ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

ESMO Clinical Practice Guideline interim update on new targeted therapies in the first line and at relapse of chronic lymphocytic leukaemia☆

B. Eichhorst[1†], P. Ghia[2,3†], C. U. Niemann[4], A. P. Kater[5], M. Gregor[6], M. Hallek[1,7], M. Jerkeman[8] & C. Buske[9], on behalf of the ESMO Guidelines Committee*

[1]Department I for Internal Medicine, Center for Integrated Oncology Aachen Bonn Köln Düsseldorf, University of Cologne, Cologne, Germany; [2]Medical School, Università Vita-Salute San Raffaele, Milan; [3]Division of Experimental Oncology, IRCCS Ospedale San Raffaele, Milan, Italy; [4]Department of Haematology, Rigshospitalet, Copenhagen, Denmark; [5]Department of Hematology, Cancer Center Amsterdam, Lymphoma and Myeloma Center Amsterdam (LYMMCARE), Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; [6]Division of Hematology, Luzerner Kantonsspital, Luzern, Switzerland; [7]Cluster of Excellence—Cologne Excellence on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany; [8]Department of Oncology, Skåne University Hospital and Lund University, Lund, Sweden; [9]Institute of Experimental Cancer Research, Comprehensive Cancer Center Ulm (CCCU), University Hospital of Ulm, Ulm, Germany

Available online XXX

Key words: BCL2 inhibitor, BTK inhibitor, chronic lymphocytic leukaemia, guideline update, time-limited targeted therapy, ibrutinib—venetoclax

INTRODUCTION

The following ESMO Clinical Practice Guideline (CPG) has been recently updated with new treatment recommendations and updated algorithms for managing early and advanced disease: Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.[1]

View the original CPG here: https://www.esmo.org/guidelines/guidelines-by-topic/haematological-malignancies/chronic-lymphocytic-leukaemia.

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

The World Health Organization 2022 classification continues to consider small lymphocytic lymphoma and chronic lymphocytic leukaemia (CLL) a single entity, while B-cell prolymphocytic leukaemia (B-PLL) is no longer recognised due to its heterogeneity.[2] Cases previously labelled as B-PLL are now classified as: (i) mantle cell lymphoma in the presence of *IGH/CCND1* fusion; (ii) CLL with prolymphocytic progression if the prolymphocyte count is >15%; or (iii) splenic B-cell lymphoma/leukaemia with prominent nucleoli if not otherwise classifiable.

MANAGEMENT OF EARLY DISEASE

Binet stage A and B without active disease; Rai 0, I and II without active disease

A recent phase III clinical trial comparing ibrutinib with placebo in asymptomatic patients with Binet stage A and unfavourable-risk CLL confirmed the lack of an overall survival (OS) benefit when starting treatment early in early-stage asymptomatic patients, despite demonstrating longer time to next treatment as expected.[3,4] Hence, the watch-and-wait approach continues to be the standard of care in early-stage asymptomatic CLL.

MANAGEMENT OF ADVANCED DISEASE

Binet stage A and B with active disease or Binet stage C; Rai 0-II with active disease or Rai III-IV

The treatment algorithms for first-line (Figure 1) and relapsed therapy (Figure 2) have been updated.

First-line treatment. Different treatment strategies are available for first-line therapy (see Figure 1): (i) continuous treatment with Bruton tyrosine kinase inhibitors (BTKis), such as ibrutinib, acalabrutinib (with or without obinutuzumab) or zanubrutinib, until progression; or (ii) time-limited therapy with the B-cell lymphoma 2 inhibitor (BCL2i) venetoclax combined with obinutuzumab for 12 cycles or three cycles of ibrutinib monotherapy followed by ibrutinib—venetoclax either fixed for 12 cycles or minimal

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 4, CH-6900 Lugano, Switzerland
E-mail: clinicalguidelines@esmo.org (ESMO Guidelines Committee).

†These authors contributed equally to the publication.

☆Note: This Clinical Practice Guideline interim update is endorsed by the European Hematology Association (EHA) through the Scientific Working Group on chronic lymphocytic leukaemia (CLL)/European Research Initiative on CLL (ERIC).

