Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/updates-on-clinical-trials-in-oncology-radiation/13390/

Released: 06/30/2022
Valid until: 06/30/2023
Time needed to complete: 75 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Updates on Clinical Trials in Oncology & Radiation

Announcer Introduction:
Welcome to CME on ReachMD. This activity titled: *Updates on Clinical Trials in Oncology and Radiation* is brought to you by the American College of Chest Physicians, and supported by an independent educational grant from AstraZeneca Pharmaceuticals, an educational grant from Genentech, a member of the Roche group, and an independent medical education grant from Merck, Sharp, and Dohme Corporation. Before starting this activity, please be sure to review the faculty and commercial support disclosure statements, as well as the learning objectives.

Dr. Edell:
Good evening, everyone. Welcome to our fourth of five webinars on updates in lung cancer management. We're thrilled to be here, and we want to thank the American College of Chest Physicians and CHEST for enabling us to put on this session. And we also want to thank our sponsors that include AstraZeneca, Genentech, Roche, and Merck, Sharp and Dohme companies. Without their help, we couldn't have accomplished and put on these seminars.

Today's program will follow the learning objectives that we have listed here. I'll give you just a couple of seconds to look at the objectives and get you excited about what program you're going to be part of.

It's really a privilege for me, Eric Edell of the Mayo Clinic, in conjunction with my co-sponsor, Dr. Murgu from the University of Chicago, to bring this seminar - this webinar to you with two internationally known medical and radiation oncologists. Dr. Florez is currently Assistant Professor at the Thoracic Oncology and Dana Farber Cancer Institute as part of the Harvard Medical School. And Dr. Rimner is Associate Attending Director of Thoracic Oncology in the Department of Radiation Oncology at Memorial Sloan Kettering.

You can see the disclosures by each of our presenters. And now, I would like to invite Dr. Flores to begin the webinar with her presentation. Dr. Florez.

Dr. Florez:
Hi, everyone. I'm delighted to be here. There's been a lot of data for the treatment of lung cancer since 2020. In 2020, we have seven different approvals. And in 2021, how we change lung cancer has changed. So I'm going to hope to make this as interactive and applicable to why you do everyday as possible. I encourage you to ask questions as we go. You can put it in the Q and A section of the – this webinar.

We're going to start with a question. Which of the following is true about the use of chemotherapy plus immunotherapy and the neoadjuvant, that means before surgery, setting for non-small cell lung cancer? Neoadjuvant therapy delays surgery in patients with resectable lung cancer, that patients that received neoadjuvant therapy had longer surgical times and require more extensive surgeries, or neoadjuvant therapy increased the rates of complete pathologic response? All right, Ooh, you're going to learn about this question.

All right, so lung cancer has significantly changed from what it used to be even 10 years ago. Before it was squamous or nonsquamous, and then now we have become to the molecular pathology level, and then a PDL-1 expression. So lung cancer is no longer one disease, but many diseases. And that's what makes the treatment more complex. My mentor, Dr. Alex Adjei, told me that for a long time, it was carbo-taxol, and that was always the right answer. That is not the case anymore.

And what is important for our pulmonology colleagues is that a lot of these therapies are moving to the early stage. What this means is that we are not - we're now doing therapy in patients that before that would only get surgery. And this is the current algorithm for the treatment of small - non-small cell lung cancer includes neoadjuvant therapy, adjuvant therapy, and for metastatic setting.

The goal of this presentation is not for a breakdown in molecular aspect, but how can our pulmonology colleagues be involved in this growing complex treatment paradigm that changes every 6 months for lung cancer.

So honestly, when you see the algorithms like where do I go, all this drug has very different names. I went to pulmonology, so I don't have to learn these drugs. What we've, for this webinar, we simplified this presentation quickly. So why is this important? Because we are required more and more tissue at the time of diagnosis. Before for early stage, we were thinking that we're going to get tissue at the time of resection, but now is changing. We need tissue before resection. And that is quite important, as many of you are essential members of the multidisciplinary team. And always, always tissue will be the issue with lung cancer, particularly now that 50% of patients have a target mutation. So for stage 1B to 3A that are resectable, nonsquamous, we need EGFR testing at the time of diagnosis. For stage 3 known squamous, they get definitely chemoradiation, we still need EGFR, because we know these patients will not benefit as much for an immunotherapy after chemoradiation. And, Dr. Rimner is going to talk about the PACIFIC study. But we need the testing so we don't put patients on drugs that don't work for them. And for advanced metastatic, all nonsquamous need to get testing. And for particularly patients, non-smokers, young patients will need that as well.

So everything changed in the adjuvant treatment, when we had the ADAURA trial. And this is different. These are patients that require tissue genomic testing at the time of diagnosis. So the ADAURA trial was presented in 2020, and changed how we treat patients with EGFR mutations that have resectable disease. So the ADAURA trial is a phase 3 trial that included patients that have limited stage disease, 1B to 3A. And we have to remember, all of these is basically a classification that is no longer up today, is the seventh and now we're in the eighth.

So these patients went to surgery. But there were - most of them were recruited before surgery, meaning genomic testing happened at the time of diagnosis, then they were randomize - they gone - they went to surgery, some of them got chemotherapy after the surgery, not all of them, and then they were randomized to osimertinib, which is an EGFR therapy for 3 years versus placebo. Their main endpoint was disease-free survival. And the study was terminated early because of the great response that was observed. And this is the benefit.

So this is disease-free survival. We're showing the group that benefit the most, the stage 2 and 3A. And the differences between disease free survival, 20.1 months versus 14.9 months. And I always joke about it, because you can put a truck in between these two lines, but that is disease-free survival, right. And the data for overall survival is still pending. And how like – I know thoracic – I know pulmonologists, how these matters. It matters because we need tissue at diagnosis for genomic testing. And it matters because these patients in osimertinib for 3 years, and osimertinib is known to cause pneumonitis. So I always work with my pulmonologists when we see these very challenging situations in these patients with osimertinib. And it's a great one, it's a great tool that we rechallenge these patients.

