# Upfront therapy: the case for continuous treatment

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**Both BTKi and BCL2i are regarded as standards of care for frontline treatment of CLL. In this paper, I present the arguments for favoring BTKi as initial therapy. Venetoclax-based regimens have the advantage of being fixed in duration, but patients with select high-risk features may experience inferior PFS relative to those without high-risk features.**

**LEARNING OBJECTIVES**

- Understand that both BTK inhibitors (BTKi) and the BCL2 antagonist venetoclax are effective treatments in frontline CLL
- Understand that BTKis are active across the breadth of prognostic subgroups but are associated with long-term toxicities and the need for indefinite therapy

## CLINICAL CASE

A 71-year-old man was observed for chronic lymphocytic leukemia (CLL) for 2 years and progressed with doubling time of 6 months and bulky lymphadenopathy. He has stable hypertension, atrial fibrillation, and osteoarthritis. Prognostic workup showed del(17p) by fluorescence in situ hybridization, unmutated immunoglobulin heavy chain (IgHV), and *TP53* mutation with complex karyotype. He lives in a rural location and travels 1.5 hours by car to see his treating oncologist. Should he receive upfront continuous BTK inhibitor (BTKi) therapy or limited-duration venetoclax-obinutuzumab?

## BTKis and the paradigm for continuous therapy

Therapy for CLL in the chemotherapy era is traditionally limited in duration due to cumulative myelosuppression and other side effects.[1] This paradigm is now challenged by the advent of targeted therapies with improved tolerance profiles. In this article, we discuss the advantages of continuous BTKi therapy relative to limited-duration alternatives.

Eight years ago, the phase 1 report of the first-in-class BTKi ibrutinib was published in the *New England Journal of Medicine*.[2] Ibrutinib was groundbreaking for patients with relapsed/refractory (R/R) CLL, achieving prolonged median progression-free survival (PFS) of 52 months and 7-year overall survival (OS) of 55%,[3] compared with historic median OS expectations of less than 1 year for similar populations.[4,5] Since then, new generations of BTKis, including more specific covalent inhibitors with the potential for reduced side effects (eg, acalabrutinib,[6] zanubrutinib[7]) and even newer "reversible" agents (eg, pirtobrutinib[8]), have emerged. Multiple phase 3 studies have confirmed the superiority of BTKi-based therapies over established comparators in CLL, in both the frontline (1L) (RESONATE-2,[9] ELEVATE-TN,[10] ILLUMINATE,[11] E1912,[12] ALLIANCE[13]) and R/R settings (RESONATE,[14] ASCEND[15]).

Although broadly effective and well tolerated as a class, the paradigm for BTKi therapy is indefinite therapy due to incomplete eradication of the CLL population, as manifest by low complete remission rates of approximately 25% to 35% and approximately 10% in the 1L and R/R settings,[3,11,16,17] respectively, and largely absent chances of attaining undetectable minimal residual disease status (uMRD; defined as <1 CLL cell per 10,000 leukocytes). The addition of the anti-CD20 rituximab to ibrutinib failed to improve PFS in 2 randomized studies in CLL,[13,18] although a slight PFS advantage to the combination of acalabrutinib and obinutuzumab to acalabrutinib alone was seen in the ELEVATE-TN study.[10,19] Thus, the nature of BTKi-based therapy remains continuous and indefinite.

## The alternative: BCL2 inhibitors and limited-duration therapy

Over the similar period, the BCL2 inhibitor venetoclax was developed.[20] Similar to ibrutinib, venetoclax showed remarkable single-agent activity in patients with heavily pretreated CLL, with median PFS of 30 months and 3-year OS of 71%.[21] Different from BTKi, venetoclax is capable of attaining uMRD as monotherapy in R/R CLL (27%–30% in blood, 16% in marrow[21,22]).

