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Treating NSCLC with Durvalumab, Chemotherapy, and Novel Agents: Preliminary Results

Announcer:
You're listening to *On the Frontlines of Non-Small Cell Lung Cancer* on ReachMD. And now, here's your host, Dr. Charles Turck.

Dr. Turck:
This is *On the Frontlines of Non-Small Cell Lung Cancer* on ReachMD. I'm Dr. Charles Turck, and today I'm joined by Dr. Thomas Egenod to discuss the efficacy and safety results of the Phase 2 trial NeoCOAST-2, which was presented at the 2024 World Conference on Lung Cancer. In addition to being a study investigator on NeoCOAST-2, Dr. Egenod is a pulmonologist in the Department of Thoracic Oncology at Limoge University Hospital in France. Dr. Egenod, welcome to the program.

Dr. Egenod:
Thank you for this kind introduction, Dr. Turck. My pleasure to be with you.

Dr. Turck:
Well, to start us off, how does NeoCOAST-2 build upon previous clinical trials studying resectable non-small cell lung cancer?

Dr. Egenod:
We need to consider the context. The gradual implementation of lung cancer screening over the past 15 years allows us to diagnose more and more lung cancer at an early stage. We know that these stages have a better prognosis, but before the era of the IO, recurrences remained too frequent. With the benefit of adjuvant chemotherapy, overall survival is estimated at 5 percent at 10 years. There was therefore an unmet need. But now, with the era of immunotherapy, we know that neoadjuvant platinum-based chemo with IO, associated or not with adjuvant IO for 1 year, prolongs event-free survival and will increase PCR rate, which is very important in patients with resectable nonvascular cancer compared to chemo alone. We also know in other settings that the combination of IOs can improve patient outcome when compared to IO alone. Nevertheless, this combination of chemo and multiple IOs have not been evaluated yet in perioperative settings.

Dr. Turck:
And would you expand further on why you studied this particular combination of treatment?

Dr. Egenod:
So as I said, this is a combination of IO. There is durvalumab. Durvalumab is a treatment that everybody knows. It helps the body's immune system by binding to PD-L1. Following the results of the AGEAN trial, we can say that the administration of chemotherapy associated with durvalumab is preoperatively followed by treatment with durvalumab for 1 year. In the adjuvant situation, this can improve the PFS and increase the rate of major pathological response in these patients, especially in patients suffering from Stage 2 to Stage 3 non-small cell lung cancer.

Oleclumab binds to protein in cancer cells, called CD-73, and this protein prevents the production of adenosine, which is a chemical stopping the immune system from attacking cancer. Monalizumab binds to NKG2A. It's another protein on immune cells, and this protein inhibits their ability to kill cancer cells.

Early studies suggest that combining as a treatment with durvalumab may be better than durvalumab alone at slowing the growth and spread of cancer in patients with non-small cell cancer.

Volrustomig is another treatment. It's a PD-1 CTLA4 bispecific drug that recently demonstrated durable response versus IO alone as

first-line treatment for patients with metastatic non-small cell lung cancer. Therefore, this combination has the potential to further improve PCR and survival outcomes in our patients.

Dr. Turck:
I was wondering if you would walk us through the methodology you employed in this trial.

Dr. Egenod:
From my perspective, NeoCOAST-2 is a very interesting study because it explores multiple possibilities of treatment. This is a randomized, open-label multicenter study for 9 months approximately and planned for 210 patients with previously untreated resectable Stage 2A to 3B non-small cell lung cancer. There is a pre-specified stratification by PD-L1.

We split the population between the negative and the positive patients. And at the beginning, patients were supposed to receive treatment chosen between an association from chemo, durvalumab, and oleclumab or chemo, durvalumab, and monalizumab or chemo and volrustomig. This was done every 3 weeks for 4 cycles in that trial prior to surgery, and then there was an adjuvant period. Only the immuno and the combination of IO without the chemotherapy for up to 1 year or until we observe disease progression.

