Evolving Paradigms in AML: Navigating New Therapeutic Opportunities in the Frontline and Relapsed Settings

Farhad Ravandi, MD – *Chair*
Professor, Department of Leukemia
Division of Cancer Medicine
Chief, Section of Developmental Therapeutics
The University of Texas MD Anderson Cancer Center
Houston, Texas

Naval Daver, MD
Associate Professor
Department of Leukemia
The University of Texas
MD Anderson Cancer Center
Houston, Texas

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

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

CHAPTER 1: Overview: The Expanding Treatment Paradigm in AML -- Farhad Ravandi, MD

Good morning and welcome to you die hard leukemia fans who are here so early in the morning to listen to this symposium, *Evolving Paradigms in AML*. I'm Farhad Ravandi from MD Anderson and I have a very esteemed panel with me. We are going to talk about some of the new therapeutic opportunities in acute myeloid leukemia. I'm going to briefly go over where we are in leukemia and then my colleagues will expand on some of the topics that I go over in the overall review.

We have always considered biology of leukemia important in terms of decision-making. We have used cytogenetics as a predictor of outcome using traditional cytotoxic chemotherapy. More recently with the availability of more sensitive assays, we have identified a number of molecular mutations which are particularly important with patients with a normal karyotype but also in other subtypes of AML. We now are actually moving towards an era that we can actually start thinking of leukemia as a constellation of a number of different specific entities. This is important because we already are developing specific therapeutic strategies for some of these entities. This is also important because the molecular aberrations are helping to refine our predictors and classification systems as you see in the recent European LeukemiaNet classification. Also, it's important to note that we are beginning to look at allelic burden as you see with FLT3. Although this is still a bit controversial, I think this is the way of the future, and we start looking at different allelic burdens of mutations in disease prognostication.

In a younger AML patient, as you know, we have made progress over the years and this has really been by tweaking the doses of chemotherapy and perhaps by using a third drug. The only third drug that has really withstood the time is gemtuzumab that is now known to be very effective in at least core binding factor leukemias, and possibly intermediate-risk leukemias. We also know that this entity – therapy-

related or secondary AMLs – tend to have a very poor prognosis but we now have specific strategies that I think Dr. Garcia-Manero will go over. This is CPX-351 which has been shown to be associated with an improved survival and is now approved for this specific population of patients.

Going back to the molecular entities, FLT3 mutations exists in about 30% of patients. Dr. Stone, I'm sure, will expand on this but there are a number of FLT3 inhibitors that have been developed. The RATIFY trial led to the approval of midostaurin because it improved the survival of younger patients with AML with FLT3 mutation who received 3+7 plus midostaurin, but there are now more effective, more potent FLT3 inhibitors such as quizartinib and gilteritinib. Perhaps these drugs will be available in the near future and will improve our armamentarium for treating FLT3 mutated AML. I'm going to go over IDH inhibitors at length. This is a population of patients which account for about 20% of AML patients and now we have specific drugs for. Also of a lot of interest is the BCL-2 inhibitor venetoclax, which you will hear about throughout the meeting and this morning later, which is showing promising activity in various areas. I think minimal residual disease is very important to think about. There are various assays used to assess minimal residual disease or measurable residual disease. This important paper from the HOVON Group in the *New England Journal of Medicine* showed that if you have the non-CHIP mutations, non-DNMT3A, TET2 or ASXL1, persisting at the time of remission it is highly associated with the higher likelihood of relapse and worse survival and you can actually use these assays together. This is with flow as well as NGS. You can see the predictability improved significantly. This is going to become more important when we have effective agents such as immunotherapeutic agents that Dr. Daver is going to go over, when we can at least try to eradicate minimal residual disease.

I think this is an exciting time in AML therapy. We have a number of strategies available. With that, I'm going to ask Dr. Richard Stone to come and talk about FLT3 mutations.

CHAPTER 2: FLT3 Mutations in AML: Navigating the New and Emerging Therapeutic Options -- Richard Stone, MD

Farhad, thank you very much. Thanks to MediCom for organizing this symposium and certainly thanks to all of you for rising at this very early hour to hear us speak. I'll be talking about FLT3 mutations in AML. Without further ado here's my disclosure slide.

FLT3, as most of you know, is a transmembrane tyrosine kinase that has a ligand called FLT3 ligand; but the key thing is that it's mutated at about 33% of AML patients. These two types of mutations are mutations in the juxtamembrane region called the length mutation or ITD (internal tandem duplication mutation) which is the most prevalent of the two types. The other one is a point mutation in the tyrosine kinase domain. Clearly, the ITD carries the adverse prognosis. The ITD patients usually are associated with a high white count but not always, and ITD patients particularly are associated with a high risk of relapse and a poor overall prognosis. Although in general FLT3 AML is a chemo sensitive disease at least initially, which is not often thought of. Obviously when FLT3 is auto activated by a mutation, it auto dimerizes and then signals down the MAP kinase pathway to cause mitogenesis.

