Imatinib: A Perspective on Its Potential for PAH Patients

We invited 4 experts to a telephone roundtable facilitated by guest editor Jim White, MD, PhD, on April 13, 2012, to discuss the results of the recent Phase III trial, the Imatinib in Pulmonary Arterial Hypertension (IMPRES) trial (NCT00902174). Investigators enrolled patients with pulmonary arterial hypertension with severe hemodynamic impairment at catheterization despite treatment with 2 background therapies. Patients were randomized to placebo or 200 mg imatinib twice daily for 6 months of therapy to assess efficacy. Participating in the discussion were Mardi Gomberg-Maitland, MD, MSc, Associate Professor of Medicine and Director, Pulmonary Hypertension Center, University of Chicago; Iona Preston, MD, Co-director, Pulmonary Hypertension Center, Tufts University Medical Center, Boston; Jeremy Feldman, MD, Director, Pulmonary Hypertension Program, Medical Director of Research, Arizona Pulmonary Specialists, Phoenix; Stephen Mathai, MD, MHS, Assistant Professor of Medicine, The Johns Hopkins School of Medicine, Baltimore.

Dr White: We really appreciate everybody's joining us today. In this issue we're thinking about the overall direction of care for patients with pulmonary hypertension and how recent advances in the laboratory could lead to new medications. The last time that we had a new class of medication go to the FDA for approval was 2004. so it's very exciting that we have very fresh clinical trial data that are headed to the FDA about a brand new class of medication. Everybody knows that the tyrosine kinase inhibitor, imatinib, was tried in a handful of patients over the last decade, and the exciting results led to a Phase II clinical trial, which had some encouraging signs of efficacy. Imatinib was then tested formally in a rather unusual group of patients in a Phase III trial design, and those results were presented last fall at the American College of Chest Physicians' annual meeting. On the call with me today is Mardi Gomberg-Maitland, from the University of Chicago, a research clinical scientist with extensive experience in studying receptor tyrosine kinases. Also participating are Ioana Preston from Tufts, Jeremy Feldman from Phoenix, Arizona, and Steve Mathai from Hopkins. All are experienced pulmonary hypertension clinicians and researchers with different perspectives on the drug development process. I thank you all for being on the call today.

I thought we would lead off today's discussion with Mardi Gomberg-Maitland, who has real expertise both in the basic research laboratory and in the clinic with this class of molecules. Mardi, how do you see tyrosine kinase inhibitors influencing treatments for our patients in the next decade?

Dr Gomberg-Maitland: Well, I first want to say that I'm excited that we're looking into these compounds. I think that, thus far, we've really been focused more on the vasodilatory capacity of our therapeutics trying to target the vasoconstrictor aspect of the disease. This is the first time that there's been any investigation in a therapy to reduce proliferation in the pulmonary vasculature. Moreover, investigators looked at how this was affecting the heart and the right ventricle. It would be great if we could do both things, and not just target the pulmonary vasculature, but also target the right ventricle. This move toward more of an antiinflammatory, anti-proliferative approach-as if PH is a cancer-is not necessarily novel, in that Dr. Voelkel talked about this in the late '90s when he found that endothelial cell expansion was monoclonal and that it mimicked a cancer. It took some time for all of us to get there, but his group's landmark 1998 publication showing this monoclonal expansion was a very important first step [1]. The subsequent demonstration that he could mimic that expansion in the animal model, with hypoxia and SU5416 (a multi-tyrosine kinase inhibitor), raised a concern about whether these drugs might be harmful, because in that model, the multi-kinase inhibitor actually produced pulmonary hypertension in the setting of hypoxia.

So, there's been a lot of back-and-forth and I think a little bit of uneasiness, which is appropriate, because these medications are currently used for oncology, and they do have significant side effect profiles. In addition, some of them have even been known to affect the left ventricle. So, it's not as easy to design trials in this area. There's a lot of complexity, and we're not sure that the doses are going to be the same for oncology. Moreover, what are our trial endpoints and goals? Because we already have current therapies, it seems to me that what we're really looking for is the blockbuster drug that can cure the disease or that can demonstrate improvement on top of our existing therapies . . . or perhaps replace them! That being said, if the toxicity outweighs the benefit, then this class of drugs is not going to be fruitful.

