Evolving Practices in AML: A Case-based Guide to New and Emerging Treatment Options

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Chapter 1

Dr. Daver: Thank you all very much again for being here. We have our excellent faculty here with us, Dr. Courtney DiNardo, who is at MD Anderson, focuses on acute myeloid leukemia, Dr. Eunice Wang at the Roswell Park, also acute leukemia expert, and myself. I am going to start with some discussion briefly on the background cytogenetic molecular information, patient stratification. I am not going into a lot of detail, Dr. DiNardo and Dr. Wang will cover more about the molecular prognostic impact and especially the target approaches with different molecular approaches in their respective talks.

I am going to move into the initial introduction portion. I think one of the major advances in the AML has been therapies in the last two years. We all are familiar, have heard about that at numerous talks, but in fact, there actually has been a tremendous amount of progress and understanding the molecular stratification, clonal heterogeneity, as well as clonal evolution. I think that really was the initial research that led to a number of discoveries that we have had, so it is important to understand the prognostication and factors we use. So we know the traditional ones: age, performance status, comorbidities, organ function, and secondary AML. We've used these for 20 to 30 years to prognosticate patients, but now we have additional and very predictive factors such as chromosomes, as well as molecular; and the molecular especially I think is critical because not only can it be prognostic, help us to decide intensity of therapy, as well as transplant/no transplant, but also can be predictive in which therapy you select for that given patient. So, one will ask, how does the molecular truly help your prognostication?

On the right-hand side, you see what we used to use, cytogenetic stratification, and this was the typical number we used throughout, 20% favorable, 20% unfavorable, and 60% intermediate. But, what we see is when you overlay the molecular prognostic value of different mutations, you can actually stratify

people much more clearly, so you could have somebody who is intermediate by cytogenetics, but could have 5-year survival of 85%. These are your NPM1 mutated, FLT3, wild-type, balletic, CEBPA and such and on the other hand, you could have some people who have what appears to be intermediate chromosomes, but could have survival of 10% or 15%. These are your people with TP53, RUNX1, ASXL1, so this really has helped us understand the prognostication.

This is one example, a paper published a few years ago. There are numerous publications by different groups in Europe, US, Australia showing that if you use all the tools available: chromosomes, FISH, cytogenetic analysis, as well as molecular, you can truly get a very diverse stratification with some people like APL having 96% to 97% 5-year survival, and some others like FLT3 high, NPM1, or TP53 having less than 10% 5-year survival.

So as an example in point, I am going to talk about FLT3. Historically, you will hear people say, off the cuff, FLT3 is bad, and actually that statement is not true in its entirety. FLT3 mutation is impacted significantly by allelic burden, co-mutations, and the chromosomes that go along with it and I will show you some of the examples. In general, the first time FLT3 was described in a large retrospective study by the German Cooperative Group, they showed that among FLT3 ITD mutations, this was a 900-patient study, 200 or so had FLT3. The ITD population had a 5-year survival of about 20% to 25%, and I think that is important to realize in the light of some of the data that Dr. Wang will talk about as to where we now are with the FLT3 inductions talking about 80% potentially long-term survival, but that was not really sufficient.

When you look at allelic ratio, which is a ratio of the mutated FLT3 to the wild-type, you can see that it really is the people who have a high allelic ratio, meaning a high burden of mutated blast with the FLT3, who have really the worse outcome, and those people have 10% or less 5- year survival. The others don't do great, but they do close to what has been done at that time with de novo AML. So, the allelic ratio on its own is quite important. We usually looked at this. It is in the ELN and NCCN guidelines and can help let you know if the FLT3 is really bad.

The second thing, which I think has even more impact and it took a few more years for us to realize, was that the allelic ratio alone was not enough. You could have somebody with low allelic ratio and some of them did not do so well and we said why is that? Then you start looking at the co-mutation. So if you have co-mutation DNMT3A, TET2, trisomy 8 with a FLT3, this is the worst of the worst. These people are as bad as your TP53. In that case, allelic ratio does not matter. These people you need to give induction, FLT3 inhibitor ideally, take them to transplant.

This is now reflected in the ELN 2017 where you can see FLT3 in all three groups it is in favorable where you have a FLT3 with a low allelic ratio with an NPM1 mutation. It is intermediate. As you see, people who have NPM1 mutated with the FLT3 ITD high, and then it is also in unfavorable, which is the one that we think of the most, which is high FLT3, NPM1 wild-type. Also, you see mutations are now incorporated in ELN. This is not Dana-Farber, MD Anderson, major academic only. This is for everybody; community

setting, commercially approved insurance will approve this, so we should be looking at these mutations across the board.

These are some of the major targets that are in development and we will talk about them in more detail. The two most well-known are FLT3 and IDH, but there are others such as KIT epigenetic targets, also targets for drugs with TP53 like APR or for MLL, and then of course Bcl-2 is not a targeted therapy in that you look for a receptor, but it works ubiquitously in large proportions of acute leukemia.

Here you can see without a microscope, the clear progress and breakthroughs for 40 years. We did have some progress, but in the last two to three years using this molecular and immune information, eight new drugs have been approved and now we have the challenge of finding the right setting, the right combination, and the right duration of these therapies going forward.

Last couple of slides, we really now are having personalized therapy. We talked about it for many years, but in fact when we see a new patient now and most academic centers are doing the same, we try to put the patient in the right treatment. APL has extremely good outcomes with ATRA-arsenic. If we find inversion 16821, we had gemtuzumab. You can see a striking benefit. This was 3+7. We have same data with FLAG-IDA showing 85% 5-year survival, and then FLT3 midostaurin is approved. It had some benefit and maybe we can do even better with quizartinib, gilteritinib, crenolanib, we have to wait and see. Even in secondary- and high-risk AML, a population that for many years we had no progress, now we are making major strides with HMA venetoclax, which we think is going to be a new backbone to further build on with other targeted immune therapies and with CPX-351, which has also shown benefit. So really a lot happening, and with that, also immunotherapies that I will talk about later in my talk, which are kind of in the most early development, but we think these will play a role, especially in low burden disease, MRD, and maintenance just like in ALL and multiple myeloma. I am going to stop there and turned it over to Dr. Eunice Wang.

Chapter 2

Dr. Wang: Thank you so much. My role now is to follow-up on that great introduction and talk to you a little bit about how to adapt some of these novel therapies and some of our older therapies for the treatment needs of the individual patient. So my part of the talk is really to discuss treatment options for newly diagnosed patients and there is a huge amount of data for this, so I am going to try to do this very quickly and then I will be followed by Courtney and Naval again to talk about some of the options for patients with relapsed and refractory disease and then new directions for AML therapy.

