State-of-the-Art Treatment and Novel Agents in Chronic Lymphocytic Leukemia

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Summary

Chemoimmunotherapy is the established first-line treatment of patients with chronic lymphocytic leukemia (CLL) who do not display the high-risk genetic features del(17p) and/or TP53 mutation: Physically fit patients without or with only mild comorbidities should receive fludarabine, cyclophosphamide and rituximab, while bendamustine and rituximab can be considered in fit elderly patients of over 65 years and in patients with a higher risk of infections. Patients with relevant coexisting conditions should receive chlorambucil with a CD20 antibody, preferably obinutuzumab. Patients with a del(17p) and/or TP53 mutation respond poorly to conventional chemo(immuno)therapies. However, the recently approved BTK and PI3K inhibitors ibrutinib and idelalisib have the best efficacy ever documented in patients with these high-risk genomic alterations and/or refractory CLL. The choice between ibrutinib and idelalisib should be based on the patients' comorbidities and concomitant medications since both agents have a distinct toxicity profile, although they are generally well tolerated in the majority of patients. For treatment of patients with a late relapse, chemoimmunotherapy instead of kinase inhibitors is still a reasonable approach, but has to be determined for every patient individually. Further targeted drugs and their combinations are currently being evaluated in clinical trials and have the potential to eradicate all residual CLL cells and thus lead to a cure of CLL.

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Management of Patients with Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is the most common leukemia in Western countries [1, 2] and affects mainly older and male patients as the median age at initial diagnosis is 67–72 years and the male to female ratio 1.7:1 [1–3].

The diagnosis of CLL is established according to the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) guidelines [4] with a peripheral blood smear and immunophenotyping. Due to frequent blood testing in clinical routine, a CLL is often diagnosed in an early, asymptomatic stage or even as its precursor the monoclonal B-cell lymphocytosis (MBL) [5, 6]. As described in detail by Langerbeins et al. [85] in a review on the management of early stage CLL in this issue of ONCOLOGY RESEARCH AND TREATMENT, patients with early stage CLL should be managed with a watch-and-wait approach outside the setting of clinical trials. Treatment is only indicated in cases of advanced CLL (Binet stage C/Rai stage III/IV) or symptomatic, active disease with massive enlargement of lymph nodes or spleen, a rapid lymphocyte doubling time or constitutional symptoms, such as weight loss ($\geq 10\%$ within 6 months), night sweats or fever without evidence of infection [4].

As described more extensively in the review on prognostication by Tausch et al. [86] also in this issue of ONCOLOGY RESEARCH AND TREATMENT, the deletion of the short arm of chromosome 17 (del(17p)) and/or mutation of the TP53 gene are associated with a worse prognosis [7]. They are also associated with resistance to most chemotherapeutic agents used for the treatment of CLL, as these mediate cell death through DNA damage and p53-dependent apoptosis [8, 9]. Therefore, an analysis for detection of these aberrations is crucial for the treatment decision. Due to the possibility of an evolution of a clone of CLL cells harboring these genetic abnormalities during the course of disease [9–13], it is necessary to perform this analysis before the start of a first-line therapy and also ahead of every subsequent line of treatment.

In addition, the patient's physical fitness, burden of comorbidities (especially renal and liver function), and concomitant medications need to be considered for treatment decisions. Elderly cancer patients can be allocated to 1 of 3 groups differing in therapeutic goals based on their physical fitness, comorbidities and estimated life expectancy not considering the limitation due to the cancer diagnosis [14–17]: (1) physically fit patients without or with only mild comorbidities, who should receive standard therapies aiming for long-term remissions and prolongation of survival (mnemonic principle of action 'go go'); (2) patients with relevant comorbidities that are likely to have an impact on life expectancy, who should receive dose-reduced or modified therapies for disease control ('slow go'); or (3) patients with a markedly reduced life expectancy due to multiple and/or severe comorbidities or frailty, who should be treated with best supportive care for symptom control/palliation ('no go').

For the allocation of patients to 1 of these 3 groups, the German CLL Study Group (GCLLSG) established the use of the cumulative illness rating scale (CIRS) score [18] and creatinine clearance, which reflect the biological age rather than the calendar age of a patient. The CIRS score rates the burden and severity of comorbidities in 14 organ systems with up to 4 points, and a total score of ≥ 6 is used as a cut-off to distinguish 'slow go' patients from 'go go' patients.

