CLINICAL UPDATE

Current Developments in the Management of Chronic Lymphocytic Leukemia

Emerging Data for Venetoclax in Chronic Lymphocytic Leukemia

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H&O What study data led the US Food and Drug Administration (FDA) to approve venetoclax for chronic lymphocytic leukemia (CLL)?

SO In CLL, venetoclax (Venclexta, AbbVie/Genentech) is approved for both treatment-naive and relapsed/refractory patients on the basis of 3 main trials. Results from phase 1 and 1b trials led to approval for patients with the 17p deletion and patients with relapsed disease.[1,2] The phase 3 MURANO trial resulted in the approval of fixed-duration therapy (2 years) with venetoclax and rituximab for relapsed/refractory patients.[3] Approval in the frontline setting was based on the CLL-14 trial.[4] Each trial helped to evolve the treatment and/or broaden the treatable patient population.

The original phase 1, dose-escalation trial evaluated doses ranging from 150 mg/day to 1200 mg/day in 56 patients.[1] In an expansion cohort, 60 additional patients were treated with a weekly stepwise ramp-up regimen, with doses that reached 400 mg/day. The trial enrolled a very refractory group of patients with CLL.[1] The patients had received a median of 4 prior regimens, so they were heavily pretreated. Treatment with venetoclax was continued until the patient developed progressive disease or intolerable adverse events, which is the same strategy used with the Bruton's tyrosine kinase (BTK) inhibitors.

The trial did not identify a maximum tolerated dose. Among the 116 patients who received venetoclax, a response was seen in 79%. A complete response was reported in 16%. Undetectable levels of minimal residual disease (MRD) were reported in 5%. Responses were seen in patients with high-risk characteristics. The overall response rate was 71% among patients with the deletion 17p, which included a complete response in 16%. Among patients with unmutated immunoglobulin heavy-chain variable region gene (*IGHV*), the overall response rate was 76%, with a complete response rate of 17%. At 15 months, the estimated rate of progression-free survival (PFS) was 69% among patients in the 400-mg dose groups. Based on the results of this trial, venetoclax received an initial approval in CLL for patients with 17p-deleted disease. The approval was then expanded to include all patients with relapsed CLL.

The phase 1b trial combined venetoclax with rituximab in patients with relapsed CLL.[2] Venetoclax was administered in a stepwise escalation to the target doses of 200 mg/day to 600 mg/day. Monthly rituximab was then added, at 375 mg/m^2 in month 1 and 500 mg/m^2 in months 2 to 6. The maximum tolerated dose of venetoclax was not identified. For the combination regimen with rituximab, the recommended phase 2 dose of venetoclax was 400 mg.

The overall response rate was 86%, which included complete responses in 51%. At 2 years, the estimated rate of PFS was 82%. Ongoing responses were reported in 89%. Treatment led to a high rate of undetectable MRD of 57%, so investigators chose to move forward with this combination rather than single-agent venetoclax.

The randomized phase 3 MURANO trial compared venetoclax plus rituximab vs standard chemoimmunotherapy with bendamustine (Bendeka, Teva) plus rituximab.[3] The dose of venetoclax began at 20 mg/day and increased to 400 mg/day throughout the first 5 weeks. In this trial design, the antibody was front-loaded, meaning that it was given with venetoclax (after the venetoclax dose ramp-up was complete), but only for the first 6 months. Treatment with venetoclax was stopped after 2 years.

