



2020 Target Therapy Forum

ALK/ROS1 Session

Sequence of ALK Inhibitors

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Dr. Luis Raez: Good morning everybody. My name is Luis Raez for the ones that are joining just now I am the President of the Society of Clinical Oncology in Florida, my thoracic oncologists. I want to talk about how we sequence the use of ALK inhibitors and I am a medical director of Memorial Cancer Institute in Miami and what we call them, a health care system is a public healthcare system. I am also a clinical professor Florida International University. I'm also a member of GRACE the board, and you can be a pressure on or to work with these great group of people helping to move the knowledge about how we can find better lung cancer eh, with all the support from the advocates as we're very happy to have a lot of people now listening and watching. And I think I know many more will do it. When we put the videos online. We need to empower the patients with all of this knowledge to help us to fund raise funds for lung cancer research.

These are the drugs the agents that we have available for the treatment of ALK translocation. So we call fusions, you know, we call it translocations because two pieces of the gene interchange material that why we call them translocations fusion, you know, and these genetic aberrations generate proteins. And that's why we know that these Alkogenes are very present because we see the product of their, of the expression. I know that so patients are new and they probably just scared the first time about ALK. And some patients have been with us for many, many years. So it's a blessing. And but in black you have the five agents that we really using now to fight ALK fusions in lung cancer and in red there are two agents that are in development. I Want to try to explain how we use them. And some of the patients are going to need more than one of them. Two of them, hopefully the patients can benefit of all of them. So, because that means that will delay treatment with chemotherapy or all other mortalities.

This is why it is extremely important, you know as a science publication is only a review of 105 patients, 110 patient for [inaudible] with ALK fusions. But the amazing thing I



want you to everybody watch is in the bottom of the months, the survival of these patients in months, and in the left side, you have the overall survival probability. If you look for the 0.5, the 50%, you can see that these patients are living 18 months, 82 months, meaning as stage four, lung cancer patient nowadays is stage four lung cancer patient. Nowadays, if he has the ALK genetic aberration, they are fusion, they are translocation as we call him, you can live [inaudible] 18 months, seven years, seven years. This is very important because, you know especially our colleagues in the medical field, when they have our lung cancer patients going to the hospital, the first thing that they always ask me when a patient presents with pneumonia is, Oh, are you going to make him be an [inaudible]?

Why? Oh, because he's lung cancer, lung cancer patients. I understand they used to live 20 years ago when they start to get lung cancer. The survival was one year. So sometimes the patient is a [inaudible] or make a complication. The survival is short, but not anymore. That's why this course, it has a lot of teaching for you because first of all, the lung cancer patients, especially the ALK ones, can live many, many years circle. You see, this is a blessing. So we need to find the genetic aberration because either the patient has a genetic aberration can live all of these years, compared with all the lung cancers that don't have these benefits. Also one is that we have used all of these ALK therapies that we're talking now in the next 20 minutes, the patient can still start chemo. The patient can still is start immunotherapy. So that is why it's so important to fight. And these genetic aberrations, one of the questions that they were asking us in online was, what happened when you have a patient that is a non smoker is young, maybe female, and you don't find any of these EFR, ALKs?

What we'll do it again, if you did a test in tissue and you don't find it, but the profile of the patient says that he may be, but you do a liquid biopsy because you want to be hundred percent sure that you don't have it, because if you have it, you see how much different can be the survival of these patients and the quality of life with all of these ALK therapies. Some cases, because I know that there are a lot of patients in the audience and you're going to get tired of all of these statistical tables that we like to do in our oncology meetings. So this morning already, we fill you with tons of statistical data. So we'll have two or three cases to make it more interesting. Okay. This is the rare patients that you have treated. This was a 50 year old lady, no smoker. She had a lobectomy in June 2008, [inaudible] Chemo. And started therapy for at that time was doing well, zero [inaudible] because we hoped that she was cured. Unfortunately in 2015 she developed two new lung nodules and MET satisfaction in the pleural.

