



Breast Cancer *Virtual Journal Club*SM

**Endocrine Therapy Plus Zoledronic Acid in
Premenopausal Breast Cancer: A New Paradigm**

**Live Question & Answer Session
with Michael Gnant, MD**

TELCON MODERATOR: Good day, everyone and welcome to today's **Virtual Journal ClubSM** question and answer session on the ABCSG-12 trial with Dr Michael Gnant. At this time, I would like to turn the call over to Dr Lee Lokey, with PRIME Oncology, for opening remarks. Please go ahead sir.

LEE LOKEY, MD: Good day to everyone and welcome. This will be PRIME Oncology's breast cancer **Virtual Journal ClubSM**. Today we will be conducting a question and answer session with Professor Michael Gnant, who is professor of surgery at the Medical University of Vienna, in Vienna, Austria. Dr Gnant, welcome to you.

MICHAEL GNANT, MD: Hello, thanks for having me on the program and hello to everybody.

LEE LOKEY, MD: Today we are going to focus on a *New England Journal of Medicine* manuscript, published on February 12, 2009, titled "Endocrine Therapy Plus Zoledronic Acid in Premenopausal Breast Cancer." Professor Gnant is the lead author of this manuscript, which is the publication of the results of the ABCSG-12 clinical trial conducted by the Austrian Breast Cancer Study Group Investigators. Professor Gnant, congratulations to you and the ABCSG-12 Investigators. This was a very well conducted trial with some very important implications for the management of early breast cancer. We have a series of questions that were submitted to us following the interview that you and I conducted about this manuscript. But before we tackle those questions, I would appreciate it if you would briefly describe the schema for the ABCSG-12 trial, the primary endpoint, and a brief conclusion of the results for our listeners.

MICHAEL GNANT, MD: Okay, I'll be happy to do so. ABCSG-12 is a trial of adjuvant treatment in patients with early breast cancer. As a matter of fact, the number of patients recruited to this trial was 1803 patients. They all suffered from premenopausal endocrine-responsive breast cancer. Meaning, in essence, that literally every single tumor in these patients was endocrine responsive, expressing either estrogen and/or progesterone receptor. There is not a single patient with unknown or negative receptor status in this trial, which I believe is important. These patients, in general, were from a low-risk and intermediate-risk breast cancer population with about 30% node-positive patients. After their local treatment including surgery (and radiotherapy where indicated), the patients received 3 years of endocrine adjuvant treatment based on ovarian function suppression using the luteinizing-hormone releasing hormone (LHRH) agonist goserelin. Then they were randomized to receive either tamoxifen or the aromatase inhibitor anastrozole, or either treatment plus the bisphosphonate zoledronic acid at the dose of 4 mg twice a year. The reason for this was, basically, two-fold. First, we have been concerned with what that endocrine intervention would do to the bone health of our patients and, second, that there was a number of preclinical reports and even suggestions from clinical trials that bisphosphonates may be able to prevent metastases.

These patients, as I said, were treated for 3 years and then followed up in a systematic way. The primary endpoint of the trial was disease-free survival. In the terms of this primary endpoint, with such a two-by-two factorial design, you can address two questions. First is: Is the aromatase inhibitor anastrozole better than

tamoxifen? Second is: Is the addition of zoledronic acid beneficial to the outcomes of our patients as compared to endocrine treatment without the bisphosphonate. And in terms of the main results, for the endocrine question, we did not find a difference; so we saw, more or less, superimposable the disease-free survival curves out to seven years. There is no appearance of a difference. More excitingly, actually, what we did find was that the treatment with zoledronic acid significantly improved disease-free survival, literally reducing the risk for relapse by about 36% in the primary endpoint. So, these are the main findings of the trial.

LEE LOKEY, MD: Thank you, Professor Gnant. Those are really very interesting and, I think, thought provoking results. Let's go to the first of our questions and I think this plays directly into the design of the trial. What was the reason for only 3 years of hormonal therapy in the ABCSG-12 trial? And this question is being asked in the context of a current trend to give longer duration endocrine therapy, generally speaking, at least 5 years. So why was 3 years chosen in this particular trial?