Question #7: Bob. I do not know why I picked the word Bob. Bob is a 72-year-old gentleman diagnosed with MDS last year. He received several cycles of azacitidine as per the standard of care and now unfortunately he has been referred to you because he transformed to AML. Initial analysis of his MDS, as well as his AML demonstrates that his AML disease arising out of prior MDS is really characterized by very complex karyotype. You know, one of those karyotypes that four lines long when you get it in the lab report. The question is, what would you recommend for treatment for Bob? Options are

gemtuzumab plus 7+3; liposomal cytarabine and daunorubicin; venetoclax and decitabine; glasdegib and low-dose cytarabine; or options 2 and 3? Both options could be feasible. So the majority of you picked liposomal cytarabine and daunorubicin CPX, followed closely by venetoclax and decitabine, or options of the two, so very consistent, great.

Second question. Mary, a 55-year-old woman. She has de novo AML. Diagnostic work-up demonstrates a normal karyotype, but the presence of both FLT3 ITD and IDH mutations, as Naval mentioned co-mutations are common and even probably expected in some of these patients, particularly those with normal karyotype. She has no prior history of cancer. No significant medical problems. The most appropriate therapy for Mary would be 1) venetoclax and azacitidine, 2) glasdegib and low-dose cytarabine, 3) liposomal cytarabine and daunorubicin, 4) midostaurin plus 7+3, or 5) ivosidenib monotherapy. Okay, 78% of you would choose midostaurin plus 7+3. Okay, excellent.

Moving onward, just a couple case presentations to illustrate the type of complexities and difficulty that we have sometimes in tailoring treatment options for individualized patients. This is a 68-year-old woman that I saw recently when I was covering my inpatient service. She had a prior history of polycythemia vera diagnosed five or six years ago and treated with intermittent phlebotomy. Over time, her hemoglobin was normalized, but her white counts started to rise. She has some comorbidities, coronary artery disease, atrial fibrillation, she is on coumadin, etc. Over time, as you can see here, her white count started to go up at the time of presentation. She has a white count of above 100,000 with 50% peripheral blasts consistent with an AML diagnosis and she is fairly symptomatic with that high white blood cell count. On exam, she is a little hypoxic. She has abnormal lung exam. Her white count is over 100, again with high percentage of peripheral blasts and your work-up of her AML is consistent with the diagnosis of a myeloid malignancy, 100% of her blasts are CD33 positive. She has, as we see in about half of our patients, a normal female karyotype and her molecular analysis comes back and she is mutated in TET2 and JAK, as well as TP53, but wild-type for FLT3 and IDH1 and IDH2.

What would be your choice for initial therapy for this patient with AML? Middle-age woman, history of polycythemia vera, treated with phlebotomy, comes in with a very high white blood cell count, and some comorbidities; cytarabine and daunorubicin; 7+3 GO, CPX351; decitabine monotherapy; venetoclax and decitabine; or venetoclax plus cytarabine. So many of you would choose cytarabine and daunorubicin + GO and actually that is what this woman got. Some of you would pick liposomal cytarabine + daunorubicin, which I think is also a good choice, although the initial trial in which the CPX351 was approved did specifically exclude individuals with secondary AML arising at a prior MPN. So, although we think that that might be a good option, that was not specifically examined based on recommend data, great.

Second case presentation: An 87-year-old woman, again this is a patient of mine. Past medical history has some comorbidities, COPD, hypertension, has a history of an MDS, with normal karyotype. She was treated with growth factors and subsequently with several cycles of azacitidine. She is now status post 4 cycles and has transformed to AML after a recent hospitalization for pneumonia. Her marrow shows a

normal karyotype, which is consistent. She has high expression of CD33 and her molecular panel of which we don't have the full results, really does not show any FLT3 or NPM1 mutations.

So, the question is, how would you treat this individual? Again, venetoclax and azacitidine; venetoclax and LDAC; glasdegib and low-dose cytarabine; CPX351, gemtuzumab monotherapy; or supportive care? The majority of people are going to give venetoclax and azacitidine, followed by low level of people with the other therapies, so certainly supportive care with transfusions alone in an 87-year-old would be completely appropriate care. This patient had a history of prior azacitidine exposure for her MDS and in the phase 1B trial led by Dr. DiNardo over here, she can tell you that patients with prior HMA exposure were excluded from that trial, so we do not know and we do not have data on how that particular regimen would do. There is data for venetoclax and low-dose cytarabine, so I do think that, and they specifically did look at response rates in patients who had prior HMA therapy and they were lower than what we saw without prior HMA, but we will discuss that a little bit later.

Moving on to the slides, now we have been very, very spoiled by what we have called an embarrassment of riches. After 40 years, and I would be the first person to say 40 years, I would say this to my trainees, of no changes of AML therapy, we have been blessed in the last couple of years with the approval of eight drugs for AML and one drug for an entity BPDCN and we will discuss all of those drugs here.

First of all, I wanted to ask a question. What is the benefit? These are elderly patient, largely about half of patients are going to be diagnosed above the age of 65, median age of 67 to 70. What is the benefit in this highly aggressive disease associated with high mortality and morbidity, of giving chemotherapy at all? This data dates back to the 1980s and 70s, where Dr. Lowenberg and colleagues did a trial, which would be unethical nowadays, where they took 60 older patients above the age of 65 and randomized them to the standard intensive chemotherapy 7+3 or a watch-and-wait philosophy. Even in this early era of treatment, there was a statistically significant improvement in overall survival, a doubling of overall survival from 11 to 21 weeks when you gave intensive chemotherapy, so despite the toxicities that we saw in that elder population, there is benefit to treatment. The Swedish study many years later confirmed this benefit across the age spectrum from younger patients to older patients and again, you need to look at the treatment results for patients that do not get treatment, 50% across the board are not alive 30 days after their diagnosis. So, this remains a highly deadly disease with a high lethality and our recommendation is when we meet these individuals that they should strongly consider therapy.

Next, 7+3, well obviously we have had decades to try to perfect our use of 7+3 and in general, as was mentioned, we know that 7+3 can be curative, younger patients, patients with favorable gene fusions, inversions 16, 8, 21 can be cured. This is 10-year data survival. You can see that there is clearly evidence of cure rates with 7+3, but the outcomes can vary dramatically based on the biology of the disease. Now, how have we improved 7+3? The first indication that we were able to improve this was in 2017 with the introduction of FLT3 inhibitors, and this data is known to all of you where we were successfully able to add a FLT3 inhibitor to standard 7+3 and improve outcomes for these patients. This was the first agent that we added to 7+3 over decades of trying that actually led to survival benefit. Now re-analysis of this data suggests that part of that benefit was the use of allotransplant in the patients as well, but certainly

a 7% difference in overall survival over four years is nothing to make fun of. Then, what about patients who were not FLT3 mutant? Well, the data came out saying that this old drug, gemtuzumab ozogamicin, can actually improve outcomes of favorable intermediate karyotype patients when added, again, to 7+3. These are patients that expressed any level of CD33, whether it be anywhere greater than 0.1% CD33 expression, and you can see a clear difference in event free survival differences with the addition of GO.

