ManagingAML

Breaking New Ground in AML: Practical Applications of Emerging Treatment Options

Guillermo Garcia-Manero, MD
Professor
Chief, Section of Myelodysplastic Syndromes
Deputy Chair, Translational Research
Department of Leukemia
Division of Cancer Medicine
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Jeffrey E. Lancet, MD
Department Chair
Malignant Hematology
Moffitt Cancer Center
Tampa, Florida

Elli Papaemmanuil, PhD
Associate Director
Center of Hematological Malignancies
Computational Oncology Service
Department of Epidemiology and Biostatistics
Memorial Sloan Kettering Cancer Center
New York, New York

Richard Stone, MD
Professor of Medicine
Harvard Medical School
Chief of Staff
Director, Adult Acute Leukemia Program
Dana-Farber Cancer Institute
Boston, Massachusetts

Dr. Guillermo Garcia-Manero:
I am Guillermo Garcia-Manero from MD Anderson in Houston, and I am very happy to be here chairing this, what I think is going to be a very interesting symposium. We have a really incredible group of speakers, and we want to do this actually quite educational, maybe with an objective to practice in medical oncology that may or may not see a lot of leukemia. So, we are going to have some cases before the talks and then at the end. So, I think this is going to be hopefully quite informative for all of you. So, let me first introduce the speakers, so again I am Guillermo Garcia-Manero from Houston. We have at the end of the table Dr. Jeff Lancet who is the Chair of Malignant Hematology at the Moffitt Cancer Center and a world leader in developmental therapeutics in leukemia. Next, we have Dr. Stone who is the Chief of Staff at the Dana Farber Cancer Center and one of the leading acute leukemia investigators in the world, and closer to me, Dr. Elli Papaemmanuil who is actually one of the leaders in molecular genomics in leukemia, he has done some seminal work in MDS and AML, so I think this is really an excellent panel of speakers.

This is the agenda. We are just a few minutes behind. So, we are going to start with a little bit of an introduction by me. Then, Dr. Papaemmanuil is going to talk about the molecular structure of acute myelogenous leukemia. I think this is extremely relevant to what our practice is going to be in the years to come. This will be followed by a talk by Dr. Stone where he is going to review current treatment strategies in AML, basically the standard of care followed actually by Dr. Jeff Lancet who is going to talk about new therapies and I think what is coming, and that is going to be a quite transformative, and then, we are going to close this talk if we have time with six or seven clinical cases that actually are true cases that I saw a month ago when I was in the inpatient service and see if we can put all the stories together. Hopefully, we will have enough time for some questions and discussions among ourselves because maybe whatever I think about my cases is not the standard, so we will figure it out, and we will adjourn at that time.

First of all, let me disclaim that there was no interaction between us and any of the sponsors that are supporting this event. They gave us an idea and opportunity, and we built it without any interference or collusion as they say now with any of the sponsors, but we have to thank Agios Pharmaceuticals, Astellas, Celgene, Helsinn, Incyte Corporation, and Jazz Pharmaceuticals. So, they are the people developing compounds in AML, and we are grateful for their support.

And with that, it is actually my really distinct honor to introduce Dr. Papaemmanuil. I first met her, I do not know if you remember this, in Edinboro when she was presenting really seminal data on splicing mutations, and she is now really a world leader on genomic annotation in MDS and AML, so we are very happy to have you here.

Dr. Elli Papaemmanuil:
That is an extremely generous and kind introduction. It is real honor to be here tonight and certainly put into context some of our recent findings in terms of what we are learning from molecular characterization of patients with AML and how we can slowly start to interpret them and most importantly translate them into clinical practice. So, I need to learn how to use this first. So, this is what I am going to touch on today, and it very much stems on the concept that the cancer genome and the mutations found in the tumor of every patient essentially dictates the tumor's biology and that in turn determines the clinical presentation and the overall clinical course and treatment response of the disease, and this is very much the premise upon which now that benchtop molecular profiling technologies in the clinic are becoming more and more routine across the world. We want to set up a platform upon which we can learn from those mutations and deliver treatment decisions that are tailored to the individual patient, and one of the promises comes from early successes in leukemia where we assume that we are going to identify the one mutation in a patient for which we are going to have the one drug for which we will be able to treat them and ultimately cure them. But we know that this narrative is much more complicated because cancer is never the consequence of one mutation, but most importantly, every cancer patient or leukemia patient at presentation has had a natural history that has resulted from an early initiating event that led to a first clonal expansion and mutation that is present in older cells and that one cooperates with additional events, secondary and tertiary events that ultimately dictate disease progression, clonal diversification, treatment response, and ultimately treatment resistance.

So, how does that lie together? Now that we are completing cancer genome sequencing profiling across most tumor types, we learn that most patients have three or five main driver mutations that they can be present in different subsets of the cells, some in older cells, some in smaller subsets of the cells. So, how would that tie in and translate with the precision medicine paradigm that we are envisioning or dreaming of where we are hoping to have the one mutation that we will treat. And bringing this into context of the clinical challenges that we are facing now in AML, AML treatment has not significantly changed over the past decade, although we are now seeing a significant surge of potential therapeutic options. It is an aggressive disease, and in standard of care, we use standard demographic and bone marrow morphology and peripheral blood counts. We are more recently tying this with karyotype data to make specific clinical decisions. It is an acute disease. We need to treat fast, and we need to consider how what we are learning and how quickly we can deliver molecular profiling data can be incorporated within clinical practice. So, the early characterization of the genomic profiles of AML have been instrumental in supporting those decisions, and this has happened from the early identification

of cytogenetic abnormalities that were recurrent, and one thing that was very specific about the cytogenetic abnormalities that they are most frequently mutually exclusive. They separate AML patients into distinct groups, and we have learned over the years that these cytogenetic subgroups also segregate with very distinct clinical outcomes, and these have enabled, over the years, refinement of both diagnostic classification and prognostication algorithms that define patients into favorable or adverse or unknown risk categories upon which we can base clinical decisions such as where do we need to intensify chemotherapy, who do we need to transplant at first CR, who do we need to transplant post relapse. These have been very much the mainstay of both diagnosing and prognosing patients, supporting clinical decisions along the way, and we have also seen the characterization of those molecular abnormalities resulting into very effective therapeutic intervention protocols. The delineation through a combination of parameters of these patients into risk groups has been very successful in one part, but on the other hand, it has been also challenging because variable clinical response, as you see here, we have separated patients between the four previous risk categories in AML and we looked how the top performers within each category perform, and you can see that the worst performers within the favorable group do pretty much as bad as patients that fall within the adverse risk group. So, while we are refining molecular risk groups to support these clinical decisions, we know that there is a lot more work that needs to be done. We have patients with favorable risk performing really well, and others that do very poorly.

So, how can we refine and improve this characterization of those patients so that we can deliver the best treatment decisions for those? So, this is a summary of how the clinical picture of AML looks. These are patients from three clinical trials from the AML-SG group in Europe, and we started with 1540 patients and you see that just over 1200 patients will achieve complete remission, but then 600 of those patients will relapse, and only 140 patients would be salvaged after relapse. How then we take each one of the risk groups and try and determine specific patients route along those different stages of the disease can be quite challenging, and also how with emerging new therapeutics we can put this into context. So, particularly, more recently, we have uncovered many more molecular alterations that through the TCGA effort there were 200 recurrently mutated genes in AML, and one thing that was immediately noticeable in this case is that contrary to the cytogenetic abnormalities, which you see on the left of the panel which are mutually exclusive, patients with gene mutations tend to have a lot of those gene mutations. These mutations like to hang out together. We are not defining discrete and non-overlapping molecular subgroups, and they seem to affect a number of pathways that implicate both transcriptional regulation, epigenetic modifiers, chromatin regulators, and more recently, the spliceosome machinery. So, a lot of new pathways that were previously unrecognized in cancer are becoming the mainstay of the interest of their abnormalities in AML and how we can incorporate them into both diagnostic prognostication, most importantly therapeutic protocols, is with this complexity and heterogeneities becoming increasingly complex. So, we have more than 100 recurrently mutated genes, many genes per patients, and also very diverse prognostic relationships emerging from each one of those genes. So, quite a lot of the work that we have been doing over the past years is to take large population studies and try and uniformly profile patients with treatment and clinical outcome annotations to try and understand what are the genomic interrelationships that define the backbone of AML, and most importantly how we can then learn from them to try and build clinical algorithms both for diagnoses as well as clinical decisions.

