Ponatinib Vs Imatinib in Patients with Newly Diagnosed CP-CML – Discontinued EPIC Phase III Trial Showed Unprecedented Early Deep Responses to Treatment

Hi, I am Dr. Stuart Goldberg from the John Theurer Cancer Center in Hackensack, New Jersey, and I am here with ManagingCML.com. I am speaking to you from the 2014 American Society of Clinical Oncology meetings where there have been several exciting presentations on the management of CML. As many of you know, ponatinib, a third-generation tyrosine kinase inhibitor, was FDA approved for the treatment of patients with CML that was resistant or intolerant to multiple tyrosine kinase inhibitors or for those patients who had developed the dreaded T315I mutation, the mutation that essentially renders the CML clone resistant to the common TKIs. Given that this agent is much more potent, there was some hope that may be utilizing it upfront may be better than our old friend imatinib. This led to the study known as EPIC. This large international randomized trial was comparing imatinib versus ponatinib as first-line therapy. However, as many of you also know in the fall of 2013, unfortunately, we started to see some cardiovascular signals with ponatinib. This led the FDA to abruptly halt the trial as well as to pull the medication temporarily from the market while safety signals were analyzed. Ponatinib is back on the market utilizing a REMS program where we now counsel our patients on the risks and benefits of utilizing the medication, especially the cardiovascular risk. So therefore, the ponatinib EPIC trial was discontinued and it is not moving forward, but we have the patients who have been treated on both imatinib and ponatinib on this trial, and so at the 2014 meetings we are now looking at some of that data. Unfortunately because of the way that study was discontinued, we will never know the 1-year outcomes, but a significant number of patients had been treated for more than 3 months. At 3 months, the NCCN Guidelines now look at a milestone, that is how many patients suppress below 10% on the international scale. We know from German and London data that patients who are below 10% at 3 months have an excellent chance of becoming long-term survivors, whereas patients who were above 10% at 3 months still could have trouble and have inferior survival. So therefore, 3-month look may give us early clues on whether a more potent tyrosine kinase inhibitor can be beneficial to our patients. What we did find in the EPIC trial? What was seen that 94%, almost everybody on the ponatinib arm made that 3-month milestone to below 10%, but on the imatinib arm 68% made, roughly one-third not hitting the milestone. So sure enough, a stronger TKI got more patients into that early milestone, but it did not come without a cost, and as expected in this randomized trial, we can now look at the cardiovascular effects early on. And what we saw using very strict guidelines on what to consider a cardiovascular event, we saw that 12 patients on the ponatinib arm but only 3 patients on the imatinib arm had some type of cardiovascular event. The agent does appear in a randomized trial to have more
cardiovascular issues which has what led the FDA to stop the trial and also to temporarily halt the use of this agent in the general population. I think the EPIC trial is very interesting because it does show us that a stronger TKI may have more patients getting to that early remission and sort of echoes what we seen in the nilotinib NS trial and the dasatinib DASISION trials that the more potent second-generations are getting more patients into the early spot, and it also confirms our suspicion that cardiovascular events are important in ponatinib and may be important in some of other TKIs and we have to follow them as more data emerges. For more information about CML, checkout ManagingCML.com. I am Dr. Goldberg. Have a good day!

Reference: