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Exploring First-Line Treatment Strategies for Metastatic EGFR-Mutated NSCLC

Announcer:
You're listening to ReachMD, and this episode of Project Oncology is sponsored by Lilly. Here's your host, Dr. Charles Turck.

Dr. Turck:
Emerging research has changed the treatment landscape for non-small cell lung cancer. But for patients with EGFR mutated disease, treatment can be especially challenging. So, what might we do to prevent disease progression and improve patient outcomes when it comes to the selection of first-line therapy?

Welcome to Project Oncology on ReachMD. I'm Dr. Charles Turck and joining me to explore first-line treatment strategies for metastatic EGFR mutated non-small cell lung cancer is pneumonologist, Dr. Nicolas Girard, who's head of medical oncology at the Institut Curie in Paris. Dr. Girard, welcome to the program.

Dr. Girard:
Thank you for inviting me.

Dr. Turck:
To start us off, Dr. Girard would you give us an overview of the first-line therapies available for metastatic EGFR mutated non-small cell lung cancer?

Dr. Girard:
Sure. Historically the treatment of EGFR mutant non-small cell lung cancer is based on EGFR TKIs that have been compared to chemotherapy and demonstrated a benefit in terms of PFS and overall survival. Our current standard of care is osimertinib which is a sub-generation TKI that demonstrated its superiority in terms of PFS and OS as compared to first-generation EGFR TKIs. With osimertinib, we may expect a median PFS of 18 months translating into a benefit in terms of overall survival with a median OS of thirty-nine months from the data of the landmark trial the FLAURA randomized phase 3 trial. The issue with osimertinib is actually that at the time of disease progression, we have limited options as a resistance mechanism to osimertinib diverse, difficult to identify, and a majority of patients actually receive chemotherapy after the failure of osimertinib.

Dr. Turck:
So, how does TKI therapy or tyrosine kinase inhibitor therapy compare with other treatment options such as amino therapy, chemotherapy, or other targeted therapies?

Dr. Girard:
Well, the TKIs demonstrated a benefit as compared to cisplatin-based chemotherapy. These TKIs have not been compared to immune checkpoint inhibitors that were not available at the time these were developed. Actually, the EGFR mutant non-small cell lung cancer is a disease that is not highly sensitive to immune checkpoint inhibitor study for PD1, PDL1, pathway. This is because EGFR is not had much in the clinic because EGFR mutations lead to an immunosuppressive microenvironment with an infiltration of TFIs that inhibit and teach more responses.

In the clinic, studies that looked at the efficacy of immune checkpoint inhibitors in EGFR mutant small cell lung cancer failed to show any benefit. And in some patients, we may have hyper-progressive disease so right now room for immune checkpoint inhibitors in EGFR mutant non-small cell lung cancer is unclear. This treatment should not be administered as first-line treatment. Maybe they may have some efficacy in combination with chemotherapy +/- anti-angiogenic but this remains to be further studied.

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Dr. Turck:
For those just tuning in, you're listening to Project Oncology on ReachMD. I'm Dr. Charles Turck and today I'm speaking with Dr. Nicolas Girard about first-line treatment strategies for metastatic EGFR mutated non-small cell lung cancer.

So, Dr. Girard, if we take a step back and focus on the overall approach to treatment what are some strategies you use to delay disease progression in patients with metastatic EGFR positive non-small cell lung cancer?

Dr. Girard:
Well, we need to obviously discuss new strategies for those patients. We have osimertinib but as I discussed, the efficacy is actually limited in terms of duration of response, in terms of duration of efficacy, especially if we look at the global treatment sequence. If we go back to available options, we have opportunities with the sequencing of first second-generation TKIs followed by osimertinib in the setting of T790M-mediated acquired resistance. And actually, with this sequencing of two lines of EGFR TKIs, we may actually prolong the overall efficacy of TKIs treatment within the global treatment strategy for patients. We need to optimize each of those TKI lines of therapy and we have data, especially from the RELAY trials that demonstrate the benefit of combining erlotinib which is a first-generation TKI with ramucirumab with a VEGFR2 inhibitor, so combination of EGFR TKI plus anti-angiogenic agents that lead to a prolongation of PFS, as compared to erlotinib alone. And which, actually, allows a subsequent treatment with erlotin with osimertinib with the second line in the setting of T790M mutation. So obviously we need to have additional follow-up from the RELAY trial to assess the actual duration of TKI treatment in those patients and whether such benefit in terms of PFS translates into an overall survival benefit.

But at this point, this strategy would probably allow a more prolonged duration of treatment with an EGFR TKI as compared to osimertinib alone. Obviously, this requires close monitoring of the patients, rebiopsy at the time of disease progression after first-line to identify the resistance mechanism, T790M mutation that predicts the efficacy of second-line osimertinib.

Dr. Turck:
You mentioned progression-free survival, are there any other outcomes we might optimize for these patients and if so, how?

Dr. Girard:
We need to optimize overall survival as osimertinib actually demonstrated a benefit in terms of overall survival. But we need, as I mentioned, to consider the quality of life and obviously, TKIs treatment are better tolerated than chemotherapy. So, if we prolonged the duration of treatment with EGFR TKIs, we may expect a benefit in terms of quality of life for those patients.

We have additional options that are currently under investigation in the first-line treatment of EGFR mutant small cell lung cancer. So, it is a combination of third-generation TKI with chemotherapy such as in the FLAURA2 trial or a combination with antibodies targeting EGFR and MET such as amivantamab that is currently under investigation in the first-line setting for those patients. So, actually, the future of treatment for EGFR mutant non-small cell lung cancer will be a combination. Maybe combination with anti-angiogenic with chemotherapy with anti-MET antibody this will be what we do for those patients. And now we need to understand what is the best treatment sequencing to optimize not only PFS but also OS.

Dr. Turck:
Finally, Dr. Girard, I'd like to open the floor up to you. are there any takeaways you'd like to share with our listeners?

Dr. Girard:
Well yes, the key takeaway is that the story is still continuing for the development of new strategies for those patients. Osimertinib is currently the standard of care but maybe we will need to revisit sequencing between first, second-generation TKIs combined with anti-angiogenic which allows the second-line treatment with osimertinib. So, maybe we will have this kind of strategies available and demonstrating an overall survival benefit. We have also to understand what is the best sequence regarding chemotherapy, should it be administered as first-line in combination with EGFR TKIs or later, maybe in combination with immune checkpoint inhibitors. And then agents targeting MET are also under investigation, both in the first-line setting and in the late-line setting. So, we have multiple options we need to address the issue of sequencing ultimately so that patients have a good quality of life but also higher efficacy of the global treatment strategy to ensure prolonged overall survival.

Dr. Turck:
Well, with those final thoughts in mind, I want to thank you, Dr. Girard, for coming on to share your insights concerning one of the most prevalent types of treatable non-small cell lung cancer mutations, worldwide. It was great having you on the program.

Dr. Girard:
Thank you.

Announcer:

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