2020 Target Therapy Forum

ALK/ROS1 Session

TKI for ROS-1

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Dr. Jessica Lin: Good morning, everyone. Thank you for joining us today on this forum. I'm Dr. Jessica Lin. I am a medical oncologist at the Massachusetts General Hospital Cancer Center and instructor in medicine at Harvard Medical School. I am very excited to be here today to review the TKIs and targeted therapy treatment options for Roswell fusion positive lung cancer. As many of you heard earlier today, there are an increasing number of oncogene drivers in non-small cell lung cancer, which have important implications on treatment options. We're focusing for the next few minutes on ROS1 fusions, which is the oncogene driver present in approximately one to 2% of all non-small cell lung cancer. Now, ROS1 fusions were initially discovered in lung cancer in 2007, and ROS1 fusion indicates that apart of the ROS1 gene is abnormally joined or fused to part of another gene.

Since the initial description of ROS1 fusions in lung cancer, the reported in lung cancer and in all of these fusions, part of the ROS1 gene, the kinase domain is preserved, and this part is very important for driving the cancer growth. We know of certain characteristics that have been associated with ROS1 fusions in lung cancer. So this is a table from a study published back in 2012, where the investigators looked at a small cohort of patients with ROS1 positive lung cancer, and also a small cohort of patients with ALK positive lung cancer, which we knew more about back then. And the key features here are that patients with ROS1 positive lung cancer tended to be younger at initial diagnosis with a median age at diagnosis of around 50, as compared to over 64 other patients with lung cancer. Many patients had never smoked before and almost all of them had adenocarcinoma type of lung cancer. In my mind, the takeaway point here is that patients of any age, even very young patients and patients with any smoking history can get lung cancer.

And so, it is critical to test for this oncogene drivers, including ROS1 infusions in all patients who are newly diagnosed with advanced non-small cell lung cancer. There are various methods that can be used to detect ROS1 fusions, the earliest method that was developed, it's called fluorescence in silu hybridization, abbreviated as FISH. Here, there are different colored proves red and green probes that bind to different areas of the ROS1 gene. And when there is a ROS1 rearrangement that results in splitting of these red and green signals, or sometimes there's an isolated red signal that is found. Now the FISH test requires relatively little tissue and it has a pretty quick turnaround, but it does depend on good interpretation of the result by a pathologist. And there can be false positives or false negatives, meaning that it is not a perfect test. Another test that has been used in some institutions is immunohistochemistry also called IHC. Here, we're looking for expression of the ROS1 protein in the tumor.

And so, in this picture, the Brown spots represent positive expression of ROS1. Now this is also an imperfect test, particularly because there can be background staining for ROS1 protein, even in normal cells. And so at least at Mass General, when we have a positive ROS1 IHC test, we always try to confirm that using another method. Next generation sequencing or NGS panels are becoming increasingly used across institutions in the United States. And the reason is that NGS assays allow for testing for multiple different oncagenes all at the same time simultaneously, including ROS1 fusions. And that's particularly important because as years go on, we're learning that more and more oncagenes in lung cancer may be targetable using terrenes and kinase inhibitors. And so increasingly NGS panels are the preferred method of detecting ROS1 fusions in clinic.

So now let's turn our attention to treatment options for ROS1 fusion, positive lung cancer. Once you're found to have ROS1 fusion in your tumor. And I would say the standard initial therapy once patients are diagnosed with advanced ROS1 positive lung cancer is a ROS1 and terrene kinase inhibitor or TKI. At this time, there are two ROS1 TKIs that are approved by the FDA in the United States for the treatment of ROS1 lung cancer. These are crizotnib and entrectinib. I will start by discussing crizotnib and then move on to entrectinib. Crizotinib you heard about earlier from Dr. Raez, crizotnib is what we call a multi targeted TKI because it is not just against ROS1, but also against ALK and MET. There's actually an interesting history here. Crizotinib was initially developed by Pfizer initially considered as a MET inhibitor, but then really developed as an ALK inhibitor. And then once ROS1 Fusions were discovered and validated as an important oncogene in lung cancer.

