Robert Mocharnuk, MD: Hello, and welcome to this education activity titled *Because You Care About Your Patients with ROS1 Non–Small Cell Lung Cancer: Revolutions in Treatment*.

I am Dr. Robert Mocharnuk, Emeritus Professor of Clinical Medicine, and I am joined today by Dr. Alexander Drilon, Associated Attending Physician at Memorial Sloan Kettering Cancer Center in New York City, New York.

Here is a disclaimer and disclosure indicating that we may be discussing off-label use of approved agents or agents that are in development.

Here is our financial disclosure information.

Here are the learning objectives for this activity. Today, we will review and evaluate the most recent clinical data and provide expert insights on *ROS1* rearrangement–positive metastatic non–small cell lung cancer.

Let's start with a brief discussion on the epidemiologic and biological aspects of *ROS1* rearrangement–positive non–small cell lung cancer.

Alexander Drilon, MD: *ROS1* fusions are structurally similar to other fusions that are found in non–small cell lung cancer such as *ALK*, *RET*, and *NTRK* fusions. As you can see in this slide, these fusions include the kinase domain shown in red, and these occupy the 3' position, whereas in the 5' or upstream position there are a variety of different gene partners. These fusions are activating in vitro and in vivo when they're in frame, include the kinase domain, and result in oncogenesis.

In terms of clinical features, *ROS1* fusion–positive lung cancers tend to look similar in terms of the phenotype to other fusion-positive lung cancers. These features include having a never-smoking history or a former light smoking history and a younger median age. In terms of pathologic features, these cancers tend to be adenocarcinomas in the majority. Although in some other fusions, such as *ALK* fusion–positive lung cancers, you may see certain typical features like signet ring cells in a proportion of cases, that's not very common for *ROS1* fusion–positive lung cancers.

So while we are seeing a phenotype of a common group of patients who might harbor *ROS1* fusions in their lung cancer, one major point is that we should not be biased when screening these patients for *ROS* fusions.

Mocharnuk: Dr. Drilon, how do clinicians detect these *ROS1* fusions in patients with non-small cell lung cancer?

Drilon: There are several different methods for detecting *ROS1* fusions in lung cancers. A common method in the past has been FISH, or fluorescence in situ hybridization, which involves break-apart probes where the presence of a fusion causes two different colored probes to break apart under the microscope.

However, more and more we're using contemporary and comprehensive assays such as next-generation sequencing, which in addition to interrogating *ROS1* also looks for other actionable oncogenic drivers in non–small cell lung cancer such as *EGFR* mutations, *ALK* fusions, *RET* fusions, and *MET* exon 14 splice site alterations, recognizing that non–small cell lung cancers harbor many of these actionable signatures.

Other assays that can serve as a surrogate for detecting *ROS1* fusions include immunohistochemistry (IHC). What we're looking for with IHC is the expression of *ROS1* or overexpression.

One thing to remember even with our more contemporary assays that are DNA-based is that some of these next-generation sequencing assays aren't perfect at picking up all possible *ROS1* fusion events. On this slide is a study that looked at patients whose cancers were "driver-negative". We used RNA-based sequencing with anchored multiplex polymerase chain reaction (PCR) to look for drivers that were not found with MSK-IMPACT. In about 15% of cases a variety of different fusions were detected, including *ROS1*, that were not picked up with prior sequencing. Moving into the future, we may need to be very thoughtful about possibly including RNA-based sequencing as a means of maximizing the likelihood of detecting *ROS1* fusions in lung cancer.

Mocharnuk: Will you take us through the available ROS1-targeted therapies for the treatment of *ROS1*-positive non–small cell lung cancer, and the data and guideline recommendations that support their use in this patient population?

Drilon: Several targeted therapies are available for the treatment of *ROS1* rearrangement–positive lung cancers, and these are tyrosine kinase inhibitors (TKIs) that are ATP-competitive or type 1 and bind the active confirmation of the ROS1 kinase, therefore shutting down oncogenic growth in these cancers.

Because You Care About Your Patients With *ROS1*+ NSCLC:

Recent Revolutions in Treatment

We're first going to start with the early-generation targeted therapies, and in this slide you see the outcomes of the PROFILE 1001 trial, which was the seminal trial that looked at the activity of a ROS1 TKI for patients with *ROS1* fusion–positive lung cancers.

