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CURRENT AND EMERGING INVESTIGATIONAL VENETOCLAX-BASED THERAPIES IN CHRONIC LYMPHOCYTIC LEUKEMIA.

Running title: Venetoclax in CLL.

Key words: CLL, venetoclax, current combinations, investigational combinations, minimal residual disease, MRD , progression on venetoclax.

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ABSTRACT

Introduction: Venetoclax has emerged as a breakthrough treatment which revolutionized the therapeutic paradigm of chronic lymphocytic leukemia (CLL). This is primarily due to the efficacy of venetoclax as time-limited, chemo-free, therapy in a therapeutic area dominated by targeted agents given on a continuous schedule. Furthermore, compelling clinical data support the use of venetoclax in combination with other targeted agents in the hope of preventing drug resistance due to the emergence of acquired mutations.

Areas covered: This review provides an overview on clinical results of newly approved or under clinical development venetoclax-based therapies for CLL. In view of current and potential roles in CLL care, the strengths and disadvantages of venetoclax-combinations are discussed. The MEDLINE database, ClinicalTrials.gov and conference proceedings were all reviewed to select the relevant literature.

Expert Opinion: While the advent of venetoclax-based combinations has significantly expanded the therapeutic options for patients with CLL, further research with longer follow-up is required to address remaining open questions such as (I) the role of venetoclax in driving the duration of therapy, (II) timing and threshold of minimal residual disease (MRD) assessment for stopping therapy, (III) the efficacy of novel triplet combinations using venetoclax as backbone, (IV) indications for re-initiating therapy with venetoclax.

Article highlights

- Targeting the bcl-2 pathway is a rational treatment approach in CLL. Therefore addition of venetoclax to the toolkit of CLL therapy represents important progress in the field.
- Double or triple, chemo-free, venetoclax-based combinations have been recently evaluated in CLL. The idea behind this regimens is to administer therapy for a defined period, rather than exposing patients to endless treatment.
- With the widespread use of venetoclax-based regimens, treatment of CLL patients who become refractory to novel agents is an area of unmet need.
- Future directions to overcome resistance mechanisms to venetoclax should explore new approach based on novel BH3 mimetic developed to interact with either MCL-1 protein or transcriptional regulator of Mcl-1 expression.
- Cellular therapies (i.e., CAR-T) are challenging in patients with progressive disease who are double-refractory.

Keywords: Chemotherapy -free combination strategies, chronic lymphocytic leukemia, continuous treatment, genetic characterization, minimal residual disease, oral targeted agent, sequencing, time-fixed duration, venetoclax

1.0 Introduction

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in the Western world with a male prevalence and median age at diagnosis of approximately 72 years [1]. In such a disease the therapeutic transition from chemo-immunotherapy (CIT) to novel molecular targeted agents resulted in a substantial increase in overall survival (OS) [2-6]. Initially, the landscape of treatment was modified by ibrutinib, the first-in-class Bruton's tyrosine kinase inhibitor (BTKi) [6]. This change not only enabled patients with the del17p/*TP53*mut to achieve previously unattainable OSs, but it also contributed to significantly reduce myelosuppression, which is a common side effect of CIT [6-10]. However, remissions induced with ibrutinib are typically partial, consequently, long-term treatment is required when this BTK inhibitor is used as a single agent. In addition, the occurrence of peculiar non-hematologic side effects such as atrial fibrillation and hypertension, as well as interactions with concomitant medications, resistance development, and

high financial costs are all disadvantages of ibrutinib therapy [10-12]. On the contrary, venetoclax, an orally bioavailable BCL2 inhibitor, induces a high rate of complete responses (CRs) which often translates into undetectable minimal residual disease (uMRD) status (13-15). Furthermore, venetoclax is peculiar in that it allows for fixed durations of therapy of 12 months in the frontline and 24 months in the relapsed/refractory (R/R) setting, which improves patient compliance and pharmacoeconomics (16-17).