I think we should first talk about tyrosine kinase inhibition. There's a tree of 478 tyrosine kinases in the human kinome. This is like a "family tree" with branches, trying to show how the different kinases are more or less related. Tyrosine kinases include src, abl,



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platelet-derived growth factor receptor beta (PDGFR), epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR-1 & 2); these have been our targets thus far. I think that tyrosine kinase-like kinases, like Raf-1, B-Raf, TGF beta receptor 1, and BMPR are going to be targets that we might be addressing with future drugs. Over time, there's been a large amount of drug development in oncology, and there is now an attempt to translate those findings to PAH. In PAH, we observe a similar mechanism as far as smooth muscle cell and endothelial cell overgrowth and dysfunction; thus, the thought process was: can we take drugs that are already developed for oncology and utilize them in pulmonary hypertension?

That was why there were some case studies looking at imatinib, which is predominantly a more selective tyrosine kinase inhibitor. Imatinib principally targets c-abl, c-kit, and platelet-derived growth factor receptor; this contrasts with sorafenib which we have evaluated here at University of Chicago, which is more of a multi-kinase inhibitor because it strongly inhibits Raf, as well as VEGF, PDGF, and c-kit, mildly. So what the oncologists-and I think the basic scientists-have developed with these "family trees" is that you could visualize the different kinases that are targeted by these different compounds. There is debate about whether or not it's good to hit one target versus multiple targets. In some ways, the debate is similar to that for endothelin antagonists: selective A versus non-selective A and B. The problem with a new field or a new area of investigation is that there are a lot of unknowns, and the need for selectivity in receptor blockade is just one unknown. Plus, unpredicted side effects may occur.



"There's a tree of 478 human kinases in the human kinome. This is like a "family tree," with branches, trying to show how the different kinases are more or less related." Dr Gomberg-Maitland

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in the human Dr White: So Jeremy, if you could summarize what nome. This is we know about the imatinib trials to date, I think that "family tree," would be a really helpful adjunct to Mardi's introduction.

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different kinases
are more or less
related."Dr Feldman: Great. So there have been two major
studies, the Phase II conducted predominantly in Eu-
rope, which overall was a negative study. But when
they looked at a subgroup analysis, there was a strong
signal that the sickest patients, as measured by pul-
monary vascular resistance, actually had some benefit.
That set the framework for the Phase III study. The
Phase III study had as primary endpoints 6 minute
walk and hemodynamics, with numerous secondary
endpoints. The robust improvement in 6 minute walk
needs to be viewed in the context of the other back-
ground therapies that these patients had. So, unlike the
previous monotherapy studies, where patients had no
background therapy, and the trials demonstrated 6

minute walk improvements of between 30 and 50 meters, in this study 40-plus percent of the patients were on triple therapy before enrollment. Thus, to show a 30 meter improvement on background triple therapy is fairly impressive; this is all the more true when one considers that recent combination therapy studies have demonstrated 6 minute walk improvements at 20 m. So there's a very strong efficacy signal with the 6 minute walk. There were also some subgroup analyses looking at whether the 6 minute walk improvement remained robust with the different background therapy groups. So whether you were on 2 oral therapies, one oral and one IV, or all 3 therapies, the 6 minute walk difference strongly favored imatinib. And sensitivity analyses, using different methods to adjust for incomplete data, also showed that imatinib produced a robust improvement in walk. The fact that we have an effective medication as measured using 6 minute walk is exciting, but even more exciting than that were the hemodynamic data at week 24. This study, in contrast to more recent trials, had a hemodynamic endpoint. The net improvement in cardiac output was impressive: it was in the order of magnitude as what has been seen with continuous prostanoid therapy. Investigators measured almost a 1 L/min improvement in cardiac output and a 379 dyne-cm/s⁵ of reduction in PVR. These improvements are very convincing, especially when you think about the background therapy that these patients were using at enrollment. Unfortunately, the secondary endpoints of functional class and time to clinical worsening were not statistically different between treatment assignments. I think that we're going to have some discussion surrounding the role of adverse events and how that made it difficult to interpret the clinical worsening, since it seems like a significant portion of the clinical worsening events were actually adverse events related to the drug.