There are a number of drugs that were made to inhibit FLT3 because this sort of discovery about FLT3 mutations occurred in the setting of the wonderful news about imatinib in CML. You figured you got an activated tyrosine kinase, inhibit it, and all will be good. Well, it's a bit more complicated in the FLT3

setting. First of all, the drugs that have been developed to inhibit this activated kinase vary in terms of potency and specificity widely. These dendrograms indicate what other enzymes are inhibited by the agents. You can just see by the amount of red, for example lestaurtinib, one of the so-called first-generation inhibitors as well as midostaurin have a lot of red on there, which means they inhibit a lot of kinases. Midostaurin actually inhibits non-tyrosine kinases (like serine/threonine kinases) but quizartinib, crenolanib, and gilteritinib are much more specific. Whether that's a good thing and a bad thing; it may depend on the setting. My colleague, Dr. Levis, from Hopkins has said that maybe you want you use a nonspecific FLT3 inhibitor early in the disease when it's polyclonal then a more specific inhibitor later in the disease when it's more addicted, when you relapsed to a FLT3 mutation.

These are the second-generation FLT3 inhibitors: crenolanib, gilteritinib, and quizartinib. They are all relatively specific compared to the first-generation inhibitors. Crenolanib and gilteritinib hit both types of FLT3 mutations; quizartinib is very specific and potent for the ITD. The drugs are given three times a day for crenolanib and once a day for gilteritinib and quizartinib. They all have little quirks like crenolanib doesn't affect KIT which means it's not myelosuppressive, gilteritinib inhibits AXL1 which may be good or bad depending on whether you like broad specificity or toxicity, and quizartinib is very specific.

Let's, for the next seven minutes, talk about the settings in which the FLT3 inhibitors have been and could be used and in some cases should be used. We'll talk about historically the first randomized trial that was done with a FLT3 inhibitor was done in a salvage setting. The trial was led by Mark Levis. It investigated whether lestaurtinib, a first-generation FLT3 inhibitor, could add to chemotherapy in terms of prolonging survival and improving remission rates in people that had relapsed FLT3 AML with an ITD. They got MEC if they had a short disease-free interval (delayed relapse) or a HiDAc if they had a long disease-free interval. They get lestaurtinib beginning after the chemotherapy and going on throughout the whole thing. As you can see, in the right hand Kaplan-Meier Curve there was absolutely no effect on survival by adding lestaurtinib. This was disappointing but Dr. Levis went on to show that many of these patients, in fact most of them, did not achieve sufficient levels of FLT3 inhibitory activity in their plasma by an assay called the PIA, plasma inhibitory activity assay. It did not achieve its original FLT3 inhibitor activities in the plasma cell. Maybe the drug failed due to pharmacologic rather than other reasons.

Arog is the maker of a drug called crenolanib which I mentioned is given three times a day. As you'll see in a second, it does have activity in the relapsed/refractory setting as a single agent, but it's being used in a similarly designed, if you will, relapsed/refractory trial with a backbone chemotherapy being mitoxantrone and relatively high-dose ara-C as placebo, or crenolanib. We'll see if this more bioavailable, more specific and potent inhibitor will affect the outcome of patient with relapsed AML given chemotherapy. Remember this in a few minutes we'll talk about single-agent use of FLT3 inhibitors in the relapsed/refractory setting. Interestingly this trial does not have another arm with the crenolanib alone, which probably would have been interesting.

What about with induction upfront? That is where we have the one approved agent, but before we talk about that agent I'll mention sorafenib which is an older drug compared to even midostaurin in terms of its use. It's approved, as many of you know, in hepatocellular carcinoma and renal cancer. Dr. Ravandi here was one of the first, as he always is, one of the first users of sorafenib in the setting of AML. We'll talk about two trials; the first one was IA, MD Anderson/IA plus sorafenib. There was a high complete remission rate. That was taken by the SAL group in Germany and they used chemotherapy plus or minus

sorafenib in older adults with AML, and that was another failure. It was not effective in prolonging event-free or overall survival and it was toxic. But then, another German group led by Cristopher Rollig did a trial with the same design except it was in younger patients. It was not restricted by FLT3 mutation status and it was a positive trial in that it prolonged event-free survival. No effect on overall survival for reasons that I can't quite tell but even though it affected overall survival positively and we like that, it's not really used commonly as upfront agent. Maybe that's because of the RATIFY trial which was a trial in which midostaurin – another first-generation nonspecific FLT3 and kinase inhibitor – was added to chemotherapy, or placebo and that was given induction, consolidation, and in maintenance if you didn't get a transplant in the meantime. The results, as you may know, showed that there was a 22% reduction in the risk of death with a significant *P*-value for those who were given midostaurin compared to placebo. There are lots of other interesting findings from this trial that I don't have time to discuss. The median overall survival was triple but do not look at that because it's not really sensibly valid. Look at the hazard ratio and look at the curves. As you can see it was not a home-run but it was important and I would say it was a double.