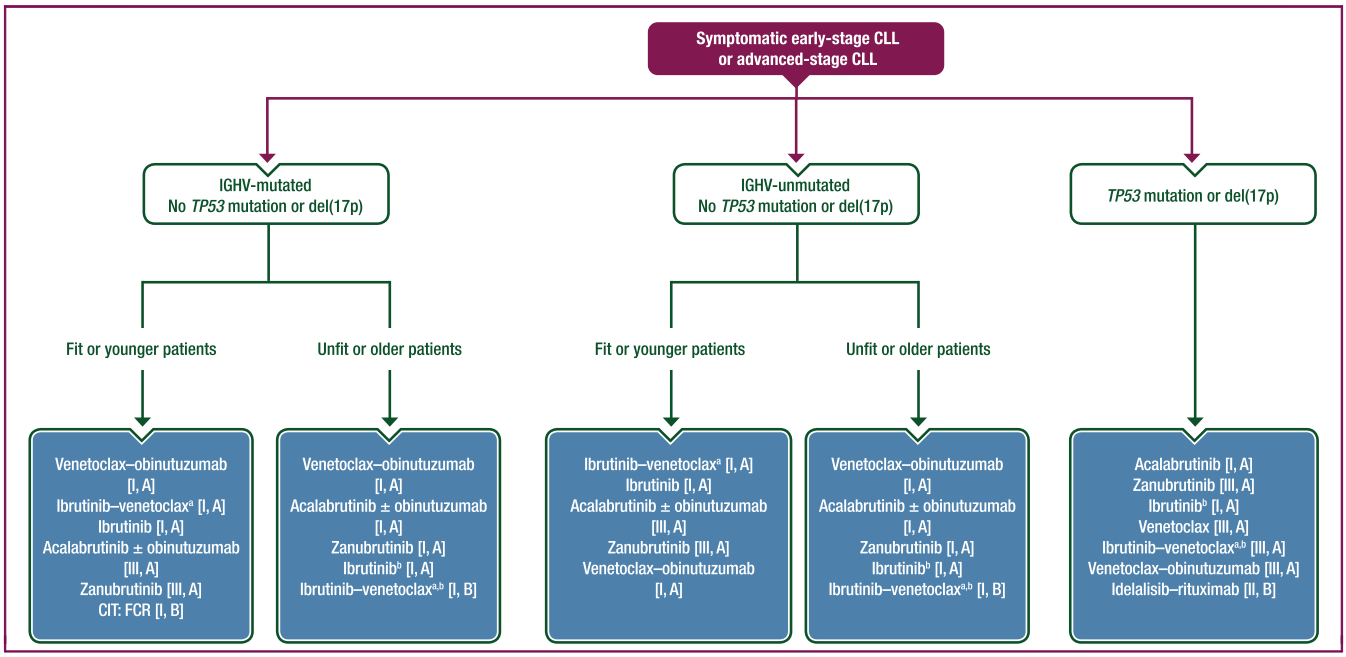

Figure 1. First-line therapy.
The order of the recommended treatments for each subgroup is based on the authors' expert opinion, which considers time-limited therapy as more valuable, if there is equal evidence for different treatment options.
Purple: algorithm title; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects.
CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukaemia; del, deletion; FCR, fludarabine—cyclophosphamide—rituximab; IGHV, immunoglobulin heavy chain variable; MRD, minimal residual disease.
[a]Ibrutinib—venetoclax with a 15-month fixed duration or with an MRD-guided duration.
[b]Ibrutinib or ibrutinib—venetoclax should be considered carefully in older patients with cardiac comorbidities.

residual disease (MRD)-driven [that produced prolonged benefit but is not European Medicines Agency (EMA) or Food and Drug Administration (FDA) approved].

Time-limited chemoimmunotherapy (CIT) such as fludarabine—cyclophosphamide—rituximab (FCR) should only be considered for patients with a good genetic risk profile [defined as mutated immunoglobulin heavy chain variable (IGHV) status and no *TP53* aberrations] and, in addition, a non-complex karyotype (defined by less than five aberrations if complex karyotype was evaluated[5]) and if targeted therapies are not reimbursed. Progression-free survival (PFS) of other CIT regimens (bendamustine—rituximab, chlorambucil—obinutuzumab or chlorambucil—rituximab) is shorter when compared with time-limited targeted agents; but this has not yet been shown for OS in most studies.[6,7] Optimal patient counselling (including information on the related risk of developing myeloid neoplasias[8]) with respect to short- and long-term toxicities is strongly recommended.

Pre-treatment evaluation when choosing one of the recommended therapies should include assessment of IGHV and *TP53* status—deletions in chromosome 17p [del(17p)] and/or *TP53* mutations—and patient-related factors such as comedication, comorbidities (particularly cardiac assessment when planning to use a BTKi), preference, drug availability and expected treatment adherence.

Subgroup analyses of the E1912 trial (~6-year follow-up) that stratified patients with CLL according to their IGHV mutational status showed a longer PFS for continuous ibrutinib—rituximab compared with FCR regardless of IGHV mutational status [hazard ratio (HR) 0.27, 95% confidence interval (CI) 0.11-0.62, $P = 0.001$ in patients with mutated IGHV status and HR 0.27, 95% CI 0.18-0.41, $P < 0.0001$ in those with unmutated IGHV].[9] In the FLAIR trial, however, after 44 months of median observation time, PFS was not significantly different for patients with mutated IGHV when comparing the two treatments (HR 0.64, 95% CI 0.35-1.16, $P = 0.15$).[10]

In the 5-year follow-up analysis of ELEVATE-TN, superior efficacy was shown for acalabrutinib—obinutuzumab versus chlorambucil—obinutuzumab (PFS: HR 0.11, 95% CI 0.07-0.67, $P < 0.0001$; OS: HR 0.55, 95% CI 0.30-0.99, $P = 0.474$).[11] PFS (HR 0.21, 95% CI 0.15-0.30), but not OS, was superior in acalabrutinib alone versus CIT.[11] The study, however, was not powered to show a difference in efficacy between acalabrutinib and acalabrutinib—obinutuzumab. Therefore, the impact of adding obinutuzumab to acalabrutinib is still unclear, although the combination shows a consistent observational benefit, with the exception of patients with *TP53*-aberrant CLL.

