Novel Therapies in AML

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

Now, hypomethylating agents, I think, and I hope everybody here is familiar with, these drugs have really become the mainstay of therapy for high-grade myelodysplastic syndrome, and in a large part in acute myeloid leukemia, at least in North America where we use them as front-line agents for the older patients, and what I am referring to is primarily 5-azacitidine and decitabine. I will just refresh you a little bit on some of the trials that have been done with these agents in older patients with untreated AML. With decitabine, as you may recall, a few years ago a phase 3 trial was completed that indicated a higher response rate with decitabine compared with investigator's choice for older patients with AML, but the overall survival did not quite reach statistical significance at the initial landmark analysis, although in later follow up there seemed to be a significant improvement compared to other agents. Azacitidine followed the same path. You can see here that there was a modest, although not quite statistically significant, benefit in survival for patients who received azacitidine compared with conventional care regimens in AML, so two studies that indicated the utility of these drugs, albeit with a very modest effect. We have also recognized through the years that hypomethylating agents, despite a lack of randomized trials against other more intensive therapies probably are just as good if not better. In this analysis of over 900 patients now from own institution and similar data were replicated previously at MD Anderson, in older patients over age 70, we found that the HMA-treated patients actually lived longer than any other group of patients after we did a propensity analysis

to match patient characteristics based on what type of therapy they would most likely receive. So, HMAs have clearly emerged as a major standard of care for older patients with AML.

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

The next agent I wanted to talk about is an agent called pracinostat. This is an HDAC inhibitor, and HDAC inhibitors are another type of epigenetic modifier that can reinstitute gene expression and perhaps allow for greater recovery of gene expression of silence genes in AML, such as differentiation genes. Dr. Garcia-Manero has worked extensively with this class of compounds and has done a lot of work in publication, and one of the most exciting compounds coming out lately is this orally bioavailable drug pracinostat, which is a selective inhibitor of class 1, class 2, and class 4 HDAC. This trial was performed, as shown here, in older patients with previously untreated AML who received both pracinostat daily, every other day, and azacitidine for 7 days in a row, every 4 weeks. The primarily endpoint again was overall response rate in patients who were, generally speaking, older and not candidates for more intensive therapy. The demographics of this study are shown here. As you might imagine, the majority of the patients were older than age 70, in fact most of them were over the age of 75, and a significant component had secondary or high-risk features in terms of secondary disease that arose from MDS or MPN. About 40% of patients with poor-risk karyotype as well. The overall response rates are shown here, and again very intriguingly high response rates in comparison with what you would expect with single-agent azacitidine, decitabine, or low-dose cytarabine, with an overall response rate of CR plus CRI of 46%. The duration of the response I think was impressive at over a year, and the time to the marrow complete response was about 60 days, so not a quick-acting agent in combination, but still something that is happening within a couple of months' time. What I think was very impressive about this trial in the preliminary stages was the fact that the median overall survival was 19 months. If you recall, the median survival in the single-arm studies

of azacitidine and decitabine were generally less than a year, and the 1-year survival at 62%. So, these are looking promising as far as perhaps altering the natural history of AML with this combination, and certainly a randomized study will help clarify that question further.

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

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

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

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

The next drug I will talk about briefly is gilteritinib. This is another class 1 FLT3 inhibitor that binds to both the active and inactive conformation of FLT3, and these are data that were presented by Dr. Sasha Perl at ASH this past year. This was a phase 1/2 trial of gilteritinib looking at a variety of doses, ranging from 20 mg daily up to 450 mg daily, and the doses that are being focused upon right now are the 120 mg and 200 mg dosing cohorts. This was a large phase 1/2 study, and just to summarize the data here, I know the charts are a little bit hard to

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

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

Now, the next breakout group within this large trial was a combination of vadastuximab plus a hypomethylating agent, and these data were presented by Amir Fathi at ASH this year and these were again patients who were previously untreated that had AML that were CD-33 positive who had declined or not deemed eligible for intensive therapy, and again no prior HMA therapy was allowed. These patients were treated with azacitidine at a dose of 75 mg/m^2 for 7 days or decitabine at 20 mg/m^2 for 5 days and received 4-week cycles of vadastuximab as part

of the treatment regimen. Here are the results, again a quite high overall response rate of 73%, which is really much higher than you would expect with azacitidine or decitabine alone, and the response rates held up across different subtypes of AML including FLT3 and older age group. So, stay tuned for a lot more on that drug. We are seeing randomized studies being developed right now for vadastuximab with chemotherapy in younger patients or in combination with azacitidine in the randomized study in older patients.

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

I will finish off here by talking about the IDH inhibitors, and for those of you who may not be familiar, IDH is a very important enzyme in the citric acid cycle. When IDH1 or IDH2 are mutated, you get an abundance and an overproduction of 2-hydroxyglutaric, which then leads to a variety of events intracellularly that lead to a hypermethylation effect in general, and that is felt to be the reason that this mutation class is bad. There are a lot of different mutations that can occur in different tumor types including AML, MDS, and solid tumors as well, and there are several different inhibitors in clinical development. The two that are I think are furthest along right now are the Agios compounds 221 and 120, which we will talk about briefly. The AG-221 drug also known as enasidenib is basically very far along, another very large combined phase 1 and 2 study that was run by Eytan Stein at Memorial, and these data have been presented at ASH over the past few years with several hundred patients treated to date. Baseline characteristics are shown here, over 200 patients. They were practically all mutated at IDH2 and most of them had relapsed or refractory AML. The response rates and the overall efficacy shown here, as you can see, there was a 37% overall response rate and about a 20% CR and CRI rate. Again, as a single-agent in relapsed and refractory disease, pretty good. A handful of patients were also untreated that did not seem to have any higher of a response rate than in the relapsed group, so very strong efficacy in this particular class of compounds, and several of these patients were also able to subsequently undergo allogeneic transplant, so the idea about a bridge to transplant has gained a lot of appeal for these newer agents that we are able to get people into remission. AG-120 is the IDH1 inhibitor that has been extensively studied by Dr. Courtney DiNardo at MD Anderson who presented her data also at ASH this past year, again a

very similar trial in relapsed and refractory AML that was IDH1 mutated. And basically, to again cut to the chase again, a fairly high and impressive overall response rate of over 30% in the relapsed and refractory group, including 30% who achieved a CR or CRI. For those of you who have not been doing this for very long, these numbers are astounding. We can barely crack 20% in relapsed disease with best intensive chemotherapy regimens that we have had for years. The fact that we can get these types of responses with a single oral agent that is just generally well tolerated is very impressive. I will point out that the AG-221 drug in particular has been associated with a differentiation syndrome as a toxicity that is in line with its mechanism of action. It is felt to be differentiating agent in large part. Dr. DiNardo also showed data giving evidence that you could actually clear the IDH1 clone in a significant number of patients who achieve response with this particular compound. So, of the patients of 14 patients who achieved a complete response, 5 of them had mutation clearance of IDH1, and I think we recognized that mutational clearance based on what we have heard from our previous speakers is a very important endpoint in AML and clearly correlates with better outcome. So, we will be looking to see more details on this in the upcoming months and years, and you can see here graphically how many of the CR patients actually cleared their mutations, but it could take time to do it. It could take up to 6 months to clear the mutation, so it is not necessarily a fast-acting drug.

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