FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC)

Tuesday, February 8, 2011

8:00 a.m. to 4:30 p.m.

P R O C E E D I N G S

(7:58 a.m.)

Call to Order and Introduction of Committee

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So for the first question, with respect to single-arm trials to gain accelerated approval, single-arm trials have formed the basis of 29 out of 49, or over half, of our accelerated approvals for oncology to date. And while they often require less resources and time to complete, they provide limited data on clinical benefit and safety.

Single-arm trials for accelerated approval have usually been performed on refractory populations where no available therapy exists. But as a greater number of drugs are approved, identification and documentation of the refractory population is becoming increasingly problematic.

In addition, marginal response rates observed in single-arm trials in a refractory setting make it difficult to determine whether the findings are reasonably likely to predict clinical benefit.

Some alternatives to single-arm trials in a refractory population include randomized trials in a less refractory population against an active control using a surrogate endpoint analyzed at an earlier time point or a randomized trial on a refractory population comparing the investigational agent to either best supportive care or a dealer's choice of various agents selected by investigators. Randomized trials provide the opportunity to look at a wider variety of endpoints and allow for an improved characterization of safety.

So the committee members are asked, given the problems with single-arm trials, discuss scenarios where randomized studies should be required for accelerated approval. Alternatively, please discuss situations where single-arm trials may be appropriate to support an accelerated approval.

DR. PAZDUR: If I could just mention a few things here that perhaps we did not mention on the slide, and that is really the need to really define the population very well in a single-arm trial. Remember, by law, these have to be controlled trials, adequate and controlled trials that lead to an approval of a drug. And in a single-arm trial, what we're looking at is really a situation where no other therapy exists, so the response rate in the control arm, this make believe control arm, is basically zero, because there's other effective therapy for this disease.

Let me give you an example of this. One of our very early uses of a single-arm trial was in irinotecan or CPT-11 for colon cancer, when only there was 5-FU for that disease. So it would make sense that a single-arm trial of X percent, I think it was about 15 percent in that situation, would be a situation where one might consider an accelerated approval, the control being there is no control. There is no other active drug in this disease, so if one did a randomized study, one would expect to see a zero percent response rate.

Some of the problems that you get into, especially with more and more drugs being approved in other disease settings, is that it might not be that cut-and-dry, especially for some of the hematological malignancies, lymphomas, Hodgkin's disease, myeloma, et cetera, leukemias, where you might get response rates even by retreating patients with drugs that they've had in the past or drugs that are on the market that may not have a specific indication but are widely used in oncology.

Here, again, the other issue that I think people have to understand is that we're probably one of the very few therapeutic areas that takes single-arm trials for drug approvals. Most other therapeutic agencies, the agencies go right away to randomized studies. And this use of a large single-arm trial of 100 to 120 patients really is a manifestation of the accelerated approval process.

One could say an alternative would be, right after the Phase 1 study, if you see some really interesting level of activity, high level of activity, maybe you want to start a randomized study very early on rather than basically just accruing large numbers of patients to a single-arm trial.

Sometimes when you get to some of the single-arm trials that have two single-arm trials with 150 patients, you're well on your way already of randomized study, and you might have been better off by just doing a randomized study relatively early on. And that's some of the issues that we really wanted to discuss.

As with everything, we feel that there is a role for single-arm studies, particularly in unique diseases or where one has very, very high response rates. But as with everything in medicine and advice that we give, water tends to seek its lowest level and we frequently find sponsors coming in saying, "Dr.

Pazdur, what's the fewest number of patients and the lowest response rate that you'll take?" Okay, that's problematic for us, and that's where we're going with this question.

DR. WILSON: So I do think that one can always make an argument in settings that a single-arm trial is okay. I think one of the difficulties you've already pointed out is the fact that in numerous settings where it is said that nothing else works, that is actually not correct.

Actually, in kind of a follow-up to that, you all mentioned that 29 of the accelerated approvals were based on single-arm trials.

What percent of the follow-up trials were randomized? Let me restate it. What percent of the follow-up trials did you require a randomized study at perhaps an earlier stage?

DR. JOHNSON: Twenty-four of 27.

DR. WILSON: I'm sorry?

DR. JOHNSON: Twenty-four of 27 that were converted were converted based on randomized trials; almost all.

DR. WILSON: So if I hear right, 29 got accelerated approval on single-arm, and of 27 that were converted, 24 of those required randomized studies.

I think this really brings to bear the very thing you said, Dr. Pazdur, which is that should small, single-arm trials be what gets you accelerated approval or should you wait for the randomized studies, because as we all know, and it's been brought up here, it's not that these drugs are not available. They can be obtained through compassionate use. There's a variety of different mechanisms that they can be made available.

Dr. D'Agostino?

DR. D'AGOSTINO: In terms of this, we were told that they can't be randomized, yet most of them at the later endpoint were, in fact, randomized. So there's sort of something contradictory here. But let me go back to the notion of the single-arm study.

In this single-arm study, is the endpoint a surrogate endpoint or is it the actual clinical endpoint?

DR. PAZDUR: It really depends on the disease setting, but most of the time, in solid tumors, we're talking about this to be a surrogate endpoint reasonably likely to predict clinical benefit. And that's where the real problem becomes, because the issue, especially when one is dealing with a low magnitude of benefit, if somebody is coming in with a 10 percent response rate here, in a solid tumor, how does one really make that jump and leap of faith here, so to speak.

DR. D'AGOSTINO: Given if it's a small population, like maybe some of the things we heard today, that you have a very small population or an offering drug situation, you could see the notion of a surrogate endpoint trying to move things along. But, again, I find the fact that later on, you can do a randomized trial and it materializes, that most of them are randomized trials that somehow or other undermines the notion. So I guess the notion that you need the single-arm -- so I guess the single-arm trial is basically to entice the company to move on with the drug; get the single-arm trial going, they get accelerated approval; then they have incentive to put more substantial controlled clinical trial together. And I don't see why they can't package that all at once to get it right on the table; this is what we're going to do. And you can handle both of these issues.

DR. PAZDUR: I really want to make this point very clear. The accelerated approval program is a patient-centric program aimed at getting drugs to the patient. It is not an incentive program, financial incentive program to the industry. And that's why I think it's very important that we pay attention -- this is why we keep on using that word over and over and over again in our presentation.

