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Earlier Use of ICIs in NSCLC: Integrating the Latest Evidence Into Clinical Practice

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Dr. Donington:
Hello, I'm Jessica Donington. I'm a General Thoracic Surgeon and the Chief of Thoracic Surgery at the University of Chicago. I'm here to talk to you today about updates for neoadjuvant therapy for resectable lung cancer. I'm joined by my friend and colleague Josh Reuss. He can introduce himself before we start our discussion.

Dr. Reuss:
Thanks, Jessica. Yes, I'm Josh Reuss. I'm a Thoracic Medical Oncologist and Assistant Professor of Medicine at Georgetown University and Georgetown Lombardi Cancer Center. Excited to be here to discuss this important data.

Dr. Donington:
Thanks. Alright, so we're going to start our discussion today with a case. This is a pretty typical case of what I see right now in my clinics. It's a 79-year-old woman. She had a smoking history in the past and she was seeing me for a second opinion. She had recently gone to the emergency room with a self-limited chest pain, and the workup revealed this kind of large central right upper lobe mass. She was otherwise really quite active, she exercised daily. She did have a remote history of an early-stage breast cancer, and she had already been scheduled to start chemotherapy and radiation before I had seen her. She'd also had a PET scan done, you can see this large central mass with an SUV of 15. There was no uptake anywhere else. She'd also had a brain MRI, which was normal. And she'd undergone an EBUS with navi bronc, and the mass was non-small cell, otherwise not specified. Moleculars had not been sent. And her EBUS was negative for mediastinal lymph node involvement.

When we saw her, the kind of the first thing I did was to send off her moleculars. We got that path from the outside. Luckily, they had a big enough sample and we didn't have to re-bronc her. She had no targetable mutations, but her PD-L1 was 90%. We then looked to see could she maybe be an operative candidate? And she had great PFTs. So you know, we had a clinical stage IIB patient, T2bN0. And we sent her off to tumor board for discussion.

And before we go over the whole discussion, I think we'll start looking at the literature that helps guide decision-making for a patient like this right now. So you know, we think of these early-stage or resectable patients, we used to always think that, you know, local therapy was the king. And that local control was enough to cure these patients. But the reality is now we have really good systemic therapies. And therefore, we're improving survival in these patients by reducing the risk for distant relapse, which means we treat these patients entirely differently than we used to; not that every patient with lung cancer isn't treated differently. But the data that we're going to talk about today with neoadjuvant immunotherapy really focuses on this kind of IB through resectable IIIA, and all the new options that we have for patients there.

This is what the landscape looks like. I think I like the fact that I have this as a, you know, an iceberg because it's changing all the time.

And let me tell you, that iceberg is coming to the top rapidly. We have new trials reported out on a really continuous basis now, but we have adjuvant trials with the IMPower and KEYNOTE-091 We have a single neoadjuvant trial, and that's what I'm going to spend most of my time talking about today. And then we have this whole huge peri-adjuvant group of trials, and I am going to include some data from them because, you know, really right now we're only seeing the effect of their neoadjuvant therapy. And we're not really seeing the benefit yet of the tail end.

This is a lot of data. This is what all these trials look like, and it is kind of hard to kind of understand everything that happens in them. I think there are some basic easy things to keep in mind. One, the three spaces, the neoadjuvant, peri-adjuvant, and then the adjuvant. When you look at trial size, not surprising, the largest trials are the adjuvant trials. They have to be; it's just harder to prove benefit in the adjuvant space. Otherwise, the design of these is all quite simple. They either each have you know one PD-1 or PD-L1 inhibitor, paired most commonly with a platinum doublet. They all have very similar endpoints, especially for the neoadjuvant and the peri-adjuvant with a pathologic endpoint along with an event-free survival endpoint. And they've all done their best at this point to exclude EGFR and ALK patients. Some of the earlier trials still included them just because we didn't really understand the importance of excluding them long ago.

So let's talk about CheckMate because this is our only neoadjuvant trial. It will probably always be our only neoadjuvant trial, and there's a lot of data here to unfold. They keep giving us more and more. The basic trial design resectable IB through IIIA's on the 7th TNM system, randomized to three cycles of either nivo plus chemo or chemo alone. And then on to resection 6 weeks later. One of the primary endpoints was path CR. This was the first piece of data we saw out of this trial. And we were, you know, all awe-shocked by this kind of 12-fold improvement in path CR with the addition of nivolumab to the three cycles of chemotherapy. We then started to see event-free survival. And we now see event-free survival for this trial out through 3 years. And I always want to remind people that events are not going to surgeries and event as is disease recurrence or death. And out at 3 years with a hazard ratio of 0.68.