At 2 years, the rate of PFS was 84.9% with venetoclax plus rituximab vs 36.3% with bendamustine plus rituximab. The median PFS was not reached vs 17

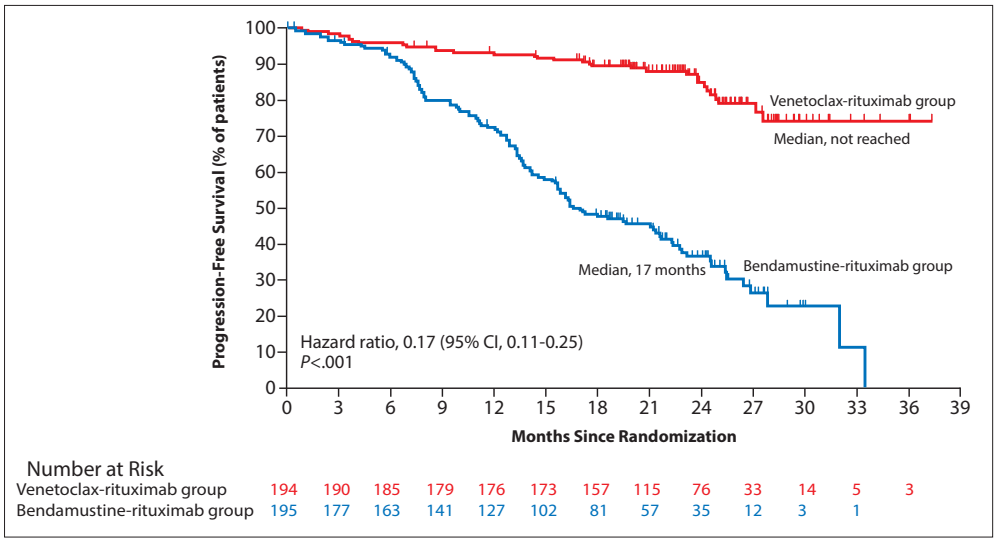

Figure 1. Progression-free survival in the phase 3 MURANO trial, which compared venetoclax plus rituximab vs standard chemoimmunotherapy with bendamustine in patients with relapsed or refractory chronic lymphocytic leukemia. Adapted from Seymour JF et al. *N Engl J Med.* 2018;378(12):1107-1120.[3]

months, respectively (Figure 1). Among patients with deletion 17p, the 2-year PFS rate was 81.5% with venetoclax plus rituximab vs 27.8% with bendamustine plus rituximab. Based on the results of this study, the combination of venetoclax plus rituximab was approved as a fixed-duration regimen. (As a single agent, venetoclax can be administered indefinitely.)

The CLL-14 trial compared venetoclax plus obinutuzumab (Gazyva, Genentech) vs chlorambucil plus obinutuzumab in the frontline setting.[4] This trial was spearheaded by investigators in Germany. Rather than combining venetoclax with rituximab, the investigators chose to use obinutuzumab because it is more potent than rituximab.[5] As in the MURANO trial, the antibody was front-loaded and given for only 6 months, whereas venetoclax was given for 12 months and then discontinued. In the CLL-14 trial, obinutuzumab was initiated before venetoclax, whereas in the MURANO trial, rituximab was started after completion of the venetoclax ramp-up.

In the CLL-14 trial, the primary endpoint of PFS was significantly longer with venetoclax plus obinutuzumab.[5] At a median follow-up of 39.6 months, the median PFS was not reached with venetoclax plus obinutuzumab vs 35.6 months with chlorambucil plus obinutuzumab. These data led to the approval of this regimen in the frontline setting. Venetoclax plus obinutuzumab was administered in a fixed duration of 1 year, rather than the 2-year schedule given in the MURANO trial. The shorter duration was chosen based on the premise that previously untreated patients would be able to achieve undetectable MRD more quickly than relapsed patients.

H&O What are the other treatments used in CLL?

