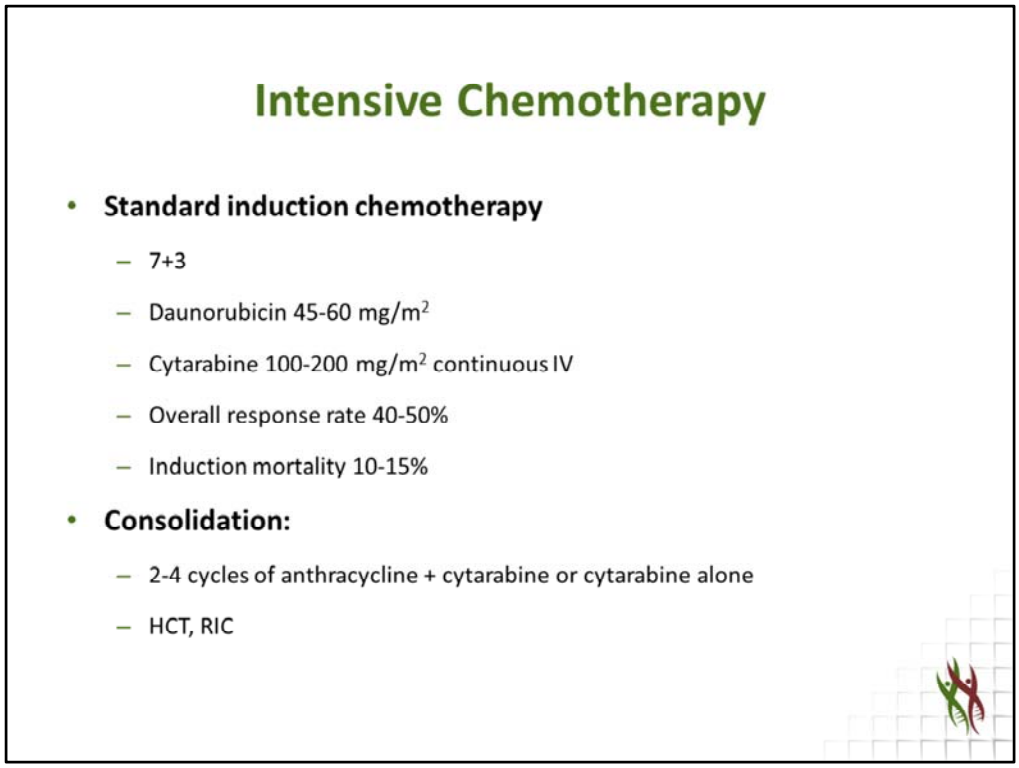

So in terms of intensive chemotherapy, outside of a clinical trial, again, even intensive chemotherapy the patient should be offered intensive chemotherapy on a clinical trial, in the absence of a clinical trial we can use standard induction chemotherapy, which is 7+3, seven days of continuous infusion of cytarabine and three days of anthracycline, daunorubicin dose of 45-60 mg/m^2, we can also use idarubicin 12 mg/m^2. The numbers I typically quote my patients are the overall response rates in terms of CR or CR with incomplete platelet recovery or incomplete hematology count recovery is about 40%-50%, and the induction mortality is about 10%-15%. In terms of consolidation, we have to make the decision whether the patient should move to receive allogeneic stem cell transplant. Typically, reduced intensity as stem cell transplant conversation happens with a transplant specialist, whether the patient can tolerate transplant, whether the patient has clinical characteristics in terms of their cytogenetics and their molecular profile that prompt the transplant options for them, or the patient can receive consolidation chemotherapy. The number of cycles, the dose, and the schedule of the consolidation chemotherapy is controversial and is beyond this presentation to discuss this controversy, but in general, it is about 2-4 cycles of treatment with anthracycline and cytarabine or cytarabine alone.

