Hello. Welcome to Managing CML. My name is Jorge Cortes, and I am a professor of medicine in the Department of Leukemia at MD Anderson Cancer Center in Houston, Texas. I am the deputy chair of the department and the section chief for CML and AML. I am speaking today live to you from 2015 ASCO Annual Meeting in Chicago, and I would like to take a few minutes to review some of the important information and key take-away messages from some of the abstracts that have been presented at this meeting. And granted, there is no earth-shaking news in terms of new studies, but I think that it is very important to review some of these abstracts because they provide either very key long-term followup that can help us understand better some of the drugs, particularly some of the ones that have been approved more recently, and also some of the emerging safety data that I think it is very important that we understand so that we can manage our patients better and offer them the best possibility of a long-term good outcome.

So, we are going to start with the first abstract which is the Efficacy and Safety of Ponatinib in Heavily Pretreated Leukemia Patients in the PACE Trial, and this is with the 3-year follow-up results. As you recall, the PACE trial was the pivotal trial for this drug, ponatinib, which as you know is a tyrosine-kinase inhibitor that inhibits BCR-ABL in the presence of any of the mutations that we see commonly in the clinic, including the T315I mutation. And in this study, patients were treated in different cohorts, chronic phase, accelerated phase, blast phase, or Philadelphia-positive acute lymphoblastic leukemia, and within each of these stages, they could have the T315I mutation or any other mutation or no mutation at all. So, we have a number of cohorts, and we know that the results have been positive, and that led to the approval of ponatinib for the management of patients with this condition in all of these stages. So, what we are seeing here now is the 3-year followup of these patients, and the results continue being very positive, certainly in terms of the efficacy, particularly focused on the chronic phase which is where we have the most information. Almost 50% of the patients continue receiving therapy with ponatinib, and the cumulative rate of major cytogenetic response is almost 60%. That is a very high response rate because you may recall that in this study over 90% of the patients had received at least two tyrosine-kinase inhibitors, and almost 60% of the patients had received at least three tyrosine-kinase inhibitors. So, this is a population that was a very heavily pretreated population where we really do not have any other good treatment options up until the appearance of this drug. So, again, the rate of the major cytogenetic response in the chronic phase was almost 60%, and importantly, we are seeing the deeper responses, the major molecular response that occurs in over 30% of the patients. We are seeing even the MR4.5, so that is 4.5-log reduction in the transcript levels in almost 20% of the patients, so we are seeing excellent responses. The responses are durable. The durability of the major cytogenetic response by the 3 years, we see that about 80% of the patients maintain the response, and the overall survival for these patients is also around 80% by 4 years. We also have an update in the more advanced stages of the disease, and although as you can imagine the responses are not
as high, we still saw about a 40% rate of major cytogenetic responses in both patients in accelerated phase and in blast phase. The overall survival is better for the accelerated phase, and it is actually very impressive in my opinion because it almost reaches 60%, which again for this very heavily pretreated patient who has progressed to accelerated phase, it is very impressive. In the blast phase it is shorter, as well as in the Philadelphia-positive ALL. Of course in that setting what is being explored is combinations and things like that. And we also have some update on the safety. The adverse events that we know for ponatinib are continuing showing. Most of the adverse events occur in the first few months of treatment. Thrombocytopenia is the most common in over 40%. Abdominal pain, rash, and dry skin, all of these things happen in around 40% of patients. The great majority of these are grade 1 and grade 2. They can be managed, but they obviously need attention, and of course, one of the key elements on this drug is the possibility of developing arterial thrombotic events, and these have occurred globally, about 20% to 22% of the patients have developed either cardiovascular, cerebrovascular, or peripheral arterial disease, approximately 12%, 8%, and 8% respectively. So, this is an important element of this drug that needs, of course, very close monitoring and very close attention. Some of the things that are being presented in these meeting is the impact that dose reductions may have on the response because of course we are using dose reduction to manage the risk, and unfortunately, when you decrease the dosage from 45, which was the starting dose, to 30 or even to 15, most of the patients who have achieved a response can maintain the response and some may even achieve the response for the first time after dose reductions. So, those adjustments are something that should be considered when it is appropriate. So, the conclusion of this followup is that ponatinib is a very effective drug. It is a drug that is very useful because it is a very potent TKI and highly efficacious in this setting of very heavily pretreated patient population. It has its safety signal, and we will talk a little bit more about this in a minute. So, therefore, number one, there needs to be the proper selection of patients, the patients who have a proper indication for the use of these drugs, and of course the proper followup of the patients, not only from the point of view of the leukemia which of course we all know, but also from the point of view of the presence of comorbidities, for example, that may increase the risk of these adverse events and properly manage their cholesterol, their diabetes, their blood pressure, etc., so that we try to minimize the risks for these patients. So, this is, I think, an important followup for this drug.