SO Frontline treatments for CLL can be classified into 2 main types: chemoimmunotherapy and newer targeted therapies. The newer targeted therapies include BCL-2 inhibitors and BTK inhibitors. BCL-2 is a proapoptotic protein that helps cells to survive.[6] Venetoclax is a highly selective inhibitor of BCL-2.[1]

In the United States, there are 2 BTK inhibitors approved for CLL. Ibrutinib (Imbruvica, Pharmacyclics/Janssen) was the first, followed by acalabrutinib (Calquence, AstraZeneca).[7-10] The BTK inhibitor zanubrutinib (Brukinsa, BeiGene) is approved for mantle cell lymphoma, and it received accelerated approval for Waldenström macroglobulinemia and marginal zone lymphoma.[11-13] Zanubrutinib is not yet approved for CLL. Results from a randomized head-to-head comparison of zanubrutinib vs ibrutinib in the relapsed setting were presented at the 2021 European Hematology Association meeting.[14] The interim analysis was based on assessment by the investigators, rather than an independent review committee, and had a limited follow-up of only a year. The patients treated with zanubrutinib had a somewhat higher response rate and longer PFS. Zanubrutinib will likely be the third BTK inhibitor approved for CLL in the United States.

Drug classes other than chemoimmunotherapy are also approved for CLL. There are 2 phosphoinositide 3-kinase (PI3K) inhibitors: idelalisib (Zydelig, Gilead), which is approved in combination with rituximab, and single-agent duvelisib (Copiktra, Secura Bio).[15,16] These treatments are approved only in the relapsed setting. Another PI3K inhibitor, umbralisib, is currently under investigation.[17]

Noncovalent BTK inhibitors appear promising, but are not yet approved in the United States. The approved BTK inhibitors—ibrutinib, acalabrutinib, and zanubrutinib—all bind at the same site: C481S.[18] A common

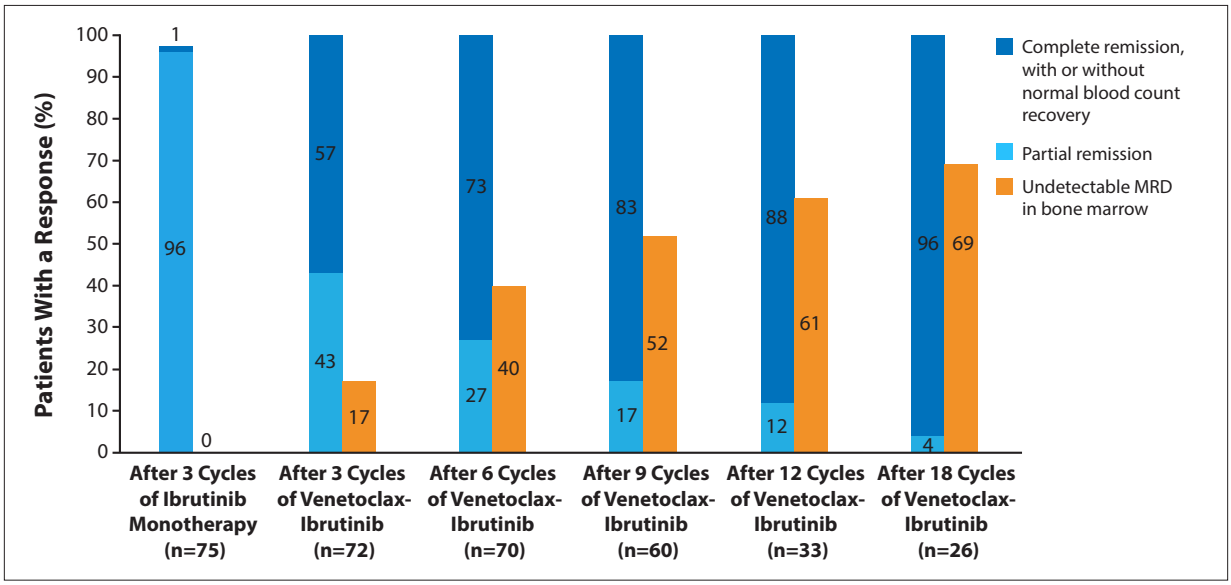

Figure 2. Response to treatment in a phase 2 trial of ibrutinib plus venetoclax among patients with previously untreated chronic lymphocytic leukemia. MRD, minimal residual disease. Adapted from Jain N et al. *N Engl J Med.* 2019;380(22):2095-2103.[23]

mechanism of clinical resistance to these drugs is a mutation at the binding site. A patient who is resistant to one of the approved BTK inhibitors is highly likely to be resistant to the others.[19] An advantage of the noncovalent inhibitors is that they bind at a different site. These novel agents have shown good efficacy, even in patients who are resistant to the approved BTK inhibitors.