Advances in Treatment of CLL and Novel Agents

Chlorambucil was the standard treatment for CLL for several decades [19–21] until combinations of different chemotherapies, e.g. fludarabine and cyclophosphamide, were used in the 1990s and improved the quality and duration of response in younger patients [22–24]. The introduction of the anti-CD20 antibody rituximab after the millennium revolutionized the treatment of lymphoma, including CLL, and a first breakthrough with a prolongation of overall survival (OS) of patients with CLL was achieved by the addition of rituximab to fludarabine and cyclophosphamide (FCR) [25]. Recently, the combination of chlorambucil with the novel humanized and glyco-engineered anti-CD20 antibody obinutuzumab proved to be feasible and effective, also prolonging survival in elderly 'slow go' patients with relevant comorbidities [26, 27]. Thus, chemoimmunotherapies have become recognized standard therapies for the treatment of most CLL patients.

During the current decade, a growing understanding of the pathogenesis of B-cell lymphomas and CLL has fostered the development of novel drugs with different targets. The 2 kinase inhibitors ibrutinib and idelalisib targeting the Bruton tyrosine kinase (BTK) and phosphatidylinositol-3-kinase (PI3K), respectively, are already licensed and available in most western countries for relapsed CLL. In the EU, these are even approved for the first-line treatment of patients with del(17p) and/or TP53 mutation, since the treatment outcome of patients with these high-risk genetic abnormalities was the best thus far documented [28, 29].

In addition to these 2 licensed kinase inhibitors, several other mostly oral agents targeting different kinases in the B-cell receptor

signaling and other pathways, as well as antibodies directed against surface antigens other than the CD20 epitope, such as CD37, are being developed and tested in clinical trials. The BCL-2 antagonist ABT-199 (venetoclax) has very promising efficacy, which appears to be independent of adverse prognostic parameters, such as a del(17p) or unmutated immunoglobulin variable heavy chain (IgHV) status and refractoriness to fludarabine [30, 31]. However, due to the overwhelming activity, which led to serious and even fatal tumor-lysis syndromes during the first trials, several safety precautions, including a very slow dose escalation over several weeks, need to be followed. ABT-199 is expected to become licensed for CLL in the next months. A summary and discussion of all other novel, not yet available agents is beyond the scope of this article.

First-Line Treatment of CLL

Current First-Line Treatment of Physically Fit Patients

Chemoimmunotherapy with fludarabine, cyclophosphamide and rituximab (FCR) is the recognized standard treatment for physically fit patients [25, 32]. Long-term results from the first phase II trial evaluating FCR at the MD Anderson Cancer Center showed a 6-year overall and failure-free survival of 77% and 51%, respectively [32]. In an update of the randomized CLL8 trial by the GCLLSG, with a median observation time of 4.9 years, 69% of patients treated with FCR were alive compared to 62% of patients treated with FC (hazard ratio (HR) 0.68, 95% confidence interval (CI) 0.535–0.858; $p = 0.001$) [33]. Furthermore, in the subgroup of patients with a mutated IgHV status in the FCR arm, the median progression-free survival (PFS) after FCR was still not reached and the Kaplan-Maier PFS curve appeared to level off to a plateau. These long-lasting remissions raise hope that treatment with FCR might lead to a cure of CLL in some of these patients.

Attempts to further increase the efficacy of the FCR regimen were made with the addition of the anthracycline mitoxantrone (FCM-R) [34, 35] or the immune modulatory agent lenalidomide (FCR-L) [36, 37], or an addition or a substitution of rituximab by the anti-CD52 antibody alemtuzumab (CFAR, [38] or FCA [39, 40]). In most of these trials, a relevant increase of toxicity, especially (opportunistic) infections, was observed and thus a wider use of these regimens was precluded.

On the other hand, regimens with reduced treatment intensity were designed in order to reduce the risk of adverse events, especially cytopenias and infections as observed with FCR; for example, in the CLL8 trial, severe CTC°III–IV neutropenias and infections occurred 34% and 25% of patients treated with FCR [25]. Less intense regimens either contain a reduced dose of the chemotherapeutic drugs (so-called FCR-Lite regimen) [41, 42], a substitution of fludarabine by the other purine analogs pentostatin (PCR) [43, 44] or cladribine (RCC) [45] or a substitution of both fludarabine and cyclophosphamide by either pentostatin (PR) [46] or bendamustine (BR) [47–49]. However, most of these alternative regimens were less effective than FCR or had a similar toxicity rate.

