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Insights from the Latest Clinical Trials in Lung Cancer

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Dr. Socinski:
Welcome to Clinical Countdown. I’m Dr. Mark Socinski.

Dr. Mekhail:
And I’m Tarek Mekhail.

Dr. Socinski:
Tarek, were you aware that in November 2019, over 3,500 healthcare professionals convened a meeting called ESMO Asia in Singapore? Actually, this meeting started in 2016, so it’s only I believe the third or fourth year. Um, and I didn’t realize it had grown to that size.

Dr. Mekhail:
Uh, I’m aware. I can’t afford the business class tickets. I would never make it, so --

Dr. Socinski:
So you weren’t in the 3,500?

Dr. Mekhail:
I wasn’t.

Dr. Socinski:
That’s why today on Clinical Countdown, ESMO Asia Edition, we’ll be taking a look at key data from the 2019 ESMO Asia conference, including how ramucirumab and erlotinib performed in the RELAY trial against the placebo erlotinib control arm, as well as diving into an interim analysis of the CASPIAN trial, looking at durvalumab in small-cell lung cancer, and a three-year peek into the PACIFIC trial. You ready, Tarek?

Dr. Mekhail:
Let’s go.

Dr. Socinski:
We begin today with a look into the results of the pembrolizumab KEYNOTE-407 Chinese extension studies. These studies were designed similarly to the other global KEYNOTE-407 trials in that they looked at overall survival, and progression-free survival with pembro plus carboplatin, in combination with either paclitaxel or nab-paclitaxel. So Tarek, what did we learn from this prespecified

interim analysis in terms of the differences in results between patients in mainland China versus other population groups?

Dr. Mekhail:
I don't think we learned much. I think it's very reminiscent of the results of the main, KEYNOTE-407. The triplet with pembrolizumab, paclitaxel, and carboplatin, which is the regimen used on the Chinese extension, versus the doublet alone, triplet is superior. Better overall survival than the doublet. Ratio seems to be better than even the original study, the KEYNOTE-407; ideally that has a ratio of 0.44, response rate is higher. So I don't think we learned much. I think triplet established itself as the standard of care.

Dr. Socinski:
I mean, I agree. And I think one of the observations we saw from this trial is that Asian populations in general tend to do better, but we kind of learned that years ago when SWOG compared some of their data with the Japanese data you know stage for stage with chemotherapy regimens, the Asian populations just in general did better. And we saw this in KEYNOTE-407.

Dr. Mekhail:
I agree with you. I mean, we have a response rate for the triplet of 75% which was much higher than that, I believe 63% on the main study. What we haven't learned is when to use the single-agent immunotherapy with pembrolizumab. For that, we are still relying on subgroup analysis, and still not sure what to do with my practice. I think triple remains the standard of care, but it's not the only standard of care for patients with PD-L1 more than 50%.

Dr. Socinski:
Agree.

Dr. Mekhail:
Well let's now go to the RELAY study. We know that adding ramucirumab to erlotinib was better than erlotinib plus placebo in patients with activating EGFR mutations. What this study is talking about is patient-focused outcomes. What can you tell us, Mark, about this?

Dr. Socinski:
So this is another trial in a series of trials. We have at least three of them with bevacizumab added to an EGFR TKI, and this is the first one that I'm aware of with ramucirumab. All of them showed the same benefit in PFS. We have to remember that EGFR mutation-positive disease is a very VEGF-driven situation. So, it's surprising that VEGF inhibitors, both bevacizumab and ramucirumab do this. The interesting thing in this presentation was that there didn't seem to be any detrimental effect. I do think adding a VEGF agent does medicalize the treatment. It's an I.V. treatment every three weeks versus just taking a pill. We haven't yet seen a convincing survival benefit in any of these trials. But this data suggests that from the patient perspective, there were really no negative effects of it, but I didn't get the sense there were really any positive effects like symptoms controls were better. There was actually more hemoptysis on the ramucirumab arm.

Dr. Mekhail:
Yeah. I actually, to be honest, I didn't know what to expect just reading the title of abstract. Are we supposed to get better patient-focused outcome because we're adding an effective drug? Or do we expect worse because we might be adding toxicity? It looks like it was a wash.

Dr. Socinski:
Yeah, and I don't know that it necessarily changes my standard of care, because again it does change the treatment paradigm from taking a pill once a day to adding an I.V. agent that does have some toxicity even though this is generally a population that would tolerate it well.

Dr. Mekhail:
You're telling me that this study did not convince you to change your standard of care from the current standard of care, which is?

Dr. Socinski:
Osimertinib. And that's one of the drawbacks of this study, is that it used erlotinib, which we'll talk about in a moment, is really not our first-line choice.

Dr. Mekhail:
I agree with you.

Dr. Socinski:
Now, Tarek let's transition. There were a couple of presentations at ESMO Asia looking at durvalumab. First, there was the subgroup analysis from Asia, the CASPIAN trial, which focused on extensive-stage small-cell lung cancer. What are your thoughts on the findings?