So now the patient has a metastatic adenocarcinoma of the lung. So patient was started right away on palliative chemotherapy at that time. The standard of care still we'll use, it was carboplatin, pemetrexed, and bevacizumab what we call them [inaudible]. But I did



the, I send the patient for a tissue analysis, despite the fact that the blood was negative. So the patient started on chemo. She didn't want to wait because, you know, the tissue unfortunately takes some time four weeks. So the patient was positive. So what we did is she only got one cycle of chemo and then we switched it to targeted therapy because I was mentioning before you have to always give them the best treatment first, you cannot say, Oh, I'll give you the [inaudible] only when she fails, we put her on the target therapy. No, you can see how great is the benefit of ALK inhibitors with the survival. I showed you in the first graphic, you don't want to put them on chemo because not everybody that gets chemo will have opportunity to get the best treatment.

You always do the best treatment first. So anyway, at that time, the only agent that we have for all was crizotinib. So we put them on crizotinib. The patient did very well for a while. And as you know, crizotinib protect the brain. So the patient had developed a solitary brain metastasis. We did a [inaudible] the brain radiation, localized radiation, and patient was fine. Again, for two years, and two years later she developed, again, two lesions in the brain. You can see in your right side, in the bottom, these are two, these two white spots are the new brain metastasis. And finally the patient was started on April, 2017 on alectinib that was already available. And she has been now in remission three years and more than 40 months actually with this agent. So the difference is that we were able to give her an agent to protect her brain. So she has not developed a new brain metastasis because now we're giving an agent that protects her brain. This patient is alive now for five years, with only two agents, two agents on that long list of ALK inhibitors that we have.

So I'm still have the opportunity to treat her with all the other inhibitors once that she progress. We have even more chemo immunotherapy, anything else and she's having outstanding quality of life. So this is a summary in this table of some of the studies that have justified the utility of these agents. You know, the first agent again, was crizotinib in the first column, second column certinib, third column alectinib, fourth column brigatinib. And then all of these agents were compared with platinum or another oral agent. But what I want you to see in the bottom, I put in a square red square is that, you know, these patients have a progression-free survival PFS. That is known, you know, so when we started to use crizotinib, we expected the patients to stay in the agent 10.9 months. When we start to use certinib 16 months. And now with alectinib is 34 months. And I'll show you the data [inaudible] and the response rates have 74%, 80%, very high response rates are even higher than chemo.

That's another important point. So we are giving you the best agent, not only because we can survive longer, but also we have a very good response to these agents, because sometimes when I tell the patients, Hey, you have a genetic aberration. We want to give you an ALK inhibitor the patient said, Oh, no, no, you know, I want something strong,



I'm in good shape. So give me the chemo first. I said, no, you know, the pills are not for palliative care. The pills are the most effective, rational way to treat cancer nowadays. So even you appeal, even if sounds weaker than some toxic chemo that make you throw up is the best treatment. As you can see in the statistics, you know, the response rate, the progression free survival, etcetera. So that is why this is very important. Also in the bottom, you can see that the three agents Ceritinib, alectinib and brigatinib, they have brain penetration. As I said, in the example of the last case, that's very important because we want to protect the brain.

That's why nowadays probably if you have a new ALK patient we don't start with crizotinib because we need an agent that penetrates the brain and protects the patient. And that's one of the reasons why we don't use crizotinib anymore. And we use the agents in the right. Finally, we have the agent number five lorlatinib. Lorlatinib was very important because in these waterfall pictures that you can see there are patients that have failed crizotinib, they are patients who have failed chemo and even failing crizotinib, and failing chemo. Lorlatinib was able to rescue these patients. And in the right side, you can see also that there is penetration delivering. And that is very important too. So this is another agent that has penetration to the brain and is able to rescue people that have orals. All those are one of the other questions that two people have raised or sent to us is how do you know which one to use first? Now you have five agents that FDA approved, which one I use first?

