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# Update on management of diffuse large B-cell lymphoma Richter's transformation

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## Abstract

Richter's transformation (RT) is defined as the development of an aggressive lymphoma in 2–10% of patients with chronic lymphocytic leukemia (CLL). Despite significant advances in the last decade, there is currently no established standard of care for RT, making its management a significant challenge. Questions regarding patients' treatment management in the era of novel agents and targeted therapies have yet to be answered. Nevertheless, several retrospective studies and clinical trials have emphasized the use of novel targeted agents to address this problem. In this review, we provide a summary of potential therapeutic options for RT.

**Keywords:** chronic lymphocytic leukemia, treatment, Richter's transformation, immunochemotherapy

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## Introduction

Richter's transformation (RT) is characterized by the development of aggressive lymphoma in patients previously or concurrently diagnosed with chronic lymphocytic leukemia/ /small lymphocytic lymphoma (CLL/SLL) [1, 2]. RT is a rare event, occurring in 2–10% of CLL patients with an annual transformation rate of 0.5–1% [3]. It is associated with clonal evolution and the transformation of the original CLL clone into diffuse large B-cell lymphoma (DLBCL) or, less frequently, to Hodgkin lymphoma (HL). The great majority of RT cases (90–95%) manifest as diffuse large B-cell lymphoma RT (DLBCL-RT), while Hodgkin lymphoma RT (HL-RT) accounts for 5–10% of cases [4]. Rare cases of Richter's transformation into lymphoid or myeloid leukemia have been reported, as well as transformation into very aggressive mature T-cell lymphoma [5, 6]. Despite similar clinical characteristics to those of DLBCL, the molecular profile of RT is distinct. RT is characterized in most cases by rapid disease onset and progression. Transformation develops due to the acquisition of multiple genetic defects that facilitate rapid proliferation, such as *TP53* aberrations, *NOTCH1*, *MYC*, and *CDKN2A*, and DNA damage response mutations [7]. An important feature of RT is the clonal relation to preexisting CLL. Clonality can be determined by comparison of the immunoglobulin heavy chain variable region (IGVH) gene by next-generation sequencing or Sanger sequencing. Nevertheless, widespread testing of the clonal relationship has been limited due to the methodological issues dependent on the accessibility of RT tissue material for molecular testing. About 80% of RT is clonally related, whereas c.20% of RT is clonally unrelated: such cases are considered as the coexistence of two diseases: CLL and DLBCL. Clonality significantly worsens the prognosis [8–10].

RT can occur at any point in the disease course of a patient with CLL, including in previously untreated patients under observation or even as the initial presentation of CLL. However, such cases are very rare, and the vast majority of RT occurs in patients either on active CLL treatment or who are progressing after previous treatment [11]. The median time from CLL diagnosis to transformation is 2–5 years [12–14]. A recent epidemiological study

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comparing the incidence of RT in the era of novel agents revealed that this disease has occurred approximately half as frequently since the advent of the widespread availability of BCL-2 inhibitors or Bruton's tyrosine kinase inhibitors (BTKi) [15].

Despite advances in understanding the molecular variations and the disease's pathogenesis, DLBCL-RT is characterized by a poor prognosis, refractoriness to treatment, and short median overall survival (OS) of less than 12 months [10, 16]. Heavily pretreated CLL patients developing RT in the contemporary era following a targeted inhibitor such as BTKi have potentially an even worse outlook, with a series of cases demonstrating an OS of only 3–4 months [17, 18]. Better prognoses may be observed only in cases of clonally unrelated DLBCL-RT, which is similar to DLBCL *de novo,* with median survival of c.5 years [8–10].

There is currently no established standard of care for DLBCL-RT, making it one of the most significant clinical unmet needs in non-Hodgkin lymphoma (NHL) treatment. Nevertheless, progress in the development of novel targeted therapies holds the potential to enhance outcomes in RT. This review concentrates on treatment options for DLBCL-RT.

## Treatment

### Immunochemotherapy

In most cases, the therapy of RT-DLBCL is based on treatment experience from the B-cell non-Hodgkin lymphoma setting, albeit with significantly poorer outcomes. The predominant approach involves immunochemotherapy such as rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) [19]. While this regimen achieves high response rates in *de novo* DLBCL, and even cures up to two in every three patients, patients with RT are rarely cured by immunochemotherapy [7, 20, 21]. R-CHOP was initially investigated prospectively in a phase II study in 15 patients, which reported an overall response rate (ORR) of 67% with a low complete response (CR) rate of only 7%. Responses were generally not durable, with a median progression-free survival (PFS) of only 10 months (Table I) [22]. Similar results were noted in a retrospective analysis by the Polish Adult Leukemia Study Group. In a cohort of 76 DLBCL-RT patients treated with R-CHOP-like protocols, an ORR of 42.3% and a CR of 32.9% were reported, with a median PFS of 16.9 months [12]. It is however most important to underscore that in this retrospective analysis, both PET-CT as well as CT, were used for response assessment, thus potentially introducing bias.

