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Precision Strikes in AML: Navigating the Evolving Landscape of Targeted Therapies

Opening:

Welcome to CE on ReachMD. This activity, titled “Precision Strikes in AML: Navigating the Evolving Landscape of Targeted Therapies” is provided by Daiichi Sankyo, Inc. and Kura Oncology, Inc.

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Chapter 1

Dr. Erba:
Hi. I'm Harry Erba, Professor of Medicine and Director of the Leukemia Program at Duke University in Durham, North Carolina.

We are going to be discussing today *Precision Strikes in AML, Navigating the Evolving Landscape of Targeted Therapies*, and specifically looking at the use of FLT3 and menin inhibitors. Let's start with an overview of this evolving landscape of AML treatment based on AML genomics.

We know that patients with acute myeloid leukemia at the time of presentation will have recurrent genetic changes that are somatically acquired that help to define the disease, define risk stratification, and actually are now targets for therapy.

For example, in this dataset, 48 genes were found to be recurrently mutated, 35 of them mutated in more than 1% of patients, but most of the patients had at least one mutation. In patients over the age of 60, mutations in RUNX1 and chromatin modifiers and DNA methylation enzymes were more common, as were the spliceosome mutations. But as you can see, the three most common mutations are in the genes FLT3, NPM1, and DNMT3A.

And we know that these gene mutations are not occurring in isolation. So from this same dataset, you can see that each vertical line represents one patient and the mutations in that sample at the time of diagnosis. Today, we are going to focus on KMT2A rearrangements, which occurred in about 6% of patients in this registry study, NPM1 mutations occurring in 33.3%, and the FLT3 mutations, the FLT3-ITD accounting for about 30% of patients, and the FLT3 TKD in 11% of patients. And what we've learned over the years is that these mutations, both cytogenetic changes, fusion genes, and mutations in these genes, actually govern prognosis and help us determine the prognosis of patients at the time of diagnosis.

But as I mentioned, these gene changes may interact with each other, and FLT3 and NPM1 are a great example of how the presence or absence of one or the other genes impacts on the prognosis associated with the other. So for example, there have been multiple studies that have shown that the impact of the internal tandem duplication in the FLT3 gene is most pronounced when patients also have

mutations in NPM1 and DNMT3A. And in fact, Elli Papaemmanuil showed on the left that it was actually the co-mutations that determine prognosis in FLT3-ITD-mutated patients more so than the variant allelic frequency or the amount of the mutation.

Chapter 2

Dr. Erba:
Mutations in NPM1 actually lead to the overexpression of the FLT3 tyrosine kinase. So NPM1 mutant protein is brought to the promoter regions of the HOXA9 and MEIS1 genes by XPO1 and helps recruit menin and the KMT2A proteins to this area, leading to upregulation of HOXA9 and MEIS1. MEIS1 in turn leads to the upregulation of FLT3, so you get increased expression of the FLT3 protein. And in fact, FLT3 is expressed on AML cells, hematopoietic stem cells, on AML blasts. And the level of expression of native FLT3 has been shown to be associated with inferior outcomes.

FLT3 is a receptor tyrosine kinase. It is activated by binding the FLT3 ligand. It is expressed, as I said, on hematopoietic stem cells, and it's critically involved in the proliferation and differentiation of hematopoietic cells. As I mentioned, high FLT3 expression on AML blasts is associated with inferior outcomes.

Now in AML, there are two major types of FLT3-activating mutations. The more common is the FLT3 internal tandem duplication, duplication of anywhere from 1 to over 100 amino acids in the protein, and this occurs in about 25-30% of AML cases and has been associated with inferior survival due to an increased risk of relapse. Previously, this was considered to represent a high-risk or adverse-risk mutation prior to the incorporation of the FLT3 inhibitors into standard treatment. FLT3-ITD is now classified as intermediate risk by ELN 2022 because of the incorporation of these FLT3 inhibitors into chemotherapy.

The effect on outcome also depends on the co-mutations, as I mentioned, as well as the allelic ratio. Now on the other hand, the less common mutations that activate FLT3 in the mutations in the tyrosine kinase domain have an unclear effect on prognosis. So for example, prior to the incorporation of the FLT3 inhibitors, you can see in these two studies that the outcome of patients receiving intensive chemotherapy for newly diagnosed AML with FLT3 mutations was worse if there was an ITD mutation than if there were no FLT3 mutation or if there was a FLT3 tyrosine kinase domain mutation at codon 835.

On the other hand, multiple studies have failed to show an impact of the FLT3 TKD on ultimate outcome of patients with acute myeloid leukemia. One dataset actually showed it was associated with a better survival to have a FLT3 TKD, but this is most likely due to the concomitant mutations such as core binding factor fusions that can occur with the FLT3 TKD.

Chapter 3

Dr. Erba:
I'm going to turn my attention to one of these genes now, the NPM1 gene. And as you can see here, the NPM1 mutation has been associated with a favorable outcome using either intensive or less intensive therapy, as long as the FLT3-ITD is not present. If the FLT3-ITD is present with an NPM1 mutation, it is considered intermediate risk with intensive chemotherapy, and patients with a FLT3-ITD mutation are felt to have intermediate risk by the ELN 2024 risk stratification for patients with AML receiving less intensive therapy.