A third BTKi, zanubrutinib, has been approved by the EMA and the FDA in first-line therapy of CLL based on the results of the SEQUOIA trial, which compared continuous zanubrutinib with bendamustine—rituximab CIT in older patients (PFS: HR 0.42, 95% CI 0.28-0.63, two-sided $P < 0.0001$).[12-14]

Phase III trials (in the relapsed or refractory setting) with a head-to-head comparison of acalabrutinib with ibrutinib[15] and zanubrutinib with ibrutinib[16] have shown an improved

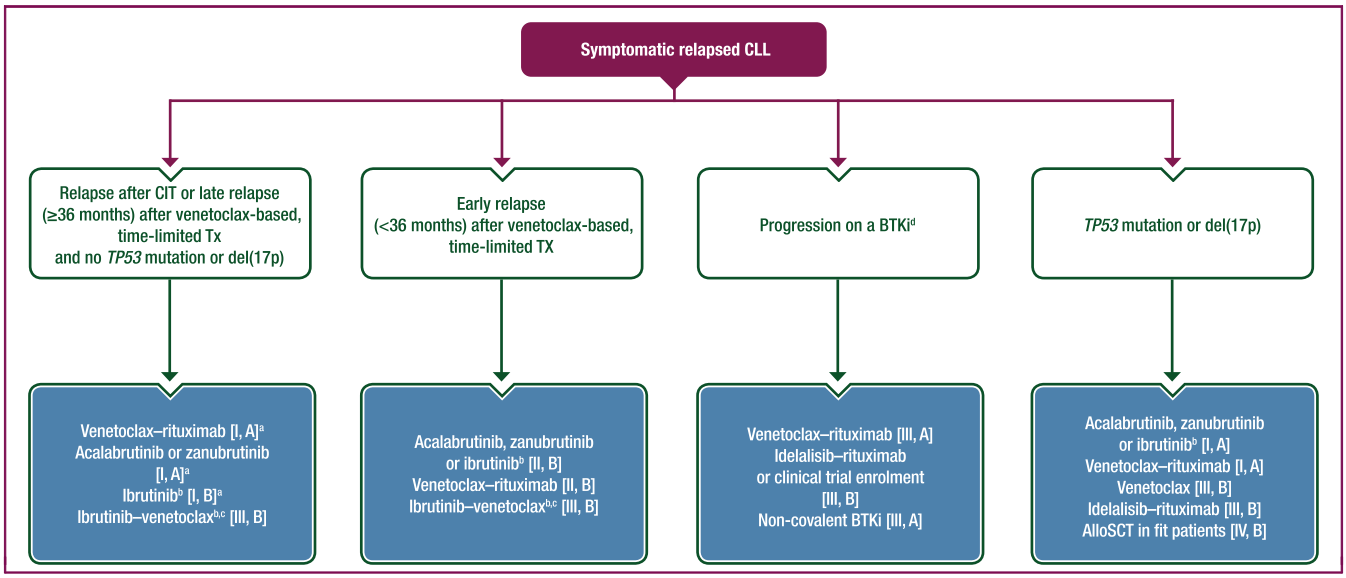

Figure 2. Relapse therapy.

Purple: algorithm title; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects.
alloSCT, allogeneic stem cell transplantation; BTKi, Bruton tyrosine kinase inhibitor; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukaemia; del, deletion; EMA, European Medicines Agency; FDA, Food and Drug Administration; Tx, treatment.
[a]For relapse after CIT, BTKis or venetoclax–rituximab should be considered equally, depending on comorbidities, comedication, access and preference.
[b]Ibrutinib should be considered carefully particularly in older patients with cardiac comorbidities.
[c]Not EMA approved, not FDA approved in relapse.
[d]If a patient relapses after prior treatment with a BTKi, which was stopped due to side-effects, changing to a different BTKi or rechallenge could be considered [III, B].

cardiovascular side-effect profile (for acalabrutinib, less atrial fibrillation and less hypertension; for zanubrutinib, less atrial fibrillation) in older patients or patients with cardiovascular disease. Therefore, acalabrutinib or zanubrutinib are preferred to ibrutinib, if available, especially in patients with an increased risk of cardiac toxicity.

Data in fit patients stratified by age from a randomised four-arm trial (GAIA-CLL13) confirmed that 12 cycles of venetoclax–obinutuzumab is superior to CIT (FCR or bendamustine–rituximab), both in terms of undetectable MRD (uMRD) in peripheral blood at month 15 (86.5% versus 52.0% of patients, respectively) and PFS at 3 years (HR 0.42, 97.5% CI 0.26-0.68, $P < 0.001$).[7] Adding ibrutinib to venetoclax–obinutuzumab resulted in a higher percentage of patients with uMRD (92.2%) and a longer PFS compared with CIT (HR 0.32, 97.5% CI 0.19-0.54, $P < 0.0001$).[7] The incidence of severe infections was higher in the triple therapy (21.2%) compared with venetoclax–obinutuzumab (13.2%). Based on these findings and that the direct comparison between venetoclax–obinutuzumab and the triple therapy was not powered, treatment with the latter cannot be recommended at the time of writing.

When patients were stratified according to IGHV mutational status in the CLL14 and GAIA-CLL13 trials, it was shown that particularly those with an unmutated IGHV status benefited when treated with venetoclax–obinutuzumab compared with other CITs.[6,7] In the CLL14 trial, venetoclax–obinutuzumab was also superior to CIT with chlorambucil–obinutuzumab in patients with a mutated IGHV status, although the impact was smaller.[6]

The time-limited combination of ibrutinib–venetoclax for 12 cycles (preceded by ibrutinib for three cycles) has been approved in the European Union based on the phase III GLOW trial and the time-limited cohort of the phase II CAPTIVATE trial.[17,18] GLOW consisted of an older population and showed that patients treated with ibrutinib–venetoclax had a longer PFS compared with chlorambucil–obinutuzumab (HR 0.216, 95% CI 0.131-0.357, $P < 0.001$).[17] The CAPTIVATE population consisted of younger patients and confirmed long-lasting remission with this regimen, including patients with unmutated IGHV and/or a *TP53* aberration.[18,19] There were a few early deaths in the GLOW trial that were likely related to cardiac toxicity; however, these were not observed in the CAPTIVATE trial. In an update of the GLOW trial, an OS benefit for ibrutinib–venetoclax over chlorambucil–obinutuzumab was observed.[20] Careful evaluation, however, should be done in elderly patients before they are considered for ibrutinib–venetoclax treatment.

Patients receiving time-limited and fixed-duration therapy, particularly those with CLL and unmutated IGHV status, may have a shorter PFS compared with continuous therapy. On the other hand, they have the benefit of a potential rechallenge and drug pause, and, to date, there are no data showing that the shorter PFS will translate into decreased life expectancy. Randomised trials will, however, show which patients benefit from continuous treatment.

An additional cohort of the FLAIR trial found that ibrutinib–venetoclax administered with personalised duration based on measurable MRD led to significant improvement in PFS compared with FCR (HR 0.13, 95% CI 0.07-0.24, $P < 0.001$) as well as in OS (HR 0.31, 95% CI 0.15-0.67) in a younger, fit population.[21] The treatment duration was personalised by determining the time to first uMRD

measurement (defined as $<10^{-4}$) in the peripheral blood and bone marrow and doubling that time for the overall treatment duration. The median duration of treatment with ibrutinib—venetoclax was 27 cycles. A non-powered subgroup analysis of patients with mutated IGHV status showed no difference in PFS and OS between FCR and ibrutinib—venetoclax. Determining the duration of the ibrutinib treatment (fixed duration of 15 cycles or personalised duration based on MRD) should take into consideration the tolerability and reimbursement of prolonged treatment.

Although CIT may be an option for patients with a favourable genetic profile, targeted therapies should be the first choice due to improved PFS and OS.[6,7,9-12] When deciding between time-limited ibrutinib—venetoclax or venetoclax—obinutuzumab versus continuous BTKis, time-limited therapy is preferred, as it is associated with reduced toxicity and retreatment would be possible at relapse (depending on current regulations and availability), would limit clonal selection and decrease adverse events in the follow-up. Long treatment-free intervals have been observed with time-limited therapy,[6,18,20] particularly in CLL with a favourable-risk profile, which is an additional benefit to PFS (Figure 1).

Patients with a *TP53* mutation and/or del(17p) should receive first-line therapy with BTKis (Figure 1). Venetoclax monotherapy (as continuous therapy), ibrutinib—venetoclax, particularly in the young population, or venetoclax—obinutuzumab may be used alternatively, although the shorter duration of response compared with other CLL subgroups should be discussed. Data from randomised studies are still pending, but reported PFS rates suggest that duration of disease control may be longer with continuous therapy with BTKis.[6,22,23] The impact of first-line continuous BTKi treatment versus a time-limited combination (venetoclax—obinutuzumab or ibrutinib—venetoclax) on OS, however, is still unclear.

Treatment of relapsed and refractory disease. CITs should not be administered in the relapse setting if access to targeted therapies exists, as CITs are inferior with respect to PFS and OS (Figure 2).[24,25]

For patients that have relapsed after CIT or late after venetoclax-based, time-limited combination therapy, there are two main options: (i) venetoclax—rituximab as time-limited therapy; or (ii) acalabrutinib, zanubrutinib or ibrutinib as continuous therapy.

The MURANO trial showed a superior PFS and OS in relapsed or refractory patients treated with venetoclax—rituximab compared with bendamustine—rituximab.[25] To date, it is unclear how long the minimum duration of remission should be for a recommendation for retreatment with venetoclax—CD20-antibody.

The 4-year follow-up of ASCEND showed that acalabrutinib maintained favourable efficacy compared with idelalisib—rituximab or bendamustine—rituximab.[26] It also had a non-inferior PFS with fewer cardiovascular adverse events compared with ibrutinib.[15] Zanubrutinib demonstrated superior PFS and fewer cardiovascular adverse events than ibrutinib in the ALPINE study.[16] Based on that trial, the EMA and the FDA approved zanubrutinib in relapsed CLL.[13,14] There are no data comparing acalabrutinib and zanubrutinib head-to-head, only indirect comparisons.