Addition of lestaurtinib to front-line chemotherapy was tried by my UK colleagues led by Steve Knapper. Lestaurtinib which was that drug that Levis used in that relapsed trial and that was used by the Brits in the upfront setting. Chemo plus or minus lestaurtinib should work, right? It didn't work but if you look at the fine print you'll see that lestaurtinib did work by prolonging event-free and overall survival in patients who had significant levels of FLT3 inhibitory activity in their plasma. Again, this drug has some pharmacologic problems. Also if you've got azoles which increase the FLT3 inhibitor level, the patients benefited, so it was a negative trial but didn't really demolish the concept of using a FLT3 inhibitor in upfront setting. The other FLT3 inhibitors are each being tested in the same setting. The QuANTUM-First trial is designed similarly to the RATIFY trial. It's chemo plus quizartinib or chemo plus nothing. The crenolanib trial is I think a very important trial because that's going to test whether using a specific inhibitor upfront is a good idea compared to midostaurin plus chemotherapy. Hopefully they'll pull that off and the Astellas folks are thinking about doing a similar trial of chemo-gilteritinib versus chemo and midostaurin.

Single agent at relapse. This is an important place to look at because we have three second-generation drugs all of which have activity. The first one of which is crenolanib which does work both in people who have been exposed to prior tyrosine kinase inhibitors and works even better than those who were tyrosine kinase naïve. As I said, that's not being conducted as a single agent in the relapsed/refractory setting but the next two are: quizartinib which Jorge Cortes, one of these faculty's colleagues, did an important trial showing that there was a significant response rate for quizartinib as a single agent in relapsed/refractory ITD patients. The QuANTUM-R was really a key trial which has just been presented by Dr. Cortes at the European Hematologic Association meeting recently. It was basically quizartinib versus dealer's choice chemo if you have relapsed/refractory FLT3-ITD. The primary endpoint was overall survival, and indeed the overall survival was prolonged with a significant *P*-value. As you can see here, a 12-month survival of 27% in the quizartinib-treated patients and 20% in the chemo patients; so that's probably going to be approved as a single agent in relapsed/refractory AML FLT3 mutant as will gilteritinib.

Dr. Perl led a trial of single-agent gilteritinib in relapsed/refractory AML. Pretty high response rate similar to quizartinib. This one hits both the ITD and the TKD. The trial comparing gilteritinib to chemotherapy, similar design to the prior trial I showed. Probably also positive. The way we know that is because a press release was released by the company saying that there was going to be an approval

NDA filed and the FDA was going to review the application for this drug as a single agent in relapsed FLT3 AML. Low-dose chemo upfront in relapse. Very interesting idea. We have a lot of combination with hypomethylating agents. Again, Dr. Ravandi was one of the first people to combine a hypomethylating agent with a FLT3 inhibitor: in this case sorafenib. This regimen is still used a lot in people that are considered good chemo candidates. The response rate was appreciable.

Another MD Anderson colleague, Dr. Swaminathan, led a trial of quizartinib plus azacitidine or low-dose cytarabine. If you just look at the overall response rate of 69%, you can see that this combination of FLT3 inhibitor plus low-dose chemotherapy let to a response rate as high as you'll hear about with venetoclax and hypomethylating agent. Interesting combination; need to follow that up. After allo stem cell transplant, less data. A bunch of trials with both old and newer agents in the post-FLT3 inhibitor transplant setting in trying to prevent relapse. There is data that sorafenib and quizartinib do prevent relapse in very small trials, but the key trial is the gilteritinib versus placebo in the pre-relapse, post-FLT3 mutant AML transplant setting. That's the BMT CTN sponsored trial and hopefully patients in America will go on that.

In summary, midostaurin is approved as an agent to be used with initial chemotherapy in FLT3 mutant patients. Does it work because it inhibits FLT3 or other things? We'll have to find out. Novartis is sponsoring a chemo plus or minus midostaurin trial in wild-type FLT3 patients. We need to learn more about potent and selective inhibitors in our relapsed patients and we'll have to learn more about using these drugs with hypomethylating agents in the post-transplant setting. That was a whirlwind tour of FLT3 inhibitors in AML.

CHAPTER 3: High-Risk AML: New Therapeutic Option and Trials in Progress -- Guillermo Garcia-Manero, MD

Good morning everybody and thank you, Farhad, for this opportunity. I was given the task to talk about three different compounds, CPX, ABT-199 and subsequently pracinostat so that's quite a bit in 10 minutes.

This is in the context of high-risk AML and basically therapy related secondary disease. For this group of patients I guess there is different modalities that you could use in the current standard of care type of perspective like high-dose araC, intensive chemotherapy approaches or more commonly, in my practice at least, the use of hypomethylating agents. Some people particularly in Europe like to use low-dose araC combinations. Now we have CPX-351 approved at least in North America and of course the investigational clinical trials. I think everybody in the room, if they are here at 6:30 in the morning, know that this is a particularly difficult group of patients where the expectations of survival are quite poor. It doesn't seem, from the slide that I'm showing you from my recent analysis from Dr. Boddu and Dr. Kadia here at MD Anderson, that the survival has been really modified or affected by any of these particular modalities, except maybe in green on the CPX curve.