So this is the overall sur - the overall population including stage 1B. The benefit is less, so the hazard ratio is still 0.20. This is the most updated data we have for ADAURA. But we still don't have overall survival, we have 30 to 40% material data.

So what happened with this drop? Well, we noticed that not everybody benefits the same. So stage 1A - B has the less benefit, and a stage 3A has the greater benefits. And that's obvious in these Kaplan Meier curves. You can see the more advanced stage, the greater the benefit for disease-free survival. So for 1B, I often have conversations with my patients, because none of these patient may have been cure, and they don't need 3 years of osimertinib, and all the side effects that comes with that. For 3A, definitely because they have a 75% chance of having recurrence if they don't go on the EGFR therapy. For a stage 2, they have a 40 to 50%. So that's right in the middle. But I usually for 2B and above I recommended therapy because the benefits are greater.

Also, these patients are quite young, EGFR mutant, they're never smokers. So they don't have competing comorbidities that, you know, will affect a survival, most of these patients will die of the disease. So you want to make sure that you give them the chance to get better, or potentially cure. There are some theories that we may be treating micrometastatic disease, but we still don't have overall survival to answer the hypotheses.

Something that's very important about ADAURA. This was presented at ESMO after ASCO, is that significantly decrease the recurrence in the CNS, from 1 to 10%. So 10% is the placebo group. The majority of these patients got chemotherapy in the adjuvant setting. And the challenges with CNS disease is just very morbid, particularly for patients that have no other comorbidities. It significantly in patient's affects patients quality of life.

So in 2020, as everything started changing after surgery for local lung cancer, these patients with EGFR mutation, which are 13% of

patients with lung cancer, now are going on EGFR for therapy for stage 1B or above, meaning tissue at diagnosis and complications for osimertinib in a new population.

Well, if things couldn't now get more confusing, we're back to where we started. So many neoadjuvant studies in lung cancer were negative. They didn't show benefit. So we didn't do neoadjuvant therapy. But that changed with CheckMate-816, what incorporates chemotherapy and immunotherapy. So the new wild factor in this combination is immunotherapy. So CheckMate-816 is neoadjuvant nivolumab, plus a platinum-based regimen for stage 1B, to 3A. So these are patients that newly diagnose, the tumor's 1B or higher than 4 centimeters, and they have to have no sensitizing EGFR or augmentation. Why is that important to me? Well, again, we're now doing NGS at diagnosis for early stage, because these patients with EGFR mutation, and an ALK alteration should not go on neoadjuvant therapy, because immunotherapy doesn't work for them. So we don't want to delay therapy or delay surgery to give the neoadjuvant therapy when the drug doesn't work.

So these patients were randomized to nivolumab plus chemo versus chemo alone, then they went on surgery. Some patients have optimal chemotherapy after, most patients do not, plus/minus radiation. And this is a new endpoint that we are learning from our breast cancer colleagues and is complete pathologic response or pathologic complete response. And the differences are clear, the people that received the chemoimmunotherapy had a complete - pathologic complete response to 24% versus 2.2%. And you can see why the neoadjuvant studies in chemotherapy were not successful. There was a difference regarding the intention to treat versus the patients that got the resection, but the difference was still very large between the patients that got the combination therapy versus the chemotherapy alone. Again, patients with ALK and EGFR mutations should not get this.

So a lot of concerns from my colleagues and surgeries like neoadjuvant therapy can delay therapy they can now allow patients to get surgery on time. So these data was later presented by a surgeon and showed that neoadjuvant immunotherapy plus chemotherapy do two things, one it reduced the time of surgery, the median time for 184 minutes to 217, but also reduced the amount of surgeries, there are no numbers that patients are needed total pneumonectomy 17 versus 25. These are numbers, not percentages. A lobectomy increased from 77 for the ___ 14:46 arm versus 61. So what we saw is the combination not only make surgery shorter, but also may allow for some patients to get less invasive surgery for a pneumectomy to a lobectomy, and complete resections were more possible. But neoadjuvant immunotherapy should not be used to downstage patients. So, neoadjuvant immunotherapy did not negatively affected surgery outcomes. And that was one of the main concerns.

What about side effects? If you give my patients all these fancy drugs, they're going to get sick and navigate to surgery. Well, there was no significant difference between adverse events between the chemotherapy arm and the chemotherapy arm, the combination experimental arm. There were more immune-related adverse events, but that all makes sense. If you get you get more immune-related adverse events. But overall, the adverse events did not significantly delay surgery for these patients.

And this is just a summary, major pathologic response, pathologic complete response, and experienced downstaging were the benefits of neoadjuvant chemoimmunotherapy in this patient population. And since then, it was approved on March 4th of 2022. Things changed. A lot of patients, particularly patients who are at higher risk for recurrence, stage 3A, stage 2B, other risk factors in the histology of the tumor are getting neoadjuvant chemoimmunotherapy. So these patients can get complications from the nivo 16:31 prior to the surgery, that we need or pulmonologist friends to help us. And also because we know immunotherapy stays in target for quite some time. They also can have side effects from the immunotherapy including pneumonitis after the surgery. And of course, we need tissue early on to do NGS so the wrong patients don't get the wrong therapy.

And I can tell you, my tumor boards completely changed after this. Because now the conversation is now, 'I will see him in the clinic when he goes to go surgery.' That's usually what we used to say as medical oncologists. Now we're being incorporated early in the conversation for these patients. Now we're requesting NGS early.

And liquid biopsy. Going back to webinar number 3 – 2 or 3. Number 3, I think. Liquid biopsies are not very good for patients that have disease in the chest only because the patient is unlikely to be shredding tumor DNA. So tissue is an issue here.