Meta-analysis data, which Dr. Daver has already mentioned demonstrates that the benefit is primarily in patients with favorable karyotype with over 20% improvement in overall survival and a meta-analysis over 3,000 patients treated with GO and five randomized trials. There is however also a benefit in intermediate risk, smaller, but definitely a 5% difference in overall survival, the difference with midostaurin is only 7% at four years. So if you believe that midostaurin improves outcomes, you need to think about whether gemtuzumab improves outcome in patients with intermediate risk. What about patients that have pre-existing MDS? We talked about that second patient of ours, an 87-year-old, prior MDS, prior HMA therapy, AML with MDS related changes or arising out of a prior history of MDS is associated with certain cytogenetic abnormalities, certain morphological abnormalities, and is associated again with poor outcome as standard 7+3. You can see here that standard 7+3 given to these older patients fit enough for intensive chemotherapy only leads to an overall survival of five to six months. Liposomal 7+3 or CPX351 can dramatically improve these outcomes and in our practice, anybody that is fit enough to get liposomal 7+3 is automatically a candidate for allotransplant, and you can see on the right-hand side, the most compelling argument in my mind to give liposomal 7+3 in an older individual with secondary or therapy related AML is this curve on the right-hand side demonstrating that when you send this poor prognosis patients in CR1 to transplant, the post-transplant outcomes are markedly improved.

What about other subsets? You can see, unlike other subsets, that you do get benefit in favor of intermediate, less good with unfavorable. You can also see however we have benefit in patients that have secondary MDS, but if you had prior HMA therapy, and this is something I'll mention, as in the second patient case, you do not do quite as well with an aggressive regimen, with overall again, overall survival of five to six months. What about hypomethylating agents? Hypomethylating agents can be used for AML. We have shown a couple of studies with low blast count as well as high blast count AML that hypomethylating agents can lead to equivalent overall survival, about half the CR rate, CR rate is about 20% to 30%, but equivalent in survival as cytarabine-based chemotherapy. So this has been our go-to for older patients.

We have also looked at trying to enrich our results by looking at hypomethylating agents specifically in specific patients. So this is data looking at decitabine in TP53 mutant patients, and then the study published in the *New England Journal*. There were very, very high reported response rates, again, in patients with TP53 mutation. However, the benefit needs to be extended across all of the mutational profiles and all of AML, so this study using venetoclax with hypomethylating agents has quickly become new standard of care based on our familiarity with HMAs and our knowledge in recognition of venetoclax from its use in CLL. This has been avidly adopted I am sure by your practices, as well as by ours, based on very high CR rates of 60% to 70%. A duration of response of almost 12 months and a median overall

survival of 18 months with about 45% or 50% of patients alive at 24 years. These were evaluated primarily in older patients at a median age of 75 and interestingly enough, we are encouraged by these results because patients with poor karyotype, as well as intermediate karyotype both benefited and patients with secondary AML. However, as we mentioned the venetoclax HMA trial did not include patients with MDS treated with prior HMAs. This trial did include that, this is a use of low-dose cytarabine and venetoclax and, again, similar CR rates, little bit lower, about 50% as opposed to 60% to 70%, a little bit lower overall survival, about 10 months as opposed to 18 months. Of note, you can see here that prior HMA therapy was still associated with a lower response, rate about 33%, but there was a response rate, so that is something that we would actively consider for patients with prior HMA exposure. You can see here that there was definitely, however, decreased overall survival in patients with that exposure.

Glasdegib low-dose cytarabine has been adopted for patients who do not want to be inpatient, who want a completely ambulatory regimen, have a regimen that is not associated with significant cytopenia. As you can see here as compared to low-dose cytarabine alone, patients with good and intermediate karyotype had overall CR rate of about 20% and almost a doubling of their overall survival. GO remains a therapy for patients that are unwilling to receive any other therapy. It is a single agent, you can give it as outpatient. It is just two doses in the first month and then transfusion supportive care. Of note, although this is an option, the median overall survival remains only 4.9%.

Lastly, to end, what about these new targeted therapies? Can we use any of our new small molecular inhibitors or kinase inhibitors for treatment of upfront AML? These have largely been explored as we expect in relapsed and refractory setting. Enasidenib and ivosidenib here are well-known for their ability to induce responses in relapsed and refractory patients are currently being evaluated with de novo AML in combination with 7+3, as well as monotherapy and in combination with azatadine. Here are some early data suggesting that as single agents, both ivosidenib and enasidenib can result in very, very similar CR rates of about 40% to 45% in the newly diagnosed setting identical to their response rates in relapsed and refractory setting, and these drugs can successfully be added to conventional upfront intensive 7+3. They are well tolerated and they result in reasonable CR rates, particularly in de novo patients. Future studies await the overall survival benefit.

The FLT3 inhibitors, of which midostaurin is in early development, are characterized by three highly specific, highly potent FLT3 inhibitors in clinical development. Again, these have largely been validated in the relapsed and refractory setting, but early studies are evaluating the benefit of these second-generation FLT3 inhibitors in addition to 7+3. As you can see here, as opposed to midostaurin, each one of the second-generation inhibitors added to 7+3 has resulted in CR/CRh rates of 80% to 90% and we are hopeful that with that 20% difference in CR rates that will translate into a higher overall survival than we saw with midostaurin 7+3.

For this study, Bob, we looked at this person, wanted to know if you had changed your answers after our discussion. So quickly we are just going to look at those results. Okay, 57% choosing liposomal

Mary is a 55-year-old woman with de novo AML. She had FLT3 ITD and IDH and again, these are your treatment options. 89% midostaurin 7+3. Take-home points as mentioned previously, knowing the biology of your disease, knowing the characteristics of your patient, allows you to make truly individualized treatment choices for patients with newly diagnosed AML. Things to consider, patient age, fitness, and goals of care. So just to keep in mind, there are a lot of options, a lot of data. You need to think about treatment options, it is not as straightforward as they used to be. Thank you very much. I am going to let Courtney take over.

Chapter 3

Dr. DiNardo: Good evening everyone. Thank you all for staying to the bitter end of the first day. It has been a good meeting thus far. So my task is to talk specifically about incorporating the new approved therapies into relapsed/refractory AML. It is a very specific task to go through just a couple different approved therapies and then Dr. Daver is going to take over and talk about relapsed/refractory AML, everything else. Over the past two years we have multiple new approvals and the various different FLT3, IDH1, IDH2 approvals talking about in particular. So, two cases for this portion of the talk that will go through.

