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Case: Peri-Operative Immunotherapy in Early-Stage NSCLC

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Dr. Reuss:
Hi, my name is Joshua Reuss. I'm a Thoracic Medical Oncologist and Assistant Professor of Medicine at Georgetown University School of Medicine and Georgetown Lombardi Comprehensive Cancer Center. Today we're going to be discussing perioperative immunotherapy in early-stage non-small cell lung cancer. And I'm pleased today to be joined by my good colleague and friend, Dr. Jessica Donington.

Dr. Donington:
Hi, I'm Jessica Donington. I'm a General Thoracic Surgeon, and I'm Chief of the Section of Thoracic Surgery at the University of Chicago. Excited for the conversation.

Dr. Reuss:
Thank you, Jessica. And I think this is probably one of the hottest topics, particularly in early-stage non-small cell lung cancer. It's great to have so many options, but now with the emerging perioperative approaches, who is getting treated with what, who do we give neoadjuvant to, who perioperative, who adjuvant? Hopefully we can have an exciting discussion.

So I want to start with a case example. This is a 77-year-old gentleman with a history of COPD, type 2 diabetes, hypertension, and hyperlipidemia, who presents to you for recommendations and management of locally advanced non-small cell lung cancer. He had been following with pulmonology with yearly CT scans for a growing right upper lobe lung nodule, but unfortunately, was lost to follow-up during the COVID-19 pandemic and recently represented. Not surprisingly, a CT imaging and PET/CT showed an enlarged 5.4 by 4.7-cm right upper lobe lung mass along with enlarged right hilar and precarinal lymph nodes. Pathology from an EBUS with bronchoscopic biopsy shows keratinizing squamous cell carcinoma of the right upper lobe lung mass with a right paratracheal and precarinal lymph nodes that are positive. So multi-station N2 lymph nodes positive. Brain MRI is negative for intracranial metastases. The patient's case is reviewed at multidisciplinary tumor board and is deemed as potentially resectable.

So the question is what is your recommended treatment approach?

And before we discuss perioperative therapy, just for those who are watching who are a little confused about neoadjuvant, adjuvant, and perioperative, just want to give a little glossary of terms here. So if we look at surgery, what we're talking neoadjuvant means giving treatment before surgery. So systemic therapies before surgery. Adjuvant means giving treatments after surgery. And then this perioperative or peri-adjuvant is a term that's kind of evolving to say giving systemic therapies both before and after surgery.

Another important term is we talk in a lot of these studies about disease-free or event-free survival versus overall survival. So what does that mean? So let's say you have a study of 10 patients, 1 year later, 5 of these patients are alive and disease free, 3 are alive, but the

cancer has recurred, and 2 have unfortunately passed away. And in this setting of disease-free survival, only 5 of the 10 patients are alive and disease free because 2 have passed away, and 3 have experienced disease recurrence. However, the overall survival here is 80% because there are additional 3 patients who are alive, but the cancer is cured but they still are alive and 2 are no longer alive. So just a little visual term for some of the things that we're going to be talking about.

So let's jump right into the data. So the first perioperative trial I want to discuss is the KEYNOTE-671 trial. This was a randomized, double-blind, phase 3 trial that included patients with resectable stage II to IIIB non-small cell lung cancer as adjudicated by the AJCC TNM 8th staging edition. Patients were randomized 1:1 to receive the immunotherapy pembrolizumab with cisplatin-based chemotherapy for four cycles, or placebo with platinum or cisplatin-based chemotherapy followed by surgery, and then an additional 13 cycles of adjuvant pembrolizumab compared to placebo, with dual primary endpoints of event-free and overall survival. This study met its event-free survival endpoint as presented at ASCO earlier this year. And then we had a more recent update just this past month ESMO conference that showed a clear event-free survival benefit with a median event-free survival of 47.2 months in the pembrolizumab arm, compared to 18.3 months in the placebo arm with a hazard ratio of 0.59.

As highlighted here, you can see some important things. Benefit observed across disease histology, both non-squamous and squamous. Benefit also observed across clinical disease stage II to IIIB. And then the benefit, while more striking in the high PD-L1 population, there was benefit observed irrespective of PD-L1 status.

