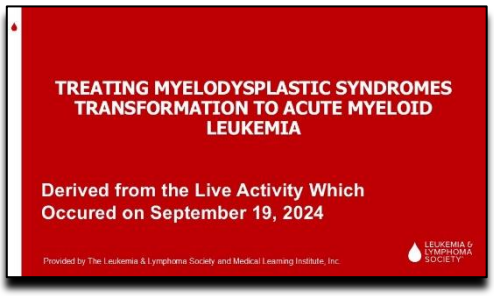


Slide 1: Treating Myelodysplastic Syndrome's Transformation to Acute Myeloid Leukemia

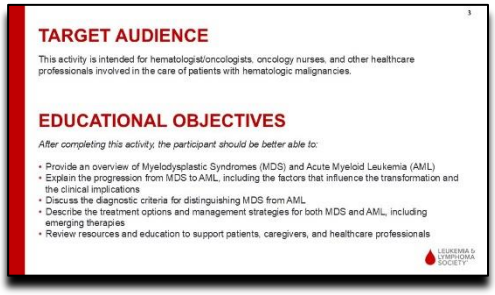
Lesley Hoerst, BSN, RN: Greetings, and welcome to treating myelodysplastic syndrome's transformation to acute myeloid leukemia, a web education program.

Slide 2: Welcome and Introductions

My name is Lesley Hoerst, Senior Manager of Professional Education Programs at The Leukemia & Lymphoma Society. On behalf of LLS, thank you for joining us. Our organization is committed to improving patients' quality of life through webinars such as this one for healthcare providers and education and support resources for patients and caregivers.

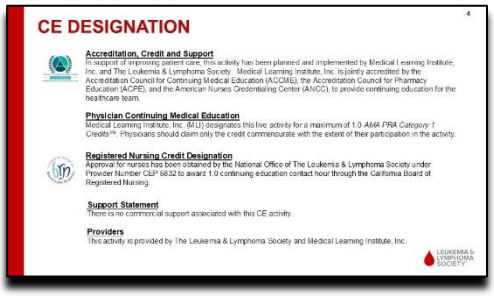
LLS advocates for funding to accelerate the discovery and development of blood cancer therapies and is the largest nonprofit founder of blood cancer research, investing more than $1.7 billion worldwide since 1949.

This webinar will provide an overview of MDS and AML, explain the progression from MDS to AML, discuss the diagnostic criteria for distinguishing MDS from AML, treatment options and management strategies, including emerging therapies, as well as additional education resources for you will also be provided.



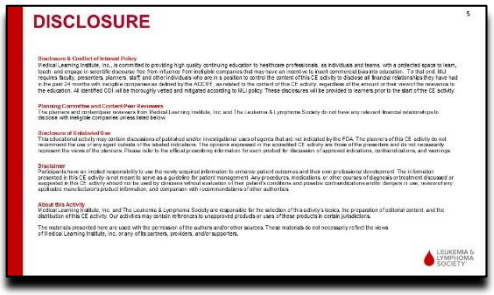
Slide 3: Learning Objectives

The learning objectives for today's webinar are listed on this slide.



Slide 4: CE Designation

Continuing education information is listed here.



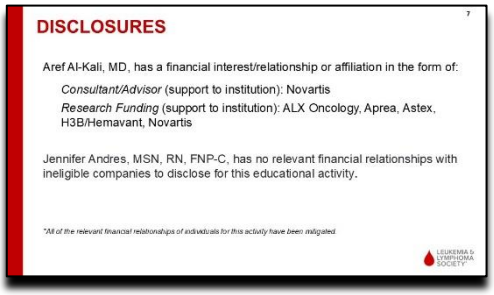
Side 5: Disclosure

Planner disclosures are listed on the slide on the screen.

Slide 6: Faculty

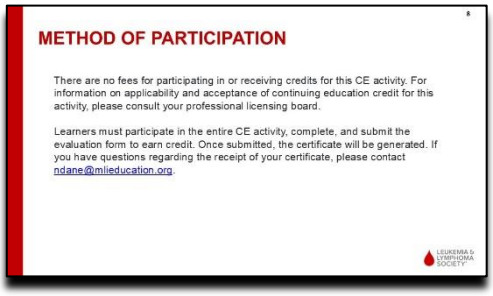
I am honored to introduce our presenters. Dr. Aref Al-Kali, Professor of Medicine, MDS Clinic Director, Acute Myeloid Group Chair, Section Head, Division of Hematology at Mayo Clinic in Rochester, Minnesota. And Miss Jennifer Andres is an outpatient hematology nurse practitioner at Mayo Clinic in Phoenix, Arizona. Thank you for volunteering your time and expertise with us.

Following their presentations, we will share information about resources from The Leukemia & Lymphoma Society.



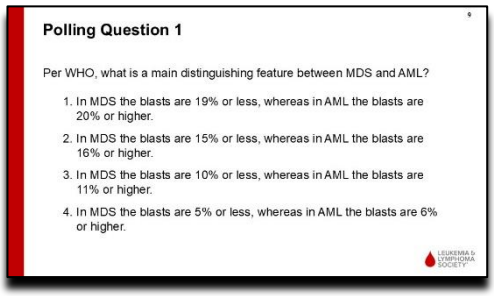
Slide 7: Faculty Disclosures

Faculty disclosures are listed here.



Slide 8: Method of Participation:
To receive credit for participating, please complete the evaluation at the end of the program. Once submitted, a certificate will be generated. Your feedback is important to us to help plan future programs and is also required for you to receive continuing education credit.

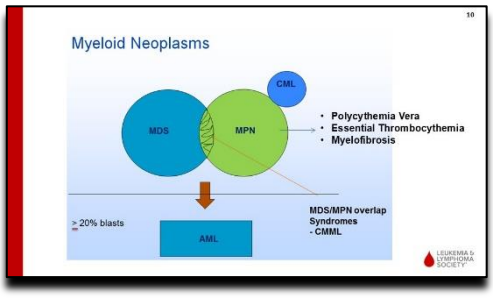
Miss Andres and Dr. Al-Kali, I now invite you to join us on camera, and it is my pleasure to turn the program over to you.



Slide 9: Polling Question 1
Jennifer Andres, MSN, RN, FNP-C: Hello, everyone. It's a pleasure to be presenting today with Dr. Al-Kali. He and I would like to thank all of you and The Leukemia & Lymphoma Society for the opportunity to speak with you about MDS and AML.

We'll go ahead and start with a Polling Question. Per the World Health Organization, what is a main distinguishing factor between MDS and AML? Is it #1 - In MDS, the blasts are 19% or less, whereas in AML the blasts are 20% or higher. #2 – In MDS, the blasts are 15% or less, whereas in AML the blasts are 16% or higher. #3 – In MDS, the blasts are 10% or less, whereas in AML the blasts are 11% or higher. Or #4 – In MDS, the blasts are 5% or less, whereas in AML the blasts are 6% or higher. Go ahead and make your best selection.

Okay. So it looks like the majority of you did get this correct, and so the correct answer is #1. In MDS and AML, one of the distinguishing factors is that in AML the blasts are 20% or higher.

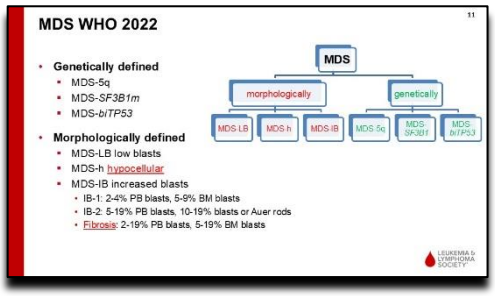


Slide 10: Myeloid Neoplasms
All right, so what are myelodysplastic syndromes or MDS? Well, it is not one disease but rather a group of clonal stem cell disorders. If we break down the name, we have myelo referring to the myeloid cells, which are the monocytes, the macrophages, neutrophils, basophils, eosinophils, erythrocyte, and platelet, and dysplasia, meaning abnormal. This abnormality results in ineffective hematopoiesis, the process by which blood cells are formed. This, in turn, leads to problems with a person's red blood cells, white blood cells, platelets, or potentially all three of these cell lines. Essentially, we have maturation defects in the bone marrow.

So if we take a look at this diagram, the green circle represents MPNs or myeloproliferative neoplasm. This would include diseases including polycythemia vera or PV where there is an overproduction of red blood cells, essential thrombocythemia or ET where there is an overproduction of platelets, or myelofibrosis where there is scarring in the bone marrow.

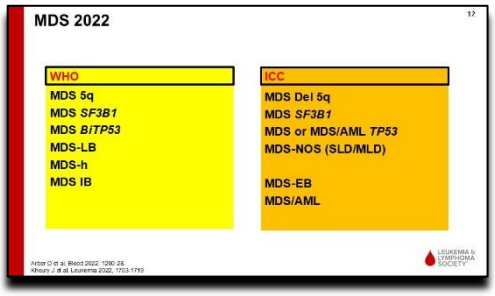
Next to that, the blue circle represents MDS, whereas we discussed, there is a dysfunction of the cells. As you can see in the middle, there is an MDS/MPN overlap syndrome, which we also refer to as CMML or chronic myelomonocytic leukemia, where they may have both characteristics of MDS and the MPNs.
Then we also have a group of myeloid neoplasms called CML or chronic myeloid leukemia. And for the purposes of today's presentation, we'll be focusing on the MDS and the AML.