MICHAEL GNANT, MD: It is a very good question, indeed. Basically when you set up a trial what you usually like to do is you like to rely on the results of other trials. And since the trials started with ovarian function suppression, we need to view this in the context of the trial that were available in the year 1999, when we started our trial, where ovarian function suppression was used for short periods of time. Basically, for 6 months in the Scottish trial, for 2 years in the German trial, and we ourselves in the predecessor trial of ABCSG-12, which is ABCSG-5, for endocrine responsive premenopausal patients we used that modality for 3 years. And what we found in that trial was that the combination of goserelin for 3 years plus tamoxifen for 5 years was superior to CMF chemotherapy in these patients. These results have been published. So, basically, when we tried to, again, improve our results based on the ASCSG-5 results, we used goserelin plus tamoxifen as a comparator arm. However, we must not use aromatase inhibitors by themselves; so we would have had to limit the aromatase inhibitor to 3 years together with goserelin. And, eventually, we decided that we would also limit the duration of the tamoxifen for the same 3 years in order to have comparability of these treatments. Otherwise, we would have had a mess in terms of statistics; like adding tamoxifen after 3 years of anastrozole, which was and still is completely experimental, very creative but no data for any such approach. Hence, this is the reason why we ended up with a somewhat unusual 3 years of treatment duration. I have to say, however, that the 5 year duration we now usually use as a standard is poorly defined in terms of evidence available. We know just what tamoxifen did: 5 years is better than 2 years. We never tried that for aromatase inhibitors. We were just, basically, taking those 5 years that were defined by tamoxifen. There is a very recent trial, BIG 1-98, suggesting that maybe a shorter duration of aromatase inhibitor treatment may be good enough. While I absolutely agree that, particularly in postmenopausal patients in the low-risk end of the endocrine responsive population, we now view breast cancer as a chronic disease and we try to extend the treatment durations, particularly in our younger patients. That is a different situation. Endocrine intervention poses some problems for their quality of life. You have implications on well being, on sexual life, and other aspects including bone health. And I believe it is also of value, particularly in low-risk patients, to get out of our patients' lives again. With the overall survival we

observed in ABCSG-12, which is close to 98% at 4 years of follow up, in this population of young breast cancer patients, I believe it is very difficult to say that we need a longer duration of treatment in that particular patient subgroup.

LEE LOKEY, MD: I think that is an extremely important point, that despite the 3 year duration of therapy, both the disease-free survival and the overall survival were extremely good in this population of patients.

MICHAEL GNANT, MD: Yes, I mean this is obviously because the treatments are effective, but it is also because it is a careful selection of patients. When you select patients by biological properties of the tumors, particularly low-risk features and endocrine responsiveness, then, I believe, even in the absence of adjuvant chemotherapy, this is a very good result and this is how you can achieve it. It is by patient selection rather than by treating everybody with the same regimen.

LEE LOKEY, MD: Alright. Let's take a second question. Why do you think ovarian function suppression plus anastrozole was not superior to ovarian function suppression plus tamoxifen? Obviously, in the postmenopausal group of patients, we have seen improved results with use of the aromatase inhibitors. But in this patient population we did not see that. What is your postulate about why that was the case?

MICHAEL GNANT, MD: I believe that the reason for this is that there is a significant difference between postmenopausal and premenopausal patients in terms of what we achieve with our endocrine intervention. Aromatase inhibitors that, as you have correctly stated, have been proven to be superior to tamoxifen in postmenopausal setting, act indirectly—blocking the enzyme aromatase—and by doing so they reduce the peripheral estradiol level. When you compare the peripheral estradiol levels of tamoxifen patients in postmenopause, the level may be around, let's say 15 to 25 picograms per milliliter. When you use an aromatase inhibitor, you basically bring that down to 5 picograms per milliliter or even sometimes below detectable limits; meaning that you really make a difference, in terms of peripheral estradiol, when you use an aromatase inhibitor in an elderly patient.

In a young patient with functioning ovaries, basically, you start out with peripheral estradiol levels of let us say 500 picograms and then you use ovarian function suppression as a basic treatment, which will bring that down to about 25 picograms; meaning that you now have already reduced the peripherally available estradiol by about 95%. When you now add tamoxifen, you will bring that down by about 97%, and with the aromatase inhibitor, relatively speaking, you will bring it down by 98%. That will make just about a 1% difference as compared to the baseline endocrinology of these patients. I believe that is the most likely explanation for why we did not observe a difference between tamoxifen and anastrozole. There are other results, however, demonstrating that, obviously, when you use an aromatase inhibitor in premenopausal women, you may have a differential situation on androgen receptors. The ovaries, while being reduced in their function, they are hopefully only sleeping but not absent. So that means that we could activate some of those androgenic mechanisms, by doing so inducing a part of the rebound. I believe that there will be, probably alongside ongoing trials of endocrine treatment in premenopausal patients, some very interesting research questions to be asked in

doing serial measurements of these hormones.