The next study that I want to discuss with you is another important follow-up study. This study is for a different tyrosine-kinase inhibitor also approved relatively recently which is called bosutinib, and this is the abstract called Long-term Bosutinib for Philadelphia Chromosome Positive Advanced Chronic Myeloid Leukemia After Prior Tyrosine-kinase Inhibitor Failure. As you recall bosutinib is, as I mentioned, a tyrosine-kinase inhibitor, the characteristics of this drug is that it is an SRC/ABL inhibitor, but in contrast to all the other tyrosine-kinase inhibitors that we use in the clinic, it does not inhibit c-kit and it does not inhibit PDGFR receptor. So, that is one important characteristic. It does not inhibit BCR/ABL in the presence of T315I mutation, so it is a second-generation TKI that we use. The study that led to the approval was a phase I/phase II and included cohorts that had received prior therapy, some just imatinib and others had received also other tyrosine-kinase inhibitors, dasatinib and/or nilotinib, and there was a cohort for chronic phase and then a cohort for advanced phase disease that included accelerated phase and blast phase which is what is being presented here. The chronic phase is not being updated at this meeting. So, here we are seeing the update with long-term followup, 4 years of followup on this patient population, and the results actually continue being very good. There are of course many patients who have left the study, mostly because of progression, some of them
because of adverse events, but there is about 20% of patients in the accelerated phase that remain on the study and only about 3% of patients in the blast phase. Now, the results are very good, the overall hematologic response was the primary endpoint for this study, and it has been maintained. There is not much improvement in the response with the long term, but the maintaining response has been very good, and the overall survival for these patients remains very positive, again considering that these patients had failed at least the imatinib and progressed to the accelerated and blast phase, and some of them actually had failed both imatinib and another second-generation TKI. One important thing with bosutinib is that just like with ponatinib, this is one drug where we have prospective data on patients that have failed more than one tyrosine-kinase inhibitor. This is another drug where we have good data for these patients in accelerated or blast phase. The safety data with bosutinib is important. The most common side effect for bosutinib is diarrhea. It happens in about 85% of the patients, but very importantly, this is a toxicity that happens with a great majority of patients, only grade 1 or 2 diarrhea, and it tends to be an early phenomenon. It is something that we see in the first few weeks, 2 to 3 weeks of therapy, and it is very manageable with interventions such as the use of Imodium or Lomotil, although many patients do not even need that, but it is something that needs attention because with proper management patients can remain on study. Actually, it was exceedingly rare that any patient had to discontinue therapy because of the diarrhea in this study. Other things to pay attention with bosutinib are elevation of liver function tests, again mostly grade 1 and grade 2 and occasionally grade 3 that would need transient treatment interruption and dose adjustments, and then there is also the possibility of rash. Of course, there is some myelosuppression, but in advanced phase that is a little bit more difficult to evaluate because most of the myelosuppression or the neutropenia and the thrombocytopenia may be related to the fact that patients have the advanced phase of the disease. So in summary, this is another study that continues to show the positive results and the benefit long-term of the use of bosutinib, even in patients that have an advanced phase disease. So it is another valuable tool for these patients once they have received prior therapy with imatinib and perhaps even with another tyrosine-kinase inhibitor with the exception of patients that have a T315I mutation.

Now I would like to discuss with you a few abstracts that have to do with safety of the tyrosine-kinase inhibitors, and the first one is the abstract that is entitled Elevated Blood Pressure and Adverse Events of Hypertension in Ponatinib Leukemia Trials. In this study, the methodology was to pool all the patients that had been included in the ponatinib trials, that included the phase 1 study, the phase 2 PACE study that we just discussed earlier, and then a randomized phase 3 study that was done for frontline therapy in CML chronic phase. That study eventually was terminated pretty early with a median followup of approximately 6 months, but we do have some data on the patients that went into that study, and also we have the control of the imatinib arm which makes its very important. As we all know, and I mentioned earlier, the hypertension is one of the important adverse events that occurs with ponatinib. So, we should remember that this drug has a VEGF receptor inhibition, and we know that VEGF receptor inhibitors tend to cause hypertension. So overall, the rates, importantly a significant number of patients, over 40% of the patients had hypertension to start with at baseline before they went into the study. So that is important because we know that that is a risk factor for atherothrombotic events, etc., so we need to pay attention to that. Now during this study, approximately 70% of patients developed hypertension or worsened their hypertension compared to the baseline, and that was very similar across the three studies – the phase 1, the phase 2 PACE, and the phase 3 randomized study. Now, importantly, in the control arm on the randomized study where we had imatinib patients, approximately 50% of patients on imatinib also developed or worsened their
hypertension that they had at baseline. So this is very important to remember because certainly the rate was higher with ponatinib, but we need to remember that the blood pressure may go up with any tyrosine-kinase inhibitors, certainly at least here we know that with ponatinib or with imatinib, and it is very important that we pay attention to these aspects of the disease. We know now that we can control the leukemia, but we need to manage all of these comorbidities so that we minimize the risk of the more serious adverse events and that we offer a good long-term outcome. Importantly, no patient discontinued therapy with ponatinib because of hypertension, and very few had to dose adjust because of hypertension. So, that is important to know that with proper management, and perhaps the management could have been even better during the study, but with proper management, you can continue the treatment with ponatinib and offer the long-term benefit for the patient. So, the corollary on this study is that we need to remember that hypertension can happen with tyrosine-kinase inhibitors, certainly with ponatinib we see a higher rate, but that with proper management the patients can continue on treatment and that we should really pay close attention to these and manage them well and aggressively so that we minimize the long-term risk of more serious events.