DR. D'AGOSTINO: Well, no. What I meant by that is that there's an incentive with an indication that they can enlarge the indication and so forth by doing it, and the single-arm study entices them into a way of getting it. But I think one of the questions, put them all together. And I think they should move from the single-arm study to the clinical study, and that should be laid out, and that should be how the approval is based.

DR. PAZDUR: And remember, nobody has to start a development program in the most refractory population. They could introduce the drug into a less refractory study and do a randomized study.

Here, again, we did point out other potential alternatives to single-arm trials, very similar to the AIDS scenario, where one has randomized study where one would take a look at a surrogate endpoint in the middle of a study or near completion of the trial, base accelerated approval on that, and then look at survival at the end.

DR. D'AGOSTINO: Can I make one more comment?

Moving to a different population, I see where you're coming from; you've got a bigger population and what have you. But there's sort of a danger in that that you're moving away from the target that you wanted and the balance of, say, you can't do a single-arm study, do a randomized trial on a different population. Then you're scratching your head at the end, is it really applicable.

So the single trial, with some kind of indication of how do you judge effectiveness, even at the accelerated level, followed by or in conjunction with the follow-through with the randomized trial seems to me like, from what you're saying, it should be possible, especially given 24 did go on to do the randomized trial.

DR. WILSON: Dr. Sekeres?

DR. SEKERES: Thank you, Dr. Wilson.

Dr. Pazdur, something that you said about the justification for single-arm studies is exactly what went through my head at the same time, and that is that it's a rare disease and that there's some type of benefit that's impressive right off the bat.

In my world, I'm a leukemia doctor, that's arsenic. Right? You have arsenic trioxide given to people with relapsed acute promyelocytic leukemia, which is an extraordinarily small population; so small that you can't justify opening a study in your center because it's not cost-effective, and you have a big magnitude benefit.

But I think the third piece to it -- and, Ralph, this gets a little bit at what you were saying -- is the either real or perceived imperative to getting a medicine out there to market, and that's a real tough balance to strike.

So then if you take that to the next level, what kind of randomized study could you propose and what would your population be, it seems to me -- and the examples we had presented to us today were great, because you saw very small patient populations where it would be difficult to do a randomized study right off the bat to get approval, and you saw relatively small, but not that small, where randomized studies were enrolled too efficiently, and that example was with GIST, which, by the numbers presented to us, looks like it affects between three and 4,000 people a year in the U.S. Chronic phase CML is very similar, about five to 6,000. Yet, they were able to accrue quickly to a randomized study.

It seems to me that if you have a patient population that's somewhere around a thousand, that becomes difficult. And maybe the type of study you have to design to encourage accrual within the U.S. gets a little vague in the comparator group, and that may be dealer's choice by the physician; because I think in the U.S., it's hard to convince somebody to not get the latest and greatest or to be randomized to a placebo when it's a very small patient population who happens to be very vocal.

DR. PAZDUR: And we have advocated that to several sponsors who said they couldn't -- there wasn't agreement on a comparator arm or there is none, and that has been used in drug approvals.

DR. SEKERES: And do you have roughly -- I know you can't give a number, but is there some sort of rough patient population where, in your own mind, you think, gee, they could probably do a randomized study; it might not be easy, but they could do it versus it ain't going to happen?

DR. PAZDUR: It's hard to say because it also depends on the treatment effect that you're seeing. If you have a very effective therapy, you can see a big effect in a very small number of patients.

I'll give you an example. Who would ever think you could do a randomized study in paroxysmal nocturnal hemoglobinuria? They did it, and it was highly successful, because they had a very, very effective drug. I've never seen a case so -- they did a randomized study on that. So it really depends on the effect size that you're talking about here.

Here, again, I think there are some issues, for example, in some of the GIST supplements that we approved on single-arm studies and gave them just a regular approval, because we knew it wasn't going to be possible to even do a randomized study, like in eosinophilic leukemias, et cetera, and other very rare tumors. It's going to be very difficult to do.

DR. SEKERES: You know, the PNH example is a great one. So there's something that that company did with a very vocal and active patient group, where they were able to accrue to that sort of study. And the same thing happened with imatinib for just our first CML. And there's probably a lesson that other companies can take out of those that did that successfully.

DR. PAZDUR: And one would hope, as we get more targeted therapies that have greater efficacy in a subpopulation, one could go more rapidly to a randomized study rather than doing this cookie-cutter approach of let's do now 150 patients on a Phase 1 study.

If you have done an expanded Phase 1 cohort in 20-30 patients and see a 70-80 percent response rate, why not just jump into a randomized study, and with an effect size that truly is what you think it's going to be, not aiming at the garden variety two-month improvement in overall survival, but really a big effect on overall survival. So one would have to deal with a small -- or one could deal with only a small trial here.

DR. WILSON: Maybe you can give us some guidance here. And I'm really caught up on the fact that 29 accelerated approvals were single-arm, of which 24 of 27 that were converted were on randomized study.

So really this is how rapidly the FDA -- I mean, this really is under your control. And if the FDA wants to, as Dr. Sekeres said, move a drug forward

quickly, then you might be willing to accept a single-arm trial. But it sounds like in the vast majority of settings, randomized studies were done; they were positive, presumably, et cetera.

So I'm trying to get a sense of what you're looking for from us, because at the end of the day, the FDA can say, "Listen guys, yes, you've got a strong signal here, but don't come forward with this, because you can do a randomized study."

DR. PAZDUR: Well, you've heard our arguments, and we've used these arguments and had, over the past 10 years, discussions with companies on this. Nevertheless, I think it's important for us to have this discussion so people hear it again in public, so to speak. So it's not just the FDA saying it, but there is some recommendation by the advisory committee of where you feel these should also be going.

I want to say, and I want to make it real clear to everybody here, we're not saying we will never accept a single-arm study. There are situations where we think it's appropriate, in homeruns, when somebody comes in and it really is a drug that we really want to get out from a public health perspective. But here, again, many times, what we have seen here is people coming in with a very small response rate, with ill-planned if no confirmatory studies, saying there's nothing else for these patients; please approve this drug.

They also may be doing themselves a disfavor, because many -- we've had circumstances where the true benefit of the drug was realized in a randomized study on the basis of survival, where the response rate was miniscule. The example that I gave to you of irinotecan, we approved that drug at 15 percent response rates. The Europeans demanded a randomized trial. It showed a survival advantage, which really put that drug in the context of how it should be used, and that was only a year after the accelerated approval, roughly, of that drug.