Despite the high rate of undetectable MRD obtained, patients eventually progress while receiving venetoclax monotherapy. Recently, much interest has focused on the combination of BTKis and venetoclax, possibly with inclusion of an anti-CD20 monoclonal antibody (16-17). The rationale for using these combinations is based on *in vitro* data indicating synergy between venetoclax and BTKis, as well as differences in clinical activity in lymph nodes versus bone marrow and nonoverlapping clinical toxicity of these agents (18). Some venetoclax-based combinations including covalent or non-covalent BTK inhibitors have been tested in phase II and are currently undergoing scrutiny in phase III studies (Table 1 and table 2) .

In this review a literature search was performed on PubMed and main hematology meeting abstracts to obtain information on phase II and III clinical trials including venetoclax-based combinations in CLL (last search date: 28 February 2021). We also discuss therapeutic options for patients who progress on venetoclax reviewing the existing literature and studies registered at ClinicalTrials.gov database.

2.0 Venetoclax monotherapy in R/R CLL

The results of three pivotal trials (i.e., M13-982, M12-175 and M14-032) allowed for the first approval of venetoclax in April 2016. These trials were heterogeneous with respect to patient del(17p)/*TP53* status and prior exposure to B-cell receptor inhibitor (BCRi) therapy. However, despite differences relating to inclusion criteria, overall response rates (ORRs) were between 65% and 75% while estimated progression-free survivals (PFSs) at 1 year were close to 75% [13-15].

A pooled analysis including four phase I or II clinical trials (i.e., M13-982, M12-175, M14-032 and M13-365) was conducted recently by Roberts at al [19] who assessed the magnitude of clinical outcome improvement obtained with venetoclax in relation to clinico-biological factors that influence the rate and durability of response. In this study which included 436 patients objective

response was documented in 75% of cases, with a 22% CR/ CRi (CR with incomplete hematologic recovery) rate [17]. Overall, 27% of the patients achieved uMRD in peripheral blood (PB) while median PFS was 30.2 months. In multiple regression analyses, lymphadenopathy ≥5 cm, presence of 17p deletion and/or *TP53* mutation, NOTCH1 mutation and poor response to previous treatment with BCRi were consistently associated with shorter duration of response (DoR) [19].

Recently, results of VENICE 1, a phase 3b trial study evaluating the efficacy of 2-year fixed duration venetoclax monotherapy in patients with CLL have been presented at the virtual European Hematological Association (EHA) 2020 meeting [20]. Most patients were BCRi-naïve (n=191), but 67 had received prior BCRi-treatment (BCRi-exposed). Site-reported genetics indicated that 17p-deletion or *TP53* mutation was present in 16.8% of BCRi-naïve patients *versus* 43.3% of BCRi-exposed patients. ORR was 85.3% for BCRi-naïve patients (CR/CRi, 35.1%) compared with 64.2% in the BCRi-exposed group (CR/CRi, 25%). Furthermore, MRD at week 48 was undetectable in 35.6% and 26.9% respectively , while median PFS was 30.5 months for the BCRi-naïve and 28.6 months for BCRi-exposed patients. Toxicity was high, but manageable; 74.4% experienced grade ≥3 adverse events (AEs) (neutropenia 37.2%, infection 19.0%); 12.4% of patients had reduced doses due to AEs, and 109 (42.2%) discontinued venetoclax (12.8% because of AEs, 10.9% with disease progression). No new safety signal was noted.

3.0 MURANO trial: a time-limited venetoclax-based therapy in R/R CLL

Enhanced activity of venetoclax combined with rituximab has already been recorded in preclinical models [18] . These preclinical data supported by results of a safety phase 1b clinical trial, suggest that venetoclax *plus* rituximab is an attractive therapeutic option for patients with R/R CLL, who may achieve deeper response which could possibly be maintained for long time after discontinuing therapy [21].