NPM mutations are one of the three most common genetic lesions in AML, as I said, 30-35% of cases. It's typically associated with a normal karyotype, and this is considered a driver of the AML or it's a leukemogenic driver. It is not observed in clonal hematopoiesis. And in fact, according to the WHO, regardless of blast percentage, if a patient has a nucleophosmin or NPM1 mutation detected, that is diagnostic of AML. By the International Consensus Classification, that classification still requires at least 10% blasts. The NPM1 mutation frequently co-occurs with FLT3 mutation, DNMT3A, and the IDH mutations.

Now, how do you recognize this at the time of diagnosis before you get back your PCR analysis? Well, one thing to look at is the morphology of the blasts. You can see here these deep invaginations in the nuclear envelope leading to the terms fish mouth or cup-like nuclei, very characteristic of NPM1-mutated AML. And also in the immunophenotype by flow cytometry, where you see a myeloid immunophenotype with decreased or absent expression of CD34 and HLA-DR, the stem cell markers. Now, acute promyelocytic leukemia can have a very similar immunophenotype but typically has higher expression of CD33 and especially myeloperoxidase.

As I mentioned, NPM1 without a FLT3-ITD mutation is considered favorable risk by the ELN 2022 risk stratification. This is recent data

from Europe in over 1,500 patients with AML who received intensive induction chemotherapy with an anthracycline and cytarabine followed by high-dose Ara-C plus or minus stem cell transplant. In the green line on the left, you can see the outcome of all of the patients with ELN 2022 favorable risk disease, but it's broken down on the right. And what you'll notice is out of the three genotypes that make up ELN favorable—core binding factor fusions, NPM1-mutated, and the bZIP domain mutation in CEBPα—NPM1 has the worst prognosis, with a long-term survival of only about 50%, but this is with treatment with 7 and 3 basically and high-dose cytarabine.

More recently, there have been studies showing that more intensive chemotherapy may improve the outcome of patients with NPM1-mutated disease, such as this data from the United Kingdom showing that patients receiving FLAG-IDA compared to any of the other induction chemotherapy regimens were more likely to have an MRD-negative remission after cycle 2 of chemotherapy, and they had a lower 3-year cumulative incidence of relapse if they achieved MRD negativity.

The patients treated with FLAG-IDA had better overall survival and a lower risk of relapse, as shown at the bottom right. Also, they showed an impact of gemtuzumab ozogamicin on outcome, as you can see on the bottom left, with an improvement in survival in those patients getting one dose of the anti-CD3/CD33 antibody drug conjugate, gemtuzumab ozogamicin.

Furthermore, venetoclax, the BCL-2 inhibitor, has been shown to improve outcomes in or be associated with improved outcomes in NPM1-mutated AML. On the left, you're looking at retrospective data from MD Anderson showing a very high complete remission rate with HMA and venetoclax in NPM1-mutated patients of 96%. And in fact, the overall survival of patients receiving HMA and venetoclax was superior compared to those getting HMA alone or even intensive chemotherapy.

More recent data from MD Anderson shows that in patients receiving intensive chemotherapy such as FLAG-IDA, CPX-351, and cladribine, idarubicin, and high-dose Ara-C, all of those with venetoclax, those patients had a very favorable outcome with an 83% survival at 3 years.

Chapter 4

Dr. Erba:
Now, turning our attention to KMT2A rearranged AML, this is found in about 5-15% of patients with newly diagnosed acute leukemia, and it could be seen in both acute myeloid and acute lymphoblastic leukemia, and it is one of the more common mutations in mixed phenotype acute leukemia. The median age at diagnosis of KMT2A-rearranged AML is lower than in all of AML. Make particular note of the fact that in neonates with acute leukemia, typically ALL, over 80% will have a KMT2A rearrangement. In adults, however, only about 10-15% of patients with acute leukemia will have a KMT2A rearrangement.

Now like NPM1, which is a driver mutation or a founder mutation in acute myeloid leukemia, the same is true for these rearrangements of the KMT2A gene that's found on chromosome 11 at band q23. This gene used to be called the mixed lineage leukemia gene or the myeloid lymphoid leukemia gene, or MLL, so it goes by different names, a variety of names in your pathology reports.

In AML, it's important to remember that KMT2A rearrangements are strongly linked to therapy-related AML, especially after the primary tumor has been treated with a topoisomerase II inhibitor such as an anthracycline or etoposide, and the latency between that chemotherapy and the development of AML, typically with a monocytic phenotype, is very short, measured in less than a year to up to 3 years.

Patients with newly diagnosed KMT2A rearranged AML have a higher risk of relapse compared to normal karyotype AML.

A recent analysis that was presented by Dr. McMahon showed that the median age of KMT2A rearranged AML was 55 with 41% of patients being over the age of 60. The most common of these rearrangements of the 11q23 band or the KMT2A gene is with chromosome 9, the 9;11 translocation found in 45% of all of these patients. On the other hand, what you can see on the bottom right, co-mutations are pretty uncommon, but when they occur, the most common are the KRAS and NRAS mutations.

