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Acquired Resistance to Targeted Therapy of NSCLC: A Global Perspective

Dr. Camidge:
EGFR tyrosine kinase inhibitors, or EGFR-TKIs for short, have resulted in dramatic improvements for patients with EGFR-mutant advanced non-small cell lung cancer. However, acquired resistance continues to limit the longterm benefit from these agents. Sometimes, that's due to T790M, but, in addition, activation of the MET pathway is now emerging as not only something we can identify but something that we can target, and that's why today we'll be discussing the use of MET inhibitors, for their role in extending the duration of benefit in EGFR-TKIs.

Welcome to CME on ReachMD. I'm Dr. Ross Camidge from the University of Colorado, and I'm delighted to have joining me today Dr. Luis Paz-Ares from Madrid in Spain. Welcome to the program, Luis.

Dr. Paz-Ares:
Thank you, Ross. Thank you for having me here today with you in this interesting activity.

Dr. Camidge:
Dr. Paz-Ares, can you start us off by describing the major classes of the EGFR mutation in non-small cell lung cancer and the different generations of EGFR-TKIs we use to manage these?

Dr. Paz-Ares:
So, briefly, you have, we have, the common mutations which had activating mutations typically around exon 18 and a point mutation on exon 21, the L858R. Also, we have some uncommon mutations. Some of them are sensitizing like the G719x or the L861Q or S768I, but also there are some, exon 20 insertion that are actually predicting, for resistance. There are still some exceptions within the, exon 20 insertion. There are some of them like the FQEA or the LQEA are sensitizing mutations. In terms of EFR-TKI inhibitors, there are third, three generations. First-generation erlotinib and gefitinib, they are reversible inhibitors. Second-generation, they are irreversible inhibitors – apatinib, dacomitinib – and they are actually not only inhibiting EFR-1 but the whole family of EFR type of receptors. And then third generation, which are the specific inhibitors of the T790M, mutation, and they do reversible, inhibit as well the, sensitizing mutations, but they are not having significant, inhibition of the wild-type receptor.

Dr. Camidge:
Oh, that's great. So, given that background, and you could be starting somebody on a first or a second or a third-generation drug, how do people become, resistant to these after they've initially benefited? What do we know about that?

Dr. Paz-Ares:
Okay. So, in terms of mechanisms of resistant, I would, briefly divide on those patients having on-target mechanisms of resistance typically having a mutation on the, EFR gene, and those in good T7090M mutation, that typically happen after first or second-generation inhibitors, but there are some other that occurs only after third generation. Those are the, C, 797S. On the other hand, that typically and those occur the T7090M in 60 percent of the cases, and there are some other, mechanism of resistance, the bypass mechanism of resistance, that include MET amplification and some others.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Ross Camidge, and today I'm speaking with Dr. Luis Paz-Ares

about whether the use of MET inhibitors can be effective in extending the duration of benefit to EGFR-TKIs. Okay, so, before getting into the deeper discussion of the, data on using MET inhibitors to extend the benefit from EGFR-TKIs in the resistant setting, let's look at what we know about MET inhibitors when they're being used as, where MET is a primary driver, so, for example, MET exon 14 skip mutations, and tell me about the different classes of MET inhibitors and the, and the data we've seen in that setting.

Dr. Paz-Ares:
In terms of MET inhibitors, and we may, taking into account molecules that typically inhibit the, kinase,the cytoplasm level. Those could be very specific selective MET inhibitors such as capmatinib or tepotinib but also some, more, multikinase type of inhibitors such as crizotinib. Then, second class of agents are those, monoclonal antibodies against the receptor, including those which are antibody-drug conjugates, and the third type of agents are those targeting not the receptor by.. the hepatocyte factor.

Dr. Camidge:
So, it sounds like we've got potentially really good tools for addressing the MET pathway. I mean, I think some of the people listening will recall that combining MET and EGFR inhibitors in lung cancers had a rather, difficult birth. There were some studies which were, which were very negative. Why should we, we be interested now? What have we learned from our mistakes, and where is the more promising data now in the EGFR-mutant setting?

Dr. Paz-Ares:
So, I think what is important here is to actually, be able to see which space in are we treating, and, to actually reinsure that we are, in which in those space in that are actually having met some mechanism of resistance. In fact, if you look at the data on those patients that have been, given EFR-TKIs MET inhibitors at the time of resistance, response rates are actually depending on the way we are defining resistance to EFR, and we are measuring, MET by immunohistochemistry. We typically are not that selective, and we are actually doing that by FISH, particularly if we are, looking for that, a significant, a, MET to, CEP, ratio from sample three, we typically will define better the population, and I think that is going to be, the clue of the succession to the future so that we are selecting those patients that are actually truly, having met, some mechanism of resistance.

Dr. Camidge:
So, what have we seen in terms of the combinations of an EGFR inhibitor and some of these next generation MET inhibitors in the, EGFR-mutant population?

Dr. Paz-Ares:
Absolutely. I think you're totally right. There are some, studies that do actually, validate this hypothesis. There are trials with gefitinib/capmatinib with, response rates in the phase I part and second part in the range of 20 to 30 percent. A similar trial, a, using tepotinib/gefitinib had median response rate in the, in the range of 42-43 percent, and actually there is still some data with osimertinib plus savolitinib, in patients progressing to first or second generation or even to third generation. If they have progressed to second generation, response rate is more in the range of 50 percent. For those cases progressing on osimertinib, the response rate is more on the 25 percent range.

It's really difficult, so I would say those are, let's say, just proof of concept data rather than mature diverse data that allow us to compare, what each other. So, I would say the main message at the present time is that, it looks like inhibiting, MET in combination with EFR inhibitor, it may help a number of patients in the resistant setting when amplification of MET is emerging, and I think that should be something that should be further evaluated.

Dr. Camidge:
This sounds like it, you can't really pull apart what's the, the differences between the drug versus who's being treated in these studies.

Dr. Paz-Ares:
Absolutely. So, here we have to consider, not only, the way we define resistance to, EFR in terms of, MET inspection or FISH or, whatever other mechanism, copy number to gain or whatever, but also, to which EFR inhibitor the patient had been exposed. It is not the same if the patient had only been exposed to a third or second generation and then you're treating with a third-generation MET inhibitor as compared to you use in those patient that had been already exposed to third-generation inhibitors, and then you just put, a MET inhibitor on top.

Dr. Camidge:
So, it sounds like there's still quite a lot of work to go.

Dr. Paz-Ares:
Absolutely.

Dr. Camidge:
Okay. Unfortunately we're almost at the end of today's program, but, Luis, before we go, can you just share some take-home messages and provide your thoughts on what we might see over the next few years with regard to overcoming EGFR-TKI resistance, focused on MET, but, you know, any other thoughts that you might have?

Dr. Paz-Ares:
So, I think that, mainly, in terms of MET, I think that it would be very important to, have better tools to recognize which are the patients that actually benefit from, the MET inhibitors on top of EFR, EFR inhibitors at the time of the resistance. That means, being able to see in which spaces MET is actually playing a main role, and I think that is the first challenge. Second challenge would be what is the best, EFR plus the best, MET inhibitor in that particular setting. Those will be the two main, for sequenced to answer.

Dr. Camidge:
Well, I think that's a great way to round out our discussion, on how we can manage EGFR-TKI resistance in non-small cell lung cancer. I'd like to thank, Luis as my guest for joining me in this discussion, and it was great speaking with you today. Stay well.

Dr. Paz-Ares:
Thank you.