AML at the Crossroads: Finding a Treatment Role for Innovative Therapeutics

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Activity Information

Activity Description and Educational Objectives
While the current standard of care in acute myeloid leukemia (AML)—cytarabine-based chemotherapy—may be an effective option for many patients, others are unlikely to benefit from this intensive strategy; this fact has prompted much clinical research into new and novel options for AML treatment, a search that may now be bearing fruit. Currently, a number of therapeutic advances, driven in part by a modern understanding of AML biology, are on the cusp of validation. This CME activity, based on an expert-driven symposium held prior to the 2016 ASH annual meeting, will feature important science on a growing wave of new options for AML, including next-generation cytotoxics, epigenetic treatments, immunotherapies, and targeted agents; in addition, the experts will discuss updated evidence on the clinical role and efficacy of emerging therapeutic options and agent classes in AML, including targeted therapies, immunotherapies, and other strategies. Presenters will inform participants of AML's changing landscape, including novel cytotoxic, targeted, and immunotherapeutic strategies.

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Dr. Ravandi: Good afternoon and welcome to this educational symposium entitled “AML at the Crossroads: Finding a Treatment Role for Innovative Therapeutics.” I'm Farhad Ravandi from the University of Texas MD Anderson Cancer Center in Houston, and joining me for this symposium are Dr. Michael Savona from Vanderbilt-Ingram Cancer Center in Nashville, Dr. Naval Daver from MD Anderson Cancer Center, and Dr. Amir Fathi from Mass General Hospital Cancer Center, Harvard Medical School in Boston.

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Dr. Ravandi: Before we start, I’d like to spend a couple of minutes remembering my good friend of 30 years, Dr. David Grimwade, who tragically passed this October. David has been instrumental in a number of advances that we have made over the last several decades in AML from the cytogenetic risk stratification in the MRC trials, to the understanding of biology of APL and APL therapies, and more recently in terms of understanding the role of minimal residual disease assessment in AML. David will be sorely missed.

However, we haven’t been silent over the last several years. We’ve actually had significant advances in the understanding, the biology of AML, especially in terms of cytogenetic and molecular aberrations that are responsible for leukemogenesis. As you know, we have used these as prognostic factors in AML therapy not only to predict survival but also in the selection of post-remission therapy. These have generally been pre-treatment factors but also a number of post-treatment factors, especially minimal residual disease assessment, are becoming much more relevant and hopefully will be available for our intensification on post-remission decision-making.
So there are a number of agents that are in development and I'm just showing you a few of them here. There are novel cytotoxics, such as CPX-351 and vosaroxin. Second generation hypomethylating agents, such as decitabine, as well as targeted therapies targeting mutations such as FLT3, IDH, as well as Bcl-2 inhibitors and nucleus transport inhibitors. Novel antibodies are very exciting. We have both antibody–drug conjugates, such as vadastuximab, as well as SL401, as well as bispecific antibodies that are in early development and hopefully will be useful and available in the near future.

So this afternoon's agenda is to look at this progress and these drugs in development. We will start off with looking at some of the novel cytotoxic strategies, as well as new epigenetic treatments, as well as new antibody-based therapies that I mentioned and targeted therapies directed at a number of the mutations that have been described. Finally, I'm going to spend a brief 15 minutes talking about minimal residual disease monitoring and how I think it's going to become more and more important in AML, as well as other hematological malignancies. After each session, we will discuss a number of available and ongoing clinical trials. Some of them are still enrolling and hopefully you will be participating by enrolling your patients in them.
Dr. Ravandi: And with that, I’m going to invite Dr. Michael Savona from Vanderbilt University to talk about cytotoxic and epigenetic therapies.

Dr. Savona: Thank you, Dr. Ravandi. [There are] a lot of people who know a lot about cytotoxic therapy, so hopefully we’ll learn something. I didn’t practice 40 years ago, but those who did treat AML 40-plus years ago listened to Richard Nixon declare a war on cancer and maybe thought we wouldn’t have cancer anymore, and certainly didn’t think they’d be using 7+3 to treat leukemia. And maybe they thought we’d be having ASH on the moon or Mars or something.

But in fact, we still do use cytotoxic therapy and that’s really the backbone of how we treat acute myelogenous leukemia. And learning how to better care for patients receiving this treatment and then maximizing the nuances of the treatment or improving upon some of the nuances of cytotoxic treatment with novel cytotoxic agents has moved the bar forward, even if incrementally.

So before I start, one thing I just want to make clear: I don’t believe that everyone over 60 is not a candidate for high-dose therapy. I don’t believe that everyone with AML should get cytotoxic therapy. Those two things are not mutually exclusive. And in fact, there are patients in the mature corral that are good candidates for cytotoxic therapy followed by allogeneic stem cell transplant and there’s some that are not.

For the patients who are candidates for high-dose or intensive therapy, there’s a new development, CPX-351. And this was an attempt to address the lack of achieving synergy due to the way that we give 7+3. We know there’s very good synergy between cytarabine and anthracyclines but giving the two drugs together didn’t always lead to the optimal stoichiometric measurements of the two drugs. And this compound is a 100-nm bilamellar liposomal construct of a 5:1 molar ratio of cytarabine to daunorubicin. And after a phase 1 study where this 5:1 molar ratio was observed even 24 hours after administration, and safety was established, a phase 2 study was started in relapsed/refractory AML patients.

What Is the Future of Cytotoxic and Epigenetic Therapy in AML?

Now Charlie Schaffer once described “MDS-y” AML as a hyperproliferative AML, and I always liked that because I think the biology of AML in most elderly patients more closely resembles MDS than the biology of a young person, hyperproliferative leukostatic AML. And in fact, although the rates of secondary or treatment-related AML have not gone up, we know that most patients in their seventies—and a good number of the patients in fifties and sixties—their AML is of the “MDS-y” variety. And we also know that those patients do poorly. They do worse than patients with de novo AML.
CPX-351 Versus IC: Randomized Phase 2 Study in Poor-Risk Relapsed AML

Randomized phase 2 study (N = 125, 2:1): CPX-351 versus investigators’ choice of first salvage tx in adults with first-relapse AML

In subset analyses of EPI-defined poor-risk strata, patients receiving CPX-351 (n = 56) vs IC (n = 29) demonstrated:

- Higher response rates (39.3% vs 27.6%)
- Improvements in EFS (HR = 0.63, P = .08)
- Improvement in OS (HR = 0.55, P = .02)
- 60-day mortality lower in the CPX-351 study arm (16.1% vs 24.1%)

And you probably are aware of this data, but this relapsed/refractory phase 2 study compared patients who received CPX-351 versus investigator’s choice in first salvage, so patients with relapsed disease but first relapse. And there were considerably higher response rates in the patients who received CPX and an improvement in survival.

CPX-351 Versus 7+3: Randomized Phase 2 Study in Previously Untreated AML (Age ≥60 Years)

Simultaneously, there was an upfront treatment-naïve AML study for elderly patients, or since that’s just 60 I’ll say mature-age patients. And though there wasn’t a difference in survival or response in the overall study, there was a profound difference in survival between the patients who received CPX-351 and 7+3 who had secondary AML.

Phase 3 Study of CPX-351 Versus 7+3 in Older Patients With Newly Diagnosed High-Risk AML

And this led to the idea of how can we capitalize on this “MDS-y” type of leukemia with this drug. These are patients who are well enough to receive intensive therapy, but they just had done miserably in 7+3 on this study. So in a phase 3 study, CPX-351 was randomized to 7+3 in the mature age category, in patients who had either MDS followed by AML, CMML followed by AML, or AML with myelodysplastic-related changes and no known previous history of MDS. They had to be between 60 and 75 years and then they were allowed two cycles of induction if the first cycle was not leading to complete remission. They were consolidated and followed for overall survival.

Equivalent Grade 3-5 Nonhematologic AEs (Event Frequency ≥5%)

There was slightly increased pneumonia, sepsis, and bacteremia in the CPX arm.

CPX-351: Complete Recovery Counts for Patients Achieving CR or CRi

And likewise, and this may be due to a late recovery, there was a later recovery in patients who did have complete remission in the CPX arm, with absolute neutrophil count over 500 and an average of 35 days in the CPX arm, and only 28 days in the control arm. Same as with platelets.

However, the response rate was significantly improved in patients who received CPX over 7+3, and the complete response plus incomplete response rate or marrow complete response rate...
without resolution of normal hematopoiesis by counts was statistically significant.

And this is revealed here in a survival analysis, which remains durable, with the median survival improved from 5.5 months to 9.5 months for patients on CPX.

When this data was analyzed with a landmark survival analysis for transplant, interestingly, the patients who were on the CPX arm who went on to receive transplant have had startlingly good survival, as you can see on this curve here, with a median survival not yet reached at 3 years.

So in short, CPX-351 did demonstrate superior efficacy compared to 7+3: 
- Overall survival, DFS, CR, CR+GR
- Early mortality lower in the CPX-351 arm, safety comparable to 7+3 though count recovery is likely prolonged
- Outcomes following transplant favored CPX-351
- CPX-351 should be considered standard first-line treatment of 60-75-year-old patients with high-risk AML who are candidates for high-intensity therapy

So next I’d like to talk about vosaroxin, which is an interesting drug. It acts like an anthracycline, it works like an anthracycline, but it’s not an anthracycline. It’s on a quinolone core and it inhibits topoisomerase, but it doesn’t create in its metabolism the number of reactive oxygen species that are created by classic anthracycline chemotherapy, and this is thought to be the reason why it has no or little cardiac signal. And in fact, in the patients treated with vosaroxin, there has been no direct-related heart failure.

After successful phase 1 and phase 2 studies, I’ll just skip to the meat and potatoes: the VALOR study, which was the largest study in AML, led by my colleague, Dr. Ravandi, who presented this data for us previously, and has been published now in Lancet Oncology. This was a study randomizing vosaroxin at 90 mg/m² plus intermediate-dose cytarabine at 1 g/m², versus the cytarabine alone. And that cytarabine is given 1 g/m² on days 1 through 5. Patients were induced and then allowed a second induction if they failed the first induction. They were consolidated in a CR/CRp and followed for survival. I’ll go over the AEs in a minute but there were some increases in adverse events in the patients who received vosaroxin. As we would expect after the phase 1/2 trial, there were increased rate of stomatitis. There was increased rate of neutropenia and febrile neutropenia.
But interestingly, there was really no difference in 30- or 60-day mortality with the one exception of patients over 60 years old with early relapse who, within 60 days, there were more patients dying in the AraC arm, which makes sense if you think about how quickly patients will relapse and then die of their disease.