Two noncovalent BTK inhibitors are in development: nemtabrutinib (formerly known as ARQ 531) and pirtobrutinib (formerly known as LOXO-305). Preliminary data for these agents have been presented.[20,21] These noncovalent BTK inhibitors are exciting because they would allow continued use of this mechanism of action in patients who are resistant to one of the other drugs. Currently, the only option for patients who are resistant to a BTK inhibitor is a switch to venetoclax-based therapy.

H&O What are some differences between venetoclax and the BTK inhibitors?

SO Venetoclax and the BTK inhibitors are both targeted therapies. They differ in their mechanisms of action and durations of administration.

Venetoclax is usually administered as fixed-duration therapy. Treatment lasts for 12 months with the combination of venetoclax plus obinutuzumab in patients with previously untreated CLL. In patients with previously treated CLL, venetoclax plus rituximab is administered for 24 months. The BTK inhibitors are administered until the patient develops disease progression or unacceptable toxicity.

Venetoclax inhibits a different kinase from the BTK inhibitors.[6] The BTK inhibitors and the PI3K inhibitors are known as B-cell receptor inhibitors. These drugs interact in the B-cell receptor pathway, albeit on different kinases. This is important because ligating the B-cell receptor sends a strong proliferative and survival signal to the cell.[22] Inhibiting that signaling would be beneficial.

There are now some data from studies combining a B-cell receptor inhibitor with venetoclax (Figure 2).[23,24] There may be some synergy in vitro. Not only do these treatments target different pathways, but the B-cell receptor inhibitors drive the cells out of the microenvironment. When BTK inhibitors are used as single agents, they initially cause lymphocytosis before the patient achieves a partial response. BTK inhibitors drive the cells out of their protective niches within the lymph nodes and the bone marrow, and into the blood. Venetoclax is particularly effective at killing circulating cells. Early data from the combination trials look promising, with high rates of undetectable MRD.

H&O What are the benefits of a fixed-treatment duration?

SO There are numerous benefits to a fixed-treatment duration. Adherence is improved. Venetoclax is generally very well-tolerated. Any adverse events that do arise will resolve after treatment ends. There are potential financial benefits to a fixed-treatment duration, both to society as a whole and to the patients, who often have a copay for these expensive drugs.

H&O Which patient characteristics guide selection between venetoclax and the BTK inhibitors?

SO Venetoclax and the BTK inhibitors are both excellent treatments in general. Some prognostic differences are emerging. With the BTK inhibitors, PFS does not differ based on whether the patient has a mutated or unmutated *IGHV*.[7] A patient's *IGHV* mutation status does appear to impact response to venetoclax plus obinutuzumab in the frontline setting. In a 4-year follow-up analysis of the CLL14 study, treatment with venetoclax plus obinutuzumab led to a median PFS of approximately 5 years among patients with the unmutated *IGHV* gene vs not reached among those with mutated *IGHV*.[25] However, even for patients with the unmutated *IGHV* gene, it is not clear if a BTK inhibitor is preferred. The patients in the venetoclax/obinutuzumab group had stopped receiving this treatment an average of 4 years before they relapsed. Patients who relapse after treatment ends will not necessarily develop a resistant clone. It might be possible to re-treat these patients with venetoclax, either continuously or with a second course of finite duration.

The BTK inhibitors and venetoclax are both generally well-tolerated drugs. Another distinction, however, is that cardiovascular toxicity, notably hypertension and atrial fibrillation, may occur with BTK inhibitors but is not seen with venetoclax. This might mean that physicians would prefer venetoclax in a patient population with significant cardiac comorbidities.

