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Highlights from Madrid on Targeted Therapy for Advanced NSCLC

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Dr. Aggarwal:
Hello, and welcome to Updates from ESMO, the European Society of Medical Oncology. There was a lot of interesting data as it relates to the management of patients with lung cancer. And we'll go over some of those updates today. I'm Dr. Charu Aggarwal. I'm the Leslye Heisler Associate Professor for Lung Cancer Excellence at the University of Pennsylvania's Abramson Cancer Center. And I'm joined today by my colleague and dear friend, Dr. Patrick Forde.

Dr. Forde:
I'm delighted to be here, Charu, and looking forward to discussing some very exciting data from ESMO 2023, one of the most exciting conferences I think we've had for lung cancer many years.

Dr. Aggarwal:
Exactly. There was just so much data and, you know, we'll try and distill some of this data into two sessions; the first of which is our segment on targeted therapies. We clearly know that lung cancer is the poster child for precision medicine. We now know that it's not just one disease, but many diseases. And we saw just that, how many different therapies are playing out in the space. For example, for EGFR, mutant non-small cell lung cancer, for those with sensitizing mutations, we saw not one but two large phase 3 trials, the first of which was MARIPOSA. Now, this MARIPOSA trial was a large trial over 1,000 patients that really asked the question of is combination therapies superior to osimertinib in the first-line setting? So the study design randomized patients with EGFR sensitizing mutations to receive ami/laz, or amivantamab and lazertinib, versus osimertinib, or versus lazertinib. The primary progression-free – the primary endpoint was progression-free survival, and the trial did meet its primary endpoint of the ami/laz combination compared to osimertinib, revealing a higher median PFS with a hazard ratio of 0.7. Median PFS

here was 23.7 months, versus 16.6. They also looked at things such as extracranial PFS with a hazard ratio of 0.68.

Some adverse events of note, there were a significant number of patients with VTEs, all very well managed. But I think this is a unique complication that we must become aware of. About 62% of the patients develop infusion-related reactions that usually come on with the first stools, but need to be managed regardless. Other EGFR-related side effects such as rash and paronychia were seen.

But for the first time, we're seeing combination targeted therapy really emerge in the first-line setting for EGFR sensitizing mutations, we also saw MARIPOSA-2. Again this was a second-line trial, which looked at quadruplet therapy. So lazertinib/amivantamab along with chemotherapy, versus chemotherapy, or versus amivantamab in combination with chemotherapy. The trial had dual primary endpoints of PFS for the quadruplet versus chemo, as well as the triplet that is amivantamab/chemotherapy versus chemotherapy. And we saw that the hazard ratios for both of those were pretty significant 0.44 for the quadruplet that is LACP versus chemotherapy, and 0.48 for

ACP versus chemotherapy. And this adverse event profile was very similar to what we had seen in MARIPOSA, as well as what we would expect in terms of EGFR-related side effects.

I think one thing of which was interesting was that lazertinib didn't quite add that much in the second-line PFS because the hazard ratio of PFS for ACP versus chemo was about 0.48, not very different from lazertinib in combination with chemotherapy.

Patrick, what do you think about this data? And how will it affect your management?

Dr. Forde:
Yeah, I think it's becoming more and more complicated in terms of managing patients with EGFR mutation lung cancer, which is welcome. I think we currently

have a tolerable therapy available to us in terms of osimertinib for most patients, which provides good progression-free survival, but nearly all patients, the tumor becomes resistant eventually. And I think now we have potentially two more intensive treatments in terms of either amivantamab/lazertinib or potentially chemotherapy with osimertinib and in terms of FLAURA2.

My personal feeling is there are probably select patients who will benefit from these intensified strategies. Perhaps those patients who are priority have more aggressive disease, perhaps brain metastasis, perhaps those patients with exon 21 alterations.

What are your thoughts, Charu, in terms of choices for these regimens?