Though promising results for ibrutinib—venetoclax have been published for relapsed CLL,[27,28] the combination has yet to be evaluated in randomised phase III trials or approved in this setting. The time-limited regimen of ibrutinib—venetoclax is shorter than that of venetoclax—rituximab but with a similar PFS. This could be an advantage in the relapse setting, even when considering the limitations of cross-trial comparisons and the fact that all patients in both trials had received CIT and not targeted therapy for prior lines. Extended data of relapse treatment beyond this regimen are not yet available, but retreatment has been demonstrated to be feasible and effective.[29]

There are limited data with no long-term observation on re-exposing patients with long-lasting remission after first-line venetoclax—obinutuzumab to a regimen containing venetoclax plus an anti-CD20 antibody.[25,30,31]

For the choice between these treatment modalities, the same aspects as for first line should be considered and discussed with the patient (treatment duration, way of administration, compliance, number and complexity of clinical controls and side-effect profile considering existing comorbidities). The impact of prior-line therapies on the expected PFS of the different treatment options, as detailed above, should also be discussed.

In patients who relapse after prior treatment with a BTKi that was stopped due to side-effects, there are data to support that a change to a different BTKi could be feasible (e.g. switching from ibrutinib to acalabrutinib[32] or zanubrutinib[33]). Switching to other classes of drugs or rechallenge could also be an option.[34,35]

In case of progression on BTKi therapy, changing to venetoclax-based therapy is the preferred treatment.[30]

Recommendations

First-line treatment

- In patients with CLL regardless of IGHV status but without a *TP53* mutation or del(17p), preference should be given to time-limited therapies and to therapies and/or combinations with longer follow-up data, if efficacy is similar.
- Fit or younger patients with a mutated IGHV status and without a *TP53* mutation or del(17p) should be treated with one of the following options:
  - Venetoclax—obinutuzumab [I, A]
  - Ibrutinib—venetoclax [I, A]
  - Ibrutinib [I, A]
  - Acalabrutinib (adding obinutuzumab is an option) [III, A]
  - Zanubrutinib [III, A]
  - CIT with FCR, but the risk of secondary neoplasia should be discussed with the patients [I, B]

- Unfit or older patients with a mutated IGHV status and without a *TP53* mutation or del(17p) should be treated with one of the following options:
  - Venetoclax—obinutuzumab [I, A]
  - Acalabrutinib (adding obinutuzumab is an option) [I, A]
  - Zanubrutinib [I, A]
  - Ibrutinib [I, A], after appropriate cardiovascular work-up
  - Ibrutinib—venetoclax [I, B], after appropriate cardiovascular work-up
- Fit or younger patients with an unmutated IGHV status and without a *TP53* mutation or del(17p) should be treated with one of the following options:
  - Ibrutinib—venetoclax [I, A]
  - Ibrutinib [I, A]
  - Acalabrutinib (adding obinutuzumab is an option) [III, A]
  - Zanubrutinib [III, A]
  - Venetoclax—obinutuzumab as an alternative to ibrutinib [I, A] (although no OS benefit has been seen yet)
- Unfit or older patients with an unmutated IGHV status and without a *TP53* mutation or del(17p) should be treated with one of the following options:
  - Venetoclax—obinutuzumab [I, A]
  - Acalabrutinib (adding obinutuzumab is an option) [I, A]
  - Zanubrutinib [I, A]
  - Ibrutinib [I, A], after appropriate cardiovascular work-up
  - Ibrutinib—venetoclax [I, B], after appropriate cardiovascular work-up
- Patients with a *TP53* mutation or del(17p) should be treated with one of the following options:
  - Preferably a BTKi: acalabrutinib [I, A], zanubrutinib [III, A] or ibrutinib [I, A]
  - Venetoclax (continuous treatment) [III, A]
  - Ibrutinib—venetoclax (particularly in younger patients) [III, A]
  - Venetoclax—obinutuzumab [III, A]
  - Idelalisib—rituximab could be selected, if the other options are unavailable or considered unsuitable for the patient [II, B]
- When selecting a first-line treatment, the following could be taken into consideration [V, B]:
  - Side-effect profile (e.g. renal impairment and risk of tumour lysis syndrome versus atrial fibrillation, hypertension and risk of bleeding versus accumulation of side-effects with continuous therapy)
  - Drug administration (e.g. intravenous application for therapies including anti-CD20 antibody infusion versus oral medication only)
  - Access and intensity of controls (e.g. 5-week ramp-up period with the use of a BCL2i)
  - Shorter follow-up