Dr White: So the sponsor and investigators are certainly to be congratulated for conducting what I think everybody would regard as a pretty risky trial given that this patient population had multiple background therapies. Moreover, the protocol required that these patients be especially sick from a hemodynamic perspective. So this is indeed a really unique trial and a unique group of patients. Ioana, can you tell us something about what your experience as an investigator was with adverse events and how that relates to the adverse event data overall?

Dr Preston: First, I'd like to point out what you've alluded to, that this population in which imatinib was studied had a very advanced disease and was taking multiple therapies. They also had very advanced he-

modynamics. The inclusion criteria set a PVR of >800 dyne-cm/s⁵. So this is a very sick and advanced population. On the other hand, this is a chemotherapy drug, so it's not devoid of side effects. If we look at the safety and tolerability of this compound in the Phase III clinical trial, the vast majority of patients reported an adverse event. Ninety-seven percent in the imatinib group and 96% percent in the placebo group had one or more adverse events, reflecting the symptom complex of a very sick population. Most side effects that were attributed to the compound were reported in the first 8 weeks. Those included nausea and edema. Peri-orbital edema or lower extremity edema were particularly important, and those occurred in the first 8 weeks of the trial. Other side effects that are associated with these compounds are thrombocytopenia; and that is something that we need to remember, especially in patients who are already on prostacyclins and start off with a lower platelet count. So it's not an easy drug to tolerate. But in those patients who tolerate it, there were some beneficial effects. As far as serious adverse events, they were reported in 44% of patients on imatinib versus 30% on the placebo. So even if you look at a placebo group, 30% of those patients reported a serious adverse event. Again, we're talking about a very sick population. As far as discontinuation, 33% versus 18% in the placebo group. So overall, as Jeremy mentioned, this drug had positive effects on a population of very sick pulmonary hypertension patients. But there are some patients who cannot tolerate the drug, and it seems that the majority of the side effects that patients experience are in the first 2 months of the therapy.

Dr White: That's a real helpful perspective, Ioana. Steve, can I ask you, as someone who was not involved with the trial, hearing about what is really a pretty remarkable efficacy profile in a sick and heavily treated group of patients–and also hearing about an AE profile that again looks kind of like a prostanoid (in terms of a difficult medication to use)–how do you see this fitting into your practice, especially at Hop-kins, where you see a lot of scleroderma patients and a lot of interstitial lung disease?

Dr Mathai: That's a great question and really remains to be determined. The concerns that I would have going forward are directly related to the risk: benefit ratio, particularly with regard to the potential disconnect between hemodynamic and exercise capacity improvement compared to quality of life and tolerability issues. I think it's important to recognize in diseases such as pulmonary hypertension, which are chronic, that we focus on aspects of the personal or patient-related outcomes, such as quality of life and whether or not the medication actually makes them feel better, regardless of what the hemodynamic or functional capacity data suggest. So particularly in our scleroderma population, where they may be more prone to experience side effects, one thing that would be concerning to me would be the peripheral edema. We have seen this with other medications that require a little more monitoring and more aggressive diuretic therapy in the scleroderma population. So those types of concerns would be at the forefront for me, from a clinical perspective.

Dr White: Jeremy, you had a number of patients in this trial, and I know followed some of them for quite a long time. And you also use a lot of prostacyclins. In the patients who stayed on the drug, what's your sense of how they perceived this as compared to an infusion prostacyclin, in terms of the overall benefit versus difficulties?

