Podcast ESMO 2011: The Tamoxifen-Exemestane Adjuvant Multinational (TEAM) Phase III Breast Cancer Trial Results

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Prof C Markopoulos

EJCMO.TV: The Tamoxifen-Exemestane Adjuvant Multinational or TEAM phase III trial was conducted in hospitals in nine countries. Postmenopausal women with hormone-receptor positive breast cancer were randomly assigned. The primary endpoint was disease-free survival at 5 years. Professor Christos Markopoulos is director of the Breast Unit, Athens University Medical School. His work includes more than 100 scientific papers published in international medical journals. He is

also credited as scientific speaker, editor, and author. Since 2000, he is president of the Hellenic Breast Surgical Society.

Professor Markopoulos, hello and a very warm welcome to EJCMO.tv. Thank you for taking the time to speak to us today.

PROFESSOR MARKOPOULOS: Hello, thank you for inviting.

EJCMO.TV: You are very welcome. Professor Markopoulos, I will start with your proffered paper session at ESMO recently. Your presentation focused on the results of the TEAM study, the randomized phase III trial. In the context of age-specific competing mortality in breast cancer patients, first, could you tell our listeners about the TEAM study?

PROFESSOR MARKOPOULOS: As you said earlier, the tamoxifen and exemestane adjuvant multinational, the TEAM trial is a phase III trial conducted in eight European countries and in the United States of America. We had a number of almost 10,000 postmenopausal patients with early-stage breast cancer, and they all had histologically confirmed invasive hormone-receptor positive tumors. The patients were randomized, one-to-one to receive either exemestane 25 mg once daily for 5 years or tamoxifen 20 mg once daily for 2.5–3 years, followed by exemestane again for 2–2.5 years for a total of 5 years of adjuvant hormonal therapy.

EJCMO.TV: How was the TEAM study originally designed?

PROFESSOR MARKOPOULOS: Originally, TEAM was designed to compare exemestane with tamoxifen, 5 years as initial treatment, and the primary endpoint was disease-free survival and that was, as we say, in the upfront strategy comparing an aromatase inhibitor exemestane to tamoxifen.

EJCMO.TV: The design of the TEAM study was modified significantly in 2004. Could you please explain to our listeners why this was modified?

PROFESSOR MARKOPOULOS: Yes, this is right. In 2004, we had the results of the IES study. In this study, patients who had received tamoxifen for almost 2–2.5 years and were free of any recurrence were switched to exemestane for a total of 5 years of hormonal treatment.

At the 56 month follow-up, the IES trial showed a superiority and efficacy in favor of the switched strategy. Therefore, what we thought that is was already proven that the switched strategy is better than tamoxifen. So, it was more important to compare the 5 years of initial treatment with exemestane to the switched strategy, and by 2004, no patient had reached that endpoint; then we had the opportunity to amend the protocol and thus TEAM trial became a sequential trial comparing 5 years of exemestane to 5 years of tamoxifen switch to exemestane about 2.5–3.0 years. By saying sequential trial, I mean that the randomization was done at the very beginning, not like in the IES, which was a switched trial.

EJCMO.TV: Right. What were the actual findings of the TEAM study itself?

PROFESSOR MARKOPOULOS: Well, the final results that was published recently in Lancet showed that there were no significant differences in efficacy endpoints between 5 years of exemestane alone versus the sequence of tamoxifen followed by exemestane. That was the intent-to-analysis at 5 years. The median follow-up was 5.1 years, and also we must notice that more than 60% of patients had completed at least 5 years of follow-up. Disease-free survival as well as overall survival was not statistically significant between the two arms and, therefore, we concluded that exemestane alone and tamoxifen switch to exemestane are both appropriate treatment options for postmenopausal women with hormone-receptor positive early breast cancer.

EJCMO.TV: What made you analyze age-specific competing mortality in breast cancer patients?