As you can see here, crizotinib was given at the recommended phase 2 dose of 250 mg twice daily, and the primary endpoint of objective response rate, which was high at more than 70%. As shown on the right in this waterfall plot, the vast majority of patients had disease progression with this therapy, several of whom had complete responses to crizotinib, highlighting that this is a very effective therapy.

Beyond response, the duration of disease control had a median of almost 18 months, and a median progression-free survival (PFS) of more than 19 months, which is longer than what we expect to see in terms of median PFS with *ALK* fusion–positive lung cancer. Patients with *ROS1* fusion–positive lung cancers seem to stay on crizotinib for a much longer time compared to those with *ALK* fusion–positive lung cancers.

The next early-generation agent is ceritinib, and this was tested in a phase 2 South Korean trial where it was given at 750 mg once daily. Similar to crizotinib, the objective response rate was in excess of 60%. The waterfall plot, albeit it having a smaller number of patients, looks similar to the outcomes that we see with crizotinib. However, we know that ceritinib compared to crizotinib has a somewhat more toxic profile in terms of gastrointestinal side effects at the full dose, so this drug is not as widely used despite the fact that these data are out there, and ceritinib is listed in the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines).

The third drug that we'll discuss today is entrectinib, which was recently approved by the FDA for the treatment of *ROS1* fusion–positive lung cancers. Results in the table are pooled from 3 different trials, the ALKA, STARTRK-1, and STARTRK-2 trials, and in this series we have patients with *ROS1* fusion–positive lung cancers who were TKI-naïve.

Entrectinib was given at 600 mg orally once daily, with an objective response rate of 77% and a median follow-up of 15.5 months for which the median duration of response was approaching 25 months.

On this subsequent slide, you see the waterfall plot of entrectinib in all patients with *ROS1* fusion–positive lung cancers. You see again that the vast majority of patients had disease shrinkage; we're again seeing complete responses. In addition, note the activity of the drug in patients with central nervous system disease, meaning those with brain metastases.

This series probably had the best characterization of the intracranial outcomes of a ROS1 TKI, as the prior series, PROFILE 1001, did not report on the outcomes in patients with brain metastases, and we have very little data from the ceritinib trial. The main point is that these patients with brain metastases also did very well on this drug, entrectinib, which was designed to be a CNS-penetrant TKI.

On this slide, we're seeing the PFS with entrectinib, which was comparable to that of crizotinib at a median of 19 months. However, what we like to see in a drug with very good CNS penetration is that possibly we're delaying the onset of CNS metastases, and as you can see in the table on the upper right the median PFS in patients without CNS disease at baseline was longer at 26 months, and in this article there was an additional analysis of median time to CNS events for which the median was not reached.

How do we put all of these data together? As you'll see in this table, we have 3 of the drugs that we discussed along with later-generation agents that we'll talk about in more detail in the next section. In terms of response, objective response rates are fairly high and comparable among all of these agents.

If you look at median PFS, although we like to see a longer median PFS for later-generation drugs, thus far in these early data we're still not seeing a very big differentiation in terms of median PFS. However, we'll see what happens with the more mature data.

With the later-generation drugs, there's been much more of an exploration of the activity in the CNS in patients with brain metastases, and thankfully with drugs such as entrectinib, lorlatinib, and repotrectinib, we're seeing very good intracranial response rates and overall disease control.

Finally, we'll note that the safety profile is somewhat different among these agents. Crizotinib is a well-known drug and is known to cause a variety of side effects including visual changes and, in some patients, peripheral edema.

Ceritinib, at the full dose of 750 mg daily tends to have substantial GI side effects; therefore, to abrogate those or to minimize the impact on the GI system, we are able to give a lower dose of 450 mg once daily with food.

Entrectinib is somewhat different in its profile from the other 2 drugs, because it is also an effective TRK inhibitor, and thus we're seeing some TRK inhibition–mediated side effects such as weight gain and paresthesias. We can see dizziness or ataxia, cognitive changes very rarely in some patients, and pain flare when patients discontinue entrectinib because these drugs are known to modulate the threshold for feeling pain.

On this slide, we see warnings or precautions that are on the labels for crizotinib, ceritinib, and entrectinib. However, these 3 agents can be very tolerable.

Summarizing the current approval data and guidelines data for these agents, with first-line therapy, crizotinib and entrectinib are preferred and have FDA approval with larger datasets compared to ceritinib, which is listed in the guidelines but is not as widely used for the reasons we mentioned earlier. There are subsequent therapies such as lorlatinib we we'll discuss in the next section.