So as I mentioned, there was an increase in febrile neutropenia, stomatitis, and sepsis in the vosaroxin arm.

Yet this was abrogated by considerably higher rates of complete remission seen in the vosaroxin arm which, with the exception of less than 60 years old, was clear throughout every subgroup: patients who were primary refractory, patients who were relapsed, early relapse, late relapse. And this is true for complete remission and for the combined endpoint of complete remission plus CRp/CRi.

Now the patients over 60 and all subgroups had a statistically significant improvement in remission rates. This was most striking in the early relapse and the refractory patients.

In fact, in the original survival analysis, there was an improvement in survival from 6.1 months to 7.5 months in all patients in the 770-patient study, which was true 94% of the time, statistically speaking, with a \( P \) value of .06. If you censor for transplant as was preplanned, the improvement in survival was statistically significant with a \( P \) value of .02.
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And this was true throughout all of these relapse and refractory categories, as I mentioned previously, and I’ll go quickly through that.

You can see here, the long-term follow-up shows the survival benefits are actually indeed durable going into 5 years. So VALOR was an enormous study and we did see a difference in survival. We’re working to try to find a way to get this drug approved because there is certainly a place to use this in AML. We don’t think that there’s a difference in 30- or 60-day mortality. We acknowledge that there’s an increased risk of stomatitis and infections.

And choosing patients carefully and using new mitigation strategies, for example, in our upfront vosaroxin/AraC study that I’m conducting with Dr. Strickland, it’s a multicenter study, we have patients chew ice before they take their vosaroxin and we haven’t seen any stomatitis. Dr. Naval Daver, who’s here with me, has recently presented the vosaroxin/decitabine upfront data, which is also very appealing and we’re looking forward to combining these types of regimens in an upfront, randomized study for vosaroxin.

The Role of HMAs in AML

So in the beginning I said to you that I think of people in the mature age category as the fit and non-fit, and I won’t get into the debate of what makes fit or not fit or what makes someone eligible for intensive therapy versus not. There’s a lot of work being done with this, but the experienced leukemia specialists can know it when they see it. And those patients who are not fit for induction therapy or patients who have a contraindication to induction therapy, DNA methyltransferase inhibition, or hypomethylating agents have really become the mainstay of therapy in the United States. And really over the past 10 years, we’ve seen the use of these agents even before approval, used because they were finding success in MDS and MDS that was similar biologically to this “MDS-y” type of low-blast hyperproliferative leukemia that we see in the older patients. In addition, this has been further tweaked with novel HMA therapy and administration, largely via new routes of administration, such as subcutaneous and oral, which I’ll talk about now.

So you’re probably familiar with the role of 5-azacitidine in acute myelogenous leukemia. So this was a paper published in Blood by Hervé Dombret and colleagues, and there was a statistically significant improvement in survival and a 1-year survival difference of 12.5%, which we consider fairly meaningful. And this has really encouraged the use of 5-azacitidine and decitabine in AML even more, and trying to find ways to combine this agent, which we know is active with other agents in patients who can’t necessarily tolerate induction therapy.
Now we do know over the past 5 years that patients have different responses to HMA and different molecular subsets, TET2, IDH1, TP53. And the Wash U and University of Chicago paper that was published in the New England Journal 2 weeks ago, patients with TP53-mutated AML had remarkably a good response to 10 days of decitabine. But as they showed in their paper, unfortunately this doesn’t change survival, so we still have a lot of work to do.

One attempt is called guadecitabine, or SGI-110, and this is a second-generation hypomethylating agent which is a dinucleotide combination of decitabine, a cousin of azacitidine, and deoxyguanosine, which basically inhibits the metabolism of, and breakdown of decitabine deamination by cytidine deaminase. So this sticks around a little bit longer.

And I’ll briefly just talk to you about the clinical data that’s so far in AML. And essentially, in a phase 2 study of treatment-naive AML that were deemed to be unfit for induction, and this is by investigator choice, and there’s some guidance in the eligibility criteria, they were randomized to one of three arms: what was thought to be the biologically effective dose of 60 mg/m² daily times five; 60 mg/m² daily times 10, mimicking that decitabine 10-day regimen; and then the highest tolerated dose from earlier study of 90 mg/m² daily times five.

And they were followed for response and overall survival. And there wasn’t really—I’ll just get to the meat of it—there really wasn’t a difference in response between the 10 and 5 days, and there was greater toxicity in the greater exposure and in the higher dose. So this has led to a study design of the 60 mg/m² days 1 through 5.

So in general, this was a very well-tolerated drug. There was common adverse events that you’d expect that are not too dissimilar to what we see with decitabine and probably improved from what we see with induction chemotherapy. We’re learning that this may be a very intriguing option in elderly/unfit patients with AML.

And this study is now close to accrual so we should hopefully be seeing that readout shortly. There are other phase 3 studies, ASTRAL-2 is relapsed/refractory AML and that’s about to start.
So another attempt to try to maximize the potentiality of epigenetic therapy—and specifically in DNA methyltransferase inhibition and increasing patient convenience—is by providing azacitidine in oral form. The problem with giving these drugs orally is that cytidine deaminase is replete in the liver and the stomach and cytidine deaminase will usually deaminate the drug and making it unavailable in circulation.

The way that we chose to pursue this development with CC-486, or oral azacitidine, was to drive the dose beyond the existing cytidine deaminase. There have been several presentations at ASH over the years since 2007, I think, Guillermo first published our first book about it then, so really this has been going on for a decade. But I wanted to present this here because we were involved in using this drug in patients with relapsed/refractory AML who had previously received azacitidine or decitabine or, in some cases, even induction. And we found that treatment with this agent was able to yield some impressive hematopoietic improvements in AML, MDS, and CMML.

There is only one CR in the AML group but [these are] small numbers. Nonetheless, an oral agent like this allows you to treat the patient for as long as 21 days, and treating the patient this long changes the method—it changes the pressure on the oncogenic cell, and changes the methylogram. And we do have evidence that the cells that are hypomethylated are, even by simple measures by line one, are vastly different than the traditional treatment with hypomethylating agents.

Another approach has been with a new compound called ASTX727. And ASTX727 is actually a combination of two drugs, oral decitabine and E7727, which is a cytidine deaminase inhibitor, which is quite clever because it shut off the cytidine deaminase in the stomach and the liver and allows the oral decitabine to become properly metabolized and reach the desired cell type.

We completed the phase 1 study and this is the pharmacokinetic analysis. And just briefly, you can see that by providing ASTX727, these two pills, you have an AUC which is comparable what’s seen with IV decitabine. IV decitabine is in the blue line and the 100 mg of decitabine and 30 mg E7727 together, seen by that dotted red line, have a similar AUC. So these pharmacokinetics are rather predictable and fairly replicative of what we see with IV decitabine. And this is a drug that you give people orally for five days in a row and they could come into the office and get the five pills and go home. So I have patients who travel 1,000, 1,500 miles coming to get their pills once a month and it cuts down on 15 hours of chair time a month, so that has served its purpose, even though it’s early, early days yet here.

In the escalation, I can just give you a brief snippet of efficacy and show you. Remember these are escalating doses and this is in relapsed/refractory and upfront [MDS] largely biased towards relapsed/refractory MDS in the beginning. And though we had responses even at the lower cohorts, which again lends credence to the point I was making before about CC-486 and differential dosing, and actually seeing response in patients where we don’t expect to see it. So when we have these agents orally available, we will enter an era where we’ll be able to try not just different routes of administration, but vastly different schedules to establish our goals with respect to hypomethylation.
Okay, at the end here I’d just like to just briefly mention MLN4924, or pevonedistat. Pevonedistat, it’s been around for several years but it’s a very novel drug, and it seemed to have found a home in combination in upfront AML with azacitidine. This drug forms an adduct with a NEDD8-activating enzyme, with NEDD8 to prevent NEDD8 activating enzyme from conjugating Ubc12 and shutting down Cullin-RING ligase, and ultimately upsetting the process of ubiquitination.

So in conclusion, I’d just like to note that I think that cytotoxic chemotherapy is not gone yet. We still rely on it. It’s vitally important in AML even in elderly patients. And it’s important to recognize that elderly patients or mature patients may qualify for induction chemotherapy. Age is no longer the clear discriminator. Hypomethylating agents or methyltransferase inhibitors are the backbone of therapy for non-fit patients in AML. And providing new modes of accessing these drugs via oral, via subQ, different schedules will greatly enhance our capacity to combine them with new novel agents, which you’ll hear about a little bit later today. And as I said before, new oral HMAs not only expand these possibilities but provide a real improvement in convenience for patients. Thank you very much.
So the current state, just to try and put everything together before we start here, is that AML is highly heterogeneous, both across a population and within individuals. And for that reason, it likely explains somewhat the reason for the poor outcomes we’ve had for the past three decades, which have been mainly cytotoxic chemotherapies. Conventional therapies have emerged in the late 1970s, have not changed. These are indiscriminate cytotoxic agents that are used in combination, so-called conventional induction chemotherapy, such as 7+3, IA, and the rest. The improvements in outcomes that we’ve seen in recent years have really been related to advances in supportive care. And therefore novel and effective diagnostic, prognostic, and therapeutic approaches are desperately needed.

So by the time these individuals are treated multiple times, relapse, have refractory disease, there’s a whole host of different subclones that end up comprising the disease and, again, make treating very difficult because some of the subclones may be less sensitive to chemotherapy than perhaps the mothership or the initial clone was, unfortunately. So this is all very new and interesting development in the field of AML.
One manner by which we could approach AML is through the use of antibodies. And antibodies are immunoglobulins that are engineered or humanized to target specific proteins on the surface of cells that might be upregulated or exclusively present on the malignant cell. This sort of targeted cytotoxic approach is very intriguing. CD33, a "Siglec" or a sialic acid-binding immunoglobulin-like lectin protein. Siglecs are a variety of protein receptors on a whole host of different cells in the variety of hematologic cells. CD33 just happens to be one of them.

And upon binding of the sialic acid, the cell is activated, and there is an inhibitory signal that's provided, leading to downstream signaling. It's on the surface and therefore it's easily accessible. It's endocytosed, so it's very conducive to perhaps using antibody–drug conjugates to get the cytotoxic drug or the radiation into the cell and allow this targeting cell death to occur. CD33 is expressed on the majority of myeloid blasts. It's thought to be expressed on the leukemic stem cell and perhaps less so on the hematopoietic stem cell, making the therapeutic window optimal.