Dr. Mekhail:
Well, the CASPIAN trial is three-arm study. The arm that I really want to find out about is the arm that's not reported, which is the CTLA-4 inhibitor plus durvalumab plus chemotherapy compared to chemotherapy alone. But let's talk about what was reported, which was durvalumab plus carboplatin or cisplatin etoposide for four cycles, followed by durvalumab versus carbo or cis plus etoposide for six cycles. PCI was allowed. Followed by placebo. And to be honest, the study was very reminiscent to the immunotherapy study with atezolizumab, IMpower-153, there is significant, statistically significant at least, improvement in overall survival and outcomes, establishes immunotherapy in addition to chemotherapy as a new standard of care for extensive-stage disease. Still, we don't know the value of adding the CTLA-4 inhibitor, but there were no surprises with that study.

Dr. Socinski:
I think this really cements the standard of care is the addition of the PDL-1 agent to chemotherapy in this particular setting. We'll have to wait on the CTLA-4 question that was asked; we don't yet know that data. My concern there is that it may increase the toxicity issue but we'll have to wait and see.

Dr. Mekhail:
You're right on this one. And the reason I stressed the point that they allowed PCI, because I personally have mixed feelings about the utility of PCI in extensive-stage disease.

Dr. Socinski:
I agree.

Dr. Mekhail:
I'm skeptical, particularly of all the people in this particular study the median age I believe was 65 or something like that, so I would like to know how many people actually got the PCI.

Dr. Socinski:
Yeah.

Dr. Mekhail:
Well, continuing on durvalumab, Mark, what did you think about the read on the probably the three-year follow-up on the PACIFIC?

Dr. Socinski:
Well this was a rehash of the data that we saw at ASCO. We saw at ASCO the three-year survival update from the PACIFIC trial to remind people this was following chemoradiotherapy for stage 3 disease. Those patients who did not progress were randomized to either durvalumab for a year or placebo. The primary endpoint was a two-year survival endpoint, but they looked at the three-year. The nice thing about the presentation at ASCO and this presentation is that there didn't seem to be any decay in the survival benefit, meaning that the – the survival curves stayed consistently separated by 12-13% or so, absolute difference. Hazard ratio was the same as we saw from the two-year endpoint, and it just really solidifies the fact that we have a new therapeutic option for patients, and now I think the standard of care – we're hoping these changes that are – seem to be persisting beyond three years, are going to really change the four to five-year overall survival and we're really curing more of these patients.

Dr. Mekhail:
Yeah, I agree with you. I think that's the main question. We have to always remind ourselves that the goal of treatment for stage 3 disease is cure. So does this data so far mean that we actually cured more people? Or do you want to wait a little longer?

Dr. Socinski:
I'd like to wait a little longer, although I'm not quite sure how many more analyses we're going to see of this particular database. The other thing that I'll point out is that there was some initial concern on this trial that giving an immunotherapy drug after chemoradiotherapy might set up patients for more lung toxicity. We really – so a little bit more grade 1 or 2 toxicity, but really no difference in the rate of grade 3 or 4 toxicity, which is actually really reassuring from this population. So, you know, again, I think it's an important study. It's really changed all of our practices. It's a beachhead in terms of incorporating immunotherapy. Now the research question is: What do we add to the immunotherapy to even make the results better?

Dr. Mekhail:
I agree with you, and I always remind myself how hard that we try to improve the outcomes of stage 3 disease over the last two decades, adding more chemotherapy, adding consolidation, changing the dose of radiation, changing the chemo; I think immunotherapy made the day for us.

Dr. Socinski:

Switching gears here a bit, Tarek, let's talk about ALK disease, specifically ALK inhibitor naïve advanced ALK positive non-small cell lung cancer. At ESMO Asia, we saw updated results from the phase 3 ALTA-1L trial. With that being said, what stood out for you in this trial?

Dr. Mekhail:
Well, it's – it's becoming a lot of fun. We have so many drugs, which is great. The main concern I have that when we compared these new generation drugs that we know are more effective, cross the blood brain barrier with CNS activity, we keep comparing it to the first generation, crizotinib, what we don't know is how do they compare to each other? How does brigatinib compare to 9:44 and so forth?

Dr. Socinski:
Yeah, the comparative doesn't seem to be crizotinib anymore, right? Because we – that is not our typical first-line choice.

Dr. Mekhail:
Correct.

Dr. Socinski:
So you know, I thought this trial – I was, you know, to be honest with you, I was hoping for a little better median PFS number. But we have to remember that even in earlier follow-up with ALKs, the number might have been roughly in the same range. So I think we know this is a population that lives for many years. Median survival now is north of five years for these patients, and so I think we still have to kind of wait a little longer before we have any final drugs. There are just so many options now.

Dr. Mekhail:
You're right. And that – you're absolutely right. This is not the final results. This is 75% of the events, is that median PFS for brigatinib going to improve over the, independent review committee of 24 months as it stands now to match what we have seen with erlotinib now with 34 months, we don't know the answer. And to be honest, I don't know which is the most effective drug. We're comparing across studies.

