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Initial BTK inhibitor-based treatment selection in a treatment-naive, symptomatic, unfit older patient with comorbidities and high-risk cytogenetics

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Dr. Shadman:
Hi, this is CME on ReachMD I'm Dr. Mazyar Shadman. Today I'm going to review and discuss initial BTK inhibitor treatment selection in treatment naïve symptomatic onset older patients with comorbidities and high molecular risk CLL.

Let's start with a case. A 68-year-old man with a diagnosis of CLL for 2 years is seeing you and patient at the time of diagnosis had deletion 17p, and also an unmutated IGHV, the 2 known high risk features in CLL. Patient now presents with fatigue and progressive lymphadenopathy over the past 3 months, and you confirm that in the physical exam, and with large lymph nodes in different areas. The spleen is not palpable on your exam and patient's blood work shows a white count of 86,000, 95% of which is lymphocytes, and they have a hematocrit of 31%, and a platelet count of 98,000. Basically, after discussing with the patient, you make the decision to initiate therapy.

In terms of the treatment options for untreated CLL patients, we have the two major classes, the covalent BTK inhibitor class, which has 3 members, ibrutinib, the 1st in class, followed by second generation drugs, acalabrutinib or zanubrutinib. And then we have venetoclax-based therapy, which is a fixed duration option for patients with treatment naive CLL. Focusing on this patient, this patient has high-risk features. When we looked at different BTK inhibitors, starting with ibrutinib, which was the first in class BTK inhibitor, a pooled analysis done by Dr. Allan showed that patients with del 17p, when they receive ibrutinib, with the median follow up of around 50 months, the progression free survival is 79% at 48 months. This is a very good progression free survival in high-risk population that have an abnormal P53 gene.

Acalabrutinib is one of the second generation BTK inhibitors. This drug was tested in ELEVATE-TN trial, and this is a study, which was recently updated at the American Society of Hematology meeting in 2023, showed that patients with del 17p or P53 when they had with the long term follow up at 72 months 56% of these patients still had progression free survival, and the median was not reached with that follow-up. And zanubrutinib is another second generation BTK inhibitor, a covalent BTK inhibitor, which was tested in frontline in the SEQUOIA trial, which had a dedicated cohort and arm for patients with del 17p. And we recently updated the 4 year follow up, and we reported that 79.4 percent, or 80% of patients, were progression free at 42 months of follow up. And that was not different from patients who had the normal P53 gene.

So, the summary is that when you use a covalent BTK inhibitor as a continuous therapy the impact of abnormal P53 gene, at least in the frontline setting goes away. Now this is not true for time-limited venetoclax-based therapy. If you look at the most recent presentation and updates from the CLL14 trial, which led to the approval of venetoclax and obinutuzumab in first-line, with a median of duration time of more than 76 months, the median progression free survival for patients with abnormal P53 was 52 months. So, the median is

reached, and when you look at those curves, it's different from the PFS that patients with the normal P53 gene have.

So, to summarize, the BTK inhibitors, the covalent BTK inhibitors are treatment of choice for patients with abnormal P53 gene and among them, covalent BTK inhibitors, and from the second-line studies, or relapse studies, we know that the safety profile of both acalabrutinib and zanubrutinib are superior to ibrutinib, and we also know that the efficacy of zanubrutinib is superior to ibrutinib. So we would argue that the choice of therapies for the patient that we presented would be a second generation BTK inhibitor namely acalabrutinib and zanubrutinib. I should mention that in the ALPINE trial, which was done in, again, in the relapse setting, in patients with del 17p or P53 gene, zanubrutinib, in a pre-planned analysis was superior to ibrutinib, and we did not see that in the ELEVATE-RR trial with acalabrutinib.

I hope you find this information helpful for your practice and thank you for listening.

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