LEE LOKEY, MD: That is a very clear and clinically rational explanation. Thanks for that. Let's move to another question. But first let me ask if there are any questions from participants on the call.

TELCON MODERATOR: Thank you. If you do have a question at this time please press star one on your touch tone phone. A voice prompt on your phone line will indicate when your line is open. Please state your name before posing your question. Once again, that is star one if you have a question. We will take our first question.

GILL: This is Gilbert from Montreal, Canada. This is kind of a technical question regarding how DFS [disease-free survival] and RFS [relapse-free survival] were defined because in the article, your disease-free survival included the local recurrence, the contralateral breast cancer, the distant metastases, the secondary carcinoma, and death. The only difference with RFS is that you did not take into account death. But when we are looking at the number of events between DFS and RFS there is only one unit difference in terms of events. But when we are looking at overall survival there was 16 deaths in the group of patients who got zoledronic acid and 26 in the group of patients who did not get zoledronic acid; a difference of 10 patients. But when I'm looking at the numbers between the DFS and RFS it is only one unit difference. I was wondering how we got to these numbers or if the data were censored at some point. I was wondering if you could give me an explanation on this?

MICHAEL GNANT, MD: Yeah, thank you very much for reading the paper very thoroughly. It is a good observation, Obviously, DFS and RFS in young population of breast cancer patients will be more or less identical, because the only difference is death from other causes.

GILL: Right.

MICHAEL GNANT, MD: And while in an elderly patient population, let's say aged 70 years plus, like we see in the ATAC or the BIG 1-98 trial, you will have 80% to 85% of all occurring deaths being deaths from other causes because the patients die from cardiovascular and other diseases. In a population like we started with, where a median age is between 44 and 45 years, a non-breast cancer death is actually a very rare occurrence. We lost a patient, this is the single patient you actually counted, by traffic accident, for example. So this is the only difference in there. Therefore, I believe there is not too much sense in differentiating DFS and RFS in that trial. The exact definitions are given in the paper. I am aware of the fact that we have different definitions of these outcome parameters in many of the trials, which is unfortunate. Remember the trial started in year 1999 when basically all the different research networks had their own definitions that had been used for centuries. There are very plausible efforts to harmonize these and I was part of the initiative lead by Cliff Hudis. Last year we published in the *Journal of Clinical Oncology* a proposal on how we would use those individual event categories in the future to allow comparability between trials. So this trial is from another era, so it is not perfect; but the exact technical definitions as they were defined by the

perspective protocol are given in the paper.

GILL: Okay, well thanks a lot for that clarification.

LEE LOKEY, MD: Thank you Michael for that. Is there another question from a participant?

TELCON MODERATOR: There are no other questions at this time.

LEE LOKEY, MD: Alright, thank you. So, Michael, let us take a second question, which was emailed to us...and that is: What was the rationale to modify the interval for zoledronic acid administration from every 4 weeks to every 6 months?

MICHAEL GNANT, MD: Basically the reason for this, as it was correctly observed by whoever asked the question, is that the trial started per protocol; in the initial protocol we wanted to use 8 mg of zoledronic acid every 4 weeks, which is kind of a huge dose that has never been used in a prospective clinical trial. The reason for this being, that at that time—at the end of year 1999 and the beginning of 2000—there were reports about safety problems when you use intravenous bisphosphonates at larger doses. There are reports about myeloma patients suffering from renal failure after repeated administration of that [dosage of bisphosphonate]. And at that time all the trials anywhere in the world—whether in osteoporosis or in oncology—were basically forced or had to, based on that information (there were even some deaths from renal failure), reduce their zoledronic acid dose. Personally, I was fighting against that reduction because I did believe at that time (and I was wrong, fortunately) that we would see an antitumor effect only when we really went to the maximum dose. And I was not so much concerned about renal safety because, again, our trial population is a population of young patients. These breast cancer patients are usually otherwise healthy and when you monitor their renal function, which we did, you can see that this is not a problem. But still, from a regulatory and, probably, ethical point of view, it was impossible at the time to maintain the original dose. So that means after, I believe it was, 93 patients in the trial, we had to reduce the dosage and to amend the trial's schema; from that point on the 4 mg twice yearly was used for the remaining 1700 patients. Obviously, what we did is we did particularly look at those patients who received higher doses. Actually, I personally treated one of the first patients in the trial and she did receive up to 100 mg and she is doing fine. There were neither renal problems nor any dental problems or other issues. We also tried to have a look whether these patients would fare differently in terms of the outcome. However, it is a limited number and we are unable to say that would make a difference. So, I would have to say that I'm quite happy with the 4 mg twice yearly because as we now know from more than 4000 patients from prospective randomized trials, that is a perfectly safe dose. You will not observe more than extremely rare occurrences of dental problems, so the outcome was kind of good. But, initially, it was just a safety concern rather than a scientific rationale.