If we follow the red arrow down, these diseases above can then transform or progress into an acute leukemia. And so as we take a look here, the blasts of 20%, again, is that distinguishing factor that we had discussed. So is MDS a preleukemia? Yes and no. That term can be a little misleading as it really depends on the subtype of MDS. Roughly about one-third of MDS cases will transform to AML.



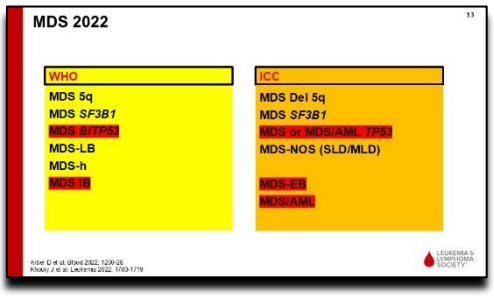
Slide 11: MDS WHO 2022

So, MDS is classified by morphology represented in red. This would be MDS with low blasts, hypocellular MDS, or MDS with increased blasts, and genetically. This is the MDS with 5q minus, SF3B1, and TP53 mutations.



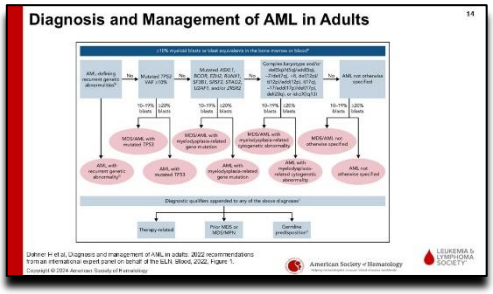
Slide 12: MDS 2022

MDS is also classified by the World Health Organization and the International Consensus Classification, which are similar but have their own unique features.



Slide 13: MDS 2022

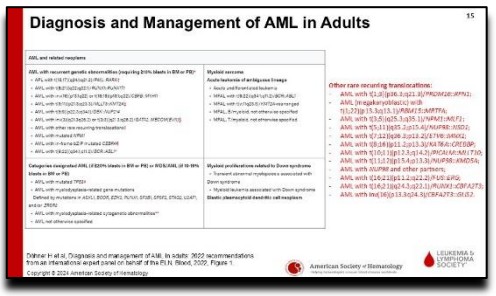
Taking a look here, we see that the high-grade MDS is highlighted in red, and these are the MDS with the biallelic TP53 location, MDS with increased blasts, or the MDS/AML with excess blasts.



Slide 14: Diagnosis and Management of AML in Adults

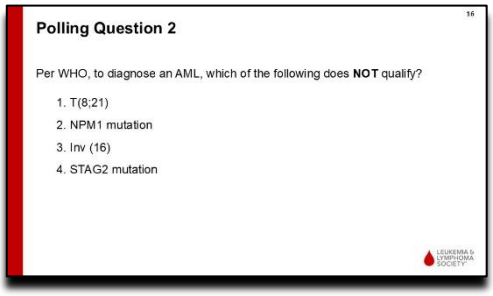
Aref Al-Kali, MD: Thank you. The ICC has an algorithm in terms how do you work up a case. This is shown here. As you can see, if you do have mutations or translocations that defines AML, then this is AML with recurrent genetic abnormalities. If you do have a p53 mutation above 10%, then the blast matter less than 20%, this would be MDS/AML. More than 20%, this will be AML with mutated p53.

Please note the WHO mandates 20% to call it AML. And then you have other mutations that will define, for example, AML with MDS-related gene mutations. For example, EZH2. And then after that, you can have complex karyotypes or other abnormalities that will define a very high risk group of cases, which is MDS with myelodysplasia-related cytogenetic abnormality. In fact, we're going to talk about a study in that category. And then if you have none of the mutations you see, then this is AML, not otherwise specific.



Slide 15: Diagnosis and Management of AML in Adults

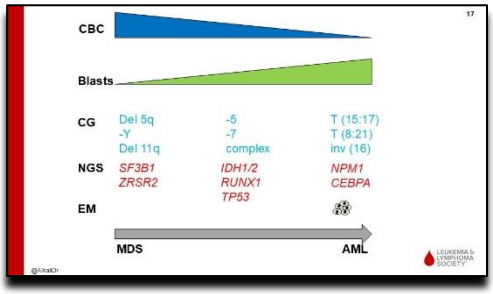
And if you go into more details, AML as I said, can be defined with those recurrent mutations. So if you have a blast above 10% and 8;21 or inversion (16), this is AML. And this is very important as you could change diagnosis and perhaps even the therapy of those patients. There's also new categories, which is mutations, which is NPM1 mutation and CEBPA mutation, the bZIP mutation. So even if you have those two with a blast of 15%, this will be considered acute myeloid leukemia. And there is actually rare genetic translocations, as you can see on the right side of the slide.



Slide 16: Polling 2

So, the next question is going to review exactly what we talked about. It's, which is the diagnosis of MDS, high grade, versus AML, which is an area of difficulty, especially because now we have the two classifications of ICC and WHO. So per WHO, to diagnose an AML, which of the following does not qualify? Does not qualify? Translocation 8;21, NPM1 mutation, inv(16), or STAG2 mutation?

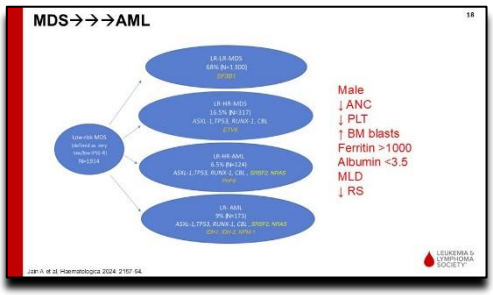
Thank you for answering that. So to review the question again, if you remember that we said if there's increased blast, then this is likely high-grade MDS. However, what could be more important is the presence of those genetic abnormalities. Translocation 8;21 and inversion (16), those are diagnostic of AML with any case of blast above 10%. NPM1 mutation is also diagnostic of AML with blast percent of more than 10%. STAG2 mutation, if you remember the picture before, it actually does not define AML on its own. However, if you do have AML, this would be AML with, MDS-related gene mutations. So the answer is 4. STAG2 does not qualify for AML.



Slide 17: Diagram

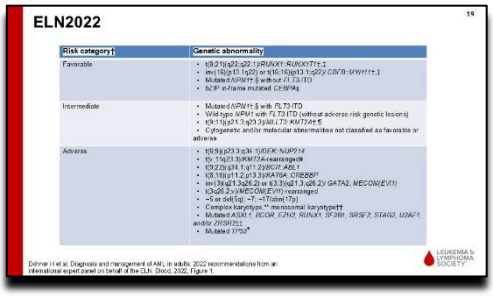
Jennifer Andres: So this diagram here is another way that we can look at the progression from MDS to AML. So starting at the top, you can see that, in general, the CBC results would worsen with lower hemoglobin, reduced white blood cell counts, and decreased platelets, while the blast percentage would increase, as we discussed, that 20% threshold typically for AML.

Then the cytogenetics can also change as we progress from MDS to AML as well as the genetic mutations that we see on the next-generation sequencing. In AML, we can also see that there can be some extramedullary hematopoiesis, which is the production of red blood cells outside of the bone marrow.



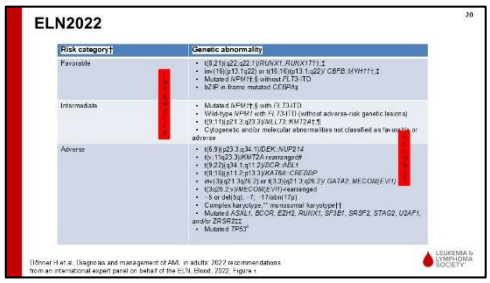
Slide 18: MDS→→→ AML

These are some of the factors seen in cases transforming to AML. So patients typically can be male with a lower absolute neutrophil count, lower platelets, increased bone marrow blasts, high ferritin levels, lower albumin levels, and multilineage dysplasia and ring sideroblasts.



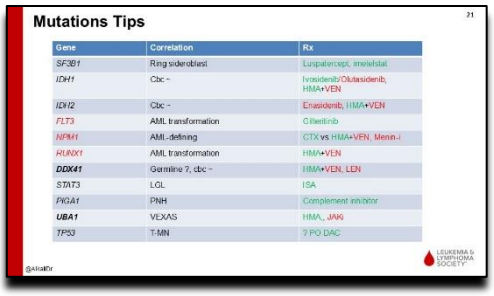
Slide 19: ELN2022

Per the 2022 European Leukemia Network, AML is classified into favorable, intermediate, and adverse risk categories based on genetic abnormalities. And Dr. Al-Kali will be speaking more to this in the next slide.