Similarly, the randomized phase III CLL10 trial of the GCLLSG comparing FCR and BR in 564 physically fit patients without relevant comorbidities showed that the BR regimen was indeed less toxic, but also less efficacious than FCR [49]. As expected, the rate of severe CTC°III–IV neutropenias and infections was significantly higher with FCR (88% vs. 68%, $p < 0.001$ and 40% vs. 25%, $p = 0.001$), especially in patients older than 65 years (infections CTC°III–IV: 48% vs. 27%, $p = 0.001$). Overall response rates were 98% in both arms, but patients treated with FCR achieved a higher rate of complete remissions (41% vs. 32%, $p = 0.026$) and more minimal residual disease (MRD) negativity (74% vs. 63%, $p = 0.024$), which translated into a longer median PFS (54 vs. 43 months, HR 1.589, 95% CI 1.25–2.079, $p = 0.001$).

Combinations with the other anti-CD20 antibodies ofatumumab (e.g. FCO [50] and PCO [51]) or obinutuzumab (FC-G and B-G), as well as the novel kinase inhibitors ibrutinib and idelalisib in the front-line setting in physically fit patients are currently being evaluated in clinical trials to define whether these should be used in the front-line setting. For the time being, chemoimmunotherapy with FCR remains the standard of care in the first-line treatment of physically fit patients without a del(17p) or TP53 mutation. For elderly fit patients of > 65 years with a higher risk of infections, BR should be considered as alternative front-line therapy, although it is likely inferior to FCR. Also, growth factor support with granulocyte colony-stimulating factor (G-CSF) and an anti-infective prophylaxis should be considered during treatment with FCR or BR and follow-up: e.g. trimethoprim/sulfamethoxazole in all patients for *Pneumocystis jirovecii* pneumonias, aciclovir or valaciclovir for viral infections in seropositive patients with recurrent herpes simplex virus (HSV) infections, and possibly also fluoroquinolones, e.g. ciprofloxacin, for bacterial infections in case of longer lasting neutropenias. An intensification of treatment or combination with novel agents can only be recommended in the setting of clinical trials.

Current First-Line Treatment of Patients with Relevant Comorbidities

Until recently, chlorambucil remained the mainstay of treatment in older patients with relevant comorbidities [19–21], as an intensification of treatment with more potent agents, including fludarabine and alemtuzumab, did not lead to a survival benefit [52–55]. However, the addition of an anti-CD20 antibody to chlorambucil proved to be beneficial in the phase III CLL11 trial that included 781 patients with coexisting medical conditions (defined as a CIRS score of > 6 and/or creatinine clearance of < 70 ml/min) [26, 27]. Overall and complete response rates (ORR and CRR) were best with the addition of the novel anti-CD20 antibody obinutuzumab to chlorambucil (G-Clb), followed by the combination of rituximab and chlorambucil (R-Clb) and was worst with single agent chlorambucil (ORR: 77% vs. 66% vs. 31%, CRR: 22% vs. 7% vs. 0%). A significant proportion of responding patients treated with G-Clb even achieved an MRD negativity in peripheral blood and bone marrow (38% and 20%). These responses translated into an improvement of PFS with G-Clb and R-Clb compared to Clb

(29 vs. 15 vs. 11 months; $p < 0.0001$) and G-Clb even improved the median OS in comparison to single agent chlorambucil (HR 0.47, 95% CI 0.29–0.76; $p = 0.0014$). However, G-Clb leads to a higher incidence of infusion-related reactions (IRR) in general and especially severe IRRs (CTC°I–IV and °III–IV: 66% and 20% vs. 38% and 4% with R-Clb). The IRRs were mostly limited to the first administration of obinutuzumab and manageable with certain preventive measures, e.g. adequate premedication, dose splitting of the first dosage and prophylactically withholding any antihypertensive medications. Also, cytopenias, especially neutropenias, were more common with G-Clb and R-Clb compared to single agent chlorambucil, but did not lead to a higher rate of infections (CTC°III–IV: 12%, 14% and 14%).