The first case is a 58-year-old gentleman, presents with a rather acute onset gingival swelling, myalgias, fevers, and epistaxis. His white count is elevated, 44,000. His hemoglobin and his platelets are low. Bone marrow was done, shows AML diploid cytogenetics, NPM1, IDH1, and FLT3 ITD. He was started on 7+3 with midostaurin. He achieved a complete remission. He received four consolidation courses due perhaps to his NPM1 mutation and his allelic ratio just under at 0.5. He was not taken to transplant. He did not receive maintenance midostaurin, that is not currently approved, and then unfortunately several months later, he was noted to have a white count of 27,000, 37% circulating blasts. Would you re-introduce 7+3 midostaurin? It has been several months. Would you re-induce him with a more intense FLAG-IDA perhaps? He has an IDH1 mutation, start ivosidenib; start gilteritinib; start gemtuzumab. He was CD33 positive or would you rush and repeat his mutational analysis prior to deciding? Alright, people are all across the board and there are many different appropriate options. My bias would be to say things can change at the time of relapse and so my plea to you all would be to please make sure, especially with FLT3 mutations which can change as resistance and relapse occurs, to check the FLT3 mutation prior to assuming your patient at relapse has that FLT3 ITD still present.

We will move to case #2 which is a 68-year-old female. She has coronary artery disease, congestive heart failure. She went in for a knee repair and I swear like half of my patients are going for a preoperative evaluation when they are found to have pancytopenia, then maybe either pains or actually leukemia related. In this case, 27% blasts, CD33 positive, 123 positive, MDS related changes, trisomy 8 on cytogenetics. This was my patient about two years ago, was started on azacitidine for AML, did well for a period, achieved a hematologic and complete remission, and then progressed and at the time of her progression, still had the trisomy 8, had a new deletion 20q, and an NGS panel at that time showed a DNMT3A, IDH2, and SRSF2 mutation.

How would you treat this patient given what you know? Low-dose cytarabine and venetoclax; gemtuzumab; enasidenib; CPX351; or hospice supportive care? And the majority would say enasidenib. This patient does have an IDH2 mutation. There is a cohort of people that would say low-dose cytarabine, venetoclax, which is certainly very reasonable, although this patient had AML at diagnosis and had had azacitidine so low-dose cytarabine and venetoclax is not strictly approved for a relapsed AML patient, but the patient of course had not had venetoclax, so potentially a reasonable option.

Moving into my slide deck just talking a little bit about relapsed/refractory patients, this again is a schematic done by two different papers showing that your leukemia at diagnosis can be modified by the treatments you receive by clonal evolution that occurs related to various different chemotherapy and other induced mutagenesis, and so there can be different clones present at relapse then were present at the beginning and so repeat genomic analysis if possible is always preferred because things can be different at relapse than they were at the beginning.

We will talk briefly about FLT3 mutations, Eunice gave a fantastic overview of FLT3 mutations in the newly diagnosed setting. Just to briefly recap, many of you have seen this slide many times before showing that FLT3 mutations are present in somewhere between a quarter to a third of AML patients, so it is the minority, but a sizable minority of patients will have FLT3 mutations in either the ITD or the TKD region or both, and these are often present in younger patients, more proliferative disease, newly diagnosed de novo AML, oftentimes with diploid or otherwise, intermediate cytogenetics. The FLT3 ITD in particular is predictive of poor prognosis with all of the caveats that Dr. Daver took us through already. Several different FLT3 inhibitors in various stages of development, midostaurin of course is the one that is approved upfront with standard intensive chemotherapy for newly diagnosed patients. Gilteritinib and quizartinib have both had positive randomized phase 3 studies. Gilteritinib is approved in the US. Quizartinib approved in Japan, and various other FLT3 inhibitors, in particular, crenolanib in later stages of development. Important to be aware of the different types of FLT3 inhibitors with type 2 FLT3 inhibitors sorafenib and quizartinib in particular, not as effective against the TKD mutation.

Taking you through some of the data leading to the gilteritinib approval in the US, now available for relapsed/refractory AML patients. This was a study of over 350 patients with FLT3 mutated either ITD or TKD mutations, relapsed/refractory AML, randomized 2 to 1 to gilteritinib at a dose of 120 mg a day versus salvage therapy, which could have been your choice, either high intensity MEC or FLAG-IDA or lower intensity low-dose cytarabine or azacitidine. Taking you through the responses in particular highlighted in red, CR rate nearly double compared to salvage chemotherapy, aCR/CRh rate of about 34% compared to 15%, and at the very bottom looking at the patients transitioning on to a transplant over a quarter of patients receiving gilteritinib. One might say that trying to do a non-inferiority study may have even been significant for a well-tolerated oral pill as opposed to especially intensive chemotherapy, so the ability to improve upon the response rate with a well-tolerated targeted therapy is certainly something of importance.

And this kind of gets to the safety profile, gilteritinib in kind of that gold color as shown here. As you can see, compared to chemotherapy regimen in general, safety is equivalent or less than many of the various

different AEs we are very used to seeing in our relapsed/refractory patient, with one exception. The AST and ALT, which you notice the second and the third from the top. Transaminitis is something that is seen with gilteritinib and needs to be monitored for. This shows the overall survival with gilteritinib as mentioned already. Overall, survival benefit shown with a 12-month overall survival now at 37% compared to 17% with salvage chemotherapy. So again, the overall survival is of course not 50% or 100%. There is room for improvement, but a clear improvement compared to the various standard of care options that we think are the best salvage therapy is, whether it is lower intensity or higher intensity for that respective patient.

A couple caveats to be aware of, the CHRYSALIS study was the phase 1 and phase 2 study of gilteritinib that was done prior to the ADMIRAL phase 3 study and one important thing to note is that there was a difference in response rate whether your patient had never seen a FLT3 inhibitor before compared to patients who had received a prior FLT3 inhibitor like sorafenib or midostaurin. So certainly in this era now where midostaurin is approved and most of our patients are receiving 7+3 with the FLT3 inhibitor, we can certainly still expect to see nice responses, but the response rate maybe diminished in patients who have already received different line FLT3 inhibitor. Moving towards molecular responses, so MRD is certainty a very important endpoint that we all want to know when our patient is in a remission, how deep is the remission or are they MRD negative. So this again is the phase 1 and phase 2 CHRYSALIS study looking at patients receiving 80 mg or higher, of these 80 patients about a quarter of patients had a molecular response to 10^{-2} or 10^{-3} considered an MMR, and on this next slide will look at the significant improvement in overall survival, seen in those patient who do obtain a higher level or depth of remission.