Dr Feldman: I think, as Ioana pointed out, that this is not an easy drug. The AE profile, simply by percentages, really is consistent with what the patients experienced. That is to say, every patient in the study had at least some problem with the medication; in general though, these were manageable. Even at the 200 mg dose, most of our patients had some at least mild degree of peri-orbital edema. And we had to reduce dose from 400 down to 200 and then push it back up in several patients. We also had some trouble with rashes that were important, but did not require patients to discontinue therapy. In general, out of our cohort of one dozen patients in this study, the vast majority of those continue now, more than a year out. The patients that felt better were willing to put up with the side effect profile. I think the concept of having dosing flexibility is very important, just as we do with our other pulmonary hypertension therapies, finding just the right dose for each patient. It's not a one-sizefits-all. And I think there is some dose responsiveness in the frequency of adverse events. We don't know whether every patient needs to be at 400 mg to benefit. Maybe in our smaller patients, the right dose is a little bit lower. Given the improvements that were seen in 6 minute walk and hemodynamics, in general our patients also echoed that, in terms of quality of life, they felt better.

Dr White: That's really, really useful information. Ioana, could you sort of tickle this quality of life issue that Steven and Jeremy have touched on? For the people that you've enrolled and in talking to other investigators, do patients perceive the quality of life to be better?



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Dr White

Dr Preston: From the short experience that we've had with this drug, in the beginning, they did not seem to notice an improvement. And in some, especially the ones who developed edema, they may feel a little bloated and worse. And then, as Jeremy said, you tweak the dose and help them to go over the first few weeks after initiation of this drug. And then once things settle, many seem to feel better.

Dr White: Mardi, can I circle back to you and ask the million dollar question? Do you think that this data set is going to be sufficient for the FDA to label the drug and move forward with approval?

Dr Gomberg-Maitland: So (laughter) before we get to the million dollar question, I think that this large imatinib experience is instructive and similar to what we found with sorafenib. Because of all the issues that we have discussed with quality of life, we might not need as high of a dose to achieve our goals. With sorafenib, we have found that patients didn't tolerate the oncology doses. The side effect profile for that drug is hand-foot syndrome, with significant calluses and pain. That profile, even when mild, sometimes produced an unacceptable change in the patient's lifestyle compared to somebody who's dying with kidney cancer or liver cancer, who might be willing to accept that side effect. So when it comes to imatinib, what was surprising to me was the design targeting the full oncology dose. I think what we've found over time and what others are reporting is that we're getting sort of equal "bang for the buck" at a lower dose in the patients who are responders. And I think, just like any other drug, that not every patient is going to respond to this medication. I do think that the sponsor took a risk going from Phase II to Phase III only looking at these really select, severe patients. However, it was a risk that the sponsor and investigators were willing to undertake because these were patients that we didn't have very much else to offer, other than transplant, if candidates.

In terms of the FDA, I think right now their concern is the interaction that appears to occur with imatinib and warfarin with intracranial bleeds, more so than the dosing issues with nausea, vomiting, electrolyte imbalances, and bloating. I only have a small sample size and didn't see these bleeds. It's difficult and I'm not sure what the FDA will do because we have a small sample size. They might say, "We need to have another study or we need to put a black box that patients shouldn't be on warfarin." Maybe with that kind of a warning, they might think that we could approve it without another trial. I think that the FDA is going to wrestle with difficult decisions because, again, these drugs are not without risk. Despite having a large sample size of patients on these medications in oncology, the majority of the oncology trials haven't done systematic ECHO, looking at the right side. Yes, some of the trials have MUGA scans to evaluate left ventricle function, which is important, but it hasn't been done systematically in their clinical trials. So these drugs present a risk, and I think that the FDA will be conservative with their decision making.

Dr Feldman: Jim, can I touch on the subdural hematoma issue?

Dr White: Absolutely.

Dr Feldman: When you drill down on those 8 patients for whom they provided data, it's a little bit murky. The majority of those patients actually had multiple risk factors for subdural, such as a traumatic head injury. A number of them were on NSAIDs concurrently with their warfarin. One of the patients had an acute leukemic conversion and was very thrombocytopenic. So while the fact that 8 patients had subdural hematomas is always a concern, I think the details are extremely important. I would be optimistic that the FDA would really look carefully at the data surrounding the incidents of subdural and the other risk factors beyond exposure to imatinib. I think that those of us with large PAH cohorts have all seen our patients on warfarin fall and smack their head and get subdurals. So the risk factors I think are particularly important here.