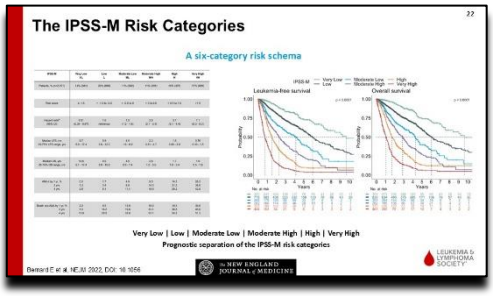
Slide 20: ELN2022

Dr. Al-Kali: Thank you. And this is an important piece of information as it could decide how do we treat those patients. So, if you have an AML with a favorable chromosomal abnormality, for example, inversion(16), you want to try to give intensive chemotherapy if the patient is fit. On the other side, if the patient has a complex karyotype where maybe intensive chemotherapy is not that effective, then that might be deferring factor, and you may decide to go with a nonintensive therapy. It also helps you to decide, do we need to send patients to transplant? Allogenic hematopoietic cell transplantation. So, if you have an intermediate or adverse-risk AML, you do want to start that referral to BMT for consideration of a curative option. On the other side, if you have a favorable AML, BMT at remission one, CR1, may not be needed.



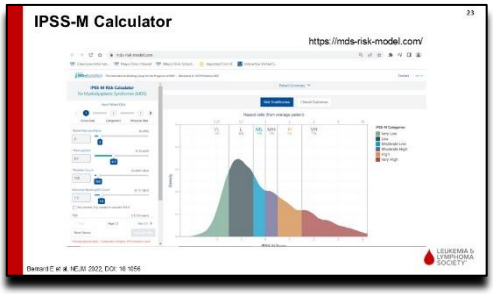
Slide 21: Mutations Tips

I do want to stress out the importance of molecular abnormalities. It's becoming now essential in the practice of a myeloid neoplasm, including MDS and AML. And briefly here, you can see that the finding of SF3B1 is now diagnostic of MDS with RS. It also could affect your treatment approved in that category. IDH1 and IDH2, they tend to come with almost intact normal counts. Even though the blasts are increased, we now have FDA-approved therapy in AML and also in MDS with the IDH1 case. If you see other markers, like, for example, FLT3, it makes you think we might be transforming into AML, although it's not yet defining for AML. And then if you see a DDX41, that's an important finding, about 1 to 2% of all cases. Then you want to think is this inherited disorder? And so forth. Also, some platforms have UBA1, which has been linked recently to the VEXAS syndrome. So, seeing those markers and mutations are important to understand the disease and may affect how you treat those patients.



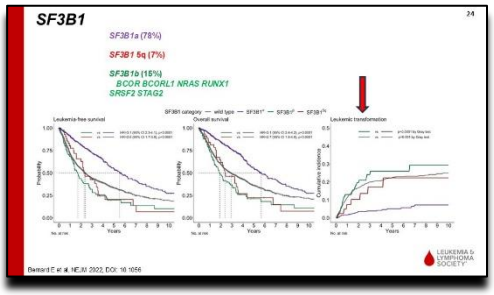
Slide 22: The IPSS-M Risk Categories

Jennifer Andres: The Molecular International Prognostic Scoring System provides risk stratification based on clinical and molecular data with six categories ranging from very low risk to very high risk.



Slide 23: IPSS-M Calculator

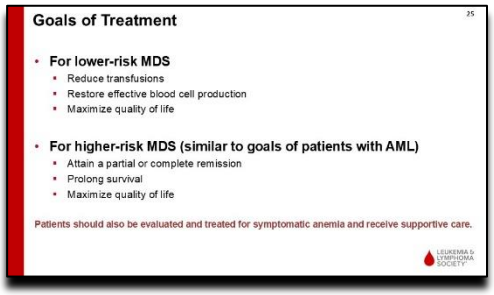
The IPSS-M calculator takes into account clinical data, including blast percentage, hemoglobin, platelet count, absolute neutrophil count, age, cytogenetic information, and molecular data. It is then able to provide different endpoints, including leukemia-free survival, overall survival, and AML transformation rate per year.



Slide 24: SF3B1

And, Dr. Al-Kali, did you want to speak more to this slide here?

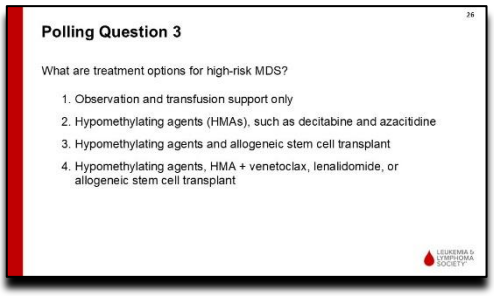
Dr. Al-Kali: Yeah, absolutely. We also need, and we also got some benefit from the IPSS-Molecular, telling us about a specific category, which is, as I mentioned earlier, the SF3B1 mutation. We now have three different groups of patients with SF3B1. The bulk of those cases are just SF3B1-mutated. And as you can see in the slide in purple, about 78% of those patients, they tend to have a good prognosis, long survival. On the other side, the presence of 5q with SF3B1 or secondary mutations like BCOR, BCOR ligand 1, NRAS, RUNX1, SRSF2, STAG2, that makes it a higher risk. And if you look on the right side where the arrow is, you can find that those patients, none in purple, have the highest risk of transformation into AML in this known to be a very mild indolent case.



Slide 25: Goals of Treatment

Jennifer Andres: So when we think about goals of treatment, it helps to know what risk category a patient is in. For some of our asymptomatic lower-risk patients without evidence of disease progression, they may not require any other treatment other than monitoring. For our lower-risk MDS patients, we certainly want to reduce their need for transfusions and help restore effective blood cell

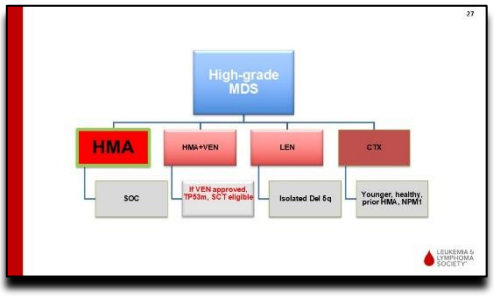
production. For our higher-risk MDS patients and AML patients, we strive to attain a partial or complete remission with allogeneic stem cell transplant and prolonged survival. And, of course, in all of these patients, we want to maximize their quality of life. If patients are having symptomatic anemia, then they should certainly receive supportive care with either blood transfusions or perhaps erythropoietin-stimulating agent.



Slide 26: Polling 3

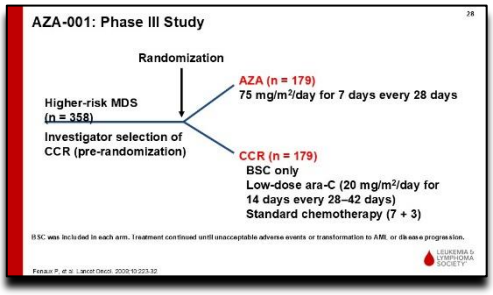
So time for another Polling Question. What are treatment options for high-risk MDS? Is it Option 1, observation and transfusion support only? Option 2, hypomethylating agents or HMAs such as decitabine or, or azacitidine. Option 3, HMAs and allogeneic stem cell transplant or Option 4, HMAs with or without venetoclax, lenalidomide, or allogeneic stem cell transplant?

Okay, and it does look like over half of you did get the answer correct, which is Option #4. So all of those can be treatment options for high-risk MDS. Good job, everybody.



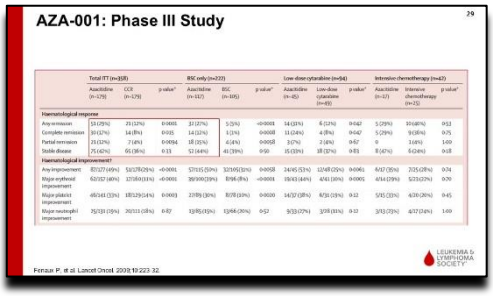
Slide 27: Image

Alright. So, in high-risk MDS, treatment options can include standard of care hypomethylating agents as we discussed in the previous slide, so that would be the decitabine or azacitidine. They can also be used in combination with venetoclax, especially if patients have a TP53 mutation. For patients that have the deletion 5q mutation, lenalidomide can be used. And then in patients who are young and fit and have had prior HMAs or the NPM1 mutation, we can treat with chemotherapy and then perhaps, stem cell transplant.



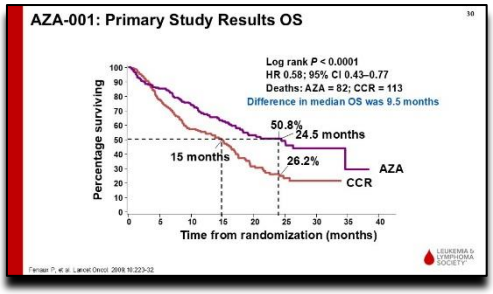
Slide 28: AZA-001: Phase III Study

So, in this landmark study, patients with higher-risk myelodysplastic syndromes were randomly assigned to receive either azacitidine at a dose of 75 milligrams per meter squared per day for seven days at an every-28-day interval versus conventional care, which includes best supportive care, low-dose cytarabine, or intensive chemotherapy as selected by the investigators before randomization. They concluded that treatment with azacitidine increases overall survival in patients with higher-risk myelodysplastic syndromes as compared to conventional care.



