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Is There a Chemo-Free Approach for Early-Stage NSCLC?

Announcer:
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Dr. Spicer:
My name is Jonathan Spicer. I am from McGill University up in Montreal, Canada. And here we will be talking about whether there is a chemo-free approach for early-stage Non-small Cell Lung Cancer. First off, why consider a chemo-free approach? Well, chemotherapy comes with its own attendant toxicity. We know from prior trials that grade 3-4 adverse events rates are occurring about two thirds of patients, and chemo itself is associated with a mortality rate of almost 1%. We know that whether we give chemo before or after there are adverse events although some of the data seems to indicate that the tolerability of chemo prior to surgery is better and in fact many of our patients, anyone practicing in the area of early-stage lung cancer knows that many patients are either ineligible for chemotherapy or will decline it altogether despite the potential survival benefits that it might offer.

There are indeed very few data about systemic therapies that do not employ chemotherapy. There are no ongoing phase 3 registrational trials that explore the possible elimination of chemotherapy from the perioperative regimen for patients who would otherwise be eligible for pre or postoperative chemotherapy in the nondriver mutated resectable non-small cell lung cancer space. And this is because of the proven overall survival benefit of chemotherapy. And so, people are very reticent to deescalate therapy and given the existence of this overall survival benefit even if it is somewhat marginal especially in the lower ends of the stage ranges. That said, there are many phase 2 data that indicate promise of the approach, and these are largely utilizing immunotherapy-based regimens and we will explore some of those approaches in the next few slides.

I think it's very important to note that chemo-free adjuvant immunotherapy does not seem to be an option at this point. We have IMpower010 which was positive for the DFS endpoint in the greater than 1% patients and positive for the overall survival endpoint in the PD-L1 greater than 50% patients. But what was very interesting to note from the KEYNOTE 091 study, is that in fact in patients who did not receive adjuvant chemotherapy there was really no benefit of adjuvant pembrolizumab. And so, this begs the question as to whether there is some synergy between the use of chemotherapy and immunotherapy in the adjuvant space even if it is in a sequential manner. But currently there is really no evidence to support eliminating the use of chemo in patients who have undergone an upfront resection therapeutic strategy.

So, as I said, there are no phase 3 data for chemo-free neoadjuvant therapy approaches but there are several promising phase 2 trials, and these include studies where immunotherapy was used as a monotherapy. There are studies looking at combinations of different immuno-oncology treatments and then also the very promising use of radiation therapy in combination with immunotherapy. Within the pipeline of treatments, there is the notion of combining targeted therapy such as against KRAS G12C mutation with immunotherapy, as well as the hope that perhaps by manipulating the microbiome we may increase the effect of immune checkpoint inhibitors.

So, the largest trial we have looking at immunotherapy used as a monotherapy in the neoadjuvant space comes from the Lung Cancer

Mutation Consortium 3 trial, where patients were given two doses of Atezolizumab prior to surgery. And in this study 183 patients were enrolled. 181 were dosed, 88% of the patients enrolled went onto surgery. It was very high complete resection rate and some compelling results.

So, I think the most important outcome of this study is the high rate of major or complete pathological response which was the primary endpoint of the study. We saw major pathological response rate in the range of about 20% of the patients and a complete pathological response occurring in approximately 8 or 9% of the patients. And although the complete response rate was not quite as high as what we have seen in other studies, such as CheckMate 816, where the complete pathologic response rate was on the order of 24%, we do see really remarkably good overall end disease free survival rates with 3-year DFS at 72% and 3-year OS at 80%. It is important to note that the study included post stage II and III patients as well as stage IB patients. But all the same, these are remarkable overall survival rates for this population of patients. And gives us some indication that perhaps monotherapy is certainly, in biomarker-selected patients may be a totally viable option but this remains to be tested in a proper phase 3 design.

Next, we have Dr. Altorki's study looking at durvalumab as a monotherapy versus in combination with low dose stereotactic body radiation therapy. This was a phase 2 randomized study and I think here what was quite striking about the publication was the 50% major pathological response rate that was seen by the addition of just eight gray and two doses of SBRT to durvalumab which greatly improved the pathological response rate. And we also saw excellent complete resection rates from this study with very acceptable surgical morbidity. So, the use of radiation as a sensitizing agent to immune checkpoint inhibition is a compelling avenue, which may provide a very effective chemo-free option. It remains to be determined whether this approach will still deliver the same systemic effect as what can be achieved with the combination of chemotherapy and immunotherapy and whether this can prove to be a viable alternative. Again, something that would need to be tested in a randomized phase 3 design.

Of course, there's the NEOSTAR Trial where we now have publication of the Arm A and Arm B findings where patients were either treated with three doses of nivolumab versus nivolumab plus ipilimumab followed by surgery. This was a highly translational trial, but also gives us some good data on the use of these pure IO regimens in the resectable stages of non-small cell lung cancer.

We saw comparable major pathological response rates to what was seen in LCMC 3. Clearly the addition of ipilimumab improved the major pathological response rate quite substantially. It is interesting to note that a similar phase 2 study conducted out of Johns Hopkins and Sloan Kettering was actually closed due to toxicity. This did not seem to be an issue in the NEOSTAR Trial although the N is quite low with only 16 patients enrolled into that arm at least from what we've seen in the Nature Medicine publication from this year. Now more and more we are trying to augment the use of immune checkpoint inhibitors to either anti PDL-1 one or PD-1 by adding additional immuno-oncology agents that may augment the response. The NeoCOAST trial was a platform trial looking at four different treatment arms on a backbone of a single dose of durvalumab in a 28-day treatment cycle. And what was very interesting of this, from this single finding exercise is that the addition of either oleclumab, omalizumab and danvatirsen all had numerically higher major pathological response rates as compared to durvalumab alone. It is also interesting that these rates of major pathological response were found with such a short exposure to immune checkpoint inhibition. So certainly, these such trials are promising though, certainly, underpowered to bring these to routine clinical practice at this time.

So, in conclusion, I think it's clear that periadjuvant chemotherapy remains a cornerstone of therapy to optimize outcomes for resectable non-small cell lung cancer. We do not yet have the evidence to omit this component of therapy when feasible. We do not have any approved therapies for our chemotherapy ineligible patients, and this is a clear unmet need that we continue to try to address and hopefully some new phase 3 trials will increase the number of options for patients in this space. We have many compelling phase 2 data that suggests that a chemo-free option could be appropriate and certainly if we improve our biomarker selection to increase the response rates as it could be a great path forward. I think there are many questions that still remain to be addressed about how the administration with chemotherapy itself can be optimized in combination with immuno-oncology. We want to minimize adverse events while optimizing quality of life, as well as optimizing pathological and survival outcomes. And I think a significant amount of work needs to be done in that area as well. Thank you for your attention. Have a great day.

Announcer:
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