Dr Mathai: Jim, I have a question for the group, regarding the long-term experience and potential concerns about long-term effects which have been noted with other tyrosine kinase inhibitors, such as the recent report about dasatinib. With imatinib and sorafenib being multi-tyrosine kinase inhibitor medications, do others have concerns about long term use in PAH?

Dr Gomberg-Maitland: First, I think that a major difficulty that we encounter trying to cross-purpose these drugs, is that the patients that are getting these therapies are typically older, and in the case of sorafenib, men with kidney or liver disease. For chronic myelogenous leukemia, there's a lot of comorbidities and risk of infection. When I've looked at the dasatinib reports, just as Jeremy said with the subarachnoid bleeds, it's very difficult to tease out a signal for the development of pulmonary vascular disease versus the possibility that these patients had left heart disease, diastolic heart failure and PH . . . or perhaps longstanding pulmonary venous hypertension that then became arterial. It's going to be hard to say.



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Dr Feldman

This is the caution and the reason why the French group wrote the editorial in the European Resipiratory Journal [2] to say, "Hey, you know, we need to go a little bit slower." And so I think ultimately what we need are well designed trials with long term extensions, understanding that even these data sets will not provide all the information. When it comes to our small trial with sorafenib, we enrolled 11 patients in a pilot Phase I, and right now I have 1 patient remaining. Of the patients that remained on therapy for 3 years, we found that the initial benefit was maintained, but we didn't get any additional benefit over a longer term. And so at the 3-year mark, as new studies were becoming available, I gave them the option to come off the medication. They were at a low dose of the medication, especially compared to what was approved. The majority of them were on 200 mg once a day instead of 400 mg twice a day. And some were at a lower dose than at the completion of the initial 4-month study. None of them has had any ill effects of discontinuing the medication, and we didn't have any unexpected adverse events in that small cohort.

I think that we're always going to be stuck with the situation that we don't know what any of our therapies really do long-term. For example, the FDA had questioned how long should our patients be using sildenafil? Do we really know if there is continued benefit? Are people going to deteriorate if we stop sildenafil? And this issue becomes especially important in kids, which we haven't really mentioned. You know, what are the toxicities of all of our therapies in the long term? In an orphan disease, I'm not sure we're ever going to get the best answer. I think that careful surveillance for adverse effects during the trials and close cooperation with the oncologists who know these medications best will be critical to understanding the short- and long-term outcomes.

Dr White: Ioana, can I point the discussion your direction and ask: "If this drug gets approved in the next year, with all the caveats that we've discussed, where will you use this drug, given the efficacy data, given your alternative therapies, and given the adverse effect profile? You've had some experience with this drug... where are you going to see it fitting into your practice?

Dr Preston: Well, that's a good question. We do have the luxury of choosing from quite a few therapies. But for this particular drug, because we started testing it in a very sick population, I think I will be conservative. I intend to gain more experience using this drug, if it gets approved, in the specific population that was studied: in the sick PAH patients already on 2 or 3 therapies, who

remain symptomatic ... that would be the population that I would target initially.

Jim, may I go back to the differences in the different tyrosine kinase inhibitors and the dasatinib connection with maybe producing PAH? Imatinib has been used for quite a number of patients with cancer. And yet, at least as far as I am aware, it hasn't been associated with PAH. Only dasatinib has been. So I would speculate, and it's only a speculation, that maybe the differences in the specificity and the pathways that each compound inhibits in the tyrosine kinase superfamily may account for one producing pulmonary hypertension and a different one having beneficial effects on the pulmonary vasculature.

Dr White: No question that that's possible. And it's also entirely possible that people who are receiving these drugs for malignancy have a different set of risks for the development of pulmonary hypertension. It's likely that those patients are very different from people who already have pulmonary hypertension with a diseased signaling pathway in their lung who might actually benefit from imatinib. So there's going to be a lot of uncertainty as these drugs are developed. I think we ought to push for very careful registries for every patient who's put on imatinib for pulmonary hypertension. If this comes to market, I hope that the manufacturer would really take advantage of the fairly sophisticated registry tools that we're already using at different centers and say, "Okay, we've got to follow each of these patients over time, to better understand the long-term toxicity."