DR. WILSON: Ms. Mason?

MS. MASON: Thank you. I wanted to go back to your comment about the ability of patients to access medication prior to approval through expanded access or compassionate use programs. And while it's wonderful that that mechanism is in place, unfortunately, it doesn't seem to be working like it might, simply because the industry does not want to take the risk or, for whatever reason, it's not out there for patients, and that's been a real issue.

DR. WILSON: Would FDA like to comment on that?

DR. PAZDUR: Well, we're very much in favor of an expanded access program, where it makes sense, especially in these situations where there is evidence of activity of the drug or the drug provides a benefit while we're developing the drug. Here, again, we cannot make a pharmaceutical company give a drug either to a single patient, to an expanded cohort, intermediate size or large size of large patient population.

So here, again, I think before the pent-up demand is realized, what we're really encouraging people to do is think randomization early rather than doing these large single-arm trials here.

DR. WILSON: Dr. Freedman?

DR. FREEDMAN: I agree with the point that you made. It seems that the default position has already been established. The standard is to do the randomized trial. But there's always going to be the exception, where you have a clear-cut response that's durable and it's associated with specific symptoms that you can direct. Take esophogeal cancer; the patient can either swallow or they can't swallow. That's the way I see it. It's going to be a minority of trials where you could consider that; but, otherwise, the usual route is going to be the randomized trial.

DR. WILSON: So far it's been 58 percent, so it's not a minority.

Dr. Logan?

DR. LOGAN: I guess I certainly agree with all the concerns that have been raised about single-arm trials in terms of the difficulty interpreting these marginal response rates that we're seeing, difficulties in assessing toxicity.

I would also just raise a concern that I think it oftentimes makes it difficult to do those follow-up randomized trials, certainly, in the same relapse refractory setting. It makes it difficult because of the accelerated approval. But I think it also -- as we've seen in several of the presentations today, it may make it difficult to do that follow-up randomized trial in a less refractory population because of the potential for crossover to the agent being studied.

The other point that I wanted to make was in terms of doing an upfront randomized trial. I think it's been alluded to in terms of setting up an upfront randomized trial where a surrogate endpoint is the primary endpoint for accelerated approval, with additional follow-up for survival.

Certainly, that's a reasonable approach. You just want to make sure that -- make sure of a couple things; first, that you're adequately powered for survival. Second of all, you want to be careful about the duration of the follow-up in terms of when are you presenting the results on the surrogate endpoint; is that done at the end of accrual so that

you're not presenting results before accrual is completed.

DR. WILSON: Dr. Martino?

DR. MARTINO: I think I'm getting old and crabby and probably that's the sum of everything I want to say to you. But I'm very disappointed in the fact that this process of approval has really become a screening process.

I'll just remind you of Dr. Pazdur's recent comments. Everyone is interested in what is the least that we have to offer. And I think that this committee and the FDA and others have allowed that to become the mood of science within the field of oncology during at least my lifetime, where we are willing to accept drugs with the most minimal evidence that they do anything at all, and move them forward.

I actually wonder whether we're having the right discussion here. I appreciate all of these procedural issues, but I'm starting to find them somewhat irrelevant. I think we have moved the whole field in absolutely the wrong direction. And the reason why a single-arm trial is so inadequate is because we're dealing with drugs that barely have any activity. And it isn't just a drug that falls into that category; it is most of our drugs. The exceptions are the ones that have more than a whiff of activity. And at some point, we have to start to take responsibility for that.

To the simple question of is a single-arm trial adequate, there's almost no circumstance where it should be adequate for approval for human beings, which is who we're dealing with. So, again, I'm wondering whether this is the right discussion to be having.

DR. WILSON: So let me try to put this into perspective, and maybe you can give us some numbers. Twenty-four accelerated applications or accelerated approvals were converted to full approval based on randomized studies.

What is the median and range between the accelerated approval and the full approval based on randomized study? And this going to be the worst case, because if these companies were told they had to have randomized studies early on, this whole thing would have been quicker, because the whole idea here is to move drugs -- is to make drugs -- as Dr. Pazdur said, it has to be patient-friendly; it's to make the drugs available.

I'm no advocate of single-arm trials either, but I think the other statistic is that only four drugs have been not confirmed that have reached the point of confirmatory trials, and that was 10 percent.

So the system seems to be working. Again, so the question is it's just a matter of a balance between how quick versus do we even know how to use these drugs in a proper manner.

But what is the median time for those 24 drugs?

DR. KLUETZ: If you're talking about the median time between the accelerated approval based on a single-arm trial and the verification of benefit based on the randomized trials, of all 27 indications --

DR. WILSON: Twenty-four that required --

DR. KLUETZ: I can't take out the 24.

DR. WILSON: Okay. Well, 27 is fine.

DR. KLUETZ: It's 3.6 years, and the range is 0.8 to 12.6. And if you take the tails, which is what happened with the longest trials and what happened with the shortest trials, it's off the topic of whether it's a single-arm trial or not, but what it looks like is a lot of the very long time for very long trials have a couple of things in common.

Number one, only one confirmatory trial was undertaken. And what we'll talk about later is if you lose on that, then it's scramble time. Do you do another trial? If you don't withdraw it, you do another trial, that's a long time before that drug is up.

Another thing that's happened that we've already seen is that there are certain populations where there's a very small amount of patients that can also take a long time. And another thing that can take a long time is if you're not looking early on in drug development and you want to do your confirmatory trial as a combination trial, moving the drug up front, and you don't have a Phase 1 trial yet, that's a big problem, too. That adds years onto the development.

DR. PAZDUR: This is why we're trying to emphasize planning, planning, planning. It's not coming to us with a single-arm trial and then let's discuss after the drug is approved. There's no reason why somebody can't -- and here, again, I think the numbers will bear this out. The successful drugs have had trials ongoing. If there needed to be a Phase 1 study, okay, you're studying the drug in a refractory setting. The other disease settings that you're going to be comparing this drug to involves combination therapies. Why not start developing those Phase 1 studies early on while you're getting the registration trial in place?

Here, again, it's this planning issue here that needs to be emphasized to the companies, and that's why we're asking the series of subsequent questions about the timing, implications of not having the trials well thought out, the number of trials, et cetera, who you're going to be using for these trials.