Treatment of relapsed and refractory disease

- For relapse after CIT, BTKis or venetoclax—rituximab should be considered equally, depending on comorbidities, comedication, access and preference.
- Patients who relapse after CIT or with a late relapse (to date, there are no data on the optimal time point of re-exposure, but it should be after at least 36 months) after venetoclax-based, time-limited therapy (venetoclax—obinutuzumab or ibrutinib—venetoclax) and without a *TP53* mutation or del(17p) should be treated with one of the following options, depending on the therapy utilised in the first line:
  - Venetoclax—rituximab for 24 months [I, A]
  - Acalabrutinib or zanubrutinib as continuous therapy [I, A]
  - Ibrutinib as continuous therapy (acalabrutinib and zanubrutinib are preferred over ibrutinib) [I, B]
  - Ibrutinib—venetoclax [III, B; not EMA approved, not FDA approved in relapse]
- If a patient experiences early relapse (<36 months) after venetoclax-based, time-limited therapy, the following treatments should be considered:
  - Acalabrutinib, zanubrutinib or ibrutinib (BTKis are preferred over venetoclax plus an anti-CD20 antibody) [II, B]
  - Venetoclax—rituximab [II, B]
  - Ibrutinib—venetoclax [III, B; not EMA approved, not FDA approved in relapse]
- If there is progression on BTKi therapy, changing the treatment to venetoclax—rituximab is recommended [III, A], though patients pre-exposed to BTKi therapy may have a slightly inferior outcome compared with those who are BTKi naive.[36]
- If a patient relapses after prior treatment with a BTKi, which was stopped due to side-effects, changing to a different BTKi or rechallenge could be considered [III, B].
- Relapsed patients after prior treatment with a BTKi, who are refractory to both BTKis and BCL2is, should be considered for treatment with the phosphoinositide 3-kinase (PI3K) inhibitor idelalisib plus rituximab, for clinical trials [III, B] or compassionate use with a non-covalent BTKi, if available [III, A]. The non-covalent BTKi pirtobrutinib has already been approved in the United States based on efficacy data from a phase II trial in mostly double-refractory patients demonstrating a tolerable and efficacious profile,[37] currently undergoing testing in a randomised setting [III, B].
- Relapsed patients with a *TP53* mutation or del(17p) should be treated with one of the following options:
  - Acalabrutinib, zanubrutinib or ibrutinib [I, A]
  - Venetoclax—rituximab [I, A]
  - Venetoclax [III, B]
  - Idelalisib—rituximab [III, B]
  - Allogeneic stem cell transplantation in fit patients [IV, B]
- Autoimmune cytopenia should be treated with high-dose corticosteroids. In patients not responding to corticosteroids or those who relapse shortly after corticosteroids, treatment with an anti-CD20 antibody with or without targeted therapy could be considered [IV, B].
- Except after allogeneic stem cell transplantation, MRD measurement is not yet recommended as a clinical routine test for clinical decision making [IV, C]. As clinical trial data on the MRD-guided ibrutinib—venetoclax

regimen suggest,[10,28] however, MRD measurement may be used to determine the duration of targeted treatment in subgroups of patients in the near future [II, C].

METHODOLOGY

This eUpdate was developed in accordance with the ESMO standard operating procedures for CPG development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing this eUpdate. Levels of evidence and grades of recommendation have been applied using the system shown in Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2024.06.016.[38] Statements without grading were considered justified standard clinical practice by the authors.

ACKNOWLEDGEMENTS

Manuscript editing and writing support was provided by Ioanna Ntai and Jennifer Lamarre (ESMO Guidelines staff); this support was funded by ESMO.

FUNDING

No external funding has been received for the preparation of these guidelines. Production costs have been covered by ESMO from central funds.

DISCLOSURE

BE reports personal fees for advisory board membership from AbbVie, AstraZeneca, BeiGene, Janssen, Kite, Lilly and MSD; personal fees as an invited speaker from AbbVie, AstraZeneca, BeiGene, Lilly and Roche; and institutional funding from AbbVie, AstraZeneca, BeiGene, Janssen and Roche. PG reports personal fees for advisory board membership from AbbVie, AstraZeneca, BeiGene, Bristol Myers Squibb (BMS), Galapagos, Janssen, Lilly/Loxo Oncology, MSD and Roche; personal fees as an invited speaker from AbbVie, AstraZeneca, Janssen and MSD; institutional fees as local principal investigator (PI) from AbbVie and BeiGene; institutional fees as coordinating PI from AstraZeneca, Janssen and Lilly/Loxo Oncology; and institutional research grants from AstraZeneca, BMS and Janssen. CUN reports personal fees for advisory board membership from BeiGene, CSL Behring, Genmab, Octapharma and Takeda; personal fees as an invited speaker from AbbVie, AstraZeneca, Janssen and Lilly; institutional funding from AstraZeneca, Novo Nordisk Foundation and Octapharma; institutional fees as coordinating PI from AstraZeneca and Janssen; institutional fees as local PI from Genmab; a non-remunerated role as member of Board of Directors of the Danish Data Science Academy (independent academy, but funded by the Novo Nordisk Foundation and the Villum Foundation); and non-remunerated membership of the Danish Hematology Society, the European Hematology Association (EHA; and past member of the Scientific Program Committee) and the European Research Initiative on CLL (ERIC) (has also published guidelines and has been responsible for workshops held by ERIC). APK reports personal fees for advisory board membership from AbbVie, AstraZeneca, BMS, Janssen, LAVA and Roche/Genentech; personal fees as an invited speaker from AbbVie; a role as coordinating PI for AbbVie, AstraZeneca and Roche/Genentech; an institutional research grant from BMS; membership of a Steering Committee at Janssen; a non-remunerated role as Chair of the EHA Scientific Working Group for CLL; and non-remunerated roles as Chair of the CLL Working Group and president of the Executive Board at Hovon. MG reports personal fees for advisory board membership from AbbVie, Amgen, AstraZeneca, BeiGene, BMS/Celgene, GSK, Janssen-Cilag, Roche, Sanofi and Servier; personal compensation for international congress attendance from AbbVie and BeiGene; institutional fees for expert testimony from AstraZeneca; and institutional fees as local PI from Lilly/Loxo (clinical study in relapsed/refractory CLL). MH reports institutional fees as an organiser and invited speaker from AbbVie for a 2023 conference (funds transferred to a non-profit organisation); and institutional funding for clinical trials from AbbVie, AstraZeneca, BeiGene, Johnson & Johnson/Janssen and Roche. MJ reports personal fees for advisory board membership from BMS, Genmab, Gilead, Janssen and Novartis; personal fees as an invited speaker from Incyte and Roche; institutional funding from AbbVie, AstraZeneca, Celgene, Gilead, Janssen and Roche; and institutional fees as coordinating PI from Bioinvent, Coordinating PI. CB reports personal fees for advisory board membership from AbbVie, BeiGene, Celltrion, Gilead Sciences, Incyte, Janssen, Lilly Deutschland GmbH, MorphoSys, Novartis, Pfizer, Regeneron, Roche and Sobi; personal fees as an invited speaker from AbbVie, BeiGene, Celltrion, Gilead Sciences, Incyte, Janssen, Lilly Deutschland GmbH, MorphoSys, Novartis, Pfizer, Regeneron, Roche and Sobi; and institutional funding from AbbVie Amgen, Bayer, Celltrion, Janssen, MSD, Pfizer and Roche (all for investigator-sponsored clinical trials and registries).