The MURANO trial is the first phase III study investigating time-fixed therapy with an oral inhibitor in CLL. From a clinical stand point this implies a change of the therapeutic paradigm for CLL from continuous to time-fixed chemo-free approach [22]. In the randomized, open-label, phase III MURANO trial, patients were assigned to receive either venetoclax for up to 2 years (from day 1 of cycle 1) *plus* rituximab for the first 6 months (VR group) or BR for 6 months (BR group) [16]. The primary end point was investigator-assessed PFS. Of note, only 2% of patients had received prior treatment with BCRi.

According to updated 5-year results presented at the ASH 2020 virtual meeting, the PFS benefit was sustained over time [23]. After median follow-up of about 60 months, median PFS was 53.6 months for VR compared with 17 months for BR (P <.0001). The 5-year estimated OS rate was 82.1% for VR and 62.2% for BR (P <.0001). Patients treated with VR who reached the end of treatment (EOT) without progressive disease and achieved uMRD had an improved PFS and OS compared with those with did not. The 3-year post–EOT PFS estimate was 61% for patients with uMRD (i.e., $< 10^{-4}$), 41% for low-MRD positivity (i.e., $> 10^{-4}$ to $< 10^{-2}$) and 8.3% with high-MRD positivity (i.e., $> 10^{-2}$). Among patients who achieved uMRD at EOT, baseline presence of del(17p), genomic complexity, and unmutated IGHV were all associated with a greater risk of MRD conversion and subsequent progressive disease [23-24]. Of note, the MURANO study's 5-year data show that fixed duration VR provides a time-to-next-treatment (TTNT) benefit, improves time to second PFS (PFS2) event, and allows for high response rates to subsequent therapies, including re-exposure to venetoclax-based regimens. No new safety signals were identified in this updated analysis [23].

Although the MURANO study established the VR time-limited regimen as a new standard of care in R/R CLL patients, there are still some open issues. The first is whether a 2-year period of exposure to venetoclax is adequate for all patients with R/R disease, or if patients with sub-optimal response should continue venetoclax beyond the planned 24 months. In a retrospective analysis of 62 R/R patients, the goal of uMRD was mostly achieved in the first 2 years of venetoclax therapy and patients with suboptimal responses had limited chances to reach deeper responses with extended therapy beyond 2 years [24]. Furthermore, in absence of direct comparisons, the superiority of VR combination over venetoclax monotherapy might be questionable. A multicentre, retrospective cohort which included 321 R/R CLL patients showed comparable results between patients treated with venetoclax monotherapy or VR [25]. However, the absence of additional toxicities caused by anti-CD20 monoclonal antibodies, the aim to achieve the deepest response possible and results indicating a long-term benefit in terms of PFS and OS with VR, all appear to justify the current use of this approach in the context of time-limited therapy for R/R CLL patients.

4.0 CLL14 trial: time-limited - venetoclax-based up-front therapy for CLL

Given its success in R/R patients, time limited venetoclax-based combination was also investigated in the frontline setting. The phase III CLL14 trial investigated the efficacy of venetoclax-obinutuzumab (VO) given for 12 months compared to CO in patients with untreated

CLL [17]. Only patients with coexisting medical conditions (i.e., Cumulative Illness Rating Scale [CIRS] score > 6 or impaired renal function [creatinine clearance <70 mL/min] or both) were enrolled. Recent update, after a median follow-up of 52.4 months, confirmed the earlier reported benefit for PFS; the 4-year PFS was 74% in the VO arm and 35% in the CO arm [26]. The improved PFS was consistent across all clinical and biological risk groups, including those with del(17p)/*TP53* mutation, unmutated *IGHV* status and complex karyotype [27-28]. It is worth noting that after a longer period of follow-up, patients with mutated *IGHV* status who were treated with VO fared better in terms of PFS than those who received CIT [29].

At the EOT, 90 (42%) of 216 patients given VO had MRD levels below 10^{-6}, versus 14 (7%) of 216 patients in the CO group [29,32]. Notably, all MRD conversions and progressions in the VO arm were encountered in patients with del(17p) and/or mutated *TP53* after venetoclax discontinuation.