The observation that some patients in uMRD remissions were able to maintain durable responses off therapy[23,24] led to the design of time-limited regimens such as the 24-month venetoclax-rituximab (Ven-R) regimen in the MURANO study of R/R CLL[25,26] and the 12-month venetoclax-obinutuzumab (Ven-O) regimen in the CLL14 study of 1L CLL.[27] These regimens have the appeal of providing a relatively short exposure to therapeutic agents and their attendant side effects.

However, emerging data suggest that limited-duration venetoclax regimens may not be suitable in all types of CLL, with particular concern for patients with genomic high-risk disease. In the MURANO study, compared with the whole-study uMRD rate of 84% following Ven-R, uMRD rates were 42% for patients with del(17p), 55% for complex karyotype (CK), 48% for *TP53* mutation, and 40% to 43% for mutations in *NOTCH1*, *XPO1*, or *BRAF*.[26] Among patients who responded to Ven-R, 25 patients have been rechallenged after initial remissions of 12 or more months.[28] Genomic analyses comparing serial samples taken at baseline (before Ven-R) and at retreatment showed selection for del(17p) and CK, and patients carrying these clones were highly unlikely to reach uMRD from venetoclax reexposure.[28]

Similarly, in updated data sets of CLL14, patients with IgHV-unmutated status, del(17p), or *TP53* mutations experienced shorter PFS following Ven-O (hazard ratio [HR], 2.14, 3.19, and 2.42, respectively), and del(17p) was additionally associated with reduced OS following Ven-O (HR, 3.52).[29] Interestingly, clonal regrowth rates were faster in patients with IgHV-unmutated CLL,[30] suggesting that continuous "suppressive" BTKi therapy may be preferable in these patients.

## BTKis are broadly effective in high genomic risk CLL

The earliest experience with ibrutinib in the PCYC-1102 phase 1b/2 trial suggested that del(17p) and/or CK may associated with inferior outcomes: compared with the whole-study R/R CLL median PFS (mPFS) of 52 months, mPFS was 26 months for del(17p) and 31 months for CK.[3] However, the adverse risk in the CK subgroup was entirely attributable to overlap with del(17p), as patients with CK alone (without del(17p)) had a favorable mPFS of 88 months. In comparing the results of this study with those reported in subsequent BTKi studies, it is important to note that the patients in PCYC-1102 were very heavily pretreated (59% had ≥4 prior lines of therapy[3]) and may be less representative of patients seen in clinic today. Indeed, a clear relationship between increasing prior lines of therapy and inferior PFS has been clearly established across multiple ibrutinib studies.[3,31,32]

The phase 3 RESONATE study compared ibrutinib and ofatumumab in a less heavily pretreated R/R CLL population.[14] Del(17p), *TP53* mutation, and CK were present in 32%, 51%, and 25% of patients on the ibrutinib arm, respectively.[31] Patients with del(17p) and/or *TP53* mutation continued to show a slight disadvantage (mPFS of 41 months) compared with other subgroups, but no PFS differences were observed in patients with and without CK.[31]

Results of ibrutinib in 1L CLL with adverse genomics were even more favorable. In the long-term follow-up of the National Institutes of Health phase 2 study of 34 patients with *TP53* mutations receiving 1L ibrutinib therapy, 6-year PFS was 61%.[33] When pooled with the results of 3 other 1L studies (RESONATE-2, ECOG 1912, and ILLUMINATE), 89 patients in total with *TP53* aberrant CLL were treated 1L on ibrutinib-based regimens; in aggregate, a 4-year PFS of 79% was reported.[34] Balancing these favorable reports, the ALLIANCE 1L study of BR vs ibrutinib vs ibrutinib-rituximab found a less favorable PFS for patients with del(17p), with a 2-year PFS of approximately 75% for ibrutinib regimens; the corresponding 2-year PFS for patients with CK was approximately 90%.[13]