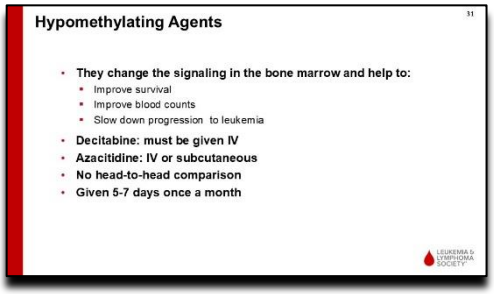
Slide 29: AZA-001: Phase III Study

Here we see that the response rate for azacitidine was 29% and complete remission rate 17%, showing that azacitidine does have efficacy in MDS.



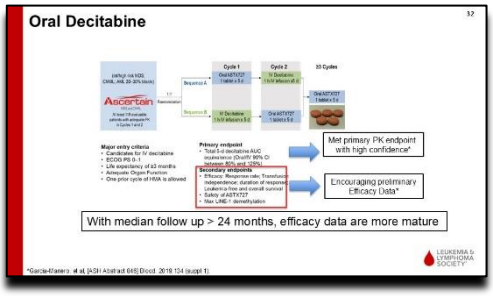
Slide 30: AZA-001: Primary Study Results OS

This slide shows that the overall survival in azacitidine was 24-1/2 months as compared to only 15 months in the conventional care group showing that azacitidine is superior.



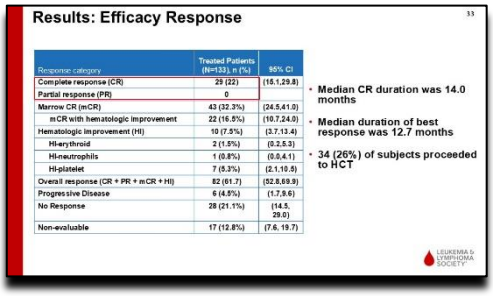
Slide 31: Hypomethylating Agents

So, just a little more about the hypomethylating agents. These work by changing the signaling in the bone marrow. So they can help to improve survival, improve blood counts, slow progression to leukemia. There hasn't been any head-to-head comparison between decitabine and azacitidine. Both are given at once-a-month intervals for five to seven days. The decitabine must be given IV, and the azacitidine can be given IV or subcutaneously.



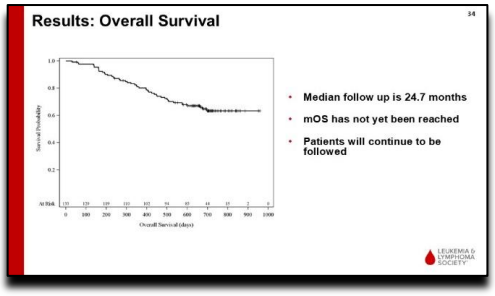
Slide 32: Oral Decitabine

Dr. Al-Kali: We also have an oral formula of decitabine that's FDA approved in myelodysplastic syndrome where intravenous decitabine is approved.



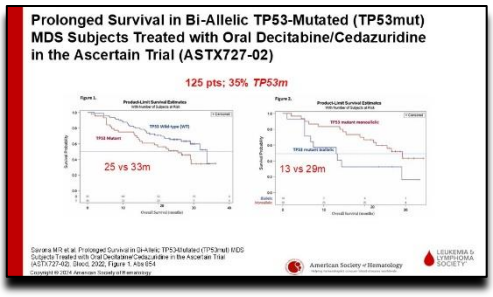
Slide 33: Results: Efficacy Response

In this study, you can see that the complete response rate was 22%.



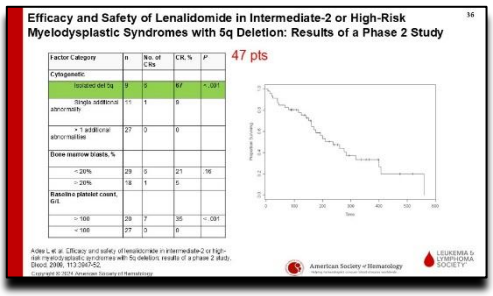
Slide 34: Results: Overall Survival

And if you look at this abstract, you can find that the survival, median survival was not reached even after 24 months of follow-up. So it is a reasonable alternative option for patients with high-grade MDS.



Slide 35: Prolonged Survival in Bi-Allelic TP53-Mutated (TP53mut) MDS Subjects Treated with Oral Decitabine/Cedazuridine in the Ascertain Trial (ASTX727-02)

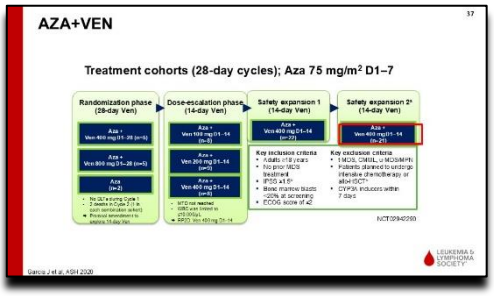
We also did an abstract in patients with p53 mutations, and you can see that there's always worse outcome with the patients in red, which is the p53 mutation versus, in blue, which is a wild type on the left side. On, in Figure 2, you can also see that the patients with two p53 mutation, biallelic p53 mutation in blue, they do worse than patients in red, which is the monoallelic p53, although their survival in our abstract was 13 months, which is a little bit better than historical data.



Slide 36: Efficacy and Safety of Lenalidomide in Intermediate-2 or High-Risk Myelodysplastic Syndromes with 5q Deletion: Results of a Phase 2 Study

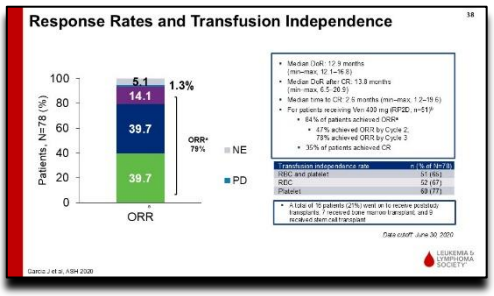
Can we do lenalidomide in these patients? And the answer is in high-grade MDS. We're not talking about low-grade MDS where it's very effective. This is actually the answer from a very small study of 47 patients with chromosome 5q abnormality and increased blast, the intermediate-2 or high-risk MDS. And you can see on the left side in the table in green, if you have isolated del 5q, even though you have high blast, 7, 10%, you actually could respond, and the response is 67%. But this is not true if you have two

or multiple chromosomal abnormality. So it seems like lenalidomide is effective even in higher blast if you have isolated del 5q.



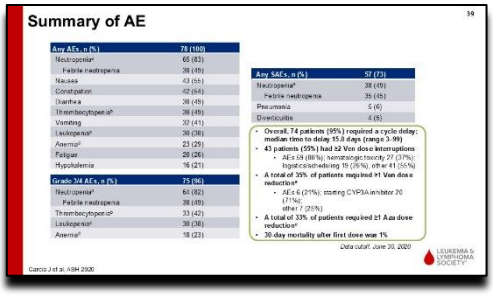
Slide 37: AZA+VEN

Now can we do combination therapy of azacitidine plus venetoclax? And the answer, this is not FDA approved yet in MDS, but it is approved in AML. And we have lots of studies showing that it's a very effective drug combination. In MDS, I need to highlight the importance that it's given for two weeks, not four weeks like we do in acute myeloid leukemia. And the reason for that, it was more toxic in MDS.



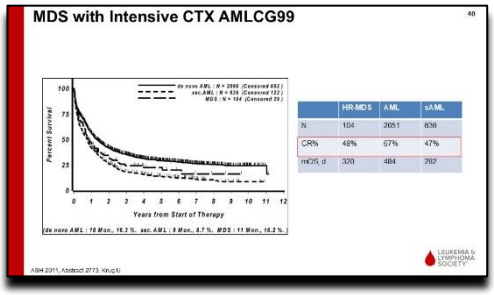
Slide 38: Response Rates and Transfusion Independence

And if you look at the CR rate that we quoted 15 to 20% previously, now is up to 39%. I do want to stress out that this is a Phase I/II study, not a Phase III study, and we're still awaiting the Phase III data. But, if you have a young patient with possible plans to go to transplant, and you're able to get the drug approved for the MDS patient with high blast, high grade, this might be a more powerful treatment option.



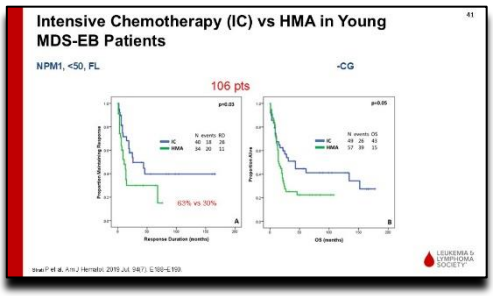
Slide 39: Summary of AE

You need to be careful though. It's much more toxic, especially in the first month of therapy.



