2020 Target Therapy Forum

Agnostic Tumor Therapy

The Future of Lung Cancer Has Arrived

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Dr. Luis Raez: Good morning, everybody. My name is Luis Raez, I am a Clinical Oncologist, I work in Miami. I'm the president of the Florida Society of Clinical Oncology and Medical Director of Memorial Cancer Institute is part of the healthcare system here in South Florida, the public healthcare system. And I am a professor in FIU. It's my pleasure to participate in this event because we really have had great commitment to help our patients. And I think the best that we can do also to move the needle for lung cancer research is to empower the patient to help us in this endeavor. I also have the privilege and the honor to be part of the world of GRACE. I think that this organization has been amazing and is doing great things for the patients and with the help of all of you, we can do more.

I want to talk about Agnostic tumor development, because you know, for many, many years, the oncology is changing. We are, I'm a lung cancer expert and somebody else is a breast cancer expert and somebody else does leukemia. But that was a very arbitrary division of our expertise, you know, and now we are getting a more rational ways to attack cancer with all of these molecular markers. And maybe these divisions are going to disappear because the treatment is not based anymore where the tumor is located. The treatment is based on which one is the genetic aberration, the cost [inaudible]. That's why we want to talk a little bit about agnostic tumor development and touching some of the topics are gong to be touched by other speakers. You saw my disclosures. And so that's why this was the introduction. Now you're going to see a lot of these articles that I wrote with my old friend Dr. Santos.

We are moving, we're causing a revolution in oncology focusing now on agnostic tumor therapy, more than location of tools. I want to give you four examples. You know, about these agents and pretty much the first three are very relevant for lung cancer, the last fourth one, nobody knows. One thing I want to emphasize a lot of my colleagues, not only that they do tumors and I say, Oh, you know what [inaudible] yes, but you know, you always have to remember lung cancer are the major risks, 230,000 new patients a year in America. So even if we are talking about 1%, 2%, and this is [inaudible] we can be covering more than 10,000 lives. So that is why it's very important to find each of these genetic alterations. We're talking about a lot of people that we do look for to find it. We will never find it. And I think Jack West has been very clear about how about other statistics, about testing, you know, and putting people on therapy.

So, for example, NTRK inhibitors, you know, we have two drugs available, larotrectinib and entrectinib. And we are hoping that these drugs LOXO 195, that is one of the adults for resistance of larotrectinib needs to get approved, because we already have patients that are failing larotrectinib because we are already using this agent for three years. Institutions, you know they're very interesting because you know, these we call them enteric. We also call them TRK. We also call them instead of one, two, three, we call them ABC, but all of these genes are related without pain, thermoregulation, memory, mood, appetite, proprioception and of course when these genes develop translocations fusions between two genes, then we have now two more so than we have proliferation. That is why they become targets for us you know, that larotrectinib was approved by the group that was led by [inaudible] in 2018.

At that time, we had to do a huge effort of many institutions because each of us was able to provide a very small number of patients, because these are not very common. I remember for this publication, I think I provide one or two patients, I have to screen like 300 to find them. But the important thing of this publication is that talking about the revolution of agnostic tumor therapy, we show how we can kill several different types of tumor with the same agent, because the molecular aberration, in this case entrik fusion is present in all of different tumors. For example, in this patient, we have a lot of patients with salivary gland, soft tissue sarcoma, fibro sarcoma in kids. We also have lung cancers as you can see, 7%, unfortunately in real life is probably 1% only, you know, we were hoping that the genetic aberration were more common in lung cancer, but after testing hundreds of patients, each of us, we see this probably around 1%.

But the [inaudible] needs regardless where the tumor is located, where the tumor is coming from, the response rate is very consistent, [inaudible] extra 75%. That is a great response rate for an oral agent that is not very toxic. At that time, we didn't have

progression-free survival data that was published later by Dr. Hall, that is around 28 months, 28 month progression-free survival for this agent. Part of these evolution of agnostic tumor therapy is the fact that you know, most of us are not only trained as experts in one type of cancer, like lung cancer, we also think as adult oncologists, you know, I have never treat a child, a kid because we consider that a totally different careers. However, now, if you can see this genetic aberration, for example, entrik expressing in kids and adults. So now the same pill that works for an adult with salivary carcinoma, lung cancer, it may help a kid with infant fibro sarcoma or congenital nephroma they're the most common aberrations.