Let's start with CPX-351. The question is what is this compound? Actually this is basically a liposome delivery molecule that allows you to actually provide the leukemia cells with a fixed ratio of your cytarabine and daunorubicin in a fixed structure. The concept here is that you have a more efficient vehicle to provide therapy to specific sites of disease, in this case the leukemia blast. As you know, this drug was approved in 2017 for the treatment of patients with therapy related acute myelogenous

leukemia. The development of this compound followed three major studies that you see in the slide that is typical for this type of process. Phase 1 where the maximum tolerated dose (MTD) was defined as 100 U/m^2. This was followed by a phase 2 study. It was a kind of global AML trial that actually allowed these investigators to identify perhaps a subset of patients with AML that could benefit the most from this therapy, and that served as the basis for the phase 3 trial that led to the approval of this compound. The slide shows the scheme of the clinical trial that was designed to test this hypothesis of comparing CPX-351 versus standard 7+3 chemotherapy. Basically you see that the key eligibility criteria was for previously untreated patients with AML ages 60 to 75. Of course these individuals should be able to tolerate some form of intensive chemotherapy with adequate performance. Then they were randomized to the investigation of compound CPX versus standard of care with the 7+3 therapy. As typical with this type of approach, two induction programs were allowed and then continue on some form of consolidation chemotherapy afterwards if they had achieved some type of response.

Overall this was a very positive trial. Here you see the comparison in terms of responses, both CR or CR plus CRi. CRi, as you know, refers to these patients that do not fully recover their platelet count. It is in favor of CPX-351, so the complete remission rate with the investigational agent was a little bit over 37% compared to 25% for those patients with the 7+3. If you combine both the CR and CRi obviously you see it's almost 50% with CPX versus a little bit over 30% for those patients with the 7+3 type of approach. Of course that's important, but what you needed to see whether this translates into improved survival or not with this type of approach. Here, they are showing you plots of event-free survival comparing CPX versus 7+3. As you can see this was in favor also of the investigational compound of this study with a hazard ratio of around 0.74.

Another issue that is critical is actually if there is a difference in terms of early mortality. There are different ways to compute this, either 30-day mortality or 60-day mortalities. As you can see in the slide there is actually a trend in terms or less toxicity or less mortality with the investigational compound in this randomized clinical trial. The key question is does this really improve the overall survival? Again, if you see the slide here, this has significant improvement in survival with CPX versus 7+3 with a hazard ratio of a little bit less than 0.7 that was highly significant. I think these are important numbers because it's really comparing what will be considered as standard of care type of therapy with a new modality with a significant improvement in survival in this group of patients. What I think is very interesting from this trial is that there is an effect in terms of the number of patients or the outcome of those patients that went to transplantation with this particular outcome. I think, actually, that if you look at this data in its totality, most of the benefit actually goes from those patients actually that eventually achieved or went o bone marrow transplantation. The question is, why these patients do so well with this modality? I think this is something that needs to be explored further in future studies. Of course this prior intervention was significant, but I don't think that the overall survival that we saw there around nine months is enough for us to say this should be 100% considered standard of care. There is a very large effort between the sponsor of CPX, Jazz Pharmaceuticals, and actually MD Anderson trying to develop a platform of potential doublet combinations combining CPX with maybe some of the targeted therapies and others that Dr. Stone was discussing earlier. I think we’re going to see a lot more clinical activity with that compound right now.

The second agent that we are going to discuss is one that many of us think is going to be very, very important in acute myelogenous leukemia and also potentially myelodysplastic syndrome. This is

venetoclax or ABT-199. As you now this is a compound that is approved for patients with chronic lymphocytic leukemia and it was tested also in AML through the efforts of Dr. Konopleva at MD Anderson. As a single agent, contrary to what you see in CLL, this drug has modest single-agent activity and you see that on the left panel on your slide. There are some specific molecular subsets of this disease. For instance, those with IDH mutations where this compound by itself may have a little bit of a higher response rate and this is something important when you use the compound in your patients. What really got our interest and I think what's really going to be transformative is this concept of combinations of this agent that modulates apoptosis with hypomethylating agents. This has been done both with azacitidine and decitabine. These are studies again done by Dr. Konopleva and Dr. Leonardo at MD Anderson. The data I think is really spectacular. This is a plot that summarizes response rate by patient subgroups so you can look at cytogenetic risk, whether they have AML, age, etc. Basically you are seeing responses that are significantly over 60% and importantly, in this older subset of patients with very high-risk features, complete remission rates that are between 30% to 40% in all subsets. We think this is important data.

What is really more important actually is the durability of these responses and the fact that this combination is truly affecting the natural history of this disease by providing a survival that is quite significant. If you look at the slide here, we're talking of almost 16- to 17-month median survival. Compare that with the prior data we saw with the intensive chemotherapy type of approach. For sure this is an agent and an approach that is going to have fundamental role in this disease. It's also interesting that the investigators that are leading these efforts are able to separate specific molecular subsets that may predict for really outstanding outcome. Realize that some of these other subgroups, perhaps those with TP53 mutation, even if they have a little better outcome compared to what the standard will be, it's still a group that we need to work with a little more with, perhaps, other combinations.