So, we have recently taken those 1540 patients for which we had cytogenetic data, peripheral blood counts, clinical outcome, treatment data, and we performed deep targeted resequencing for the 100 or so most frequently mutated genes in AML. These let us identify 5234 mutations. What is quite critical here is that for a disease that is predominantly stratified on the basis of cytogenetic abnormalities, mutations in genes are accounted for 75% of the overall mutation burden seen in AML patients. What we saw was cytogenetic abnormalities also accounted for just over 50% of the patients. We found at least one abnormality, one in 97% of the cases and two or more in 86% of the cases, and this suggests that we now have at least one if not more biomarkers for pretty much every patient that comes in to the clinic. So, how can we use this information? We performed a statistical and supervised analysis to see whether these gene mutations, if we consider secondary and tertiary genetic groups interactions, segregate distinct and non-overlapping groups. Remember, the TCGA study of 200 or so cases could not really delineate distinct molecular groups. There was a very heterogenous landscape, but with the analysis of 1540 patients, we have significantly more power to study both patterns of cooperativity as well as mutual exclusivity. This led us to characterize 11 non-overlapping molecular subgroups. We validated many of the previous and very well-recognized cytogenetic groups. We validated two provisional categories, one AML defined by NPM1 mutations as well as C/EBP alpha balletic mutations, but most importantly, our analysis identified three distinct molecular subgroups. One which overlaps very much with one of complex karyotype or monosomies, but here it includes in general chromosomal aneuploidies and TP53 mutations which was a very distinct group. The second which in fact was the second largest group in AML was characterized by mutations in the chromatin and spliceosome machinery, and another group defined by IDH2 mutations in a particular codon. This has now been validated in an extra set of 3000 AML patients from the UK MRC trials. Here I present to you the 11 groups where every column represents a patient and every row represents one of the lesions. The advantage of next-generation sequencing data is that we can use very intelligent fraction matrix to estimate the proportion of cells that carry each one of those mutations. If you remember the early map that I showed of the first, second cooperative events that lead to disease overall in cancer, we were able to ask, can we see similar patterns in AML? Within those groups, can we identify which gene is mutated first, which mutation comes second, and which mutations come third? And quite strikingly, what we saw here is that amongst 1540 patients, we identified 1060 distinct genotypes, but those 1060 distinct genotypes segregate in 11 common themes, those 11 molecular subgroups, and each molecular subgroup in turn seemed to have a very consistent pattern of which genes were mutated early, like the founder clones, the genes that generate the founder clone, the secondary, and the late events. This can become very important as we are thinking the clinical management of AML whether we want to treat the late lesions, the early lesions, or the combination of the two lesions that come together most frequently. And this is schematic that represents while we consider AML as one disease, we are now learning that there are distinct paths that can lead to AML. Each of the paths can invoke a very distinct pathway, and we can now learn what are the critical nodes of each one of those pathways that we can both learn to use, both for disease surveillance protocols, but most importantly therapeutic protocols.

So, beyond the biological significance of those molecular groups, we wanted to test whether they were clinically relevant, and indeed, each one of those molecular subgroups segregated distinct clinical outcomes and this is published data. So, if you want to digest it in more detail, please do. You can find it available. So, now, whereas previously we could categorize 50% of

AML patients in a risk group, now 85% of the patients are accounted by one molecular subgroup for which we have recognized very distinct clinical overall survival outcomes. Beyond overall survival, we have here asked the question. We have this bar plots where we indicate on the top bar the proportion of patients within the group that achieved complete remission and on the bottom bars, the lower bars, the proportion of patients that relapsed in light blue that was alive after relapse or alive without relapse at last follow up. What we found was that we now are seeing these common themes emerging for each one of those subgroups beyond overall survival as well as in the patterns in which patients might achieve complete remission in the first instance, the proportion of patients within each group that might relapse or not, and then the proportion of patients that will be alive within 3 or 5 years. Bringing it into more context of novel and emerging therapies that we are very interested in, and we are going to hear a lot more about today, I took the review from Ross Levine, which indicates potential gene markers that are currently in either phase 1 to phase 3 clinical trials or that result in stratification of patients in clinical trials, and I asked how many patients have at least one, and this is like the upper level of what could be considered in the clinic and an optimistic level, but how many patients have at least one mutation that could stratify them if the worlds of clinical trial was available to them, how many have two and how many have three? I was actually pretty stricken by the results in that, in this overestimate of potential targets that we could explore clinically, we had 74% of the patients that had at least one that could be a FLT3 mutation and IDH mutation, 45 that have at least two, and 16% that have three or more. This is important because we need to start, if there are consistent patterns in which these mutations come together, perhaps we can start using this information on both how we interpret outcomes from clinical trials, but also how we might in the future rationalize combination therapies. So, this is the representation of each one of the molecular subgroups, just to give you a flavor how the commutation and the overall composition within the group is important and how we can use this in the NPM1 context. We see that 75% of patients are mutated in one of the genes affected in DNA hydroxy methylation machinery or receptor tyrosine kinase pathways or GTPase of which there are numerous targets both through IDH inhibitors or FLT3 inhibitors or RAS inhibitors that we could consider for that subgroup. If we were to subset the patients that carry these alterations, and while NPM1 is considered a favorable prognostic group, here we see that patients with NRAS mutations, particularly codon 12, seem to have consistently good outcomes in accordance with what we know and expect from NPM1 mutations. However, patients that have mutations in IDH, one of the IDH genes, show increased refractory disease in patients that have the combination of DNMT3A and FLT3-ITD, have increased refractory disease and increased relapse rates. Clearly, the numbers of each of those subsets are small, but we can now start validating these and learn which ones of the subgroups, as we are doing with FLT3 for example in the NPM1 context, we can stratify and consider additional therapeutic modalities.

I would like to draw the attention to the chromatin spliceosome group which accounted for 18% of the patients in our cohort. So, this was the second largest molecular group. This group performed really poorly, has very poor survival. The majority of those patients would be currently considered as intermediate-risk AML that present with de novo disease, they are generally older with a median age of 58 years old, and they are associated with poor survival and a high relapse-related mortality, and less than 20% were alive at the last follow up. So, this group is one that we immediately recognized as a novel or high-risk group in AML, and there has been a lot of population genomic studies to show that there is a number of gene mutations within the spliceosome machinery that determined the backbone of this disease, and these

mutations are mutually exclusive. This observation has recently led us to postulate that two mutations within the spliceosome machinery are probably not viable within the cell, and this has led to the development of spliceosome complex inhibitors that are currently being trialed for both MDS and AML because there are recurrent molecular abnormalities in both diseases. These are showing early promising results, and here, we see the on-target effects of two of the agents that are currently underinvestigated, an SF3B1 mutated context as well as the preferential effects that they have on splicing factor mutated CMML in this context which you see in patients with the blue line and the same is here where they have a very specific and selective effect in reducing the overall blast count in F3B1 and splicing factor mutated CMML. So, we are going to hear a lot more about IDH mutations and FLT3 mutations, but we are all startled by the fact that we are dealing with hundreds of molecular alterations that we need to learn and incorporate within our clinical algorithms. But with population studies, we can now learn how these gene mutations come together, how they define distinct clinical groups, how mutations and key pathways that we can target come together, they help us rationalize potential clinical trial protocols, and while we may have 1500 individual patients, we are now recognizing more and more distinct molecular and clinical subgroups that we can deliver more personalized or group-tailored therapy that is more relevant to the biology of the disease. This is an example whereby joining forces through collaborative efforts we can learn from a large proportion of AML patients to individually treat each of the patients and how we are thinking and learning as we are expanding the studies of incorporating the molecular markers and the pathways into logical algorithms upon which we can interpret. So, I would like to thank all of my collaborators and the funding bodies and everyone in the lab. It is impossible to just mention everyone, particularly all the physician scientists that enroll patients in trials and then submit samples and clinical information into such population studies because without this effort it would be impossible to extract messages that we can then bring back into every individual clinic. So, thank you very much.

Dr. Richard Stone:
It certainly is an honor to speak in this, let me say, this august panel. You can see from Elli's talk the genetics is a little bit outpacing our ability to deal with that from a clinician's perspective, but I will give you my take on the current treatment paradigms in AM because her papers were all done with many countries, the samples from many patients from many countries. That is what we need to do in a rare disease AML. AML as you all know from my perspective is unbridled proliferation of immature hematopoietic stem cells or leukemic stem cells that result in patient death unless we figure out a way to treat that properly. The most important risk factor for AML is age. The median age is about 68 to 70. There are about 5% to 10% of patients who have a risk factor such as a chemo for other cancers, exposure to radiation, and as usual therapeutic nowadays or industrial solvents. A very important subgroup that we are beginning to understand more and more, thanks to work done by people in his town like Dr. Godley and Dr. Churpek is the importance of familial leukemias which was something I did not think about until very recently, so I just want to bring that up. So, most patients are diagnosed after age 60, which brings into our eyes importance about comorbid diseases and frailty and things like that. It is a heterogeneous disease. You just heard how heterogenetic it is from a genetic and molecular standpoint. Obviously, we are talking about older people. Some 70-year-olds play basketball. Some are confined to wheelchairs. It is true for younger people, but particularly for older adults, you can see from the bar graphs it is a disease of older adults. If we diagnose that more often in

80- or 90-year-olds, the thing on the right would probably be higher, we just do not diagnose it that much.