Here you see the survival in this retrospective analysis, overall survival on the left and disease-free survival on the right was superior with intensive chemotherapy compared to patients receiving HMA and venetoclax or HMA alone.

So why are we discussing specifically the NPM1-mutated patients and the KMT2A rearranged in this program? Well, it's because both of

those share a common gene expression pattern. Both the KMT2A fusion proteins and the mutated NPM1 protein lead to the high expression of HOX and MEIS1 genes, which creates a leukemogenic phenotype with inhibition of differentiation, increased cell proliferation, and a block in apoptosis. And this recruitment of the transcriptional complexes to HOX and MEIS1 genes is through the chromatin scaffolding protein, menin, which we will talk about later.

Chapter 5

Dr. Erba:
So how are we going to identify these patients with these mutations so we can take advantage of inhibitors that we now have available? I'm showing you here a schematic of the FLT3 gene. And as I said, about 25-30% of those patients will have an internal tandem duplication, and 5-10% will have tyrosine kinase domain mutations. These can be identified by your local diagnostic lab, the ITD mutation with a short turnaround time, and that's what we do at Duke University in order to identify patients who may benefit from a FLT3 inhibitor more rapidly.

The FDA-approved diagnostic companion assay, LeukoStrat, has also a turnaround time of 3 to 5 days and can detect both tyrosine kinase domain mutations and the internal tandem duplication. However, the LeukoStrat test only identifies mutations at the codons 835 and 836, whereas your next-gen sequencing panel, which has a longer turnaround time, will identify tyrosine kinase domain mutations not only at D835 and I836 but other noncanonical mutations that actually might be sensitive to a variety of FLT3 inhibitors. Now over time, these next-gen sequencing panels have gotten much better at identifying and actually quantifying the internal tandem duplication as well.

So what do you see in a typical NGS report for a patient with AML? Well, there are a variety of mutations that can be identified. What I'm showing you here are first mutations that seem to be founder mutations, DNMT3A, WT1. These mutations will affect epigenetic modulation of gene expression, so they're DNA methylation enzymes, chromatin modifiers, for example.

And then you have a cooperating mutation like NPM1 followed by the presence of a signaling mutation. And sometimes you can glean some understanding of the acquisition of these mutations by looking at the variant allelic frequency. However, pathologists will tell you that there are a lot of caveats in making big conclusions about the ontogeny or the development of these mutations in the hematopoietic cells over time just based on the variant allelic frequency.

So let's consider then how are we going to do these evaluations? Well, you could use either a peripheral blood sample or a bone marrow aspirate. If I have a patient coming in with a white count of 100,000 and it's mostly blasts, there is no problem in sending that sample for immunophenotyping by flow cytometry, cytogenetic analysis, FISH analysis, PCR tests, and next-gen sequencing. Okay? But the sample must contain the blasts if you want to see what are the mutations that are driving the leukemic cells. And you have to be careful, because if you don't have blasts in the sample, then you are very unlikely to find mutations such as NPM1 or FLT3, which are typically not seen in clonal hematopoiesis, whereas other mutations, such as in chromatin modifiers and DNA methylation enzymes, spliceosome enzymes, those gene mutations can be seen not only in clonal hematopoiesis but in myelodysplastic syndrome.

Polymerase chain reaction will allow you to get a much more rapid turnaround on mutations, and we find it very useful in identifying patients with FLT3 mutation so that we can add a FLT3 inhibitor to chemotherapy. Next-gen sequencing, however, detects a broader array of mutations in these genes that are recurrently mutated, but it can take some time to get this data back.

Specifically looking at NPM1, the mutations in NPM1 first identified by Falini and colleagues are typically out-of-frame or frame-shift mutations in the last coding exon of the NPM1 gene, which happens to knock out a nucleolar localization signal and to create a nuclear export signal. So unlike wild-type NPM1 shown in green on the left that's in nucleoli and in the nuclear envelope, the DNA being stained red, you can see in the mutated cells the nucleophosmin protein, or NPM1, is in the cytoplasm. And so NPM1 mutations can be detected by PCR tests, by next-gen sequencing, even by immunostaining. However, these mutations are very small, typically tetranucleotide or maybe slightly longer frame-shift mutations shown at the top of the slide that are not detected by FISH or cytogenetics.

Now, the KMT2A gene can be rearranged with a multitude of other genes. There are over 100 different genes that have been shown to be able to fuse with KMT2A. It's always the 5 prime end or the amino terminal end of the KMT2A protein that is fused to another protein. The most common of these, as you can see in the table, is the KMT2A-MLLT3 fusion, which is the 9;11 translocation, which I mentioned

earlier.

And although there are over 100 different fusion partners, there's a short list of only about eight that are associated, that do fuse with KMT2A and may be targets then of menin inhibitors, as we will discuss. These mutations can be detected in a variety of ways. Cytogenetic analysis can detect them, but the turnaround time is longer. The FISH analysis is typically done using a break-apart probe, where fluorescently tagged probes for the 5 prime and 3 prime ends of the KMT2A are used to hybridize to nuclei. When there is a fusion or a rearrangement, those two signals are separated. They call this a break-apart probe. But even FISH and cytogenetics may miss some of these fusions. RNA sequencing techniques will be able to detect the KMT2A fusions with all of these known partners.