I guess everybody agrees, crizotinib may not be the first choice, because there is no brain penetration, but we still have four options. Okay. So after the approval of these agents we started to do study to compare. And as you know, very well, this is a very famous study called Alex. You know, there was a J Alex in Asia, and this is a Western Alex study. Both of them showed the same thing. You know, that when we compare alectinib the agent number three with crizotinib, agent number one, there was a benefit in the survivor. There was significant, in favor of alectinib. So it's not only the valid, that it penetrates the brain and protects the brain of the patient. As I show you in my personal experience is that the survival is better. For these reasons alectinib was placed as a preferred agent in the orange [inaudible] when we have a new ALK patient. And that's why it's not a surprise now, if you have a new patient with ALK in America, usually, they offer you alectinib or brigatinib.

Alectinib based on this study. And the other study that was a more recent is the ALTA, where we compared brigatinib [inaudible] with crizotinib and we have the same good results. There was a benefit in the progression-free survival, brigatinib also is approved. And for that reason also brigatinib is a consideration when you have a new patient with ALK. Well, Encartinib, because, you know, Encartinib is not FDA approved, but everybody, I already have two or three questions about Encartinib people that have



raised, because I guess you guys saw this presentation that beautiful that we did in our world lung last month you know, Dr. Leah Hong from Mandeville show that these new ALK inhibitor is better than crizotinib [inaudible]. So it show also that this agent has been on crizotinib. The only thing I have to remind you is it is not reapproved. That's why it's not widely available.

After I presented the data from the last three agents beating crizotinib, they always get a question. But what happened with certinib, certinib was the second agent that came to the market on why there is no study? Well unfortunately there is not a head to head study that we compare crizotinib and certinib saying it's better. This is a study that was published by Out of Time from Singapore in the GTO four years ago, basically, you know, we're not supposed to compare two different studies because you know there are different studies, but he tried to make them equivalent [inaudible] and compare them. And, you know, I think it's more or less obvious that certinib is superior, so these results are not a surprise, you know. Also certinib penetrates the brain. That's why, it's not a surprise that has some advantages over crizotinib.

So in summary you know, I show you that the head to head comparisons have shown that alectinib and brigatinib are beating crizotinib. certinib I put only across there by a retrospective review. And ensartinib also, I show you that beats crizotinib, but it's not FDA approved. Okay. So, but in summary, we still have these five agents in our inventory. And most of the time we start treatment with alectinib, or brigatinib nowadays. However most of us that are not considered experts, I have survivors who certinib. I have people on certinib for five years, doing very well. I haven't had the need to change the agent yet. And so another case is that another one of my patients at 34 year old, this patient gave him a second opinion because he was started by his primary oncologist on crizotinib. After three months, he failed and the cancer progressed. So he went for certinib, he fail again and the cancer progressed. He went for alectinib, and unfortunately he fail again and came to me for second opinion when he was on brigatinib.

This was a very weird tumor presentation because I show you in the statistics that each of these agents are supposed to give us like a one year of before there is progression, I even show you my patient on only two agents is already benefiting for five years. So how coming one year the tumor has been able to beat three of the best drugs that we have. So what I did is I did a biopsy and I found this ALK resistant mutation G1202R that was two or three years ago that we didn't need a lot about these resistant mutations. And but we already know that very well now. This is a chart you probably are getting familiar, in white, in the first column, when you're treating a patient with ALK, these patients develop resistant mutations as well as the mechanics of resistance. And in



white, there are all the least resistant mutations that are identified until the time of the publication, we have more.