So, I am going to begin by a couple of minutes about a very important story. Hopefully, in 5 or 10 years, we can say everything is a success story. Right now, APL is, because we can cure virtually all patients who develop APL. When I started training, it was a horrendous disease. The word unmet need is often used when we are talking about cancer therapy. It is sort of jargon word, but it means we do not do very well. I think most people know that in younger patients most of them need allogeneic stem cell transplant which is dangerous and causes infertility. It does cure a lot of people but not as many as we would like. There is still toxicity and relapse. Old adults do miserably as we all know, and once the disease relapses, we salvage very few as Elli showed. I would say one new thing is the importance of, I will call it, measurable residual disease. We want our patients to achieve remission after initial therapy. We want them to do so at a level where we cannot detect the disease by morphologic means, yes, but also by molecular and/or immunophenotypic technologies. Here is the usual summary of how we have done over the years with AML. On the right, you can see that older adults have done miserably. The median survival is no more than a year. In younger adults, we have done better over the years. The cure rate is now about 50%, and that is probably not so much due to better antileukemic therapies but rather due to safer transplants and antifungal agents where less of our patients die of neutropenic complications. So, a few things about APL, very important, especially if you want to avoid lawsuits, if you suspect the disease, treat it with retinoic acid before you can make the diagnosis because you can ablate the coagulopathy that goes along with APL and you can save the patient a lot of morbidity and possibly even mortality. Then, you document the disease by FISH looking for the 15;17 translocation by molecular techniques looking for the PML-RAR fusion transcript or indeed by routine cytogenetics. Then you assess the risk, it is very easy. If the white count is greater than 10,000, they have high-risk disease, and less than 10,000, they do not. That is a kind of simple stuff that I can almost remember, and if they have a white count less than 10,000 and maybe if they have a white count greater than 10,000, you can cure them without chemotherapy based on the amazing work led by Dr. Lo-Coco from Rome, who compared the then popular PATHEMA, or Spanish regimen, which involved heavy anthracyclines plus retinoic acid, versus the regimen developed by Drs. Ravandi, Estey, and Kantarjian at MD Anderson with chemo-free ATRA and arsenic trioxide. It was a non-inferiority trial which was restricted to people up to age 70. It was restricted to those who had a white count of less than 10,000, but the Brits have shown this probably applies with a little bit of chemotherapy to even patients with higher white counts and older adults. You can see here it was a non-inferiority, but the chemo-free regimen won out after arsenic curing virtually everybody. There is an art form to doing it, how much steroids to use, when do you hold the drugs looking at the QT interval. We can talk about that later if we have time, but you can cure virtually everybody with this disease. Now, what about non-APL AML? What do we care about today as a clinician, age, comorbid disease, all that stuff I refer to, cytogenics and molecular studies. What molecular studies? Everybody says what do we send now? Well, I think most clinicians know that you need send FLT3-ITD, you need to send NPM1 and C/EBP alpha. The last one is not so common. Now, the European LeukemiaNet and the Europeans, who were ahead of us on this, have recommended additional mutations to look for, even though the NCCN Guidelines do not actually include these right now, but RONEX-1, TP53, SXL1, each of which were bad, and I would also say c-KIT and CBF because about 24% of the favorable core binding factor and cytogenic patients have a mutation c-KIT which is probably

unfavorable. What we do about that right now, I do not know, and I listed on the bottom things we are going to be doing based on what Elli just talked about. As new drugs emerge, we will need to know these, and also, we might want to refine the prognosis. I mean it is one thing to talk about prognosis. It is more important to have a better therapy. So, of course, the bottom line is what do I do? Recommend next-generation sequence panel. At the Brigham where I work in the Farber, we get 96 genes back in 5 days, and we can make therapy decisions very rapidly, and that is where the field is going. So, the European LeukemiaNet led by Hartwood Döhner from Ulm has come up with three subcategories. Favorable, which is basically inversion 16, 8;21, and also NPM-1 mutant that does not have a FLT3-ITD. That is an important subgroup, normal karyotype with C/EBP alpha balletic mutations also, but I want to just point one thing. It is a little bit of trick thing here. If you have got NPM1 mutation but no FLT3-ITD, okay that is favorable. In Europe, they also do what is called the allelic ratio. We do not always do that in America. The allelic ratio has to do with how much normal FLT3 have to abnormal FLT3-ITD, and if you have a low ratio under about .4, it varies 40% or less is the bad kind. Then, they do pretty well and maybe they do not need a transplant in first remission, that is controversial. Then over on the right, you have the adverse risk, they do very badly, and they are enriched with things that I consider killer cytogenetics like 3q26 abnormalities, 9;11, certainly T53, as we say in Boston, wicked bad, and complex karyotypes are highly enriched with p53 mutations. Everybody else is in the middle, and I will just say this very simply. If you are on the left-hand side of that, you probably do not need a transplant. If you are on the right-hand side, we do a transplant even if we have to go to a haplo donor or a double umbilical cord. That is a little controversial. Some centers will even do a haplo for the people in the middle, but I think you get the point. The ones in the left do not need transplant probably. All right, what is the goal? Goal of induction is to reduce the high leukemic burden at diagnosis, maybe 10 to the 12th cells down to undetectable levels, and I said earlier, and I am stressing it, the goal really now in 2017 is to reduce it to a level below detectability by common means. We do not all do that. We do not know what to do if it is positive because if you give induction therapy and you still have evidence of disease by molecular or immunophenotype, you take them for transplant, they do not do very well. If we had a drug or drugs that can erase the MRD after induction, then we might be making some strides, or if we had drugs we can add upfront where we had a higher level of MRD negativity, we would probably make some strides. I think when you listen to Jeff's talk about CPX-351, think about that, and think about that when we talk about midostaurin in a second. Once you are in remission, at least morphologically, the goal is to eradicate residual leukemic burden either by allogeneic transplant or chemotherapy/autologous transplant. For people under age 60, it is true things have not changed very much in a long time; 3 and 7, we have learned to give higher doses of daunorubicin. We do not really offer the dose of ara-C, and Guillermo can talk about the inferiority of idarubicin and ara-C compared to 3 and 7 in at least good-risk patients with AML. Consolidation, I already told you that I would give adverse cytogenetic patients allotransplant no matter what that is the only chance for long-term survival, really favorable risk, 4 cycles of HiDAC, or something intensive at least, intermediate-risk allo preferably, and maybe I would extend that to a sibling donor and match unrelated.

Here is the data from E1900 led by Marty Tallman that showed that if you intensify dose of daunorubicin to 90, compared to what we usually use is 45, you do better, but again the unfavorable cytogenetics with those people, chemotherapy does not work very well. It is not a chemo-responsive disease, but intermediate- and low-risk do well with a higher dose. We do not use 45 mg of daunorubicin anymore, really. Now, this is the data. It is almost 10 years old now.

It is from the same people that cooperated with Elli on the paper she wrote. It showed that, this was not a randomized trial, but if you had a donor, you did better unless you had MP1 but no FLT3-ITD, and again, the ITD burden may be important in this. So, that is the data supporting not doing transplants on people with normal karyotype, NPM1 mutation, no FLT3-ITD. What about the changed landscape? Well, FLT3, right? You saw from Elli's talk that FLT3 mutations occur in about 30% of people with AML. It is especially the IDT subtype, which is the greater subtype of the FLT3 group, do poorly. Unmet need if you like. Let's add a FLT3 inhibitor to chemotherapy, I do not have time to go through the history of this, but it was a long gestational period. The first study with midostaurin was done at around 2000, and this trial which is a huge randomized effort done internationally because it was restricted to people who had the FLT3-IDT or the FLT3-TKD mutation, the point mutation, and it was for adults under age 60. Basically, it was a simple design. The control arm got 3 and 7 for induction, high-dose ara-C for post-remission, and maintenance with placebo, and the experimental arm got 50 mg of midostaurin twice a day after the chemo was finished during induction and after the chemo was finished during consolidation, and they did not get it after transplant. The transplant was not specifically called for, although as the study went on based on the data that I showed you a couple of seconds ago, the paradigm shifted to doing transplants to FLT3-ITD patients anyway. This is the top line result of that trial that resulted in the approval about 2 to 3 weeks ago, maybe a month ago now, of midostaurin to be used with chemo-fit patients with chemo, who have a FLT3-ITD mutation or FLT3-TKD mutation. Now, if you are an optimist, you can say, "Hey, this is great. It has met its endpoint. There was a 23% reduction in the risk of dying in those who are randomized to midostaurin." If you are a pessimist, you can say, "Look at those curves, how different are they? You really did not make a home run here, it may be just single or double." But there was a 7% increased cure rate. To me, the tail of the survival curves in AML is what is all about. We want to cure more patients. So, if you compare to the old data with FLT3, 50% cure rate was not so bad compared to the historical data. About 25% of these patients were transplanted in first remission and about 26% were transplanted down the road. It turns out that if you were transplanted in first remission and you got exposed to midostaurin, you had a pretty good outcome, and you did better than the group who were transplanted in the first remission who got placebo. You will see similar data when it comes to CPX-351. Although we did not prospectively measure it, to me that says perhaps the addition of midostaurin to chemotherapy meant that we were getting them to transplant at lower-level disease, a lower likelihood of measurable residual disease that remains to be proven, and that is why it is important. Hopefully, all of you know about the IV paper that was done in cooperation with Dr. Grimwood who sadly died last year, talking about the importance of getting MRD negative. If you have MRD positive disease, at the end of induction, they use 2 cycles of induction in Europe. If your MRD is still positive, this is by NPM1 mutation positivity in people who had an NPM1 mutation diagnosis. It is about like not going into remission at all. It is pretty miserable. So, we need drugs to drive the MRD burden down more than we can get with looking at the light microscope. Older patients, tough disease as I have already said. This is old data, but the reason why older folks do not do as well, they have a higher death rate, maybe not 25% now, but it is higher than younger patients. If they go into remission, but they do so less often, they are less likely to stay in remission. So, I tried to transplant all my older patients who are fit enough to do that. I have already mentioned this. They have intrinsically resistant disease due to a lower likelihood of having a favorable cytogenetic abnormality, higher exposure to drug-resistant proteins, and a higher instance of hematologic abnormalities that predate their diagnosis of AML. Also, they are older, so their kidneys and livers have been around for 7 decades, and so they do not clear the