Dr. Socinski:
Let me ask you this question. It's a land of plenty. We have, what, five, ALK inhibitors approved. They all work, right? Are you – any toxicity concerns for you with brigatinib?

Dr. Mekhail:
Repeatedly, brigatinib has shown to have increased incidents of ILD, compared to other agents. On this particular study, it was around 5% or so. We need to recognize that. Yes, it is manageable. It might be a different type of permanent toxicity, I mean, there are patients who get it after two doses in the first couple of days, is that ILD is the permanent toxicity, I don't know, but it's clear to me that there is a slight increase in the incidence of ILD. Mark, so now let us move on. We have the final results of the FLAURA study. Which compared osimertinib versus EGFR tyrosine kinase inhibitor. On that particular study, it was gefitinib or erlotinib. What do you make out of the results?

Dr. Socinski:
Well yeah, so this – and you know, again, this is a standard of care changing phase 3 trial. Osimertinib, a third-generation drug, the advantages of this is a very good sensitizing mutation drug. It also is a very good T790M drug, which is where erlotinib, gefitinib, and dacomitinib kind of fall off, at least in clinically achievable doses. Most of the patients on this trial in the control arm got gefitinib. I don't think that's a major issue except it might be a little less toxic. There was a clear advantage in overall survival in this population that was, to me, not only clinically significant, but it just reminds us that with our cancer patients, we really need to give the best drug first. You can't rely on giving your best drug or wait to use your best drug. This was a nice example. Doesn't address the issue of how does it compare to the second generation drugs. I'm not aware of any trials that are doing that, and I don't think we should be doing that. The nice thing about osimertinib too is that it has a very nice toxicity profile because of the lack of really wild type inhibitions that we would tend to see with the first and second generation drugs. So I think this has changed practice, it's changed guidelines in the United States. And I think it is a new standard based on the FLAURA data. Would you agree?

Dr. Mekhail:
I agree 100%. And the more – the other exciting thing about osimertinib is the CNS activity.

Dr. Socinski:
Yes.

Dr. Mekhail:
Uh, which is I think is very relevant in patients with EGFR, uh, that are living for years almost, as we have on that study.

Dr. Socinski:
Yeah, we didn't focus on this in the ALK population, but then that's another advantage of the new ALK drugs, is that they have really good CNS activity, like osimertinib has in the EGFR space.

Dr. Mekhail:
Frustrating thing, we don't totally understand the mechanism of resistance, they vary we don't know how to conquer it if patients progress on osimertinib.

Dr. Socinski:
We had a nice story after the first generation agents; that was the T790M story, osimertinib was a good second-line drug. It's actually a better first-line drug at this population.

Dr. Socinski:
The TATTON study I think is was a very nice abstract. We are beginning to understand, and have understood that MET amplification is a mechanism of resistance to the first and second generation, and also is part of a resistance to osimertinib. This agent added a MET inhibitor to osimertinib, it was tolerable, it was active, it needs further study before we consider it the standard of care. But it does reinforce the concept that retesting to understand the mechanism or resistance may open up specific options for patients in this setting.

Dr. Mekhail:
Well, that's - the abstract I would like to comment on is Entrectinib. It's a selective potent inhibitor for NTRK A, B, and C as well as ROS1. This particular abstract looked at the activity of entrectinib in patients with NTRK fusion based on RNA testing regardless of what the type of the tumor. So it's all solid tumors. Nice to do a study that's directed, but there's genomic profile of the patient by the type of the cancer of the patient. Patients have 59% response rate, crosses the blood brain barrier, it's a new standard of care for patients with NTRK16:29 fusion.

Dr. Socinski:
So key takeaways from me for the 2019 ESMO Asia population are it's important to do comprehensive genomic testing to identify these subsets of patients. We have a growing number of active, targeted agents. If you find the target, and we've talked about ALK and EGFR, NTRK, and ROS1 we've mentioned here. We have immunotherapy incorporated in, uh, stage 3 non-small cell, a new standard of care in small cell. So compared to when we started in lung cancer, this has become a very complex disease with lots more therapeutic options. And I think in my personal experience, I think you'll probably agree with me, we are just seeing longer longevity in survival and better quality of life as a result of these therapeutic options in the general lung cancer population.

Dr. Mekhail:
I second that. My takeaway from, uh, this particular meeting – we can't have enough meetings to talk about new data in lung, which is great. And we'll talk about two things. We'll talk about the incorporation of immunotherapy, and targeted therapy, precision medicine. We're not talking about chemotherapy anymore. It's very exciting and a lot of fun.

Dr. Socinski:
Yeah, and just I want to reinforce. You can't use a targeted therapeutic agent unless you find the target. So it's the importance of comprehensive genomic testing at the time of diagnosis in the advanced stage of disease. So that's it. We're out of time. Thank you for joining us.

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