Chapter 6

Dr. Erba:
Let's get into now some details of the inhibitors that we're using. And this all started with midostaurin. Rick Stone gets a lot of credit for his work of combining a first-generation type 1 FLT3 inhibitor with chemotherapy in phase 1 studies done in Boston. Once the optimal dosing of midostaurin with intensive chemotherapy was worked out, an international trial was launched called the RATIFY trial, in which patients 59 years of age and younger and those with a FLT3-ITD or TKD mutation—and 22% of them had a TKD mutation—were randomly assigned to receive 7 and 3 followed by 2 weeks of midostaurin or placebo. And if they achieved remission, high-dose cytarabine followed by 2 weeks of midostaurin or placebo and then up to 1 year of midostaurin or placebo. Patients could undergo allogeneic transplant once they have achieved a remission.

This study showed an improvement in survival of patients receiving the midostaurin. The difference in the median survivals is quite dramatic, 75 months versus 25 months. I think a better way of looking at the data is survival at 48 months was 51% with midostaurin and 44% with placebo, or a 22% reduction in the risk of death, a hazard ratio in favor of midostaurin of 0.78. And this was regardless of the fact that equal numbers or similar numbers of patients actually achieved a response in the two arms of the study.

However, it seems that it was only the patients who received midostaurin who then went on to get a stem cell transplant in first remission who had the improvement in survival, as shown on the right. Patients who did not get a stem cell transplant in first remission did not have any benefit of midostaurin.

However, this study then raised a question: Should patients with AML be treated with a FLT3 inhibitor such as midostaurin that is not specific for FLT3 but inhibits other kinases, both tyrosine and serine-threonine kinases that might be involved in AML pathogenesis? Or is this benefit really due to the fact that FLT3 is being inhibited?

Chapter 7

Dr. Erba:
And this led to the study of quizartinib, a second-generation type 2 inhibitor of FLT3. Second-generation, meaning it was rationally designed, and it's a type 2 inhibitor which only binds to the inactive conformation of the FLT3 protein. Now, because the tyrosine kinase domain mutations cause the protein to fold into its active conformation immediately, there is no activity of quizartinib in FLT3 TKD-mutated patients.

So this study, the QuANTUM-First study, was very similar in design to the RATIFY trial, with some important differences. The chemotherapy was similar. Daunorubicin or idarubicin, it was 50% had received daunorubicin, 50% received idarubicin, and either 100 or 200 mg/m^2 of cytarabine in a 3 and 7 schedule. And this chemotherapy could start while the patient was being screened centrally for the FLT3-ITD mutation, and the randomization actually occurred on day 7.

Patients achieving a remission could then go on to get quizartinib or placebo for 2 weeks following high-dose cytarabine, and then up to 144 weeks of quizartinib or placebo as a continuation or maintenance. And as you can see, allogeneic transplant was also allowed once the patients achieved a remission.

Now, what's different about this study is that it was only FLT3-ITD-mutated patients based on the activity of quizartinib as a type 2 inhibitor. We included in the study patients up to and including the age of 75 who were fit for intensive chemotherapy. And as I said, the chemotherapy could start before it was known if the patient was able to actually be randomized based on the central review.

The primary endpoint of the study was reached with an improvement in survival. With quizartinib, it was 32 months. With placebo, the median survival was 15 months. These curves look very similar to the RATIFY trial. In fact, the hazard ratio in favor of quizartinib for survival was 0.78. However, what's different here is that in patients who either did receive an allotransplant in first remission on the left or did not receive an allotransplant in first remission on the right, there was a benefit of quizartinib. Now, these are post hoc secondary analyses, but in the analysis of this data, we found that both quizartinib and transplant were important for improving the survival of patients with FLT3-ITD mutated AML.

The CR rates were similar between the two arms. There were more CRi's with quizartinib, likely due to the fact that there's more delayed neutrophil count recovery with quizartinib after 7 and 3. And the median duration of those CRs and relapse-free survival was three times longer with quizartinib than placebo.

And again, if you look at the continuation of quizartinib or placebo after the completion of consolidation, the hazard ratio in favor of quizartinib on overall survival was 0.40, or a 60% reduction in the risk of death without an allotransplant.

This was also the first prospective international randomized phase 3 study that incorporated a very sensitive MRD assay. In this study, we used a NGS-based FLT3-ITD assay to look at how it correlated with outcomes. On the left, what you can see is that at the end of induction, the median FLT3-ITD variant allelic frequency was lower with quizartinib than with placebo, and that was statistically significant. And importantly, more patients achieved a completely negative assay result using this FLT3-ITD MRD assay, 22% versus 14%. On the right, what you can see is regardless of what the patient received, MRD negativity was associated with a better survival regardless of treatment, but again, more patients achieved MRD negativity with quizartinib.