Now, the first-line of studies are with the hypomethylating agents but there are other studies going on. One that is going to be very important is this combination of low-dose araC with ABT-199. I think this is a very smart doublet that probably will lead to approval of this compound because in our experience the activity of low-dose araC in this context is pretty low and the data that Dr. Wei from Australia has shown is actually quite significant if you combine venetoclax with low-dose araC. The next goal also will be, for instance, to combine this not just with low intensity modalities, low-dose araC or hypomethylating agents but actually with standard high-dose araC type of approaches. This is the design of a trial combining FLAG-IDA with ABT-199 that could be a really powerful and robust form of induction chemotherapy. There is really a potential rational to combine this agent with multiple other agents in different diseases and this is a slide that Dr. Konopleva gave me showing some of the ongoing and planned clinical trials. As you can see, this is probably one of the largest research portfolios I've seen for a single agent, and reflects the interest and the potential activity of this compound.

In the last couple of minutes I'd like to go through a combination that is kind of in the background. I don’t know if a lot of people in the room are following this study but this is dear to me because I helped in development of this compound. Pracinostat is a second-generation histone deacetylase inhibitor that we developed at MD Anderson with a group in Singapore; both as a single agent, first in MDS where the drug actually did not show improvement in terms of survival in a randomized trial, but interestingly this data in AML presented at ASH a couple of years ago led to an ongoing major phase 3 trial that is now going through basically almost every continent in the world.

Here, what we did was a small pilot trial of 50 patients combining azacitidine with pracinostat. You know the hypothesis that these two epigenetic drugs are synergistic, and we tested this in a group of patients with AML using the standard dosing of azacitidine. The dose that we have derived with a number of phase 1/2 trials at MD Anderson using this compound pracinostat at a dose of 60 mg orally three times a day. In terms of the overall endpoints, the first thing that we saw is that we were achieving a response rate of around 50%, a little over that, with 42% of these patients achieving complete response rates. This is actually a really high response rate if you compare that with prior doublets with HDAC inhibitors and with the hypomethylating agents as a single agent. Of course there were some subsets that did better. Those with worse cytogenetic characteristics did a little bit worse than those that were intermediate group. But what was really interesting from this pilot trial is in the slide here, that the median survival that we saw was actually close to 20 months. That is similar to what you just heard with the ABT type of combination with 62% of these patients being alive at one year. This is a very intriguing data, the only data with actually the HDAC inhibitors that has this durability of survival. The study actually is now ongoing in multiple countries, is actively accruing and I think is going to be, again, perhaps the last chance for an HDAC inhibitor to prove its value in combination with an HDAC inhibitor.

To finish my summary slide, very simple, I think it's obvious that CPX-351 is a new approach that is approved at least in North America for patients with high-risk AML, particularly also in the older setting. I think although the ABT-199 is not approved, it's going to be an asset that is going to transform the care of our patients with leukemia, not just AML, MDS, and other diseases. I think it's going to be very interesting to see what happens finally with this pracinostat trial that, hopefully, we'll be completing in the next few months. With that, Farhad, thank you very much.

CHAPTER 4: Recent Developments and Current Status of Immunotherapy in AML -- Naval Daver, MD

Thank you very much Dr. Ravandi and the MediCom team for the invitation. I'm going to go through some of the immune therapies.

When we talk about the immunotherapies, I think there is two big groups that we look at. We have the antibody-based drug conjugates. These are hugely antibodies that target particular antigens on the leukemia surface and these are usually linked to either a bacterial or a chemical toxin. These are direct way of cytotoxicity. Then you have what we call the T-cell based therapies. These include bi-specific antibodies, immune checkpoints, CAR T-cells and vaccines. Those are the two kind of sections of the talk that I'm going to give.

First, talking about the targeted antibodies, I think most of the focus now has been on antibody drug conjugates. We haven't been focusing much in the recent times on the naked antibodies because we haven't seen a good level of activity in trials with these agents. There's a number of targets emerging, I think the two best known ones are CD33, CD123. As you know, there is a drug approved, a CD33 antibody drug conjugate with the bacterial toxin clarithromycin. This is gemtuzumab ozogamicin also called Mylotarg. There are other CD33 targeted ADCs as well as bi-specifics that are in development. For CD123 at this time, there is nothing approved but as you can see there are a number of agents and active clinical development in phase 1/2 studies. There are some new targets, one of them especially that I think could be interesting is called CLL1 or CLEC12. This seems to have a more specific distribution on the mature AML blast with less expression on the hematopoietic stem cell based on some preclinical

data published by German colleagues. There are ADC as well as bi-specific approaches that are targeting this now in clinic.

Gemtuzumab has had a very long history. I'm not going to go through the full details but as you know it was previously approved in the United States based on large phase 2 studies. Unfortunately, a confirmatory phase 3 in the front-line setting combining gemtuzumab with induction chemotherapy did not show survival benefit and there was some concern for increased early mortality, four-week mortality. There were issues with the trial and a lot of discussions and reviews have been written, concerns with the dosing as well as the early mortality in the control arm being lower than what would be expected for standard induction. Nonetheless, the drug was withdrawn from the market in 2010.