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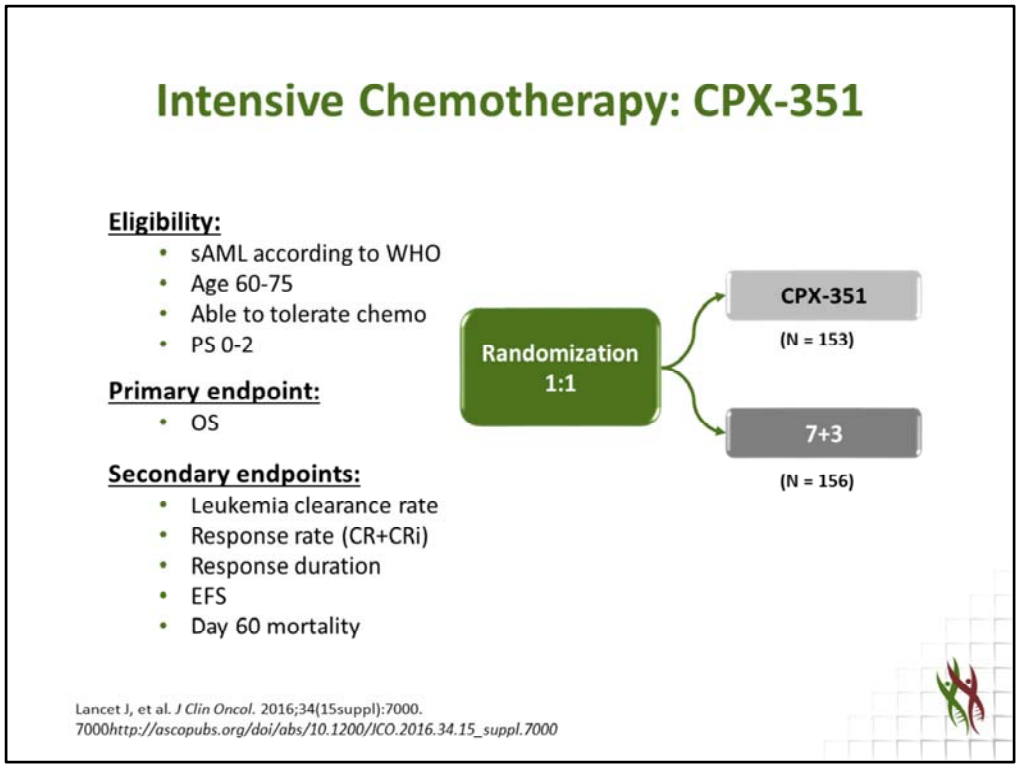

Most recently, there has been a drug, that is CPX-351. This is a liposomal formulation of daunorubicin and cytarabine in a ratio of 5:1 of five cytarabine and one daunorubicin. There has been a phase 3 randomized clinical trial that took patients with higher-risk AML, higher risk defined by secondary acute myeloid leukemia arising from prior hematologic malignancy, or therapy-related acute myeloid leukemia by WHO criteria. Patients age 60-75 who were thought to be able to tolerate chemotherapy with good performance status were randomized to receive CPX-351 or standard chemotherapy 7+3. The primary endpoint of this study was overall survival. The secondary endpoints were leukemia clearance rate, response rate defined by CR or Cri, response duration, event-free survival, and induction mortality after 60 days of induction.