DR. WILSON: So the numbers are median -- you're shaving 3.5 years off availability on the median. If

these things were preplanned to be randomized upfront or even preplanned to be approved on single-arm, but randomized is already starting, you might be able to move this up even more.

So I think that Dr. Martino makes a very good point that things have probably slid way far over to not planning, to allowing single-arm trials too often, and there's got to be some middle ground moving this back.

Dr. Loehrer?

DR. LOEHRER: I wasn't going to initially comment, but I agree with Dr. Martino on this. There was a journal years ago that Rick knows about cancer treatment reports. If it was zero for 14, it was a negative trial, and if it was one for 25, it was a negative trial.

DR. PAZDUR: The Gehan rule.

DR. LOEHRER: Yes. And now one for 25 is promising results.

DR. PAZDUR: No; it's a drug approval.

DR. LOEHRER: Right. And move for approval, right.

A couple points I wanted to make. One has to do with the second point, situations in which a single-arm might be appropriate.

So an example from our institution that hasn't been raised is in refractory testes cancer. When a patient is cisplatin refractory, when I was a boy, there was no drug that had activity until etoposide came around, and then that, again, moved into a randomized trial and was approved that way.

The next generation drug was ifosfamide, and ifosfamide got approved by the FDA not based on a randomized trial, but because in third-line therapy in patients who were refractory, there was a 15 percent long-term survival and a cure rate for that patient population; impossible to do a randomized trial on that. There's probably two or 300 patients in the country. But yet it was a population in which you could clearly show people were alive that wouldn't have been alive, and so there are situations in which this occurs.

The next bullet point, to follow-up with Mikkael, is that if you look at the website for the Office of Rare Diseases by the NIH, it's defined as a disease that is less than 200,000 people, which encompasses colon cancer. And I think logic would dictate that we could probably define some diseases in which there are less than a thousand patients that are, really, very rare diseases, and some of the examples were brought today, in which the bar in terms of doing a randomized trial may not necessarily have to be there, but the endpoint needs to be solid.

If you have clear historical data that there is a zero percent one-year survival and now you have a 20 percent one-year survival, something like that, I think you could do it. But the progression-free survival is a very soft endpoint, I think, and some of the trials in which we have a two-month improvement or 1.5-month improvement is a little shaky.

Then the final bullet point has to do with something I think we all have to wrestle with is this era of personalized medicine, and that with the genomics and pharmacogenomics and all the other aspects of the cancers, we have to think of a different way than the randomized trial. If I get colon cancer and Kevin gets colon cancer, just because we're different people, it's going to have different responses.

Now, the randomized trial is supposed to correct for that, but I think ultimately we need to correct for the randomized trial by coming up with better genetic markers. And so the point would be in KRAS mutant patients, for example, in which we know that EGFR antibodies don't work, great, we've got this unique population. If we had an EGFR antibody that suddenly had a 30 percent response rate, that would be meaningful; probably not enough to be approved, but it certainly would be meaningful. And I think down the road, in rare diseases, we're going to have to use these kinds of genetic markers to help us.

DR. WILSON: Dr. D'Agostino?

DR. D'AGOSTINO: The comment I was trying to make, I was going to make it earlier, I think it has been answered. But back to the 24 randomized trials that follow the single-arm, were the 24 on expanded populations or were they the same population?

DR. JOHNSON: Nine of the 24 had a randomized trial at a higher stage, lesser resistant. Think about it. You were talking about randomized trials and they couldn't do randomized trials in refractory patients. And if you can't do it initially, just think, after the FDA has given it accelerated approval, it's likely to be better than anything that's available, and then you're going to approach a patient and say, "How would you like to be randomized?"

DR. D'AGOSTINO: I think that's the dilemma that some of us are facing is that once you give accelerated approval, why would anybody go into a randomized trial. And so you have to do something to entice them, and one of the things is to broaden the population so you get a different group of individuals where it's not proven.

So it makes a lot of sense, but it does impact on what the single-arm trial looks like and then how you expand. It's not basically solely the same

population. When you present to the FDA, when you're designing, as Dr. Logan was saying, you have to worry about the fact that you're going to have a maybe single arm which you're working, but then you're going to go into a randomized on probably a broader population. So there are, obviously, lots of things to think about that are not necessarily typical in putting a randomized trial together.

DR. PAZDUR: But here, again, I think that's why the regulation clearly states that these trials should be underway at the time of approval. And here, again, you saw the AIDS paradigm, where the trials, two trials, large trials, are underway looking at a surrogate endpoint and then verifying clinical benefit in the identical trial here. So there's not this issue of let's start a new trial after the drug is approved.

DR. D'AGOSTINO: And it's not the issue with saying, well, the indication we're looking for in the single-arm is we can put a randomized trial together. Maybe you really can't, but then you can move to a broader population in the context of a research program.

DR. WILSON: Dr. Curt?

DR. CURT: If a sponsor goes to the agency and asks whether a single-arm trial will lead to approval, you'll be told it's a review issue, which is the right answer. But I would just like to add that I agree that in rare diseases or large areas of unmet medical need, there may be, in some cases, a need for a single-arm trial. I agree entirely with Dr. Pazdur that planning beyond that is a must.

But the one question I had for the agency is, in some way, do you think that your decisions were flawed in approving drugs with single-arm trials? Because most of them went on to randomized trials, and most of them went on to prove their worth. So is the message that we shouldn't be doing that or that you regret having approved 29 out of 49 by single-arm trials?

DR. PAZDUR: No. I don't think we want to go into that, that we have regrets about the approvals. We're looking at ways to improve the program here and not go backwards, so to speak, and learn from lessons, because here, again, remember, there are outliers here of 10 years of doing randomized trials and us finding out that the drug didn't work, and even one of these is a painful experience.

So, yes, and we've stated this repeatedly. We really believe this is a successful program, but we're interested in improving the program. And, yes, if one takes a look at the medians, it looks good, relatively, three years. Could that be improved? Yes. Do we want to avoid the outliers? You better believe we want to avoid the outliers. And how can we do that is by looking at how to optimize the program.

DR. WILSON: Dr. Sekeres?

DR. SEKERES: If you take kind of a broad look of this program and, again, fold into one of the things that has to be considered, is either the imperative or perceived imperative of getting a drug to patients, to say 90 percent of the time that the initial decision was proven in a well designed follow-up study, I think, is, frankly, a success for getting drugs to people who have a terrible disease, which is cancer.