Dr. Aggarwal:
I think we – this is definitely a step in the right direction. We are seeing that targeted therapies and combination targeted therapies can yield improved PFS? I think these are two positive trials. We do have to factor in patient preferences. I think toxicity is something that we have to look at. But I think definitely a step in the right direction.

In the future, I think, in first line, we will be looking at combination strategies, be it with chemotherapy, be it for targeted therapy. So I think this is a step in the right direction.

And in fact, EGFR classical mutations were not the only players in the field at ESMO. We saw data from the PAPILLON clinical trial as well. If you remember, this is a phase 3 clinical trial for EGFR exon 20 insertion mutations. In the first-line setting currently we treat them with either chemo or chemo IO, chemo bev; I think there is no wrong or right answer here. But this trial evaluated the efficacy of amivantamab in combination with chemotherapy versus chemotherapy alone with the primary endpoint of progression-free survival. And this clinical trial was significantly positive. Our primary endpoint of PFS improved with combination targeted therapy and chemotherapy with a hazard ratio of 0.39 in the first-line setting. Overall survival benefit has not yet been shown. But interim overall survival also shows a trend in the favor of amivantamab and chemotherapy with a hazard ratio of 0.6. Benefits seen across all major subgroups. And I think this may be one of the clinical trials that helps change the frontline standard with that hazard ratio. What are your thoughts, Patrick?

Dr. Forde:
Yeah, I agree. I think exon 20 is historically a much more difficult tumor to treat in terms of the available systemic therapies. Amivantamab has been approved in the second-line setting, as was mobocertinib before being recently withdrawn. However, our targeted therapies overall have been limited. And I think this trial is probably the first to show this, by giving these therapies upfront, we can really achieve significant benefits for our patients. And I think it is, to my mind at least, practice changing in that first-line setting.

Dr. Aggarwal:
Absolutely. And we are all hoping for an approval soon and we can start to combine this.

I want to change gears and talk about a RET fusions. We've all been aware of TKIs that have been available and approved. We have selpercatinib of course, which was the first RET TKI to be approved, and many of us use it in the first-line setting. However, as was mandated, there was a clinical trial that was conducted called the LIBRETTO-431, which was a phase 3 open-label study to evaluate head-to-head efficacy of selpercatinib versus either chemo or chemoimmunotherapy. And for the first time we saw that, yes, this hypothesis that targeted therapy will be better is better. We saw PFS for selpercatinib in patients with RET fusion with a hazard ratio of again 0.46 compared to chemo IO. Response really seen across all subsets, cumulative incidence of CNS progression was less in selpercatinib. And overall just I think affirms our practice to use this drug. I don't even know if this trial was really warranted. But I think it just goes to show that targeted therapies can go a long way.

Dr. Forde:
And I think that was a good point raised by Dr. Bass, who is the discussant at the meeting, whether these randomized trials are necessary for these highly active targeted therapies. And I think it's going to be an ongoing question as we thankfully we have very effective targeted therapies for several other very rare mutation groups within non-squamous non0small cell lung cancer.

Dr. Aggarwal:
And I also think that I think we have to, again, in keeping in mind personalization of these therapies, keep in mind that not everyone needs that high dose. We've all seen our fair share of adverse events related to selpercatinib use. So, if we can dose modulate, but still afford that efficacy benefit, we're doing a great service to our patients.

So a lot was happening in targeted therapy in the metastatic space but not to leave behind the adjuvant space, we saw data from the ALINA clinical trial. This was the first time an ALK drug was being evaluated in the adjuvant setting. We all know data from the ADAURA trial that led to approval of adjuvant osimertinib for EGFR classical sensitizing mutant non-small cell lung cancer. ALINA was very similarly designed, again in patients with stage IB to IIIA ALK-positive resected lung cancer, so were randomized to receive either alectinib or platinum-based chemotherapy. Interesting that chemotherapy was not included for those patients with an ALK translocation. And what they found was that amongst these patients, the disease-free survival hazard ratio was 0.24 for patients with stage II to IIIA, even though these patients did not receive chemotherapy, significant improvement in disease-free survival. Even if you throw in the stage IB's into the equation, you still saw a hazard ratio of 0.24. Benefit seen across all subgroups really. Stage IB is looking a little immature right now. And then of course, CNS disease-free survival was huge.