With respect to safety issues, the most common grade 3 or 4 adverse event in VO group was neutropenia (53%), however, only 4% of patients had febrile neutropenia [29].

Although results of the CLL14 trial established fixed duration VO as an effective upfront therapy in CLL, future studies should determine the efficacy of this regimen in younger patients. The ongoing phase 3 CRISTALLO trial (NCT04285567) which enrolled fit, treatment-naïve patients without del(17p) or *TP53* mutations, is now evaluating the efficacy of time-fixed (i.e.12 cycles) VO *versus* FCR or BR.

5.0 Venetoclax combination with other targeted agents

There are currently numerous studies in various stages of clinical development that are testing venetoclax-combination approaches (Table 1 and table 2). Venetoclax added to ibrutinib improves responses obtained with ibrutinib monotherapy, potentially increasing the proportion of patients with uMRD in the peripheral blood (PB) and bone marrow (BM), and providing a clue to guide therapeutic decisions based on MRD status. This novel, individualized, MRD-driven approach was used in the phase II CLARITY study, which enrolled patients with R/R CLL. The primary endpoint of study was the eradication of MRD after 12 months of combined therapy [30]. The duration of treatment was determined by the confirmed MRD response in flow cytometry; accordingly, patients discontinued ibrutinib and venetoclax when <0.01% MRD (i.e.,uMRD) was reached. uMRD was achieved at the PB and BM levels after 12 months of ibrutinib plus venetoclax in 28 (56%) and 19 (38%) of 50 patients, respectively. Despite discontinuation of therapy in patients with uMRD, the response to ibrutinib plus venetoclax is sustained after a longer follow-up (i.e., 38 months).

Estimated PFS and OS at 36 months were 95.9% and 97.7%, respectively [31]. Ibrutinib plus venetoclax was also tested in 80 previously untreated and high-risk, older CLL patients. After 12 cycles of combined treatment, 88% of patients achieved CR/CRi, while 61% achieved uMRD. [32]. The the German CLL Study Group (GCLLSG) is currently evaluating ibrutinib and venetoclax against ibrutinib monotherapy and venetoclax plus obinutuzumab in the phase III CLL17 trial (NCT04608318).

CAPTIVATE (PCYC-1142) is a multicenter phase II study (NCT02910583) in which treatment-naive patients younger than 70 years were randomized to receive double-blind treatment with placebo or ibrutinib after 12 cycles of ibrutinib plus venetoclax and confirmed uMRD [33]. Of the 149 patients enrolled, 86 (58%) had confirmed uMRD and were randomly assigned to placebo or ibrutinib, while the remaining 63 (42%) did not have confirmed uMRD and were randomly assigned to ibrutinib or ibrutinib plus venetoclax. After a median follow-up of 31.3 months, the one-year disease-free survival (DFS) of patients who achieved uMRD was similar regardless of randomization arm (i.e., placebo,95.3%; continuous ibrutinib,100%).

Given the high number of infectious complications associated with ibrutinib [1] , a venetoclax combination substituting ibrutinib for acalabrutinib in CLL patients at high risk of infection is going to be explored. The PreVent-ACaLL study (NCT03868722) is a randomized, phase II trial that is currently underway to investigate the potential of short-term treatment combining venetoclax and acalabrutinib, a second-generation BTKi, to reduce the risk of infection in newly diagnosed patients with CLL.

Shorter triple chemo-free combinations have also recently been investigated in CLL. The idea behind this triplet regimen is to administer therapy for a defined period of time rather than subjecting patients to indefinite treatment [34]. Preliminary findings from a phase Ib trial suggest that time-limited therapy for CLL with the triplet combination of ibrutinib, venetoclax, and obinutuzumab (IVO) leads to promising rates of CR with high rates of uMRD, especially in R/R patients with TP53 mutations [35]. Later, the IVO combination was tested in two separate cohorts of 25 treatment-naive (TN) and 25 R/R CLL patients [36]. A total of 14 (56%) TN and 11 (44%) R/R patients achieved uMRD in both PB blood and BM. Both TN and R/R patients have a 36-month PFS of 95 percent. It is worth noting that these findings are based on the longest follow-up period ever reported with a triplet chemo-free combination in CLL.