So let's make things a little bit more complicated. Neoadjuvant therapy is approved, targeted therapy, adjuvant therapy is approved. Now we added immunotherapy in the adjuvant setting with IMpower010. So IMpower010, as atezolizumab, an immune checkpoint inhibitor for a year for a patient after they get resected. So this trial is completely resected patients 1B to 3A, you can see their recurring team here 1A to 3B, tumors higher than 4 centimeters because the classification changed. So they got surgery. These patients did not get neoadjuvant therapy. Then they get adjuvant chemo for one to four cycles. And then they were randomized to follow-up, because that's what we used to do, follow up and pray that the cancer doesn't come back, or elotuzumab for a year which is 16 cycles because it's every 3 weeks. The primary endpoint was disease-free survival, same outcome as the ADAURA trial for EGFR. This trial was a little bit more immature than the ones that we have seen.

So this is the data for a stage 2 to 3A non-small cell lung cancer with a PDL-1 higher than 1%. So for these patients don't we only need NGS, we also are needing PDL-1. We didn't need PDL-1 for early stage before, because what are you going to need the PDL-1 for? Didn't really affect much, but now we need it because it atezolizumab in the adjuvant setting, meaning after surgery, is only approved for patients with a PDL-1 higher than 1. If it's less than 1, they cannot get the drug. So these patients are getting atezolizumab for a year. What that entitles - I have two patients already getting this drug. These patients are - some of them are cured, but the immunotherapy adverse events are still there. And those are relevant I think for any internal medicine specialty, because we need an endocrinologist, a rheumatologist, a pulmonologist; all of them to help us deal with these adverse events. Because now, some patients are a stage 1B to a stage 4, are going on immunotherapy. Many institutions are developing clinics specialized for immune-related adverse events.

So what about overall survival data? Still very immature. So the three studies that we just discussed do not have overall survival data. So this is like approve, hurry up, and wait for overall survival data. For neoadjuvant and adjuvant trials, it takes quite a longer to get these results. I won't make any actual conclusions of these overall survival data curves, because the data is still very immature. But we don't have data for any of the three trials.

IMpower110 more immune-related adverse events compared to placebo, because as best supportive care you cannot drug. There were grade 3, grade 5 immune adverse events in the experimental arm, that means were a few deaths, jury for pneumonitis. And grade 3 and 4, around 22%. So these patients are going on these drugs with more adverse events than no drug, and systemic steroids around 12% of them. And atezolizumab was approved. So now we have three different regimens by three different trials that change how we treat lung cancer in less than two years.

And just to add to this, there's also, which is very similar to IMpower10. The difference here is the agent. So instead of being atezolizumab, it's pembrolizumab. These results were also very promising. So immunotherapy in the adjuvant setting is probably here to stay. We don't know yet because we don't have overall survival data. But that increases the pool of patients that are going to be in immunotherapy to close to 90%. Because we have 60% of patients that are stage 4, that even if you have a target mutation, eventually they will get to immunotherapy when they develop a resistance to the mutation or to the targeted therapy. Then we have the patients with squamous cell and patients with small cell that also get immunotherapy, and now we have a stage 1B to 3A that can get immunotherapy before surgery, three cycles, all can get after surgery.

And let's put the cherry on top of the cake. There is a study done in China that is actually combining the neoadjuvant and the adjuvant. It is not approved in the United States, and the FDA said it will not approve it until the study's done in a population that looks more like the U.S. But this study is including neoadjuvant chemoimmunotherapy, surgery, and then immunotherapy for a year. So you are going to see all the immune-related adverse events during that interval treatment.

So additional updates outside of the immunotherapy window, we're going to go back quickly to the targeted therapy. And as the CODEBREAK-100. This was presented in last year and is currently approved. This is KRAS G12C. And why is this important for me as a pulmonologist? Well, patients with KRAS G12C tends to have higher prevalence of smoking history. They're still nonsquamous, they're mature almost all of them, but they have a higher smoking history. So these are patients that we always collaborate with our pulmonologists because they tend to have COPD, or many other lung issues and they're going KRAS G12C, which was found to be untargetable. But there's always a joke that the GI oncologists say, 'We cannot target KRAS,' and then the thoracic oncologist said, 'Hold my beer,' and then we developed KRAS therapy. I don't know if that really happened, but it's a good joke.

So KRAS therapy, it is approved in lung cancer. This is around 12% of patients, making that 50% of patients with a target mutation. The agents can be hard to tolerate, and a big pill burden.

And let's make things more complicated, we have a drug that soon will be approved for HER2-mutant non-small cell lung cancer. So this is around 1 to 2% of patients with lung cancer and that we make that 50% or 52%. This comes from the DESTINY trial that was done by Dr. Janne, here at Dana Farber, and this shows that patients with HER2 mutation can go on these. This is a drug conjugate that includes a monoclonal antibody with a linker and a topoisomerase inhibitor that has a payload. What this means to us - what this means to a pulmonologist, well, around 11 to 13% of these patients develop ILD as a side effect. We expect that this compound is going to be approved in the second line setting probably in the next 4 to 6 months. So with 11 to 13% of ILD, we are going to need definitely all of you because these patients with HER2-mutant non-small cell lung cancer are usually never smokers, majority woman. So the first line therapy is chemoimmunotherapy and then they go - if - when this drug gets approved to HER2-directed therapy with 11 to 13% of ILD. And they actually had several deaths due to ILD in this study. And that's going to be a new ballpark for many of us. We didn't see these toxicities with HER2-directed therapy in breast cancer, and it's just because the patient population is very different compared to lung cancer. But that just increased the amount of collaboration and importance of multidisciplinary teams.