chemotherapy as well. Their bone marrow stem cells are not as robust, and that has been shown in breast cancer. This is data I really, really like because I contributed to it some. I did not just contribute to it, Dr. Lindsley did all the work. The reason why I like it is because these were 100 patients that came to Dana-Farber, who were over age 60. We said they had de novo AML, us smart clinicians, right? None of them had a history of anything, but if you just asked how they did according to the mutations, if they had a p53 mutation or secondary-type mutation, largely the epigenetic stuff and the splicing mutations that Elli showed, they did miserably. But if they had a pan-AML mutation like FLT3 or RAS, they did okay, so not all de novo AML patients are alike, that is really shown well by this, the genetics trump, no offense, the clinical aspects of the cure. What we do with older adults now? We give them 3 and 7 if they are fit. If they are not fit, we kind of give up and give a lower dose of therapy, but I think that is okay, especially in the groups that I showed you in the last slide. If they are not going to do well with chemotherapy, why subject them to that if it is not going to help them? Dr. Kantarjian and Dr. Garcia-Manero at their institution came up with four or five things that say you are not going to benefit from 3 and 7. If you are over age 70, if you have a poor performance status or comorbidities, bad chromosomes, and I would add bad genetics as I just showed you, or if you have had a history of another bone marrow problem, you are not going to do well. Maybe, we should give hypomethylating agents like we do for MDS to those patients. Dr. Dumbre, in a Celgene-sponsored trial, led this trial call the AML-001 trial which was the sort of an idea, well, everybody says, "Okay, you said we should not give them 3 and 7, what do we do?" This was a trial of older patients over age 65. They had to have a white count less than 15 grams at the time they started, and they were randomized to azacitidine and conventional care. Now, this was not a comparison of azacitidine to 3 and 7. Most of the patients could not get 3 and 7. You had to put your cards on the table before the patient was randomized. You would say, "I am going to give this guy 3 and 7," get on the experiment of the control arm, or whatever. So, most of them ended up getting low-dose ara-C or supportive care. The complete remission rate was no different, but the median overall survival was actually higher in the azacitidine group. Why? I think, I do not know because this group of patients is with lower white counts. Older adults were enriched, people with bad mutations, that is being looked at now, and they did a little bit better. They did not meet the primary endpoint of extending a little bit more, but it seemed like it was a good idea to give azacitidine to these patients, but it needs to be looked at according to mutations. What about if azacitidine for 7 days, which is what they did in that trial, it is good, how about 10-day decitabine? This is really interesting data that needs to be confirmed. MD Anderson has some counter arguments to this, which maybe Guillermo would get into, but this is 10-day decitabine in a whole bunch of older adults or some were even older, and I do not know if you can see here, but all the responders were people who had a p53 mutation. That is really strange because p53 is really bad with 3 and 7, but they were getting responses with the 10-day decitabine. Is it the 10-day decitabine or is it just decitabine, we do not know that yet, but if you look at the right-hand side, you can see that getting the 10-day decitabine seemed to ablate the negative prognostic impact of having a p53 mutation. So, even though it certainly was not curing them, to me this says okay, we probably should never give 3 and 7 to a patient with p53 mutation, but we will see what others say about that. So, in relapse disease, this is obviously very bad, flag item, MEK, and then for people who cannot tolerate chemotherapy, hypomethylating agent. If you look at the response rate according to some of the salvage regimens, if you do the literature search, you will see a wide splay because no matter all relapse patients are the same, are they all bad, but some are worse than others. If you had a long disease interval, you have a better chance to respond to chemotherapy. If you cannot give them

chemotherapy, Max Stahl from Yale just reviewed some retrospective data about HMA therapy which we sometimes do for relapse patients. There is a small CR rate, and if a patient cannot get salvage, then you want to get something that is not unreasonable. Obviously, the overall goal if you are trying to cure somebody who is relapsed is to get them into second remission and transplant them. The fact of the matter is, many of these relapse after a transplant, and that is very hard to get them to a second transplant. So, we have a lot of unmet needs, I said before, older adults almost all die of the disease and younger adults we still do not cure nearly enough, and we have very toxic treatments by and large that are very expensive and resource intensive.

So, 2017 is the year of hope. Midostaurin was approved. Again, you can see the benefit that it accrued, it was a real benefit and not a dramatic one perhaps, maybe approved in 2017, CPX-351 which you will hear about from Jeff, and enasidenib for IDH2 mutant patients and maybe gemtuzumab will come back from the discord pile. We are not sure about that, but there are a lot of interesting drugs that are undergoing phase 3 testing that could be part of the armamentarium in the not too distant future, which you will hear about in a second. So, having said that, I would like to thank you for your attention, and there is a little bit of excitement. So, let's get into it. Thanks.

Dr. Jeffrey Lancet:
I have been tasked with a difficult opportunity here in the next 25 minutes to review a whole lot of drugs that are really exciting in this disease and they reflect what we just heard about from both Elli and Rich, and I apologize in advance if I have to skip over some of these drugs in great depth because of the number of the drugs there are to talk about. I guess it is a good problem to have. Twenty years ago, if this topic were introduced at the podium and Rich were giving the talk, you would hear a whole lot about politics in Boston sports but probably not too much about AML, which could be entertaining but not the greatest for the patient. So, it is nice to be able to talk about some novel agents that really have an impact. So, why don't we get started here. So, a lot of these new drugs are being developed across a wide array of indications, and I was asked initially to the kind of try to pigeonhole these new drugs towards different disease types, and you really cannot do that. Many of these drugs are targeted towards different patient populations and different targets, and even some of the targeted agents themselves are not necessarily helpful in only patients with that particular target, there are off-target effects that we have to think about that probably come into play with agents such as midostaurin and others where you may have benefit in patients that do not necessarily carry that specific target. But as you can see from this diagram here, many of the new drugs are looking to have an impact in fit patients, in elderly patients, in relapsed patients, patients with specific targets, and others, so I think we are going to see a lot of diversity in how these drugs are used over the years and there is not going to be one specific population for which any one drug is targeted.

Now, hypomethylating agents, I think, and I hope everybody here is familiar with, these drugs have really become the mainstay of therapy for high-grade myelodysplastic syndrome, and in a large part in acute myeloid leukemia, at least in North America where we use them as front-line agents for the older patients, and what I am referring to is primarily 5-azacitidine and decitabine. I will just refresh you a little bit on some of the trials that have been done with these agents in older patients with untreated AML. With decitabine, as you may recall, a few years ago a phase 3 trial was completed that indicated a higher response rate with decitabine compared with investigator's choice for older patients with AML, but the overall survival did not quite reach

statistical significance at the initial landmark analysis, although in later follow up there seemed to be a significant improvement compared to other agents. Azacitidine followed the same path. You can see here that there was a modest, although not quite statistically significant, benefit in survival for patients who received azacitidine compared with conventional care regimens in AML, so two studies that indicated the utility of these drugs, albeit with a very modest effect. We have also recognized through the years that hypomethylating agents, despite a lack of randomized trials against other more intensive therapies probably are just as good if not better. In this analysis of over 900 patients now from own institution and similar data were replicated previously at MD Anderson, in older patients over age 70, we found that the HMA-treated patients actually lived longer than any other group of patients after we did a propensity analysis to match patient characteristics based on what type of therapy they would most likely receive. So, HMAs have clearly emerged as a major standard of care for older patients with AML.

Now, what about the next steps in hypomethylating agents? I do not think we have reached the ceiling. Certainly, the response rates and the survival are modest, and we can do better, and we are. So, for example, a new drug, guadecitabine, also known as SGI-110, is the next-generation hypomethylating agent, and this is a dinucleotide of decitabine and the deoxyguanosine. This is pharmacokinetically advantageous because this particular compound is resistant to cytidine deaminase. So, it sticks around for a lot longer in the circulation and therefore has the advantage of maybe having more of an antileukemic effect. These are data from the MD Anderson Group that were presented at ASH about 1-1/2 years ago based upon prior phase 1 data. In this particular trial of guadecitabine in treatment-naive patients with AML, patients were randomized in the initial phase of the study to receive either the biologically effective dose, in other words, the dose that led to the most robust and reliable demethylation effect at 60 mg/m^2 daily x5 against the highest well-tolerated dose of 90 mg/m^2. Then at the end of the first phase of the study, they introduced biologically effective dose given over a 10-day regimen to try to extend that pharmacokinetic advantage, and the primary endpoint was the overall response rate in this phase 2 study. And the results are shown here. If you compare the 5-day regimen to the 10-day regimen, there was really no significant difference. If anything, perhaps a slight improvement in the 5-day outcomes compared to the 10-day outcomes, but not statistically significant, and an impressively high CR, CRI, and CRP rate, certainly higher than what you would expect with either azacitidine or decitabine alone. So, these data are encouraging whenever you see higher initial response rates. So, I will leave it at that for that drug. You will be hearing a lot more about that, and there is randomized phase 3 trial going on right now comparing guadecitabine against investigator's choice of single-agent azacitidine or decitabine.

The next agent I wanted to talk about is an agent called pracinostat. This is an HDAC inhibitor, and HDAC inhibitors are another type of epigenetic modifier that can reinstitute gene expression and perhaps allow for greater recovery of gene expression of silence genes in AML, such as differentiation genes. Dr. Garcia-Manero has worked extensively with this class of compounds and has done a lot of work in publication, and one of the most exciting compounds coming out lately is this orally bioavailable drug pracinostat, which is a selective inhibitor of class 1, class 2, and class 4 HDAC. This trial was performed, as shown here, in older patients with previously untreated AML who received both pracinostat daily, every other day, and azacitidine for 7 days in a row, every 4 weeks. The primarily endpoint again was overall response rate in patients who were, generally speaking, older and not candidates for more intensive therapy. The demographics of this study are shown here. As you might imagine, the majority of the patients

were older than age 70, in fact most of them were over the age of 75, and a significant component had secondary or high-risk features in terms of secondary disease that arose from MDS or MPN. About 40% of patients with poor-risk karyotype as well. The overall response rates are shown here, and again very intriguingly high response rates in comparison with what you would expect with single-agent azacitidine, decitabine, or low-dose cytarabine, with an overall response rate of CR plus CRI of 46%. The duration of the response I think was impressive at over a year, and the time to the marrow complete response was about 60 days, so not a quick-acting agent in combination, but still something that is happening within a couple of months' time. What I think was very impressive about this trial in the preliminary stages was the fact that the median overall survival was 19 months. If you recall, the median survival in the single-arm studies of azacitidine and decitabine were generally less than a year, and the 1-year survival at 62%. So, these are looking promising as far as perhaps altering the natural history of AML with this combination, and certainly a randomized study will help clarify that question further.