I think this also, Patrick, is practice changing. What are your thoughts?

Dr. Forde:
Yes. I think most definitely probably the most, the clearest result, I think from the entire conference probably in that where, in this study, 2 years of therapy seems to be delivering sustained benefit even at more than 2 years, potentially up to 3 years in follow-up. So I think for patients with ALK fusion-positive resected lung cancer, I think this is the new standard of care.

I think one question is the trial did not administer chemotherapy, which does have a proven survival benefit to the alectinib-containing arm. And I think that'll be an ongoing question for us when we see our patients: Should they have chemotherapy followed by alectinib? Or go directly on to alectinib? And we won't have a direct answer to that for some time.

Dr. Aggarwal:
Absolutely. It's shifting gears back to our metastatic space with one of the large common mutations, KRAS G12C. We've seen a lot of movement over the last 3 or 4 years in terms of approvals. We now not – just not have one, but two drugs, sotorasib and adagrasib. And we've all been itching to move these drugs into the first-line setting and we see data being revealed at ESMO from KRYSTAL-7. This was phase 2 cohorts or combination of an adagrasib with pembrolizumab. Recall that combination of KRAS G12C inhibitors with immunotherapy has been quite challenging because of associated hepatotoxicity. So the study reported safety data from 148 patients and efficacy data amongst cohorts of patients with PD-L1 greater than equal to 50%. And what we found was that overall response rate in the greater than 50% PD-L1 cohort was 63%. Duration of treatment was quite long with a median time to treatment response of 1.4 months and a median duration of response not reached. Median PFS for this cohort was not reached. And the safety profile adagrasib plus pembro was actually consistent with either drug as monotherapy. Low rate of TRAEs, low rate of discontinuation. And I think these data are encouraging as we think about moving these drugs in the first-line setting.

Patrick, anything unexpected for you?

Dr. Forde:
No, I agree. I think it's enough to support further investigation here. And I think it's encouraging overall.

Dr. Aggarwal:
And then a few posters that were presented that I think were interesting. Repotrectinib has been a drug that has been used. We saw data from the phase 1 and 2 TRIDENT-1 trial that evaluated the efficacy of this drug in NTRK fusion-positive advanced solid tumors. And we basically saw activity and, you know, these drugs are coming in, we already have drugs for NTRK fusion lung cancers, but I think as we think about resistance mutations and other drugs, it's just very encouraging to see newer data in large. I think all I will say is that it's important for us to test anything.

About repotrectinib, Patrick, that caught your eye?

Dr. Forde:
No, no, I think there's new options coming along all the time, thankfully. And I think this is one of those options that we have for our patients.

Dr. Aggarwal:
Absolutely. And targeted therapies are not just limited to small molecules. We saw a lot of data on antibody drug conjugates. And if you ask anybody at ESMO what the buzz was, it was all about ADCs.

The first thing that we heard was on DESTINY-Lung01 and Lung02. Intracranial responses of trastuzumab deruxtecan. We all know that this drug is available and approved for the management of HER2 mutant lung cancer in the second-line setting. But we have not been aware of intercranial responses, at least in lung cancer as opposed to breast cancer, where these had been reported. Pooled data from these two studies showed that systemic responses to T-DXd are seen. However, they found that this monotherapy can demonstrate intracranial efficacy. In an exploratory analysis, they found intracranial overall response rate of 50% with the 5.4-mg/kg cohort, which is the dose that should be used. And this efficacy was similar in both treated and untreated brain metastases amongst those patients with brain metastases at baseline.

Patrick, do you think this is going to change how you use this drug?

Dr. Forde:
So I think at the moment, it's our preferred agent of choice. And I think it's reassuring to know that patients with brain metastases, which are not uncommon in HER2 mutant lung cancer, can have responses. And that's been my personal experience as well with this agent, it's well tolerated in general and is highly active.