Among the first anti-CD33 antibodies that were developed was lintuzimab. It's a humanized anti-CD33 antibody. It was naked. It had very limited activity as a single agent in relapsed AML. As you can see, there were some reductions in blasts in some of the patients on study, the three that responded out of the 49 that had reductions but there was no significant benefits seen in subsequent studies where the drug was combined with conventional therapies. And ultimately, folks thought maybe there was a role perhaps in lower-burden disease.

Then came the famous gemtuzumab ozogamicin. It was a humanized antibody similar to lintuzimab, but it was an antibody drug conjugate with a linker and a cytotoxic antibiotic called calicheamicin, which was bound to it. Calicheamicin was hydrolyzed in the lysosome after internalization into the cell. And there was much excitement, initial trials showing a very impressive response rate in relapsed/refractory patients.

In 2000, as mentioned by Farhad, there was FDA approval in expedited fashion, and people were excited and it was increasingly used, especially in older patients in the relapsed/refractory setting. But soon thereafter, multiple studies revealed the presence of hepatotoxicity and what looked, at least, like veno-occlusive disease, which is a condition in the post-transplant setting affecting the liver. Multiple questions about why this was happening. Was it related to dose? Was it related in some fashion to the mechanism of the antibody–drug conjugate?

The so-called sinusoidal obstruction syndrome, alarmingly shortened "SOS," was seen actually in a fairly large percentage of patients. And it was specifically seen in individuals or susceptible individuals seemed to be those who had had extensive prior chemotherapy, those who had received higher doses or at increased frequency of dosing, as well as those individuals—and this is something probably you guys have heard—that had previously had bone marrow transplant. So it was an unfortunate finding that limited, in some sense, the use of the drug.
The SWOG study was a 600-person study that compared induction chemotherapy without an induction chemotherapy with gemtuzumab. It showed no difference in overall survival. And that was certainly a knock against the combination with chemotherapy in this study of younger patients. But in addition, in the arm that included gemtuzumab, there was a higher proportion of patients dying, five times as much. Now, it was 1% versus 5%; 1% in an induction study is, I would say, relatively low. But nevertheless, because of these reasons, because of the challenges with the drug, as well as this increase in mortality seen on this study, at least in the arm that had gemtuzumab, the drug was voluntarily withdrawn by Pfizer.

This then takes me to the newer kid on the block, SGN-CD33A—also now known as vadastuximab, that’s a V, vadastuximab talirine—which is a novel anti-CD33 antibody drug conjugate. It’s a little bit different, has a different linker and it’s coupled to a different cytotoxic agent, a highly potent cytotoxic agent called pyrrolobenzo-diazepine, also known as PBD. The cross-linker is very stable. That means the conjugate is stable in circulation. The toxin is not released into the circulation, which is important. Pharmacokinetically it is less affected by P-glycoprotein, which is important.
There was some early suggestion of efficacy in early preclinical studies and then there was a phase 1 study of monotherapy with vadastuximab [talirine], and that’s ongoing. There was dose escalation across all doses in this relapsed/refractory population. The remission rate was in the 20s. But looking at the stable dose that we found, which was 40 mcg/kg, which was thought to be safe and somewhat efficacious as monotherapy, about 47% of patients, about half achieved blast clearance.

This sort of gives you a general idea of the patients on study at various doses. And as you go up in dose, you tend to have greater bone marrow blast clearance in these patients. Now you have to also be careful; as you go up in dose, you tend to also have more on-target myelosuppressive effects with patients having cytopenias. But this was quite encouraging. Doses of up to 50 mcg/kg appear to be well tolerated.

In preclinical studies, vadastuximab was also looked at in combination with hypomethylating therapies. And as was previously mentioned, HMA therapy is now being increasingly used among older patients who are not appropriate for, or eligible for, or decline induction or more aggressive cytotoxic chemotherapy, with a very promising improvement in overall survival. When cells are exposed to hypomethylating therapy, whether it’s decitabine or azacitidine, there does appear to be a modest increase in CD33 expression on cells. In addition, the exposure to HMA therapy appears to increase the incorporation, when antibody drug conjugate is then administered, of PBD dimer into the DNA and in this fashion, preclinically at least, there was a rationale to combine these two drugs.

And thereafter, a cohort of this phase 1 study specifically looked at vadastuximab talirine, the antibody–drug conjugate, in addition to a hypomethylating therapy in our patients. And this gives you a schema here about how this was done. Patients would be either given decitabine, which would be given over 5 days at a dose of 20 mg/m² or would be given azacitidine, either subcutaneously or intravenously at 75 mg/m² times 7 days. That’s the standard dosing for these agents. On the last day of hypomethylating therapy, on day 5 for decitabine or day 7 for azacitidine, the antibody–drug conjugate would then be administered at a lower dose of 10 mcg/kg. This would repeat for four cycles of combination therapy, with intermittent assessment, marrow biopsy and assessment for response. Those individuals who achieved response, a CR or a CRi, could thereafter continue to receive maintenance therapies and subsequent cycles, as well as follow-up every 3 months.

In this cohort of patients—53, which is a decent number for this phase 1 study—the median age was 75, with a range of 60 to 87, so this was an older patient population. But also note that the...
majority of patients were over the age of 75. The majority were treatment-naïve. The folks that were not treatment-naïve had received treatment for MDS prior to coming on study but had not received treatment for AML. A sizable percentage of patients, 38%, had adverse-risk AML, and 45% had prior myelodysplasia.

These are the treatment-emergent adverse events that were seen in 20% or more of the patients. As you can see, the large majority of greater than grade 3 events occurred as on-target effects that were thrombocytopenia, neutropenia, anemia and such. There were other non-hematologic toxicities that were lower grades and were more commonly seen across a variety of therapies we give AML patient, such as fatigue, gastrointestinal toxicities, nausea, and so on.

The drug appeared to be fairly safe; 30- and 60-day mortality rates were 2% and 8%. This is from data presented at the European Hematology Association this past summer. No dose-limiting toxicities or infusion related reactions were observed. These are the infusion-related reactions have been seen with other antibody-based therapies. Many folks have asked whether doses have been delayed or not given as a result of toxicity. In our study, the majority of doses were given, but 34% of doses were delayed and the majority of the reasons for dose delay were actually on-target effects, such as neutropenia, thrombocytopenia, and related sequelae. There were no grade 4 or grade 5 bleeding events.

This is the so-called money slide. Remission rates for patients that were efficacy evaluable at this last presentation here shows that the remission rate in this patient population, the composite remission rate, CR plus CRi across all patients was 71%. Now, now if you look at the trials that have been done with azacitidine alone or decitabine alone, the rates of remission hover anywhere between 15 to 25 percent. So this is really comparing apples and oranges but it gives you an idea of what appears to be a higher rate of response compared to historical values.

We also specifically looked at some subsets of higher risk among this patient population. Those included those with high-risk karyotypes or those with antecedent myelodysplastic syndromes. The high remission rates were also preserved in those populations of patients. The lowest row there shows the overall response rate, which is, I feel, the most controversial response rate mechanism because it includes, in addition to complete remissions, partial responses as well as MLFS, which is morphological leukemia-free state. Many folks do not feel those are real responses but, as you can see, if you include those as well there is also a very robust rate of remission that’s presented or evidence of blast clearance that is also represented there.

Just to hammer home the point here, as you can see, almost every patient on this study of almost 50 individuals had a reduction in blasts, the large preponderance of which had significant reductions in blasts. It did not matter whether they received azacitidine or decitabine in combination. The diamonds on the bottom, the black diamonds, are complete remissions. The white ones are CRis.
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This is the estimated overall survival as of the presentation last summer. The median follow-up at that time was 8.4 months. The median overall survival at that time was 11.6.

Okay, this slide is not very surprising but suffice it to say those individuals who responded did better than those individuals who did not, with a median overall survival that was double those individuals who did not achieve a response.

So the preclinical synergy of 33A plus HMA appears to translate into some clinical benefit. There does appear with this combination to be a favorable balance of activity and tolerability among patients who are not eligible for aggressive cytotoxic chemotherapy, the majority of whom are older patients, and given the median age of AML being 67, it’s going to be a large number of our patients. There was a low early mortality rate, as well as a safety profile consistent with on-target myelosuppression. The responses were seen across a host of high-risk patient populations and the remissions appear to be durable.

Finally, there is a phase 3 study, a randomized, placebo-controlled study of 33A, or vadastuximab, plus HMA versus HMA plus placebo in patients 18 and up but who are not eligible for induction chemotherapy.

So just for completeness sake, [gemtuzumab ozogamicin] and vadastuximab talirine are not the only antibody–drug conjugates that are under development. They’re certainly the ones that are furthest along in development in clinical trials but there are others that have been studied with my colleagues sitting at the table here. Lintuzimab, which is a drug I mentioned earlier, has recently been combined as a radioisotope conjugate, lintuzimab-iodine-131, or lintuzimab-yttrium-90 have been used as transplant conditioning regimens. Actinium-225, which emits alpha particles, has been studied in combination with chemotherapy, cytarabine, with some promise but there also some impact, myelosuppressive effects.

There is a whole host of engineered compounds that have also been developed, the so-called BiTE compounds, the bispecific T-cell engagers, that bring CD33 on the surface of malignant cells close to CD3 on T-cells, and in that fashion lead to immunologic cell death. They have also been very promising in preclinical models and entering clinical trials as we speak.
CD123 is another target on leukemic blasts that is now receiving a lot of attention. It appears to be on leukemic stem cells, but less so on hematopoietic stem cells. And it seems to be involved in the process of self-renewal and decreased sensitivity to chemotherapy. So certainly targeting it would make some amount of sense.

A variety of drugs are now under development. Hu7007, the James Bond drug, it looks like, humanized unconjugated CD123 antibody. It’s being tested in clinical trials. SGN-CD123 as well is just now entering clinical trials. We’re opening that study in Boston soon. Xmab CD3/CD123, as well as MGD006, that is a dart molecule as opposed to a BiTE compound, which is a dual-affinity retargeting molecule shown here, again bringing T-cells in close proximity to the target cell and causing immunologic cell death.

The immune-based approaches are not only going to be the antibody-based approaches. Checkpoint inhibitors, as you guys probably know, are extremely exciting across oncology and there are a variety of drugs that are currently being developed, nivolumab, pembrolizumab, in various solid tumor malignancies. Only now we’re starting to see some suggestion of efficacy and promise in hematologic malignancies, including MDS and AML. And there’s a whole host of targets on T-cells that potentially can mediate this pathway and impact treatment for patients.
New Molecular Targets in AML: Overview and FLT3 Inhibitors

Naval Daver, MD
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Houston, Texas

**Dr. Daver:** When we look at AML and prognostic factors, we look at it in two ways. We look at patient-specific prognostic factors, and these are things such as age of the patient, comorbidities, cardiac function, performance status. And then we look at disease-related risk factors or prognostic factors, and these include things such as cytogenetics, as well as prior antecedent hematologic disorders. And now emerging and potentially one of the most powerful prognostic markers are molecular markers.