Now, in parallel, a number of European studies, actually five large randomized studies, were initiated in the early- or mid-2000s and all of these looked at different induction-based combinations with gemtuzumab. One of the big differences compared to the US studies were most of these used a lower fractionated dose of gemtuzumab, usually 3 mg/m^2 either once when it was given in combination with FLAG-ida-like regimen in the British MRC phase 3s or three times as was given in the ALFA-0701 studies when it was given on day 1, 4 and 7, but this was with 3+7.
What was seen, and this is a very nice meta-analysis published in *Lancet Oncology* a few years ago was there was an improvement in EFS as well as OS across the board. There was no increased early four-week or eight-week mortality that was seen previously in the US cooperative study. Actually the most striking findings that are going to be discussed later in the AML session, there is going to be a debate on this with Dr. Roboz and Dr. Walters, was that the benefit seem to be the most in core binding factor. Indeed at MD Anderson our standard and best regimen that we have published on has been FLAG-ida with gemtuzumab in core binding factor giving us about 85% four-year-plus survival rates. There is some benefit in the intermediate group. It is statistically significant, clinically maybe not of great impact yet but this is a reasonable option even for the intermediate group, of course, taking out FLT3 for which Dr. Stone mentioned there is a standard FLT3 inhibitor.

This was the approval of gemtuzumab in the United States by the FDA. It was approved in the frontline setting to be used in combination with induction. Very important, it was approved at the lower dose, 3 mg/m^2. This was predominantly based on the ALFA-0701 study which used gemtuzumab with 3+7 on day 1, 4 and 7. It also was approved in the front line setting as a single agent in patients above 75 years of age who were not considered candidates for intensive chemotherapy, and there are very specific parameters for what would be considered non-candidates for intensive chemo. In this situation, this was based on a large Italian study that randomized patients in the frontline setting with gemtuzumab versus investigator choice therapy. In the end, the median survival was five months versus two and a half months for the gemtuzumab, so this is a reasonable option but I think, as Dr. Garcia-Manero mentioned, we are much more interested in things such as the HMA or low-dose araC with venetoclax. There also is an approval as a single agent in relapsed/refractory AML. I think this is one that is causing a lot of confusion in the community. We get a lot of calls about this. It can be used as a single agent. There are efforts to combine it with HMA. I think in reality we think the way this will be used in a lot of trials we're developing in MD Anderson is in combination with newer agents such as CPX-351 or with venetoclax. I think in the frontline setting, in the core binding factor, and possibly in the intermediate, that probably is the best way this drug can be used.

CD123 is another very important target. It is expressed heavily on AML mature blasts as well as in AML stem cells, but also is expressed on the hematopoietic progenitor cells. There are a number of CD123 trials that went into development. Some of these are on hold. There are some newer ones such as immunogen compounds targeting 123 and 33 that are showing some activity and will be updated at ASH. There are two bi-specifics that are being developed at this time, one of them is a MacroGenics bi-specific that targets CD3, CD123; and the other one is a study with XmAb, a multicenter study that is ongoing which has similar approach.

Bi-specifics, why is there interest in this? I mean, one of the big reasons is in ALL we do have a bi-specific called blinatumomab which is targeting CD3, which is present on the surface of T-cells, and CD19 which is expressed on the surface of ALL blast. The idea is that by bringing the T-cells in close proximity to the mature leukemia blast, you activate T-cells, result in cytotoxic death of the mature leukemia blast. The similar construct, it is hoped, will be working in AML, and there are many bi-specifics now in development. One of the first ones that Dr. Ravandi from our group has been working on a lot is AMG330. Amgen is the same company that developed blinatumomab in ALL and they are looking at a bi-specific now in AML. There are some early signals of activity and responses that we have seen and this will be shown at ASH. One of the bi-specifics, and this is the only one that I'm aware of where data actually has been released, this was at the ASH meeting last year, is a drug called flotetuzumab. This was presented by Dr. Uy who works with Dr. Dipersio. They did show – at the higher dose levels, mind you – this was a large dose escalation and that the dose levels below 500 actually did not see any activity but once they got above 500 they do see response rates, about 30%, as a single agent in relapsed AML. These are people who had a median of two salvages, so this is quite interesting. Another thing they did see was that there was up regulation of PD1, PDL1 and so there is a concept that maybe you can combine these bi-specifics with the PD1, PDL1 inhibitors and these approaches are being looked at.