Next-generation covalent BTKis such as acalabrutinib and zanubrutinib show improved tolerance compared with ibrutinib in head-to-head studies.[35–37] In one of the largest prospective series of patients with del(17p) reported to date (SEQUOIA Arm C, n = 109), 1L treatment with zanubrutinib resulted in and overall response rate of 95% and an 18-month PFS of 91%.[38] Importantly, for those patients with the highest risk category of del(17p) and concomitant CK, a favorable 18-month PFS of 94% was maintained.[38] Similarly favorable 1L results for *TP53* aberrant CLL were reported in the ELEVATE-TN study of acalabrutinib vs acalabrutinib-obinutuzumab vs chlorambucil-obinutuzumab, with an 18-month PFS of more than 80% for acalabrutinib arms in patients with del(17p) and/or *TP53* mutation.[10]

Finally, all BTKi studies to date showed no disadvantage for patients with IgHV-unmutated status, with consistently overlapping PFS curves irrespective of setting (1L or R/R), *TP53* status, or agent studied.[10–13,15,17,31,33,38]

In aggregate, available data across the covalent BTKi experience suggested that the impact of adverse genomics (particularly *TP53* aberrations) is limited mainly to patients with heavily pretreated CLL, with largely favorable outcomes observed in phase 2 to 3 studies of patients treated in the 1L.[10,13,33,34,38] Conceptually, one can argue theoretically that the patients with the highest genomic risks (ie, del(17p) with CK) may be best served by indefinite suppression of the CLL clone at a time early in the treatment sequence rather than being challenged by intermittent therapies that may give rise to subclonal complexity later in the disease course.[39]

## Other advantages of continuous BTKi therapy

In general, BTKi therapy is straightforward to commence and broadly applicable across a range of patients, including those with mild to moderate organ impairments, with a low risk of tumor lysis syndrome.[10–13,15,17,31,33,38] Therefore, BTKis may be particularly suitable in patients with high tumor burden disease, those with renal impairment, or those situations (eg, patients residing in rural communities) where real-time monitoring for tumor lysis syndrome for venetoclax step-up may be logistically difficult. Their relatively broader "coverage" against genomic high-risk CLL also makes them easier agents to administer in community-based clinics where advanced testing for CLL genomics may be less available. Indeed, emerging data from real-world registries show low rates of testing for *TP53* and other high-risk features in patients with CLL managed in the United States.[40]

## Drawbacks of continuous BTKi therapy

Continuous BTKi therapies do have their price in terms of potential for emergence of resistance, side effect burden on patient

quality of life, and economic cost. Addressing the potential of resistance emergence, it is theoretically possible that intermittent exposure to a drug may have a lower risk of inducing treatment resistance compared with long-term exposure. However, as we have seen in the early MURANO retreatment experience,[28] even fixed-duration venetoclax exposure appears to induce the emergence of genomic high-risk, treatment-resistant clones. To date, there are no data on whether limited-duration BTKi exposure (eg, in trials combining ibrutinib and venetoclax)[41] may have less impact on the subsequent emergence of BTKi-resistant mutations.

Many patients on continuous BTKi experience side effects that may be tolerable in the short term but cumulatively represent a substantial impact on their quality of life in the long term.[42] Real-world studies suggested that up to 41% of patients discontinue ibrutinib after a median of 17 months of follow-up, largely due to side effects.[43] Balanced against these chronic toxicity considerations, it is noteworthy that all 3 recently reported head-to-head comparisons of ibrutinib vs acalabrutinib or zanubrutinib were concordant in reporting reduced cardiovascular and musculoskeletal complications in favor of the second-generation agent.[35-37] Therefore, the tolerance profile of indefinite BTK inhibition in the second-generation BTKi era is likely to be substantially improved compared with that of the ibrutinib era.

## CLINICAL CASE (Continued)

After discussions between the physician and patient, our 71-year-old patient was started on frontline BTKi due to his rural location and poor-risk genomic features. Acalabrutinib was chosen over ibrutinib due to a lower risk of cardiovascular toxicities.

### Conflict-of-interest disclosure

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Constantine S. Tam: none discussed.

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