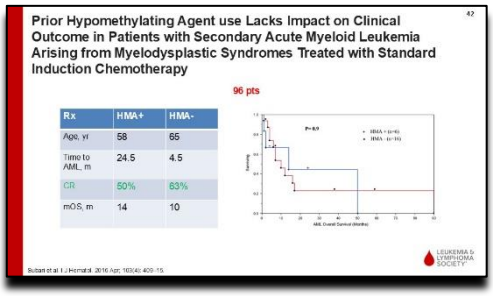
Slide 40: MDS with Intensive CTX AMLCG99

Can we do chemotherapy in patients with MDS? It's very uncommon, but every now and then you'll find a younger patient with a blast, for example, of 15%. And you can say, maybe I should give him an intensive chemotherapy rather than HMA alone where the response rate in HMA is 15% for a complete remission. But as you see in this abstract, the response rate is almost 50% if you give intensive chemo for a young fit patient with high blasts with your intention to take them to transplant.



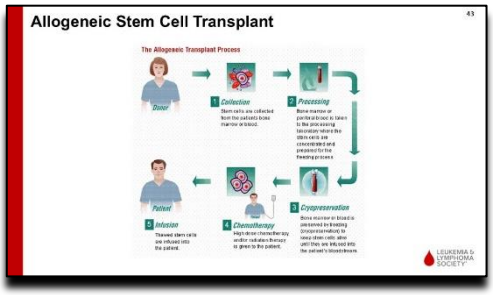
Slide 41: Intensive Chemotherapy (IC) vs HMA in Young MDS-EB Patients

Now, who benefits most from intensive chemo versus just single HMA? Just like I said, young patients in this study, younger than 50. If they have an NPM1 mutation, which they behave like an AML, and if we're giving those as a frontline therapy right at the beginning in diagnosis. Remember, with high blasts. On the other side, do you remember where I talked before? If you have complex karyotypes, that may not really respond nicely to chemotherapy, and HMA or chemotherapy in that population may be just similar.



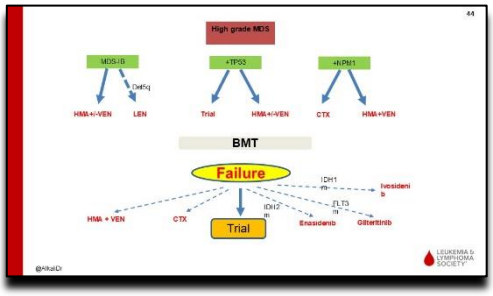
Slide 42: Prior Hypomethylating Agent use Lacks Impact on Clinical Outcome in Patients with Secondary Acute Myeloid Leukemia Arising from Myelodysplastic Syndromes Treated with Standard Induction Chemotherapy

In this paper that we wrote, we also found if we gave chemo for MDS patients who progressed into AML, it didn't matter significantly if you've had prior HMA or not.



Slide 43: Allogeneic Stem Cell Transplant

Jennifer Andres: This slide gives an overview of the allogeneic stem cell transplant process where a patient gets stem cells from a matched related donor such as a relative or a matched unrelated donor from our donor registry, which could be national here in the US or international. Once an appropriate and healthy donor has been identified, they are given filgrastim to help with the mobilization of the stem cells. The stem cells are then collected from the donor, processed, and infused fresh into the donor or cryopreserved for later use. During this time, the MDS or AML patient is receiving chemotherapy and/or radiation therapy to prepare their body to accept these donor cells, which are typically infused via central line.



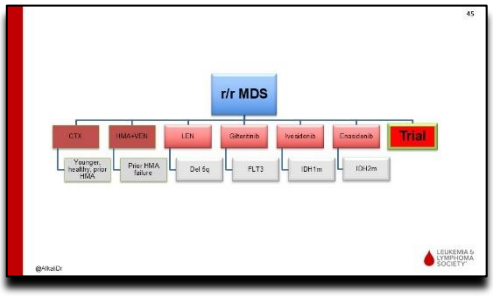
Slide 44: Diagram

Dr. Al-Kali: So, how do I manage high-grade MDS transforming almost into acute leukemia? So, if the MDS, is increased blasts as I mentioned, HMA is the standard of care. If the patient is young, fit, healthy, and I'm able to get venetoclax approved, I could try to give the combo again with a caveat of giving up to 2 weeks of venetoclax only. If they have del 5q with high blast, then lenalidomide is an option. These are just a small minority of patient, probably 1 to 2%.

If you have a patient with TP53 mutation, this is a very tough disease. The current therapy is not great, so we always like to send this patient to a trial, a novel therapy that could improve both response, CR duration, and survival. However, if a trial is not an option, then HMA would be the standard of care; and you can try to see if you can add venetoclax if approved for this patient.

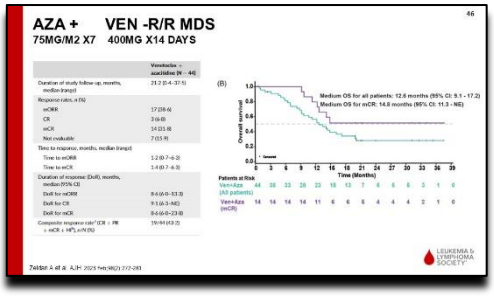
There's a small population of patients, again, about 2 to 3%, where they have the NPM1 mutation, and they still have a blast of 18 or 17%. If you remember, this is defining of AML, although by blast percentage, it's less than 20%. There is now good data that chemotherapy or HMA plus venetoclax, if approved, both are very effective with a very high response rate. So if the patient is a bit young, I'll go with the chemotherapy. If the patient is older and frail, I will probably try to get HMA plus venetoclax. And you can use the definition of AML based on the NPM1 to use the venetoclax in this case. If they go to remission, this is a high-grade MDS. You need to send them to the stem cell transplant if they are young and fit, although there is no specific age as a cutoff for stem cell transplant.

On the other side, if they fail transplant or their current therapy, then we are in trouble. Relapsed/refractory MDS is a trouble. We always recommend trial for those patients. But if a trial is not available, we can do chemo if they're younger, although the data with chemo is better as a frontline therapy rather than a second- or third-line therapy. We can do HMA plus venetoclax if they have not achieved venetoclax. If they have IDH1 mutation, you can do ivosidenib. It's now FDA approved in patients with MDS who failed frontline therapy. Or, if you have other markers like IDH2 or FLT3, you can see if the insurance will approve those patients for targeted therapy like gilteritinib for FLT3 and enasidenib for IDH2. But those are approved for relapsed AML, not MDS.



Slide 45: Diagram

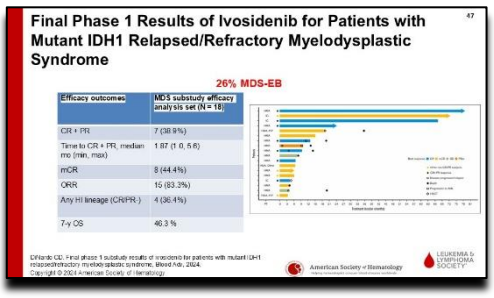
Jennifer Andres: And so just to review what Dr. Al-Kali mentioned for relapsed/refractory MDS, these are the different treatment options that we can provide for our patients. So, again, in our younger healthy patients who have had prior azacitidine or decitabine, we can utilize chemotherapy. We could also utilize the HMAs plus venetoclax. In patients that have the del 5q, we can utilize lenalidomide. And then we have our targeted oral therapies. So if they have that FLT3 mutation, they can utilize the gilteritinib. If they have an IDH1 mutation, they can utilize the ivosidenib. IDH2 mutations, they can utilize the enasidenib. And then, of course, if there is a clinical trial option, we can certainly refer the patients there.



Slide 46: AZA + VEN -r/r MDS

Dr. Al-Kali: Thank you. I do want to share now the data of HMA plus venetoclax in the relapsed/refractory MDS. And the take-home message is that this great regimen as a frontline therapy is not as great when the patient has been exposed to HMA already. So, if you look in this slide where they treated patients who relapsed from HMA with AZA plus venetoclax, and as I said, the bend is only for 14 days, the CR rate is only 6.8%. This was 40% as a frontline therapy. So, the problem with this regimen, it causes more of marrow CR, basically drop of the blast, but not much of counts recovery. You can see here that the marrow CR was 30% in this population.

On the other side, if you think you have a transplant option and you're trying to bring the blast down to debulk the disease, it may not be a bad option. The outcome of those patients, still not that great if you look at their survival for those patients.

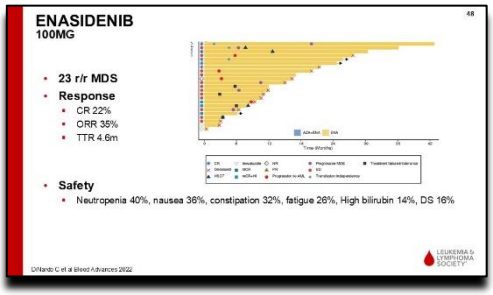


Slide 47: Final Phase 1 Results of Ivosidenib for Patients with Mutant IDH1 Relapsed/Refractory Myelodysplastic Syndrome

As Jennifer talked about, we do have now ivosidenib approved in patients with relapsed/refractory MDS with IDH1 mutation. And if you look at the CR and PR rate, it's almost 40%. So this is an active option, but you need to know the molecular signature of your case. And remember that some mutations may not be present at diagnosis but could be present later on at relapse or progression.