And in fact, correlating the MRD negativity using a cutoff of the variant allelic frequency of less than 0.01, or 10^4 cutoff, in patients who remain positive at the end of induction, shown on the right-hand side of the slide, overall survival in the top right and relapse-free survival in the bottom right were superior with quizartinib in those patients. The benefit in the MRD-negative patients after induction was not as clear, suggesting that quizartinib continued to provide benefit for the patients.

Now, unlike the RATIFY trial, we included patients up to the age of and including the age of 75. Forty percent of the patients in the study were 60 years and older. Now, if you just look though at the patients who are 59 years of age and younger who had a FLT3-ITD, the hazard ratio in favor of quizartinib on survival was 0.68, or 32% reduction in the risk of death, which I believe compares favorably with the 22% reduction in the risk of death as seen in the RATIFY trial. But again, all the caveats about comparing between two large phase 3 studies. But the data on the right suggests that quizartinib might not have a benefit in patients who are older. And in fact, we saw higher induction mortality with quizartinib compared to placebo in patients 60 years of age and older.

However, I refuse to believe it's only about age, and genomics have to be important. Remember I said patients with NPM1 and DNMT3A mutations with a FLT3-ITD have a worse outcome than patients with FLT3-ITD who do not. Well, the QuANTUM-First study showed the same thing. On the left, patients treated with placebo only, when we looked at those with the triple mutation FLT3-ITD, NPM1 mutation, DNMT3A, the survival was worse. However, when we then looked at only the patients who had FLT3-ITD with those two mutations who got quizartinib or placebo, again, you could see the benefit of quizartinib, and in fact, that benefit was seen even in patients over the age of 60.

Now what I haven't spoken to until now is the very abrupt mortality or decrease in survival in patients receiving quizartinib. And all I can say about that is, as we analyze the data from the study, it became clear that it is very important for patients receiving intensive chemotherapy with quizartinib to receive guideline-directed prophylaxis and guideline-directed therapy for febrile neutropenia.

Chapter 8

Dr. Erba:
Let's turn our attention to the relapse setting. The ADMIRAL study looked at the use of gilteritinib 120 mg a day, versus salvage chemotherapy for adults with FLT3-ITD or TKD-mutated AML that was relapsed or refractory after prior chemotherapy. There was a higher response rate both CR and CR plus CRh with gilteritinib than standard chemotherapy. The approval of gilteritinib came because of an improvement in the median overall survival with gilteritinib, a single-agent oral therapy, compared to chemo with a median survival of 9 months versus 5.6 months for chemotherapy, or a hazard ratio of 0.67, or a 33% reduction in the risk of death.

However, you can see these curves on the long-term follow-up come close to being superimposable. And it's important to recognize that there were 26 patients that were still alive 2 years later, and 18 had undergone allotransplant, and 16 of those 18 restarted gilteritinib. So clearly an important part of treatment for FLT3-mutated AML that has achieved a second remission.

So these studies have led to the FDA approvals of midostaurin for patients who are FLT3-mutation positive in combination with standard induction and consolidation chemotherapy. It's given at 50 mg twice daily with food on days 8 through 21 of induction and consolidation. It is not approved in maintenance therapy, but could be. In the study, it was continued as maintenance therapy.

Gilteritinib approved in relapsed/refractory AML, as I just mentioned, 120 mg once daily in the absence of disease progression or unacceptable toxicity. And then quizartinib approved again for FLT3-ITD-positive patients who are newly diagnosed in combination with 7 and 3 and consolidation, then continued as a maintenance. And you can see the doses of quizartinib there, again 2 weeks of quizartinib after induction or in consolidation, and up to 144 weeks, 36 28-day cycles as maintenance, and that is an FDA approval.

Current guidelines and sequencing are shown here, and for the sake of time, I'm going to leave this for your reference.

Chapter 9

Dr. Erba:
What are some of the more current considerations and future directions? Well, here are some recently reported or completed studies. The PreCOG 0905 study was performed in newly diagnosed FLT3-mutated AML patients. Patients received intensive chemotherapy with either gilteritinib or midostaurin. And although there was a higher remission rate with gilteritinib than midostaurin and higher rates of moving on to transplant with midostaurin, the primary endpoint in the study was achievement of post-induction mutational MRD negativity, which was not superior with gilteritinib versus midostaurin, suggesting maybe we're just looking too early.

Now, we're awaiting the final reported results of the HOVON study of gilteritinib versus midostaurin with intensive induction, consolidation, and maintenance in FLT3-mutated patients. However, the sponsor of that study released on the top-line result saying that that study did not show a survival benefit associated with gilteritinib compared with midostaurin. The details of course are yet to be seen.

Combining gilteritinib with azacitidine led to a higher response rate in newly diagnosed FLT3-mutated AML, but that did not translate into a survival benefit compared with azacitidine.

The GOSSAMER study evaluated gilteritinib as a single agent as maintenance therapy after completion of chemotherapy, and it did not show an improvement in survival or relapse-free survival.

And then finally, the MORPHO trial looked at maintenance with gilteritinib versus placebo for FLT3-ITD mutated AML patients following allogeneic transplant. There was an overall improvement in relapse-free survival that just missed statistical significance. The *P* value was just over 0.05. However, relapse-free survival was higher for those patients who had detectable FLT3-ITD by this NGS-based MRD assay either just before or a few of them just after stem cell transplant. Overall survival was not improved.