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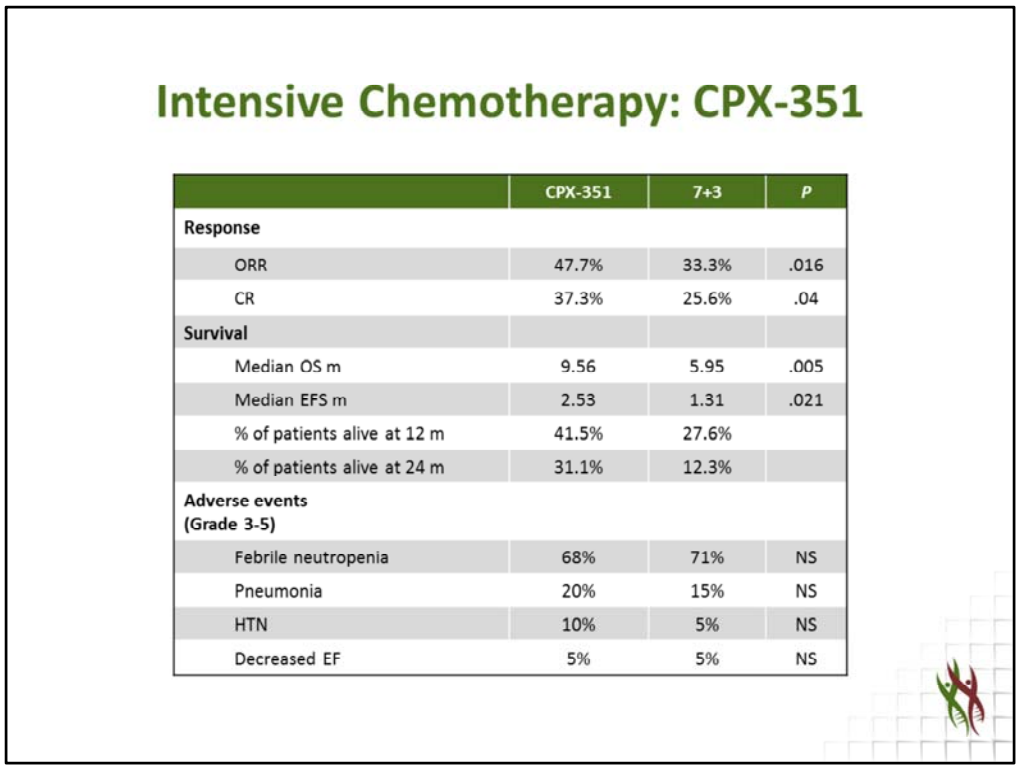

The overall response rate for the CPX-351 was higher compared to 7+3. The overall response rate was 48% for patients treated with CPX compared to 33% for patients treated with 7+3, and that was statistically significant. Even the rate of CR was higher in patients treated with CPX compared to 7+3. Most importantly in terms of survival, the median overall survival for patients treated with CPX-351 was 9.56 months compare to 5.95 months for patients treated with 7+3. This was statistically significant and lead that the trial met its primary endpoint and lead the approval of CPX-351 by the FDA on August 3, 2017 for this patient population -- higher risk AML. You can see here, interestingly about 31% of the patients treated with CPX are alive at 24 months after their treatment compared to only 12% of patients who were treated with 7+3. Most importantly, in terms of adverse events, mainly grade 3-5, were similar in the two patient cohorts, in terms of febrile neutropenia, pneumonia, hypertension, and cardiomyopathy, as you can see here on this slide. Again, based on this data, the FDA approved CPX-351 for newly diagnosed therapy-related acute myeloid leukemia or secondary acute myeloid leukemia age 60-75 who are able to tolerate intensive chemotherapy.

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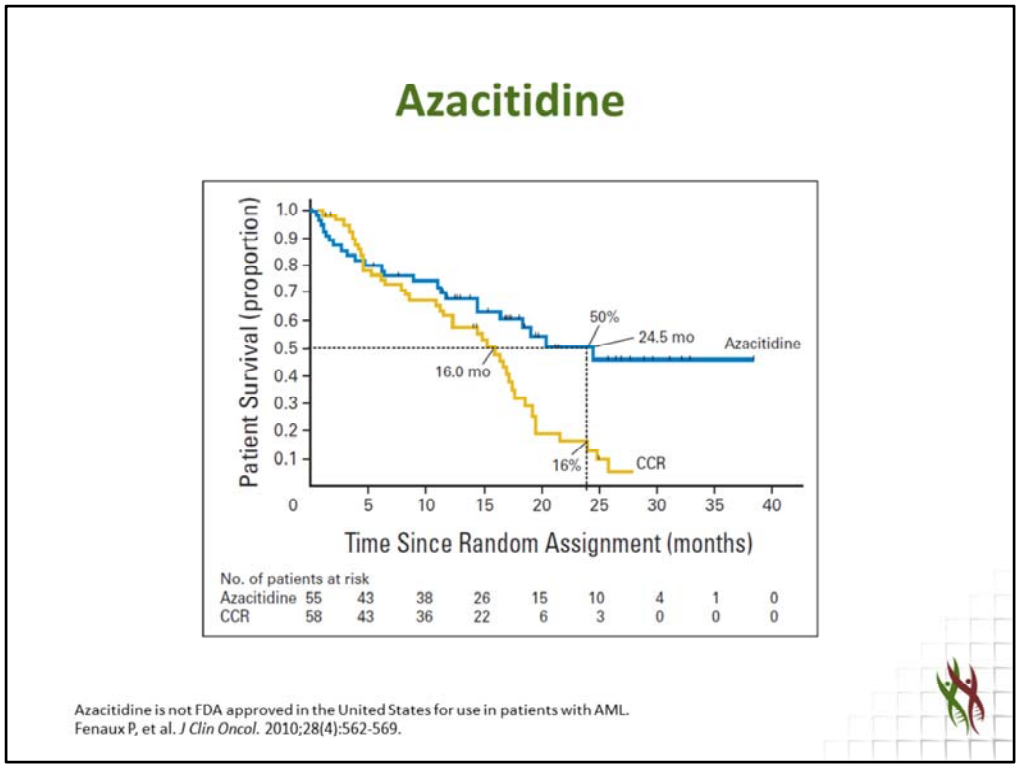