So, in summary, with the epigenetic agents that we have currently available, we know that they are active as single agents and they certainly appear to provide similar if not more benefit to traditional intensive therapy, although there are really a lack of data to really support one versus the other because the randomized studies have not been done comparing 7+3 against azanucleoside therapy. The pharmacokinetically advantageous agents such as guadecitabine may offer further advantages and lead to higher response rates and survival, and then secondly dual epigenetic modification such as combining HMAs and HDAC inhibitors might further augment response rates and overall survival benefit, and hopefully future randomized studies will allow us to better understand the place and therapy for this combination.

So, we will move on now to something else. It has been a project that I have been involved with for a number of years now, and this is a compound called CPX-351, also known as VYXEOS, and the amazing thing about this drug is it is really nothing more than a liposome that encapsulates two very old drugs, daunorubicin and cytarabine, but the beauty of it is that there is fixed molar ratio between the two drugs, cytarabine and daunorubicin, that is synergistic ,and the synergy has been proven in preclinical models, and when you incorporate this synergistic combination at the proper ratio within a liposome, you can actually deliver the two drugs at their intended ratio to the target cells, something you cannot do with three-drug cocktail. So, just to cut to the chase, we performed phase 1 and phase 2 studies that revealed promising results in relapsed and refractory disease and then a randomized phase 2 study that showed a survival advantage signal in patients with secondary AML or AML primarily from MDS. So, we took it on to a phase 3 randomized trial in patients with secondary or high-risk AML comparing CPX-351 against 7+3. We presented these data at ASCO last year, and these were patients over age 60 who were fit. These were not unfit patients, but patients who were fit enough to go through intensive therapy, they were stratified based upon the type of AML they had, MDS related adverse cytogenetics or cytogenetics related to MDS and age as well. Patients went through up to 2 cycles of induction followed by up to 2 cycles of consolidation, and the primary endpoint of the study was overall survival, and I would like to point out patients in this particular trial were not excluded from receiving a transplant along the way since we recognized many of these patients would go that route. So, the primary results are shown here that we presented last year, and as you can see, there was an overall survival advantage favoring CPX compared to 7+3 by about 3-1/2 months at the median and decrease in the risk of death by 31% over the entire course of the study, which was statistically significant. We also wanted to understand how

transplant might impact the overall survival advantage seen from CPX, and we did a survival analysis landmarking patients at the time they received the transplant. As you can see here, data we presented also last year at ASH as well that the CPX treated patients who underwent transplant had a better outcome than transplanted patients who had received 7+3. Again, not a randomized prospective analysis or subgroup analysis of a larger study, but nonetheless very intriguing and suggesting that maybe with CPX you can achieve a better and deeper response prior to going into a transplant that could lead to better overall responses and results, but these data need to be verified as to the reason why transplant seems to work better in the CPX-treated patients.

So, in summary for this part of the talk, I believe that utilizing a novel drug delivery mechanism such as CPX-351 can allow you to augment leukemic cell kill by introducing the proper synergistic ratio into the target cell, which is not achievable with three-drug cocktail. CPX-351 is currently at the FDA and will likely gain, I think, approval for secondary- or high-risk AML before the end of the year, and probably, most importantly, is this type of an approach may provide a very important platform for future combination drug development if you can really take advantage of the synergy, whether it is a targeted agent or a more empiric agent. So, stay tuned for more on that particular platform.

Next, I move more into the targeted therapy realm here. We have heard a lot of about this so far from our previous two speakers. I will touch briefly upon FLT3 mutations because Rich went into that in detail. So, FLT3, as you know, is a receptor tyrosine kinase that is frequently mutated in AML up to 30% of the time, mostly with an internal tandem duplication mutation in the juxta membrane domain, but occasionally a tyrosine kinase domain mutation can occur as well, and these are leukemias that are characterized by high rates of relapse and overall poor prognosis. I will just make brief mention of midostaurin. Rich went into that before, but midostaurin in my opinion now is unequivocally the new standard of care for any newly diagnosed patient with AML under age 60 who has a FLT3 mutation either at the ITD or the TKD locus. So, what is really interesting also is the development of next-generation FLT3 inhibitors that are quite a bit more potent selective than the earlier generation inhibitors, and these new drugs such as crenolanib and gilteritinib, which I will talk about briefly, have the advantage of being able to inhibit FLT3 both in its inactive conformation as well as its active conformation, and when FLT3 mutations develop as of means of resistance to prior FLT3 inhibitor therapy, such as what you may see with midostaurin or sorafenib, they often acquire a DA-35 mutation that leads to active conformation that these old drugs cannot bind to very well, but the new drugs can actually bind to the active conformation of FLT3 and have an effect. So, one of these drugs is crenolanib and you will be hearing a lot more about that drug at this meeting and others as well. This is a highly selective type 1 inhibitor. Again, it inhibits both the active and the inactive conformation of FLT3. And without getting into too much nitty-gritty detail, a recent trial was presented by Dr. Eunice Wang from Roswell Park at ASH this past year where patients who had FLT3 mutations at baseline were randomized to either 7+3 plus crenolanib with either idarubicin or daunorubicin, so not really a true randomization in the true sense of the word, but patients who went into remission were then treated with high-dose cytarabine plus crenolanib and then went on to receive maintenance with crenolanib. These were patients, again, with newly diagnosed AML that included patients with secondary AML and any FLT3 allelic burden was permitted, and these results are indicative of a high response rate, which is not overly surprising for newly diagnosed AML patients, but nonetheless, the majority of patients did achieve remission. Most

of them occurred after the first induction, and only a small minority of patients were non-responders and a significant number of patients went to transplant. Randomized studies are now being planned with crenolanib plus daunorubicin and cytarabine in the upfront setting as well.

The next drug I will talk about briefly is gilteritinib. This is another class 1 FLT3 inhibitor that binds to both the active and inactive conformation of FLT3, and these are data that were presented by Dr. Sasha Perl at ASH this past year. This was a phase 1/2 trial of gilteritinib looking at a variety of doses, ranging from 20 mg daily up to 450 mg daily, and the doses that are being focused upon right now are the 120 mg and 200 mg dosing cohorts. This was a large phase 1/2 study, and just to summarize the data here, I know the charts are a little bit hard to read, but the take-home message is that in the FLT3 mutated patients, the overall response rate in this relapsed and refractory cohort was almost 50%, including 37% of patients who had either a CR, CRP, or CRI, so a very high response rate for single agent. But what I thought was even more interesting was that in patients who had previously received treatment with a FLT3 inhibitor, as shown in the bar graph here to the far right, 40% of them actually had responded to gilteritinib after having failed therapy with a prior TKI, suggesting that this is a drug, along with crenolanib, that can overcome resistance conferring mutations in AML and could be the platform for future earlier therapy to prevent the development of such mutations that leads to FLT3 inhibitor failure. This is data showing the biologically effective dose as measured by the plasma inhibitory assay developed by Dr. Mark Levis at Hopkins showing that at levels of 120 mg a day and higher, you almost have complete inhibition of phospho FLT3, and this is the basis for carrying forward with these doses in the next generation of trials. So now, we have a whole slew of trials testing FLT3 inhibitors in a confirmatory fashion. We have gilteritinib versus salvage therapy for relapsed and refractory disease. We have chemotherapy plus or minus crenolanib and relapsed and refractory FLT3 AML, and quizartinib which is a class 2 drug, it does not bind the active conformation or binds the inactive conformation, but it is very selective and potent and is being tested against salvage chemotherapy for FLT3 positive relapsed AML as a single agent. So, a whole slew of trials that are coming down the pike to really outline what the role of these drugs will be, both in upfront and in relapsed disease.

Now, vadastuximab is another targeted agent, and I like to think of this as kind of the new and improved version of gemtuzumab or Mylotarg, and this is an antibody-drug conjugate where you have an anti-CD-33 antibody that is conjugated to a very potent compound known as pyrrolobenzodiazepine dimer that is highly intrinsically binding to DNA and is extremely cytotoxic at higher levels than what you can achieve with calicheamicin, which is the conjugate in gemtuzumab. So, this compound is moved forward in a humongous trial, probably the biggest phase 1 trial I have ever been involved with, that has kind of sprouted multiple subsets of trials that has yielded a lot of data in the last couple of years, and one of these subsets within the original trial was looking at vadastuximab as a single agent in patients who were older and treatment naive and who were ineligible or declined high-dose induction therapy. So, single-agent therapy for patients with newly diagnosed AML in the older group. Patients received 3-week cycles of vadastuximab at a dose of 40 mcg/kg, which was the preferred dose in this particular trial based on the earlier dose escalation phase, and the results were presented by Dr. Dale Bixby at ASH this past year and as you can see here, an overall response rate that was quite high of 58%, and this included patients that had underlying MDS in their initial diagnosis. These were not patients that had received HMA therapy, so they were also HMA naive, but nonetheless, a high response rate in this particular group of patients which I think is

always a very important finding. Most patients had significant blast reduction, and to date the survival curves are not overly impressive, but nonetheless, the response rates and the blast reduction I think provide a platform for a lot more to come.