You know, as Dr. Ravandi said, I totally agree that we’ve been lagging in progress in drug development. But when it comes to molecular. Actually I think AML is doing very, very well and is leading the field, because when we go to other meetings with other heme malignancies, the degree of detail that we have in our molecular stratification and prognosis is very, very powerful. And hopefully this will now in the next few years lead us into approvals using some of these agents.

So this is the same diagram in one of the seminal studies. But to be noted, it’s only one of many studies that have been published looking at different molecular mutations. But the take-home message from it is that it’s a very heterogeneous disease. And more importantly, if you look at this graph, as you can see, the most common mutations are FLT3. And these include two types of mutations. You have a FLT3-ITD mutation that’s seen in about 25% to 35% of patients, and then you have the FLT3-TKD, or DB3S, that’s seen in 7% to 10%. And this difference is not only semantic but it’s actually prognostically important. So it’s the FLT3-ITD patients who do poorly. They often come with high white count. They have a good response to chemo but they usually have early relapse and a poor overall survival. So that’s why it’s important. With the DB3S, we have not seen this negative impact, so we usually target the ITD patients initially, although the story is a little bit more involved because when we target ITD, we can later see that the DB3S emerges and becomes a mechanism of resistance.

The other mutation that’s very frequently seen is NPM1, and this is a favorable mutation when it occurs as an isolated phase. And at this time there’s not too many approaches targeting it but there are some new things that are coming along. Then going down the list looking more at what’s clinically evaluable, IDH1 and 2 are emerging and I think everybody here who is treating AML has heard about them. So like Dr. Savona said, there is the “MDS-y” AML and I think there’s an “IDH-y” and a “FLT-y” kind of AML as well emerging, which is good because I think we need to subcategorize these.

So again, talking about what are the prognostic groups here. So FLT3, clearly when you have an ITD, is unfavorable. It’s frequently seen in diploid-mutated patients. So, what’s important is we used to put the 60% group of AML patients who are diploid as one group but now we’re breaking them down because we saw that some people did very well and some did poorly, and the molecular is helping us stratify this group further. NPM1, in general, is favorable when it occurs alone. IDH has been neutral in general, although some studies show it may be unfavorable. And then some of these others for which there are targeted drugs emerging or already available, such as Bcl, MLL are poor.

Now at the bottom of the list are the two that are the worst, which are P53 just like in solid tumors. These people do extremely poor. And unfortunately, we have to say that at this time we don’t have...
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anything that clearly overcomes this negative factor, but there’s a huge effort looking at antibody checkpoints, Bcl-2, to see if they could improve these outcomes. And the last one is ETV6, which is associated with a translocation 3Q. And these patients also do very poorly and we don’t have any great leads yet in that area.

At a Glance: Major Targets of Past and Future Therapeutic Development

- **AML with FLT3 internal tandem duplication** • Impact on both therapy and prognosis
- **IDH mutations in AML** • IDH1/2 mutations confer a gain-of-function, affect DNA methylation and cellular differentiation
- **KIT mutations in CBF AML** • KIT mutations found in 30%-35% of CBF AML cases, but rare in other AML subgroups
- **Bcl-2 inhibition** • Bcl-2 binds and sequesters pro-apoptotic molecules; inhibition of Bcl-2 primes cancer cells for death
- **Epigenetic targets (EZH2, MLL)** • Novel agents in early clinical trial development

So looking at the targeted groups, FLT3 is the one which is more further along, and we have a few slides that are going to review the multiple FLT3 inhibitors that are in phase 3 studies and also many more in phase 2, and hopefully some that reach approval soon. IDH as well, there are now a number of these drugs. Bcl-2, many of you may have heard of venetoclax or ABT199, which is a Bcl-2 inhibitor. And by inhibiting Bcl-2, it enhances the pro-apoptotic pathways, allowing more apoptosis to take place, and is showing very, very exciting data, especially in combination with epigenetic drugs such as azacitidine and decitabine. And then some new targets and drugs that are now in phase 1 that are coming along targeting MLL and EZH2, both of which are new epigenetic targets that are also usually inferior outcomes in AML.

In fact, this is one of those situations very similar to Philadelphia-positive ALL where you have a mutation that is historically an adverse mutation with a 5-year survival of 25% and with a good targeted therapy, we’re getting these people now equivalent survival to what you would see with de novo AML. I think we often say in our group that prognostic markers are very important but only in the absence of targeted active therapy. So hopefully these things will continue to progress.

So here, this is the first study we have to talk about when we talk about FLT3 inhibitors because it is the only phase 3 study that has been completed and has shown survival benefit. So this is RATIFY study that was presented last year by Dr. Stone, it’s not yet published. And this basically took patients with AML out with activating FLT3 mutations.

Overall Survival in FLT3 Mutated AML by Era (MDACC 2003-2013)

![Overall Survival in FLT3 Mutated AML by Era](Image)

<table>
<thead>
<tr>
<th>Era</th>
<th>Total</th>
<th>Died</th>
<th>%</th>
<th>Median, mo</th>
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<tbody>
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<td>46</td>
<td>57</td>
<td>12.5</td>
<td>63</td>
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<td>77</td>
<td>13.2</td>
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<tr>
<td>2009-2011</td>
<td>56</td>
<td>72</td>
<td>12.8</td>
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<tr>
<td>2012-2013</td>
<td>67</td>
<td>87</td>
<td>12.9</td>
<td>71</td>
</tr>
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</table>

Overall Survival: 0.5 to 0.1

Phase 3 RATIFY Study: Chemotherapy + Midostaurin in Newly Diagnosed AML

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Arm 1</th>
<th>Arm 2</th>
</tr>
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<tbody>
<tr>
<td>Control group</td>
<td>Cytarabine (3 g/m²)</td>
<td>R</td>
<td>M</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Rituximab (1 g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midostaurin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-dose cytarabine (8 mg/m²)</td>
<td>M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midostaurin</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

So here, the statement about FLT3 inhibitors is because it is the only phase 3 study that has been completed and has shown survival benefit. So this is RATIFY study that was presented last year by Dr. Stone, it’s not yet published. And this basically took patients with AML out with activating FLT3 mutations.

So it’s important to note here that this was not specific to ITD. It did include ITD and D835, although the majority of patients were ITD. And the patients received standard inductions, cytarabine and daunorubicin alone, or they would receive cytarabine/daunorubicin plus the FLT3 inhibitor midostaurin on day 8 through 22, so during the middle of the induction. And then, once they went into a remission, they would get three to four consolidations with high-dose AraC, which is again the standard given 3 g/m² twice a day on days 1, 3, and 5. But in the treatment arm with the investigational agent, they would again get midostaurin from...
day 8 to 22. And then there was a 1-year follow-up maintenance period, I guess you could call it, where they would get midostaurin alone. And the primary endpoint was to look at overall survival. And here, as you can see, there were a large number of patients, 700 patients, so one of the larger studies that we’ve done in AML.

And you can see that the CR rate actually improves marginally. And like I said in the beginning, the FLT3 patients actually do get CRs; that’s not the problem, they’re not resistant to getting into remission. But where we start seeing the difference is when you look at survival. So 5-year survivals started going up. You’re getting 51% alive versus 43%, which for a patient I think is meaningful, that you have a 25%, 30% better chance of being alive. And then when you look at censoring for transplant, that benefit was continued to be maintained.

Another thing we’re seeing with FLT3 inhibitors is they’re also very good to get patients to transplant. What we’ve seen in the past is in the salvage setting we would have to give high doses of chemo, like MEC, FLAG-IDA, etc. And a lot of times patients would get infections, toxicities, complications and never make it to transplant. So I think this, what we have been calling a bridge to transplant, when you can use a less-intensive treatment, get people into remission and transplant, is actually quite important and will actually lead to improved outcomes.

So here you look at the survival curves and you can see that there is a clear difference between these two groups. It’s being maintained. We continue to follow these patients out. Overall, the other good thing is midostaurin is well tolerated. There were no major toxicities that were seen in the trial and count recovery was also not significantly delayed.

### Midostaurin ± 3+7: Efficacy Outcomes From RATIFY Study

- 3,279 newly diagnosed patients (age 18-60), 7:17 with FLT3-mutated AML
- 3+7 ± midostaurin 60 mg BID days 8-22, then HDAC ± midostaurin days 8-22, then midostaurin x 1 year, 50% had BCT (1/2 post CR1)

<table>
<thead>
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<th>Results</th>
<th>M (n = 369)</th>
<th>No M (n = 357)</th>
<th>P (HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>56</td>
<td>54</td>
<td>0.18</td>
</tr>
<tr>
<td>5-y OS</td>
<td>51</td>
<td>43</td>
<td>0.007  (0.77)</td>
</tr>
<tr>
<td>5-y OS SCT censored</td>
<td>63</td>
<td>58</td>
<td>0.47 (0.77)</td>
</tr>
</tbody>
</table>

And so then going to some of the other FLT3 inhibitors, sorafenib is one that we at MD Anderson have been using for a long time and with Dr. Ravandi, who is here, has been published a study with azacitidine and sorafenib. We’ve also done it with high-dose chemo, which is IA plus sorafenib. And this study was very interesting and I think we have to put it into perspective.

So these were patients who were salvage patients, a median of two prior therapies, and older groups, so 60-plus. And what we were looking at is if you use sorafenib with azacitidine, what would be the response rate. So if I had such a patient where I used only azacitidine decitabine, on epigenetic therapy alone, we’ve looked at this at MD Anderson, our retrospective database. We were expecting somewhere between 15% to 18% CR/CRi rate. So when we saw this CR/CRi rate of about 42%, 43%, I think that’s quite encouraging.

One of the things that we do see is the responses are short-lived and this brings us to what are the potential mechanisms of resistance. And one of the things that has been seen across multiple FLT3 inhibitors has been that there’s an emergence of secondary FLT3 mutations. So you target ITD but then you can get a D835 or a 691 or other mutations. And there are also many other pro-survival pathways, such as Bcl-2, PI3 kinase, MAP kinase, that are upregulated. And so maybe if we combine them or if we use ITD plus D835 inhibition, you could see better outcomes.