What about less intensive approaches? We talked about one option can be azacitidine. Azacitidine is FDA-approved in myelodysplastic syndromes, it is not FDA-approved in acute myeloid leukemia; however, there are some data that can support the use of azacitidine in patients with acute myeloid leukemia. This study is a randomized phase 3 trial that randomized patients with myelodysplastic syndrome to receive azacitidine compared to conventional care. This conventional care arm included patients who received best supportive care just like transfusion, low-dose cytarabine, and about 19% of this patient population received intensive chemotherapy. When the trial was conducted originally, the definition of MDS included patients with bone marrow blast percentage up to 30%. In 2008 the WHO changed the definition of acute myeloid leukemia arising from MDS to 20%. The investigator of this trial looked at the older patients that received azacitidine versus conventional care therapy and they have bone marrow blast percentage of 20-30%. So 55 of those patients received azacitidine and 58 received best available therapy. In terms of response rate, azacitidine was about 18% compared to 16% of patients on the conventional care arm. However, the median overall survival for patients who received azacitidine was longer than patients who received other therapies. It should be noted however, one of the critique of this trial is the subset analysis, is a small number of patients, and it is not direct comparison of azacitidine to intensive chemotherapy because a small fraction of these patients in the conventional care arm received intensive chemotherapy. What we can conclude from this is azacitidine can produce about 18% response rate in older adults with AML and may prolong survival compared to the other conventional care arm, but not certainly compared to intensive chemotherapy.

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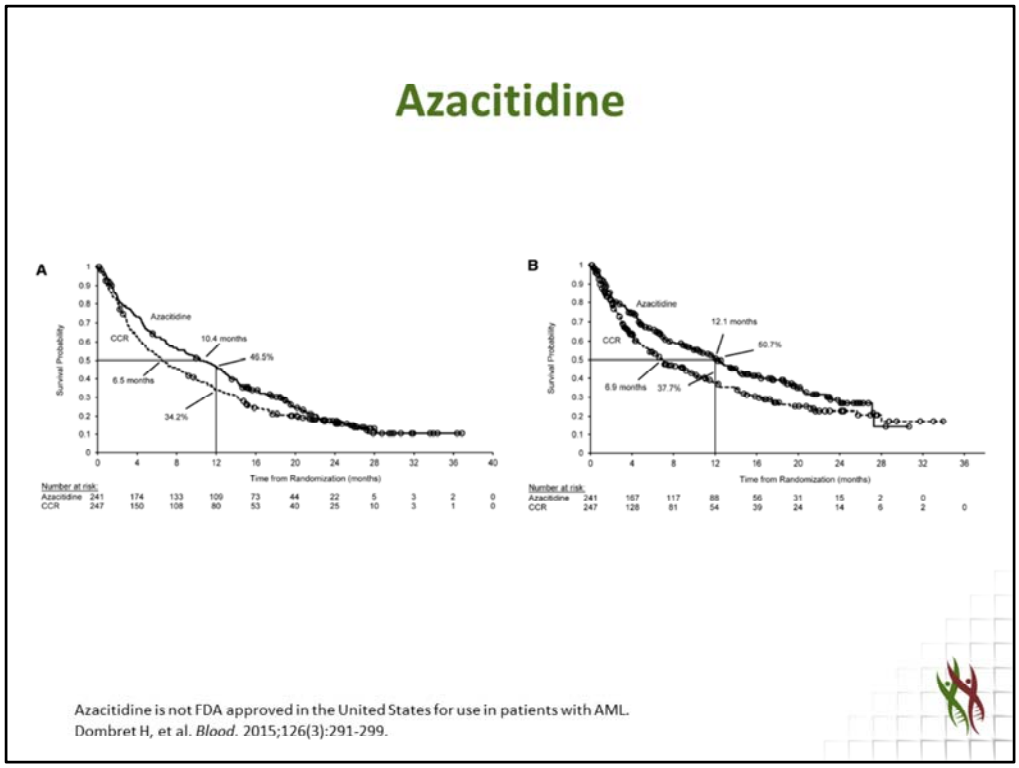