Quizartinib is also being studied in patients who do not have a FLT3-ITD. Quizartinib is also able to inhibit native FLT3, and the QUIWI trial in Spain showed an improvement in survival of patients up to the age of 70 who did not have a FLT3-ITD but received intensive chemotherapy with quizartinib 60 mg daily versus placebo during induction, consolidation, and as maintenance. What's remarkable about that study that's soon to be published is that there was no increased induction mortality in younger or older patients with quizartinib, even though it was a higher dose of the quizartinib.

So this has led to a global trial, phase 3 trial of quizartinib versus placebo in addition to intensive induction, consolidation, and having a third arm that will evaluate whether quizartinib needs to be continued during the maintenance.

Quizartinib is actually approved in Japan based on the results of the QuANTUM-R trial that was similar in design to the ADMIRAL trial. Patients with FLT3-ITD-positive AML in relapse or those refractory to chemotherapy had improved survival compared to salvage chemotherapy.

The hot topic now is moving towards less intensive therapies and incorporating FLT3 inhibitors with those less intensive therapies. This data has been presented at ASH for patients with FLT3-ITD-mutated disease. They received decitabine and venetoclax with quizartinib. You can see the schedules there. A bone marrow is done on day 14, and if the bone marrow is clear of blasts, both venetoclax and quizartinib are stopped, and then patients can continue decitabine for 5 days, venetoclax and quizartinib.

Here you can see the results. The composite complete remission rate was 94%. Most were CRs and many were MRD negative. However, there may be some extra myelosuppression associated with that.

Nick Short has already published data from MD Anderson on 30 patients who received aza, venetoclax, and gilteritinib for newly diagnosed FLT3-mutated AML. You can see the schedules of azacitidine, venetoclax, and gilteritinib. And again, the venetoclax was stopped early on day 14, as was the gilteritinib if there were less than 5% blasts in the marrow, and patients went on to receive consolidation here with only 7 days of venetoclax and continuation of gilteritinib. And note the dose of the gilteritinib is not the 120 as approved as a single agent but 80 mg. Very high composite CR rate. Most of those, 27 out of 30, had a CR as reported, and many were MRD negative by both flow cytometry and the FLT3-ITD NGS-based assay.

However, now in the long-term follow-up of that study of those 30 patients with a median follow-up of almost 42 months, you can see that the relapse-free survival at 2 years is only 50%. It's very similar to the overall survival, and there's no clear plateau on the curve.

The VICEROY trial was a multicenter trial attempting to replicate the results from MD Anderson but also to study the optimal dosing of the venetoclax. This was presented by Jessica Altman at the ASH meeting in 2025. This again was for adults with FLT3-mutated AML, both ITD and TKD mutations. The patients had to be unfit for or ineligible for intensive chemotherapy. Again, the dose of gilteritinib was only 80 mg daily, and you can see the two different doses of venetoclax, 200 or 400 mg daily.

The response rates, so the CR rate was similar with 200 or 400, 70% of patients, and the majority of patients had either a CR or a CRi. The overall survival at 12 months was 60% and 78%. The median was 23 months and 22 months. But it's important to note that of the roughly 20 patients, 5 of them in each cohort underwent allogeneic transplant.

Chapter 10

Dr. Erba:
Now turning our attention to targeting KMT2A rearrangements and NPM1 mutations in acute leukemia. So as I mentioned earlier, both KMT2A fusion proteins and mutant NPM1 are able to recruit the chromatin scaffolding protein menin in complex with the histone lysine methyltransferase KMT2A to the promoters of the HOX genes, HOXA9 and MEIS1, and increase expression of those, producing a leukemogenic phenotype with a block in differentiation, block in apoptosis, and proliferation. However, the inhibitors block the interaction between menin and KMT2A native protein and the fusion proteins, leading to decreased expression of HOXA9 and MEIS1 and allowing differentiation to then occur.

Patients with NPM1-mutated AML have a more favorable prognosis with intensive chemotherapy. As you can see from this data from MD Anderson, patients with NPM1-mutated AML receiving first salvage chemotherapy had a 56% response CR/CRi rate. If they got intensive chemotherapy—high-intensity chemotherapy—it was 67%. If they got low-intensity therapy alone so epigenetic-modulating therapies like azacitidine and decitabine was only 38%. But it was 76% in this small cohort of patients who received low-intensity therapy with venetoclax. So again, venetoclax has activity in these patients with relapsed disease. And here you can see the median survival in patients in Salvage 1, the median relapse-free survival on the left and median overall survival being 8.3 or 7.8 months, respectively.

For relapsed/refractory, the outcomes are much more dismal. Again, data from MD Anderson of 112 patients with relapsed/refractory KMT2A rearranged AML, and they were compared to 217 age-matched patients with normal karyotype. In this population of patients, you can see that the overall response rate was 9%. Most did not respond in the relapse setting, with a median survival of 2.4 months and only 7% of patients alive at 1 year and an 85% cumulative incidence of relapse.