All right. So what is the summary all of this? Lung cancer treatment keeps changing. Now have neoadjuvant chemoimmunotherapy that is approved. Patients get around 2 to 3 cycles prior to surgery. And patients need to be tested for NGS or next gen sequencing or

biomarker or genomics. We have so many names, but the point is they need to be tested prior to getting the therapy. So we need the tissue to get a least EGFR and ALK testing. Then they go on the neoadjuvant therapy, then they go on surgery. Then we have adjuvant immunotherapy, where you need a PDL-1 to be higher than 1%. Here the needle tissue is less. And then we have the adjuvant EGFR therapy. Finally, there's one new drug that is expected to be approved for HER2-mutant non-small cell lung cancer that has a higher frequency of ILD. And, of course, the 3 years of osimertinib comes with pulmonary complications.

I tried to summarize all these trials in 25 minutes, and it can feel quite overwhelming. But the point of all of this is that our patients are going to live longer, and they're going to live better, but they're going to need us more because there's more and more patients. The overall survival in non-small cell lung cancer in the early 90s was 6 months. Now in patients with ALK-mutant non-small cell lung cancer, the median survival is 8 to 9 years. So you see how the amount of patients are increasing. And it's a wonderful thing, but we need to be prepared for them.

So takeaway points. genomic testing is a critical part of the initial workup. And should be completed before starting immunotherapy in the neoadjuvant setting. And also prior to any clinical trial enrollment in the neoadjuvant or adjuvant setting. Immunotherapy has become the standard of care for patients to the entire continuum for stage 1B to a stage 4. There is new targeted therapies. And there is new side effects we are learning. As a rapid evolving treatment landscape, for my collaborators, CHEST and other organizations are here to keep you updated.

And finally, question two, which of the following targeted agents is approved and is the preferred agent for treating EGFR-mutant non-small cell cancer after complete surgical resection? Osimertinib, or atezolizumab? And you need to - I don't want to say the answer. You need to do the homework. Thank you so much.

Dr. Murgu:
Very nice. Thank you, Dr. Flores, for a great review of the landmark studies. Yet I do believe, as you said, it does affect what we do weekly in our multidisciplinary tumor board.

As I'm reflecting on your talk, I have a couple of questions that as a pulmonologist, I'm thinking when I do a biopsy for lymph nodes, we always know that we get pretty reliable material for molecular testing and for PDL-1. But before looking at even more limited disease, stage 1A, B, but no lymph node involvement, that sometimes become a challenge to assure adequate material for comprehensive genetic testing. For PDL-1, I don't think people struggle that much anymore given that only 100 cells are needed. But you mentioned the need for obtaining NGS at diagnosis, regardless of the stage. Can you please comment again, and just clarify for us how that impacts management, independent of OC 30:30, for the EGFR-mutated tumors? Because I think it's different than if we have a target for an early stage, given only one mutation. You know, maybe people can just do directed EGFR testing versus getting a large panel. Although we don't have targeted agents in the neoadjuvant settings. Can you clarify the need for large panel NGS for very early stage?

Dr. Florez:
So I am a proponent of NGS because we are always to include patients in other adjuvant trials that are going on for other target mutations. But if you have very limited tissue for 1B, 2A, EGFR should be done as a rapid EGFR, so you need less tissue. So if you know you couldn't get enough tissue, then EGFR alone is for targeted - for approved therapies. If you do have more tissue, then of course, we're going to advocate for NGS and you're never going to find a medical oncologist was going to tell you no, don't do the NGS, right. So if you have limited tissue, EGFR and ALK should be prioritized outside of the panel, because those patients should not get neoadjuvant or adjuvant immunotherapy.

And there is a question here in the Q and A that is very important. And it’s that, are you concerned about the delay in getting the NGS prior to the start of 32:00 neoadjuvant? Yes, it's quite concerning, particularly in areas in which getting genetic testing is challenging, right. So that if you think the turnaround time is going to be too long, then just doing a spot EGFR and ALK should be the way to go

Dr. Murgu:
And then one more question, as I’m just learning about the CODEBREAK-100, that was for stage 4, I suspect.

Dr. Florez:
Yes, it was only for stage 4.

Dr. Murgu:
And that is non-small cell, nonsquamous or non-small cell allcomers?

Dr. Florez:
The majority of the KRAS mutations by far happen in nonsquamous. But it’s a different patient population that other patients with target mutations, because these patients usually have a heavy smoking history compared to the EGFR, ALK, ROS1, that usually never

smokers. So you have more comorbidities with a drug that's already toxic.

Dr. Murgu:
And maybe last question from my standpoint, I don't know, Eric, if you have any or Andreas. In your institution, just to bring your institutional bias into discussion, do you perform NGS for squamous cell, independent of the younger population non-smoking, you know, that's in the guidelines, but outside of the guidelines, do you routinely do NGS for squamous?

Dr. Florez:
So we don't do NGS for the - as a clinical NGS. So we have our own protocol called 17,000. That's the name of the protocol - the number of the protocol in which we're able to do NGS within our research study. So we have that privilege, that patients won't get charged. Because the problem about doing squamous NGS is that sometimes it doesn't get approved by the insurance. But here, I'm able to do that. And because my clinic consists of mostly younger woman, I do NGS on the majority of my disclaimers, because our 50, 48-year-old with very limited smoking history. But yes, we have the privilege to do NGS in squamous through our research protocol. But it's very challenging outside of these privileges to do it because insurance coverage for those patients.

Dr. Edell:
Excellent, excellent job. Very nice presentation, very thorough. I just want to make - you made this point a couple of times, but I want to reinforce it for our viewers that - and I think we've discussed this at our tumor board, particularly since these studies have come out this year.

First of all, the overall survival, we're waiting for. It's a work in progress, and we need to ensure that patients see both our medical oncologists and surgeons as we go down this pathway. And secondly, this is really for stage 2 and greater. As you said, stage 1B is now stage 2A, at greater than 4 centimeters. So we don't want our viewers to get confused. The 1B's, very few are - of the team are going to be giving neoadjuvant with immunotherapy for a true 1B in the eighth edition.

So, but exciting times. It's really wonderful that we're able to see this advancement. And I'm excited now to hear from Dr. Rimner regarding the changes and the advancements that he's seeing in radiation oncology.

Dr. Rimner:
Thank you very much for having me. It's my privilege to present to you the updates on clinical trials in advanced lung can - locally advanced lung cancer in radiation oncology.

Here are my disclosures. Of note, I do have several investigator-initiated trials, mostly related to this presentation from AstraZeneca and Merck. I'll be as objective as I can.

Here's question number one. Which of the following treatment paradigms is the current standard of care for unresectable, inoperable stage 3 non-small cell lung cancer? Is it concurrent radiation therapy and durvalumab followed by durvalumab? Is it concurrent chemotherapy, radiation therapy, and durvalumab followed by durvalumab? Or is it concurrent chemotherapy and radiation therapy followed by durvalumab? And please enter your responses now.

Okay, it seems like the audience is very much on the same page, so maybe I don't need to give my talk.

So when it comes to multimodality therapy, here is an overview over what we can do. You heard from Dr. Flores about the resectable patients, here on the left column, and the neoadjuvant therapy, definitive therapy, and adjuvant therapy. And when it comes to deciding between resectable and unresectable, I always teach our fellows that you have to start with deciding on the definitive therapy and whether you take a patient down the surgical approach or the nonsurgical approach. And based on that, you can build the other components around the definitive therapy as building blocks. If it is surgery, you consider new adjuvant or adjuvant therapy. If it's not surgery, then radiation therapy is the definitive therapy and can be combined with concurrent chemotherapy, sequential chemotherapy, or with chemotherapy first or after radiation therapy.

Now, this has gotten more complicated as you've heard by the role of immunotherapy, which is now being entered into all of these different components and plays a role in the neoadjuvant setting or adjuvant setting as you heard. And the same thing is happening and actually happened first in the unresectable patients and we will go over the data for that in the definitive radiation therapy or chemoradiation therapy setting.

And this is what my talk will focus on, on the unresectable patients that are being treated with definitive radiation therapy.

It's been known for quite a while that radiation therapy is a great tool to increase tumor immunogenicity, in that it can increase the available tumor antigens to the antigen-presenting cells. And it can upregulate MHC-1 and alter the tumor microenvironment to really attract dendritic cells and tumor specific T-cells also tumor-infiltrating lymphocytes. And it goes together with a whole change in the

cytokine milieu in the tumor microenvironment. And it does that by really breaking down the cells and, as the cells die, they set - release you know, all their different components in a inflammatory environment that then really activates the immune system.

Now, tumors traditionally have had escape mechanisms that by releasing immunosuppressive signals, and that is really where the anti PD or PD1 or PDL-1 therapy came in, that really releases those breaks to make the immune system then recognize the cancer cells again or their antigens. And by doing so, then attacking even the live cancer cells.

And the PACIFIC trial was really the key trial that put immunotherapy on the map for stage 3 lung cancer. And that was a trial on unresectable stage 3 non-small cell lung cancer who were treated with chemotherapy and radiation. And were then enrolled after completion of chemoradiation, and randomized to the addition of durvalumab, an anti-PDL-1 antibody versus placebo and in a 2 to 1 randomization. And they had to start within 42 days after concurrent chemoradiation. The primary endpoints were PFS and OS co-primary endpoints, and we now have 5-year overall survival data that were just published in the JCL.

And these are the updated overall survival curves. You see that the overall survival had a hazard ratio of 0.72 with the addition of durvalumab, and it increased the 5-year overall survival from 33% to 43%, a 10% increase. And that's been the largest increase that we've seen in the management of stage 3 unresectable lung cancer in the last 20, 30 years. And this was accompanied by an improvement in progression-free survival, about 14, 15% from 19 to 33% at 5 years, so about a third of our patients now are free of disease progression at 5 years with stage 3 locally advanced non-small cell lung cancer.

Now, one of the questions was, now we have an effective drug, but does it improve survival by improving distant metastatic rates and preventing distant metastases or by intrathoracic local recurrences? And the PACIFIC trial did not enroll patients prior to chemoradiation, so we don't have detailed chemotherapy and radiation data. And so we couldn't determine exactly local control in the sense of is the primary tumor or the lymph nodes that were initially involved, what recurred. But what we do have is the intrathoracic versus the extrathoracic progression. And this is what was presented in 2019 at ASTRO. And you can see that durvalumab improved the intrathoracic progression, which includes, let's say, you know, metastatic lung nodules, but also, of course, lymph nodes and the primary tumor, as well as extrathoracic progression, meaning distant metastases. So it is effective on both. And that is likely what adds up to the progression-free survival and to the improvement in overall survival. And so we finally have a drug that can work on distant as well as intrathoracic disease control.

Another aspect that was really interesting when diving deeper into the data was that about two-thirds of the patients that did progress after the PACIFIC protocol of chemoradiation and durvalumab, progressed only in one or two lesions. And that is particularly relevant as local therapies, such as surgery or radiation therapy now play an increasing role in the treatment of what we call oligo progression, meaning patients that when they progress, only progress in one or two metastases. And so this is based on two or now three phase 2 randomized trials that showed a 6-month benefit just with the addition of local therapy in the oligo metastatic setting. And it's remarkable how similar these trials were even though there were three independent trials. And if this was a novel drug, it would get approved right away with this kind of benefit.

Now, what are the open questions at this point? Building on these data, can we give immunotherapy concurrently with chemoradiation? And how do we balance that against toxicity? How do we treat patients that are not fit for concurrent chemotherapy and radiation and consolidative durvalumab so they are not fit for the PACIFIC regimen? We also are looking into questions of what the optimal radiation dose and fractionation is whether we can elicit an even more effective immune response. And on the industry side, there's a lot of interest in combining anti-PDL-1 and PD and PD-1 drugs with other immune modulators, co-stimulatory drugs. And then lastly, which are the optimal drugs? And can we do dual checkpoint inhibition? Now, I'll present some of the trials that are ongoing.