The next study is an interesting analysis. This abstract is called *Cardiovascular Events in Patients with a Chronic Myeloid Leukemia Treated with Tyrosine-kinase Inhibitors: Systematic Review, and Meta-Analysis*. In this study, the investigators, what they did is they looked at all the reported studies in the literature that used the tyrosine-kinase inhibitor and that reported any cardiovascular adverse events. They put all this data, any of the tyrosine-kinase inhibitors that we use in the clinic, that is imatinib, dasatinib, nilotinib, bosutinib, and ponatinib, they looked at all these studies. They found a large number of studies and then they analyzed the frequency based on those reports of the cardiovascular adverse events. What they found is that the rate of adverse events was approximately 8% with nilotinib, 1% or 2% with imatinib, 1% or 2% with dasatinib, about 10% with ponatinib, and about 13% with bosutinib. One important thing to consider when we review these data from this study is that we need to take with significant caution these rates that are being reported, and the reason for this is several fold. Number one, we need to remember that these events have to do also with the time of exposure. The cardiovascular events can happen perhaps a little bit more in the first year, but they can continue to happen throughout the exposure of the patient to the TKI. Therefore, the longer the patient is exposed, the risk will continue to increase. So, these rates have to be adjusted by patient-year exposure, and of course, most of these studies did not report it that way. So, it is difficult to make that adjustment. Number two, the way these reports are being presented in the different manuscripts even for the same drug but with different studies from different investigators varies how much they are looking, for example, at hypertension, how they are reporting not only the main cardiovascular events, for example, myocardial infarction or angina, but perhaps others that are more or less likely to be related. So, it is very difficult to compare from study to study the rates of cardiovascular adverse events. You can compare within a study, for example, the studies that had a control arm, and they do present for example the data on the nilotinib versus imatinib randomized study because they are treated with the same inclusion criteria, they are reported in the same way. You can draw conclusions, and the rate was higher with nilotinib than with imatinib as we all know. That can be done. The comparison across different studies is very difficult, but I think that the message of this study is that we need to be aware that these events can happen with any tyrosine-kinase inhibitor. Perhaps, some have higher risks than others. We need to define exactly what the rate is for each one of them. We still do not understand the mechanism of these events, but we need to keep this in mind and manage the things that we
can manage, again the hypertension, the cholesterol, etc., and when it is appropriate, even refer them to a cardiologist or somebody who can follow properly these patients to minimize these more serious adverse events.

The last study that I want to review is one that is called Vascular Occlusive Events and Mortality Among Elderly Patients with Chronic Myeloid Leukemia. These are retrospective analyses of linked SEER and Medicare data. So, this is a very interesting database analysis, and this SEER and Medicare combination merger of these databases is very important because it provides complementary information, SEER more epidemiologic, Medicare more about the management because they have reports of what patients are being prescribed, etc. So, they give us an idea of what is happening across the spectrum of patients, not only the ones going to clinical trials but those treated in different settings in the community, in academic institutions, etc., in or out of the clinical trial. So, they found a number of patients with CML and then they tried to match them one-to-one to patients in the same age group, of course, that do not have CML, and there are several interesting messages in this way. Number one, only about 15% of patients had a claim for Medicare Part D for a TKI, and that is very interesting, and of course there could be reasons why there is not a claim, they could have supplemental insurance and other ways to access the drug or whatever, but 15% is a very low number of patients that are having a TKI, and even if the adjustment brings it up some, it could be that many of these patients are not being treated with tyrosine-kinase inhibitors. That probably deserves further investigation and looking at what is the actual rate and why. Number two, they showed the risk of death during the followup. The followup is longer the non-CML population, and yet, the risk of death was significantly higher for the patients with CML than for the non-CML population. This is also very important and we need to understand why. It could be that because of the leukemia these patients are having a shorter survival, but again, if not all the patients are being treated, well that certainly would explain why the survival may be less than we would expect. There have been analyses looking at the survival of patients, specifically those treated with tyrosine-kinase inhibitors in different age groups and compared to the expected survival in the general population for the same age group, and those have shown that the actual survival is very similar to the expected survival within every age group. So, it could be perhaps that this is affected by the low penetration of the TKIs. Another aspect of this study is the higher incidence of these being occlusive events, myocardial infarctions, and strokes, etc., on the CML patients compared to the general population, and this is treated, they then separate by TKI just in general all of these patients whether they were treated or not. So, there is a higher incidence. Bottom line, our patients in this age group, they are over 65, they deserve obviously good care, and we need to make every effort to offer a good treatment for all of these patients, that includes tyrosine-kinase inhibitors to all of them, and of course we need to pay particular attention to comorbidities and other things that are more perhaps prevalent in this particular age group so that we also offer them the good possibility of long-term outcome that the younger patients may have. So these are the studies that I wanted to discuss with you, and I want to thank you for participating in this activity, and if you want any more information, please visit ManagingCML.com. Thank you.

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