Now the last area that I've been working on a lot is the immune checkpoint and PD-1 based therapies. This is a paper that will be published in a couple of weeks where we looked at T-cell expression and expression of different immune checkpoints in a large set of about 100 AML patients including new and relapsed. What we found, and others from Moffit and Wash U have also shown, is that the T-cell numbers are actually quite well preserved in the bone marrow in AML patients both new and early salvage as compared to healthy donors. Among the immune checkpoints we looked at about 10 different ones, we saw that PD-1 seemed to be one of interest which was highly expressed in new AML and even more so in relapsed AML. Another one that might be of interest is OX40 but that's probably in a phase 1 development at this time. This was one of the larger studies. We have started a number of different combinations with immune checkpoints. You heard some of these data at MDS. We have this in AML in combination with HMA as well as in combination with high-dose chemo and in maintenance, and now there are some phase 2 and phase 3 studies looking at this. The overall response rate that we saw with this combination is 35%, CR-CRi is about 25%. What's really interesting is we're kind of seeing what's been seen in solid tumors and lymphoma where there is about 15%-20% patients who do not achieve the traditional IWG-ELN responses but have more than one, one and a half year survival. I think it's going to be very important in the phase 2 and phase 3 studies to capture these stable disease hematological improvements because a lot of these people actually become transfusion independent and are being outpatient. The other thing that we have seen is that the timed response is about two to three cycles which fits with a lot of HMA combinations, and the response rate does seem to be higher than what was shown in the recent very large study with single-agent AZA. But I think more than

response, what we're interested in is the survival impact that we see with these agents. I think there is a discrepancy in the survival and the response rate. When we looked at a historical group of patients at MD Anderson as well as a large historical group of 600 patients from the Yale institution we do see, especially in salvage 1, that the one-year survival seems to be improved. I think with a lot of these immunotherapies the focus should probably be on early salvage as well as people with lower blast and burden disease. This was shown with blinatumomab as well with CAR T-cells, and that is where we're looking to develop these in the subsequent larger studies.

Another important thing is biomarkers. We did see that people who had high bone marrow CD3 infiltration (we were able to find the cutoff of 13% by logistic regression), had about a 55% response rate, and this made up about half of the population. One of the ways this could be developed, and this is where some of the companies are looking at, is like we do for FLT3 and IDH where we select patients who have high bone marrow peripheral blood CD3. I'll talk a little bit more about this in the main session when we talk about the immunotherapy, but I think that is how these agents will be more successful rather than treating the entire population.

This was some data shown in MDS by Dr. Garcia-Manero who just spoke before me. What's interesting, and this is I think a little bit different from what we have previously expected, is that IPI is emerging as an important drug. This was shown in AML in a post-transplant setting published in *New England Journal of Medicine* a couple of years ago by Dr. Matt Davids from Dana-Farber. Again, we're seeing this in MDS, that in the post HMA failures which as you know is a very, very high-risk, poor outcome group we are getting single-agent responses and some durable survival, granted this is small numbers but we're seeing this with IPI, not with Nivo. The doublets of course are looking good with 60 to 70% response rates. The CAR T-cells I think are very, very early in AML. Not as mature, let's say, as in ALL. There is one published represented data set from the City of Hope by Dr. Budde and her group where they did show some exciting results. Now, this is seven patients so we would like to see the update, but they had responses. Four out of seven patients, median fourth salvage. Actually when I spoke to them, the durability has been maintained at one year in four of the responders, so this is interesting. I think the study is being expanded.

In conclusion, I think gemtuzumab does have an important role for sure in core binding factor. I think also a reasonable approach in intermediate cytogenetic patients, in adverse cyto or most of the large studies don't show benefit. The lower dose is the dose to use. There is lower incidence of VOD, but precautions and close monitoring are still required. The bi-specifics, I think, are showing some interesting activity. I think they may go very similar to ALL where they work well in the lower burden and maybe in early salvage. With the immune checkpoints, there are now two phase 3 and a phase 2 study looking at frontline as well as maintenance setting. I think these agents, also like the bi-specific, should be used in the salvage 1 setting and maybe we can have biomarker driven studies like we do for FLT3 IDH, and we will see how those go. Thank you very much.

CHAPTER 5: The Impact of New and Emerging IDH Inhibitors on Clinical Practice -- Farhad Ravandi, MD

I'm going to talk about a couple of very exciting drugs that are already available and these are IDH inhibitors.

Isocitrate dehydrogenase is a normal enzyme in the normal Krebs cycle in the cells and it's been shown to be mutated in a number of malignancies. In acute myeloid leukemia there are two enzymes, IDH1 and IDH2, and you can see the incidence of mutations in AML in this slide, as well as in this slide that shows that these mutations can occur in a number of cancers. They were first described actually in colorectal cancer but they are also seen in glioblastoma multiforme, for example, as you see. Again, in AML IDH2 mutations occur in about 15% of patients and IDH1 mutations at about 7% of patients. These are tested by assays such as PCR or next-generation sequencing. Most academic centers are doing this and this is available. Also a number of private laboratories also performed this. It's very important for you to consider doing this testing both at the time of diagnosis but also at the time of relapse because now we have effective drugs that are available for treating these patients.