REFERENCES

1. Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2021;32(1):23-33.
2. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: lymphoid neoplasms. *Leukemia*. 2022;36(7):1720-1748.
3. Langerbeins P, Zhang C, Robrecht S, et al. The CLL12 trial: ibrutinib vs placebo in treatment-naive, early-stage chronic lymphocytic leukemia. *Blood*. 2022;139(2):177-187.
4. Langerbeins P, Robrecht S, Nieper P, et al. Ibrutinib versus placebo in patients with asymptomatic, treatment-naïve early stage chronic lymphocytic leukemia (CLL): final results of the phase 3, double-blind, placebo-controlled CLL12 trial. *Hematol Oncol*. 2023;41(S2):56-58.
5. Furstenau M, Thus YJ, Robrecht S, et al. High karyotypic complexity is an independent prognostic factor in patients with CLL treated with venetoclax combinations. *Blood*. 2023;142(5):446-459.

6. Al-Sawaf O, Zhang C, Jin HY, et al. Transcriptomic profiles and 5-year results from the randomized CLL14 study of venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab in chronic lymphocytic leukemia. *Nat Commun*. 2023;14(1):2147.
7. Eichhorst B, Niemann CU, Kater AP, et al. First-line venetoclax combinations in chronic lymphocytic leukemia. *N Engl J Med*. 2023;388(19):1739-1754.
8. Benjamini O, Jain P, Trinh L, et al. Second cancers in patients with chronic lymphocytic leukemia who received frontline fludarabine, cyclophosphamide and rituximab therapy: distribution and clinical outcomes. *Leuk Lymphoma*. 2015;56(6):1643-1650.
9. Shanafelt TD, Wang XV, Hanson CA, et al. Long-term outcomes for ibrutinib-rituximab and chemoimmunotherapy in CLL: updated results of the E1912 trial. *Blood*. 2022;140(2):112-120.
10. Hillmen P, Pitchford A, Bloor A, et al. Ibrutinib and rituximab versus fludarabine, cyclophosphamide, and rituximab for patients with previously untreated chronic lymphocytic leukaemia (FLAIR): interim analysis of a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2023;24(5):535-552.
11. Sharman J, Egyed M, Jurczak W, et al. Acalabrutinib ± obinutuzumab versus obinutuzumab + chlorambucil in treatment-naïve chronic lymphocytic leukemia: five-year follow-up of ELEVATE-TN. *J Clin Oncol*. 2022;40(suppl 16):7539.
12. Tam CS, Brown JR, Kahl BS, et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2022;23(8):1031-1043.
13. European Medicines Agency. Brukinsa: Summary of Product Characteristics. 2023. Available at https://www.ema.europa.eu/en/documents/product-information/brukinsa-epar-product-information_en.pdf. Accessed June 13, 2024.
14. Food and Drug Administration. Brukinsa. Prescribing Information. 2023. Available at https://www.ema.europa.eu/en/documents/product-information/brukinsa-epar-product-information_en.pdf. Accessed June 13, 2024.
15. Byrd JC, Hillmen P, Ghia P, et al. Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: results of the first randomized phase III trial. *J Clin Oncol*. 2021;39(31):3441-3452.
16. Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med*. 2023;388(4):319-332.
17. Kater AP, Owen C, Moreno C, et al. Fixed-duration ibruitnib-venetoclax in patients with chronic lymphocytic leukemia and comorbidities. *NEJM Evid*. 2022;1(7):EVIDoa2200006.
18. Tam CS, Allan JN, Siddiqi T, et al. Fixed-duration ibrutinib plus venetoclax for first-line treatment of CLL: primary analysis of the CAPTIVATE FD cohort. *Blood*. 2022;139(22):3278-3289.
19. Wierda WG, Allan JN, Siddiqi T, et al. Ibrutinib plus venetoclax for first-line treatment of chronic lymphocytic leukemia: primary analysis results from the minimal residual disease cohort of the randomized phase II CAPTIVATE study. *J Clin Oncol*. 2021;39(34):3853-3865.
20. Niemann C, Munir T, Moreno C, et al. Residual disease kinetics among patients with high-risk factors treated with first-line fixed-duration ibrutinib plus venetoclax (Ibr+Ven) versus chlorambucil plus obinutuzumab (Clb+O): the glow study. *Blood*. 2022;140:228-230.