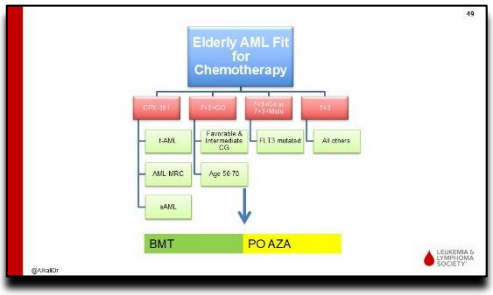
You can see that another 40% had marrow CR, and the overall response rate is 83% in this population. You need to be careful for the possibility of differentiation syndrome, anywhere between 10 to 20%, depending on which paper you read at. Those patients may also have mild-to-moderate elevation of their bilirubin. You just need to be watching that and observing it. It doesn't really need to be holding the therapy. On the differentiation syndrome, you need to be very careful – having fevers, pulmonary infiltrates, hypoxia, kidney or creatinine elevation, edema, weight gain, all of this concerning that you might be dealing with differentiation syndrome; and you may need to give dexamethasone for these patients, and you may also need to hold the treatment if the case is very severe.

If you notice in this picture, some of the patients on the right, some of the patients who actually responded to therapy responded for several years. And this is something unique about IDH1 and IDH2. There is some patient who would actually respond and respond for a long time, although we're not yet sure who those patients who have this nice and prolonged response even in the relapsed/refractory setting.



Slide 48: Enasidenib

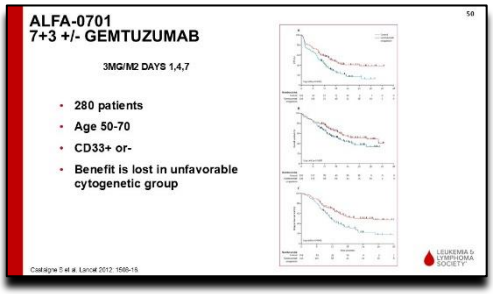
Enasidenib is not FDA approved in MDS, but it is approved in relapsed/refractory AML with IDH2 mutation. You can see even in the relapsed/refractory setting, the response rate was 22% with an overall response rate of 35%. This drug also could cause elevation of the bilirubin, as I mentioned, and could cause differentiation syndrome. So for those, both drugs, enasidenib and ivosidenib, you need to be careful about these toxicities. You also need to be patient. They don't respond right away. As a single agent, it takes several months for that patient to respond.



Slide 49: Diagram

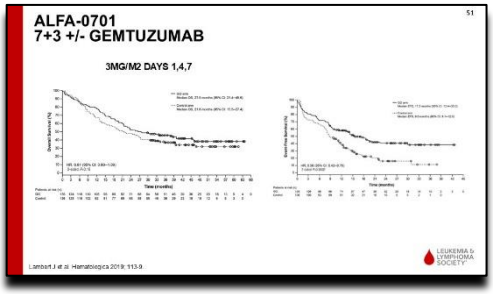
So how about if the patient already progressed to classical AML with a blast above 20%? We want to show here some of the data, not all the data. We want to focus on a few trials that may be important in this population. So a patient who has MDS and then progressed to AML and they have secondary mutations or they have cytogenic abnormalities, t-AML or AML-MRC, CPX-351, which is liposomal cytarabine and daunorubicin, is an excellent option in those patients. Or, if they have favorable chromosomal abnormality, 7+3, classical cytarabine and idarubicin or daunorubicin plus gemtuzumab may be a great option for them. All other patients, they usually get 7+3. And if you have a FLT3 mutation, you could consider gilteritinib or midostaurin.

If you go to remission in this population, then you should consider transplant unless you have a favorable AML. If transplant is not an option, and this is not favorable AML, oral azacitidine is FDA approved for patients with AML who were induced with chemotherapy and were given up to two cycles of consolidation which showed survival advantage.



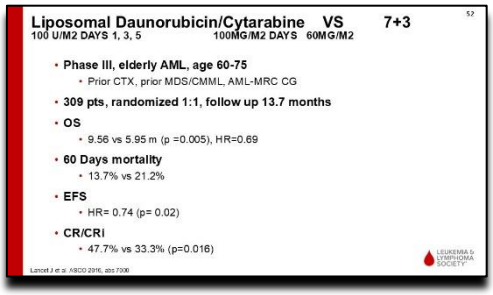
Slide 50: ALFA-0701 7+3 +/- Gemtuzumab

I'm going to focus on the two trials, which is basically adding gemtuzumab to 7+3. And you can see that those patients who got gemtuzumab plus 7+3 compared to 7+3 did well. The benefit was mainly in the favorable and the intermediate. However, for the unfavorable cytogenetic group, that benefit was not seen.



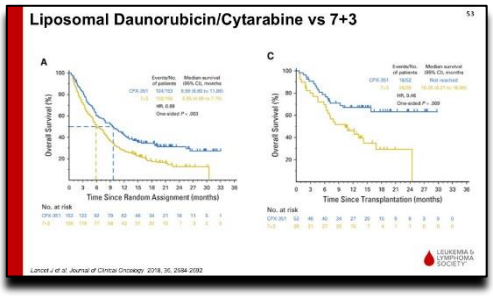
Slide 51: ALFA-0701 7+3 +/- Gemtuzumab

On the follow-up publication of the same study, the survival benefit, the overall survival benefit was lost, but the event-free survival benefit was still maintained. If you look now at the guidelines, it is recommended in patients with favorable cytogenetic abnormalities and fit for intensive chemotherapy.



Slide 52: Liposomal Daunorubicin/Cytarabine vs 7+3

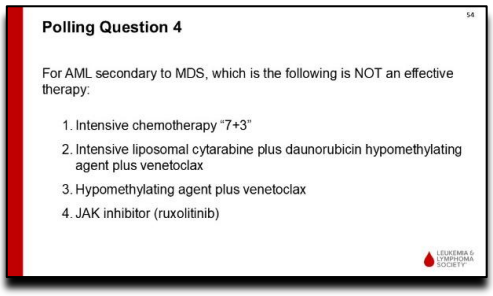
How about liposomal daunorubicin and cytarabine? This is a landmark Phase III study where patients between the age of 60 to 75, and they are either considered to be t-AML, therapy-related AML, or secondary AML, or they have chromosomal/mutation abnormality that's consistent with AML with MRC. Those patients were randomized to 7+3 versus liposomal chemotherapy. And you can see that the liposomal chemotherapy wins. In terms of the CR/CRI, it was 47% compared to 33% in patients with AML between the age of 60 to 75.



Slide 53: Liposomal Daunorubicin/Cytarabine vs 7+3

And if you look at that survival there, it was even much more pronounced in the patients who went to transplant in Figure C. You can see that since transplant, the blue line is the patient who got liposomal daunorubicin, while the yellow line is the patient, is the patients who had 7+3. So that means

it's not just the remission. Even the patient who went to transplant from either arm, the liposomal intensive chemotherapy patients did well.

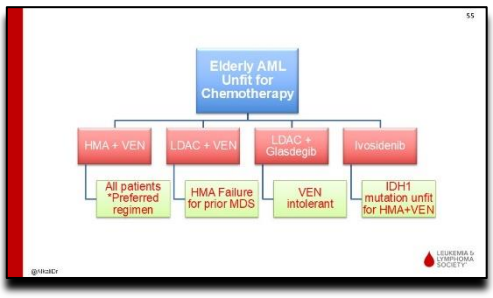


Slide 54: Polling 4

So, I'm going to move now to our Polling Question #4, and this is our last question. For AML second day to MDS, which is, of the following, is not an effective therapy? So, for secondary AML from MDS, which is not effective therapy? Intensive chemotherapy, like 7+3, intensive liposomal cytarabine plus daunorubicin, hypomethylating agent plus venetoclax, or option number four, which is JAK inhibitor, for example, ruxolitinib?

This question is meant for everybody to know the options that you can share with your patients depending on the appropriate setting, the patient fitness for intensive versus nonintensive therapy, and sometimes the patient will in terms of being hospitalized versus not having prolonged hospitalization.

And I agree with the answers. A JAK inhibitor in AML secondary to MDS has not, does not have a role for those patients. So I think of 7/3 if the patient is fit for chemotherapy, no comorbidities. I think of liposomal cytarabine plus daunorubicin if the patient has secondary AML from MDS, age between 60 to 75, and fit for chemotherapy. Potentially looking for a transplant as the data is very robust in the transplant cohort. I think of hypomethylating agent plus venetoclax, which is approved in AML in patients who are not fit for intensive chemotherapy. So all first three options would be correct, but not JAK inhibitor.