So a little bit of change in gears, and this is a discussion we often have in our group as to are these FLT3 inhibitors specifically working towards the FLT3 mutation or are we getting benefit because these are multikinase inhibitors. So sorafenib, for example, inhibits VEGF, it inhibits RAF, it inhibits KIT, and that’s why it’s been approved in renal cancer, in liver cancer, some forms of medullary thyroid.

### Azacitidine + Sorafenib in AML FLT3 ITD+

- 43 patients with AML (40 FLT3 ITD+); median age 64 (24-87); median prior Rx 2 (0-7)
- AZA 75 mg/m² IV daily x 7 + sorafenib 400 mg BID
- OR 16/43 = 46%; CR, 6 (16%); CRi, 10 (27%); PR, 1 (3%)  
- Median CRD, 2.3 mo; median OS, 5.7 mo
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And so this was a very interesting study that was published in *Lancet Oncology* last year by Dr. Röllig and his colleagues. What they did is they took people, all patients—not FLT3-specific—all patients with AML who were younger patients, so 18 to 60 years, and randomized to receive either [7+3]–like therapy, which is standard, or [7+3] with sorafenib. And they wanted to see how did this impact the overall survival, the event-free survival, and the remission rates.

And so what was very interesting is that they saw very clear and marked improvement in the event-free survival. It was 23 months versus 9 months. However, the overall survival actually did not show a clear difference. And this is, I think, a very intriguing study that we also reviewed at MD Anderson, and we don’t know exactly what happened.

So I think there are two possibilities. One is if you use very, very active therapy upfront, so [7+3] with a multikinase inhibitor, it is possible that under the pressure, therapeutic pressure of very effective treatment, you’re going to get more resistant or aggressive disease emerging. Dr. Röllig and his colleagues are looking at the molecular profiles pre- and post-treatment and it will be very interesting to see. The second thing we saw when we talked to them and reviewed the study is that more patients who were on the non-sorafenib arm went to transplant; it was almost about 18% more. So what you could see is that in the sorafenib-treated patients, less of them needed transplant but got the same survival, which is quite interesting. But this still needs to be teased out and I don’t know the final answer as to whether you can use these FLT3 inhibitors in non-FLT3 settings.

The other study that we’ve looked at has been with quizartinib. So this is also a very active FLT3 inhibitor. It’s gone through randomized phase 2 studies and now there’s a large, randomized phase 3 ongoing. Overall, as you can see, the CRc response rate is about 53%, which is quite good. But majority of these are CRs with incomplete count recovery, so you don’t see as many CRs, only about 5%. However, a lot of these patients can go on to transplant. Again, we see that the response durations are the same, 2.5 to 3 months, and so we need to improve on that.

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The other FLT3 inhibitor that is in development at this time is gilteritinib, and this is a very interesting and overall very active drug. And this targets both ITD as well as the D835 mutation. And one of the hopes is that this does not target other kinases as much, such as c-KIT, which actually mediates the neutropenia and cytopenia, so maybe you’ll get less neutropenia and cytopenia.

So this study completed. It’s a phase 1/2 trial and we found that the most active dose is around 120 to 200 [mg per day], where again you see that the CRc or composite remission rates are about 50% to 52%.
So quickly going through, this is the phase 3 study here where we're going to be looking at gilteritinib alone versus salvage chemotherapy in the salvage patients, first and second salvage group of patients. And this is open, accruing, so if you have this kind of patients, I would strongly urge to look for the FLT3 mutation, IDH mutation and consider them for these trials.

Crenolanib is another one that is a FLT3 inhibitor that's in development at this time. And this one also, like gilteritinib, inhibits both ITD as well as D835. We have this at our center, we’ve been treating patients and we do see that it has activity, especially in the D835, where we’re getting about 20%, 25% response rates in patients who have become resistant to prior FLT3 inhibitors, such as sorafenib, quizartinib. So an interesting one but it’s earlier in development at this time.

We’re getting responses in the range of 50% to 60% with these FLT3 inhibitors but we need to improve on these responses. And a number of different strategies are looked at in the lab, but also many of these have now become clinically translationable. So we’re combining FLT3 inhibitors, for example, with MEC inhibitors, a study of a drug called E6201 that inhibits both these pathways. There are combination studies now coming with Bcl-2 inhibitors with ABT that we’ll be opening at our center, as well as with PIM-kinase inhibitors. And then there are the new, broader FLT3 inhibitors that block both ITD as well as D835. So the hope is with these newer combinations, or broader FLT3 inhibitors, we will be able to not only keep the response rate the same or better, but get that durability higher.
New Molecular Targets in AML: IDH, Bcl-2, and Nuclear Export Inhibition

Naval Daver, MD
The University of Texas MD Anderson Cancer Center
Houston, Texas

Dr. Daver: Now moving on to the next group, the IDH mutations, which actually is more of a recent clinical development, they’ve been around for about 3 to 4 years. And these are more metabolic drugs. So you know, I think we need to differentiate the FLT3 from the IDH group. The FLT3 really works more at the level of the mutation, whereas with the IDH group, when you have these IDH mutations, what you see is that these patients do not go through the normal pathways and produce alpha-ketoglutarate, but they start producing hydroxynitrile glutarate. And this compound is known to block differentiations, so this is kind of a similar situation as to what you see in APL, there’s actually a differentiation blockade. And what you see when you use these drugs clinically, IDH inhibitors, is that the differentiation then progresses through the normal means. And so we sometimes do see these differentiation syndromes.

So now there have been a number of patients who have been treated on these IDH inhibitor trials, and overall what we see is the incidence of these IDH mutations is about 18% to 20%. IDH2 is about 8% and IDH1 is about 6% to 8%, as well. Very important is that we never see acquisition in IDH mutations. We looked at this in our center as well as others have looked at it. It’s a founder mutation. On the other hand, FLT3 we can sometimes see that it is acquired later on.

And the other important thing to note here is that the IDH mutations are often seen in patients who have diploid cytogenetics, just like FLT3. So these are important, especially when you have patient who is diploid, to both stratify them prognostically as well as to consider them for clinical trials. And one thing that has been shown by our colleagues at Sloan-Kettering is that in patients who had myelofibrosis, or MPN, who progressed to AML, there seems to be very high incidence of these IDH mutations. We don’t know clearly why, but up to 30%, 35% of these patients may have it. So definitely if you see a myelofibrosis or a PV or ET patient progressing to AML, please consider checking these patients for IDH because there’s a good chance, one in three, that they could have it. And as we know, these patients do extremely poorly so they would be very good candidates to consider for such clinical trials.

So here’s an overview of the IDH inhibitors that are now in clinical trials. The two that started the earliest are AG-221 and the AG-120, IDH2 and IDH1 inhibitor, respectively. And now there is in a phase 1 a dual-IDH inhibitor, AG881. There’s also another, IDH305, which is in the early trials, looking at both solid tumors, basically brain tumors as well as in leukemias, and other new compounds.

So the AG-221 I think is the first one that started about 2, 2-and-a-half years ago. It included patients who had very broad group
of advanced heme malignancies. As you can see, this was the expanded phase 1 with four different cohorts that were looked at, including older patients, younger patients, also patients who didn’t have necessarily AML but had MDS or other hematological malignancies. So the dose escalation was done and they actually were able to go up to doses of 600-plus [mg], and there were actually no major DLTs or toxicities seen. So overall, it was quite a well-tolerated drug.

Here, as we mentioned, the main effect of these drugs is to remove that differentiation blockade, and so a lot of times we start seeing more mature cells. And we also sometimes clinically see this differentiation syndrome, which was very unique to us when we started treating these patients about a year and a half before. But it’s a little different from the differentiation syndrome that we’re used to seeing with APL when we use ATRA. It doesn’t coincide as well with the level of white counts, so it can happen even at low white counts, and it does respond though to steroids. So this is something to be aware of as these drugs are being used more and more if they become available to be used in the community.

So going back here, what is the response? That’s always the big question. So as a single agent, when you look at these, and we’ve highlighted the relapsed/refractory AML group, and a good number of patients now have been treated and this will probably be updated later on at this ASH, 160 patients treated. The overall response rates—so looking at CR, CRi, PRs, hematological improvement—was about 37%, which as a single agent, non-toxic, orally available, is quite good. The CR rate was 20%, which also I think is good because eventually these drugs are all going to be used in combination.

What’s interesting is that even as a single agent, a lot of these responses have been durable. And as you can see, the response durations can be anywhere from 7 months, 10 months. We actually have some patients who are now 2 years out that we are following and treating who have maintained this response as a single agent.

So the other one is the IDH1 inhibitor, AG120. This one is a little bit later in—the trials started later, so fewer patients on it. Also this is an expanded phase 1b study with about 150 patients who have been treated on it. And here you can see almost a mirror image for the responses in the previous slide. So even in the IDH1 we see very similarly overall response rates, somewhere between 30% and 35%, and the CR rates are somewhere between 18% to 20%, 22%. This drug also is equally well tolerated. We did see a few cases of transaminitis but that was well-controlled with dose reduction or slight interruptions. But all in all, no major toxicities, no mucositis, no nausea/vomiting, no diarrhea, and quite easily tolerated.
AML at the Crossroads: Finding a Treatment Role for Innovative Therapeutics

So the IDH inhibitors are in development. There is an expanded phase 1b ongoing and we’re hoping that some of these may become available very soon. There are discussions ongoing with the FDA and there are also combination trials that have begun, both in elderly frontline using epigenetic agents, like azacitidine and decitabine with these drugs for untreated older AML as well as for younger AML, using [7+3], plus IDH1 or 2 versus [7+3], very similar to the RATIFY midostaurin design.

So the next very exciting drug is ABT199, or venetoclax. It’s a Bcl-2 inhibitor. And we did a lot of preclinical work with this drug at MD Anderson with Marina Konopleva in our group. And basically the Bcl-2 pathway is a group of families that blocks apoptosis. So if you release these drugs then you get more pro-apoptotic signals and then you can get more apoptosis of the leukemia cells.

We did a phase 1 multicenter study with this agent and the overall response in 32 patients, CR/CRI was about 20%. What was interesting is among this group, we did have molecular adaptations for all the patients at baseline and of the six IDH-mutated patients, we saw responses in four of them, so that’s also a very interesting finding, that this drug did have good activity and there have been some preclinical data published on this as well.
then the dose has been established for this at between 400 and 800 [mg/m²] for the venetoclax. And the study has now been expanded and some of the data has actually been presented both at ASH last year by Dr. Dinardo and then this year by Dr. Pollyea at the EHA meeting that was in the spring.

So again, when we think about these patients, we have to see what the age is. These are patients, so 75 years is the median age so definitely a high-risk group of patients. A lot of them did have adverse cytogenetics and some with antecedent hematological disorders. And this is kind of the group of patients we would expect to see at our institute or any other institute for an older AML population.

If we had azacitidine or decitabine alone, we would be looking at 22% to 28%, 30% overall CR/CRi rates. And here we can see the CR/CRi rates are in the range of 60%, 65% on some more recent updated data. So very encouraging.

The next drug that is a little bit different from the ones we’ve talked about that target only one pathway predominantly is a drug called selinexor. And this drug actually has a very unique mechanism of action. So what it does is it works at the nuclear pores to prevent efflux of a number of tumor-suppressor proteins. And so you can actually have activity through multiple pathways by keeping tumor suppressors, such as NF-kappa B, B53, FLT3, all of these within the nucleus. The idea is maybe you don’t block each one individually, which is not logistically possible, giving people many drugs, but maybe you can activate multiple pathways at once. And this drug is being used in many different diseases, in myelomas, in lymphomas, as well as in AML study that we’re participating in.
So the phase 1 study has been published with the selinexor. So again, if you look at this group, what’s clear is this is a high-risk group. The median age is about 67 years, and these [patients] had a lot of prior treatments, so this is median of third salvage. So again, when we see a third salvage patient with AML who is above 60, expected response rates with standard chemotherapy are somewhere between 12% to 15% or lower, and these patients don’t really tolerate it well. And a lot of these patients also did have intermediate or adverse cytogenetics.

And what was seen is definitely the agent had activity in blast reduction. A large number of people, about 60%, had reduction in blasts and the overall CR/CRi/PR rate was about 17% to 18%, which as a single agent, again, is reasonable. I think the money is going to be about what happens with the combinations.

And one of those combinations that is ongoing is combining selinexor with idarubicin and cytarabine in relapsed/refractory AML. So this at last presentation was a small study but there are more patients that have been enrolled, and we should have some updates on this. And this was for all patients who had any kind of relapsed disease, including prior transplants.

And at this time in this population, we’re getting a response rate about 50%, which is very, very encouraging. With high-dose AraC alone or IA alone in such a population, salvage two or beyond, we would expect a response rate of somewhere between 15% to 20%, 22%. So we need to continue to follow this data and see how this progresses.
**Clinical Trial Showcase on Novel Therapy in AML**

Farhad Ravandi, MD  
The University of Texas MD Anderson Cancer Center  
Houston, Texas

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**Phase 3 Study of Guadecitabine Versus Treatment Choice in Adults With Previously Treated AML**

Dr. Ravandi: So we are going to actually show you some of the ongoing clinical trials, larger trials. So you heard about ASTRAL-2, which is a randomized phase 3 trial of guadecitabine versus treatment choice in patients with relapse and refractory AML. And as I mentioned, this is an ongoing or about to begin trial, so again we welcome and encourage your participation.

**ASTRAL-2**  
Adults with previously treated AML  
- ECOG PS 0-2  
- Prior tx with standard-intensive induction  
- Refractory to initial induction (primary refractoriness) or on relapse  
Estimated N = 404

**Guadecitabine**  
- 60 mg/m² SubQ in 28-day cycles  
- Cycle 1: 61-12 and 61-12  
- Cycle 2: 61-6 and 61-6 only

**Treatment Choice**  
- HDAC: MEC or FLAG/IDA  
- LDAC: decitabine or azacitidine  
- BSC

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**CPX-351: Phase 4 Expanded-Access Protocol**

And there is a phase 4 multicenter, single-arm, expanded-access trial of CPX-351, another agent that you heard a lot about from Dr. Savona. And this is, again, patients with secondary AML who are suitable for treatment. So I think we hear a lot about patients who are unsuitable for chemotherapy, but these are patients who are suitable for treatment and they can two get cycles of induction and four cycles of consolidation.

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**Phase 3 CASCADE Study: Vadastuximab Talirine + Azacitidine or Decitabine in Older Patients With AML**

Okay, the next clinical trials showcase, you’ve already heard about this study, which is the CASCADE study. As Dr. Fathi mentioned, this is a randomized trial, actually in any patient over 18 who is not fit for chemotherapy. But obviously the younger patients should be very few, if any. But again, this study is looking at either azacitidine or decitabine based on physician’s choice, plus or minus vadastuximab talirine. And so this is already started in a few centers and it’s going to be a multicenter study, so I’m sure there are centers near you that you can enroll patients through.

**Vadastuximab Talirine: Other Ongoing Studies**

- Phase 1/2: Vadastuximab talirine and azacitidine in previously untreated IPSS int-2 or high-risk MDS
- Phase 1/2: Vadastuximab talirine in relapsed chemoresistant AML; in sequence with standard treatments before a planned HSCT or as maintenance therapy after HSCT

Vadastuximab [talirine] is also being looked at in high-risk MDS. This is a study that is ongoing, a phase 1/2 study putting patients again with higher-percent blasts, bone marrow blast MDS. And also being looked at post-transplant and in the maintenance and pre-transplant [settings], so this is a drug that is generating a lot of interest at the moment.
As you heard, there is interest in checkpoint inhibitors in AML. We are lagging behind solid tumors. As you know, these drugs have been revolutionary in solid tumors. But there is interest in myeloid malignancies and there’s a few studies open at our center.

And there is also other checkpoint inhibitors like pembrolizumab that are being evaluated initially in phase 1 and phase 2 studies, either in combination with azacitidine or with chemotherapy. So, again, some of these studies may be open in a center near you and, again, we highly invite your participation in those.

You already heard about this study, gilteritinib in relapsed and refractory [AML], a randomized phase 3 trial. And the comparison is to conventional salvage chemotherapy. Obviously patients have to be FLT3-mutated and there are about 370 patients that will be enrolled.

There is the IDHENTIFY study, which is AG-221 in patients over the age of 60. And again, they have to be IDH2 mutated and this drug is going to look at the efficacy of AG-221 as a single oral agent as compared to conventional care regimens, such as azacitidine or similar strategies, or chemotherapy, intermediate-dose chemotherapy.

And there are studies with selinexor that are ongoing, mainly phase 2 studies. And these are in combination with chemotherapy. [Note: In combination with cytarabine and idarubicin.] And again, they may be available in centers near you so I would again encourage your participation.
From the Chair: MRD and the Path Forward for Novel Therapy in AML

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Minimal residual disease is becoming more and more important. It’s not new. Particularly flow cytometry has been used for probably more than 2 decades but this is again a measure of what happened to the patient, especially to the leukemia or the AML in the patient when you gave them induction therapy and then consolidation therapy. What was the interaction? That’s governed by the biology of the leukemia, its drug-resistant mechanisms and also the way that the patient handles the drug. We’ve never looked at this in detail over the last 2 or 3 decades when we’ve been using chemotherapy but obviously chemotherapy is metabolized differently in these different patients.

So minimal residual disease is essentially showing you what’s left behind after you’ve given the patient induction therapy and consolidation therapy. And you can use different assays to assess this. Even cytogenetics can be used, I’ll show you a slide next but this is obviously not very sensitive. And more recently, assays like flow and PCR and even next-generation sequencing are being used to detect minimal residual disease and as some people may call it, measurable residual disease.

And these are all pre-treatment covariates. There are obviously interactions between the treatment that you give the patient, the induction treatment, as well as the disease and the leukemia. And post-treatment predictors are very important as well. The most important obviously is achievement of complete remission but we’ve used things like blast clearance day 15, etc., to try to predict the outcome of the patients. I actually also use them to signpost remission therapy.

This is just to show you about cytogenetics. We looked at this a few years ago at our center, essentially looked to see who had cytogenetic analysis at the time of CR. And we showed clearly in these slides if you have abnormal cytogenetics at the time of CR/ NCCR, you did significantly worse in terms of relapse-free and overall survival than if you had normal cytogenetics at CR/NCCR. So even the simple cytogenetic analysis can be a good marker of minimal residual disease.
As I mentioned, that’s not very sensitive and we do have more sensitive assays, PCR particularly, which is particularly useful in patients who have fusion transcripts, patients with core binding factor leukemia, translocation(8;21) and inv(16), as well as patients with MLL-rearranged leukemias, 11q23 leukemias. So clearly you can use the PCR to detect residual leukemic cells that are harboring these fusion transcripts. As this slide shows, again by Dr. Grimwade, that these more favorable core-binding factor leukemias tend to occur in younger patients and, as such, there is a bigger portion of pie in the younger populations that could be susceptible or prone to using PCR for MRD monitoring.

Similarly, in the inv(16) population, they found copy number reduction in peripheral blood to be predictive, and these are actually translating to survival. So in the core-binding factor leukemias we were getting more and more data of the usefulness of this PCR monitoring for MRD. But as I mentioned, they occur only in about 15% or 20% of AMLs and so we do need more common markers that are more widely present in AML patients.

NPM1 mutations occur in about 30% of AML patients, so significantly more frequent, and about half of normal karyotype AML. And there have been a number of studies looking at NPM1 mutation clearance in NPM1 mutated patients. This is a study from the German group that showed that persistence of NPM1 mutations after induction, as well as after the completion of therapy, is associated with a much higher likelihood of relapse, which translated to significantly worse overall survival.

But core-binding factor leukemias account for only about 15% or 20% of leukemias at best and they have been assessed in a number of studies. This is from MRC again showing that using PCR, if you actually get more than a certain degree of log reduction in the bone marrow in t(8;21) patients, you have a very low likelihood of relapse, whereas if you don’t get much of a log reduction, your patient will eventually relapse.
This is another study, again from Dr. David Grimwade’s group that was published in *New England Journal of Medicine* last year. They actually found that using the peripheral blood assay for NPM1 mutated PCR, in patients with NPM1 mutated AML clearance of peripheral blood is actually a most important predictor of outcome on a multivariate analysis. This translates to a much higher likelihood of relapse in the patients who remain positive and a significantly worse overall survival.

So as you know, we have now identified a number of significantly mutated genes in AML. This is data from the Washington University group that looked at 200 patients with AML and did whole genome and whole exome sequencing. And they found significantly mutated genes to be present in patients, and there are 23 significantly mutated genes, including the ones we know about, FLT3 and NPM1, which are the commonest, as you see in this slide. So these genes can potentially be markers for MRD analysis. However, to be a useful marker of MRD analysis, the gene or the mutated gene has to be stable and also not to be gained at the time of relapse. So for example, as you see here, FLT3-ITD can be gained frequently at the time of relapse. So the patient starts off with a FLT3-negative disease and actually gains it at the time of relapse. And the stability is not so great. But as you see, NPM1 is highly stable and has become considered as a useful gene for assessing MRD.