I wanted to play off of something Dr. Loehrer said, also, focusing on the personalized medicine. I think as we start to define cancer on a progressively more molecular level, we're going to start to cut into smaller and smaller patient populations who then will claim to be a true rare disease and, therefore, would qualify for a single-arm study.

So maybe an approach to that would be if it's truly this astounding size effect and truly a rare disease, it might be appropriate to approve on a single-arm study; prior to that approval, negotiating a much bigger study that even could include patients with and without that molecular defined lesion and kind of have a long-term follow-up of those patients and a validation of the initial, while having a well designed study that could maybe identify other patient groups who could benefit from that drug.

DR. WILSON: Ms. Mayer?

MS. MAYER: I want to go back for a moment to Dr. Martino's eloquent, not crabby at all, statement and talk about the issue of patient benefit and how we look at that, particularly as advocates, or at least how some of us look at it.

It's not only about getting access at the earliest possible moment to the newest drugs. It's about making sure that the treatments that are approved make a really significant difference in the disease, and those are not necessarily the same things. And I think we've seen a number of instances where they are not the same.

So I'm really concerned that we don't get into the business of lowering the bar in the name of compassion, in the name of thinking that that is something that benefits patients, when there are many, many more other patients who will be diagnosed in the future or who don't have access to treatments early on, who actually may be harmed by an influx of drugs that have very, very minor effects. I think that sends a message to the industry at large that you don't have to work very hard to make a difference and to help us, and that's not a

message I, as an advocate, would ever want to send.

But getting to the question, I think single-arm trials should be really reserved for circumstances where there are so few patients and such an unusual -- I like the phrase that was used in the EMA presentation about exceptional circumstances. I think they should be reserved for exceptional circumstances. And I think it's possible to almost come up with an algorithm of the factors that might make those circumstances exceptional, and then require -- since we don't get now a way beyond comparing groups to require randomized trials pretty much across the board outside of those circumstances.

Not to be rigid about it, but, again, it's really important not to lower our standards and create a sort of de facto, low level route to approval, which we've had at least up to FDAAA, in place, because there has been no action taken to withdraw indications.

Anyway, that's my statement.

DR. WILSON: Thank you.

Dr. Balis?

DR. BALIS: I think other people have said this, but what's apparent is that this process of accelerated approval has an impact on the drug's subsequent development. And so just subtracting the time from accelerated approval to when it's finally approved may not be an accurate reflection of what would have happened if that had never occurred at the beginning.

Clearly, it can impede subsequent randomized trials, and if a drug has a very narrow spectrum of activity, it may actually prevent its final approval, if you can't accrue to those studies. And I think that's something that needs to be -- I don't know how you would measure it, but needs to be somehow evaluated in evaluating this program overall; in some way get at what impact it's having on the drug development process.

The other point I wanted to make in response to the issue about where our bar is currently set is that, at least from the perspective of somebody who is a pediatric oncologist, it is becoming more and more difficult to detect any drug effect in patients who have gone through standard therapies and second-line therapies, because we have so many drugs that are currently available.

So although the bar may seem lower, I think it's different now giving drugs to patients that have come off intensive front-line therapy and expecting to see an effective and new drug that may actually be quite active if it's given in a front-line setting. So I think we have to be careful not to also set the bar too high in some circumstances when you consider the population of patients that are being looked at in these initial studies.

So I guess the other point I wanted to make, actually, was I agree that these single-arm studies, because of the potential impact of these approvals, must be restricted to a very narrow clinical setting.

DR. WILSON: Dr. Mortimer?

DR. MORTIMER: I think inherent in doing a single-arm study is a presumption that there is good over doing nothing. And I just want to point out that there have been five randomized trials of best supportive care compared to therapy, largely in non-small cell lung cancer, where the best supportive care arm had a survival advantage.

So I think doing studies with best supportive care versus an investigational agent is a really good way of doing a study.

DR. WILSON: Dr. Lyman?

DR. LYMAN: I'm basically saying the same thing I think we're all saying, and that is randomized, controlled trials should be the default position for approval of any type, including accelerated approval, recognizing that there has to be some flexibility in terms of exceptions.

As Ms. Mayer said, I think we could come up with some very explicit criteria, including the rarity of the disease, the magnitude of treatment effect, some evidence of low toxicity or safety, and there are probably others. But I think if industry understands that it's only under those exceptional circumstances that they'd be able to come forward and expect accelerated approval, I think that helps them just in terms of the reality and what they're going to need to do in advance.

Also, as Dr. Balis said, I think we also could be doing some harm with more rapid approval based on limited evidence, because it clearly does impact on completing the definitive trials and the validation study. So I think we're not necessarily doing anybody any service by using single-arm studies when clearly randomized trials with some type of control can be done.

DR. WILSON: So maybe the agency could comment. I've sat on this committee through some drugs that were focused on regulatorily defined unmet medical needs, and they were single-arm trials. And I think that's another slippery slope, because sometimes these things are simply defined by what's been previously approved and may not really be the best thing from a clinical point of view.

But how do you view unmet medical needs that are the kind that fit within a regulatory definition based on what's been previously approved for that sector?

DR. PAZDUR: It's really kind of a -- what you're really getting at is the definition of available therapy, where there's no available therapy, and we have a guidance on available therapy.

Generally, it focuses on approved therapies and there's an asterisk with an exception for oncology drugs, and it said where there's standard oncology treatments. And that comes to a definition of kind of interpretation -- or interpretation rather than a strict definition.

In general, when we've tried to clarify that, it's been stated, "Well, the level in the literature, for example, should meet the criteria for drug approval or an NDA." So in other words, there should be multiple trials here.

So that is kind of the regulatory stance on what available therapy is. It doesn't necessarily have to be approved therapy, but the body of evidence in the literature, in the scientific literature, should meet some expectation where there are multiple trials that one could come into for approval of the drug; so it's not one trial that shows a 10 percent response rate.

DR. WILSON: Dr. Richardson?

DR. RICHARDSON: I was taken by Gary's comment on randomized trials being kind of the default position. And particularly when it comes down to the issue of best supportive care, the field has changed so much over the years, when you think back on the old 5-FU leucovorin studies in colon cancer, when the comparative arm was, in fact, observation, those things would be, I think, difficult to do in today's environment.