And in the rest of the columns, you see the names of the names crizotinib, certinib, alectinib, brigatinib, lorlatinib the first five approved agents. My patient developed, unfortunately, the resistant mutation that I have highlighted in purple, my patient developed that resistant mutation G12O2R. And you can see red and yellow means no response. And that's why this patient didn't benefit from a crizotinib, Ceritinib, alectinib or even brigatinib. The patient needed oral lorlatinib. But unfortunately, where that was the time three years ago, or something like that, when we were opening the study for Lorlatinib. So we couldn't enroll him because he developed a pneumonia and he died. But that brought to me the importance to check for resistant mutations, because more patients are being treated with these agents, we need to be aware that they may be resistant mutations that can compromise the benefit that we are having with these agents.

And so that's why when some of you are asking yourself, or asking me how we are going to use these agents. This is one way that we can use them a rational way, not empirical way. It's not like before we used to give everybody drug number one, crizotinib. And then when the patient first [inaudible], if you know, the second drug is called ceritinib , then the patient uses the third row alectinib. And now I really have to show you with these studies that we compare two roles that they are not the same. Some of them are more potent than others, but now with these resistant mutations, maybe we have to develop some algorithms like this ones that we have here, that based on the first agent that we use, based on the resistant mutations, we see what happen. For example, let's pick up alectinib the second row in blue. Alectinib is a very strong as we know, but the patient, for example, may develop three types of resistant mutations and a patient with alectinib can be rescued with crizotinib, as you can see, because if they are resistant mechanism is met amplification, even a drug that's supposed to be weaker like you crizotinib, may work.

So that's amazing. So that's a very rational way to use these agents because we're using the agent based on the molecular aberration at the time. And it's not the empirical choice of agents anymore. And we have one more case before I finish. This is a 62 year old patient with ALK fusion. Another second opinion. This patients was a little bit difficult because he already had finished crizotinib, alectinib, and he was on an lorlatinib when she came for second opinion after she has failed lorlatinib. So what I did again, I like to do these things. I know it's not standard of care, but I like to look for resistance. Resistant mutations are not in everybody, but a lot of times I've been lucky finding the resistant mutation, so we can try to understand how to treat the patient better next time. This patient has several resistant mutations, as you can see there, including the



ALK EML4 in red. So that's why this patient was resistant to lorlatinib even, and that he was not going to benefit from the other agents. So we need new drugs for ALK [inaudible] patient is that we have served patients [inaudible].

Well, we haven't found a good one yet. Reprotrectinib, the next drug. This is a drug that is very good for us, as you can see in the chart down below is in red, the amount of drug to inhibit this malignancy, malignant tumors is much less compared with crizotinib, certinib, alectinib, brigatinib, lorlatinib, ensartinib, entrectinib meaning that these agents are more potent against these resistant mutations. But these are examples with [inaudible]. We need a better examples with for ALK. So that's the [inaudible] system mutations. You know, if you use a drug like in the Pie A, crizotinib, you don't generate a lot of resistant mutations because it's a weaker agent, but if you use for example alectinib that is now our standard of care, you develop a larger number of resistant mutations. Some of them very bad, like the first one that G12O2R that needed lorlatinib to rescue. So that is why we have to be familiar with is comfortable resistant mutations. So that's all to finish with this algorithm, you know, we have a patient with ALK being treated and the progression is minimal in the bottom, you know, the patient gets only one brain metastasis, one liver metastasis.

That's very easy. We do ablative therapy with radiation, stereotactic radiation. We continue with the same agent for one or two metastasis. We're not going to deprive the patient or the benefit to continue on the same agent. And we can easily control that with the stereotactic radiation, but the aberration is systemic in red. We need to do a new biopsy. This can be a liquid biopsy, doesn't have to be a tissue biopsy. And if there is no [inaudible] system mutation, because they are [inaudible] independent we need to put the patient on chemo immuno, but the patient has a ALK resistant mutation, we can try to choose the next agent based on the mutation that we have identify as have show in examples with my patients before. It's very important that we do all of these extra miles, because that's the only way that the patients are going to benefit of all of these agents. And as I said, once that all of these rounds out, we can still start with the chemo immuno and keep benefiting our patients.

