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Released: 09/25/2023
Valid until: 11/15/2024
Time needed to complete: 39m

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# Highlights from Singapore on Targeted Therapies in NSCLC

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**Dr. Aggarwal:**
Hello, I'm Dr. Charu Aggarwal. I'm the Leslye Heisler Associate Professor for Lung Cancer Excellence at University of Pennsylvania's Abramson Cancer Center. Today I'm joined by my colleague Dr. Patrick Forde as we discuss results and new data from recent medical oncology conferences, including the World Conference in Lung Cancer. But before we begin, I'd love to introduce Dr. Patrick Forde.

Welcome, Pat.

**Dr. Forde:**
Hi, Dr. Aggarwal, it's good to be here. So, I'm an Oncologist at Johns Hopkins, and I'm looking forward to discussing the recent data from World Lung. It was a very busy meeting and lots of new data to plow through.

**Dr. Aggarwal:**
Definitely. So, I thought we will begin with targeted therapies. These therapies have completely revolutionized the way we treat patients with advanced metastatic non-squamous, non-small cell lung cancer and there have been recent developments that continue to improve our ability to personalize therapy. I think the breakthrough news, of course, was the FLAURA2 trial. This is a trial that I think needed to be done as the benefit of adding chemotherapy upfront in combination with osimertinib, a 3$^{rd}$ generation TKI in patients with metastatic EGFR-mutant lung cancer. Only sensitizing mutations were included, that is exon 19 and 21. About 557 patients randomized to receive either platinum doublet chemotherapy with pemetrexed for 4 cycles or osimertinib alone. And as we saw, PFS, which was the primary endpoint, was improved in the chemotherapy plus osimertinib arm with a hazard ratio of 0.62. Overall, I think benefits seen in every subgroup, including ones with CNS metastases. Low overall rate of receipt of second-line therapy, I thought, and AEs were significant with 48% discontinuation rate in the arm of patients that received osimertinib and chemotherapy.

Patrick, what was your impression of this trial? Would you incorporate it into clinical practice?

**Dr. Forde:**
Yeah, I think you've summed it up pretty well there, Charu. I think there may be selected patients who would benefit from this, but I think it's going to be an important discussion to have with patients because we're definitely going to add some toxicity, and the question is whether we can modify patients' longer-term survival as well. And now, we don't yet have any signal of overall survival from the study, but the hazard ration for PFS was significant. But as you said, with added toxicity, there may be some subgroups who derived more benefit, perhaps those patients with more aggressive disease or with brain metastasis. But I think longer-term follow-up is probably needed from this study in order for it to become a routine management strategy.

**Dr. Aggarwal:**

I completely agree. I think, definitely, a signal there, but not a homerun for all. I'd like to turn to repotrectinib. A very select subgroup of patients with ROS1 fusions. This is a novel TKI. We saw results from the TRIDENT-1 study that evaluated the activity of this agent in both pretreated, as well as TKI-naïve patients. Median PFS for this was almost 36 months. Durable intracranial activity, very manageable safety profile. And when I say manageable, I want to be mindful that it's consistent with previous reports, and I think this will be approved and available for use by all of us because it's pending FDA approval potentially late November, early December.

Patrick, would you incorporate this into your practice?

**Dr. Forde:**
Yeah, I think the results were very encouraging. A really high response rate, close to 80%, very long duration of response, and also significant intracranial responses. And I think it's going to be one more really good option for these patients. A rare disease, obviously, but a significant number given the overall incidence of lung cancer. And I think it will be very welcomed to have an FDA approval soon.

**Dr. Aggarwal:**
Absolutely, and I think as we learn more about emergent resistance patents, this will be a great drug to have in our armamentarium.

CHRYSALIS 2, keeping in the theme of EGFR-mutant lung cancer, CHRYSALIS 2 was a subset of the amivantamab and lazertinib clinical trials that evaluated this combination with chemotherapy in patients' post-progression on a third-generation, or an oral TKI followed by chemotherapy. Smaller subset of about 20 patients. Primary endpoint of overall – primary endpoint was looking at adverse event profiles. Overall response rate of about 50% noted in this category. Median PFS of 14 months. Again, this is technically a third-line regimen. And we saw safety data not surprising, but, you know, the usual what we would expect with amivantamab, lazertinib, as well as the chemotherapy. And then the phase 3 MARIPOSA trial is going to address this question in further detail. I personally have put a lot of patients on these clinical trials, and I think that this, while it represents a good option, I feel like the toxicity is something that definitely needs a lot of supportive care.

Patrick, what are your thoughts?

**Dr. Forde:**
Yeah. I think the big questions there, as you said, Charu, are going to be with toxicity, and also the frequency of infusion of amivantamab. I think a lot of patients who have been on a TKI, they're used to relatively infrequent visits to the clinic, so it's somewhat a change in their lifestyle as well.

But I think overall, similar to a lot of the studies we're seeing presented, it's important to get these initial data so that we can build on them and hopefully design more registrational studies going forward.