The combination of chlorambucil with ofatumumab (O-Clb) [56–58] achieved an ORR of 82% with 12% CRs (compared to 69% and 1% with single agent chlorambucil, $p < 0.001$), which translated into an improvement of the median PFS of 9 months (22 vs. 13 months, $p < 0.001$). So far, no randomized head-to-head comparison of ofatumumab and the other anti-CD20 antibodies has been performed; the results achieved with O-Clb in this trial compared favorably to those achieved with R-Clb but less positively compared to G-Clb in the CLL11 trial [26, 27].

Combination treatment with bendamustine and ofatumumab (BO) [59, 60] was evaluated in a small number of patients; 1 of the 2 trials was prematurely stopped due to adverse events. Although the combination of BO is now approved for the use in CLL, it cannot be recommended because of a lack of comparative data suggesting an advantage for the use of ofatumumab instead of rituximab in combination with bendamustine. Other regimens proposed for elderly patients include different dose-reduced FCR treatment schedules, e.g. the so-called FCR-Lite regimen with a reduced dosage of fludarabine and cyclophosphamide and an increased frequency of rituximab infusions (day 1 and day 15 of each cycle), followed by 3-monthly rituximab maintenance treatment [41, 42, 61], as well as the FCR² regimen with lenalidomide (FCR-Lite with a slow dose escalation of lenalidomide, followed by a maintenance with lenalidomide) [37], the FCR3 and FCR5 regimens designed by the Australian group consisting of either 3 or 5 days of orally administered fludarabine and cyclophosphamide combined with the usual dosage of rituximab [62], as well as the Q-Lite regimen with a dose reduction by 50% for fludarabine and cyclophosphamide and the full dosage of rituximab [63]. Most of these different dose-reduced FCR regimens proved to be feasible and less toxic than the conventional FCR regimen; however, the patient collectives of these trials were younger and fitter than the collective evaluated in the CLL11 trial.

Thus, the different dose-reduced regimen might serve as an alternative treatment for elderly but rather fit patients, as discussed above for the BR regimen, which should be considered in physically fit patients of > 65 years due to an increased risk of infections. For patients with a relevant burden of comorbidities or an impaired renal function, the current therapeutic standard is a chlorambucil-based chemoimmunotherapy. Among the different combinations of chlorambucil with CD20 antibodies, chlorambucil

combined with obinutuzumab achieved the longest PFS so far documented in this patient group, and also led to an improvement of OS. However, no data are yet available regarding the head-to-head comparison of chlorambucil plus ofatumumab and chlorambucil plus either obinutuzumab or rituximab, and a comparison of chlorambucil-based chemoimmunotherapy and other regimens, such as the dose-reduced FCR regimen. The evaluation of the novel kinase inhibitors ibrutinib and idelalisib in the first-line treatment of elderly patients with comorbidities might further change the therapeutic options of these patients.

Current First-Line Treatment of High-Risk CLL

Patients with a del(17p) and/or TP53 mutation often have a very aggressive course of disease resembling an acute leukemia and respond poorly to chemo(immuno)therapy [7, 8, 64]. Despite a considerable risk of serious (opportunistic) infectious complications due to T-cell depletion, the anti-CD52 antibody alemtuzumab was, until recently, the only efficacious agent in patients with these adverse genetic abnormalities [65]. Fortunately, the outcome for these patients was revolutionized with the introduction of the novel targeted agents, which act downstream of the B-cell receptor signaling pathway and thus independently of the p53 pathway [66, 67]. Both single agent ibrutinib [68] and idelalisib combined with either rituximab [69] or ofatumumab [70] were found to induce high response rates, and promising PFS and OS in all patient groups. Treatment outcomes achieved with these drugs are the best ever reported in patients with del(17p)/TP53 mutations [28, 68, 69]. However, del(17p) and TP53 mutations appear to retain their adverse prognostic impact as the treatment outcome is inferior with regard to quality and duration of response compared to patients without these genetic abnormalities [28, 68, 69].