Now, the next breakout group within this large trial was a combination of vadastuximab plus a hypomethylating agent, and these data were presented by Amir Fathi at ASH this year and these were again patients who were previously untreated that had AML that were CD-33 positive who had declined or not deemed eligible for intensive therapy, and again no prior HMA therapy was allowed. These patients were treated with azacitidine at a dose of 75 mg/m^2 for 7 days or decitabine at 20 mg/m^2 for 5 days and received 4-week cycles of vadastuximab as part of the treatment regimen. Here are the results, again a quite high overall response rate of 73%, which is really much higher than you would expect with azacitidine or decitabine alone, and the response rates held up across different subtypes of AML including FLT3 and older age group. So, stay tuned for a lot more on that drug. We are seeing randomized studies being developed right now for vadastuximab with chemotherapy in younger patients or in combination with azacitidine in the randomized study in older patients.

I would like to touch briefly on another very exciting area. We all know that BCL2 has been a key target for therapeutic development over the past several years based on the importance of BCL2 as an anti-apoptotic protein, and in the case of venetoclax, you can actually competitively bind and replace the proapoptotic protein such as Bim or Bax and basically negate the function of BCL2 that allows for apoptosis to take place. The earlier studies done by Dr. Konopleva at MD Anderson in a phase 2 single-agent study showed that there was impressively, I think, high rate of response in relapsed and refractory disease with about 20% of patients responding to this drug as a single agent, and there seemed to be a stronger signal on IDH mutated AML for reasons that are unclear. This initial study has paved the way for a number of combination studies, one of which I will show here. This was presented by Dr. Wei at ASH this past year combining venetoclax plus low-dose cytarabine. Other studies have combined azacitidine or decitabine with venetoclax as well, and at the recommended phase 2 dose of 600 mg was where they expanded the phase 2 component of the study. And as you can see here again very high response rates in the older age patient group, especially 70%, and what I think is most important is that the survival curves are looking good. Now, the follow up is short, but the fact that the 1-year survival is hanging out at a fairly high rate is impressive and I think will be very important in the future of this disease because certainly overall survival is what we are trying to achieve for these older patients.

I will finish off here by talking about the IDH inhibitors, and for those of you who may not be familiar, IDH is a very important enzyme in the citric acid cycle. When IDH1 or IDH2 are mutated, you get an abundance and an overproduction of 2-hydroxyglutaric, which then leads to a variety of events intracellularly that lead to a hypermethylation effect in general, and that is felt to be the reason that this mutation class is bad. There are a lot of different mutations that can occur in different tumor types including AML, MDS, and solid tumors as well, and there are several different inhibitors in clinical development. The two that are I think are furthest along right now are the Agios compounds 221 and 120, which we will talk about briefly. The AG-221 drug also known as enasidenib is basically very far along, another very large combined phase 1 and 2 study that was run by Eytan Stein at Memorial, and these data have been presented at ASH over the past few years with several hundred patients treated to date. Baseline

characteristics are shown here, over 200 patients. They were practically all mutated at IDH2 and most of them had relapsed or refractory AML. The response rates and the overall efficacy shown here, as you can see, there was a 37% overall response rate and about a 20% CR and CRI rate. Again, as a single-agent in relapsed and refractory disease, pretty good. A handful of patients were also untreated that did not seem to have any higher of a response rate than in the relapsed group, so very strong efficacy in this particular class of compounds, and several of these patients were also able to subsequently undergo allogeneic transplant, so the idea about a bridge to transplant has gained a lot of appeal for these newer agents that we are able to get people into remission. AG-120 is the IDH1 inhibitor that has been extensively studied by Dr. Courtney DiNardo at MD Anderson who presented her data also at ASH this past year, again a very similar trial in relapsed and refractory AML that was IDH1 mutated. And basically, to again cut to the chase again, a fairly high and impressive overall response rate of over 30% in the relapsed and refractory group, including 30% who achieved a CR or CRI. For those of you who have not been doing this for very long, these numbers are astounding. We can barely crack 20% in relapsed disease with best intensive chemotherapy regimens that we have had for years. The fact that we can get these types of responses with a single oral agent that is just generally well tolerated is very impressive. I will point out that the AG-221 drug in particular has been associated with a differentiation syndrome as a toxicity that is in line with its mechanism of action. It is felt to be differentiating agent in large part. Dr. DiNardo also showed data giving evidence that you could actually clear the IDH1 clone in a significant number of patients who achieve response with this particular compound. So, of the patients of 14 patients who achieved a complete response, 5 of them had mutation clearance of IDH1, and I think we recognized that mutational clearance based on what we have heard from our previous speakers is a very important endpoint in AML and clearly correlates with better outcome. So, we will be looking to see more details on this in the upcoming months and years, and you can see here graphically how many of the CR patients actually cleared their mutations, but it could take time to do it. It could take up to 6 months to clear the mutation, so it is not necessarily a fast-acting drug.

So, in summary, and I am out of time, but fortunately, I do not think anybody here is going to the U2 concert tonight. Maybe I am wrong. So, we have a little bit of flexibility. The next-generation HMAs, especially those with favorable pharmacokinetic profiles, such as guadecitabine or even oral azacitidine, which I did not get into, appeared to build upon the previous single-agent activity that HMA has demonstrated and I think will be absolutely indispensable as a future platform for drug development in older adults. Novel drug delivery vehicles such as CPX-351 I think are going to revolutionize not just AML but cancer care in general through their ability to deliver two drugs simultaneously at the optimal ratios, and in AML in particular, I think we are going to see a new standard of care for older secondary AML patients within the next few months. FLT3 inhibitors are very active in combination and as single agents. In FLT3 mutated disease, midostaurin is now the standard of care for mutated FLT3 patients who are under age 60 and next-generation inhibitors are very effective. As single agents, they can overcome resistance mutations and may provide their proverbial bridge to transplant which so many of us are looking to as a way to get our patients cured. IDH inhibitors are very strong single-agent actors as well in the relapsed setting, also with potential for bridging the transplant, and the BCL2 inhibitor approach also appears to be very promising at a more empiric level. You may not need to have a specific target to get an effect as evidenced by the very high response rates, and the combination of venetoclax in low-dose agents such as HMAs or low-dose cytarabine are showing very promising results and early evidence of prolonged survival. So, I have covered

a lot of material. I apologize for hitting some of it superficially, and I would be glad to answer any questions afterward. So, I think we have to move on to the esteemed Dr. Garcia-Manero Guillermo. Thank you.

Dr. Garcia-Manero Guillermo:
So now we are going to go to the clinic. I am not sure if we are going to be able to review all the cases. I do not know how much time we have. I really like to go through the questions at the end, and again, these are actually real cases. Of course, these photos I did not get them, and they are not the real person, but this lady looks like the patient I just saw a couple of months ago, but I think they reflect actual situations and they have a little bit of some twist on them and I am trying to going to go through them fast. Actually, this is my own opinion. I am pretty sure that Jeff and Dr. Stone may or may not agree totally in whatever I say, which will be fine. So, if you do not agree or you want to comment, please be happy to. So, Dr. Stone started his talk talking about APL and how we cure 100% of these patients. So, this lady, that I saw literally around 6 weeks ago, a 41-year-old lady from Mexico, and you will say why is he talking about Mexico, why is he pointing to this particular group? Well, if you live in Texas like I do, you will see that there is actually a tendency for people of Mexican origin, particularly what we call the Rio Grande area, the Valley as we call in Houston where there is a high frequency of these kind of patients. So, you get a phone call from someone let's say McAllen. This is a city in the border. There is like we have young female, maybe a little bit overweight with a little bit of white count. The first thing you are going to think if you practice in Houston is this is potentially acute promyelocytic leukemia. This is actually something that is very important. I do not know if it is the same thing in Massachusetts or in Florida. So, she is admitted to a local facility there because of low counts and she has been kind of easy bruising for again a few weeks. They do a CBC that I think will be standard. White count is low. She is anemic, has a low platelet count, and then, the reality is actually like at least Texas that is almost as big as Spain, that is where I was born. Not all hospitals are equipped to treat this type of leukemia. Now, the question is what do you do? I did not really rehearse with Dr. Stone, but this is really crucial because he showed you, and I am going to show you in a minute, the survival of patients with APL that go to a place that I have experienced is equipped to treat this type of patients, but the reality actually probably the survival of those patients in the overall, in the intent-to-treat population, I think, is around 60%. I think Martin Tallman has this kind of data. So, unfortunately, many patients will die early on in their diagnosis a few days where they are in some hospital trying to be actually diagnosed or treated. So, the take-home message, as Dr. Stone said, is you really need to like start therapy as soon as possible, even if you do not have a final diagnosis. And of course, the standard of care is to start all-trans-retinoic acid immediately. So, the question is, what do you do? Try to correct the coagulopathy that will characterize this disease, arrange for ambulance, or basically start therapy as soon as possible? And the answer is, and this may be obvious to many of you, but this is not so obvious in the general practice. You want to start therapy. There is nothing wrong if the patient actually ends up not having APL, you just used some tablets with basically no side effects. So, basically, you told the doctor to start that therapy in McAllen or Brownsville. Patient comes the next day, your ER is full. You do bone marrow. It looks like there are a lot of progranulocytes and Auer rods, these are morphological characteristics of the disease. But now, we come into the tricks of what happens here and that is may be what Elli and her group will probably at some point change this, because you heard Dr. Stone telling you that at Dana-Farber it takes you 3 or 4 days to get these genomic test, the same thing at the MD Anderson. So, you actually do not get this data immediately. I do not know about Memorial, but

