



## **Controlling Brain Metastases in Patients with Molecular Driven Advanced Non-Small Cell Lung Cancer (NSCLC)**

**Presented by Alice Shaw, MD, PhD**

**Associate Professor, Medicine, Harvard Medical School**

**Attending Physician, Thoracic Cancer Program, Massachusetts General Hospital**

### **TRANSCRIPT**

My name is Alice Shaw, I am director of the Center for Thoracic Cancers at Massachusetts General Hospital in Boston.

CNS metastases are a very common problem in patients with metastatic non-small cell lung cancer and in particular for patients who have driver oncogenes like EGFR mutation, ALK or ROS1 rearrangements, and other drivers.

ALK positive patients in particular have a very high propensity for having spread to the central nervous system or CNS. We've seen in a number of studies over the years that at the time of diagnosis patients with metastatic ALK positive lung cancer about 40% of them may have brain metastases even at the time of diagnosis so very common issue. And what we've also seen in clinical trials of first and next generation ALK inhibitors is that as patients continue on these ALK inhibitors that the chance of developing CNS metastases rises even further. So, in many of our studies now of next generation ALK inhibitors that allow multiple prior ALK inhibitors as treatments we see that over 60-70% of patients may have brain metastases so it's a very common problem and it is a critical issue that we've been trying very hard to address.

For ROS1 we also have patients who can develop brain metastases. However, the incidence of brain metastases for this particular molecular subset seems a little bit lower than that of ALK.

We recently published a study comparing this exact question: the frequency of CNS metastases in ALK versus ROS1 patients. What we found is ROS1 patients at diagnosis are less likely to have brain metastases than ALK patients; a little less than 20% of our ROS1 patients were found to have brain metastases when they were first diagnosed. What we also showed is that over time, accumulated incidence of brain metastases was higher for ALK compared to ROS.

Nevertheless, for a significant proportion of patients with ROS1, brain metastases can be a very important issue that must be addressed. Now, fortunately over the last five years or so we have developed a number of next generation ALK and ROS1 inhibitors that actually are very CNS penetrable. So Crizotinib, the first generation ALK/ROS1 inhibitor that has been the standard of care since 2011 at least for ALK positive patients, is a very good drug but it has relatively weak CNS activity because it is limited by the blood-brain barrier. We do see relapses in the CNS quite commonly for the ALK and ROS1 patients while they're on Crizotinib. However, what we've now seen with the more potent ALK and ROS1 inhibitors is that these drugs can get into the CNS at much higher levels and we've seen remarkable activity in the CNS. So as an example, with Alectinib, used after failure of Crizotinib, the intracranial response rate is pretty much the same if not higher than what we call the systemic or the body response rate. In the brain we often see a response rate of 60% or more meaning really significant shrinkage or response in the CNS metastases. Often times we can see a complete response where all the CNS lesions are no longer identifiable on scans. We have had very good success in treating patients with CNS metastases with these new targeted agents and this has really allowed us now to actually postpone or entirely forgo the use of radiation therapy and I would say particularly whole brain radiation therapy.

Whole brain radiation therapy has been the standard of care for patients who develop multiple brain metastases. That was done very frequently in the past however fortunately with the CNS penetrable drugs that we now have many of my patients will actually forgo whole brain radiation. Their CNS disease will be entirely controlled by these new next generation drugs. Occasionally, we will need to use radiation and often times we can use more focused radiation like Gamma Knife or stereotactic radio surgery and those more focused approaches tend to be much better tolerated than whole brain radiation therapy.

<http://cancergrace.org/lung/2018/03/29/lung-cancer-video-library-controlling-brain-metastases-in-patients-with-molecular-driven-advanced-nscl/>