Dr. Aggarwal:
And I think it's an unmet need. We often find that these patients with mutations, harbor brain metastases, they've been previously treated, they're remits that we haven't treated. So I think any drug with intracranial efficacy really gives us a lot of armamentarium to benefit our patients. So trastuzumab deruxtecan was not the only drug to demonstrate intracranial efficacy. We also saw data from HER-3-DXd. You will recall that we discussed this trial from World Conference in Lung Cancer, where the results of HERTHENA-Lung01 were presented. This is a drug that is being actively evaluated in the EGFR mutant lung cancer space. And those were classical EGFR sensitizing mutations. And we saw data from the third-line clinical trial setting where patients had progressed post osimertinib, as well as chemotherapy.

At ESMO, we heard data from the intracranial response rate with the use of this drug. And what we found was encouraging durable intracranial responses with just this particular agent that was used. This was obviously very, very encouraging. We found also that the rate at which the CNS was the first site of progression, with and without a history of brain metastases was very low with the use of this drug. And again, I think, anything that brings with it CNS penetration is a welcome agent in my clinic.

Patrick, what about you?

Dr. Forde:
Yes. I think it's really good that we're seeing, even though these are not small molecules, they're rather big proteins antibodies, they're having intracranial activity, and I think that's encouraging as a class as well.

Dr. Aggarwal:
And I'd like to finally close with one drug that was presented in two different settings, Dato-DXd. This is a TROP2 antibody drug conjugate we saw for the first time results from TROPION-Lung01. This is a phase 3, open-label clinical trial amongst patients with non-small cell lung cancers with any histology, any genomic alteration, randomized to receive either Dato-DXd or docetaxel. So this could be a second or third-line drug with a primary endpoint of PFS and OS, dual primary endpoints. And we saw that this drug did improve overall PFS with a hazard ratio of 0.75 against docetaxel. PFS seemed to be much better in nonsquamous with a hazard ratio of 0.63, but squamous population did not do well with the hazard ratio 1.38. So actually, patients did worse on Dato-DXd. I think interim overall survival data show us a hazard ratio of 0.9. I think there have been concerns about safety of this drug. There were some ILD-related deaths that I think we need to bear in mind, but overall seems like this drug had fewer all-grade TRAEs is compared to docetaxel. Grade 3, TRAEs about 25% with the drug compared to 41%.

Patrick, if this drug were to be approved, how would you in your setting?

Dr. Forde:
Yeah, I think it's going to be a difficult one to interpret, you know, because the benefit does appear to be almost completely in the non-squamous population. And even within that group, we have the breakdown in the patients with actionable genomic alterations were permitted to enroll as well. And so, we have both the AGA population and non-AGA. And I think people will look closely at those hazard ratios. Also at the alternatives in particular for those patients who have actionable genomic alterations in this setting, whether there are other ADCs, there are potentially combination targeted therapies as well. But overall, I think where this drug may have a significant role is in the non-squamous, non-actionable genomic population, at least initially, because that's a group where we don't really have good options. But whether this trial and the way it's been designed and the way it's reading out at present will support approval, I think that's still to be determined.

Dr. Aggarwal:

And you highlighted one of the key points of the next trial that I was going to discuss, which is TROPION-Lung05, which basically evaluated the activity of this drug in patients with actionable genomic alterations, heavily pretreated patients, but we found that this drug is quite active, particularly amongst those with EGFR mutations and ALK rearrangements. I think the AE profile is something that we will have to learn how to manage. You know, in addition to ILD, nausea and stomatitis seem to be the predominant AEs. Less great of hematologic toxicities as compared to other ADCs. But I think I completely agree that this may be a pair in the non-squamous non-small cell lung cancer, maybe as an option even for our patients with actionable genomic alterations.

Well, Patrick, this was great to discuss all of this exciting data. I had to speak fast to get all of this in. I appreciate you weighing in with all your expertise. Thank you.

Dr. Forde:
Great to be here, Charu.

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