you probably are going to have a little bit of a delay. You have to remember that there are alternatives to genomic testing. So, for instance, there are very specific, very fast tests that we use commonly at the MD Anderson. I do not know this is actually a test that is used all over the world, but this immuno type of stain immunofluorescence. It is called the spot test. You get this basically in 30 minutes, I believe. So, in our practice if a patient comes with suspected APL, you will do this test, get a phone call, and basically, it is almost 100% sure that you will have that answer. You can do other assays like real-time PCR assays that in some places may be actually a little bit faster than true genomic testing, and of course you may pick most of this translocation by conventional FISH, that in many hospitals if you can do that you probably can have this kind of information in 2 or 4 hours after you order it, and of course, you have already started your patient with all-trans-retinoic acid (ATRA). So now, they come with your spot test. It is positive. You gave this nice lady the first dose of ATRA, and now, the question is what to do? Basically, you will have a couple of options, right? Something like 7+3 ATRA. I hope nobody does this anymore. We have the so-called AIDA programs that are the AIDA based on Italian, European, and Spanish data with some type of chemotherapy with all-trans-retinoic acid, or basically just a known chemotherapy type of approach, let's say arsenic trioxide and ATRA that are basically in general considered as non-chemotherapeutic type of approaches. Of course, the answer is today you will be using the last option. You will do arsenic and ATRA as your first-line therapy. In patients with a high white count that are what we consider high-risk disease, there is a role for an anthracycline. Maybe, Mylotarg (gemtuzumab) will come back. It has an important role in that group of patients, and Dr. Stone was very gracious actually naming Dr. Ravandi who led a lot of the studies at the MD Anderson and serve as the basis for these randomized trials performed in Europe, and basically, you see the survival curves if patients make it to a center that has expertise in this type of disease. So, of course, really great story, but it is not that easy. So, you need a level of expertise. There are some complications when you give these therapies. So, if you do not see a lot of these patients, my suggestion is actually try to transfer them to a place where they have volume and enough experience and support to treat them. So, this is probably the best leukemia you can have right now.

CASE #2

The next one probably is also very good. So, this is a young man. This is actually a patient that came the next day after I saw this lady who is a good man because all the patients have good prognosis in general. So, young guy, 29-year-old man from Louisiana, he comes with a diagnosis of acute myelogenous leukemia. Bone marrow shows a very high percentage of blasts. So, there is no doubt about it. He is otherwise healthy. No comorbidities, no major issues, but he has leukocytosis. He has a white count of 87,000, is anemic, has low platelets. You ordered a bone marrow evaluation. You ordered your cytogenetic as Elli was showing. You ordered your whatever the 1G1 panel is. Every institution seems to have a different panel, but another question is what to do, and this actually has a trick because I would like to have at least data stat, in like 20 minutes. I would like to know if they have this splicing chromatin pattern or not or do you have a targetable mutation. So, I think one of the challenges that we are going to have is rapid incorporation of this type of testing into our clinics, because now you have a young man, symptomatic, but this person has a white count of 80,000. Are you going to sit on him until you start some formal therapy? So, we will see what we decide to do. So, wait or you just go ahead and start some type of therapy right away. So, because basically your patient has a high white count, I think most of us will probably not see sit on a patient like that and you will start some type of therapy. To be honest, we do not use 7+3 in our center. We use high-dose ara-C

type of induction with some combination with nucleoside analog, but I put 7+3 because I agree that that will be the standard for most of the institutions. Now, 2 weeks later when you get your cytogenetics, actually in our hospital this will take 3 or 4 days if we rush them, but I think in general my impression is that most people will get cytogenetic information 2 to 3 weeks after you order this kind of test. So, he comes with a very good cytogenetic lesion, in this case an inversion 16, but this patient actually has also an addition of chromosome 22 just by chance, and this is the actual karyotype of this particular patient. So, another question is what do you do with this young man? So, let me put all the options here for time sake. So, in remission, once you achieve that, if you achieve that will you offer a high-dose ara-C type of consolidation? Maybe, and I get this phone call or email very frequently. "Hi, my patient has an inversion 16 or 8;21, but I have a couple of cytogenetic abnormalities, is this good, bad, does it really matter?" And as Dr. Stone was saying, it is possible that this patient will achieve a very deep response by cytogenetic, by molecular, by minimal residual disease. You are going to ask this question, do I really need to consolidate this patient? I do not know. So, I think this is a very important group of patients, and there is a study that we presented on behalf of the Alliance and SWOG at ASH this year, a huge North American effort trying to look at different forms of chemotherapy, but the lesson actually that we learned very clearly is that I do not know if IA is inferior or not to 7+3, that is for another day, but it is clear that you need a high-dose ara-C consolidation type of approach for this kind of patient with inversion 16, 8;21, and if you want to cure them. If you look at this graph, the black bar on top, that is actually the survival of these patients, and what is beautiful about this is this is done all through North America. So, we are not taking about the APL story I was telling you, you may get into Dana Farber. These are hospitals right that are through the country, so we are not talking about tops, so people actually know how to use this high-dose ara-C. This is the standard of care for this group of patients, and actually you can achieve really dramatic results, almost as good as you see in this figure compared to that APL data. So, I think that is quite straightforward and two very nice stories in acute myelogenous leukemia.

Now, this case is a little bit complicated, and I'll see what Dr. Stone, Elli, and Jeff think. This is a young woman, 39, who comes to see me because she has this weird diagnosis of myelodysplastic syndrome. There is 13% blast. She has no past history and no exposures. The doctor in India is kind of hesitating. There are no symptoms and no comorbidities. She comes to see us with white count of 7.4. She has anemia, some thrombocytopenia, you order this bone marrow, and of course with cytogenetics and some genomic markers, and then your decision is, do I wait? Do I start? What do I do? So, one approach is just wait and see what happens with your genomic test and cytogenetics. This is a young lady, very fit, why do not I give her 7+3 type of program, treat her like acute myelogenous leukemia, even if she has only 13% blast that all of you know this is basically in the realm of myelodysplastic type of syndrome, or you know what, she has MDS, let's treat her with MDS with a hypomethylating agent type of approach. So, because she is young, maybe we will also consider her allogenic stem-cell transplantation, and she came from India, so I think she was stable enough to wait for a few days. I can dial 2660, this is the cytogenetics lab in my hospital, rush it, and then 3 or 4 days later, I get the results. And it turns out that this person with diagnosis of myelodysplastic syndrome has normal karyotype for a female, and her genomic pattern actually 3 or 4 days later comes with an NPM1 mutation without a FLT3 mutation and no other mutation. So, now you have NPM1-mutated patient with "myelodysplastic syndrome" 39 years of age. So, what would you recommend here? Treat with a program like acute myelogenous leukemia, treat with a program like

myelodysplastic syndrome, and take this person to allogenic stem-cell transplant. Many of you may be thinking, well, how does her bone marrow look like, does the bone marrow look like myelodysplastic syndrome or does this bone marrow look like AML? Well, actually the bone marrow looks like myelodysplastic syndrome, flow cytometry has an MDS pattern, this frank dysplasia, etc. So, it looks like an MDS. So, the first issue is that this a huge controversy, and I am going to go tangential here, I will come back, and Dr. Stone or Dr. Lancet, one of them showed that in many patients with MDS or an AML-like MDS type of situation, this hypomethylating agents at the end result in a longer survival, probably because you have less toxicity at the beginning, and there are many data sets that basically have shown this. Going back to the SWOG 1203**,** and I use this not because I had the honor to lead this, it is just I think is the most recent randomized AML kind of ara-C type of data that we have out there, and because I had easy access to the slides. We actually see the same phenomenon. In the black bar there, just show the outcomes of patients with AML in this case with an NPM1 mutation without FLT3, and again, a very acute rate, suggesting that an ara-C type of program is good in this group of patients. So, when I saw this lady, a little bit before because I had seen a few patients like these, I thought what is the story of NPM1-mutated MDS? I have no clue. So, we look at it. It is extremely rare, MD Anderson of 3000 patients or something like this, I think we have 20 with this particular mutation. So, of course, this is not a very frequent event, and I am not trying to tell you about this particular disease. What I am trying to illustrate here is that this particular mutation trumps in this type of situation, the morphology, and other characteristics of the disease. So, when we went back to the history, what I actually saw is that some of my colleagues already knew that, even if we have not published on this, and had treated some of these NPM1-mutated MDS patients with an ara-C based program. And you see in red that this is a 100% cure rate in this group of patients. So, the point that I am trying to illustrate here is that you have to pay attention to this molecular data, and the trick again in the first patient, the white count is high, you cannot wait. This patient you have some time to wait and it is actually a tremendous benefit for this lady that was ready to start on a program with azacitidine that may not be bad, but you are talking about chronic non-curative therapy on a young patient, so we were treating her at the end with ara-C based program, and she has been complete remission for a couple of years. So, I think this is really important analysis from this type of genomic annotation.

Dr. Richard Stone:
Guillermo, I would like to make one comment and ask Elli a question. The comment is the WHO has for a long time, said if you got CBF abnormality and less than 20% blasts, that is AML, so maybe we should think about asking our pathology colleagues to change again and consider patients like this AML. But Elli, you showed some very intriguing data about the heterogeneity of NPM1 patients. So, in relapse, you showed what you think about that in regard to this? What do you think about that in regard to survival curve that Guillermo just showed? It looks like obviously that NPM1 group at the top that got 7+3 probably included a bunch of different other mutations.