I prefer to use a BTK inhibitor in one specific population: patients with a 17p or *TP53* mutation. Data for the largest cohort of frontline 17p-deleted patients with CLL treated with ibrutinib, drawn from a pooled analysis of 4 randomized trials, were recently published.[26] The 4-year PFS was 78%, analogous to the PFS seen in all-comers treated with ibrutinib in the RESONATE-2 trial (which compared ibrutinib vs chlorambucil).[8,26] In the CLL-14 trial, venetoclax plus obinutuzumab was associated with a median PFS of approximately 3 to 4 years in these patients.[4] However, it is not known whether venetoclax is a less effective agent in patients with a *TP53* aberration or whether it was the finite duration of therapy that decreased remission durability. Patients may need continuous exposure to venetoclax to achieve a longer response. Currently, there are no data to address these questions. The trial of venetoclax plus obinutuzumab was designed to evaluate a fixed duration of therapy, and no subset of patients continued treatment beyond 1 year. Without data to address these questions, my preference is to treat patients with a 17p deletion or *TP53* mutation with a BTK inhibitor, which is given continuously. Other than this high-risk subset, it is possible to make a case for either a BTK inhibitor or venetoclax in most patients, with the noted caveat of patients with cardiovascular comorbidities, in whom venetoclax-based therapy might be more desirable.

H&O What is known about resistance to BTK inhibitors?

SO After long-term use of the BTK inhibitors, many patients develop a point mutation at the C481S binding site that renders them resistant to treatment.[18] There are other mechanisms of resistance as well, since not all resistant patients have mutations in BTK. In contrast, inherent resistance is not expected in patients who develop progressive disease many years after treatment with fixed-duration venetoclax.

There is a possibility that a finite duration of BTK inhibitors might also allow these agents to be used again after several years. No clinical trials have evaluated single-agent BTK inhibitors in a finite duration, but this strategy might be worth investigating. Treatment for 3 or 4 years usually leads to a good remission. What if treatment were stopped at this point? If the patient then relapses after a certain amount of years off treatment, perhaps the drug could be initiated again. This strategy could extend the shelf life of BTK inhibitors. Trials evaluating the combination of ibrutinib and venetoclax tend to administer a fixed-duration regimen, or at least provide the opportunity for patients to stop therapy at different time points, depending on when they achieve undetectable MRD.[23,24] Other than that, all of the trials of BTK inhibitors have evaluated continuous therapy.

H&O Are there data supporting the use of BTK inhibitors after venetoclax?

SO There are emerging data for this approach. There are clinical trials and real-world data for patients treated with ibrutinib followed by venetoclax.[27-29] The FDA approved ibrutinib long before venetoclax. A clinical trial evaluated the response to venetoclax in patients previously treated with either a BTK inhibitor or a PI3K inhibitor.[30,31] The trial was for patients treated unsuccessfully with ibrutinib or idelalisib, and the data for each of these cohorts were published separately.

Data are more limited for patients treated with venetoclax followed by a BTK inhibitor. The MURANO trial of venetoclax plus rituximab enrolled patients with relapsed disease.[3] However, the median number of prior regimens was 1, and the prior treatment was chemoimmunotherapy in nearly all cases. Almost no patients in the MURANO trial had received a BTK inhibitor. Data