Another interesting point is one thing that we look at is how does the benefit differ for those who achieve a pathologic complete response? And what that means is that at the time of surgery, pathologic complete response equals no residual viable tumor. There is no discernible tumor left at the time of surgery. And what this figure shows is that for those who achieved a complete pathologic response, those patients did best regardless of whether or not they got immunotherapy or placebo, the majority got immunotherapy. But there was a benefit for the pembrolizumab arm in those who achieved a pathologic complete response and in those who did not, which is important to determine and to really determine who benefits most from these therapies.

Importantly, very recently, we got our first significant overall survival benefit from one of these perioperative trials. And it was in this KEYNOTE-671 study, which showed that the addition of pembrolizumab actually improved survival for patients compared to placebo with a hazard ratio of 0.75. And so, what that means hopefully, is that by adding in immunotherapy, we are able to cure more patients with resectable non-small cell lung cancer, which is really incredible.

Again, these are some key subgroups, and you could see that this benefit in survival was observed irrespective of disease histology, irrespective of clinical stage, lymph node status. And then I think a big question still needs to be bared out here is that the benefit was most pronounced in those with high PD-L1 expression status.

Moving on to the phase 3 AEGEAN trial. So similarly designed study, patients with stage IIA to IIIB resectable, non-small cell lung cancer as adjudicated by the AJCC 8th edition staging, were included, though notably, patients, potentially for planned pneumonectomy were excluded. Patients were randomized 1:1 to four cycles of durvalumab with platinum-based chemotherapy, a noticeable difference compared to the KEYNOTE study where it was specifically cisplatin, randomized to that versus placebo with platinum-based chemotherapy followed by surgery, and then additional 12 cycles of durvalumab versus placebo with dual primary endpoints of pathologic complete response and event-free survival.

This study too met its event-free survival primary endpoint, though with a bit of a shorter EFS median follow-up of 11.7 months, but you could see here a statistically significant clinically meaningful improvement in event-free survival with a hazard ratio of 0.68. When looking at subgroups, you could see here also benefit appeared to be irrespective of disease histology, disease stage, PD-L1 expression status, and importantly, choice of neoadjuvant platinum cisplatin versus carboplatin, with the majority of patients receiving carboplatin.

Moving on in our march of phase 3 clinical trials that showed significant benefit is the Neotorch study. This was a Chinese study that looked at patients with newly diagnosed resectable stage II to III non-small cell lung cancer who randomized 1:1 to the immunotherapy, toripalimab, with chemotherapy for three cycles, or platinum-based chemotherapy plus placebo for three cycles, then followed by additional adjuvant toripalimab versus placebo with primary endpoints of event-free survival and major pathologic response. You could see this study, which was presented at the ASCO plenary and then later at ASCO earlier this year, event-free survival hazard ratio of 0.40, favoring the addition of toripalimab. And you can see here, benefit across particular strata, most clearly pronounced in the squamous population, though this study did include a majority of actually squamous non-small cell lung cancer patients.

Then the last study we're going to discuss in detail today is the phase 3 CheckMate 77T trial. Similar to some of the prior discussed studies. This trial did include patients with resectable stage IIA to IIIB non-small cell lung cancer as assessed by the TNM 8th staging edition. Patients were randomized 1:1 to four cycles of nivolumab with platinum doublet chemotherapy, or platinum doublet chemotherapy with placebo followed by surgery, and then 1 year of nivolumab versus 1 year of placebo, with a key primary endpoint of

event-free survival. We recently saw this data, and not unsurprising, this too achieved its primary endpoint with the addition of nivolumab to platinum doublet chemotherapy, showing an improved event-free survival with a hazard ratio of 0.58, favoring nivolumab.

Subgroups here, you could see benefit more clearly pronounced in the stage III. Hard to say whether that's just because it's a population at higher risk for relapse, but either way, a more pronounced benefit there. Benefit observed across whether it was single station N2 or multi-station N2. Interestingly, a more pronounced benefit in the squamous population, and then a more clear benefit in the PD-L1 positive. Importantly, this benefit was observed in both those who achieved the pathologic complete response and those who did not. You could see though that overall, those who achieve a pathologic complete response, do have numerically higher event-free survival and tend to do better in the long run.