Gilteritinib has also been evaluated in this study. People can go to transplant and then if they were on the gilteritinib arm, restart gilteritinib after transplant any time after day 30. If they had engraftment count recovery without severe acute graft vs host disease, and you can see in those patients that were able to resume gilteritinib. So, again many reasons why a patient who was not able to start gilteritinib would do less well given infections, acute graft vs host disease, things of that sort, but those able to resume gilteritinib post-transplant seem to have a significant improvement in survival. And that is also replicated in the SORMAIN study, which was presented at ASH this past year looking at sorafenib after allotransplant. This was done in just over 80 patients randomized to placebo versus sorafenib in patients with FLT3 ITD mutated disease, and again a significant improvement in relapsed free survival. I think really showing the importance of FLT3 inhibition post-transplant which will become I think more and more standard of care over the coming years. So, FLT3 inhibitors, safe, effective targeted therapeutics, well tolerated, leading to improved outcomes, response as well. They are impressive. I think will most likely become more impressive when we are using them in combinations and that will be potentially discussed I think by Dr. Daver

And so moving on to the other area of approved targeted therapies in the relapsed setting, IDH1 and IDH2 mutations, which occur in about 20% of AML patients. So again, a minority, but a significant minority of patients and what is important about the IDH mutations as opposed to FLT3, which happen in our younger patients, on average the older your patient is the more likely they are to have an IDH mutation, so important to be aware of, and they can be identified at the time of progression, in particular

patients with MDS or MPN, when a patient with myeloproliferative neoplasm transforms or progresses to AML, almost a quarter of those patients will have an IDH1 or IDH2 mutation. So it is important to think about testing patients who fit into that category. IDH mutations are of interest because they lead to accumulation of 2-HG, which is an oncometabolite, which leads to DNA and histone hypermethylation, it blocks differentiation and so the IDH inhibitors go in and help to reverse this process and lead to a reversal of that aberrant differentiation. They are different drugs. They have different side effects. They are not the same, but the response rates which are shown in blue in the center of this curve are relatively similar, so it is easy to kind of think of it in these numbers as CR rate of about 20% and overall response rate and about 40% in the relapsed/refractory setting, with survival in a relapsed/refractory patient. On average, these patients in both of these study have had two prior therapies including hypomethylating agents and cytarabine-based therapy, median overall survival of nine months, with of course patients who respond well with the CR or CRh doing significantly better a year and half or more on average.

In addition to the response rates, you also see transfusion independence, which of course especially in our older patients is clinically significant. This is shown with ivosidenib here, but it is true with both of these therapies, so in blue are the CR/CRhs, but also in patients who have non-CR responses over half of them become transfusion independent. The definition was about two months or more of transfusion independence, so clinically meaningful. This is an example with enasidenib now looking at the differentiation response. So again, not cytotoxic therapy, and responses do evolve with time and many patients with the CRs at the bottom in red, you can see that that these responses do evolve. So if your patient is tolerating it well, there is no need to stop after 1 or 2 cycles because you can obtain maximum benefit, and this is true with the FLT3 inhibitors too to a degree, that continued therapy can lead to optimized responses.

Because they are differentiating agents, you can see differentiation syndrome. We are used to seeing differentiation syndrome in APL patients treated with All-trans retinoic acid, but also important to be aware of. We talked about transaminitis with gilteritinib. This is the kind of rare, but important side effect to be aware of with the IDH inhibitors, that non-specific constellation of fevers, pulmonary infiltrates, effusions, shortness of breath, and the most important thing to do is start steroids. Holding the IDH inhibitor of course is warranted if the patient is ill and in the hospital, but the half-life is really long. So symptoms are not going to get better for a couple of days, unless you start steroids. So just keep that in the back of your mind always.

We talked about MRD quickly with gilteritinib, again here in blue along the top are those patients receiving ivosidenib for an IDH1 mutation who were able to obtain molecular clearance, this time to a very deep level of 0.02% to 0.04% by digital droplet PCR, and again you can see that as you would anticipate people who have a deeper level of remission are those patient who seemed to have a more durable response and improve overall survival. Co-occurring mutations, certainly important so along the top in red in that first box are those patients who have multiple different co-occurring mutations. You can see on average five or six. Those are the non-responding patients compared to those patients with true CRs in blue who seem to have less co-occurring mutations, and that is shown further in the pie chart. Next to it where those patients who have three or less co-occurring mutations, have a much higher

chance of obtaining a CR or a CR-like response as opposed to those patients with six or more mutations where the likelihood of a CR is far less, so the co-mutational burden is important when using IDH inhibitors as a single agent. This again is enasidenib, but very similar with ivosidenib, with RAS mutations in particular shown along the bottom being particularly important, and while it is not 100% predictive, patients with RAS mutations tend to have trouble responding to the IDH inhibitors, a single-agent and so I think in this category in particular, combination strategies, are really going to be kind of the future for patients with signal transduction co-occurring mutations.

Similar takeaways to what we talked about with the FLT3 inhibitor where we have safe and we have effective oral targeted therapies now which are improving the responses of our patients, and hopefully in the future, both in the frontline and in the relapsed refractory setting combinations will be improving this even further. And just two slides just show a study that is moving forward combining ivosidenib with venetoclax. We have now treated 12 patients at two different dose levels of venetoclax with ivosidenib with really impressive overall response rates of 75% including 42% CR rate. So again, you cannot compare ivosidenib compared to ivosidenib with venetoclax, but certainly compelling overall response rate with several patients now continuing on and really nice remission, so just providing hope that combining therapy you are going to provide even more durable responses for our patients.

So we have a 58-year-old gentleman who had FLT3, NPM1, IDH mutated AML, was treated with 7+3 with midostaurin, went into remission and then relapsed. So, what are you going to do? I want to say, I think it is about 20% to 30% of the time that a FLT3 mutation, 20% right, will be lost or gained at the time of relapse.

Dr. Wang: Just to keep in mind also when you use 7+3 midostaurin you might lead to eradication of the FLT3 clone with the upfront TKI, so you can get recurrent disease from a FLT3 negative clone and that is something that we have also seen.

Dr. DiNardo: So we are moving into an era of precision medicine, right? So in addition to being better able to diagnose and prognosticate our patients, which Dr. Daver took us through, it is really nice to be able to know how well our patients are going to do. We are actually now finally at the point where we are able to use this information, to really guide and inform our clinical practice. So that is the focus of my talk and I will transition over to everything else.

