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https://reachmd.com/programs/cme/case-adjuvant-immunotherapy-in-localized-nsclc/16496/

Released: 11/30/2023
Valid until: 11/30/2024
Time needed to complete: 59m

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Case: Adjuvant Immunotherapy in Localized 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 the MedStar Georgetown Lombardi Cancer Center. And today I'm pleased to be joined by Dr. Jessica Donington, Chief of Thoracic Surgery at University of Chicago. Jessica, it's nice to see you.

Dr. Donington:
Josh, nice to see you. Thanks for inviting me.

Dr. Reuss:
Of course. And in today's discussion, we'll be talking about adjuvant immunotherapy for localized non-small cell lung cancer. So, obviously, a lot of data has exploded in this population. Thankfully, we now have a lot of options for our patients. And in today's discussion, we're going to focus specifically on the adjuvant therapy options for our patients and how those are fit into the sequence of other possibilities.

So to start on a case. So this is a patient, a 75-year-old patient with a history of prior tobacco use, chronic atrial fibrillation on apixaban, and hypertension who presents to you for a medical oncology consultation following resection of a localized non-small cell lung cancer. He originally underwent a chest CT for intermittent chest tightness that revealed 1.3 x 1.3-cm left upper lobe lung mass. PET/CT showed that this mass was hypermetabolic, SUV 4.4, but revealed no hypermetabolic lymphadenopathy or distant metastatic disease. A bronchoscopic biopsy of the left upper lobe lung mass was positive for a TTF1+ adenocarcinoma; however, left hilar, subcarinal, and right hilar lymph nodes were all negative for malignancy. So this did appear to be a very early stage, non-small cell lung cancer.

This patient subsequently underwent a robotic left upper lobe lobectomy with mediastinal lymph node dissection with pathology revealing a 1.4-cm invasive mucin-producing adenocarcinoma. Margins were negative with no lymphovascular invasion but 2 of 12 lymph nodes were positive for malignancy, both peribronchial with final disease stage of a pT1bN1 stage IIB non-small cell lung cancer. NGS testing revealed that KRAS G12C mutation and PD-L1 of 60%.

And the question and what we will come back to is what is your recommended systemic therapy approach for this patient?

So, that is a good segue to move into a discussion of our adjuvant therapy options that we have for patients who do not have driver mutations. So, the first trial I'd like to discuss is the IMPower010 study. This was a large phase 3 clinical trial that evaluated patients with completely resected stage IB to IIIA non-small cell lung cancer as adjudicated by the AJCC 7th staging edition. So a little bit different staging than our 8th edition, where perhaps some of these stage IB are now considered stage II. But other than that, a very similar population. Patients enrolled to this study received one to four cycles of histology-specific chemotherapy and subsequent to that

were randomized 1:1 to atezolizumab immunotherapy or best supportive care, stratification factors are listed on this slide. And the primary endpoint was tested in a hierarchical fashion; first disease-free survival in the PD-L1 positive stage II to IIIA population, then DFS in the entire randomized stage II to IIIA, and so on and so forth.

So what we've known now for over a couple of years is that adjuvant atezolizumab did prove disease-free survival in the primary efficacy population, that is the PD-L1 one positive, so 1% or greater staining, stage II to IIIA population with a hazard ratio of 0.66, favoring atezolizumab over best supportive care.

When looking at the subgroups, you could see consistent benefit across disease stage, lymph node status, perhaps less clear benefit in those who underwent bilobectomy or pneumonectomy, though I will say the large majority of patients in this study did undergo lobectomy, and then an interesting signal of a gemcitabine regimen, perhaps being not quite as prominent benefit.