During the study, a fourth arm was added evaluating the interest of a new adjuvant chemo with chemotherapy with durvalumab and datopotamab/deruxtecan, which is for me very interesting because it's an ADC directed by Trop2. And this arm stands out because it evaluates for the first time the benefit of an ADC in this neoadjuvant situation.

In the trial, surgery needed to be done at least 40 days after the last dose, and the adjuvant therapy should start within 10 weeks after the surgery. The primary endpoints are PCR rate, the safety, and tolerability. There are also some secondary endpoints, including investigator-assessed event-free survival, overall survival, feasibility of surgery, and, of course, pharmacokinetics, immunogenicity, and changes in circulating tumor DNA.

Dr. Turck:
For those just tuning in, you're listening to *On the Frontlines of Non-Small Cell Lung Cancer* on ReachMD. I'm Dr. Charles Turck, and today I'm speaking with Dr. Tomas Egenod about the efficacy and safety results from the NeoCOAST-2 trial on treating resectable non-small cell lung cancer.

So now that we have some background on this study, Dr. Egenod, let's explore the results. What were the key findings concerning the pathological complete response and major pathological response rates?

Dr. Egenod:
If you're looking at the result from oleclumab, monalizumab, and the ADC, the data was presented, as you said, during the WCLC conference this year. First thing we need to note is that more than 90 percent of the patients are able to benefit from their surgery in each arm. So there is no effect on the feasibility of the surgery by adding new immunotherapy. If you are just looking to the major pathologic response rates, they are respectively estimated at 45, 53, and 65 percent of the patients respectively in the oleclumab, monalizumab, and datopotamab arm. And if we now look to the complete response, the PCR rates are respectively estimated at 20, 26, and 34 percent of the patients in the datopotamab arm. So we can assume, therefore, there is maybe an advantage in favor of the use of the ADC and the datopotamab/deruxtecan when compared with the other arms.

Dr. Turck:
And how prevalent were treatment-related adverse events in this study?

Dr. Egenod:
So if I want to summarize, there is nothing really special coming from the side effects. Approximately 25 to 30 percent of the patients will experience Grade 3 or more adverse events in each arm. These adverse events mainly occur in the neoadjuvant situation, and this is related to the addition of the chemotherapy, leading to hematological disorder. Around 10 percent of the patients didn't have the complete treatment due to these adverse events. After the surgery, in the four arms, we observed that 7 patients died during this postoperative period, but only 1 due to cardiorespiratory arrest, possibly related to the association of durvalumab and oleclumab, and the others were directly related to the surgery and to postoperative complication.

Then, if you move to the adjuvant situation, we only observed that 5 to 10 percent of the patients will experience a grade 3 or more adverse event. We can observe the usual side effects of the immunotherapy: diarrhea, colitis, and arthralgia. They are found, but it's important to highlight that there is a specificity for datopotamab/deruxtecan leading in 20 percent of the cases to stomatitis, which are sometimes disabling for patients. Prophylactic measures are being evaluated to prevent that complication. Nevertheless, no adverse event in the adjuvant period led to treatment discontinuation.

Dr. Turck:

And as we approach the end of our program, Dr. Egenod, would you share some conclusions we can draw from this study and where do we go from here?

Dr. Egenod:
So I think that first, we can say that treatments in all arms demonstrated a manageable safety profile and surgical rates, at least comparable to current triple-regimen. Second, and it's for me one of the major findings of the study, this is the first Phase 2 study showing encouraging efficacy and manageable safety profile of an ADC for resectable non-small cell lung cancer, and this study probably paves the way for the use of ADC in that setting. Nevertheless, I want to highlight that we can assume that not all the patients will need in the future adjuvant treatments, maybe those achieving a PCR, and we do need to work on that to identify them. And finally, two new arms evaluating rilvegostomig, a PD-1 TD bispecific antibody, will be soon open for infusion and could improve the result observed yet with these four arms.

Dr. Turck:
With those forward-looking insights in mind, I want to thank my guest, Dr. Thomas Egenod, for joining me to discuss the efficacy and safety findings of the NeoCOAST-2 trial. Dr. Egenod, it was great having you on the program.

Dr. Egenod:
Thank you. It was my pleasure.

Announcer:
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