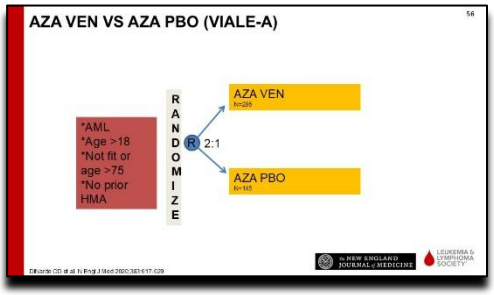


Slide 55: Diagram

So, when I look at the current schema for me treating elderly AML unfit for intensive therapy, I do think that HMA plus venetoclax, which is FDA approved in this cohort, is appropriate for almost every patient. It is now the most commonly used regimen that we do. You can use azacitidine or decitabine, although the major Phase III trials used azacitidine.

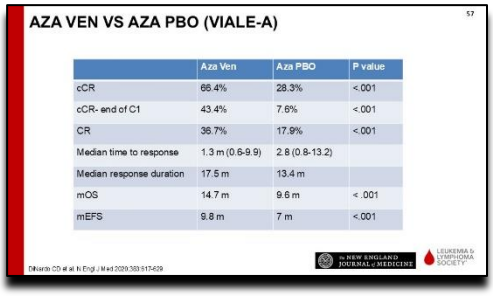
On the other side, you can also use low-dose Ara-C/venetoclax. The response rate in that paper was less, but the reason for that is a third of the patients had prior HMA. So, if you've had HMA for MDS and you progressed to AML, I think either option one or two in this case, the ven-based regimen with HMA or low-dose Ara-C would be reasonable in that case.

I do want to mention that low-dose Ara-C plus glasdegib is approved for patients with elderly AML, unfit for chemotherapy, but the response rate and survival numbers seem to be less compared to the HMA plus venetoclax data. So we've used it in case we have a patient, has a venetoclax intolerance for whatever reason. And remember that ivosidenib is approved for IDH1-mutated frontline AML.



Slide 56: AZA VEN vs AZA PBO (VIALE-A)

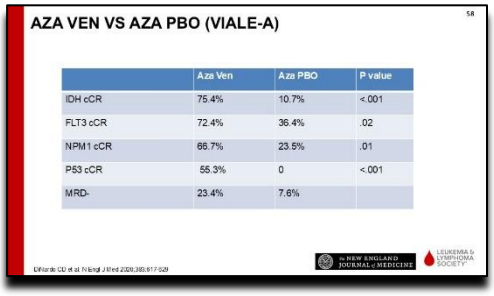
This is based on the landmark Phase III trial, which is the VIALE-A. These were AML patients, older, not fit for intensive chemotherapy. They did not have prior HMA exposure, which again explains the data behind low-dose Ara-C plus venetoclax. And they were randomized in a 2:1 fashion for aza alone or aza plus venetoclax. Please note again the venin this case is given for four weeks because we are treating an AML case.



	Aza Ven	Aza PBO	P value
cCR	66.4%	28.3%	<.001
cCR- end of C1	43.4%	7.6%	<.001
CR	36.7%	17.9%	<.001
Median time to response	1.3 m (0.6-9.9)	2.8 (0.8-13.2)	
Median response duration	17.5 m	13.4 m	
mOS	14.7 m	9.6 m	<.001
mEFS	9.8 m	7 m	<.001

Slide 57: AZA VEN vs AZA PBO (VIALE-A)

And if you look at the response rate, HMA ven, aza-ven beats aza alone in almost every category. So, the response rate is higher, the median time to response is faster, and the median overall survivor is actually better. And the story's almost complete.

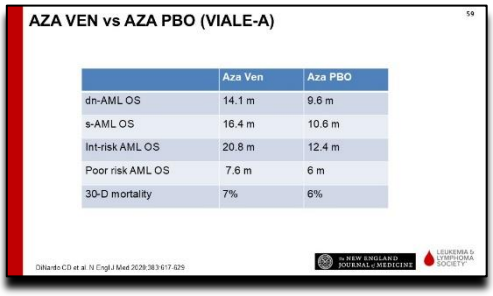


	Aza Ven	Aza PBO	P value
IDH cCR	75.4%	10.7%	<.001
FLT3 cCR	72.4%	36.4%	.02
NPM1 cCR	66.7%	23.5%	.01
P53 cCR	55.3%	0	<.001
MRD-	23.4%	7.6%	

Slide 58: AZA VEN vs AZA PBO (VIALE-A)

But if you look at the next slide, there are a couple of groups that may give us a trouble. For example, patients with p53, they do respond better with HMA ven than HMA alone, but the survival is almost identical to aza alone. So, you get more responses, but the disease relapse. And that's why p53 disease continues to be a trouble. We think of this that it's a bridge to transplant. So as long as I get more response and I can get my patients to stem cell transplant, I'd like to use the combination, knowing that on its own may not improve survival.

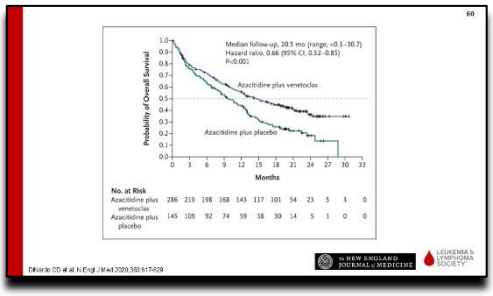
Also, FLT3, they will actually relapse more commonly. On the other side, if you have IDH1 or 2 or NPM1, and you look at the response rate, it's about 60 to 70%. The composite CR is actually very high. Those patient tend to do the best with HMA ven.



Slide 59: AZA VEN vs AZA PBO (VIALE-A)

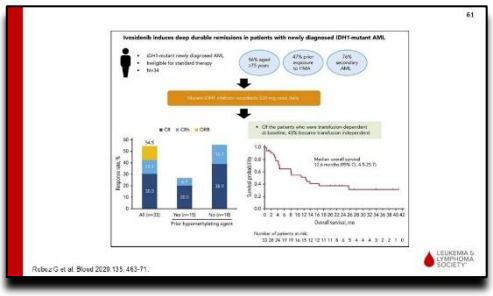
So do I restrict my patients to HMA, ven, and AML in any group? The answer is no. I just do tell my patients if they have complex karyotype, full-risk AML, their outcome is not as good. You can see here, full-risk AML, the survival is 7.6 months in the combination arm and 6 months in the aza arm. So, they don't do well in this group even though the response rate is better. And if you think is the mortality higher, not that much, but you need to be careful on those patients. The level of neutropenia and cytopenia is significant.

A lot of times, we start those patients in the hospital for five to seven days; and if they're stable and fit, they can then leave the hospital to be monitored on a daily or every other day, especially for their counts, transfusion needs. The first month is essential in managing those patients.



Slide 60: Graph

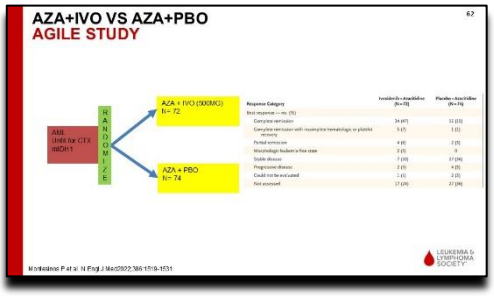
And if you look at the survival for all-comers, you can see that the azacitidine plus venetoclax did much better in terms of survival compared to the azacitidine alone. So, response is better, and then survival is improved.



Slide 61: Diagram

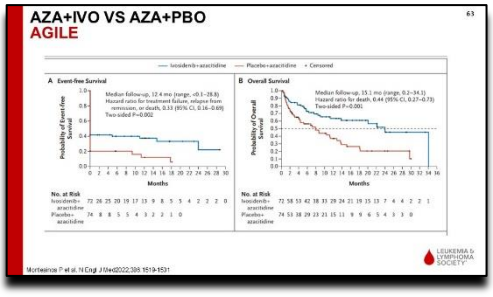
But you can also have the option of single-agent ivosidenib. It's FDA approved as a frontline therapy in IDH1-mutated AML with a good response rate. The CR rate in this population is about 30%, and the overall response rate is about 50%.

So, who would I give IDH1 single agent? Probably, if I have a, a patient who's not even fit for the combination therapy, they have the IDH1 mutation, I could consider definitely giving ivosidenib single agent. The problem with this, it will take few months for the response to happen. You also need to wait if you can and you're not in a rush on the gene results. There was a study showing that the gene results usually come within 7 to 14 days, and it was really used to change the treatment decision. So, if you think you can wait for a few days to get the gene results, it may have an impact on your patient treatment and on the patient options for therapy.



Slide 62: AZA+IVO vs AZA+PBO AGILE Study

Now, could you give the same drug, ivosidenib plus azacitidine? This is based on the AGILE study. And you can see it was a randomized study in patients with mutated IDH1 unfit for chemo, and in this case, they gave either aza alone or aza + ivosidenib. The complete remission has gone up from 30% as in the previous slide to 50%. So, this shows you that HMA + is a, HMA + ivosidenib is also another powerful option.



Slide 63: AZA+IVO vs AZA+PBO AGILE

And you can see that in this population, patients who were treated with the combination did better in terms of event-free survival and also overall survival. And you can see a lot of those patients, they could actually last for years on the combination therapy, especially about 20%, 25% of the patients. They can have a prolonged response.