Similarly, there has been a phase 3 randomized trial, multicenter, that randomized older folks 65 years and older to receive azacitidine 75 mg/m^2 for seven days, to again compared to conventional care. The arm of conventional care similarly included those who received best supportive care, which is blood transfusions, low-dose cytarabine, and intensive chemotherapy. When the investigators looked at the median overall survival for the patients who received azacitidine compared to the conventional care arm, the median overall survival was 10.4 months for patients who received azacitidine compared to 6.5 months for patients on the conventional care arm, which was not statistically significant. However, when the investigators focused their analysis on the patients who received subsequent treatments after the failure of initial drug in intent-to-treat analysis, the median overall survival was 12.1 months for patients who were treated with azacitidine compared to 6.9 months for patients treated with conventional care. The response rates were also similar, about 18% in general, but again, the same critique to this trial, although it has larger numbers of patients, did not directly compare azacitidine to intensive chemotherapy. As a matter of fact, if we look carefully in the paper, patients who received intensive chemotherapy have a higher response rate compared to azacitidine and their survival was exactly similar. What we can conclude from this is that azacitidine is a good treatment option for patients who may not receive or do not want to receive intensive chemotherapy. It can produce a response rate of about 18%-20% and may prolong survival compared to other less intensive approach treatments.

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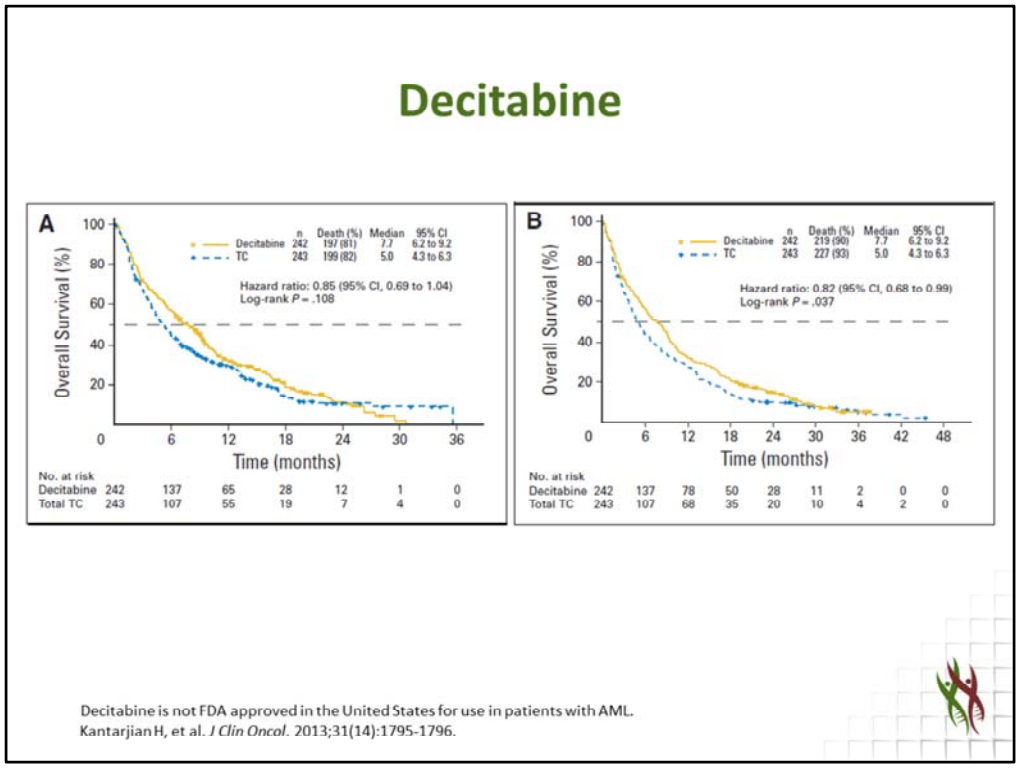