In the CLL2-GIVe, a prospective multicenter phase II trial, the IVO combination given on a time-fixed schedule in the first-line treatment of CLL with del(17p)/*TP53* mutation provides a

58.5% CR rate, with 80.5% of patients achieving uMRD [37]. Currently IVO is compared with standard CIT (i.e., FCR or BR), VR, and VO in fit patients with previously untreated CLL without del(17p) or *TP53* mutation (i.e., phase 3 GAIA trial, NCT02950051).

The AVO (acalabrutinib, venetoclax, and obinutuzumab) phase II study results show that after 15 months of time-limited therapy, 78% of patients achieve BM uMRD in a frontline CLL population [38]. In an upcoming phase III trial, the AVO combination will be directly compared to CIT and acalabrutinib–venetoclax (NCT03836261). The association of venetoclax, obinutuzumab and zanubrutinib has been tested in 39 previously untreated CLL patients [39]. Treatment duration was determined by a prespecified uMRD endpoint. Most patients achieved rapid uMRD: 92% PB uMRD and 84% BM uMRD at a median follow up of 14 months. Twenty-nine (77%) patients achieved the prespecified MRD endpoint and discontinued treatment.

There have been few studies on the efficacy and safety of venetoclax in combination with phosphoinositide 3-kinase inhibitors (PI3Kis) [40]. A phase I/II trial is evaluating the combination of venetoclax with the second-generation PI3Ki duvelisib in patients with R/R CLL or SLL or Richter syndrome (RS)(NCT03534323). This combination is of potential interest for patients with cardiac diseases and/or increased bleeding risk, for whom therapy with ibrutinib is challenging.
Barr et al. presented at 2020 ASH virtual meeting results of a phase I/II study of umbralisib, ublituximab, and venetoclax (U2-ven) in 43 patients with R/R CLL [41]. After 12 treatment cycles, the ORR was 100% (59% CR rate,41% PR rate). MRD was undetectable in the PB in 96% of patients and in the BM in 77%. Only one patient underwent disease progression after a median follow-up of 15.6 months. Grade 3/4 AEs of special interest consisted of lung infection/pneumonia (7%), colitis (5%), tumor lysis syndrome (2%), and rash (2%). The ongoing phase II ULTRA-V study (NCT03801525) is evaluating U2 plus venetoclax in treatment-naive and previously treated patients.
While more research is needed to determine the proper role of venetoclax associations, several questions about the best combination, duration of therapy, and predictors of therapy discontinuation remain unanswered. Furthermore, it is unclear whether MRD-driven approaches will be translated into clinical practice in the near future.

6.0 Venetoclax discontinuation and reasons for progression

Venetoclax is primarily discontinued due to progressive disease (PD) rather than to adverse events [22]. Generally, previous treatment with a BCRi, bulky disease, del(17p)/*TP53* mutations, *NOTCH1* mutations, and unmutated *IGHV* status were associated to shorter DoR [19]. MRD status

is also a significant predictor of disease progression in patients treated with time-limited venetoclax-based therapy [16-17,23]. In the MURANO trial 19 of the 47 patients (40.4%) who converted to MRD showed disease progression at a median time of 25.2 months. It is important to note that these 19 patients had more rapidly increasing rates of MRD after completing treatment than patients with no disease progression. Shorter MRD doubling times after the EOT were observed in patients with 17p deletion, genetic complexity, and unmutated IGHV relative to patients without these risk factors [23].