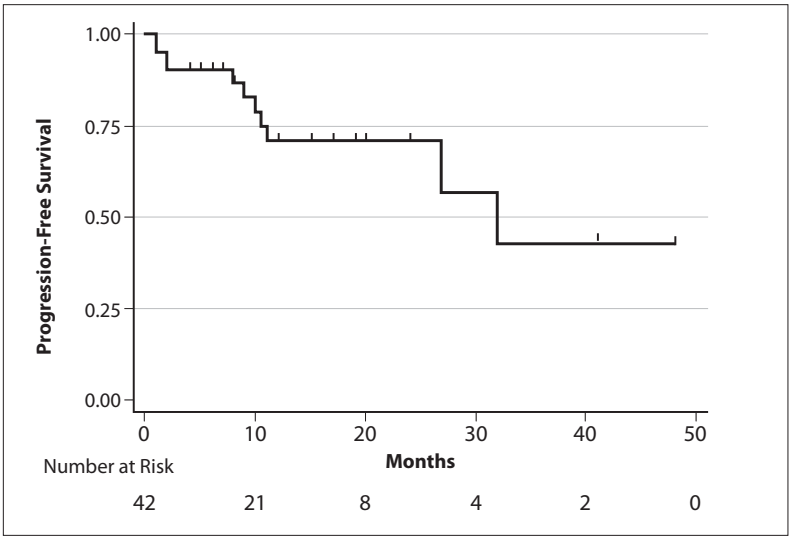

Figure 3. Progression-free survival in a retrospective study of patients with chronic lymphocytic leukemia who received a BTK inhibitor after treatment with venetoclax. Data are shown for patients who had not received previous treatment with a BTK inhibitor. BTK, Bruton's tyrosine kinase. Adapted from Mato AR et al. *Clin Cancer Res.* 2020;26(14):3589-3596.[33]

from the MURANO trial are generally updated annually. In addition to the long-term follow-up of the primary cohort, we are now beginning to see data for subsequent treatment with a BTK inhibitor and even retreatment with venetoclax.[32] The number of patients who have received retreatment is relatively small. Approximately 50 patients have received treatment with a BTK inhibitor, and they had a very high response rate.

In 2020, Dr Anthony Mato and colleagues published real-world data for 44 patients who received a BTK inhibitor after venetoclax.[33] At a median follow-up of 7.7 months, the estimated median PFS was 32 months in BTK inhibitor–naive patients (Figure 3), not reached in BTK inhibitor–intolerant patients, and 4 months in patients who were resistant to BTK inhibitors. The overall response rate was 84% in BTK inhibitor–naive patients and 54% in BTK inhibitor–exposed patients. Therefore, it appears possible to achieve good responses when moving from a B-cell receptor inhibitor to venetoclax or vice versa.

H&O What do data suggest regarding the use of MRD in the management of patients with CLL?

SO There is no question that patients who reach an MRD-negative state have deeper responses and very durable remissions. The MURANO trial of venetoclax plus rituximab in relapsed or refractory CLL evaluated outcomes according to MRD levels that were undetectable, low-detectable, or high-detectable. All of the PFS curves were dramatically different. PFS was best in patients with undetectable MRD, followed by those with low-grade detectable levels.[3] Patients with the worst PFS were those in the high-detectable group.

Measurement of MRD can also help conduct a trial of finite therapy. High rates of MRD undetectability can provide confidence that the remissions will last years. Some patients might even be cured.

Any of the regimens that produce high rates of MRD undetectability have the potential for use in a finite duration. Among the small molecules, venetoclax-based therapy is the only therapy associated with MRD undetectability. There is the possibility that venetoclax could be used again after the patient relapses while off of therapy. In contrast, BTK inhibitors can lead to durable remissions, but when the patient relapses, that class of drugs is no longer effective. (This may change with the approval of the noncovalent BTK inhibitors.)

H&O Do you have any recommendations regarding the use of MRD to monitor patients with CLL?

SO The premise behind these fixed-duration trials is the knowledge that the treatment led to high rates of MRD undetectability. However, treatment was stopped after 1 year in the frontline setting and after 2 years in the relapsed setting, regardless of the patient's MRD status.[3,4] Therefore, based on these trials, clinicians do not have to monitor MRD.