Dr. Elli Papaemmanuil:
So, two really important points. I think having had the experience to profile MDS and AML, we know that the diagnostic criteria and the boundaries that we set as MDS and AML can be much refined by the molecular basis because ultimately what drives the disease is this mutation. So, in my view, an NPM1 mutation provides the evidence for NPM1-based treatment and inclusion into an AML-type protocol. Now, you mentioned you treated this patient two years ago. So, I would imagine that the panel you have used then would have not included the splicing factor

genes, and one of the questions is, could this patient also have mutations in the splicing gene that would be the modifier for the phenotype we are observing? Ad this is a very interesting group that we could go back to profile and then evaluate whether this early upfront chemotherapy would benefit this cohort as a whole.

Dr. Richard Stone:
If you go to that slide; look at the top curve. That subsumes all the different subtypes, so I do not know, it is just a trial, the follow-up is not long, but obviously, some of these people having splicing mutation they are doing okay, but I think we need longer follow-up probably.

Dr. Guillermo Garcia-Manero:
But I learned something. Now, you see total MRD, negative flow, no NPM1 mutation. So, she has all the molecular traces of major molecular response. Now, we move on. So, again, that point was not to teach you about this very rare disease you probably are never going to see, but it is to teach about the point of the importance of some molecular events in a particular subset of patients. Now, this is maybe of course a more frequent situation. A 59-year-old gentleman comes with a high white count, you run your peripheral smear analysis in the ER, has a white count over 90,000, low platelets, etc. You order of course your bone marrow with your test and then the question is, what do you do? It is the same question, and I do that not because I repeat myself, well I kind of do, but because I want to elaborate on this point, the importance of this test, I am trying to get them as soon as possible, so you will start therapy or not or you wait for some of the tests. Of course, I do not think that anybody basically is going to just sit on this individual. So, you start your therapy with an ara-C based program, and now two weeks later, your patient comes with a normal karyotype. Again, this is a man. He has this isolated alternation in FLT3 gene that Dr. Stone and Dr. Lancet showed. So, now the questions are what do you do with this? So, in remission, offer high-dose ara-C consolidation or because the patient has FLT3 mutation, you go on and try to rush into an allogenic stem cell transplantation, but actually, you saw earlier some of these results with the transplant in this group of patients not so really positive, or tried to use some type of targeted approach with a FLT3 inhibitor. We have seen these many, many drugs in development, one that was just approved a few weeks ago. So, basically, the decision here is that you probably will do all that we discussed. So, you are going to add FLT3 inhibitor. You have one approved, midostaurin. I think you are going to still consider that patient for an allogenic stem cell transplantation, and what I think we should start thinking as myeloid physicians, like the myeloma people do, and think about total therapy. I think this idea that the therapy is dichotomized between pre-transplant and post-transplant is actually not right. I think what we need to think about now is the total continuum of this disease, and I think what we are going to do, I do not know if the indication is going to allow this or not, but actually to put back those FLT3 inhibitors post-transplant in those patients that you have been able to take to transplantation, and I do not know if Jeff or Rich want to comment on this.

Dr. Richard Stone:
Well, midostaurin is not approved as a maintenance or as a post-transplant drug. However, after transplant they should be placed on the BMT CTN trial comparing gilteritinib to nothing, so we rearrange the question, after transplant.

Dr. Guillermo Garcia-Manero:
I totally agree with this. I have to mention also that we have quite a bit of experience with this drug that is approved for other indications but that you can actually use in AML that is called sorafenib. Many studies from Europe and MD Anderson have shown significant activity of this compound, and this is our standard of care in this group of patients before midostaurin was approved. But let's go now to a more difficult case, and I think this actually is something that is I deal in my practice quite a bit. So, 70-year-old gentleman basically at the limit of stem cell transplantation, comes with a diagnosis of acute myelogenous leukemia. Bone marrow at home showed 25% blasts, something that we have called actually myelodysplastic syndrome a few years ago, has the cytopenia that characterizes this disease, you order your test. Again, the same question, do you wait, or do you start? I think in this situation most of us will wait for the studies. Now, I am impatient, so I harass these people in the lab to give me this data, and then basically you get these results where again you were not sure, you wait. The bone marrow repeated here in your local hospital shows 32% blasts. So, there is no doubt this is AML MPO positive, but this patient now has very complex karyotype with a 5, 7, 17, etc. You get your p53 assay. I think if you live in a place where you cannot do this kind of very sophisticated genomic analysis, I think if you want one test beyond the FLT3 is this p53. I think this is actually transforming our approach to AML and myelodysplastic syndrome, so you get that, and this patient has a mutation on this gene, and now your question is, what do you do with this information? Again, he is 70 and let's say in good shape, has AML, do you treat it like AML, with 7+3? Do you treat it like an MDS with a hypomethylating agent like azacitidine? You probably are going to think about transplantation. Would you consider a clinical trial? So, I would be interested to know what Jeff or Rich think about this.

Dr. Jeffrey Lancet:
It is a real conundrum. We see this all the time and there is probably not a right answer. I guess I would agree with everything you said about preferably utilizing a lower dose or lower-intensity regimen in this type of patient, and I would be especially cautious about approaching transplant in a p53 mutated AML or MDS for that matter because these patients do exceedingly poorly, and to subject in older patient who had allogenic transplant where there is an extremely higher risk of failure to me is something that you have to do with a lot of trepidation, so I am very reluctant to offer transplant to these patients outside of the context of a clinical trial or at the very least being able to demonstrate clearance of the clone. Because if they have any presence of the clone, they do just miserably, as you know.

Dr. Richard Stone:
I will answer the question, then I would open it up to the audience because we're almost done, but yes, I would give this patient 10-day decitabine. Actually, if he was fit, I would try to get venetoclax, even though that is totally unapproved, and I probably should not say that, but I have been impressed by the combination, and I would transplant him if he was fit and knew the risks. Coleman presented wonderfully in ASH and the *New England Journal of Medicine* about the lack of good outcome with p53 MDS going to transplant. On the other hand, there was a tail in the survivor curve, and if the patient knows what they are getting into, I would be aggressive. So, I would use prolonged decitabine, venetoclax if I get it, and transplant if everything was in order.

Dr. Guillermo Garcia-Manero:
So, what I am learning from the two experts is that maybe traditional 7+3 therapy would not be your first choice. For sure, this will be something that we will not consider in our program. We will really approach this patient more from an MDS type of perspective.

Dr. Jeffrey Lancet:
I would point that though that this is a patient that would fit the criteria for CPX-351 when approved with a high-risk cytogenic subtype, and the data are still unclear as to what the role of p53 will be, but this is a patient you could conceivably treat with a more intensive approach if you have that drug available and he is fit.

Dr. Guillermo Garcia-Manero:
I actually tend to disagree with this concept because what the data that you are referring to is comparing it with 7+3 not with a hypomethylating agent per se. So, I am not 100% sure. I agree with Dr. Stone that in this p53 subset of patients, I think this hypomethylating agent seems to be having a little bit of open advantage, but I think this is a very valid point.

Dr. Richard Stone:
We need to see the data. We argue that trial should be analyzed prospectively based on genetics. It was not done. Hopefully, it is being done now and we can get that kind of data.

Dr. Guillermo Garcia-Manero:
So, what is the data for the hypomethylating agents? Dr. Stone showed this in the first MDS 001 trial. There was already a very strong hint that these people with 20% to 30% blast, they actually did well on this particular trial. One thing that we know but it was very nice to see on this randomized trial, and you cannot see the animation here, is that this benefit was irrespective of complex karyotype. So, you saw actually a benefit with the hypomethylating agent in this group of patients with 7, etc., and then this issue of the p53 was very nicely shown by the Washington group in this paper in *the New England Journal of Medicine*, but actually a few months earlier, our group had published on some 300 patients with this disease showing that response to hypomethylating agent is not mediated by p53 mutation. Now, what we kind of disagree a little bit and we wrote as smoldering in the *New England Journal of Medicine* when that paper came out that this is not dependent on 10-day decitabine. We see these with 5-day decitabine. We see this with different schedules with azacitidine, etc. So, it seems to be a phenomenon related to some form of hypomethylating agent. I agree with Dr. Stone that probably combining these with some other agent will make this even more powerful, but I think that these epigenetic modulators may work in an agnostic way related to this p53 mutation status. So, we discuss this. Nothing wrong with doing 10 days of decitabine. We use this quite frequently in our practice as well, and we already saw the data from the Dombret trial. So, I am going to go a little bit fast through this. But actually, it is possible that this patient will tell you, "Well doctor, I came to Dana-Farber for something beyond azacitidine or 10-day decitabine, so what is up there?" So, of course, clinical trial, and I think what we need to do as people treating this patient is it is good that we are approving a lot of these drugs. We need to continue to do more research and consider more of our clinical trials and keep advancing the field, and I agree that CPX is an option there and maybe this patient could have some other mutation or modalities. I am not going to go through the pracinostat data, but I think that these doublets with azacitidine are intriguing, and this shows the survival curve with this particular combination, and this is actually

an ongoing phase 3 trial that is starting worldwide comparing azacitidine plus/minus this HDAC inhibitor in older patients with acute myelogenous leukemia.

Make a point here, time of relapse fundamental. Actually, Elli went very fast through what I thought it was a critical slide where you were shown the dynamics of relapse, timing on the relapse fundamental, first year relapse, but this is more than 24. Probably, you can rescue them with similar type of therapy that you did at the beginning in between, it depends.