This is the first one, enasidenib, that was investigated initially in a phase 1/2 study. There were several cohorts in this study, relapsed and refractory AML, elderly unfit AML upfront and other hematological cancers such as MDS, but the focus is really on the relapsed and refractory AML. All of these patients had to have IDH2 mutation. The overall result of the study was very exciting because as a single oral agent it was able to produce about 40% response rate, including about 20% complete remission. Considering that this is actually an oral and quite nontoxic, easily taken and well tolerated as compared to chemotherapy in relapsed/refractory AML where we see responses in the region of 30% overall, you can see that this is obviously a drug that is making an impact at least in the subset of IDH2 mutated patients. Another important thing is, as you see, the proportion of patients with complete remissions increases with time. As I mentioned, the patients can take this oral drug daily without significant problems in the majority of cases, and if you continue the therapy, you improve your responses, so you should not be giving up on the drug early and just say, "Well I'm going to give it one cycle and if it doesn't work I'm going to move on." You can actually see responses after two to three months of therapy and even longer. Obviously the patients who have achieved a complete response tend to do best as you can see this with every drug. You can see the overall survival is actually quite impressive in patients with complete response at the red line. In terms of toxicity, the one that you need to be aware of is the IDH differentiation syndrome which is actually somewhat similar to ATRA differentiation syndrome. Patients develop sometimes leukocytosis, fever, shortness of breath, pulmonary infiltrates, chest x-ray changes. It is actually managed very similarly using steroids and perhaps if you need to, by holding the drug and reducing the dose later.

Now, the second drug is ivosidenib which is an IDH1 inhibitor. It was also investigated in a similar phase 1/2 trial. Again, several cohorts, mainly patients with relapsed and refractory IDH1 mutated AML, but also untreated unfit patients as well as other diseases such as MDS. The majority of patients that are enrolled where in the relapsed and refractory. The phase 1 actually found the dose of 500 mg daily as the recommended phase 2 dose. The data that I'm showing is for the relapsed and refractory patients who were treated with the recommended phase 2 dose. You can see this is a population with a median age of 67 but as low as 18 and as high as 87. About two-thirds of them were de novo and about a third secondary AML. As you can see, the median number of prior therapies were two but as high as six and a number of patients have had prior allogeneic stem cell transplant. These are the comutations that existed with IDH1 mutation. This is important because some of these are already being shown to be mechanism of potential resistance, for example presence of RAS mutations or FLT3 mutations does portend a lower response to the IDH inhibitors.

The adverse events reported within the study were really what you see with any population of relapsed and refractory AML who is myelosuppressed and there are really infections and bleeding issues, but also differentiation syndrome as was seen with the enasidenib or IDH2 inhibitor is also seen in about 10% of patients with ivosidenib. Again, similar features — fever, shortness of breath, unexplained fever, pleural effusions, and pulmonary infiltrates. Again, it's managed by using corticosteroids and perhaps, if necessary, by interrupting treatment. You can see in the green box that even when they developed this differentiation syndrome, patients can actually have excellent responses. As you can see, there are five patients with CR and a number of patients with CRi. Developing differentiation syndrome should not make you move on to something else. You should persist and the patients may benefit in terms of response.

With ivosidenib also there was overall response rate of about 32% including about 24% complete response, which is again very impressive for an oral nontoxic agent which the patient freely takes at home and has very little other toxicity that we commonly see with cytotoxics in the relapsed and refractory setting. Again with this drug you need to persist and continue the therapy and the patients stay on the therapy. Some of the responses can occur after a couple of months or three months. You can see that patients can stay on the drug for a lengthy period of time and improving their responses. Patients who achieve a complete response do get a significant overall survival benefit. Some of these patients obviously will go on to other transplant, but without even transplant, patients can stay on this drug and remain in complete remission for a lengthy period of time. More importantly, transfusion independence. You can see the patients in CR almost 100% become platelets and red cells transfusion independent, but even some of the non-responders who didn't have the actual classical response criteria become transfusion independent during the course of this therapy.

What about clearance of IDH mutations? I talked about minimal residual disease. Obviously this is something of interest. As you see with this IDH1 inhibitor study, about a quarter of the patients with CR did clear IDH mutation at the time of achieving CR. This was, in this small subset of patients, it’s a small number of patients but still significant that you can see patients who do achieve IDH mutation clearance at the time of remission tend to do better. I think this will become significant in terms of measurable residual disease assessment in larger studies.

How about moving on further and as has been practiced with all targeted agents, we are now combining IDH1 and IDH2 inhibitors with hypomethylating agents. This is a study combining azacitidine with either enasidenib for IDH2 mutated patients or ivosidenib in IDH1 mutated patients. Early results were reported in the last ASH meeting by Dr. DiNardo. You can see this is a small number of patients, only 23 patients in terms of ivosidenib and even fewer in terms of enasidenib, but the response rate is actually quite impressive. I'm sure that we will hear more about this with the expansion of the number of patients and further patients enrolled on the trial.

I think in conclusion we are, again as I mentioned earlier, this is an exciting era in AML therapy. There is a number of very effective agents and some of them oral nontoxic agents. IDH mutated patients do benefit not only in the relapse but potentially in the future when we combine these IDH inhibitors with either hypomethylating agents or with chemotherapy. There are studies, as you see at the bottom, that are investigating these prospects, but also there are also next set of IDH inhibitors in development such as the drug mentioned at the last line of the slide. Clearly we are making a major impact in AML therapy with all of these agents and it's exciting to be doing AML these days. Thank you.