The appearance of Gly101Val recurrent mutation precipitates resistance to venetoclax, followed by CLL progression. Of note, Gly101Val mutation decreases BCL2 affinity for venetoclax by ~180-fold [42]. Given that the appearance of *BCL2* mutations is generally a late-onset event during venetoclax therapy, a 12- or 24-month fixed-duration venetoclax regimen may prevent venetoclax resistance; however, additional factors are likely at play. In a small, 6-patient CLL cohort, resistance to venetoclax was associated with MCL-1 overexpression, rather than to the presence of *BCL2* Gly101Val mutations [43].

7.0 Treatment of CLL patients who relapsed after venetoclax

The treatment option for patients who progress after venetoclax treatment is difficult to determine. Physicians must consider three scenarios, each of which reflecting the timing of CLL progression (during or after treatment with venetoclax) and/or prior BCRi exposure. (Fig 1).
The first scenario relates to patients who relapse after completing a program of fixed-time venetoclax-based therapy lasting 12 (i.e., CLL14) or 24 months (i.e., MURANO). In phase Ib trial of VR, 4 of 18 patients in deep response experienced CLL progression after ceasing venetoclax, and were then re-treated with a venetoclax-based therapy. All three patients suitable for response assessment obtained at least a PR [44]. In a retrospective multicentre study, 25 patients pre-treated with a venetoclax-based regimen (Ven1) were re-treated in a later line of therapy with a second venetoclax-based regimen (Ven2). The median time between the end of Ven1 and the start of Ven2 was 8.7 months, and 60% of patients had prior exposure to a BTKi. Assessment of response for Ven2 was available in 18 patients. The ORR was 72.2% (CR, n=4; PR, n=9; SD, n=4; and PD, n=1), and the estimated 12-month PFS was 69.1% [45]. Harrup et al. evaluated the clinical outcomes of 32 patients enrolled in the VR arm of the MURANO trial who were treated after progression (i.e., median treatment-free interval of 23.7 months) with a venetoclax-based regimen [46]. The best overall response (BOR) after Ven2 treatment was 72.2% (CR/CRi and PR/nPR rates were 5.6% and 66.7%, respectively). No new safety data were observed. Overall, these preliminary

findings indicate that re-treatment with venetoclax may be a reasonable option in patients who had a relatively longer treatment-free interval after venetoclax-based therapy. REVEAL (REtreatment With VEnetoclax and Acalabrutinib After Venetoclax Limited Duration) (NCT04523428) is an ongoing phase II trial that combines venetoclax and acalabrutinib with the goal of possible discontinuation after uMRD for treating patients who have previously been treated with a time-fixed venetoclax association and have achieved at least a clinical PR.

Scenarios 2 and 3 refer to patients who progress while receiving continuous venetoclax (Fig 1). In this setting, prior exposure to and resistance to BTKi is a significant factor influencing patient outcome. Among the 326 patients who discontinued venetoclax, 188 (58%) required a subsequent treatment, and BTKis were the most common post-venetoclax therapy for 39.3% of patients (44 BTKi-naïve, 30 with previous exposure to BTKis). The estimated PFS after BTKi post-venetoclax therapy was 32 months in BTKi-naive patients, whereas the median PFS was not reached in BTKi-intolerant patients and it was only 4 months in BTKi-resistant patients [47]. These findings suggest that a BTKi agent can induce long-term remissions in BTKi-naive or BTKi-intolerant patients who progress on venetoclax. In patients with known BTKi resistance who progress on venetoclax, however, responses to BTKis are disappointing [47]. In the setting of ibrutinib-resistant CLL mediated by *BTK*^{C481S} and PLCG2 mutations only reversible, noncovalent BTKis, including GDC-0853 , pirtobrutinib (formerly Loxo 305) , ARQ 531 , and vecabrutinib may overcome BTKi resistance [48,reviewed by Thompson MC and Mato AR]. In particular, pirtobrutinib, a highly selective, non-covalent BTKi is capable of inhibiting both wild-type and C481-mutated *BTK* with equivalent low nanomolar (nM) potency [49-50]. The BRUIN, a multicenter phase 1/2 basket trial (NCT 03740529) was designed to define the safety and efficacy of pirtobrutinib in patients with advanced B-cell malignancies who had received >2 prior therapies. The most common adverse event of grade 3 or higher was neutropenia (32 or 10%) [50-51]. Grade 3 atrial fibrillation or flutter was not observed, and grade 3 haemorrhage was observed in one patient in the setting of mechanical trauma. In 121 efficacy evaluable patients with CLL/SLL previous treated with a covalent BTKi (median previous lines of treatment 4), the ORR with pirtobrutinib was 62%. The response rate was not influenced by the presence or absence of a pre-treatment *BTK* ^{C481S} mutation, by the reason for prior BTKi discontinuation (i.e., progression vs intolerance), or by other previously received therapeutic classes (including a covalent BTKi and BCL2 inhibitor) [51]. These results suggest that pirtobrutinib may be an ideal post-venetoclax treatment in patients with recognised BTKi resistance (Fig. 2).