What about decitabine? Decitabine is FDA-approved in patients with myelodysplastic syndromes, is not FDA-approved for patients with acute myeloid leukemia, but is actually approved in Europe for patients with acute myeloid leukemia based on this trial. This trial randomized elderly folks 65 years and older with bone marrow blasts more than 30% with acute myeloid leukemia to receive decitabine 20 mg/m^2 for five days compared to patient choice or physician choice of treatment, but that only included best supportive care or low-dose cytarabine, it did not include intensive chemotherapy. You can see similarly the response rate to decitabine is about 18% overall response rate, but the median overall survival was 7.7 months for patients treated with decitabine compared to 5 months for patients treated with best available therapy, which was not statistically significant. However, in a longer follow up after the landmark analysis have shown median overall survival of 7.7 months for patients treated with decitabine compared to 5 months for patients treated with best supportive care, and that was statistically significant. Despite that, the FDA did not approve decitabine for treatment of elderly AML in the United States, again it is only approved in Europe, but can be used off-label. Treatment with hypomethylating agents such as azacitidine and decitabine, although it is off-label, it is not FDA approved, can produce about 20% response rates in older adults with acute myeloid leukemia typically is very well tolerated and may prolong survival compared to just supportive care or low-dose cytarabine.

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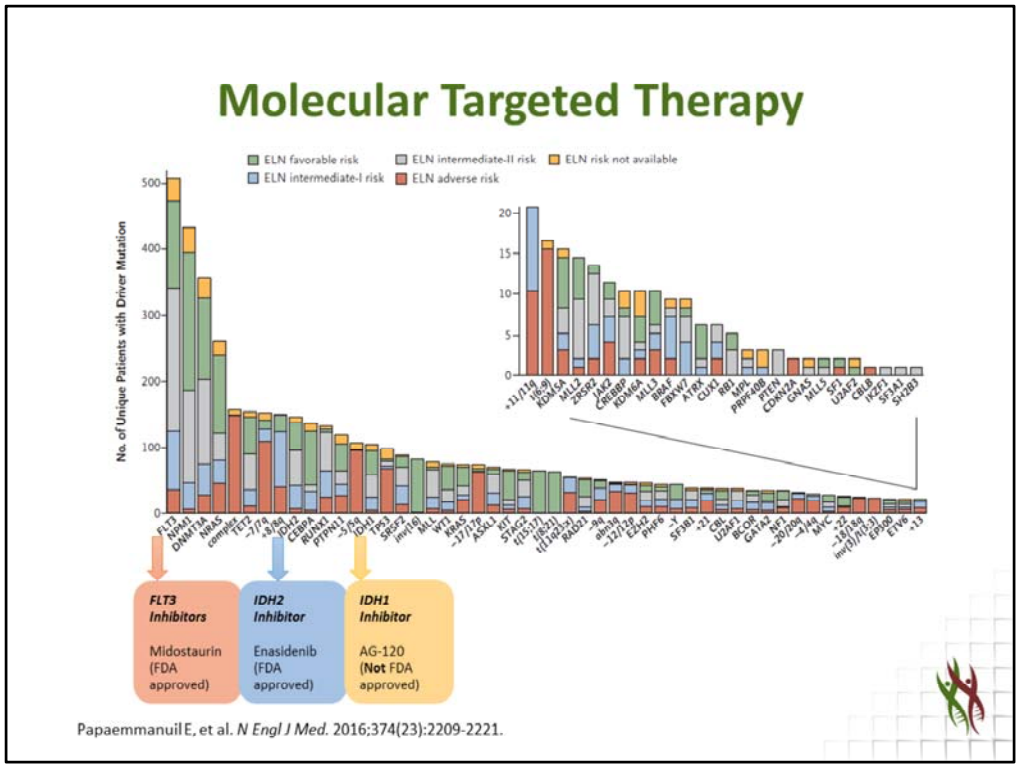