LEE LOKEY, MD: Okay, understand. And that is reassuring to know that the every 6 month dose was not only safe but effective. Let's turn to the issue of the risk category of patients who were included in this trial. We have a question indicating that only patients who did not get postoperative adjuvant chemotherapy were eligible for the trial. There were a small number who received neoadjuvant chemotherapy but no postoperative chemotherapy. So what does this mean? What does this imply, in your mind, for patients who are at higher risk of recurrence at diagnosis and who would be deemed to need chemotherapy in addition to endocrine therapy? In other words, can these results be applied in some way to that higher risk group?

MICHAEL GNANT, MD: I believe we need to be really cautious with extrapolating results from clinical trials from one patient group to the next patient group. As we saw in ABCSG-12, you cannot just easily translate the postmenopausal aromatase inhibitor benefit to younger patients. And so, likewise, I would personally prefer to stay on the cautious side with extrapolating the exciting zoledronic acid benefits to other patient subgroups that were studied.

I should say, however, that there were a number of patients, in fact it is about 30% of patients, with node-positive disease—most of them not really high risk because, even in Austria where we have a very good endocrine treatment tradition, high-risk patients obviously would receive adjuvant chemotherapy. But what we do is that if there are just one or maybe two involved nodes and the patient has an absence of any risk factors like vascular invasion or HER2/*neu* overexpression and perfect endocrine responsiveness, we would still go ahead and, if the patient decides so, we would treat her without adjuvant chemotherapy. And I realize that even in environments where for young patients, more or less, everybody was offered chemotherapy, this is now changing because we are learning that the biology of the disease may be more important than just the numerical age.

I should also say, probably, that we will need to be patient only for several months because there is a large trial, the AZURE trial, that has finalized recruitment and will probably report, I hope, by the end of the year. The AZURE trial recruited 3300 patients, all of them in stage II or III—so all of them node-positive—and all of these patients did receive adjuvant chemotherapy plus/minus zoledronic acid. So we are going to know pretty soon whether the zoledronic acid benefit is also present in the high-risk breast cancer population.

LEE LOKEY, MD: Excellent, we look forward to that AZURE publication or presentation. I would like to ask you, Professor Gnant, about the number-needed-to-treat analysis. This was reported in the manuscript for zoledronic acid and it was compared to other commonly used adjuvant therapy agents. Would you comment on this and what significance you found from that number needed to treat.

MICHAEL GNANT, MD: Yes, with pleasure. I believe that what we learn from health economists, basically, is that it is valuable information in order to somehow assess the relevance of a scientific finding to general clinical practice. Because, it may be easy to find the significant results somewhere, but you have to put that into the context of what everybody needs to do in his or her clinic or office setting every

given day. I believe that numbers needed to treat is a valuable addition in that assessment. And, in fact, that figure for the adjuvant zoledronic acid is 31—meaning that you need to treat 31 patients with these 7 infusions in order to prevent one disease relapse. And this is, in oncology, in fact very good because we have some standard treatments which have much higher numbers needed to treat. And just for comparability, to put that into perspective for our colleagues who may not be so familiar with that calculation, we just compared that to what figures have been reported for the use of taxanes, which are considered standard of cytostatic chemotherapy in breast cancer nowadays, and they are absolutely comparable. Obviously, taxanes do bear a different side effect profile than that low intensity intervention like we have with the bisphosphonate. So I believe it kind of puts the result into the perspective of how valuable the addition of that treatment modality could be in the future.