So silently, you know, oncologist, can be the doctor of a child or a young adult. You know, that's why that differentiation between child and adult is becoming relative because it doesn't matter the age of the patient. What matters is the genetic aberration. And in the New England Journal publication, basically, that's what we saw that pretty much there is a great response around 75% lung cancer tumors, and all of these 17 other tumors do respond to this agent and the quality of life and everything is fine. But then we were very blessed that we have a second agent that works for Entrik fusions. This is Entrectinib, it is already FDA approved, as you know, but the difference with Larotrectinib, is that Entrectinib it also coerce, or has the effect in ROS and maybe ALK fusions.

So, in Entrectinib is approved now for TRK and ROS, it is not approved for ALK here, but at least we have a port for the other two indications. This is a data published really in [inaudible]. You can see lung cancers have a response for this agent. So nowadays we're using both agents Larotrectinib and Entrectinib for lung cancer patients with Entrik fusions. One thing I want to emphasize for the patients is that this is the best treatment for an Entrik fusion. So we have to test the patients, find it, and treat them first. You know, a very, we do a lot of second opinions as Jack was mentioning before [inaudible] one person. And one person is, Oh, maybe I should give him chemo immuno first and then reserve the best treatment for later. You will reserve the best treatment for later, because if you don't give the best treatment first, the patient may not have a second chance. That is why we have to find these genetic aberrations in lung cancer. We have to give the treatment with the target therapy first.

And then later when we run out before options, maybe we can start the chemotherapy or immunotherapy. Another important thing of these Entrik inhibitors is that they penetrate the brain. So we don't have to send everybody now for brain radiation, you know we used to send a lot of patients for a stereotactic radiation when they have one, two or three metastasis. We don't have to do that because some of these agents, most of the agents that we're discussing today, we will talk about EFR, ALK, ROS, they have penetration in the brain. So can spare the patients for brain, I'm not advocating not to

use radiation. So radiation colleagues don't get scared. I'm only saying we can use them late. You know, we can just later because we have to give a chance to these agents to treat the patient and to cure the patient maybe, or to at least take care of these brain metastases that maybe will come back later when the patient developed resistance.

All of these agents are well-tolerated. I only put in one picture here, one table with Entrectinib you know, for the audience there is not very familiar with is what you can remember from this table, because, you know, fatigue, everything causes in lung cancer, lung cancer causes fatigue. So for me, [inaudible] that, you know, if you want to guess what's a side effect of a cancer drug, you can say fatigue, but for example, this agent causes these here. Some patients have a little bit of dizziness and these are side effects that are we also have seen some cognitive changes. But you remember at the beginning, I told you, these agents are related with many of these areas of the brain. That's why it is not a surprise that we have [inaudible] changes. Some patients complaining about increased weight for a cancer that's great news. We want the patients to put some weight on them to be strong, not to lose weight. But they are in general, very well-tolerated. We, don't have to discontinue because of side effects.

Finally, the patients develop resistance and you know, this is that they will have resistance in the first column in the left. You can see these inside these fusions, the tumor mutations after it's being treated or attacked. And then we have for example, Loxo 195 in the right third column, two from the right, we hope to rescue patients because the drug has been in development for going on three years. And the trial is open. And these are examples of patients with colorectal cancer, lung cancers, or coma. These have the resistant mutations that are arising and how in the picture, you can see how the patients are responding to this new treatment. Another exciting area for us running here, because you know Celpercatinib was recently approved by the FDA and Pralsetinib was approved last week. So this was a great year for RET inhibitors. We have two new drugs for our patients, if the genetic aberration is present in lung cancer.

As you can know, and it's very interesting because it's not only pressing in lung cancer, but these fusions can be pressing in all of these cancers that are listed in this life. Like salivary gland tumor, colorectal cancer, even myeloproliferative disorders, but this is a very interesting genetic aberration because these drugs target two different genetic aberrations. You remember for example, for EFR, most of the patients have mutations and we target mutations in the EFR. Very rarely we target fusion in EFR, but we have already identified fusion, but very rarely. When we talk about ALK or ROS we targeted fusions, we don't target mutations until the patient develops a system. However, this agent, it targets both, you know, so it targets mutations, but were talking about [inaudible].

And like in the case of lung cancer, you know, [inaudible] is the most common mutation, so most of the patients are already treated do very well. And this is study was recently published. If you remember [inaudible] amazing. This is the study that we were doing, because it's already finished, to enroll these patients are basically to show. Not only the lung cancer patients respond, as you can see here. We also have in that study, Thyroid patients and pancreatic patients, I personally have a also colon cancers here. And that's exactly what I'm trying to mention from the beginning. I'm a lung cancer doctor, the way I'm treating colon cancer is because we have this study open and the community colleagues refer patients to us with colon cancer, because they know that we have a study for, with lots of clinical for RET. So that's why now we are doing agnostic tumor treatment because doesn't matter where the tumor is located, the genetic aberration is going to respond to the inhibitor.

Like in this case, the drug is only approved for lung and Thyroid. We still don't have approval for pancreatic or colon genetic aberrations that we put in a study. Again, like most of the targeted therapies, the drug is well tolerated. The only side effect that is not here, but I have more than 12 patients on this. They can tell you is hypertension. Some patients develop high blood pressure that is very easy to control. We only have to give an oral agent. But these are very manageable side effects. I don't remember, I had had to discontinue the treatment in anybody. And then the other agent that was approved is BLU-667, that's how we were very happy for our patients because now we have more options. The data is very similar. When we have a patient with a RET fusion in this case lung cancer, you can see that even if the patients have been treated before, you know, you have two quarters there of patients that already have platinum, and then they received a drug and they respond and patients without platinum naive.

So that is why we are advocating in all of these patients with all genetic aberrations to use the target agent first don't wait until we given chemo first. Of course, they will still respond. But as I said, not every patient in second or third line will have the chance to get the targeted therapy if you respond to treatment. Also, there is a response there is a CNS penetration, something that is happening with all the agents, and that's what we advocated the use of this treatment and the delay in the stereotactic radiation therapy that improves the quality of life for the patients. And another genetic aberration that we have that they also applied for lung cancer is a BRAF and MEK is amazing. You see the number of cancers that are covered here. They are not 18 as Entrik inhibitors, but there is a large number of cancers, including some early and high [inaudible]. Most of the colleagues will not even know what, that's a hematologic disorder, but these agents can cover different diseases despite the fact that they are in different parts of the body.

For us, the most important one is the combo Dabrafenib Trametinib because it's already approved for lung cancer. The other two combos are not approved for lung cancer, but they are approved for melanoma for example. Basically the idea here is that we are using two agents because two agents in the same pathway, we block two steps. As you can see in the picture, the NRAS and the BRAF. We will look two steps, you know, and the NRAS and BRAF, and then the patient can escape through MET. So we block two different steps, the chance of response is higher. And that's what in real life we have seen that the patients have better benefit. We use a combination of [inaudible], instead of using a single agent and that's the standard of care. And you can see that the response rates are very good for all cancers. And we did combination and the duration is around nine months. These drugs are well-tolerated.

The only thing is sometimes patients develop fever. That is a little annoying because the patients develop fever, it doesn't mean they are infected, it is only they develop fever. But it's something that we also have learned how to manage. Finally, are we running on time? This was very important because actually the first agnostic, the first agnostic indication that the FDA gave in history was the use of pembrolizumab based on these genetic alterations. Nowadays doesn't matter too much for us because lung cancer doctors are now are using pembrolizumab for everybody. And Nivolumab Ipilimumab is already approved also for lung cancer. But historically speaking, this was the, what started the revolution because at the beginning, the only way that we can use pembrolizumab for our lung cancer patients was based on this indication or on this indication, basically to me, one minute. I will mention that this is based on the mismatch repair proteins that are in science that participate in the repair on the DNA.

And when we have the deficiency of these proteins, you know, that we have a high chance of response. Most of these data was based on colon cancer. As you can see here, if you have a mismatch repair deficient tumor, your BFS and your overall survival is better. And we learned this from patients with colon cancer, you can see the responses are better if you are a deficiency and these prepared enzymes. And the progression-free survival overall survival is better, but the reason why the FDA approve these for many other tumors is because the fact that we learned that this mechanism of ontogenesis was also present in other tumors like especially in [inaudible] cancer is probably the one that it benefits the most because they have a highest number probably of mitchmatch repairs efficiency. And the lung caner is unfortunately only 1% of our patients used to benefit from this indication. And now this, as I said, because we use pembrolizumab with other indications like PD-L1, and we don't need to really with all of these data now, and this was a data for nivolumab and ipilimumab. Basically the same thing, this time [inaudible], patients will respond better. And but nowadays we don't need it for lung

cancer because we just had our own indication with PD-L1. Thank you very much. Looking forward to answer any questions within the Q and A session.