Allogeneic hematopoietic stem cell transplantation (HSCT) can serve as a curative option, but is only feasible in a minority of selected younger and physically fit patients, with a matching donor [71]. As this procedure is associated with a significant mortality and morbidity, the indication and optimal timing of an allogeneic HSCT needs to be redefined with the novel drugs available [72]. Previously, the first remission was considered the optimal time point [71], but today treatment with the kinase inhibitors may be also continued and the allogeneic HSCT may be deferred to the time point of relapse. According to a consensus paper by the European Society for Blood and Marrow Transplantation (EBMT) and the European Research Initiative on CLL (ERIC) [72], the risks of the disease (cytogenetics and relapsed/refractory situation) and the transplantation (patient's age and comorbidities, donor match) should be carefully weighed and discussed with the patient, considering his/her wishes and expectations.

Treatment of Relapsed CLL

To make the choice of therapy after a relapse, the intensity of the previous therapies with potential toxicities, the quality of achieved response, and especially the duration of the response need

to be taken into account, in addition to the result of del(17p)/TP53 mutation status assessment and the above-described patient-specific factors.

Current Treatment in Case of Early Progression

Patients with an early relapse of CLL after first-line therapy are known to have a very poor prognosis [73, 74], which cannot be overcome by intensification of the chemotherapy backbone in relapse treatment [74]. This poor outcome might be related to an evolutionary acquisition of adverse genetic alterations due to the selection pressure and additional DNA damage through previous chemo(immuno)therapy [12, 13]. In line with this, in relapsed CLL, an increasing proportion of CLL cells harboring a del(17p) or TP53 mutation can be detected [9–11].

In the past, allogeneic HSCT was the only treatment option resulting in long-lasting remissions in this situation [71]. However, the majority of CLL patients do not qualify for this intensive treatment regimen. Formerly, for those patients, treatment with the anti-CD52 antibody alemtuzumab was available, resulting in relatively good response rates of 34–88%, but also in high rates of infections (37%), including CMV infections [75, 76]. In early relapsed and genetic high/ultra-high-risk CLL, B-cell receptor kinase inhibitors yield very promising results. Ibrutinib yielded an ORR of 90% with 7% complete remissions in pretreated CLL patients [77]. At 30 months, 69% of the patients were still in remission with this continuous treatment. Also patients with ultra-high-risk relapsed CLL with del(17p) showed a promising response duration with 79% being in remission at 1 year [28]. Ibrutinib showed superiority in a head-to-head comparison to ofatumumab in pretreated CLL patients with regard to all efficacy parameters including OS [78]. A randomized study comparing BR versus BR plus ibrutinib also showed the superiority of the ibrutinib-containing treatment arm with regard to response rates and PFS [79].

The PI3K inhibitor idelalisib combined with rituximab was compared to rituximab plus placebo in elderly CLL patients with relapsed CLL. The majority of the included patients had had multiple lines of therapy, and 42% had a del(17p) or TP53 mutation. Idelalisib plus rituximab yielded not only a significantly longer PFS but also a longer OS. Because of these new promising treatment options, allogeneic HSCT is now frequently postponed, and mostly performed in patients with non-response or non-tolerability of the new substances or in ultra-high-risk CLL with excellent physical fitness, young age and matched related donor [72].

Current Treatment in Case of a Late Progression

Because of the good prognosis of patients with long-lasting first remissions, a repetition of the previous treatment can be considered in case of a remission duration of 24–36 months after chemoimmunotherapy according to the European Society for Medical Oncology (ESMO) guidelines [80]. The data of the HELIOS study favor the additional administration of ibrutinib to the BR regimen in comparison to BR alone [79]; therefore, new substances represent an alternative treatment option in this situation. Since no statistically significant difference in OS has so far been observed, the

Stage	Fitness	del(17p) p53mut	Therapy
Binet A-B, Rai 0-II, inactive	Irrelevant	Irrelevant	None
Active disease or Binet C or Rai III-IV	Go go	No	FCR (BR above 65 years)
		Yes	Ibrutinib, Idelalisib+R, Allogeneic SCT (?)
	Slow go	No	Chlorambucil + Obinutuzumab or Ofatumumab or Rituximab
		Yes	Ibrutinib, Idelalisib + R, HD Rituximab or Ofatumumab, Alemtuzumab

Fig. 1. Therapeutic algorithm of the German CLL Study Group (GCLLSG) for first-line therapy.

choice between chemoimmunotherapy of 6-month duration or continuous treatment with oral kinase inhibitors has to be discussed individually with every patient. However, genetic analysis is also mandatory in patients with late relapse of CLL, since detection of a del(17p)/TP53 mutation demands therapy with one of the new kinase inhibitors.