Mocharnuk: Thank you, Dr. Drilon. Very exciting data with crizotinib, ceritinib, and now entrectinib in *ROS1*-rearranged lung cancers.

I understand that there are also additional data for other TKIs in *ROS1*-positive non–small cell lung cancer. Can you review these available data?

Drilon: Unfortunately, disease resistance to earlier-generation ROS1 TKIs can develop, and on this slide we have one series showing us the profile of ROS1 kinase domain mutations that can occur after the acquisition of resistance to crizotinib. In many patients in the red slice of the pie, a solvent-front mutation can occur such as the *ROS1 G2032R* mutation. However, there are a substantial proportion of cases, as you'll see in the blue slice, where we don't see a *ROS1* mutation emerge.

We still need next-generation or later-generation agents that hopefully address these resistance mechanisms, and one such drug is cabozantinib, which is a type 2 inhibitor that's approved for other indications in the cancer world.

In this particular series on this slide, there was a patient with disease resistance to crizotinib whose cancer acquired one of these solvent-front substitutions who was then

put on a trial of cabozantinib. As you can see on the right, this patient had a robust response noted not just in terms of the computed tomography scan, but also in terms of metabolic response on this positron emission tomography scan. A phase 2 trial is ongoing to address the activity of cabozantinib in a larger number of patients.

The second drug is lorlatinib, a drug that has activity against ROS1 and ALK. As mentioned, these later-generation drugs have been explored in the ROS1 TKI-naïve setting, and those results are shown in this slide where we're seeing an objective response rate of more than 60%, with a median duration of response of almost 17 months for lorlatinib.

Here we have the summary of the activity of lorlatinib in patients who have received prior ROS1 tyrosine kinase inhibition. In comparison to the data we presented earlier, the objective response rate in these patients is 26%, so much lower than the 60% to 80% response rates that we saw in the TKI-naïve setting. The median PFS is also lower at 8.5 months and less than half of what we saw earlier with some of the agents where the median PFS was 19 months.

Even though we know that lorlatinib can work well for patients who have had a TKI, it's important to know that the drug has not been shown to work extremely well against all kinase domain mutations. At least in this early series, we're not seeing dramatic responses to *G2032R*-containing cancers with lorlatinib. So we're looking hopefully at other agents that may have activity in this space.

There is another next-generation drug called repotrectinib, and the results in TKI-naïve patients are shown in this slide. Not surprisingly, we're seeing a high response rate at more than 80%. This drug was also explored in the CNS, and you'll see the waterfall plot on the very right, with a small number of patients; however, in all 3 patients we saw intracranial disease regression.

However, what we're looking to see with this drug is its activity after disease has progressed on a prior TKI, and as seen on the table on the left, we're seeing a similar pattern to what we were seeing earlier with lorlatinib where the objective response rates are lower, and in this series at approximately 40%. As you'll see in the waterfall plot, many of these patients have disease regression with therapy, and we're also seeing disease regression intracranially with this agent.

So putting these data side-by-side, the response rate to later-generation TKIs is lower than what we see in the TKI-naïve space. We're seeing earlier data cuts for these patients, as you can see on this slide only 18 patients for repotrectinib, 34 patients for lorlatinib. Therefore, it would be good to see what happens as we get more patients into these trials.

We are comforted by the fact that these drugs do have activity against CNS disease. The main distinguishing feature between repotrectinib and lorlatinib thus far has been the likelihood of the drug working against some of the trickier solvent-front mutations such as *ROS1 G2032R*. As you saw in an earlier slide, lorlatinib did not work against cancers that harbor these mutations; however, we know that repotrectinib has activity against the solvent-front mutation, and several patients whose cancers harbor these mutations after progression on a prior TKI have had confirmed responses to repotrectinib. Of course, we'll see what the data look like when more patients are accrued to these drug development programs.

Repotrectinib continues to be explored in a phase 1/2 trial for patients with *ROS1* fusion–positive lung cancers. This is called the TRIDENT trial and it is open for patients who have not had a ROS1 TKI in addition to patients who have disease progression on a prior ROS1 inhibitor.

Mocharnuk: Dr. Drilon, can you share with us a case example of a patient with *ROS1*-positive non–small cell lung cancer?