So KEYNOTE-799 was the first trial trying to give concurrent anti-PD-1 therapy using pembrolizumab with concurrent chemoradiation. And this was a two cohort trial not randomized. Patients were given a carboplatin paclitaxel backbone or a cisplatin pemetrexed backbone in nonsquamous patients only. The Cohort A was combined squamous and nonsquamous cohort. And this was published by Dr. Jabbour, in *JAMA Oncology* and the results were quite promising with an overall response rate of around 70%. And you can see the curves here with, you know, that are really quite remarkable for, you know, a stage 3 patient population. And this was regardless of PDL-1 status.

The toxicity overall was manageable, though slightly increased compared to what we saw with concurrent chemoradiation or the PACIFIC regimen with grade 3 pneumonitis, meaning requiring oxygen or hospitalization of somewhere around 7, 8%. In the PACIFIC trial, that was more around 3, 4%. In the real world, the data are likely is a few percent higher again. So this is important information again for you as a pulmonologist, just as we combine these drugs, as we pile on more and more drugs and combinations, the pneumonitis rates are going to inch higher.

The PACIFIC-2 trial is looking at a similar question, but in a randomized fashion, 2 to 1 randomization of adding the durvalumab to the

chemoradiation versus placebo and chemoradiation, but followed by placebo. So this is essentially moving up durvalumab by about 8 weeks to start together with concurrent chemoradiation, but it compares it to the old chemoradiation-only approach. And so this will probably read out later this year, and will be interesting; however, it will be difficult to compare to PACIFIC-1, because PACIFIC-1 is now the standard. And we will not know exactly should we now, let's say this works, give the durvalumab up front or only after chemoradiation. And so we don't know exactly how they will compare to each other.

However, an important advantage of this trial will be that patients are randomized from the beginning. So we will have detailed chemotherapy and radiation information. And we will be able to answer some of those questions that were not possible to be answered by PACIFIC-1.

Now this ECOG trial will answer exactly that question because it randomizes patients off essentially PACIFIC-1 versus PACIFIC-2. So PACIFIC-1 is concurrent chemoradiation followed by durvalumab versus concurrent chemoradiation plus durvalumab followed by durvalumab. So this will be really the tiebreaker trial if you will to give us the final answer of how these two compare to each other in terms of toxicity as well as efficacy. And we look forward to these results.

The CheckMate-73L trial is essentially a similar trial looking just at a different compound, nivolumab. And it's given either concurrently with chemoradiation, followed by a dual checkpoint inhibition, ipi/nivo, or by nivolumab alone, which is essentially PACIFIC-2, just with nivolumab. And it compares this in a three-arm trial to the PACIFIC-1 regimen, concurrent chemoradiation followed by durvalumab.

Of note, there was a small trial looking at ipi/nivo combined with concurrent chemoradiation and that was too toxic. So ipi/nivo as a dual checkpoint inhibition, combined with concurrent chemoradiation is too toxic. We'll see how it works in the consolidation setting.

Now this is all nice and good for the patients that are the fittest and the best and the strongest out of the nonsurgical patients. But the reality is depending on how aggressive your surgeons are that many of the patients who are not fit for surgery may also not be fit for concurrent chemoradiation, followed by durvalumab or in the future maybe for quadruple therapy of concurrent chemoradiation, durvalumab, and X. So what do we do with these patients? They don't have an approved indication. And about - at our institutions about 50 to 60% of patients who are not fit for concurrent chemoradiation, because they're too old, have organ dysfunction, or the tumor is just too large and bulky. And so traditionally, we will treat them with sequential chemoradiation or just radiation by itself, which has a 5-year survival or 5%. So that's really not, you know, that's barely better than palliative therapy. And so we need to find solutions for that.

PACIFIC-6 is one of those attempts. And it's looking at these stage 3 patients that are frail, it's a phase 2 open-label trial. And it's looking at sequential chemo RT followed by durvalumab. We have taken a different approach. This is our phase 2 study. And it's a single-arm study and we combined definitive thoracic radiation with durvalumab. The concurrent chemotherapy adds about 5% overall survival over radiation alone. But as you've seen, the durvalumab, especially early on, added about 15 to 20% progression-free survival and 10 to 15% overall survival. So in this already frail population, we're essentially trying to replace chemotherapy with durvalumab concurrently. And this trial is two-thirds accrued and we will have a planned interim analysis presentation as well as lung in August of 2022. So stay tuned. I can't say more than that because the data is embargoed.

And OGLU004 49:40 is a trial from my colleague Dr. Lin 49:43 at MD Anderson where he tested a different type of radiation or different dose of radiation, 60 Gy and 15 fractions as opposed to the standard for just 60 Gy and 30 fractions over 6 weeks. So cutting the treatment duration in half to 3 weeks and giving a higher dose of radiation each time. And the initial endpoint was to first prove that that is safe to give a higher dose per fraction in combination with durvalumab without chemotherapy, and it turned out it is actually safe. But it was a small first initial trial to look into that in this patient population. So we'll likely see another trial building on this through the NRG Cooperative Group, that will look into fractionation and combination of radiation and durvalumab.

Now, there are a whole bunch of immunotherapy-enhancing compounds and this is only a small selection. This is by no means complete. That are ongoing, COAST, SKYSCRAPER, ___ 50:45 and ___, just a few of them. And these are all combinations of different antibodies like anti-TIGIT, or anti-CD73 that are trying to enhance the anti-PD-1 or anti-PDL-1 effects.