Dr Preston: Right. And I should add, this drug should be, at least in the beginning, used in PH centers, where the physicians already have experience with the other therapies.

Dr White: Steve, let me ask you a more focused question, and perhaps others want to pick up on it. Will you use this before or after an infusion prostacyclin, given everything that's been said?

Dr Mathai: Very good question. I think it's going to depend on the individual patient. We tend to have more patients on combination therapy with oral and inhaled prostacyclins rather than intravenous or subcutaneous prostacyclins in our scleroderma population, as compared to our idiopathic PAH population. So I think that's going to play some role in who would potentially receive this medication. I would view it as an option, particularly in a patient who, for one reason or another, is not a candidate for intravenous or subcutaneous prostacyclin therapy. I think that this med-



"I intend to gain more experience using this drug, if it gets approved, in the specific population that was studied: in the sick PAH patients already on 2 or 3 therapies, who remain symptomatic . . . " Dr Preston ication might make sense in that situation. In patients who have maxed out on intravenous therapy or subcutaneous therapy, I think it would be an option in that case, also. I don't see it moving up higher in my personal treatment algorithm until more data are available, particularly relating to patients with less severe disease who don't have the severe hemodynamic parameters of the patients who benefited in the two trials to date.

Dr White: Jeremy, how do you view imatinib in relation to infusion prostacyclins?

"I would view it as an option, particularly in a patient who, for one reason or another, is not a candidate for intravenous or subcutaneous prostacyclin therapy."

Dr Feldman: For us, the backbone of therapy for our sickest patients continues to be continuously infused prostanoid therapy. And every patient that we put into this study, with one exception, was on continuously infused prostanoid therapy. I think we would look at it as add-on to oral plus continuous prostanoid. And then, depending on what the experience is down the road, as we learn more about it, we might broaden that indication. But certainly in the beginning, I think that we would use it after patients have already been exposed to a continuous prostanoid therapy.

Dr White: Ioana, Mardi, do you have commentary on where you're going to see this in your practice?

Dr Gomberg-Maitland: Well, based on our practice patterns, we tended to enroll patients that were already on prostacyclins and were either stable or starting to experience some signs of progression. And I think that that's probably the group in whom I would continue to use the medication. But again, I just don't know if I have enough data to say which therapies are best in combination with imatinib. And it might be that, hey, it is in lieu of prostanoid. I'd like to see more of the Phase III data before I make that decision.

Dr Preston: The type of patients enrolled in the trial would be my population in whom I would first start using it. And, as we gain experience, as Jeremy said, we may be able to broaden the indication and the type of patients for whom we can use this drug.

Dr White: So Mardi, I'm going to just ask you, and others can chime in, are there other receptor tyrosine

kinases that are in the pipeline, about which you're particularly excited? Or is there something that you'd like to share as we close out?

Dr Gomberg-Maitland: I think that there are many potential compounds that are in development for oncology at different phases. I think that we're going to need the PH community to work in unison to get the pharmaceutical companies to see the benefits of crosspurposing these drugs because I think that it is a risk to the company–unless it's something that's been out for quite some time–to take their newer therapies and broaden their horizons to get a team that is knowledgeable in pulmonary vascular disease. So my first instinct would be to work with an industry that has compounds and is already working with PH investigators, because they're going to have the most knowledge of the disease process.

Dr Preston: Yeah, it makes sense. I should add that there is another compound that's being tested in a Phase II trial and its name is nilotinib.

Dr Gomberg-Maitland: Which is the next generation of imatinib.

Dr Preston: Correct.

Dr Gomberg-Maitland: With a little bit more favorable side effect profile.

Dr White: Oh, that's exciting. Well, I thank everybody for their time this morning. I think this was a really instructive conversation for me and I hope for the readers of *Advances* as these data get published and presented to the FDA. When decisions are made about whether we have enough information to move forward or whether we need more information, I think readers are going to come back to this conversation and thank our insightful panelists for providing perspective. So I thank you all for your time this morning.

References

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