What's interesting though, is that it appeared while these results ultimately lead to adjuvant atezolizumab being approved for this population, so being approved for those for stage II to III resected non-small cell lung cancer that's PD-L1 positive, you can see that the DFS benefit appeared to be largely driven by those with high PD-L1 expression of 50% or greater, where you can see that hazard ratio, really quite prominent benefit of 0.43, and then when looking at the 1 to 49, and then the negative, really not a clear separation from one. Similarly, while we don't have overall survival results for this trial yet, you could see clear separation of the curves here. That is primarily also driven by that high PD-L1 population 50% or greater where again, we see an interim overall survival hazard ratio of 0.43. But again, we still await further data for the long-term overall survival results from this trial.

The next study I'd like to discuss is the phase 3 PEARLS or KEYNOTE-091 trial. So some similarities and notable differences between this study in the IMPower010 study. This, like the IMPower010 trial, did enroll patients with stage IB to IIIA non-small cell lung cancer as assessed by the TNM AJCC 7 staging addition criteria, and had some very similar stratification factors. However, in this study, chemotherapy was not required, it was just recommended for those where it is otherwise indicated. And then patients were randomized rather than from intervention to supportive care, in this case, patients were randomized to pembrolizumab versus placebo.

And there were dual primary endpoints in this study; one of disease-free survival in the overall population. And then secondly, disease-free survival in the PD-L1 high 50% or greater population. So when looking at this, it was also a positive trial. And you could say in the overall population, there was a DFS benefit seen for pembrolizumab compared to placebo, with a hazard ratio of 0.76, favoring pembrolizumab. And based off of this data, the FDA has approved adjuvant pembrolizumab irrespective of PD-L1 status for those with resected stage IB to III non-small cell lung cancer.

But when diving a little bit deeper into the data, you could see here are some interesting subgroups. Number one, benefit more clear in those who received adjuvant chemotherapy. Now this might be reflected of a higher stage population that had higher risk for recurrence. But I think it highlights that immunotherapy does not replace chemotherapy here. We know that there is an overall survival benefit for chemotherapy after surgery and we don't view immunotherapy as replacing the need for the chemotherapy. The benefit was also more pronounced in those with non-squamous compared to squamous histology.

And then we're looking at the PD-L1 status, there were some interesting trends here that we want to discuss in greater detail. So what was interesting is that this study did not meet the second primary endpoint of improved disease-free survival in the PD-L1 high population. And what's interesting is that numerically, pembrolizumab performed quite well across the board. But what was interesting is that the placebo arm also performed better in those that were PD-L1 high. And we don't tend to think of PD-L1 as being positive for improved prognosis. In fact, if anything, we tend to think the opposite. So this was just one interesting wrinkle from this trial. I personally don't view that pembrolizumab has any less benefit in those with high PD-L1 status. But just the data is the data and that was an interesting point from this study.

So when looking just at some key information about these trials, just this is a summary slide for your reference that highlights the design of the studies, the percentage of stage III populations, and then some of the disease-free survival hazard ratios broken down by PD-L1 status, and then ultimately, the FDA approval for adjuvant atezolizumab, which as I mentioned is PD-L1 positive stage II to IIIA disease and then adjuvant pembrolizumab, which is stage IB to IIIA, irrespective of PD-L1 status.

So as we move into our – or get close to our discussion here, there are just some interesting questions, I think. And number one is, who is adjuvant therapy most appropriate for? I think absolutely like the case that we highlighted in the beginning postsurgical upstaging, where you think it's an earlier stage cancer, but then at surgery, you realize there were occult lymph node metastases that were not diagnosed on PET or bronchoscopy. Patient-provider preference and discussion is important, and then also concern for tolerability of a neoadjuvant approach. And then there are many important unanswered questions. You know, what's the ideal duration of adjuvant therapy? Who truly needs it? As I tell my patients, you know, I don't know if adjuvant therapy is curing you. I don't know if you were cured by surgery alone or the chemo or the immunotherapy. We need better tools to assess this. And again, what is the best way to

monitor treatment response? And then lastly, what do you do at the time of recurrence? If someone recurs on adjuvant immunotherapy, what's your next steps?