Chapter 4

Dr. Daver: Okay. Thank you very much Dr. DiNardo and Dr. Wang. I am going to talk more about some of the new things that are coming. You heard about the approved agents and now you are going to start seeing in the next couple of years lot of movement towards novel, novel-novel, or novel-novel-novel combinations, even if you can say that, but we will be saying that. So we are going to try to compete with myeloma where we have all the new therapies combined with triplet, quadruplet, and quintuplet, whatever.

So these are the treatments that you already saw in yellow. These are the approved ones, but you can see there is a huge pipeline of drugs that are coming along, novel cytotoxic, novel HMA agents, and a number of immune therapies that we think will find a role just like in myeloma in combination with new backbones. Also, some interesting targets such as things targeting TP53 that we talked about, APR, and then pathways of resistance to venetoclax, which we think is the next big area of research because we do see very high activity, but in the end it is not curative. People are relapsing at 12 months, 14 months, 18 months, and now we need to find new strategies to target these patients.

So one of the new epigenetic agents that is in development is the drug called guadecitabine. This is a more potent methylating agent than decitabine. This did complete recently a phase 3 study. Some of you may have heard about it. It was presented at the EHA meeting as an oral presentation. Unfortunately, it did not meet its primary endpoint, which was disappointing. We have used this drug quite a bit in the phase 1 and phase 2. We were one of the lead sites and we actually do believe that is has some efficacy potency beyond the standard HMA and hopefully there will be continued development there. In fact our two phase 3s in MDS and we are waiting for the results of those. One of the interesting things that was seen is that when you do look at the overall endpoint, which is the middle curve, there was no survival benefit, but as would be expected, I think also makes an important clinical point is that with HMAs, just like with IDH and FLT3, unlike cytotoxic therapy, continued treatment, even in the absence of early remission induction, can improve survival, so the curve on the right shows that people who got more than 4 cycles of HMA where the physician persisted as one should, we know the median time of responses three to eight months for HMA. Actually, they did have a survival benefit and this shows the importance of continued therapy. So we have to wait and see how the MDS studies, the two phase 3's come out, MDS and relapsed AML, but that is an interesting agent.

Now moving more towards relapsed/refractory AML and treatment with venetoclax. If you remember one of my questions was, which drug is not approved? HMA Ven is not approved in the relapsed/refractory setting. There have been a number of studies that have been looking at the outcomes, off label in the relapsed/refractory setting. Our group has done one, City of Hope group has done one, Sloan Kettering. They were all presented in the last year or so and we definitely all agreed that in the relapsed/refractory setting, the response rates are significantly lower, somewhere maybe in the range of 30% to 40% for CR/CRi, and median survival six to seven months. So absolutely not the same blockbuster effect we are seeing in the frontline, so how can we improve this?

Are there pathways that we know of? We do know that there are three major mechanisms of resistance to venetoclax. This is simplification. There are tons of papers talking in detail about this, but the main pathways are upregulation of other antiapoptotic proteins, so when you block the BCL2, you promote apoptosis, but the cancer is smart. It learns how to escape by upregulating other antiapoptotic proteins and protecting itself. One of those is MCL1, others are BCLXL, etc. So just like we do with the immune checkpoints in solid tumors, if you block PD1 and CTLA-4 maybe we are better because tumors cannot escape. The same concept here, can you block both the antiapoptotic pathways, and we are trying to do this with either MCL1 inhibitors or MDM2 inhibitors, or CDK9, all of which block MCL pathways. The second major mechanism resistance are the FLT3 and I will talk about that, and then TP53. So a lot of

our strategies are looking at either concomitant or sequential inhibition of these pathways hoping we can convert that 18 months to 24, 30, so on and so far make it curative. Very similar again to the myeloma paradigm.

One of these studies is more advanced, a number of them are very early phase 1, but we do have one that has a good number of patients, it is a combination of an MDM2 inhibitor. There are many, and this one here is idasanutlin in combination with venetoclax, and this study was done in elderly 60+ relapsed/refractory AML, which is a very difficult population, they are older plus relapsed and we find encouraging response rate with two oral agents up to 45%/50% CR/CRI. So this study is maturing and ongoing. It will be going to expansion, and hopefully eventually can be combined with HMA and move upfront to further improved the median survival of HMA Ven.

Idasanutlin is I think an important drug, especially because at this time, we are waiting for some important phase 3 results. This was the phase 1/2 data that was presented almost three years ago now showing that in the relapsed AML population, a combination of intermediate dose ARA-C, IDAC plus idasanutlin could give you about 38%/ 40% CR/CRp, so not CR/MLFS. These are CR and CRps, which is considered a pretty good response in this relapsed population. So based on this, there is now a phase 3 study that should be completing enrollment very, very soon and hopefully will show us results very soon after maybe early next year is what we hope, and if this is positive, this is a 450 patient study, then potentially the ninth drug to get approved in AML and hopefully also a very good combination partner based on the preclinical data for venetoclax and also maybe for FLT3 inhibitors. So we have to wait and stay tuned.

Now, FLT3, we heard a lot, both from Dr. Wang and Dr. DiNardo about frontline relapsed setting. I think all of us agreed that FLT3 inhibitor single agents are required to get FDA approval, but really in the end if you look at two-year survival, the cure rates are less than 10%, so we do not envision, and actually at MD Anderson we never are using these as single agents; we are using them in different combinations with HMA with induction and of course, we have to check with venetoclax. Venetoclax is very, very potent priming agent. This was some data from our lab by Dr. Marina Konopleva, Dr. Jeff Tyner at OHSU has very similar data showing that when you combine venetoclax, this study was done with quizartinib, we have done with sorafenib and also with crenolanib, there is a very high degree of synthetic lethality and a very potent synergy, more than we have seen with most other agents combined with venetoclax. So we are quite excited about this and these combinations are now are in clinic. More importantly than just the synergy, is that both FLT3 and other transduction pathways like RAS, PTPN11, are major mechanisms of resistance. So in this single-agent relapsed study where venetoclax was given alone, we saw that one of the major mechanisms of both primary and secondary resistance was presence of a FLT3 ITD, so you see people who had FLT3 ITD at the beginning, none responded, and even some who responded at relapse now emerged with the FL3 ITD. So given the synergy and the fact that alone using venetoclax or even in combination, there is data with low-dose ARA-C Ven, the responses are low in FLT3, the next logical step is can you combine either as a doublet or as triplet venetoclax with either gilteritinib, quizartinib, or crenolanib? And these studies are ongoing and I would encourage you to look out for some of the ASH abstracts. The data is very, very encouraging, very similar to what we are seeing

with the Ven IDH inhibitors. So we do think clinically this is going to become the next strategy for development combining targeted with Ven, with or without HMA and hopefully taking us further.