LEE LOKEY, MD: So that is really a clinically very relevant analysis.

MICHAEL GNANT, MD: I would believe so and because the way to put it in that perspective came from health economy. And I can even add another figure, I have recently been invited to be a co-author on a health economy abstract that is going to be reported in a couple of weeks. And I believe I can say that what these colleagues found that the cost for equality adjusted life-year, which is a health economy variable, for treatment with zoledronic acid and the way it was used in ABCSG-12 is about 2600 euros, which is around 3000 US dollars. This is for quality adjusted life-year, relatively inexpensive figure when you compare it to some of our efficient, but also sometimes very expensive, treatment interventions including antibodies and tyrosine kinase inhibitors in oncology.

LEE LOKEY, MD: Thanks for that explanation. Do we have any questions from our listeners?

TELCON MODERATOR: Once again, it is star one if you do have a question at this time. And no questions at this time.

LEE LOKEY, MD: Alright. So, Professor Gnant, I'm now going to ask you a couple of difficult questions, where you need, perhaps, to give your opinion and where there might not necessarily be data. So in this trial, there was a statistically significant improvement in disease-free survival associated with zoledronic acid administration. Do you anticipate that that benefit will become an overall survival advantage with longer follow up?

MICHAEL GNANT, MD: As you said, it is difficult and I have now, in my now aging history for clinical trials in oncology, become more and more cautious in judging future results. But, obviously, the numbers are small and this may be the reason why the overall survival is currently not reaching statistical significance. When you calculate it, it's a risk reduction of 40%, which is quite significant, and if we have just 50% more deaths on the trial then it would reach statistical significance. Obviously, as a physician I am glad that we did observe so few of dead patients in this trial so far. But I'm afraid this will change with further follow up. What we also see is that when you look at this disease-free survival curves they start separating at the very

beginning and they actually keep separating long after the cessation of treatment. So, we have depicted the curves in the manuscript out to 7 years—the median follow up is now 4 years and the treatment duration is 3 years—and a very brief visual check gives you the clear-cut impression that these survival curves keep diverging. So, I would, yes I would evidently expect that we are going to see a difference in overall survival.

LEE LOKEY, MD: And could you comment on when the next planned analysis is scheduled.

MICHAEL GNANT, MD: Yes, the statistic analysis plan of the trial basically called for the final analysis of 124 events. That analysis eventually was done at 137 because always you “hit the trigger” and more events are coming in while you clear the data. I believe that we obviously have several very interesting questions to discuss in the scientific future of this trial, particularly with respect to certain subgroups and that will require about twice the number of events. I would expect that the next reasonable point in time, and we have done some calculations together with our independent data monitoring committee, may occur in the year 2010, probably in the second half of next year.

LEE LOKEY, MD: Very good, we look forward to that report. I have one final question and that is, for premenopausal patients who meet the eligibility criteria of the ABCSG-12 trial, would you currently offer those patients adjuvant zoledronic acid outside the context of a clinical trial?

MICHAEL GNANT, MD: Within that patient subgroup you described, patients who actually fit into that population, I am recommending this treatment and that is what I actually do in my personal practice. Obviously, there is no label yet, there may be a label in the future but this treatment has not been approved for that indication in the present time...so patients need to be informed about that. I am in a fortunate situation where our healthcare environment will give permission to do an off-label use of such a drug, particularly in the presence of strong scientific data, which I believe we have provided. There is initial confirmation from other trials coming in from other settings; so this is good enough for me to actually offer this treatment to my patients, when they fall into those particular inclusion-exclusion criteria. I have to say, I do get more requests from other patients from other subgroups, either treated with other treatments or late Intervention or other age groups, and I am still very cautious, as I said, in terms of extrapolating to other treatment settings. I believe we should, as physicians, try to base our recommendations in counseling patients on actual scientific data and this is what I try to do in my own practice.

LEE LOKEY, MD: Well, that is very helpful and very practical advice. Professor Gnant, I'd like to thank you very much for your time today and once again to congratulate you and the ABCSG investigators for an outstanding clinical trial and a very interesting manuscript. We look forward to working with you again in the near future.

MICHAEL GNANT, MD: Thank you very much. Good day to everybody.

LEE LOKEY, MD: Thank you.

TELCON MODERATOR: Thank you everyone.