PROFESSOR MARKOPOULOS: Well, there are a lot of reasons. First of all, we should mention that breast cancer incidence, as we all know, increases with increasing age, and we also know that the number of elderly women who are diagnosed with breast cancer is increasing due to change in demographics and also continuously increasing life expectancy. So, elderly women with breast cancer are a very important population. At the same time, we know that elderly women with breast cancer have lower odds of receiving standard care, and we know this from a number of observational studies. We also know that elderly patients are not included in clinical trials. So, we do not have a lot of data about them and they are very rarely included in guidelines.

Now, going back to the TEAM trial we noticed that the vast majority of women with early breast cancer in the TEAM survive breast cancer but had an increased risk of dying from other unrelated causes and that was strongly related to aging and because we had exactly no difference between the two treatment arms and also we did not have any difference between the number of deaths between the two arms. Therefore, we had the opportunity to analyze the causes of deaths and also to explore the competing risk of deaths and the disease-specific death in the TEAM trial population.

EJCMO.TV: Were there any other specific parameters that you explored in this analysis?

PROFESSOR MARKOPOULOS: We also explored the possibility of recurrences, but the main aim of this analysis was the competing risk, just as I have said or in other words, the risk of death from another cause that is not related to breast cancer or therapy for breast cancer and of course to see what happens, and this is the most important thing; what happens to these elderly women who do not die from co-morbidities or other causes; do they go well with breast cancer with adjuvants or not?

EJCMO.TV: What were the findings of the analysis presented at ESMO this year?

PROFESSOR MARKOPOULOS: There are very interesting findings because we saw that regardless of a high-risk of mortality from other causes and independently of tumor in patient characteristics. Disease-specific mortality increases with aging in women with breast cancer; that means, although the risk of dying from causes other than breast cancer is much higher in elderly patients. The risk of dying from breast cancer also increases with age and this probably means something.

EJCMO.TV: How do you explain these results?

PROFESSOR MARKOPOULOS: In order to avoid bias of a lot of factors, we did multivariable analysis and included a number of factors that could alter our results, but we did not find any difference or any alterations of the results. Factors included were tumor size, biological factors, and also including the first year adherence to therapy.

The only difference we found is that first, radiotherapy is administered less frequently in elderly patients and the most important was in relation to chemotherapy. From histological data, we know that about 50% of the whole population in the TEAM trial are lymph node positive, and we found that only 5% of women at the age of 75 or older received chemotherapy compared to about 50% younger women, 65 years old or younger; that means that probably this kind of undertreatment of elderly women is the main cause underlying these results. Of course, we could not exclude reasons like decreased immune system response in the elderly and, of course, we could not address these questions in this trial but our findings are supporting undertreatment behind the results.

EJCMO.TV: What do you think is the likely significance of your findings on clinical practice?

PROFESSOR MARKOPOULOS: In clinical practice, our data underlie the need for individualized treatment of elderly breast cancer patients, of course taking into account the biological age and life expectancy, in order to improve breast cancer outcome in all age groups. We must think about elderly women who are not suffering from other conditions or survive other conditions and to those women we should give the best treatment so that they will do well with breast cancer.

EJCMO.TV: In light of this clinically important combination of greater effectiveness and fewer side effects, as stated by the study findings; do you have any specific clinical recommendations that you would put forward?

PROFESSOR MARKOPOULOS: Generally speaking, I would say that when we come across an old lady with breast cancer, we should not forget that elderly patients deserve adequate treatment similar to younger patients. That means that old treatment modalities, such as surgery, radiotherapy, hormonal therapy and chemotherapy, should be used according to international guidelines. Treatment decisions should be based on risk of recurrence in terms of local and systemic recurrence. On biological age, in terms of co-morbidities and on life expectancy in

terms of age of the patient in relation to co-morbidities as well. So, taking all the above into consideration, we should decide the optimal treatment for our patient.

EJCMO.TV: Excellent. Professor Markopoulos, thank you so much for taking the time to address some of these very important developments today. We do hope to continue to follow the TEAM trial further and certainly hope to invite you back very soon with more news and developments. Thank you so much.

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