The other drug that I think is interesting although we cannot conclusively yet say if this will go all the way. We hope it will. It is a drug called APR-246, which impacts the folding of TP53. This is one of many drugs that have been tried for TP53. This TP53 is are the biggest. We are spending a lot of effort, all of us in leukemia in research. This drug actually has shown clinical data at the recent ASH meeting, response rates of 100%, believe it or not, when CR/CRIs were combined were shown, but even for CR 80% real CR with full count recovery in AML. Small numbers, but there is a phase 3 that was launched appropriately so on this exciting data in frontline MDS TP53 and efforts also looking in AML again, potentially combining this with HMA Ven, the new backbone. So now, you are seeing triplets, not only being talked about but all coming in the next year.

Next, I am going to speak about some of the immunotherapies, which I think are going to fill another hole potentially like they did in ALL targeting low-burden disease, MRD positivity or maintenance. When we talk about immunotherapies, there are two different approaches. It is very important to conceptually understand this. To the solid tumor people immunotherapy means one thing; checkpoint inhibitor. That is their immunotherapy. They do not know about ADCs. We use a lot of ADCs, but when we use antibody drug conjugates, we are really delivering a toxic payload to the leukemia cells. We do not care about the immune system. So this is a targeted cytotoxic or chemical delivery whereas with the T-cell based approach we're actually trying to harness your own immune system, which usually is preserved in the early tumor setting, but once you get very relapsed disease, your immune system is gone, and so T-cell therapies may not be ideal.

There is a number of antibodies. You heard about gemtuzumab, the approved one. There is now three or four other CD123, CD33 targeting antibodies. One that we have been working on at Anderson with a number of other centers is a drug that targets CD123, which we think potentially could be a better target than CD33. This uses a cytotoxic payload, which we prefer in general to bacteria toxins because of lower rates of capillary leak syndrome and infections. Here we see with this agent, we are starting to see some higher response rates, maybe 25% to 30%. I do not think single agent in AML in any case should be the way to take it forward, but the safety is good, so this will combined again with HMA and HMA Ven. The recurring team that is being developed in the frontline and the relapsed setting. The good thing was the safety profile was well tolerated. We did not see much hepatic problems, as well as the myelosuppression infection rates seemed to be good. So maybe we will have additional ADCs in the next couple of years coming in.

Another approach here is the bispecific antibody, so if you were here today morning, I am sure you heard a lot about blinatumomab. This is the only bispecific approved in leukemia and I actually think in all of oncology, which uses your CD3 cells and attaches them to CD19 on the leukemia cells in ALL and results in the T-cell mediated death of your leukemia cell. So we said if we can do this in ALL, why not in AML, multiple myeloma, and so on and so forth. This is a similar approach in AML. There are three or four bispecifics; one of them is flotetuzumab, the one most advanced targeting CD3, CD123, and we do see

that there is some activity with this agent. About 20% response rates. The issue with the bispecifics like in ALL, is that the delivery often has to be every other day requires 10 to 14 day inpatient and there is CRS, but in the end, if we can find a way to make them effective, maybe in the MRD setting, low burden disease where I think they may work best and trials are moving that way, we will find a way to work over the logistics. There are extended half-life formulations, etc., being developed. So still, we are not sure but there are approaches combining these with other immune agents.

One of the other immune agents that of course if you go to lymphoma or solid tumor, is posted everywhere is nivolumab, so we have a number of trials and this is the one of the trials that has been presented and published combining HMA, again, which is the usual backbone that we use with PD1 inhibitor showing that there is some improvement of response rates compared to HMA alone, which was recently published by the Yale group, as well as maybe similar to what you get in the relapsed setting to HMA Ven. I think what is more important than responses of 35% to 40% that we see with all of these is the improved survival, especially in early salvage, and I think with the immunotherapy, we have to start reconditioning our thinking and using these in the early relapsed maintenance, low burden setting where you have a nice immune system that can be harnessed just like blinatumomab and MRD early salvage, and CAR T cells in ALL, which worked in the MRD setting the best.

Biomarkers I think are going to be important for both the bispecifics and the immune checkpoints and they actually are simple biomarkers that can be incorporated into floor immunohistochemistry such as baseline T-cell and people who have more T-cells to begin with, guess what? They do much better because you have actually an immune system to harness and I think this is probably how these agents will be developed rather than trying to treat everybody with one approach. Another important thing is management of toxicities. There are two phase 3 studies ongoing; one in the US and one in Europe with these immune checkpoints and we do hear of issues with toxicity management. There is no doubt that the toxicity profile is different. Immune toxicity is different from cytotoxic in targeted agents. We have been able to manage them with a learning curve over the last two to three years and I think actually our solid tumor colleagues are very good experts and we should take input from them and identifying and treat early when we use both bispecific and immune checkpoint.

The last drug I am going to talk about is one similar to APR that we are very excited about, maybe one of the next breakthroughs for the AML, but again is quite early, so this is a macrophage checkpoint antibody. Solid tumor you have heard, as well from me about T-cell PD1. Now, here the group from Stanford, Ravi Majeti and Irv Weissman, showed in very high impact papers and very elegant work that if you enhance the macrophage activity, especially in hem malignancies, both follicular lymphoma and acute leukemia, you could get very potent preclinical activity. So this led to a clinical trial combining the CD47 antibody which unleashes the macrophages in combination with HMA. When we saw these data, we were all quite excited. You are talking about 65% response rates in frontline AML and nonfit and 100% in MDS. So when you see that waterfall plot, I do not think you cannot ask for much better. Again, early though, we have to see if this will hold true with 1500 patients, but if it does, then this drug could have a very rapid path to approval.

So in conclusion, I think in frontline, we have a good backbone. I think HMA Ven is not the end of the story. It is the beginning of the story. I like to equate this to RVD, which when I was in the fellowship 14 years ago was the first breakthrough that moved chemo out of myeloma. We forgot about VAD and melphalan, but then RVD led to addition of ELO, addition of DARA, etc., and we kept building on them and I think this is the path we are seeing. FLT3, we will add FLT3 inhibitors to HMA Ven, IDH rule out IDH. Others, we will find the drugs, maybe MDM2, MCL1 antibodies and then try to keep pushing and then maybe we will sequence triplets. So hopefully we can get increased median survival without having to use high-dose cytotoxic therapy. I think that is the goal of lot of leukemia physicians. As I said the two drugs in phase 3 right now, MDM2 inhibitor and there is a E-selectin inhibitor in the phase 3 from Glycomimetics relapsed setting. This trial has just started, but in the next one or two years, look out for those results and then immunotherapies, which I think could be very nice in MRD or potentiating. And with that, I am going to stop.

Okay, thank you all very much. Thank you for the battle, excellent. We can take maybe two questions, if anybody has a burning question. If you turn to the microphone, please sit down. There are some questions. Okay, so excellent, so maybe they put this before my talk. Are there any effective treatments for P53 which is not responded to the decitabine and venetoclax or the other study APR246+Aza? So Dr. DiNardo and then Dr. Wang thoughts?