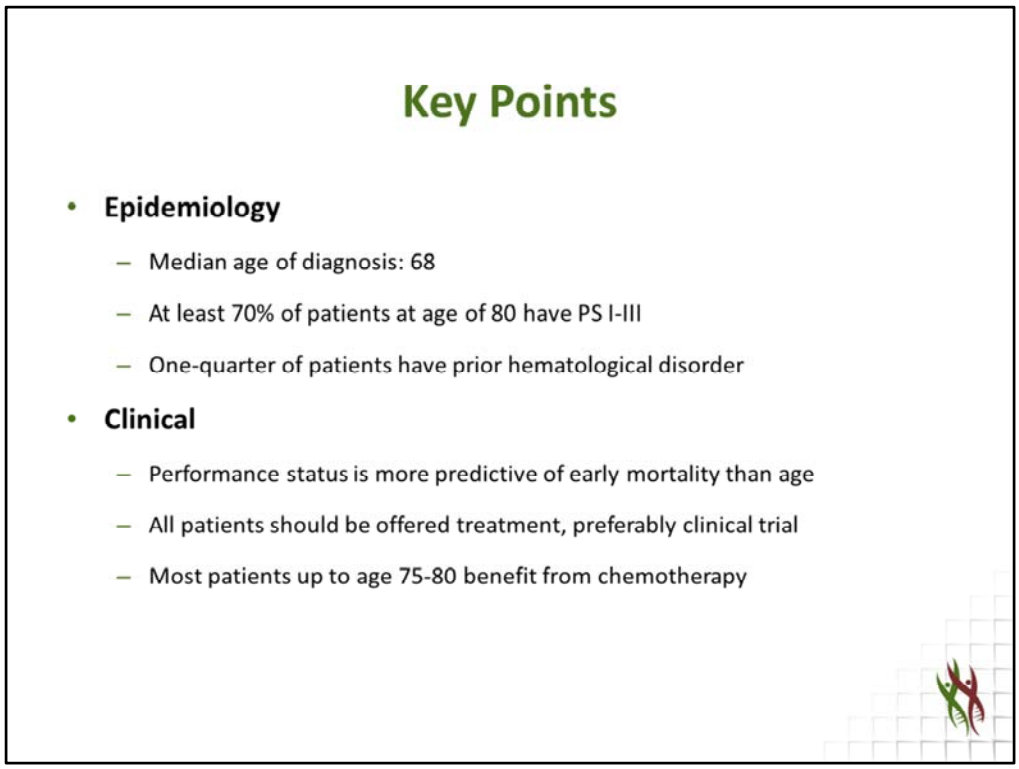


Finally, I will touch base on molecular targeted therapy. AML is a clonal disease that is derived from complex genomic abnormalities. This study looked at about 15,000 patients with acute myeloid leukemia and sequenced their bone marrow samples or peripheral blood for the presence of 111 genes. You can see there are certain molecular abnormalities that are common in AML and includes FLT3, NPM1, DNMT3A, IDH1 or IDH2, etc.; however, there are only few targeted therapies for these mutations. These are, including FLT3 inhibitors, there are multiple FLT3 inhibitors in clinical trials alone or in combination with less intensive chemotherapy or intensive chemotherapy, but only one the drug is FDA-approved. To date it is midostaurin that was approved in April 2017 in combination with chemotherapy 7+3 plus midostaurin and in combination with consolidation chemotherapy followed by a year of maintenance of midostaurin. Midostaurin, again, is the only FDA-approved FLT3 inhibitor in this setting although there are multiple FLT3 inhibitors still in clinical trial, again with chemo or without chemotherapy. The other targeted therapy that is available for patients with AML is IDH2 inhibitor enasidenib that was recently FDA-approved for patients with primary refractory or relapsed acute myeloid leukemia who carry IDH2 mutation. Another molecular targeted therapy in AML is IDH1 inhibitor, that is the AG-120, this drug is in clinical trial but not yet FDA approved. There are multiple other IDH1 and IDH2 inhibitors that are in clinical trials now, but the only FDA-approved IDH2 inhibitor is enasidenib.



