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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Guideline-recommended treatment options for patients with CLL/SLL and MCL that have progressed following a covalent BTK inhibitor

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Dr. Bhat:
This is CME on ReachMD, and I am Dr. Seema Bhat.

Dr. Abramson:
I'm Dr. Jeremy Abramson.

Dr. Bhat:
Dr. Abramson, let's begin by reviewing guideline recommended treatments for patients with CLL/SLL and mantle cell lymphoma who have progressed following a covalent BTK inhibitor.

Dr. Abramson:
Sure. By way of background, I think it's important to consider what initial treatment is, so standard initial treatment of CLL/SLL is typically with either a covalent BTK inhibitor, usually either zanubrutinib or acalabrutinib administered as continuous therapy, or time-limited treatment with venetoclax and obinutuzumab, which lasts for one year in the absence of progression or intolerance. Standard initial treatment of mantle cell lymphoma has historically been chemoimmunotherapy followed by a covalent BTK inhibitor at first relapse, but based on the TRIANGLE trial, covalent BTK inhibitors are increasingly being incorporated into frontline therapy.

So, when we think about treatment at relapse for CLL patients who are relapsing, it really depends on what their initial treatment was. If they were treated with a covalent BTK inhibitor and have discontinued that treatment due to intolerance rather than progression, then we would typically change to a different covalent BTK inhibitor which may be better tolerated. If a patient is on a continuous BTK inhibitor and progressing on that treatment, then we would typically change to venetoclax and obinutuzumab.

For a patient progressing on venetoclax and obinutuzumab, or shortly thereafter, we would typically go to covalent BTK inhibitor. But if a patient has a prolonged initial remission of venetoclax/obinutuzumab, we can always retreat them with that therapy. The biggest challenges today are for patients who are progressing despite both venetoclax/obinutuzumab and a covalent BTK inhibitor. But for those patients, we actually have a couple of available options, primarily being either pirtobrutinib, noncovalent BTK inhibitor, or a CAR T-cell with lisocabtagene maraleucel.

For patients with relapsed mantle cell lymphoma, similarly, if they stop a covalent BTK inhibitor due to reasons other than progression, we would try an alternative BTK inhibitor. But if they're progressing despite a BTK inhibitor, meaning they're refractory to a BTK inhibitor, then our available options today include pirtobrutinib, again, the noncovalent BTK inhibitor, or a CAR T-cell treatment with one of two available CAR T-cells, either brexucabtagene autoleucel or a lisocabtagene maraleucel.

Dr. Bhat:
Great overview. We do see patients with relapsed/refractory CLL who have previously been treated with chemoimmunotherapy or novel

therapies. Targeted inhibitors, including BTK inhibitors, or venetoclax, have transformed the treatment landscape not only for frontline CLL, but also in the relapsed setting. Choice of treatment at progression largely depends on what the previous treatment was. While both classes of targeted agents are effective for relapsed/refractory CLL, potential side effects and the logistics should be considered. The selection and sequencing of these therapies for relapsed disease should include patient preference just like in the frontline setting, as well as consideration of patient's comorbid conditions.

With progression on a covalent BTK inhibitor, which is largely due to the presence of BTK mutations, it's very important to remember that the other covalent BTK inhibitors will not work. Venetoclax with an anti-CD20 monoclonal antibody is definitely the right thing to do but given the results from the BRUIN CLL-321 study presented ASH 2024, pirtobrutinib, which is a noncovalent BTK inhibitor, could also be considered.

Other fixed duration therapies are being tested. We have the VenR +/- pirtobrutinib study (BRUIN CLL-322) ongoing. Then, there is a similar study with the other noncovalent BTK inhibitor, nemtabrutinib (BELLWAVE-010).

So, we know that from the available data, CLL patients with TP53 mutation or deletion 17P do much better with a continuous treatment with a covalent BTK inhibitor. But when they progress on a covalent BTK inhibitor, the approved treatment that we have is venetoclax plus an anti-CD20 monoclonal antibody. But given the data from the BRUIN CLL-321 study, we could even consider a noncovalent BTK inhibitor. But again, this continues to be an area which is actively being researched, and hopefully we'll have better treatments in the future for these patients with high-risk features.

Dr. Abramson:
Yeah, I agree with Dr. Bhat. When we approach a patient with TP53-mutated CLL at the time of initial diagnosis, I'll often favor a continuous BTK inhibitor as these patients are likely to progress after discontinuing their time-limited venetoclax/obinutuzumab. Now, that said, the progression-free survival for the TP53 mutated patients on venetoclax/obinutuzumab is actually quite good, just not as good as TP53 wild-type patients. And so, I still have a conversation with patients and if they prefer time-limited therapy, then venetoclax/obinutuzumab is entirely appropriate treatment for them, with the understanding that they would likely require a covalent BTK inhibitor at the time of progression.

Dr. Bhat:
Well, this has been a great review of guideline recommended treatments for patients with CLL/SLL and mantle cell lymphoma who have progressed following a covalent BTK inhibitor. Thanks for tuning in.

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