Drilon: We have a 34-year-old woman, never-smoker, who presents with worsening shortness of breath. She sees a local provider who orders a workup that includes a CT scan and a magnetic resonance imaging (MRI) of the brain. Unfortunately, the CT scan reveals a left lung mass, lymphadenopathy, and several liver metastases, and the MRI reveals multiple sub-centimeter brain metastases. The patient is asymptomatic from an CNS perspective and denies any neurologic symptoms or worsening headaches.

A biopsy of one of the liver lesions is performed and results reveal adenocarcinoma consistent with a lung primary, and the unused tissue is sent for molecular profiling, which does not reveal a sensitizing *EGFR* mutation or an *ALK* fusion.

For this case, it's important to keep in mind that non–small cell lung cancer can harbor many different actionable signatures. It is thus critical to consider a comprehensive next-generation sequencing test to look for these other drivers.

Next-generation sequencing of the remaining tumor was performed, which showed a *CD74-ROS1* fusion, one of the most common events in the *ROS1* fusion space that we know can be activating and lead to oncogenesis. The question, of course, is now that we've found a *ROS1* fusion in this patient, how do we proceed with treatment?

We know that there are 3 TKIs that have been tested in this space—crizotinib, entrectinib, and ceritinib. The first 2 have FDA approval, and if we look at the topline data for these agents side-by-side we'll note that the overall response rate and median PFS do not look very different. However, one distinguishing feature of the entrectinib regulatory dataset is that it featured a high proportion of patients with brain metastases. More than 40% of patients had brain metastases at baseline, and we know that there was a high intracranial response rate in excess of 50%, and also very good and durable disease control in patients who had brain metastases.

Therefore, the choice for this patient was to use entrectinib. The patient had a very durable overall response to therapy, not just extracranially but also intracranially, with multiple brain metastases shrinking, and the patient stayed on treatment for 2.5 years.

Unfortunately, as is what occurs with early-generation therapy, progressive disease developed. This first manifested as solitary site progression with a single brain metastasis, and the patient was asymptomatic at the time this happened. This patient was sent for local therapy and underwent stereotactic radiosurgery and had a good response.

This kept things quiet for another half year, after which the patient showed additional multifocal disease progression extracranially with growing disease in the lung, lymph nodes, and the liver, along with new bone metastases. At this point, the patient did not have worsening disease in the CNS and remained asymptomatic. So the subsequent question would, of course, be how would you treat this patient moving forward?

We know that in this situation we can give a patient a next-generation TKI, either lorlatinib that's currently in the NCCN Guidelines or repotrectinib, which is currently in an ongoing clinical trial. We know that if you were to do sequencing at this point and found a *ROS1* mutation such as the *G2032R* that that might push us to give this patient repotrectinib if that's available based on the data against solvent-front mutations where we see activity with repotrectinib and not with lorlatinib.

However, first-line platinum doublet-containing chemotherapy is a viable treatment option for these patients. For this particular patient, lorlatinib was available on a clinical trial at the time of progression. The patient responded with 1 year of disease control. Disease progression developed thereafter and she was switched to carboplatin, pemetrexed, and pembrolizumab, and she remains on this therapy with a durable ongoing response 2 years into therapy with maintenance treatment.

Mocharnuk: Finally, can you provide us with some key takeaways from today's presentation in the treatment of patients with *ROS1*-positive non–small cell lung cancer?

Drilon: The key take-aways from this session are that *ROS1* fusions are oncogenic drivers of non–small cell lung cancers. Although they're found in 1% to 2% of unselected cases, when you consider the fact that there are a lot of lung cancer cases diagnosed globally each year, this adds up to a substantial number of patients.

We also know that there are very active targeted therapies for these patients. In the early-generation setting, we have crizotinib and entrectinib, and we also recently have data on later-generation TKI therapies such as lorlatinib and repotrectinib that can be effective in select situations. It's also important to point out that we know that chemotherapy can be very useful in these patients with *ROS1* fusion–positive lung cancers.

So rolling all of that together, the important message is that you should pay attention to screening for *ROS1* fusions in patients with non–small cell lung cancer, and hopefully this would be done in the context of a comprehensive assay that also looks for the many other actionable oncogenic drivers that are found in these tumors.

Mocharnuk: Thank you, Dr. Drilon, for this excellent review in *ROS1*-positive non–small cell lung cancer and thank you to our audience for your participation in this activity.

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