So this is a table, quite busy, that just highlights some of the similarities and differences amongst these studies. And I think one important point here is that the consistency. The consistency of the benefit, it shows that adding perioperative or neoadjuvant immunotherapy leads to an improved event-free survival and will hopefully cure more patients and see more patients living longer. You can see that the follow-up is longest for the 816 study, where we see an overall event-free

survival hazard ratio of 0.68. For KEYNOTE-671 hazard ratio 0.59, also long follow-up of 36.6 months. Interesting, if the cisplatin requirement may have selected for a more robust population, it's hard to say. And then going down the line, you could see consistent benefit across these studies. Though the only approvals currently are for the CheckMate 816 neoadjuvant regimen of nivolumab with chemotherapy for those that have tumors of 4 cm or greater in size or node-positive disease, and then the KEYNOTE-671, four cycles of perioperative pembrolizumab with chemotherapy, followed by adjuvant pembrolizumab, that again, is approved in the same population.

So moving forward, I think there are some very important questions that we need to unpack. You know, what factors will allow us to select for neoadjuvant versus perioperative? That is the big question. Can disease histology play a role? PD-L1 status? Other molecular markers? Ultimately, I think we're going to need to utilize a response-adaptive approach. Pathologic response, is that enough to stop after neoadjuvant? Minimal residual disease assessment. You know, we went from not having enough treatments for patients with resectable lung cancer to saying, Are there patients that we actually can now de-escalate therapy for? It's pretty incredible to see that big switch. And then for those who experienced recurrence, you know, what are we going to offer next? Is it going to be a platinum IO backbone? Do we need to add an additional IO checkpoint? Do we need to throw in a new antibody drug conjugate? Some other novel approach? I think these are key questions.

Just some interesting things here. I think PD-L1 status is one interesting question. When you look at event-free survival, this is a population that did not have as clear benefit in the PD-L1 negative. However, for event-free survival from the other perioperative studies, perhaps little more signal of benefit, it's so difficult to do cross trial comparison. But perhaps that's a population where we're really deploying a perioperative upfront that makes the most sense. Same can be said about disease histology. You know, again, it's hard to make cross trial comparisons but the squamous population did not appear to do quite as well in the neoadjuvant

CheckMate 816 study. But that benefit clearly was there in the other perioperative study. So just some interesting food for thought moving forward.

So just to quickly return to our case. So this patient was discussed. He did receive three cycles of neoadjuvant nivo carbo pac, followed by resection. At the time, this was the only thing approved. Pathology at resection, so 10% residual viable tumor in the resection bed, as well as residual tumor in 4R, 7, and 10R lymph nodes. NGS did show a PD-L1 to 50%, mutational burden of 9. And so, the question is, would we recommend any additional treatment at this time? I think this is a big open question that we'll talk in greater detail.

In this case, we did elect to begin adjuvant pembrolizumab, and he continues that at this time with excellent tolerability and no recurrence.

So with that, I know this was a whirlwind, but I'd like to welcome in my colleague, Dr. Jessica Donington. And Jessica, how do you approach the big question, neoadjuvant versus perioperative? How are you looking at this data? And what do you think are some key take-homes that we can utilize to tease out who deserves what?

Dr. Donington:
I think it's really hard. And it's really challenging right now. I think there are a couple of important points. One, you showed that we just don't have a lot of follow-up from most of these trials right now. You know, AEGEAN, Neotorch, you know, they reported with follow-ups that the median follow-up matched the length of the treatment, so not that it's not going to be great data. And I bet, you know, it's going to look just like our other trials, because we're seeing that with these agents, this, you know, very consistent findings. But it just makes it a little harder to know what we're going to expect long-term because we're just starting to get 18 months past treatment. Where the CheckMate 816, we're now, you know, almost 3 years past treatment. And so, what we're seeing looks real.

I think it's hard. I mean, this patient, 10% residual viable tumor, I don't know, you know, right now, one thing I love seeing path responses, but so far, we've only seen them as a yes/no. You're either path respond, you know, path CR or you're not. You know, in someone with 5% viable tumor, the same as 95% viable tumor? I don't think so. So I think I would really love to see that become a much more nuanced to really tell us about what's going on in these patients. Because my bet is that the cut-off for where we're really going to see long-term results is not going to be at 100% dead tumor. So - but you know, is it 10, 15, 20? I think this is where I'd love to see data from all the trials together to really help us tease that out.

I think the other important point is that some of these patients can't get through all this. This is a lot of treatment; more than we'd typically give lung cancer patients. So you know, all of the perioperative trials have significant dropout with only about somewhere between 40 and 60% of patients completing all the therapies. So I do think we have to be selective. You know, at the same time, I've had a number of healthy patients who tolerate their induction well. I have no problem with continuing if that's the conversation.

Dr. Reuss:
Yeah, no, I agree. It's such a challenging question. And I guess another question then is, you know, so a patient has a pathologic complete response, right? We don't see any tumor at the time of surgery, like, is that enough? Like, I mean, I know this is just kind of us talking back and forth, so some discussions, we don't have the data to suggest that, but in your opinion, if you see a pathologic complete response, like how are you going to approach that patient? You know, if they come and talk to you about, alright, should I continue IO? Like, what if you started with pembrolizumab chemo four cycles, you know, and then you have a pathologic complete response, like, how are you going to approach this patient?

Dr. Donington:
So it's so funny. I don't have this answer, but it's very funny how I have, you know, a group of oncologists and they live on opposites sides of this, so you have to like think to yourself, okay, who are they seeing, where do they come from? Because I've got to steer the conversation a little bit in that direction. Because I don't think any of us know, we don't, you know, you can read this half empty, half full data however you want. You know, in 5 years, the picture may be clear, but right now, it's not.

Dr. Reuss:
Yeah. I couldn't agree more. I mean, I think, you know, as we alluded to in this discussion, perhaps there are some patients where at least the data subgroups suggest like alright, if their squamous, or their PD-L1 negative, you know, maybe those are ones where clearly there's a perioperative benefit, at least the studies so far suggest it. But for pathologic complete response, do we have the data to say, you know, should we continue? Should we stop? Especially if you give a perioperative regimen. If you give pembro chemo that study wasn't designed to stop. You know, it wasn't designed to say, alright, we'll stop with PCR. I mean, these are trials that we need to have.

I mean, when you think of it kind of logically, at least when I think of it, I think of two extremes where I question the utility of additional adjuvant. One is that pathologic complete response, and we need to see more data there. But the other to me is those who have like no pathologic response. Like if you have 100%, residual viable tumor, I think you've essentially proven that that's an immunotherapy-refractory tumor.

Dr. Donington:
Yep, I totally agree.

Dr. Reuss:
And is more adjuvant immunotherapy really going to help that patient? I would say probably not. And I think that's where you need to design the escalation studies of additional checkpoints, antibody drug conjugates, things like that.

Dr. Donington:
Yeah, I guess I'm hoping that, you know, in our new world, that'll be another point, you know, we'll do our induction, we'll see what our path response is, which I guess is, you know, it's way better than radiologic responses, it's a great marker. And then, you know, I still think that group with residual viable tumor is going to be the group that needs the next point of attention. Because it's a lot of patients, 75% of our patients have residual viable tumor after resection, and we still have a ways to go in finding an answer. And you're right, for a lot of them, it might be changing therapy. What do we get to add at that point? What's different?

Dr. Reuss:
Exactly. I mean, clearly, we're still not curing the majority of patients, you know, and we can't stop until we can't improve anymore. And I think we're still a ways away from that. And I mean, I agree, and I think the minimal residual disease assessment is going to be key. I don't know if the technology is quite there yet, because it's different than our traditional ctDNAs, right? It's looking at methylation signatures, or can you do a tumor-informed approach where you take the resected tumor and then you're really doing a patient-specific MRD detection? And so, I think these are technologies that are developing, but you know, they're clearly not primetime yet.

Dr. Donington:
Yeah, well hopefully soon, but I agree. And I do think, you know, tumor-specific is going to be the answer. And it's the same thing; if you've resected the tumor, you got a lot of antigen, a lot of antigen you can work with to find that that marker.

Dr. Reuss:
Exactly.

Well, I guess, you know, with that, I'd like to close the discussion. Really, I thank you for this fruitful conversation and hopefully we will continue to get more answers to help more of our patients moving forward.

Dr. Donington:
Awesome. Thank you.

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