MRD is monitored in clinical trials, and I anticipate that assessment will reach a deeper level. The standard measure of MRD undetectability uses 10^4, but there are assays that can measure MRD levels at 10^5 or 10^6. Some combination trials of small molecules have added an antibody, namely obinutuzumab. Combination regimens will lead to high rates of MRD undetectability, but how will we know in a timely fashion if one combination small-molecule regimen is better than another? Since we already achieve high rates of MRD undetectability with

small molecules, how will we determine whether the antibody is needed? An early clue might be provided by rates of MRD undetectability that are much deeper. In other words, say there are 2 regimens that produce MRD undetectability at 10^4 in 75% of patients. However, one of the regimens produces MRD undetectability at 10^6 in 50% of patients, whereas the other regimen does not produce any patients with MRD undetectability at 10^6. Hypothetically, this type of difference between regimens might help guide selection of the best treatment to study in a large randomized trial.

H&O What have these drugs added to the treatment armamentarium?

SO Compared with 10 years ago, these small molecules have revolutionized the treatment of CLL. They clearly prolong survival compared with chemoimmunotherapy, the previous standard of care. Both classes of drugs are excellent agents to have available.

Disclosure

Dr O'Brien has served as a consultant for AbbVie, Alexion, Amgen, Aptose Biosciences Inc, Astellas, AstraZeneca, Autolus, Bristol Myers Squibb, Celgene, DynaMed, Eli Lilly and Company, Gilead, GlaxoSmithKline, Janssen Oncology, Johnson & Johnson, Juno Therapeutics, MEI Pharma Inc, Merck, NOVA Research Company, Pfizer, Pharmacyclics, TG Therapeutics, Vaniam Group LLC, Verastem, and Vida Ventures. She has received research support from Acerta, Alliance, BeiGene Ltd, Caribou Biosciences, Gilead, Kite, Loxo Oncology Inc, Mustang, Nurix Therapeutics Inc, Pfizer, Pharmacyclics, Regeneron, and TG Therapeutics.

