

# CLL IN FOCUS

Current Developments in the Management of Chronic Lymphocytic Leukemia

## Choosing Between Novel Agents and Chemoimmunotherapy in CLL



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**H&O** Which novel agents are available for physicians treating patients with chronic lymphocytic leukemia?

**JW** Right now, we have Bruton tyrosine kinase (BTK) inhibitors, phosphoinositide-3 kinase (PI3K) inhibitors, and B-cell lymphoma/leukemia 2 (BCL2) inhibitors. The BTK inhibitors ibrutinib (Imbruvica, Pharmacyclics/Janssen) and acalabrutinib (Calquence, AstraZeneca) have US Food and Drug Administration (FDA) approval for the treatment of chronic lymphocytic leukemia (CLL) in both the up-front and relapsed/refractory settings. The PI3K inhibitors idelalisib (Zydelig, Gilead) and duvelisib (Copiktra, Verastem) are approved for relapsed/refractory CLL; idelalisib is approved specifically for use in combination with the monoclonal antibody rituximab. Finally, the BCL2 inhibitor venetoclax (Venclexta, AbbVie) is approved for use in both the up-front and relapsed/refractory settings; it is usually given with an anti-CD20 monoclonal antibody. All of these agents offer an alternative to chemoimmunotherapy regimens such as fludarabine/cyclophosphamide/rituximab (FCR).

**H&O** Can any other novel agents be used in CLL?

**JW** The BTK inhibitor zanubrutinib (Brukinsa, BeiGene) is approved for use in mantle cell lymphoma and theoretically could be used off label in CLL, but I am not sure if there is much of a place for this indication currently because 2 other BTK inhibitors have been approved to treat CLL.

**H&O** What are the advantages and disadvantages of using novel agents in place of chemoimmunotherapy?

**JW** The efficacy of novel agents has been shown to be superior to that of chemoimmunotherapy in both the relapsed/refractory setting and the treatment-naïve setting. Novel agents also tend to have better safety and tolerability.

The only time I might consider chemoimmunotherapy in CLL is when a patient is younger than 65 years and has very good genomic-risk disease.

**H&O** In what circumstances do you use chemoimmunotherapy in CLL?

**JW** I virtually always recommend a novel agent for my patients with CLL. The only time I might consider chemoimmunotherapy in CLL is when a patient is younger than 65 years and has very good genomic-risk disease, meaning

that the immunoglobulin heavy chain gene (*IGHV*) is mutated and no high-risk cytogenetic abnormalities are present. In such patients, very long-term remissions, and possibly cure, are possible with FCR. A practitioner might also choose chemoimmunotherapy if a patient is having difficulty taking a daily medication and is not adhering to treatment, or possibly for financial reasons, but I have not encountered either of these situations.

In the rare cases in which I use chemoimmunotherapy, I choose FCR rather than bendamustine (Treanda/Bendeka; Teva)/rituximab (BR). BR has been shown to be less effective than FCR and ibrutinib, and it also has been shown to be less effective than acalabrutinib in the setting of relapsed disease.

### H&O How do you select which of the novel agents to use in your patients?

**JW** When I see somebody with treatment-naïve CLL who is in need of first-line therapy, we have a discussion about BTK inhibitors and venetoclax in combination with the anti-CD20 monoclonal antibody obinutuzumab (Gazyva, Genentech). Right now, we do not have much data to show superior efficacy for one drug class vs another. We have more long-term data for the BTK inhibitors than for the venetoclax regimen, but the available data suggest that they are pretty similar. However, they do have different side effects; the BTK inhibitors tend to cause more cardiac effects, such as hypertension and sometimes atrial fibrillation. BTK inhibitors also carry a risk for bleeding and can cause joint pain. The side effects that we worry about with BCL2 inhibition plus obinutuzumab are tumor lysis syndrome, neutropenia, and infusion reactions.

In addition to side effects, we discuss the fact that BTK inhibitors are taken for an indefinite time, whereas venetoclax/obinutuzumab is taken for a defined period. BTK inhibitors are simpler to take initially, however; the patient receives the medication and begins taking it at home, whereas the dose of venetoclax must be ramped up to avoid tumor lysis syndrome, and the administration of CD20 antibodies requires infusions.