I honestly find myself in a real quandary trying to take care of some patients where best supportive care is one of the randomizations, and you're trying to discuss that with a patient who is desperate for some kind of treatment, trying to put that patient on that type of observation arm gets to be a pretty difficult discussion.

I can give you a good example of kind of a similar situation that we were presented with not long ago, a study that was offered to us looking at an investigational drug in patients who had failed in treatment of their prostate cancer and they had to have failed dosetaxel and prednisone, and the control arm, in fact, was continuing the prednisone. It's a difficult sell in that circumstance when you've got a patient who is looking for something other than what isn't working.

I wonder whether, in fact, we'll end up going back to the old Tom Fleming two-stage stopping rules, where ultimately you end up putting a group of patients on a particular study and, as you say, if you go 3 for 15, it's of interest. If you're 1 for 15, forget it. Maybe that's what we need to go back to.

DR. WILSON: Dr. Smith?

DR. SMITH: Speaking to the pediatric setting, the interpretation of single-arm studies is as problematic in that setting as it is in the adult setting, and so randomized trials should be the default in the pediatric setting, as well.

A couple of exceptions. The arsenic trioxide is the obvious one that you would think of as saying, obviously, you don't need to randomize when you have something as active as that.

There is one more in the pediatrics arena that I would call attention to, and that's brainstem glioma in the pediatric setting, where in the setting of a national clinical trials group, where there's recent historical experience, the opportunity for patient selection bias is minimal, because most patients will enroll in one of the national group studies; and where the outcome is so reproducibly poor over decades, that would be one case where I think the pediatric oncology community would put forward that a substantial treatment effect could be reliably detected in the absence of the single-arm trial. But there you do have a national group, and you've taken away much selection bias.

I think in terms of the pediatric setting, a couple of adaptations, and we do randomize trials all the time in the newly diagnosed setting with patient populations that are in the 200-300 nationwide per year, diagnosed per year. And so it's possible to do it with small numbers.

In the relapse setting, it gets even more challenging, though, as was discussed in the morning presentations. And there, I think adaptation, such as reducing the type one error in a randomized trial would -- you need to think about adaptations like that.

A challenge in the pediatric leukemia setting and the relapse setting, again, as discussed this morning, is patients are going to transplant, and so you have to factor in that that's going to happen, as well. And so how are you going to account for that.

There's a case where the intermediate endpoints may be useful to corroborate survival or progression-free survival endpoint after transplant. But something like minimal residual disease before transplant as a measure of treatment effect could help corroborate outcome after transplant and give more confidence that the treatment that was being investigated was appropriate. But, in general, randomized studies should be to the default in the pediatric setting, as well.

DR. LEWIS: Malcolm, I just wanted to follow-up on that, because we just heard about nelarabine and

clofarabine, and we've heard from the COGs that they don't feel they can do randomized studies in these third-line. And then, of course, some of them are following up as transplant.

I can't help but feel that this is kind of the way they do business as opposed to the fact that randomized studies couldn't be done in settings like that. It just seems like if they're not upfront in the pediatric setting, all of the eggs are really being held by the COGs, and FDA has to go along with whatever they say.

DR. SMITH: Right. And I think that makes another point I did want to make, is that in the pediatric setting, whatever plan goes forward, if it's going to be a randomized trial or even a large single-arm trial, it's going to really take most of the patients that are diagnosed over as a several year period. And so it needs to be with the full support of the pediatric research community and that community at the table from the get-go of discussing the research project.

I think large randomized trials with conventional levels of significance that night take five or six years in the relapse setting, I agree with the comments this morning that those may not be something that would be desirable from the pediatric community, but smaller trials, perhaps, again with reduced type I error that could be done more quickly, perhaps could be done.

Relapse trials have been done in solid tumors in the first relapse setting, like neuroblastoma and rabdomiosarcoma. So there is a history of being able to do it, but it does need to be with the input and buy-in of the pediatric research community, whether it's in the U.S. or Europe or elsewhere.

DR. WILSON: Dr. Mortimer?

DR. MORTIMER: I just wanted to address the comment about best supportive care. Best supportive care is not ignoring somebody or observing them. Best supportive care is providing the psychosocial support, controlling people's symptoms. It is not inactivity. There is activity associated with it, and perhaps this is why those patients live longer, because they have more peace, comfort, and so forth at home rather than being addressed and onslaughted with new agents.

So I think the best supportive care study really is a great option in the randomized trial.

DR. WILSON: Dr. Loehrer?

DR. LOEHRER: Actually, I have two questions. The first one is, are we going to go to question number 2?

[Laughter.]

DR. LOEHRER: But before we do, actually, just to echo what you're saying. I was thinking of a friend of mine who died of breast cancer years ago who needed to get on -- she felt she had to get a bone marrow transplant for her breast cancer, and finally got an attorney to sue to get this to happened. And I think we all felt it was ethical, in fact, morally responsible to get her treated with bone marrow transplant at the time, and, obviously, we were wrong on that.

The point that was brought up earlier about the difference between accelerated approval and provisional approval I think opens up a door that's not asked by all these questions. But when a drug has accelerated approval, it's now many times used off label for many other indications, and there's a lost opportunity to study drugs in a different way. And I brought up the capecitabine as one example. It may be dose and duration. And this expanded access I think gives us the opportunity to -- instead of opening it up for everyone with provisional approval, these are the studies that absolutely need to be done before it is just widely used.

The difference between the Children's Oncology Group and the adults is that 70 percent of their patients go on clinical trials and 95 percent of the adults don't. And if the drugs were limited to be available for these trials before it got full approval, then it might give us the opportunity to answer these questions and minimize some of the delays in terms of helping other people.

DR. WILSON: So I did want to tell Dr. Loehrer that there is a little rhyme and reason to this first question taking so long, because it really has direct application to 2 and 3. So the longer we spend on 1, the less you have to spend on 2 and 3. So don't despair.

Dr. Kelly?

DR. KELLY: I just want a clarification. In the EMA, do I understand it correctly they only prove, under accelerated approval, only new agents that have not been proved before?

DR. PAZDUR: For new molecular entities.

DR. KELLY: New molecular entities. In the 29 that were approved, how many were new molecular entities versus those that had prior approvals?

DR. PAZDUR: Mr. Number?

DR. MURGO: I do know that there are certain applications that have had multiple indications. So imatinib is one, had four or five; pemetrexed had a couple. So off the top of my head, I would say that the majority are new molecular entities, but there's certainly cases where there are multiple indications that we're counting as approvals in that 27 number.

Give me a moment. I actually have a spreadsheet, and I'll get you that in a second.

DR. WILSON: I also think that, as everything in science, this is going to be a moving target. I think as we do move into prospectively identifying targets, such as alc in lung cancer, that very small studies, one arm being alc positive, the other one being negative, they're not randomized but their molecularly directed studies can probably address some of these questions in a very rigorous way with a very small number of folks.

Rick, I wanted your thoughts on that, because I do think that we're going to see -- hopefully, we're going to see more therapies that really are hitting targets. And so the nature of these - they won't be randomized studies, but they'll be molecularly directed studies.

DR. PAZDUR: Here, again, I totally agree with you. I think you know everything is effect size, and it's much different when we're talking about a response rate, somebody coming in with a response rate of 15 percent versus somebody coming in with response rate of 60 percent in a refractory disease setting or a therapy that has marginal therapies available to it.

But it's very hard to recognize that early on in the drug development scheme. And here, again, what do we really get out of doing a 200-patient single-arm trial? Would it not be better very early on to start the randomized trial, looking at a big effect size, answering a survival question, because here, again, once you deem that as the drug in a particular disease, it's going to be very difficult to go back and do randomized studies. I'm not talking about large randomized studies; I'm talking about small studies with big effect size.

We've been -- I'll be quite honest with you -- been somewhat disappointed with some of these trials that have claimed big effect size or promoting themselves as very effective therapies, and then when the randomized trials were being done, they were looking at conventional improvements in overall survival of one or two months and be powered for such. You can't have your cake and eat it. So either you have an effective drug, and let's take a look at it and develop it appropriately.

DR. WILSON: Yes, Dr. Martino?

DR. MARTINO: Rick, it occurs to me that the one thing that I got out of the presentation from the European system is this concept of knowing that there is a very specific timeline when you are meeting with me again, and it's a year from now; not two or three years or when we get around to you. And I wonder if that alone doesn't give one the opportunity to evaluate these issues. And maybe that's' really the key here is to have that

DR. PAZDUR: I'm glad you brought that up, Silvana.

DR. MARTINO: I'm glad you're glad.

DR. PAZDUR: That's why we plan on having this meeting on a yearly basis and to go over these trials. There's nothing like the light of day that brings people to contrition, so to speak. And we've seen several sponsors come up to the table when we announce this meeting and say, "We really don't want to attend this meeting. We're going to consider withdrawing our drug."

DR. MURGO: So it's just 21 out of 27 are new molecular entities.

DR. WILSON: So anymore discussion on this? If you raise your hand, Dr. Loehrer is going to hit you.

[Laughter]

DR. WILSON: Kidding.

Anything more?

[No response.]

DR. WILSON: Okay. So let me just kind of give my own phrasing of this question, then I'd like to have you go around the room and give us in a very tight, short statement how you would view it.

I think the issue here, obviously, is that when should single-arm trials be considered to be acceptable for accelerated approval. We've already heard that 58 percent of accelerated approvals up to this point have been based on single-arm trials. And so the implication is that perhaps we would like to see this less.

The other side of it is that if we start to require randomized studies for approval, then it's going to also take longer to get the drugs to patients. And the accelerated approval was set up in order to be, as Dr. Pazdur said, patient-friendly, so there is a balancing act here.

So I don't know. Dr. Curt, do you want to start?

DR. CURT: Yes. I think the accelerated approval process has been a success, as well, and I think the evidence says that's been an equal success for the drugs that received accelerated approval with the single-arm trials versus randomized trials. But I would agree with the committee that single-arm trials are done at your own risk and should be done either in very rare diseases or areas of significant unmet medical need.

DR. MARTINO: I think a single-arm trial, for me, would be acceptable for accelerated --

DR. WILSON: Can I stop you? Can everyone say their name first and then -- sorry.

DR. MARTINO: Silvana Martino. I think that, for me, a single-arm trial would only be acceptable for

accelerated approval as an exception in circumstances where the patients are few and the activity of the drug is considerable. Unless both of those are met, for me, it would not be acceptable.

DR. RICHARDSON: Ron Richardson. I like Dr. Martino's comment. On the other hand, I think that one can make a strong case for approval of a single-arm study even in diseases that are very common, such as, say, non-small cell lung cancer, if you demonstrate activity above a certain threshold. And how high you set that threshold I think is going to depend on your patient population, the kinds of toxicities that these kinds of treatments entail, as well.

Looking at the issue, again, of randomized using the comparator arm, I think that remains a problem, and that also gets back to the patient population that you're looking at. If you're looking at patients with refractory disease, I would agree that -- in spite of my comments, I think there still is a role for best supportive care in that population.

DR. MORTIMER: Joanne Mortimer. I think the only indication I would have for a single-arm study is an agent that has incredibly high efficacy.

DR. LYMAN: Gary Lyman. I agree randomized trials should be the standard. The exception should be limited to rare disease situations, situations where the treatment effect is quite pronounced and/or the balance of risk and benefit clearly suggests a beneficial effect compared to risk. I think part of that is the durability of the response, so a strong treatment effect and evidence for quite a durable response. These might prompt a single-arm study for approval.

DR. D'AGOSTINO: Ralph D'Agostino. Given the discussion, there seems to be the real possibility in a lot of these situations of running a randomized trial, and I think that should be the first item on the table in terms of putting these together. There are situations, however, where a single-arm study might be necessary and certainly warranted, things like orphan drug situations, very rare conditions.

But I think in those situations when you're doing that, you have to ask the question, how do I interpret this single-arm study and how do I link that single-arm study to the confirmatory aspect later on where I'm dealing with a real clinical endpoint. So it's a big drug development program, I think, that has to be attached to a single-arm study. It also has to be attached even to a randomized trial, but in particular, the single-arm study, I think it just can't run by itself. You have to have it in this clinical drug development setting.

DR. LOGAN: Brent Logan. I share Dr. D'Agostino's concerns that it's crucial at the single-arm trial to be able to interpret the outcome that's being collected. So I think in many settings, that that is very difficult. So the default should often be a randomized trial, with certain exceptions that have been raised before, rare diseases, where there's substantial activity, as well as reasonable toxicity.