21. Munir T, Cairns DA, Bloor A, et al. Chronic lymphocytic leukemia therapy guided by measurable residual disease. *N Engl J Med*. 2023;390:326-337.
22. Moreno C, Greil R, Demirkan F, et al. First-line treatment of chronic lymphocytic leukemia with ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab: final analysis of the randomized, phase 3 iLLUMINATE trial. *Haematologica*. 2022;107(9):2108-2120.
23. Sharman JP, Egyed M, Jurczak W, et al. Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naive chronic lymphocytic leukemia. *Leukemia*. 2022;36(4):1171-1175.
24. Munir T, Brown JR, O'Brien S, et al. Final analysis from RESONATE: up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *Am J Hematol*. 2019;94(12):1353-1363.
25. Seymour JF, Kipps TJ, Eichhorst BF, et al. Enduring undetectable MRD and updated outcomes in relapsed/refractory CLL after fixed-duration venetoclax-rituximab. *Blood*. 2022;140(8):839-850.
26. Ghia P, Pluta A, Wach M, et al. Acalabrutinib versus investigator's choice in relapsed/refractory chronic lymphocytic leukemia: final ASCEND trial results. *Hemasphere*. 2022;6(12):e801.
27. 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.
28. Kater AP, Levin MD, Dubois J, et al. Minimal residual disease-guided stop and start of venetoclax plus ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia (HOVON141/VISION): primary analysis of an open-label, randomised, phase 2 trial. *Lancet Oncol*. 2022;23(6):818-828.
29. Kater A, Dubois J, Brieghel C, et al. S148: Time-limited venetoclax and ibrutinib for patients with relapsed/refractory CLL who have undetectable MRD − 4-year follow up from the randomized phase II VISION/HO141 trial. *Hemasphere*. 2023;7(S3):e10648ed.
30. Mato AR, Hess LM, Chen Y, et al. Outcomes for patients with chronic lymphocytic leukemia (CLL) previously treated with both a covalent BTK and BCL2 inhibitor in the United States: a real-world database study. *Clin Lymphoma Myeloma Leuk*. 2023;23(1):57-67.
31. Kater A, Harrup R, Kipps T, et al. S201: Final 7-year follow up and retreatment substudy analysis of MURANO: venetoclax-rituximab (VenR)-treated patients with relapsed/refractory chronic lymphocytic leukemia (R/R CLL). *Hemasphere*. 2023;7(S3):e492813f.
32. Awan FT, Schuh A, Brown JR, et al. Acalabrutinib monotherapy in patients with chronic lymphocytic leukemia who are intolerant to ibrutinib. *Blood Adv*. 2019;3(9):1553-1562.
33. Shadman M, Flinn IW, Levy MY, et al. Zanubrutinib in patients with previously treated B-cell malignancies intolerant of previous Bruton tyrosine kinase inhibitors in the USA: a phase 2, open-label, single-arm study. *Lancet Haematol*. 2023;10(1):e35-e45.
34. Gribben JG, Bosch F, Cymbalista F, et al. Optimising outcomes for patients with chronic lymphocytic leukaemia on ibrutinib therapy: European recommendations for clinical practice. *Br J Haematol*. 2018;180(5):666-679.
35. O'Brien SM, Brown JR, Byrd JC, et al. Monitoring and managing BTK inhibitor treatment-related adverse events in clinical practice. *Front Oncol*. 2021;11:720704.
36. Kater AP, Arslan O, Demirkan F, et al. Activity of venetoclax in patients with relapsed or refractory chronic lymphocytic leukaemia: analysis of the VENICE-1 multicentre, open-label, single-arm, phase 3b trial. *Lancet Oncol*. 2024;25(4):463-473.
37. Mato AR, Woyach JA, Brown JR, et al. Pirtobrutinib after a covalent BTK inhibitor in chronic lymphocytic leukemia. *N Engl J Med*. 2023;389(1):33-44.
38. Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *Clin Infect Dis*. 2001;33(2):139-144 [adapted from: Gross PA, Barrett TL, Dellinger EP, et al. Purpose of quality standards for infectious diseases. *Clin Infect Dis*. 1994;18(3):421].