Dr. DiNardo: I wish I had a great answer for that question. If the patient with P53 mutations are still I think among the hardest to treat, especially those who are failed kind of hypomethylating, Aza or decitabine with venetoclax-based therapy. We are all excited about the APR246 data, so it is open in MDS glioblastic AML and soon an AML study. Certainly, I am hoping that will be the next thing for P53 mutated. Outside of that, there really are no great effective therapies unfortunately.

Dr. Wang: I would agree with that. I mean even when you look at the outcomes of transplants or when you look at the outcomes of some other regimen, P53 is universally horrible. I think that we are very cautiously optimistic about the APR studies.

Dr. Daver: I think the APR and maybe some of the early data with some other of the CD47, etc., we hope, it looked good when they presented it on eight or nine patients, P53 agnostic. I think, we hope the immune therapies, but actually there is a data that even the immune system depends on TP53, so that is the tough one. Let me ask one question. For post-transplant maintenance, what is your approach for FLT3 patient, for IDH patient, and for non-mutated? Are you doing it and if so, for which patient and for what drug? Eunice?

Dr. Wang: We believe very strongly based on the data that Dr. DiNardo showed that there is significant benefit to the addition of the FLT3 inhibitor, so we have upfront used, resumed the same FLT3 inhibitor that we use for upfront therapy in the post-transplant setting and my inclination is to continue that indefinitely. If you look at the some of the FLT3 inhibitor maintenance studies, post-transplant, when you stop the maintenance after 12 months, there is a significant drop off and the gilteritinib ADMIRAL study showed that as well, when you stop the inhibitor. So we tend to do FLT3 maintenance indefinitely

because of the high risk of relapse in that patient population with IDH1 and IDH2 inhibitors. We also have attempted to restart the IDH inhibitors. Again post-transplant. Obviously that is a less common group, so we do not have long-term data. I don't know if Dr. DiNardo has any from her practice.

Dr. DiNardo: The same, I mean in general, IDH mutation patients tend to be a little bit older. So there aren't as many of them going to transplant, so there is even less data in the post-transplant setting, but certainly there is a strong rationale that that would be worthwhile and there are trials ongoing to evaluate that. I think certainly hypomethylating agents are also compelling. I mean patients do well post-transplant, but there is still a high risk of relapse in most of our intermediate- and high-risk patient going on to transplant, so trying to optimize, especially in that first one to two years when they're at highest risk for relapse, azacitidine or our institution is moving forward with the azacitidine/venetoclax, post-transplant maintenance that hopefully maybe particularly effective as well.

Dr. Daver: So if you do Aza Ven, would you be concerned a lot about myelosuppression and what kind of dosing would you consider doing or have we done?

Dr. DiNardo: I think it is something at this point best done on the clinical trial because I do worry about the myelosuppression and I certainly would hate to have some sort of myelosuppression related graft failure early on, so I would be kind of cautious and wait until of course you have full engraftment count recovery or at least maybe 30 to 60 days post-transplant and then start, maybe even 7 to 14 days of venetoclax with lower azacitidine regimen like 44 mg per m^2 that is often used.

Dr. Daver: Okay, anybody else have any questions left?

So you are saying somebody who is proliferative, a lot of blast, FLT3 mutated and relapsed setting, would you treat them with a FLT3 inhibitor?

Dr. Daver: No, I will let Eunice and …. I mean you know FLT3 in general inherently are proliferative, they, come with pack marrows, high blast, high white count in the blood, as well as peripheral blasts and in fact, there is no data to show that the kinetics of response are significantly depressed or effected by the burden of the disease. In fact, drugs like quizartinib, gilteritinib are very quick, within seven to nine days we start seeing reduction or clearance of peripheral blasts. I again think combos are optimal. You may want to watch for tumor lysis of course in this situation, but I actually think that is the perfect typical patient where I will use a FLT3 inhibitor in combination. It depends, gilteritinib, I will start with the standard 120, midostaurin of course in the frontline setting is 50 mg b.i.d. I will just admit those people watch them for the first five to seven days, some hydration, tumor lysis, labs, etc. Anything different Eunice?

Dr. Wang: One thing to keep on mind with gilteritinib is when you start gilteritinib, one of the major side effects that was described given the ADMIRAL trial is a significant amount of cytopenias. Actually the myelosuppressive quantity, maybe because of its ability to inhibit KIT, leads to rapid clearance of the blast, but also leads to patients developing profound pancytopenia. So it is important when you start

gilteritinib people become pancytopenic to potentially repeat the marrow and when they have cleared, similarly to venetoclax you may need to hold or dose-reduce the gilteritinib in that setting. You may go from a packed marrow with pancytopenia to an empty marrow with the pancytopenia, so it is important before not noticing count recovery, which you would expect with the CR, to just check in the marrow because you would hate to conclude that it is not working because the peripheral counts are unchanged.

Dr. Daver: I think that is the class effect of both the gilteritinib, quizartinib, the KIT inhibition, and myelosuppression is seen, and we did not talk about that with HMA Ven and that is something we do, we always check the marrow end of cycle 1 because often these people are in remission morphologically but their counts don't recover because of the cytopenia of the agents and so you can wait cautiously maybe give a few days break and then restart at a lower dose if needed.

Yes, they can both acquire both and this is a true statement, but the accusation of the FLT3 we had published this about eight years ago. Dr. Naza is the first author. It is in *Leukemia and Lymphoma,* I think 2015. So we looked at about 150 patients who had no FLT3 at diagnosis, got induction with various regimens at out institution FLAG, IDA, etc., and then at relapse about 15% of them, 15% had a detectable FLT3. So that was the accusation. With the IDH, I think it is much lower, 2% to 4%, 2% to 5%.

Dr. DiNardo: Yes, AML to AML, but it is about 10% to 15% MDS transforming to AML and like 20% to 25% myelofibrosis transforming to AML, so those groups it is higher, but yes.

Dr. Daver: So both should be checked and with the FLT3 what Eunice mentioned is very important, that if you get induction and you relapse, they actually showed this in the midostaurin, which I thought was way higher than I might have guessed, but almost 40% of people at relapse did not have a detectable FLT3 after getting 3+7 midostaurin. I do not think that number is that high in our experience and we actually looked that this is well, but the point is that 15% to 20% could acquire 15% to 20% or more could lose it, so you have to check it because what you do not want is to give 3+7 midostaurin, a year later the guy relapses and you just reach and give gilteritinib or whatever and he doesn't have the mutation.

OK, I am not going to give another chance, so good night everybody.