The first one to read out is the COAST study, which was a phase 2 randomized study that was presented at ESMO 2021. And combined - compared to patients getting the PACIFIC regimen with durvalumab and oleclumab, or durvalumab and monalizumab. And the results were this, another big jump in progression-free survival from 39% to, you know, the 70% range at around, you know, close to a year. Now, some people say that the PACIFIC arm in this trial underperformed, but nevertheless, this is a big improvement in a randomized phase 2 trial. The numbers are still a little bit on the small side. We'll see whether it holds up in a larger trial. But still, you can see how the immune therapy enhancing compounds really may very well push the curves higher, which is great for our patients.

We are currently performing with my colleague Dr. Shaverdian, an anti-IL-1 beta trial in combination with PACIFIC. IL-1 beta is important in tumor promotion and decrease that immunosuppressive microenvironment that I mentioned earlier. It can also interestingly, suppress pneumonitis and pulmonary fibrosis. So it has the potential of making, you know, the chemoradiation and durvalumab more

effective, but also decreasing toxicity, which is - would be a great combination and sort of the ideal combination, which rarely happens when we combine new drugs or add more drugs. But this is why we're very excited about this trial. And we're essentially adding kind of canakinumab to standard chemoradiation followed by durvalumab, the PACIFIC backbone. And, yeah, this is an ongoing trial, it's about halfway accrued. And we do not have formal results yet.

Not to forget, even in the unresectable patient population there is - there are patients with EGFR and driver mutations. So this is the LAURA study. And it's looking at, similar to the ADAURA study, adding osimertinib on the back end after chemoradiation versus placebo. And this is specifically for patients with EGFR mutations.

On the radiation oncology side, I would be held accountable as a radiation oncologist, I wouldn't be talking about what we are improving on the radiation side. There are novel technologies that allow us to target the tumor even more precisely, avoid the lungs even more than we can do right now. There are increasing MR linear accelerators that really allow soft tissue imaging to a degree that we haven't been able to do. In the thorax, it's a little bit challenging because of all the tissue density differences. But we are making progress and especially for the mediastinum and the heart, the esophagus, it can be very beneficial to be able to see those, even during the treatment and adapt the radiation as the tumor shrinks. It also has functional imaging capabilities, which might be very interesting in the future to detect early responses.

And then there's proton therapy, which is a specific radiation technique that allows the radiation to stop and maximally spare organs that are distal to that stopping point. And there is an ongoing randomized trial RTOG-1308, which compares protons versus photons. So that can be very beneficial in some patients when the anatomy and the geometry is right.

Talking about new biomarkers, circulating tumor DNA is a hot topic and it is not quite ready for primetime in the stage 3 settings, mostly because of detection issues. You heard from Dr. Flores how we all need more and more tissue because we're doing more and more genomic testing. And we do it early on earlier but it is challenging, especially in the unresectable patients. And so CFDNA would be a great way to circumvent that issue. We just presented a poster at ASCO a few weeks ago, where with, we were able to identify a tissue and form patient specific-assay, and develop that to detect 100% of stage 3 patients and even close to 60% of stage 1 and 2 patients, which really has not been described before. And we could see that it really separates between the patients that progress and recur, and those who don't. And you can see how these curves separate, especially when you get longitudinal testing, multiple testing points. And yeah, so there's great hopes that this will allow us to circumvent some of the tissue challenges that we have in these - in this frail patient population.

So in conclusion, concurrent chemoradiation followed by consolidation durvalumab is the standard of care for unresectable and inoperable locally advanced non-small cell lung cancer. We are looking at different fractionation of radiation, combination of immunotherapy and radiation without chemotherapy, or other immunotherapy-enhancing combinations. Future developments certainly on the radiation side include novel technologies such as the MR-linac and proton therapy and biomarkers such as CTDNA.

And that brings me to the second and last question, what is the 5-year overall survival with concurrent chemoradiation followed by consolidation durvalumab, the PACIFIC regimen? Is it 33%, 43%, or 53%? Please enter your responses now. And I thank you for your attention. Happy to answer any questions.

Dr. Murgu:
Thank you, Dr. Rimner. I again, I appreciate you updating us on what's new in radiation oncology trials. And as again, as a pulmonologist who also does Intensive Care Unit medicine, I unfortunately encounter patients that sometimes suffer toxicity both from radiation or radiation plus IO. And, you know, in the ICU setting, the severity is such that we always treat, right, with high-dose steroids. The challenge comes mainly in our clinics. And as Dr. Flores mentioned, you know, at the University of Chicago, we also have a dedicated clinic, just on IO toxicity, but occasionally they need people like me to go and do a biopsy or a lavage. And I always wonder, does it matter if people have an IO-related toxicity or XRT-related toxicity, since you end up placing everybody on steroids anyway? It's a very pragmatic question. As long as they don't behave infected, I feel like there is always this request for bronchoscopy with lavage, maybe even biopsy. And can you share what's in the guidelines in regards to that, if there are any? And maybe your institutional bias on how you address IO and XRT-related toxicity, especially when in combination, we know that the percentage is higher? And I think we've all seen that.

Dr. Rimner:
Yeah. The short answer is no, we don't. And I agree with your pragmatic approach. Unfortunately, steroids are the only treatment that we really know of. And it works for both, at least in most people before they get to the ICU setting. So the vast majority when you initiate steroids early enough, when they develop grade 2 pneumonitis will reverse quickly within a few days, and then it's just a matter of keeping them on the steroids long enough, especially for the radiation pneumonitis until it's settled down over time. I think it's my sense that radiation pneumonitis can hang around for a little longer, and maybe it's tapering slower is more important. Ultimately, it is really

tapered to patient's symptoms and trying to prevent a rebound of symptoms.

In terms of determining whether it's from radiation or immunotherapy, I think the pattern radiographic can help. It doesn't necessarily change the management but when it's very diffused bilateral, it's more likely immunotherapy. If it's sort of restricted to the radiation field, it's more likely radiation or a combination of the two. But there are examples also, where, you know, even before the immunotherapy era, you would see a diffuse bronchiolitic picture from just radiation alone or chemoradiation. And so it's not a perfect measure.