But how about a more widely-available assay, like flow cytometry? This is actually a useful assay because it can cover about over 95% of cases with AML. What it does is it identified aberrant antigen expression on the leukemic blasts, and these are an expression of lymphoid antigens or aberrant levels of antigens that are normally present. Also co-expression of early and late antigens. And what people typically do is comparison to normal, but if you have the original leukemic blast available you can use that as a sort of a support to identify minimal residual disease.

This is data from our center. We looked at [324] patients who had analysis for FLT3 internal tandem duplication mutations. You see on the left there were patients who were positive at diagnoses. They achieved the remission and some of them relapsed but you see at the bottom, a few of these actually relapsed with FLT3-negative disease. And similarly on the right, patients who were negative at diagnoses, at remission and then relapsed, about 10% of them, or eight of them, actually gained FLT3-ITD. So this tells me at least that perhaps FLT3 is not a good MRD marker.

This is not a perfect assay. This is data from St. Jude’s in pediatric AML patients. As you can see on the left side of the slide, patients who had less than 5% blasts, a significant proportion of them were MRD-positive by flow cytometry, 100 of them. But patients who had more than 15% blasts in their bone marrow, there were a few of them who were flow negative. So again, this is not an absolute and it’s not a perfect assay. And on the right it just relied on the pathologists and, again, there was not an absolute correlation between flow negativity and what the pathologist felt to be a negative bone marrow or a positive bone marrow. So this is why when you see data on MRD, you never see a complete, straight curve for the patients who are negative because the assays that we have are still imperfect. And obviously, to some extent, this is dependent on the sensitivity of the assays.
The pediatricians, especially in terms of flow, have been ahead in the game. This is again data from St. Jude’s looking at flow MRD after induction one and two. And they showed that being positive was associated with a higher likelihood of relapse and failure. And on the right they looked at various levels of flow positivity, less than 0.1%, between 0.1% and 1%, and more than 1%. And you can see, particularly after the second induction course, the higher the level, the more likelihood of relapse.

Importantly about the last study is that they did show that with intensification, as well as use of agents like [gemtuzumab ozogamicin], they could get outcomes in the pediatric AML population that were significantly better than all of the previous studies, as well as all the published pediatric AML studies. So they actually translated this to intensification and use of the other agents to try to clear the MRD and improve outcomes.

We did this study a few years ago. Actually the main aim of this study was to look at the role of decitabine versus conventional care strategies in maintenance in patients with AML who had achieved a complete morphological remission. Now at the time of going onto the study, so these patients were all in CR, they all had assessment of MRD by flow.

And interestingly, we saw that patients who remained positive or were positive at the time of entry to the study, had a significantly worse outcome, worse event-free and relapse-free, as well as overall survival. This was a small study but despite that, on multivariate analysis a positive flow at the time of entering to the study was the most important predictor of outcome. And actually use of decitabine didn’t matter. So clearly it means that we really need good agents to try to eradicate persistent disease at the time of CR.

This study is by the MRC in older AML patients, patients over the age of 60. And again they used flow assay to look at persistence of MRD after course one and course two. I'm just showing you course one. And again, they showed that persistence of MRD was associated with a higher likelihood of relapse that did translate to a worse overall survival.
And this is from the Hoven group now in the younger AML population. These are all patients younger than 60. And again, they showed that after induction cycle one and after cycle two, as well as after consolidation, if you had persistent flow-positive MRD, you are much more likely to relapse. And this was true for favorable, intermediate and adverse risk cytogenetic groups. So again, clearly showing a distinction by flow.

This is data that we recently published from MD Anderson in younger patients. Here, we use a much more intensive induction regimen, using higher dose of AraC than the [7+3] regimen that some of you or many of you use. But here again, we showed that after induction, which is month one and two, during consolidation, which is the middle two Kaplan-Meier curves, and at the completion of therapy on the right side, patients who are flow-positive are much more likely to have a worst relapse-free and overall survival. It clearly means that if you can actually do something about these flow-positive patients at this time, potentially you can significantly improve their outcome.

Dr. Walter from the Fred Hutchison Cancer Center did this really interesting study published just a few years ago. This is patients who were referred to them in complete remission, either CR1 or CR2, for transplant, for allogeneic stem cell transplant. And he showed that patients who were flow-positive, it didn't matter if they were CR1 or CR2; they did better both in terms of relapse-free and overall survival, the blue curves as opposed to the red curves. But more importantly, the failure was mainly related to relapse.

As you can see in box C, the patients who were MRD-positive or flow-positive relapse post-transplant, significantly higher than the ones who were negative. And on the D, it shows you non-relapse mortality. So they weren't failing because of toxicity or anything else; they were failing because they were still relapsing post-transplant.

They actually show that there is various levels of flow MRD positivity. Again, less than 0.1%, between 0.1% and 1%, or more than 1%. The blue curve is the patients who were completely negative by their assessment. The other three curves are the patients who had those various levels of positivity. Again, they showed that any positivity was bad, both for relapse-free and overall survival. And again, the failure was because of relapse. Non-relapse mortality was the same on all four subgroups.

So the advantages of flow MRD are that you can do it in a vast majority of AML patients and it is a relatively rapid test. The disadvantage is that you do need a very experienced flow cytometrist who does this all the time. This is very highly dependent on your operator. And obviously the other disadvantage is it’s not as sensitive as PCR. Most studies have used the level of 0.1% as showing it to be prognostic. And as I mentioned, there are now studies, particularly in the pediatric population, where we are using strategies to intensify therapy for patients for MRD-positive disease and hopefully we will do this also in the adult population.
What about next generation sequencing, a mutation clearance? There are very few studies of this. This is probably one of the few published studies from Washington University that they looked at the time of remission to mutation clearance as being a predictor of outcome. And they showed that in the top two curves, event-free and overall survival was significantly better in patients who cleared the mutations. On the bottom two curves they only looked at the intermediate-risk patients; again, mutation clearance was associated with a better relapse and overall survival.

But as you heard from the previous speakers, we obviously know that this situation is very complex, particularly relapse in AML is very complex. There are clones that become dominant, and the question is, “Are all mutations the same in these patients and do we have to clear all the mutations to be sure that the patient is not going to be relapsing?”

This is a very nice study from the Stanford University group that showed presence of these landscaping mutations in preleukemic stem cells. As we now believe, AML is a multi-step process. So perhaps some of these mutations may be present in the preleukemic stem cells and we don’t necessarily have to clear them to have long-term relapse-free survival in these patients.

And the same group did show the persistence of these mutations and remissions, which actually was responsible for clonal hematopoiesis, but did not produce eventual leukemic relapse. So again, we really probably need to know a lot more about these mutations to decide whether complete clearance of mutations is absolutely necessary for long-term relapse-free survival.

Similarly, the Boston Group has shown these mutations to be present in normal individuals. Their incidence increases with age and there is some association with a higher likelihood of development of hematological malignancies. But clearly, not all these patients who have these mutations as a background clonal hematopoiesis will eventually develop leukemia, at least they may not develop it in their immediate future.
AML at the Crossroads: Finding a Treatment Role for Innovative Therapeutics

So this has some implications for using mutation clearance for MRD detection. As I mentioned, there may be mutations that develop as late events, such as occurrence of FLT3 mutations. And these preleukemic stem cell mutations may be present without the patient developing a relapse and so we clearly need to know more about the effects of all of these mutations before we actually require the mutation clearance to be a necessity for long-term cure and long-term survival.

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<th>Implications for MRD Detection</th>
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<tr>
<td>• Subclones with different mutational profiles may cause relapse</td>
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<td>– Potentially with different “late” mutations</td>
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<td>– Can appear as “loss” (e.g., FLT3 mutants)</td>
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<tr>
<td>– May be responsible for phenotypic shifts by MFC in some cases</td>
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<tr>
<td>• Early mutations in preleukemic stem cells problematic for MRD assays</td>
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<tr>
<td>– May persist during CR, in mature populations</td>
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<tr>
<td>• Certain mutations (e.g., DNMT3A, ASXL1, TET2) could reflect background clonal hematopoiesis</td>
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Most importantly, we now are going to have potentially new agents that can clear or eradicate minimal residual disease. This includes monoclonal antibody–based strategies that you heard about, antibody drug conjugates, such as SGN-CD33A, as well as SL-140, as well as bispecific antibodies and targeted therapies, small molecule inhibitors and perhaps even oral azacitidine. There is a randomized study of oral azacitidine in maintenance therapy of AML, which we’ll hopefully hear about in the near future. And potentially even the checkpoint inhibitors, although the data on this is extremely limited. So clearly we will be able to have relatively non-toxic and potentially effective strategies that we can use in remission to eradicate MRD and hopefully improve relapse-free and overall survival.

<table>
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<th>Agents to Eradicate MRD</th>
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<tr>
<td>• Monoclonal antibodies</td>
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<tr>
<td>– SGN-CD33A, AMG-330, SL-140, others</td>
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<tr>
<td>• Demethylating agents</td>
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<td>– Oral azacitidine</td>
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<td>• Checkpoint inhibitors</td>
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<td>– Nivolumab</td>
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<td>• Small molecule inhibitors</td>
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<tr>
<td>– FLT3 kinase inhibitors, IDH inhibitors, ABT-199</td>
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<tr>
<td>• Vaccines</td>
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<td>• CAR-T cells</td>
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So these assays are getting our assessment of MRD better, particularly perhaps the more sensitive assays, such as PCR and next-generation sequencing. These are likely to potentially lead to different definitions of response. We’ve always been using complete remission, morphological remission as considering a patient as doing well, but maybe in the future we will require patients to be MRD-negative before we consider them to be relatively safe in terms of relapse. The most important thing is, when you have MRD monitoring, it’s only relevant if you have effective strategies to deal with it. And with these new novel agents, hopefully we’ll have in the future agents that we can give to your patients when they are persistently positive by flow or by PCR and try to at least convert them to negative perhaps before going to allogeneic stem cell transplant.