**Dr. Aggarwal:**
Absolutely. I think a lot of movement in the third-line space, we'll discuss a little bit more in detail with ADCs. But while remaining on the theme of CHRYSALIS, you know, CHRYSALIS study, of course, has several different cohorts that have been studied. One notable cohort that was presented was amivantamab monotherapy in patients with MET exon 14 skipping mutations. And this is not surprising because amivantamab has activity against both EGFR and MET, and their reported overall response rate of about 33%, 56% in treatment naïve, and 46% in those who had not received a previous TKI, 19% if they had received a previous MET TKI. It certainly offers us an option for MET exon 14 skipping mutations. I think it's encouraging data to see that if somebody has received capmatinib or tepotinib, perhaps we can go onto this next. Thoughts?

**Dr. Forde:**
I agree. I think this is a specific population of patients, many of them are older, so there's definitely a balance between aiming for a response and also management of toxicity. But I think it's encouraging to have potentially one more option for these patients in terms of targeted therapy.

**Dr. Aggarwal:**
And I'd briefly move on to KRAS G12C TKIs. At this years' World Lung Conference, we saw updated data from KRYSTAL-1, which is looking at adagrasib monotherapy. Two-year data looks very similar to what we would expect. You know, that there's no new safety signals that have emerged. The overall survival is holding up at about 12 to 14 months, and the same for CodeBreaK 101. And I think, while nothing new to report, what I'm personally looking forward to in the KRAS space is how do we move these drugs up into first line, as well as how do we combine them.

I know there has been concern about toxicity with combination. Patrick, where do you think we will go with these drugs?

**Dr. Forde:**
Yeah, I think it's been a challenge in particular with sotorasib, trying to combine it with immunotherapy. And I think we're seeing activity

in the second line. And as you said, no major updates here other than confirming that activity. I think the question is whether there's a new generation of these agents which can perhaps be at least an incremental benefit. We saw a recent publication with divarasib in the *New England Journal of Medicine* perhaps suggesting some slightly high response rates, so I think it'll be a very exciting space over the next couple of years, and I hope that at least one of these agents will successfully migrate to first line.

**Dr. Aggarwal:**
Definitely. I think lots to look forward to and watch in this space.

I'm going to move our discussion to antibody drug conjugates. This is a space that was previously not occupied, you know, in our medical conferences, but really, but has become a cornerstone of all meetings. We're learning a lot from the breast world. But antibody drug conjugates are, I think, going to be a game-changer in terms of our delivery of cytotoxic chemotherapy for patients with actionable mutations. There were 2 major updates in terms of targeted therapies. HERTHENA-Lung01 was a study evaluating patritumab deruxtecan (HER3-DXd). Overall response rate we saw about 28%. Again, this was strictly third-line study in patients with EGFR-mutant lung cancer following post-osimertinib, or a third generation TKI as well as post chemotherapy. And I think we are seeing PFS of about 5.5 months here, and I think more to come with this agent.

Anything to add, Patrick? Your experience with this?

**Dr. Forde:**
Yeah. We've been involved in some of the trials. I think one of the encouraging things is that we also see some intracranial responses. They reported about 33% intracranial response rates. So, though these are relatively large molecules, there appears to be some activity in the brain, which is key for some of these mutational subgroups.

**Dr. Aggarwal:**
Absolutely, and I think that's one critical need, so thank you for highlighting that. Another ADC that was discussed was trastuzumab deruxtecan. This has already become standard of care in the breast cancer world. But in non-small cell lung cancer I think this is increasingly important as we recognize more patients with HER2 mutations. And we saw available data for continuing responses as well as overall tolerability. I have incorporated this into my practice in the second-line setting.

Patrick, have you used this drug much? What is your experience?

**Dr. Forde:**
Yes. Yeah. So, I think, since the approval, it's been a preferred agent in the second-line setting. We had been using T-DM1 given that it had an NCCN guideline recommending it for that population, but I think since the approval, it's become the preferred agent. And the data presented at World Lung were encouraging. Response rates in the region were 50%, and manageable toxicity. Significant, but manageable toxicity. And I think this is a good drug for these patients given that we haven't had really tolerable small molecules thus far for this population.

**Dr. Aggarwal:**
And then I'll end with 2 novel ADCs that are being combined with immunotherapy and/or chemotherapy. So, sacituzumab as well as datopotamab. So, the EVOKE-02 trial and the TROPION-Lung04 trial. I think these are both drugs that are going to read out with results in the second-line space, but we saw some preliminary activity of these agents, either in combination with pembrolizumab on the EVOKE-02 trial or in combination with a platinum as well as durvalumab as in for the TROPION-Lung04 trial. And again, I think very small cohorts of patients. So far, the safety signals look as expected, and I think we need more longer follow-up, as well as larger patients to review this.

In any case, I think antibody drug conjugates are here to stay. More data coming up, but overall, a very promising meeting. Thank you, Patrick, for sharing your insight on targeted therapy. This was a great program. Thank you

**Dr. Forde:**
Thank you.

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