8.0 CONCLUSIONS

The addition of venetoclax to the toolkit of CLL therapy represents important progress in the field [13-21,23,52].. In comparison to BCRi agents, which are administered on a continuous basis, venetoclax-based therapies represent a "*back to the future*" in the treatment paradigm of CLL, providing the opportunity to obtain a deep response with the possibility of discontinuing treatment, an objective that BCRi agents cannot achieve. Results of clinical trials of continuous and time-limited therapy in the setting of R/R or upfront therapy for CLL leave the dilemma concerning the choice between these different approaches unresolved (Figure 2). It is debateable, indeed, whether a time-limited approach of venetoclax-based therapy, is a reasonable option for patients with del(17p)/*TP53* mutations or whether continuous treatment with ibrutinib should be used in this setting. In the CLL14 study clinical progression in patients with *TP53* disruption occurred after venetoclax discontinuation [17,29]. Results of the 5-year analysis of the MURANO trial, indicate that presence of del(17p), was associated with a greater risk of MRD conversion and subsequent progressive disease [29]. However, an indirect comparison of median PFSs between patients with del(17p) receiving ibrutinib as a single agent in the RESONATE trial (with 6-year follow-up) and patients with del(17p) treated with VR in the MURANO trial (with 5 years follow-up) show similar results (RESONATE, 40.7 months versus MURANO,47.9 months) [23,53]. However, it could be hypothesized that doublets or triplets including venetoclax given in a time-limited program and directed by MRD status, would be most useful in patients with high-risk disease in whom rapid eradication of the disease may translate into the abolition of clones promoting CLL relapse [22,37-40].

Another unresolved issue is the clinical relevance of adherence to therapy with different regimens [54]. While data in the literature suggests that ibrutinib discontinuation and interruption for reasons other than CLL progression are associated with poor survival outcomes [55] there is still limited information available on this issue for venetoclax. In a retrospective analysis conducted in patients assigned to receive VR in the MURANO trial inferior PFS was observed in patients prematurely discontinuing venetoclax for reasons other than disease progression, however, treatment interruption had no impact on PFS or OS, regardless of duration of discontinuation [56]. Venetoclax's distinct mechanisms of action from ibrutinib appear to mitigate the impact of venetoclax discontinuation on clinical outcome [57].

In conclusion, the absence of head-to-head trials comparing the time-limited and continuous approaches of therapy precludes physicians from having evidence-based indications. Two recently published network meta-analyses reveal a similar PFS in upfront therapy for these different

strategies [58-59]. When the ongoing trials (CLL17) addressing the issue will be completed, more definitive results will be provided and some of the ambiguities of the dilemma relating to continuous or time-limited therapy in CLL may well be resolved . Until then, therapeutic choices and decisions should take into consideration and rely on patient comorbidities and potential toxicities associated with the different targeted agents [60].