I also make a point of discussing clinical trials with my patients because these are an excellent option for most of them.

### H&O Which clinical trial data are the most helpful in guiding treatment decisions?

**JW** Multiple studies have established that novel agents are superior to chemoimmunotherapy. An important phase 3 study of frontline treatment is RESONATE-2, which compared ibrutinib with chlorambucil in patients who had CLL or small lymphocytic leukemia. This

study is not a great choice for showing the superiority of ibrutinib because chlorambucil is fairly ineffective. It is notable, however, in that more than 5 years of follow-up were published in *Leukemia* this year, information that is helpful for clarifying the long-term side effects and long-term efficacy of ibrutinib.

Now that we have established novel agents as the treatment of choice rather than chemoimmunotherapy, the interesting questions relate to novel agents vs other novel agents.

The defining studies that have shown ibrutinib regimens to be better than standard chemotherapy are A041202, from the Alliance for Clinical Trials in Oncology, and E1912, from the Eastern Cooperative Oncology Group and American College of Radiology Imaging Network (ECOG-ACRIN). A041202, which was published in the *New England Journal of Medicine* in 2018, found superior progression-free survival (PFS) with ibrutinib regimens vs BR in older treatment-naïve patients, and E1912, which was published in the *New England Journal of Medicine* in 2019, found superior PFS and overall survival with ibrutinib/rituximab vs FCR in younger treatment-naïve patients. Another important study is ELEVATE TN, which was published in the *Lancet* this year; the researchers found that PFS was better with acalabrutinib—with or without obinutuzumab—than with the chemoimmunotherapy regimen of chlorambucil/obinutuzumab. The defining study regarding venetoclax is CLL14, in which venetoclax/obinutuzumab significantly improved PFS compared with chlorambucil/obinutuzumab in the frontline setting. The benefit of venetoclax persisted 2 years after treatment cessation, according to results published in *Lancet Oncology* this year.

### H&O How do you decide on treatment duration when using fixed-duration venetoclax?

**JW** The CLL14 study used 1 year of venetoclax/obinutuzumab, so that is what I use in treatment-naïve patients.

Our trial data regarding venetoclax in the relapsed/refractory setting come from the MURANO study, which used 2 years of venetoclax/rituximab, so that is what I use in the relapsed/refractory setting. Results appeared in the *New England Journal of Medicine* in 2018.

**H&O** What additional questions do clinical trials need to address?

**JW** Now that we have established novel agents as the treatment of choice rather than chemoimmunotherapy, the interesting questions relate to novel agents vs other novel agents. For example, is a combination of 2 novel agents superior to a single novel agent? If so, is a combination better in all patients or just in certain ones, such as those who have high-risk disease or are younger? How do new drugs in these classes compare with older agents, and can we get even better results by using new classes of agents? We also need to learn the best way to sequence these agents—is it better to use a BCL2 inhibitor first and then a BTK inhibitor, or the other way around?

**H&O** What are some of the ongoing trials that are looking at these questions?

**JW** Two important studies that have opened through the National Clinical Trials Network (NCTN) are looking at ibrutinib/obinutuzumab vs ibrutinib/obinutuzumab/venetoclax. The Alliance A041702 trial is looking at patients 70 years of age and older (NCT03737981), and the EA9161 trial from ECOG-ACRIN is looking at patients who are younger than 70 years (NCT03701282).

Trials are not currently looking specifically at the sequencing question to my knowledge, but I think we are likely to get the answers by examining follow-up data from current ongoing studies.

**Disclosure**

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**Suggested Readings**

Al-Sawaf O, Zhang C, Tandon M, et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 2020;21(9):1188-1200.

Burger JA, Barr PM, Robak T, et al. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. *Leukemia.* 2020;34(3):787-798.

Ghia P, Pluta A, Wach M, et al: Acalabrutinib vs idelalisib plus rituximab or bendamustine plus rituximab in relapsed/refractory chronic lymphocytic leukemia: ASCEND final results [ASCO abstract 8015]. *J Clin Oncol.* 38(15)(suppl).

Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med.* 2018;378(12):1107-1120.

Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. *N Engl J Med.* 2019;381(5):432-443.

Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. *Lancet.* 2020;395(10232):1278-1291.

Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. *N Engl J Med.* 2018;379(26):2517-2528.