What we're starting to see now is a little bit - I'm sorry, here are the subgroup analyses. And we can see that, you know, there's no one who did better with chemo alone in those prespecified groups. And we see some patients who appear to have done better than others, the carboplatin, PD-L1 high expressors, never-smokers, we're still kind of sorting out what all of that means. And I think we'll learn more about all these subgroups as we start to see more data from the peri-adjuvant trials.

We are now really starting to see some important subgroups with regard to more than just basic characteristics. So here we, this year, we saw, you know, survival based upon whether patients got definitive surgery or not. And it really does talk to the importance of surgery in this population with pretty dismal looking survivals for both the nivo plus chemo and chemo arms in those patients who didn't undergo surgery. You know, this initial quick drop is the fact that not going to surgery wasn't event, but overall survival, those curves are not pretty, even after that event.

We also see time to distant metastasis. This is really nice, because it doesn't necessarily take event – you know, the surgical event into play – into account. And we are seeing nice survivals here.

And then the same thing, by the use of surgery or no surgery. And again, you can see that in patients who don't have definitive surgery, even when surgery is not an event, these patients are metastasizing fairly quickly and have pretty poor outcomes.

And then this was just presented at ESMO this year. And I think really nice data. And this is looking at event-free survival by PD-L1 expression. And in those patients who are PD-L1 positive, we see a very significant improvement in event-free survival at both – at 1, 2, and 3 years, and a hazard ratio of 0.46. The PD-L1 negative population is a place where we might have to do some work, this group does not seem to be seeing the benefit that we would hope. These patients all get this now because the approval wasn't based on PD-L1 status. But this does make some of us all think that maybe we need to be looking for something else here.

And then the overall survival improvement. Again, it's looking quite good. It's a relatively small trial, we may need to mature before we see a, you know, statistically significant improvement, but I think most of us are excited to see that difference between 64 and 78% at 3 years.

This is the recurrence pattern. And again, what we would expect from a good systemic therapy paired with surgery is that local recurrence, almost the same. The real benefit is in the reduction of distant recurrences. And especially in places like the brain, really important to our patient populations. The little box all the way over on the side shows us a little bit more about those patients who did develop brain metastasis. And it is nice to see that most of those patients were stage III patients. None of those patients were path CR patients, and in general, the amount of residual disease in those who developed brain metastasis was quite high.

So I'm quickly just going to run through these peri-adjuvant trials. And there are so many of them right now and they are being presented fast and furious. The first one we saw was the AEGEAN trial, durvalumab before and after surgery, and we saw an early event-free survival curve from them. This has now been published in the *New England Journal* just this past month.

The KEYNOTE-671 trial, perioperative pembrolizumab in a very similar protocol. And again, a nice hazard ratio for event-free survival also published in the *New England Journal of Medicine* this year.

Neotorch out of China, not one that probably we see the most in the United States, but again, really nice data.

And CheckMate 77T, the most recent presented at ESMO this year, and very similar-looking survival curves for perioperative nivolumab. So it may be the closest comparison to the CheckMate 816 will be this trial. One key difference to recognize it was four cycles preop and not three.

I put them all up together, because I'm doing the, you know, not-allowed cross-trial comparison. But these trials are all really quite similar. I don't feel so guilty here. But looking at like, again, what we would be seeing from a neoadjuvant trial, and that's the pathologic responses. This is the effect of the neoadjuvant portion of those perioperative trials. And I actually - I don't know whether all the pharmaceutical companies are as excited as I am. I'm excited because we see very similar results. We're adding a new class of medicines, we're adding agents that should react similarly. And we're seeing that. And that is, in my opinion, exciting. I don't think we see anything more insightful in major pathologic response than we do in path CR, which I think is going to become our new standard.

So where am I on these neoadjuvant trials? I think we have to be, you know, recognize that CheckMate 816 is our only neoadjuvant trials, it's probably going to stay or only neoadjuvant trial. There is growing evidence for perioperative care, but that's still maturing. So, I think we take what we can on the early part of those disease - of that data. I think the EFS and pathologic data is really exciting. The overall survival stuff is very early, but again, encouraging. I think it's safe. Well tolerated, I have to kind of say, I don't know. You know, it's really hard for patients to get through all of this, so we might have to think about being more careful about who really needs the full court press and who doesn't, because it's hard to really know the benefit of the perioperative yet. In terms of what surgeons do, it's more work, there's no doubt about it. We have to do more than we did before. We need to know more. And biomarker testing, I do think is something we hadn't always thought of preoperatively, but it has to be part of what we do.