9.0 EXPERT OPINIONS

In an era characterized by widespread use of targeted therapies, treatment of CLL patients who become refractory to novel agents is an area of unmet need [61]. At this point, patients who are refractory to BTK and BCL-2 inhibitors have few options. LOXO-305, a noncovalent BTK inhibitor, has been very promising in patients with the BTK ^{C481S} mutation [50-51]. A phase 3, randomized, open-label study comparing LOXO-305 to the investigator's choice of idelalisib plus rituximab or BR in CLL/SLL patients who have received at least one covalent BTK inhibitor (BTKi) is now enrolling patients. (NCT04666038). Of note, patients who had received venetoclax are eligible for the study.

MCL-1 overexpression has been linked to the development of venetoclax resistance [62]. Therefore, therapies targeting MCL-1 could offer a novel treatment approach for CLL patients relapsing on venetoclax therapy [62-63]. AZD5991 is a novel BH3 mimetic that was developed specifically to disrupt MCL-1 protein complexes while sparing BCL-2 and BCL-XL protein complexes [63]. Similar preclinical results with another MCL-1 inhibitor support the findings with AZD5991 [64]. The purpose of first-in-human phase 1 study is to assess the safety and tolerability of AZD5991 alone or in combination with venetoclax in R/R hematological malignancies (NCT03218683).

CDK9 is the transcriptional regulator of Mcl-1 expression, and the CDK9 inhibitor voruciclib has been shown in preclinical studies to effectively reduce Mcl-1 expression [65-66]. A phase 1, open-label, dose escalation study has been designed to determine the safety and preliminary efficacy of voruciclib in subjects with relapsed/refractory B cell malignancies and acute myeloid leukemia (AML)(NCT03547115).

Nowadays we need to understand how cellular therapies work in the context of CLL patients who have progressive disease and are frequently double-refractory [67]. At the 2020 virtual ASH meeting have been presented results of a phase 1 study that used the association of CD19-directed CAR T-cell therapy and ibrutinib, with two different doses of liso-cel, in 19 patients with R/R

CLL/SLL [68]. All patients had received prior ibrutinib, in addition, 58% had received a prior BTK inhibitor and venetoclax (double-refractory). The ORR was 95%, with all patients responding to the highest liso-cel dose, and 75% responding to the lower dose. Neutropenia, anemia, and febrile neutropenia were the most common grade 3 to 4 treatment-emergent adverse events (TEAEs). These preliminary data show the tolerability and safety of liso-cel combined with ibrutinib for patients with R/R CLL analyses of long-term efficacy are ongoing [68].

Bispecific antibodies, which bind antigens on both effector and malignant cells, have also shown anti-leukemic activity in CLL [69]. Epcoritamab (DuoBody-CD3xCD20, GEN3013),a novel bispecific IgG1 antibody redirecting T-cells toward $CD20^+$ tumor cells, demonstrated activity in non-Hodgkin lymphomas and is presently being evaluated in CLL [70]. A phase Ib/II trial has been designed to determine the recommended phase 2 dose (RP2D) and the maximum tolerated dose as well as establish the safety profile of epcoritamab in patients with R/R CLL (NCT04623541).

Finally, the management of CLL patients during the COVID19 pandemic represents a major challenge. The occurrence of COVID-19 infection in patients with CLL is associated with negative clinical outcomes [71-72]. However, no general agreement on the management and treatment of patients with CLL during the COVID outbreak has been reached . The recommendations in this regard primarily reflect the first wave of the outbreak and include editorials, opinions, letters to the editor, commentaries, and conference proceedings [73-74]. Furthermore, the majority of the data used to develop these recommendations came from patients who were on BTKi therapy at the time of COVID19 infection, whereas information obtained from patients receiving venetoclax-based therapy at the time of COVID19 infection are limited [71-72,75]. Since our understanding of the COVID-19 pandemic is constantly evolving updated and more comprehensive recommendations are awaited.

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LEGEND OF FIGURES

Fig 1
Treatment algorithm for CLL patients who progress after discontinuing or while still taking venetoclax.

Fig 2
Vantages and disadvantages of time-limited versus continuous therapy in CLL patients

Declarations of interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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