So there are some studies looking to assess this. One is the MERMAID-1 trial, which is looking at patients who have undergone resection and then randomizing 1:1 based off of residual MRD, meaning minimal residual disease detected on blood to chemoimmunotherapy, in this case durvalumab with chemo or chemotherapy alone, with a primary endpoint of disease-free survival in that MRD-positive population.

A similar, yet somewhat different trial, the MERMAID-2 study is looking at patients who receive appropriate adjuvant therapy and then once off therapy, determining who has MRD-positive disease, meaning residual – a minimal residual disease and then randomizing these patients, those who don't have gross recurrence, to durvalumab or placebo. So some very important trials that will hopefully help to tease out what treatment is best for which patients.

So just to lastly revisit the case. As we discussed, this was a patient that had upstaging at the time of surgery to stage IIB non-small cell lung cancer with lymph node involvement. Based off of the NGS profile, there was no contraindications to immunotherapy. And this patient actually went on to receive four cycles of platinum doublet chemotherapy followed by 1 year of pembrolizumab. His course was complicated by grade 1 pneumonitis that was not clinically significant, but did warrant a brief cessation of immunotherapy. And I think highlights that these therapies are not benign immunotherapy. There are patients that can experience significant toxicities. And at this time, he continues to remain recurrence-free.

So with that, I'd like to welcome back in my colleague, Dr. Jessica Donington. And so Jessica, I guess my first question for you is, in your practice, what are the scenarios where you're typically seeing adjuvant fit into the treatment approach? Are there particular patients where you're recommending this from the outset? Or is it more common in a case like this where there's surgical upstaging, and that's really when the therapy is indicated?

Dr. Donington:
I would say in our practice, in my practice, I tend to do a lot of neoadjuvant therapy. I do like 3 cycles as opposed to 12 cycles. I like having the tumor in place for an immunotherapy. That being said, surgical upstaging is a real thing. I mean, it is not going to go away, you know, with PET/CT, EBUS, all those things, this kind of 1 to 1.5-cm tumor, we expect upstaging in, you know, 10 to 12% of our patient. We just, you know – we don't see every cell that has spread. So this is I think, you know, kind of that poster child for adjuvant therapy, and I would most definitely be sending this patient for adjuvant. And I think the fact that, you know, obviously, we need NGS in all of these patients now that we have such good, you know, targeted therapies to use in this space. But without that, I'm thrilled to have another, you know - another piece to add for these patients.

I think the PD-L1 less than 50% and the PD-L1 negative are definitely, you know, a lot more of a discussion about benefit or not benefit. I don't know, how does your group feel about those kind of low expressors or non-expressors?

Dr. Reuss:
Yeah, no, it's a good point. I think, you know, kind of the way that the data fell where the adjuvant atezolizumab, that PD-L1 high population seems to be where there's that clear benefit. And that was where the benefit was less pronounced in the pembrolizumab trial. I think there's almost kind of a natural separation there where you can, you know, prescribe adjuvant atezolizumab after chemo for the PD-L1 high, and for the other populations, you know, consider pembrolizumab.

You know, in my practice, I'm not inclined to withhold pembrolizumab, even if PD-L1 negative. I mean, I don't think we've really teased out where there's - who has a true benefit, and who doesn't. You know, that population still didn't clearly not benefit, you know, in the PEARLS/KEYNOTE trial, you know, outside of those who have, you know, clear autoimmune disease or something where we wouldn't really want to risk the immunotherapy. But I think we still need more data here. Are there patients that won't benefit from this? Are there those with other, you know, molecular profiles where we actually need to escalate the therapy to additional IO agents to some kind of novel antibody drug conjugate? I think those are open questions.

So with that, I think we're going to conclude today's session. I want to thank Jessica for this really insightful discussion and looking forward to additional topics. Thank you.

Dr. Donington:
Thank you.

Announcer Close:
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