Slide 64: Thank You

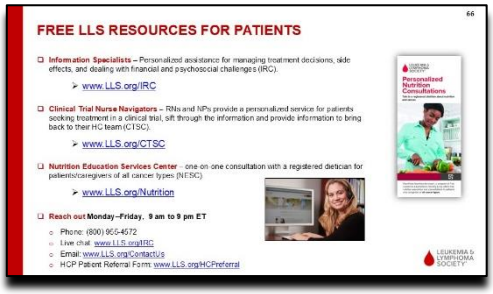
With that, I would like to conclude my presentation.

Lesley Hoerst: Thank you, Dr. Al-Kali and Miss Andres, for your very informative and comprehensive presentations.

Slide 65: Free LLS Resources for Healthcare Professionals

I am now pleased to share free resources from The Leukemia & Lymphoma Society for you and your patients.

The Leukemia & Lymphoma Society offers free CE and CME online courses as well as a podcast channel where you can listen to healthcare professionals discuss treatment, side effect management, and strategies to support your patients. New and interesting topics are added every few weeks. To access these, as well as our videos, fact sheets, and fact sheets on a variety of topics, please visit LLS.org/CE.

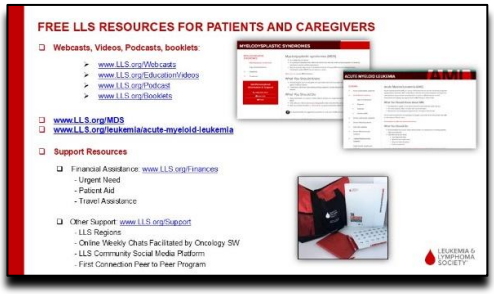


Slide 66: Free LLS Resources for Patients

The Leukemia & Lymphoma Society Information Specialists are highly trained oncology social workers and nurses who provide accurate, up-to-date disease treatment and support information, including financial information. Patients can contact them directly, or you can complete a referral form. Information Specialists can also help you access or order multiple free copies of booklets to give to your patients. Our Clinical Trial Support Center Nurse Navigators are registered nurses and nurse practitioners with expertise in blood cancers. They work one on one with patients via telephone to provide user friendly information, help find appropriate clinical trials, personally assist them through the clinical trial process, and provide information for the patient to go back to their healthcare provider.

This is a unique service from LLS. The goal is not to enroll every patient into a clinical trial, but rather to provide information, understanding, and options.
For information or to refer and connect a patient with an Information Specialist or Nurse Navigator, use the URLs listed here. We encourage healthcare professionals to refer your patients to LLS within the first 90 days of diagnosis.

Refer your patients for a free one-on-one nutrition consultation with one of our registered dietitians through The Leukemia & Lymphoma Society's Nutrition Education Services Center. Consultations are by phone, available for patients of all cancer types and all ages, and are available in many languages using our interpretation services.
I hope you will consider all of these specialists as an extension of your healthcare team.



Slide 67: Free LLS Resources for Patients and Caregivers

LLS offers blood cancer disease-specific information and support resources for patients and caregivers, including telephone and web education programs, videos, podcasts, and booklets.

You may know about LLS's financial assistance programs, and I encourage you to stay up to date on the availability of funds as well as additional support resources using the links on this slide.

Slide 68: Free LLS Resources for Your Patients

Here are some examples of booklets and informational cards you can order from LLS at no charge to give to your patients, or they can access them on the LLS website. Also available are LLS survivorship workbooks. If you have any questions on any of the LLS resources, please contact an Information Specialist.

Slide 69: Questions

It is now time for the Question & Answer portion of the program. Okay. So we will take the first question. The first question was what about a case with 5% blasts and NPM1 mutation? Would it be considered an AML?

Dr. Al-Kali: I'll take that. It's a tricky one. It does exist. Per current recommendations, this is not considered AML. However, we do know that some of this does exist. The question would become then, what is the VAF, which is the allele frequency of the NPM1? Are we talking about a 5 to 10% NPM1? So it's a very small mutation, or is this truly at 30 to 40%? Number two, it would be how the counts are doing? Are the counts so, almost intact? Some cytopenia? Then we, in those cases, actually, what we have done, we repeated a bone marrow biopsy after four to eight weeks and then saw what happened with the blast. In the cases that the blast went up from 5 to 10 or 12%, then this is basically evolving AML. In the cases that the blast, for example, was 5 to 6 or 7%, we treated those as MDS; and we shied away from chemo and rather did HMA +/- venetoclax. If the blast are 5 or less, may not need that much of ven. But if the blast is above 5%, I would definitely consider adding venetoclax. The data has been very interesting in the combination therapy, regardless whether the blasts were 10% or 30% when you combine venetoclax + HMA.

Lesley Hoerst: Okay. Our next question is are MDS or AML hereditary?

Dr. Al-Kali: Usually, about 5 to 10% of myeloid neoplasm MDS and AML can be inherited. There's disagreement on that number – maybe 5% in some papers, maybe 15 to 20% in other papers. That question's excellent. Sometimes the gene sequencing, the NGS that we use, could tell us, "Careful, this could be a germline case." For example, DDX41. For example, GATA2. Other examples, RUNX1 as a sole mutation in those cases or RUNX1 with a BCOR. It makes you think that this could be actually inherited disorder. But you do have also other cases that you may not get a common mutation to be considered a germline. There, there are specialized clinics in the country for germline workup, and you should consider that if you see, for example, a first-degree relative with MDS and AML. It's

extremely uncommon to see an MDS and then a sister, or a parent has also MDS or AML. Those patients, even if they don't have a classic germline mutation, we send them to those specialty clinics because they could find other rare mutations to explain the possibility of germline.

Lesley Hoerst: Our next question is can a person have MDS for years without knowing they have it? If so, why might a patient remain unaware of their condition despite regular doctors' visits and blood tests?

Dr. Al-Kali: That is an excellent question. In general, MDS tends to be a disease that progresses within few months. Meaning, once the cytopenia, the low blood counts happen, within a year or two, they usually become much more symptomatic. Some patients, especially the high risk, if you have a RUNX1 mutation, an IDH1 as Jennifer mentioned in her slide, those will progress fast, within months into AML. But on the other side, if you remember the slide that talks about the SF3B1 mutation, those patients can have actually MDS for years. And the way you know it, you'll find abnormal MCV, and then they have mild hemoglobin drop. And it's been two or three, four years. They're not feeling different, but there is cytopenia for years. In fact, if I see a patient who comes to me in referral and I see there is cytopenia, low hemoglobin – 11, 11.5, 10.5 – for three, five years, I can guess right away that this is likely SF3B1-mutated because it's indolent, and it does not progress. So the answer is yes, not common, but possible.

Jennifer Andres: I will say that we do sometimes see patients like this in clinic who will come to us for a consult. And some patients, because they're feeling well, their blood counts look good, they actually defer a bone marrow transplant. So they may go several years, and we may just be following them for this high MCV, slight anemia, and they, for a variety of reasons, will defer the bone marrow biopsy, so we don't have that official diagnosis.

Lesley Hoerst: Okay. The next question is severity of anemia considered as a prognostic factor for progression from MDS to AML?

Jennifer Andres: So, certainly, the hemoglobin is one of the factors that does get put into that calculator. So, the lower the anemia, the higher their potential for progressing to AML.

Dr. Al-Kali: If I may add also, one thing that's very important to practice is do not assume that anemia is always MDS. We've diagnosed a couple cases of colon cancer in MDS patients. So, the drop of the hemoglobin may actually be driven by another cause. And exactly the MCV that Jen talked about when it drops rather than goes up with MDS, it makes us concerned that they may have iron deficiency. We diagnose the iron deficiency, and then we look for a colon cancer, and we can find it.
So that's a great question. But one caveat in your practice, be careful that not to assume that every drop of the hemoglobin is MDS progression. It could be something else.

Lesley Hoerst: And we'll take one final question. Is there a way to prevent MDS from developing into AML?

Dr. Al-Kali: That's also an excellent question. So, cancer interception is now a new area of interest. So that can happen in MDS. That can happen actually in pre-MDS, so, the new entity called CCUS or clonal cytopenia of unknown significance. So there are some trials right now to see can we control the disease early and prevent even progression into a frank MDS and acute leukemia?

Now number two, if you do have a higher grade MDS you are treated, and you responded, you actually are preventing the acute leukemia. But are you going to cure the disease with simple therapy? The answer as of today is possibly no, at least as of the current data. There's a question about that in some areas of interest, especially in the NPM1, IDH1, IDH2 area in the AML area. But short of a transplant, I cannot find an easy answer to say that we can prevent MDS from becoming AML if it was going to happen.

Slide 70: Thank You

Lesley Hoerst: Thank you to the audience for all of your questions.

Again, thank you, Dr. Al-Kali and Miss Andres, for your continued dedication to patients and fellow healthcare professionals. This concludes our program. Thank you all for participating. We hope the information presented will be useful in your work with patients and families. We look forward to your participation on future LLS programs.