The phase one trial of crizotinib profile panel, one, which had already been open and active at the time was amended to allow the enrollment of patients found to have ROS1 fusions in the tumor. And so there were 50 patients evaluated in that trial. And as we go through some of these data, I will highlight two key points, which are objective response

rate here. And the median progression-free survival. And objective response rate is really referring to percentage of patients who were involved in the trial and were found to have significant enough shrinkage in their measured tumor to call it a response in that trial. And so the higher, the response rate, of course, the better, and then the progression-free survival is looking at the length of time between the initiation of therapy in this case crizotnib and the time point at which the patient had disease progression. And so, again, longer the PFS progression-free survival, the better.

And so, in this trial with crizotinib, the objective response rate among ROS1 positive lung cancer patients was exceeding 70% with a median PFS exceeding 19 months, which are very good data. Now on the left is what we call a waterfall plot. And so here each colored bar represents a patient who generously participated in this trial. And the Y axis represents the percentage of decrease in their tumor and so deeper, the bar, the lower down the bar goes, the more significant response the patient had. And you can see that many of these patients had very deep, significant tumor responses. And so based on this data crizotinib received approval by the United States and European agencies for ROS1 positive lung cancer, and subsequently crizotinib has received approval by multiple additional agencies across the globe. I wanted to show you an example of the type of response we can see to crizotnib in a patient with ROS1 positive lung cancer. These are representative CT images.

So, the top images are looking at slices of chest going from front to back. The bottom images are looking at slices of chest taken from head to toe. And so the images on the left are what we call the baseline images, looking at the tumor before the patients started on crizotinib, I've highlighted the tumor with the red line here, and then on the right, you can see the significant decrease in the tumor after six weeks on therapy. And so this is the type of response we can see with these rationally targeted therapies in lung cancer. Last year, there was an updated analysis that was published from the crizotinib trial, looking at the survival of patients with ROS1 lung cancer who had received crizotinib therapy. And what I want you to highlight here is that at four years over 50% of patients were remaining alive. Now, if we have this cost over a decade ago about median survival of patients with metastatic lung cancer, back then the prognosis was quite poor. And we talked about median survival less than a year, but now we are able to say, we can expect that half of the patients live longer than four years.

And of course, now what we're trying to do is improve upon this number to get that to be much, much longer possible. I would like to now discuss the data for entrectinib, excuse me, which is the other FDA approved agent in ROS1 positive lung cancer. Entrectinib is also a multi targeted parnas kinase inhibitor. So it is put in against ROS1, but also against TRK and ALK. The approval was granted based on an integrated analysis of three different phase one and two trials. And so in this analysis, there were 53

patients with ROS1 positive lung cancer. And among these patients, the response rate to entrectinib in it exceeded against 70% with a median PFS of 19 months. And so entrectinib received approval last year in the United States and in Japan this year for the treatment of advanced ROS1 positive lung cancer. Now some of you may recall that these numbers for response rates and median PFS look pretty similar to what we saw earlier with crizotinib and that is true.

However, there are two differences between the drugs that I would like to mention today. One is that for the trial, with entrectinib, there were patients who were evaluated, who had brain metastasis at the time of assessment. And the trials showed that interact and have had good activity against those spread metastases. So that is better than what we've seen with crizotinib, which as Dr. Raez mentioned has limited activity against brain metastasis, meaning that if we have a patient who is known to have cancer, that has spread to the brain, that may be one reason to favor and entrectinib more so than crizotinib. Another difference between the two drugs has to do with the side effects. Remember that crizotnib inhibits net protein in addition to ALK and ROS1, whereas entrectinib inhibits TRK protein in addition to ALK and ROS1, and that can manifest as different side effects. So crizotnib the most common side effect we see in our patients is vision impairment.

So, most of our patients may describe this as seeing squiggly lines in the periphery of their vision, especially when going from dark to light. There may be gastrointestinal side effects like nausea, diarrhea, or vomiting, and then there can be swelling in the legs or arms or edema, which is pretty common. And this side effect can accumulate over time and can be challenging for some of our patients to manage. With entrectinib, the most common side effects include dizziness, feeling dizzy with, for example, position changes, less balanced dysgeusia, meaning changing the way foods taste in your mouth gain in weight or paresthesia, which means burning or prickly sensation. For example, in the fingertips. And this side effect actually have to do with the activity of interacting against the track protein. And so these differences in side effects are also important to consider and discuss with our patients in clinic. In this table, I have summarized that data that is available for different TKIs in TKI, naive, ROS1 positive lung cancer.