So with that as a background for relapsed/refractory disease, let's talk now about the two drugs that are now FDA approved for patients with KMT2A rearranged and NPM1-mutated acute leukemia.

I'm going to start with revumenib that was studied in the AUGMENT-101 study. It was a phase 1/2 design and it included patients 1 year and older with relapsed refractory KMT2A rearranged leukemia, acute leukemias, and NPM1-mutated AML. You can see that these patients, 72% of these patients had prior treatment with venetoclax. Half of them had undergone allogeneic transplant for the KMT2A, and the same was true for the patients with an NPM1 mutation. Forty percent had a FLT3 mutation in addition to NPM1, which is expected. Seventy-five percent of the patients had previously received venetoclax. Those patients who had FLT3 mutation had received FLT3 inhibitor, and 22% had an allotransplant.

The overall response rate in KMT2A rearranged acute leukemia was 63% with a CR/CRh rate of 23%. And the duration of response with these single agents is short and the median overall survival only 8 months, but almost 40% of the responders were able to get to allotransplant, and this was the first labeled indication that was granted by the FDA for the KMT2A rearranged patients.

In the NPM1 subset of patients, the overall response rate was 47%, and again only about 23% had CR/CRh, and again very short duration of remission and median overall survival with 16% of patients undergoing allotransplant.

In terms of toxicity that was seen, there is some grade 1 and 2 nausea and vomiting. A differentiation syndrome was seen in 10-15% of patients. This drug has been associated with QT prolongation, and you can see that there was a high rate of dose interruptions and dose discontinuations in both groups.

The evaluation of revumenib is ongoing in combination with chemotherapy, including in newly diagnosed patients with NPM1-mutated AML, a randomized trial of revumenib or placebo with 7 and 3, followed by consolidation with high-dose cytarabine, optional transplant, and then maintenance with revumenib or placebo.

The study that led to the approval of ziftomenib, the second menin inhibitor to be approved, was the KOMET-001 study, again in adults with NPM1-mutated AML. Now in this study, we also did study patients with KMT2A rearrangement, but with the single-agent ziftomenib in KMT2A rearranged disease, we saw a very high rate of serious differentiation syndrome, including deaths, which led the sponsor to stop enrollment of the study for KMT2A rearranged patients of a single agent, but to continue development and analysis of ziftomenib in combination with chemotherapy for those same patients. So it has activity, but as a single agent, the toxicity with differentiation syndrome in KMT2A was felt to be too great. That was not true, however, in the NPM1, where we found the recommended phase 2 dose of 600 mg once daily to be preferred.

Again, most of these patients had prior exposure to venetoclax, 59%, 1/4 had a prior allotransplant. A peculiar side effect, adverse event with ziftomenib is grade 1 and 2 pruritus, which typically gets better over time. Again, about 15% had differentiation syndrome and 9% had grade 3 QT prolongation. A third of patients required dose interruptions, but few patients discontinued treatment.

Ziftomenib's overall response rate in NPM1-mutated disease was 33%. Again, the CR/CRh rate was 22%. The median duration of those responses, 4.6 months, and median overall survival, 6.6 months. And so very, very similar CR/CRh rates with both ziftomenib and revumenib in KMT2A and NPM1-mutated relapsed refractory disease.

However, the evaluation of ziftomenib is ongoing. There are three studies that are currently accruing. KOMET-007 is in newly diagnosed patients with KMT2A and NPM1-mutated disease getting ziftomenib in combination with 7 and 3 or azacitidine and venetoclax. KOMET-008 is a phase 1 study looking at the activity of ziftomenib in combination with chemotherapy in relapsed patients.

The pivotal phase 3 study has been launched, KOMET-017. In this study, there are two components, non-intensive chemotherapy with venetoclax and azacitidine with a randomization between zifto and placebo in patients with NPM1-mutated disease who are unfit for intensive chemotherapy, the primary endpoint being CR and overall survival. Andin the KOMET-017 intensive chemo arm is for patients with both NPM1 or KMT2A rearranged AML. They cannot have a FLT3-ITD mutation, and they are randomly assigned to receive ziftomenib or placebo during induction and consolidation, and again a third arm evaluating a placebo instead of ziftomenib during the maintenance. And the primary endpoint is a composite for CR, MRD negative CR, and event-free survival.

So the FDA approvals are shown here. I mentioned ziftomenib only approved for relapsed/refractory NPM1 mutation at 600 mg daily. Revumenib is approved for both KMT2A and NPM1 mutation. Again, KMT2A is seen in ALL, is seen in mixed phenotype leukemia, so any acute leukemia with KMT2Acan be treated with revumenib. The dosing is a little bit more complex with revumenib based on patient

weight. It was partly a pediatric study and also based on whether the patient is receiving strong CYP3A4 inhibitors or not. There is no dose adjustment that is necessary with ziftomenib for CYP3A4 inhibitors.

So again, here are the current guidelines that reflect the FDA approvals.