So I'm going to go back to our case now. So, Josh, we've got a, you know, stage IIB. This is an N0 case. She's been, you know, well staged by EBUS. We don't have nodal disease. If you were sitting in my tumor board with me, what would be your recommendations for an otherwise healthy patient like this?

Dr. Reuss:
Yeah, no, thank you, Jessica. And thank you for that really insightful presentation. I guess I would probably turn the question back on my surgical colleagues and say, you know, what is the operability at right now? I mean, I will say I'm a big-time believer in the neoadjuvant space, at least giving a chemo IO treatment before surgery, I think there's something important about that intact tumor burden, and eliciting a significant immune response. So, I'm always going to be a champion for that approach, specifically, if there's a patient where there's no clear contraindications to giving an immunotherapy-based approach. But I would definitely want to, you know, get my - get the opinion from our surgical colleagues to say, alright, are they are they operable right now? What would giving neoadjuvant, how could that affect the operability? So, I guess I would turn it a bit on its head here.

Dr. Donington:
Yeah. So I think you know, the stage II data's not quite as robust as it is in stage III. But she's operable right now. What do I think the chances are that we're going to make her inoperable with this therapy? I mean, when you look at the data, it looks like about somewhere between 10 and 20%, or maybe 10 and 25% of patients, you know, might become inoperable, between starting therapy and getting to surgery. But most of those patients aren't really - they're not progressing in the chest. It's not like we took someone who was, you know, we waited and suddenly the chest disease tripled and now they're - we lost our opportunity. They're either patients who were kind of borderline physiologically or who have progressed somewhere else. And you know, if someone's going to present with a brain met, you know, 3 months later, that patient didn't belong in my OR anyhow. Josh, what if she said, 'Well, can I just do adjuvant?' How would you be - what would you be telling her?

Dr. Reuss:
Yeah, I think this is where definitely a patient-specific discussion is important. I think, you know, we don't have any – and probably never will, have direct comparison data of a neoadjuvant versus an adjuvant approach. I would probably lay out the pros and cons. I mean, I think, and correct me if I'm wrong, I'm curious for your opinion, too on this Jessica, is that I think a lot of patients still view surgery as like, that's how you cure the cancer. That's how you get it out and get rid of it. And so, I think providing appropriate education of, no, you know, there are more therapies than just surgery needed to really enhance the chances of cure. And again, you lay out the pros and cons. Say, you know, you probably feel a little bit better getting the therapies before surgery than you do getting surgery and then getting the therapies. If we're comparing a neoadjuvant to an adjuvant approach, you know, I think one of the notable positives to the neoadjuvant approach is it's three cycles and you're done. Obviously, that's evolving now as we move into a perioperative peri-adjuvant,

and I'm sure there's going to be a lot further development and hopefully a lot more trials to really pare down who needs additional adjuvant therapy. But I think that's where I'd focus the discussion. I mean, ultimately, if a patient says I'd rather, you know, pursue adjuvant, I'm not going to fight them on it. I want them to get a therapy that we know is beneficial. And we know adjuvant helps. But I think in most cases where a perioperative therapy is indicated and we know that before surgery, I'd be inclined to give it before surgery.

Dr. Donington:
Yeah, I have to say we're like-minded. I have not had a very - even though I seen many patients now who had been offered resection and I'm their second opinion, and I'm putting the brakes on something that was already in place, I haven't had patients say, 'no, no, no, I only want this.' You know, you show them the numbers, you show them the number of patients who recur with their stage of disease. And you say, you know, this is what it is. And so just, you know, I use the words all the time, it takes more than good surgery, it's going to take more than good surgery to cure your disease. Not that good surgery is not part of it, but it's not the only thing. And you know, how do we find the best partner and the best pair in the best order? Right now, I do think neoadjuvant might be the stronger order. But you're right that, we just have to kind of see what evolves over the next couple of years.

Dr. Reuss:
Absolutely.

Dr. Donington:
Great. Well, thank you for the discussion. I think we're going to move to our next segment.

Dr. Reuss:
Thank you, Jessica.

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