Future Developments and Clinical Trials

As a therapeutic principle, the use of the most efficacious treatment in the first-line situation of CLL is beneficial, e.g. an improvement of OS with FCR was only achieved in the first-line and not in the relapse situation [25, 81]. Also, the outcome of patients treated with obinutuzumab and chlorambucil as a salvage regimen after an early relapse or failure to respond to single-agent chlorambucil was worse compared to patients treated with G-Clb in the first-line situation [82]. Similarly, the PFS was significantly longer in patients receiving the novel agent ibrutinib at second-line therapy compared to patients receiving ibrutinib in a later line of treatment [83].

Therefore, the addition of the novel agents to chemoimmunotherapy or the rational combination of agents with different mechanisms of action, e.g. an antibody with 1 or even several agents targeting the B-cell receptor signaling and other pathways that play a role in the pathogenesis of CLL, might with have the potential to achieve deeper remissions, potentially eradicate all residual CLL cells and thus lead to a cure of CLL. One of these approaches is the so-called ‘sequential triple-T’ concept of the GCLLSG, which is a tailored and targeted treatment aiming for a total eradication of MRD and consists of an optional debulking treatment with 2 cycles of a mild chemotherapy with bendamustine or fludarabine, followed by a 6–12 month induction treatment with an antibody and a kinase inhibitor or bcl-2-antagonist, followed by a MRD-tailored maintenance [84]. The BXX trials according to this triple-T concept and several other trials were designed chemo-free or with reduced dosages of chemotherapy, and appear to have more favorable toxicity profiles and promising efficacy. Therefore, patients

Response to First-Line Therapy	Fitness	Therapy	
		Standard	Alternatives (trials)
Refractory or progress within 2 years	Go go	Ibrutinib, idelalisib + R, A- Dex, FA, FCR, → Allogeneic SCT (?)	Lenalidomide, BR, (Ibrutinib, idelalisib, ABT-199)
	Slow go	Change therapy (see alternatives; if possible in trial)	Ibrutinib, idelalisib + R, Alemtuzumab for del(17p), ABT-199, FCR-lite, BR, lenalidomide, ofatumumab, HD rituximab
Progress after 2 years	All	Repeat first-line therapy	

Fig. 2. Therapeutic algorithm of the GCLLSG for relapse therapy.

with and without comorbidities might be treated with the same regimen to achieve a deep long-lasting remission, and the discrimination between fit and less-fit patients might become less relevant. Instead, the treatment will become more personalized, e.g. with an optional debulking in the case of a high tumor load and the duration of treatment tailored to the patient’s response. Furthermore, attempts should be made to define the biological parameters that are predictive of the patients’ response to certain treatment options to guide therapeutic decisions.

Whenever possible, patients should be offered participation in a clinical trial to offer access to new chemotherapy-free treatment regimens and to improve the treatment of CLL constantly. This is particularly important for patient groups without a defined therapeutic standard, e.g. for patients with relapsed/refractory CLL and with del(17p)/TP53 mutations.

Conclusions

The management of patients with CLL is undergoing significant changes; during the last decade outcomes were markedly improved with the addition of CD20 antibodies to well-established chemotherapies. Whereas in physically fit patients rituximab is combined with either fludarabine and cyclophosphamide (FCR) [25, 49] or bendamustine (BR) if the patient is older than 65 years or has a higher risk of infections [48, 49], patients with relevant comorbidities should receive chlorambucil with obinutuzumab (alternatively ofatumumab or rituximab) (fig. 1 and 2). In addition to the patient’s age and comorbidities, the presence of a del(17p)/TP53 mutation needs to be taken into account for treatment decisions, as these chemoimmunotherapies lack efficacy in patients with these high-risk features. In 2014, 2 novel agents targeting the BCR signaling pathway were approved for the first-line treatment of patients with these adverse prognostic parameters and for the relapsed situation because of high efficacy and a favorable toxicity. These and other novel agents may enable further advances and may revolutionize the treatment of CLL.

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