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Advances in Early-Stage Breast Cancer Treatment: A Recap of the NATALEE Trial

Dr. Chalasani:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani, and joining me today to talk about the NATALEE trial is Dr. Nicholas McAndrew, who is an Assistant Professor in the Division of Hematology and Oncology at the UCLA David Geffen School of Medicine in California.

Dr. McAndrew, thanks for being here.

Dr. McAndrew:
Thanks so much for having me today.

Dr. Chalasani:
All of us are aware of the data of CDK4/6 inhibitors, which showed improvement in progression-free survival, and a couple of them did also show benefit in overall survival. And we have been anxiously waiting to have some data in early-stage breast cancer. Obviously, we did have some initial data and FDA approval for abemaciclib, but we are excited to get data from the second CDK4/6 inhibitors.

So with that background, Dr. McAndrew, can you kind of give us the rationale and the study background for the NATALEE trial?

Dr. McAndrew:
Yeah, absolutely. So in terms of the rationale, we have seen from the metastatic trials of ribociclib, which were the MONALEESA-2, 3, and 7 trials which were in a combination of first-line and second-line metastatic, ER-positive, HER2-negative breast cancer in the postmenopausal and in the premenopausal setting as well. And as you noted, we did see those studies showing improvement in progression-free survival as did many of the other studies with the other CDK 4/6 inhibitors: palbociclib and abemaciclib. The PALACE clinical trial and PENELOPE-B as well had initially reported as showing no improvement in invasive disease-free survival benefit for adding palbociclib in the early-stage setting.

I think that further underscored the need to really identify which settings these drugs were most beneficial in trying to further define and clarify exactly the role for each of these drugs as it sort of became increasingly clear that maybe they were different drugs with different degrees of efficacy and effect on cancer cells. And so the design of the NATALEE clinical trial was such that patients with high-risk estrogen receptor-positive, HER2-negative breast cancer, anatomic stage II and III were randomized to receive either a nonsteroidal aromatase inhibitor, such as anastrozole or letrozole, and in men and in premenopausal women, they also received goserelin for five years, and so all patients received that backbone of endocrine therapy and the investigational arm also received ribociclib as well.

Dr. Chalasani:
Can you expand on the design of the study for NATALEE and highlight some of the key differences from monarchE and the palbociclib studies?

Dr. McAndrew:
Sure. So in terms of the key differences between the NATALEE trial and the other two larger studies of CDK4/6 inhibitors—the PALACE study being the study of adjuvant palbociclib and the monarchE study being adjuvant abemaciclib—the key differences I would say would be in both dose of the drug as well as duration of administration of the drugs. So the way that we think CDK 4/6 inhibitors help eradicate cancer or help kill estrogen receptor-positive breast cancer cells is by driving them into senescence, so by inhibiting the cell cycle in transition from the G_1 to S phase enough so that the cancer cell goes into cell cycle arrest and senescence. Because that's the way we believe that it works, the design of the NATALEE trial actually was slightly different in that we had administered the drug for

three years rather than two years, but in order to try and improve the tolerability of adding a drug for three years, the starting dose was slightly lower at 400 mg. We had seen lots of data in the metastatic setting showing that when patients had to dose reduce and oftentimes did dose reduce to 400 mg, there was no tradeoff in terms of efficacy, and so that seemed to be still a very effective dose of the drug. So the 400 mg, 21 days on 7 days off dose was chosen for administration for three years rather than two years, as was the case in the PALACE and the monarchE trials. And in those studies, the dose was given at a full dose, and full dose being the same dose that was approved in the metastatic setting.

Dr. Chalasani:
So can you tell us the primary endpoints of the study?

Dr. McAndrew:
Sure. So the primary endpoint of the NATALEE trial was invasive disease-free survival using the standardized DEEP criteria. There were a few secondary endpoints as well, including recurrence-free survival, distant disease-free survival, overall survival as well as patient-reported outcomes, safety and tolerability, as well as PK data. And there were a few exploratory endpoints as well, including local regional recurrence-free survival and also correlative biomarker studies including gene expression and alterations in circulating tumor DNA and RNA samples as well.

Dr. Chalasani:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani, and today I'm speaking with our guest Dr. Nicholas McAndrew about the NATALEE trial.

So, Dr. McAndrew, now that we know about the study and we covered the background and what the primary endpoints were, let's focus on the results. So what can you tell us about the key findings?

Dr. McAndrew:
Sure. So in terms of patient enrollment in the trial, about 60 percent of patients with stage III disease and 40 percent of patients with stage II disease were enrolled. About 56 percent were postmenopausal women, with 44 percent being men and premenopausal women. There were a total of 5,101 patients who were enrolled, and about 70 percent of them had been on prior endocrine therapy for up to a year prior to enrollment in the study, which was allowed per protocol.

So the study did meet its primary endpoint of improved invasive disease-free survival in patients on the ribociclib and nonsteroidal aromatase inhibitor arm with a three-year invasive disease-free survival rate of 90.4 percent at the time of the ASCO reporting in the first interim analysis, which was absolutely 3.3 percent improved over the nonsteroidal aromatase inhibitor-alone arm at 87.1 percent. There was slightly over a 3 percent improvement in invasive disease-free survival at the time of analysis, and that was associated with a hazard ratio of .748 with a significant P value of .0014, which did exceed the alpha level that the study was powered based on.

Dr. Chalasani:
Exciting to know that there are positive studies coming, which could make a clinical impact for our patients. So if we look ahead, what do you think is next for the results of this trial and where we go from here?

Dr. McAndrew:
Yeah. So I agree. It's very exciting. I mean, when you look at the relative reduction in risk of invasive disease, there's a 25 percent reduced risk of invasive disease by adding ribociclib to standard endocrine therapy. I think we have to continue to watch these patients as they continue on the study because at the time of reporting, almost 80 percent of patients on the ribociclib arm were still on treatment. They were still receiving therapy, so this is early, so we'll have to continue to follow it. But it's also exciting that we're seeing benefit early on in patients where although they were high-risk patients, stage II and stage III, we know that this is a population where many of the recurrences may not be early, as is the biology of ER-positive breast cancer. So I think that we do need to continue to watch this population.

Dr. Chalasani:
Completely agree. Considering the positive results ribociclib has had overall in patients with hormone receptor-positive HER2-negative metastatic breast cancer, we are hopeful and looking forward to more results from the NATALEE study and how this might be a potential treatment option for early-stage breast cancer.

And as that brings us to the end of today's program, I want to thank my guest, Dr. Nicholas McAndrew, for joining me today to help break down the data from the NATALEE trial.

Dr. McAndrew, it was a pleasure speaking with you.

Dr. McAndrew:

Thanks so much for having me today.

Dr. Chalasani:
I'm Dr. Pavani Chalasani. To access this and other episodes in our series, visit ReachMD.com/ProjectOncology where you can Be Part of the Knowledge. Thanks for listening.