DR. FREEDMAN: Ralph Freedman. I guess there's less and less for me to say at this point. Clearly, there needs to be quality associated with those surrogate endpoints, and people can reasonably agree that a single-arm study is appropriate in that circumstance. But it's going to be unusual. And I think that the track record that you have over this period, obviously, the agency has been learning since accelerated reviews were introduced, and one would expect the number of single trials to reduce with time.

DR. SEKERES: Mikkael Sekeres. I echo what that side of the table has already said. There's a role for single-arm studies in extraordinarily rare populations where there is an extraordinarily large benefit, but only when it's been negotiated that the post-marketing study is going to enroll a much larger patient population, where there will be longer-term follow-up, and that that study be completed in a timely manner.

DR. WILSON: I think we all agree that randomized studies are the way to go. I have to say that I'm a little bit conflicted by this question, because I'm thinking why is accelerated approval there, and we've heard why. We then heard the data, and we've heard that the vast majority of single-arm trials have been approved, and they've been approved with randomized studies. And many of the single-arm studies didn't -- in some cases we've seen here, the activity wasn't that great.

So I'm not really sure of the issue. I'm not sure what the issue really is here. I myself share the concern that's been voiced here and that is that we are seeing many, many drugs with extremely marginal activity getting approved, because they prolonged survival six weeks. To me, that is a bigger issue than this.

One thing that does concern me about having the bar for single-arm trials too high and to be rigid about it is that you have small companies out there that may be developing very targeted therapies, that might have some very interesting activity, but if you start to say you need a randomized study, these drugs may simply die. And I don't know how you walk that line.

In no way would I want to open the gates or lower the bar to prevent drugs from moving forward, but at the same time, I think it's a very difficult call. And I think that one can say, yes, it's got to be a very small population. I think response rates need to be very high, but we're seeing single-arm trials

that our response rates aren't high, and they're being approved through randomized study that we don't see very much either. However, they're being approved because they prolong survival six weeks, or maybe in some cases haven't even been able to show any prolongation.

So I guess the longer you talk, the more it means you really aren't sure. But 58 percent sounds like a very high number, so I would say that they should probably shore it up.

DR. LOEHRER: Just as a point of order, there's no question mark on this statement whatsoever, so I'm not sure where the question is. So I, like the rest of you, will just ramble on.

[Laughter.]

DR. LOEHRER: So , again, obviously, we all believe in randomized trials, and I think one of the aspects of the importance of randomized trial is the safety part; how do you judge the standard care versus a new treatment. So there's the efficacy and whether or not you have a response rate, but the other one is how toxic is it and you need to have that comparison.

I do think it behooves the FDA to come up with, if they can, a better working diagram of a rare disease and what the number of patients should be that would fit this. My fear, again, dealing with a number of different rare diseases, is that industry will abandon rare diseases and not study them because it's not going to be fruitful.

So I think if one is transparent on this process, and whether it's 500 patients, a thousand patients, whatever it is, it would be helpful to have this generally as benchmarks for what we would really call a rare disease. And for those, I do think that we need to be sensitive to doing single-arm trials.

DR. KELLY: William Kelly. Again, I think that there is a role for single-arm trials, but it has to be part of a good, well thought out drug development plan. And I think that's what the agency is really saying, what is the whole overall plan for development here so it's continuous. I think that -- again, I agree with Pat -- it is that we have to define what rare populations are. You can redefine that in multiple ways, but I think that going forward we have to do that. But we also have to define what is a significant treatment effect. I can pick up the Wall Street Journal or New York Times and say brand new drug, fantastic results, and keep on reading; 12 percent response rate. You know? So I think that we have to be able to define what we really mean as significant treatment effect for these type trials. Thanks.

MS. MASON: Virginia Mason. I'm not sure I can add a lot to what's been said. But I do appreciate that the current system seems like it's -- we're moving even to be more dynamic and allow for flexibility, and I appreciate that, as a patient myself and representing the patient population. And I would hope that with this annual review, it will help us to move further and further toward looking at what really constitutes good evidence to move things forward. So I agree. I still think there's a role for some single-arm trials, but clearly a randomized larger trial has real benefit to giving us more information.

MS. MAYER: Musa Mayer. I think if what we're looking for is strong, durable responses, another way of approaching that, perhaps even with the agents that we've seen so far, is through doing the biomarker research to select the responders so that we have predictive biomarkers developed with therapeutic agents. That simple thing may change the dynamic in such a way that we may need fewer randomized trials. I don't know. That's a sort of unexplored territory, but at least a possibility.

In breast cancer, which I represent, we certainly have seen a strong effect of co-development of biomarkers and drugs, and I'd like to see that happen in all cancers, and see no reason why that couldn't happen if the will is there. And I think the will could be there if we provide the incentives and restrict single-arm trials to very exceptional situations.

DR. SMITH: Malcolm Smith. Moving forward in the pediatric setting, I think the standard should be randomized trials for accelerated approval, and that the response to modest response rates in a single-arm trial isn't accelerated approval, but further research to see how the agent fits into the overall treatment paradigm for that particular childhood cancer.

I think there does need to be some accommodations in terms of study design and study endpoints to take into account the smaller patient sample sizes that will be available in some of the pediatric settings. But with that flexibility, that would be the general gold standard.

Finally, that all of this would need to be done in the context of discussions with the pediatric research community to really make sure this is a priority and the thing that would best serve a particular patient population for which it's being considered.

DR. BALIS: Frank Balis. I think that what we're really talking about, in some sense here, is the level of evidence required for accelerated approval. And I think when we make that consideration, it needs to go, at this point, beyond just considering what demonstration of benefit to the patient there is.

For example, in addition to probably having a better idea about benefit from a randomized study, I think we can learn more about toxicity from a randomized

study. When we have a control arm to compare to, we have a much better idea of what the incidence and what are real side effects of a drug compared to what we get from a single agent study, where we're obliged to report anything serious that happens, related or unrelated.

Then the other thing I brought up earlier is the impact it's going to have on the development of the drug itself, and that is potentially a negative one. But on the other side, what effect does it have on people making the decision to approve a drug knowing that it just got accelerated approval. Is that somehow impacting on the decisions that are being made at the point in time that we are looking -- although we think we're objective, that we're looking at the definitive studies.

So I think there are a number of factors to be considered, and, because of that, I think we need to have, at this point, until we know more about this process, a pretty high bar for what we use to determine if a drug should have accelerated approval.

DR. WILSON: Thank you very much. So why don't we move on to the second question? ///