So ROS1 positive lung cancer patients who had not received prior TKI therapies. I have already discussed crizotinib and entrectinib, which are the two FDA approved drugs that can be commercially prescribed. And then there are these other drugs that have also been assessed, but are not approved. For example, Ceritinib, which Dr. Raez discussed in the setting of ALK positive lung cancer also has activity in ROS1 lung cancer. Although the data looks pretty comparable to what we've seen with crizotinib and then entrectinib. Teletrectinib is another TKI, which was assessed in a Japanese trial, in a small number of patients and has shown efficacy. Again, not approved in the United

States. Lorlatinib you also heard about earlier in ALK positive lung cancer. This is a next generation ALK and ROS one inhibitor, which in Roswell lung cancer has shown efficacy pretty comparable. You can see in this table compared to entrectinib and crizotinib.

The one key factor about lorlatinib is that it gets into the brain really well and has excellent activity against brain metastases. And then finally, repotrectinib is a next generation Roslyn inhibitor that is demonstrating very encouraging data in ROS1 positive lung cancer. So hear in a small number of patients you consider response rate with repotrectinib exceeded 80% and the progression-free survival has not yet been reported. Repotrectinib has also shown activity against brain metastasis. And so we're pretty excited about this drug, and I think it remains to be seen whether the efficacy of next-generation ROS1 Inhibitors like repotrectinib will prove to be superior to that with crizotinib or entrectinib. Now let's shift gears and move on to what may be second line options. Meaning once you have received crizotnib or entrectinib as initial therapy, what could be the next treatment option?

And here in my mind, options would include Lorlatinib or repotrectinib, and in very small subsets of patients, perhaps cabozantinib or in some areas of the globe, Teletrectinib. And here are the factors that are important to consider include what we would anticipate to be the potential duration of response to these drugs in the patient. What is the dune ethicacy of these drugs against brain metastasis? Especially if the patient in front of us has brain metastasis at baseline, and then spectrum of activity against ROS1 resistance mutations. And so what do I mean by this? When our patients initially responded to drugs like crizotnib or entrectinib, and then experienced disease progression, we presume that there is a mechanism by which the tumor has become resistant to the drug that is given. So if some of you are able to join the earlier sessions today, Dr. Yanni described various types of resistance that can be seen in the tumor.

And at Mass General, we have studied in depth mechanisms of resistance to crizotinib as initial TKI in ROS1 lung cancer. And so this is a pie chart looking at different new ROS1 mutations. In addition to the known ROS1 fusion that can be detected in the tumor at the time of disease progression on crizotnib. You can see that about a third of these resistant cases are found to have a new ROS1 resistance mutation. And the most common one by far is this G 2032 R mutation in ROS1. This is an important one to know about because it confers resistance to many of the available ROS1 inhibitors today. And then two-thirds of cases are not found to have a new ROS1 mutation. And that is important information to know as well, because it tells us we really need to figure out what the mechanisms of resistance are in these cases. So now let's consider some of the clinical data that are available for different TKIs on crizotinib pretreated patients.

Lorlatinib has shown some activity in this setting with a response rate of 35%. You can see the median duration of response for those patients that did respond was quite encouraging exceeding 13 months. Again, as I highlighted earlier, lorlatinib is a very good drug against brain metastasis. And that is shown here again with a response against brain metastasis of 50%. And so for a patient who is progressing, for example, on crizotinib in the brain with active brain metastasis, lorlatinib could represent a good option. Another key factor is that lorlatinib does not have activity against that mutation that I mentioned earlier, the ROS1 G 2032R mutation. And so if a patient is known to have a ROS1 G 2032R mutation after progression on entrectinib or crizotnib, that would make me lean against using lorlatinib as a next line option. Repotrectinib is the next-generation ROS1 inhibitor that has also shown promising effectiveness in patients that had received prior ROS1 inhibitors.