References

1. Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2016;374(4):311-322.
2. Seymour JF, Ma S, Brander DM, et al. Venetoclax plus rituximab in relapsed or refractory chronic lymphocytic leukaemia: a phase 1b study. *Lancet Oncol*. 2017;18(2):230-240.
3. 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.
4. 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.
5. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med*. 2014;370(12):1101-1110.
6. Souers AJ, Leverson JD, Boghaert ER, et al. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. *Nat Med*. 2013;19(2):202-208.
7. Byrd JC, Brown JR, O'Brien S, et al; RESONATE Investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med*. 2014;371(3):213-223.
8. Burger JA, Tedeschi A, Barr PM, et al; RESONATE-2 Investigators. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med*. 2015;373(25):2425-2437.
9. Byrd JC, Wierda WG, Schuh A, et al. Acalabrutinib monotherapy in patients with relapsed/refractory chronic lymphocytic leukemia: updated phase 2 results. *Blood*. 2020;135(15):1204-1213.
10. Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. *Lancet*. 2020;395(10232):1278-1291.
11. Tam CS, Opat S, Simpson D, et al. Zanubrutinib for the treatment of relapsed or refractory mantle cell lymphoma. *Blood Adv*. 2021;5(12):2577-2585.
12. Tam CS, Opat S, D'Sa S, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. *Blood*. 2020;136(18):2038-2050.
13. Opat S, Tedeschi A, Linton K, et al. Phase 2 study of zanubrutinib in patients with relapsed/refractory marginal zone lymphoma (MAGNOLIA) [EHA abstract EP783]. *Hemasphere*. 2021;5(suppl).
14. Hillmen P, Eichhorst B, Brown JR, et al. First interim analysis of ALPINE study: results of a phase 3 randomized study of zanubrutinib vs ibrutinib in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma [EHA abstract LB1900]. *Hemasphere*. 2021;5(suppl).
15. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2014;370(11):997-1007.
16. Flinn IW, Hillmen P, Montillo M, et al. The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. *Blood*. 2018;132(23):2446-2455.
17. Gribben JG, Jurczak W, Jacobs R, et al. Umbralisib plus ublituximab (U2) is superior to obinutuzumab plus chlorambucil (O+Chl) in patients with treatment naïve (TN) and relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL): results from the phase 3 UNITY-CLL study [ASH abstract 543]. *Blood*. 2020;136(suppl 1).
18. Sawalha Y, Bond DA, Alinari L. Evaluating the therapeutic potential of zanubrutinib in the treatment of relapsed/refractory mantle cell lymphoma: evidence to date. *OncoTargets Ther*. 2020;13:6573-6581.
19. Gu D, Tang H, Wu J, Li J, Miao Y. Targeting Bruton tyrosine kinase using non-covalent inhibitors in B cell malignancies. *J Hematol Oncol*. 2021;14(1):40.
20. Woyach J, Stephens DM, Flinn IW, et al. Final results of phase 1, dose escalation study evaluating ARQ 531 in patients with relapsed or refractory B-cell lymphoid malignancies [ASH abstract 4298]. *Blood*. 2019;134(suppl 1).
21. Mato AR, Pagel JM, Coombs CC, et al. LOXO-305, a next generation, highly selective, non-covalent BTK inhibitor in previously treated CLL/SLL: results from the phase 1/2 BRUIN study [ASH abstract 542]. *Blood*. 2020;136(suppl 1).
22. Nemazee D. Mechanisms of central tolerance for B cells. *Nat Rev Immunol*. 2017;17(5):281-294.
23. Jain N, Keating M, Thompson P, et al. Ibrutinib and venetoclax for first-line treatment of CLL. *N Engl J Med*. 2019;380(22):2095-2103.
24. Hillmen P, Rawstron AC, Brock K, et al. Ibrutinib plus venetoclax in relapsed/refractory chronic lymphocytic leukemia: the CLARITY study. *J Clin Oncol*. 2019;37(30):2722-2729.
25. Al-Sawaf O, Zhang C, Robrecht S, et al. Venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: 4-year follow-up analysis of the randomized CLL14 study [EHA abstract S146]. *Hemasphere*. 2021;5(suppl).
26. Allan JN, Shanafelt T, Wiestner A, et al. Long-term efficacy of first-line ibrutinib treatment for chronic lymphocytic leukaemia in patients with *TP53* aberrations: a pooled analysis from four clinical trials. *Br J Haematol*. 2022;196(4):947-953.
27. Brown JR, Davids MS, Chang JE, et al. Outcomes of ibrutinib (Ibr) therapy in Ibr-naïve patients (pts) with chronic lymphocytic leukemia (CLL) progressing after venetoclax (Ven) [ASH abstract 4320]. *Blood*. 2019;134(suppl 1).
28. Lin VS, Lew TE, Handunnetti SM, et al. BTK inhibitor therapy is effective in patients with CLL resistant to venetoclax. *Blood*. 2020;135(25):2266-2270.
29. Greil R, Frasher G, Leber B, et al. Efficacy and safety of ibrutinib in relapsed/refractory chronic lymphocytic leukemia patients previously treated with venetoclax in the MURANO study [EHA abstract PS1161]. *Hemasphere*. 2019;3(suppl).
30. Jones JA, Mato AR, Wierda WG, et al. Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2018;19(1):65-75.
31. Coutre S, Choi M, Furman RR, et al. Venetoclax for patients with chronic lymphocytic leukemia who progressed during or after idelalisib therapy. *Blood*. 2018;131(15):1704-1711.
32. Kater AP, Kipps TJ, Eichhorst B, et al. Five-year analysis of MURANO study demonstrates enduring undetectable minimal residual disease (uMRD) in a subset of relapsed/refractory chronic lymphocytic leukemia patients following fixed-duration venetoclax-rituximab therapy [ASH abstract 125]. *Blood*. 2020;136(suppl 1).
33. Mato AR, Roeker LE, Jacobs R, et al. Assessment of the efficacy of therapies following venetoclax discontinuation in CLL reveals BTK inhibition as an effective strategy. *Clin Cancer Res*. 2020;26(14):3589-3596.