I will leave you with those messages at the end of this talk. In conclusion acute myeloid leukemia is a disease of elderly, the median age of diagnosis is 68, at least 70% of patients at age of 80 will have performance status 1-3, and a quarter of those patients will have secondary acute myeloid leukemia or therapy-related acute myeloid leukemia which is typically associated with worse outcome. Performance status is very important and is predictive of early mortality rather than age. All patients, as we discussed, should be offered treatment and the preferable treatment for this patient population should be a clinical trial. Even patients from ages 75-80 may benefit from chemotherapy and that should be again discussed with the patient based on his or her goal of therapy and goal of treatment in general.

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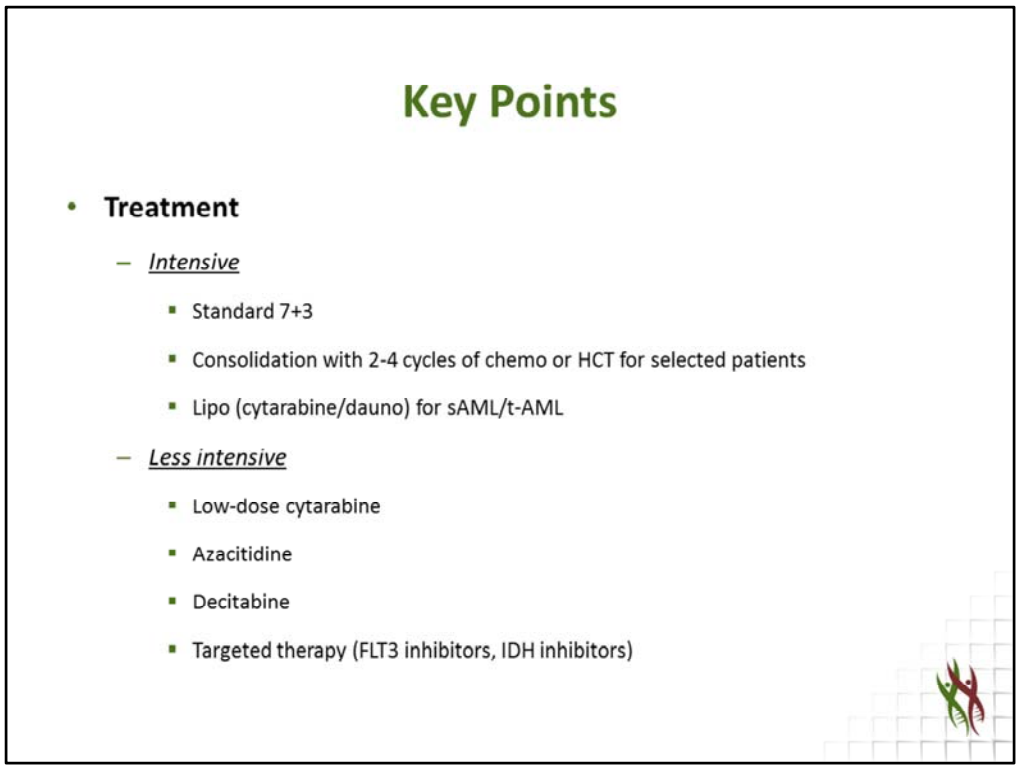

Treatment options can include intensive chemotherapy. Again, it is encouraged to be on a clinical trial but if a clinical trial is not available or the patient does not want to participate in a clinical trial, intensive chemotherapy with 7+3 followed by consolidation chemotherapy, whether it is allogeneic stem cell transplant or just chemotherapy based on the patient's characteristics, can be discussed with the patient. Recently, liposomal cytarabine and daunorubicin and CPX-351 have been FDA-approved for the treatment of higher-risk AML, that is secondary acute myeloid leukemia and therapy-related acute myeloid leukemia, that is not FDA-approved for de novo acute myeloid leukemia. Less intensive approaches can also be discussed with the patient that may include low-dose cytarabine, although the response rate to this approach is low, it's about 10%, but it is generally well tolerated. Other treatment options are azacitidine and decitabine, the overall response rate to these agents are about 20% and may prolong survival compared to the other best supportive care, but that does not include intensive chemotherapy, targeted therapy such as FLT3 inhibitors, and IDH inhibitors can be also explored in patients who carry these molecular abnormalities. Thank you very much for viewing this activity.