<table>
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<th>MRD Monitoring in AML and Emerging Agents: Take-Home Thoughts</th>
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<tbody>
<tr>
<td>• Improved assessment of residual disease</td>
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<td>– MFC, PCR, NGS</td>
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<td>• Better definitions for response are likely to evolve</td>
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<tr>
<td>• Increased complexity of MRD assessment</td>
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<tr>
<td>• Standardization of techniques crucial</td>
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<tr>
<td>• MRD monitoring in CR increasingly important</td>
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<td>• More potent strategies to eradicate MRD may soon be available</td>
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Audience Q&A

Farhad Ravandi, MD
Naval Daver, MD
Amir T. Fathi, MD
Michael R. Savona, MD

**Audience Question**

*Is there an impact of human genomics on cytotoxic therapy responses?*

*Can we use mutations to identify patients who respond to cytotoxics?*

**Dr. Ravandi:** So we do have a lot of questions. I’m going to go through some of them fairly quickly. “Is there an impact of human genomics on cytotoxic therapy responses? [And] can we use mutations to identify patients who respond to cytotoxics?” Perhaps Dr. Savona can answer that perhaps using the ECOG study.

**Dr. Savona:** Yeah, I think that there is not a lot of data that we have any mutation that shows an improvement in survival with cytotoxics, but we do have several mutations seen in several studies that help predict response that I’ve alluded to. And most recently TP53 with the 10 days of decitabine in the paper in the *New England Journal* published 2 weeks ago.

**Dr. Ravandi:** And there was the ECOG trial that suggested that there were some mutations that would do better with high-dose of daunorubicin. That data still has to be reproduced. So for example, in that study they showed that a presence of DNMT3A or NPM1 or MLR rearrangements, patients did better with higher dose of daunorubicin. But again, the data is very limited in terms of selecting cytotoxics based on mutation.

**Audience Question**

*Should antibody–drug conjugates in AML be used in high tumor burden settings or as maintenance therapy?*

**Dr. Savona:** The next question is, “Antibody–drug conjugates should have a better therapeutic window when tumor burden is highest. Why are they using them in maintenance therapy?” I guess Dr. Fathi can answer that, if you like.

**Dr. Fathi:** Well, all I can tell you is that, at least in the case of vadastuximab talirine, which is the Seattle Genetics compound, it is being studied in pretty much every setting that you can imagine in combination with HMAs, in combination with induction, in combination with high-dose AraC during consolidation, in maintenance at lower doses. Many of these are actually going to be oral presentations at this year’s ASH, so I think it is going to be used in various settings. As far as whether it’s best utilized in the upfront setting with highly proliferative disease, I’m not sure if there is sufficient data to say that is the case. I think the particular toxin that is attached to the SGN drug, in particular, is highly potent. At even very low doses, it can lead to significant blast reduction. So it is being used across all settings.

**Audience Question**

*Can you please address what is needed to get approval of vosaroxin in the United States?*

**Dr. Ravandi:** “Can you please address what is needed to get approval of vosaroxin in the USA?” Positive trials?

Well, I can tell you that it is being evaluated in Europe by EMEA for potential approval in patients over the age of 60 who are in relapse. The US authorities require more supportive studies before it can get approved, so that hopefully answers your question.
What, if any, is the significance of loss of FLT3-ITD at the time of relapse?

**Dr. Ravandi:** “What, if any, is the significance of loss of FLT3-ITD at the time of relapse and are the patients still sensitive to FLT3 inhibitors?” Dr. Daver?

**Dr. Daver:** So I think that, as Dr. Ravandi said, FLT3 is more dynamic than NPM1 and we definitely see that it’s acquired or lost. The simple answer would be that for a trial, if the FLT3 was negative, I would not put them on a FLT3 inhibitor trial. Although as we showed, this is evolving because some of the SORAML data showing that you may have benefit in non-FLT3. But I would say if they don’t have a mutation at this time I would go for another trial approach.

**Dr. Savona:** And I think it depends on the FLT3 inhibitor. I mean, some of these FLT3 inhibitors are fairly specific and some of them are fairly nonspecific. And some of the best data for response in FLT3-ITD–negative AML is in patients who receive more broad-spectrum FLT3 inhibitors, likes sorafenib or midostaurin.

**Dr. Daver:** Or quizartinib, which had about a 32% response in non-FLT3. But the good thing is we have so many new drugs, I say for a trial I would go for something else.

**Dr. Fathi:** I would just add, although perhaps it’s obvious, a lot of assays across the country may not specifically look for the TKD alteration. So if you lose the FLT3-ITD mutation, you may very well have a point mutation, especially if that individual was previously on a FLT3 inhibitor.

**Dr. Daver:** Yeah, I think that’s a great point because that may be the mechanism of resistance, and then you could put them on a broader FLT3 inhibitor.

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For Dr. Fathi: Can you comment on the durability of response with the newer antibodies (such as vadastuximab talirine)?

**Dr. Ravandi:** This next question is specifically to Dr. Fathi. “Can you comment on the durability of response with the newer antibodies, vadastuximab [talirine]?”

**Dr. Fathi:** The remissions, at least, on this cohort from the phase 1 trial are fairly durable. And we will have to see what ultimately happens with the randomized study that compares it to HMAs alone. But I would say there is early suggestion of durability of these remissions among mainly older patient populations. I would say more durable by a few months in comparison to historical data with HMA therapy alone.

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For Dr. Daver: Can you reconcile clinicians using HCT versus, say, a FLT3 inhibitor in AML?

**Dr. Daver:** So then this next question is for Dr. Daver. How do you reconcile that healthcare providers are using stem cell transplant? I assume this is in FLT3-negative mutated patients, instead of getting them midostaurin for long-term overall survival benefit with midostaurin maintenance.

**Dr. Fathi:** The remissions, at least, on this cohort from the phase 1 trial are fairly durable. And we will have to see what ultimately happens with the randomized study that compares it to HMAs alone. But I would say there is early suggestion of durability of these remissions among mainly older patient populations. I would say more durable by a few months in comparison to historical data with HMA therapy alone.
**Dr. Ravandi:** Yeah, I mean the best sort of example for that is Philadelphia-positive ALL. So initially you’re not going to exclude patients from transplant. As you get better inhibitors, like now we are hopefully getting with ponatinib, you can actually eventually think about not transplanting patients. But at the moment, I think FLT3-mutated AML continues to be a disease that should be still considered for transplant in first remission.

**Dr. Daver:** Next question is for anyone. “Any interest in combining selinexor with hypomethylating agents in AML? And has any synergy been reported?”

**Dr. Daver:** So there was an IST trial, I was not enrolling but maybe Mike may know. But there was data showing that the response rates could be higher. Do you know what the updates were?

**Dr. Savona:** I don’t know what’s been published but yes, certainly that’s been explored and there is another part of the issue has been tolerance. And with all the patients treated with selinexor now and the experienced, we found very tolerable once-a-week type dosing. And this will be explored now with oral hypomethylated agents and alternative dose of hypomethylated agents. Selinexor is a nice combination agent with several different drugs and it’s being combined with venetoclax in MDS and AML, and also being combined with PD-L1 inhibition.

**Audience Question**

*Any interest in combining selinexor with hypomethylating agents in AML? Has any synergy been reported with these approaches?*

**Dr. Ravandi:** Actually, we have a question.

**Audience Member:** Can we say that the variability of these new molecules can induce the start of a new era of maintenance therapy in AML?

**Dr. Daver:** I am actually a big advocate for maintenance therapy in AML. Historically the reason why I think there hasn’t been a lot of interest in maintenance because we only had cytotoxics. As you know, the Germans actually used to give as a part of their program cytotoxics, and they published many years ago their study where they get monthly cytotoxics for about 3 years. And they only had about 50% adherence or even less, and the only thing they improved was event-free survival, not overall survival.

Tolerability. The last thing you want to give AML patients in remission, further cytotoxics. So that has been an issue. These new agents obviously are much better tolerated and much more targeted and directed at the leukemic cells. So yes, definitely. As I mentioned, there has been interest off hypomethylating agents, which I actually don’t think are going to be the best maintenance strategies. But there is an oral azacitidine study that I mentioned that is a randomized study and hopefully will end after many years and we’ll hear if there is a role for oral azacitidine in maintenance.

And I think there will be studies, hopefully, of these other agents. The only problem is any maintenance study is very difficult to conduct. The oral, the randomized oral azacitidine study has been slow to accrue and it’s going to take a long time. So that’s been the major issue. But yes, I totally agree with you, these drugs will be used in maintenance.

**Dr. Fathi:** I concur with what Dr. Ravandi said. I would just add that I think the molecular development has also led us to kind of
understand that we need to have faster, more accurate, dynamic disease profiling. So companion diagnostics, along with the actual development of these new drugs is very important.

**Dr. Ravandi:** And actually one last thing about that is that many of the studies of these drugs continue to give it for a long time. So even, for example, the midostaurin trial had about a year of maintenance at the end of therapy. So people are beginning to believe in maintenance and MRD in AML but we probably still are a little bit away from full enactment of these strategies.

**Dr. Ravandi:** And the next questions are a bit related [to the] presence of different mutations in core-binding factor leukemias and whether they’re relevant to prognostic. “At what level of PCR would you refer a patient with core-binding factor leukemia for allogeneic stem cell transplant?” Any of the speakers.

**Dr. Savona:** So this is really controversial. I think specifically we’re referring here to c-KIT–mutated, core-binding factor leukemic patients. And clearly the patients who relapse are c-KIT–mutated patients. There are some of us who are very aggressive to take these patients to allogeneic stem cell transplant at CR1. Hopefully the MRD data that Dr. Ravandi presented will help us sort this out because not all patients with c-KIT mutations that are core-binding factor need to be transplanted; we just don’t know which ones. And so maybe the MRD-negative patients who had a mutation may end up being good patients to watch after chemotherapy. But my practice is to send core-binding factor, c-KIT–mutated patients to allogeneic stem cell transplant if they have a reasonable donor.

**Dr. Daver:** And I think the other thing is, the German group is doing a large study looking at dasatinib to see if that could abrogate the negative impact of c-KIT. So at Anderson, I think we have been depending more on the PCR after three cycles to determine whether we’re going to send them to transplant or not. So if they’re c-KIT-mutated…

**Dr. Fathi:** The imatinib trial failed. But the dasatinib may very well not, so that’s a good point.

**Dr. Ravandi:** And actually I think the best drug in core-binding factor leukemia is in terms of, in addition to chemo was gemtuzumab, and perhaps vadastuximab [talirine] is a drug that is going to be important. And in terms of referring for transplant at level of MRD, as far as I know there is a study from the Chinese group in Blood that they suggested that when they transplanted people who were positive, their outcomes improved. But this really again is controversial. Not everybody completely believes in still sending these patients for transplant. But I think as we get more and more data, we will know more about it. And again, I think addition of agents like vadastuximab [talirine] hopefully will make these people MRD-negative anyway.
AML at the Crossroads: Finding a Treatment Role for Innovative Therapeutics

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