For - I don't use radiographic pictures really to determine who needs to be initiated on steroids. I think it's a clinical diagnosis. Almost every patient who gets radiation has a radiographic inflammatory picture to some degree, but most patients, 80%, 85% do not ever develop symptoms related to that and that's okay that. You know, that's as if you had surgery and you have a scar from surgery, you know that you had surgery, you know that you gave radiation. That's not something I would jump on. But it's based on clinical presentation.

There's only - we just completed actually a randomized phase 2 trial at Memorial on the use of nintedanib in combination with steroids. Nintedanib has been approved for IPF, and has been quite promising. And the manuscript is hopefully to be accepted sometime in the next week or so. It's under review. And that was promising. We presented the results and that showed promise in reducing pulmonary exacerbations in the following year compared to steroids alone. So that might be an avenue in the future. I don't think - that was only in radiation patients, that was before the immunotherapy era when we performed that trial. How that applies to immunotherapy pneumonitis, I don't know.

Dr. Murgu:
And my follow-up question, then - and I don't know if Dr. Flores has - wants to chime in on this as well.

Dr. Florez:
A quick add-on I think something that helps me with immunotherapy pneumonitis versus radiation is the response to steroids tends to be a quick, faster for the immunotherapy-induced pneumonitis. They tend to feel better also. Only a few patients that give steroids don't feel great, you know, like the tiger from the commercial and the cereal. But I think, right, I feel great. I'm ready to go home as soon as he starts is on 1 milligram per kilogram. But their response to steroids is faster. I have seen it with neo-related toxicities that are radiation.

Dr. Murgu:
And my question maybe for the end here on this, as Eric has other questions. In this combination trials of immunotherapy and XRT, it looks like the outcomes are always the same as in oncology, right? Disease-free survival, overall survival, etc. Do people look at the quality of life at all? Is that measured and objectively documented? I'm looking more for a patient-centered outcome in trials that have a higher risk for toxicity. Can you comment on that?

Dr. Rimner:
I can say for our own trials, definitely I have PROs included in all of them. I have not seen a lot on the ongoing trials yet I think they usually take a little longer to read out. And obviously you want a little bit more follow-up. Also, the challenges that they're not always the most sensitive instruments, so you need large trials to really see a difference. So I think while I think it is very important to include in all the trials, to really see a difference in a randomized trial, you need a big difference in effect to see that in a PRO. But I completely agree with you. I don't think you'll - they are sensitive enough to see like a 3, 4 difference in grade 3 pneumonitis or so. You'll have to look at larger references.

Dr. Edell:
In that same vein, is there any work looking at any sort of predictor, whether it's a biomarker or just a - the individuals that are getting radiation and immunotherapy now where we can say these have - this population has a higher risk so that we can keep an eye on them, because some of these people, they'll get a grade 1 or 2 and we won't know about it, and all of a sudden they came in with a grade 3 or 4. And by then, they're in big trouble. So is there any predictions that are used? Or any biomarkers are predictors that we can use?

Dr. Florez:
There is, to my knowledge, and Andreas, you can help me, there is no other biomarker who would tell us who developed a toxicity. I think, also has to do with long reserve and the patient's lung capacity prior to treatment because those patients are a little bit more careful. And I tend to watch them very closely. Because if they lose a tiny little bit of lung capacity, the symptoms are catastrophic compared to a marathon runner that has to go through that.

Dr. Rimner:
Yeah. Yeah. From a radiation perspective, I mean, we - we have prediction models, that's what we use when we designed the radiation fields. And the dose of radiation and the volume of lung receiving radiation definitely correlates with the risk, but it's not a perfect system. We also found that radiation dose to the heart correlates with survival and sometimes with pneumonitis in some studies, for reasons that

are pathophysiological not clear. But so, we pay attention to that when we design the radiation field.

In terms of predictors, there are no biomarkers that I know of. Some people have looked at CT density of the lung tissue or at PET avidity of the normal lung tissue and sort of the inflammatory ground state. And some studies have found some correlation there. But you know, ultimately again, it, you know, they're predictors, but they're not perfect. And you would - we wouldn't put patients on steroids prophylactically because you don't know whether or not they will develop it, even if they're at high risk.

Dr. Florez:
Yeah. And the medical oncologist is going to call you, yelling at you, 'Why did you start this patient and more than 10 milligrams of prednisone and immunotherapy?']

Dr. Rimner:
Exactly. So if we had an intervention that could prevent pneumonitis, which we don't have yet or minimize the risk prophylactically, then maybe that would be more important to be able to predict that.

Dr. Edell:
Well, this discussion could go on for quite a bit of time. This is, as usual, the time flew by. I again, want to thank CHEST for allowing us to put this webinar together, our sponsors for providing the resources. My co-host, my co-chair, Dr. Murgu, and our esteemed panelists, Dr. Flores and Dr. Rimner, thank you very much for your expertise and your time.

And I'd like to invite the audience to join us for our fifth webinar. It's been loaded up in the box. So I'm not going to share the slide – well, actually, let me see if I can share the slide for completeness. It's the fifth in this series of five of our webinars. And we would encourage you to join us on June 28th for the fifth and final presentation. And with that, thank you again, panelists. Thank you again for the attendees for your attention, and I hope everyone has a pleasant evening.

Announcer Close:
This activity was part of a seven-part series brought to you by the American College of Chest Physicians, and supported by an independent educational grant from AstraZeneca Pharmaceuticals, an educational grant from Genentech, a member of the Roche Group, and an independent medical education grant from Merck Sharp and Dohme Corporation. To receive your free CME credit or to view other activities in this series, go to reachmd.com/CME. This is CME on ReachMD. Be part of the knowledge.