Chapter 11

Dr. Erba:
Finishing up with adverse events, quizartinib can cause QT prolongation. This signal was first seen in the phase 3 study where very high doses of quizartinib, much higher than what was needed to actually turn off FLT3, were used, and that's where the signal came from. It is an inhibitor of the slow rectifier channel in cardiac muscle, and so there is a REMS program and a black box warning because of this QT prolongation. So of course for any drug that can cause QT prolongation, before administration and periodically, you should monitor for hypokalemia, hypomagnesemia, and correct those deficiencies before starting quizartinib and during quizartinib therapy, monitor the EKG, and try to avoid drugs that will also prolong the QT, such as the fluoroquinolones and certain azole antibiotics, and dose reductions for strong CYP3A4 inhibitors.

Regardless of this, in my practice, we use isavuconazonium or isavuconazole, since it does not prolong the QT interval, and it's only a moderate CYP3A4 inhibitor, and so we have not had to adjust the dose of quizartinib when using that drug. If you use posaconazole, you have to adjust the dose of the quizartinib and monitor the QT.

Warnings for gilteritinib also include QT prolongation along with differentiation syndrome, posterior reversible encephalopathy syndrome, and pancreatitis.

The menin inhibitors, as I mentioned, you need dose adjustments for revumenib for CYP3A4 inhibitors that are strong, but not for ziftomenib. And for both, because you can see QT prolongation, make sure the potassium and magnesium are replete. I already mentioned the dosing, and also because of the risk of differentiation syndrome, these drugs should not be initiated unless the white count is brought down below 25,000 first with, for example, hydroxyurea.

Differentiation syndrome we should be accustomed to dealing with based on our experience in APL and with the IDH inhibitors. But to remind you, the diagnosis of differentiation syndrome should be entertained and considered in your AML patient receiving a menin inhibitor who develops fever, weight gain, edema, pulmonary infiltrates and hypoxia with dyspnea, pleural and pericardial effusions, and hypotension or acute renal failure due to basically a capillary leak syndrome.

And if it is suspected with the menin inhibitors, you need to begin dexamethasone 10 mg IV twice daily, and hold the menin inhibitor.

Chapter 12

Dr. Erba:
So I want to finish with one case to go through. And this is actually one of my patients presented with fatigue, fever, night sweats, and dyspnea. Prior to this, just 2 months prior, he was exercising daily, working full time, but he shows up with acute hypoxic respiratory failure with a white count of 150,000, 90% blasts, anemia, and thrombocytopenia. The peripheral blood had these immature mononuclear cells with Auer rods, so diagnostic of AML, the majority of cells were these blasts with those deep nuclear invaginations. So I wasn't surprised when the peripheral blood flow came back showing a myeloid immunophenotype with absence of CD34 and HLA-DR, and I was already suspecting that this patient would have an NPM1 mutation. And you can see the comorbidities there.

So we gave him hydroxyurea at high dose, allopurinol, IV hydration. And with this, his DIC is getting worse, his fibrinogen declines, his D-dimer is going up, he actually requires more oxygen. The absolute blast count has not come down. We've considered leukapheresis, but at Duke, we've actually stopped doing leukapheresis. There's no prospective data showing a benefit, and retrospective data also shows no apparent benefit of leukapheresis in patients with hyperleukocytosis, and it actually might make DIC worse. It requires catheter placement, which might be difficult in the setting of DIC, and I've seen it lead to worsening hypoxic respiratory failure.

So the first question is, what would be the next step in your management of this patient? Perform a bone marrow biopsy and continue supportive care? Order peripheral blood studies and continue supportive care pending the results? Perform a bone marrow biopsy and

start induction therapy immediately? Order peripheral blood cytogenetics, PCR, and myeloid gene panel and start induction immediately?

Well, in this case, we decided to do all peripheral blood studies and to start induction chemotherapy for what I felt was going to be NPM1-mutated acute myeloid leukemia. So the patient is fit for intensive chemotherapy, the morphology, the immunophenotype is consistent with NPM1, so a potentially curable acute leukemia. So we were going to treat him with intensive chemotherapy.

So which chemotherapy regimen do you choose? Would it be cytarabine and daunorubicin; IDA-FLAG; cytarabine and daunorubicin and gemtuzumab; IDA-FLAG and venetoclax; aza/ven; decitabine/ven; A and C; B and D? What would you decide for this patient? And all you know at this point is what I have told you.

Well, we started 7 and 3 induction chemotherapy. And on day 5, the PCR assay reports the presence of FLT3-ITD with a very high allelic ratio. So now I'm suspicious that there's an NPM1 mutation. There's a FLT3-ITD mutation. The QTcF is normal. The potassium and magnesium are normal. Your next intervention includes which of the following: Order midostaurin 50 mg by mouth twice daily days 8 through 21; order quizartinib 35.4 mg by mouth once daily on days 8 through 21; order gilteritinib 120 mg by mouth once daily on days 8 through 21; none of the above.

And so what happened for this otherwise very healthy 65-year-old man is that we did add quizartinib. We monitored the electrolytes and the QT interval. We started isavuconazonium sulfate for fungal prophylaxis, and we used cefdinir in place of a fluoroquinolone and monitored the QT interval. He actually achieved a complete remission. He went on to get cytarabine at 1.5 g/m^2 for six doses and quizartinib. And I referred the patient to actually my own academic center.

Closing:

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