At the dose that will be used in the phase two trial, which is currently open and occurring patients. The drug showed response rate exceeding 50% in patients that had received prior ROS1 inhibitors, which is quite promising data. Importantly repotrectinib has shown clinical activity in patients with a new moon ROS1 G 2032R mutation in their tumor. So this is a good option for patients who've had repeat biopsies showing this otherwise refractory mutation. Here, I've highlighted the forest level of view of these two drugs comparing the key point. Both drugs have shown activity against brain metastasis. Lorlatinib does not have activity against the ROS1 G 2032R mutation, whereas repotrectinib does. And then again, as with any TKIs, it's very important to consider the side effect profile, and the side effect profiles are different for these two drugs. Lorlatinib, the most common side effect is high cholesterol levels or triglyceride levels.

That is a very common side effect with this drug. Patients may have swelling in their legs, experienced neuropathy like numbness, tingling, or pain because the drug gets into the brain. So well, there can be what we call cognitive side effects, which can manifest as difficulty with multitasking or concentrating, or sometimes with mood swings or irritability. With repotrectinib, this drug is a ROS1 track inhibitor. So again, there can be side effects related to TRK inhibition, similar to what we see with entrectinib, so dizziness, changing the way foods tastes, paresthesia, burning prickly sensation, all of which I mentioned earlier with the entrectinib TKI. Finally, cabozantinib, I wanted to mention because it could be considered as an option in certain instances for select few patients. And so cabozantinib is an interesting drug. Cabozantinib is what we call a dirty drug, quote-unquote, because it so many different proteins. That includes ROS1, but also for example, MET, it inhibits RET, VEGFR and several others.

And because of that, it can cause various side effects, which for some patients can be very, very challenging to tolerate. That includes things like bad rash, diarrhea, blood

pressure, elevation, and so forth. And many of our patients end up needing interruption of dosing or reduction of the dosing in order to help ameliorate those side effects. The reason I wanted to mention it today is because cabozantinib is one of the few TKI options where we think it has activity against that refractory ROS1 G 2032R mutation. So I mentioned that mutation is not sensitive to crizotnib and entrectinib, also Ceritinib and other ROS1 inhibitors. The repotrectinib drug, which is currently in phase two trial. Those have activity against that mutation and cabozantinib could be another options to consider for a patient where there's a tumor with the G 2032R mutation. It also has activity against this other resistance mutation in the solvent front called ROS1 D 2033N.

So, this is an example of a pet scan, where there was a patient who progressed on whose tumor progressed on crizotinib with this D2033N mutation. The patient went on to receive, receive cabozantinib. And after four weeks, all of this hot tumor spots resolved, as you can see in these images. So again difficult drug for many patients, but an option to consider in select instances. All right. So here I have summarized what I consider to be the current treatment approach to advanced ROS1 positive lung cancer. And I think we are seeing in ROS1 positive lung cancer, a sequential TKI treatment approach, similar to what's been modeled in EGFR mutant or ALK positive lung cancer. The standard initial therapy when patients are newly diagnosed with this disease are crizotnib or entrectinib, and after disease progression on these drugs, next generation ROS1 inhibitors, could it be considered, followed by chemotherapy, other clinical trials, perhaps have combination regimens or other ROS1 inhibitors.

And in selecting between these different therapy options, some key factors to think about and discuss with your oncologist include what are some of the resistance mechanisms to the prior ROS1 inhibitor that may be at play in my tumor, repeat biopsies, either tumor biopsy or liquid biopsy can help with delineating that further? What is the status of brain metastasis and what is the known brain metastasis activity of these different options? What are the side effect profiles? Because these do differ between the different TKIs and how fast, what is the availability of these different options, including trials and how fast could I access those? So these are all factors to think about in summary crizotinib, and entrectinib or FDA approved ROS1 TKIs in advanced ROS1 positive lung cancer, and then next generation ROS1 inhibitors are in active development and could be considered for second line use. Going forward we need a better understanding of Roslyn independent resistance mechanisms. For example, changes in genes outside of ROS1, and what strategies can be used to overcome those mechanisms of resistance. The first and most important step in ROS1 positive lung cancer and in all lung cancers, truthfully is to detect these potentially actionable gene alterations. So we have to test, test, test the tumors using right methods. Thank you very much for your attention.