Intensification of immunochemotherapy to hyper-CVAD (fractionated cyclophosphamide, vincristine, liposomal daunorubicin, and dexamethasone with or without methotrexate), OFAR (oxaliplatin, fludarabine, cytarabine, and rituximab), dose-adjusted R-EPOCH (rituximab, etoposide, prednisolone, vincristine, and doxorubicin), or other intensive protocols may deliver improved responses. However, these have not proved durable and OS has remained <12 months in the studies published to date. Moreover, the significant toxicity of such intensive chemotherapy is an important limitation [23–26].

A novel potential therapeutic option worth mentioning is polatuzumab vedotin (monomethyl-auristatin E conjugated CD79b antibody), which showed improved PFS when combined with R-CHP compared to R-CHOP in previously untreated DLBCL patients [27]. There is an ongoing trial with polatuzumab vedotin in combination with dose-adjusted R-EPOCH in RT (NCT04679012) (Table II) [28].

### Hematopoietic stem cell transplantation

For patients who achieve response after induction treatment, hematopoietic stem cell transplantation (HSCT) still has a role to play as a consolidation in selected patients with no significant comorbidities and who are transplant eligible. Published data that supports HSCT consolidation in RT has come predominantly from retrospective and single-center studies, while prospective data is limited. Remarkably, there have been no prospective studies comparing autologous HSCT (auto-HSCT) versus allogeneic HCT (allo-HSCT). However, given that patients with RT have concomitant CLL, only allo-HSCT can achieve durable remissions for CLL , and therefore it remains the preferred transplantation approach [11].

Tsimberidou et al. in 2006 was one of the first studies to report the outcomes of allo-HSCT and auto-HSCT in RT. Seventeen patients underwent allo-HSCT and three auto-HSCT. The estimated 3-year OS was 75% for patients who underwent allo-HSCT after achieving at least a PR, 27% for patients responding to induction therapy but not undergoing allo-HSCT, and 21% for patients with relapsed/refractory (R/R) DLBCL-RT who underwent allo- or auto-HSCT as salvage therapy (Table I) [29]. Furthermore, one large recent retrospective study on allo-HSCT in patients with RT (118 patients) also confirmed that the disease status at the time of HSCT significantly correlates with the outcomes. The 3-year PFS for patients with CR at the time of allo-HSCT was 66%, 43% for those with PR, and only 5% for patients with resistant RT. Interestingly, in this study, the 3-year PFS and OS results were superior in the group of auto-HSCT recipients (48% and 57%, respectively) compared to allo-HSCT recipients (43% and 52%, respectively). However, as the authors note, it is not possible to compare outcomes after auto-HSCT against outcomes after allo-HSCT because of the differences in cohort characteristics (e.g. more patients in CR, few patients receiving prior novel agents, and few with high-risk cytogenetics in the auto-HSCT cohort, including nearly half with missing cytogenetic data), as well as the potential biases in selecting one transplant approach over the other [30].

**Table I.** Treatment outcomes for Richter's transformation

| Author | Treatment regimen | Study | Number of patients | ORR (with CR) | Median PFS (months) | Median OS (months) |
|---|---|---|---|---|---|---|
| Langerbeins et al. [22] | R-CHOP | Phase II study | 15 | ORR 67% (CR 7%) | 10.0 | 21.0 |
| Tsimberidou et al. [29] | Chemotherapy or chemoimmunotherapy with or without stem cell transplantation | Retrospective study | 130 in total | ORR 39% (CR 12%) | 7.0 | 8.0 |
| Tam et al. [36] | Zanubrutinib, alone and in combination with tislelizumab | Phase I/II study | 13 | ORR 62% (CR 15%) | 17.3 | 29.3 |
| Wierda et al. [11, 28] | Pirtobrutinib | Phase I/II study | 75 | ORR 52% (CR 10%) | 3.7 | 13.1 |
| Davids et al. [39] | Venetoclax plus dose-adjusted R-EPOCH | Phase II study | 20 | ORR 62% (CR 50%) | 10.1 | 19.6 |
| Ding et al. [48] | Pembrolizumab | Phase II study | 9 | ORR 44% (CR 11%) | 5.4 | 10.7 |
| Jain N et al. [50] | Nivolumab combined with ibrutinib | Phase II study | 24 | ORR 42% (CR 34%) | | 13.0 |
| Frustaci et al. [54] | Venetoclax, atezolizumab and obinutuzumab | Phase II study | 28 | ORR 67.9% (CR 28.6%) | 16.2 | 31.6 |
| Guieze et al. [65] | Blinatumomab | Phase II study | 25 | ORR 36% (CR 20%) | – | – |
| Kater et al. [67] | Epcoritamab | Phase I/II study | 10 | CR 50% | – | – |

CR — complete remission; ORR — overall response rate; PFS — progression-free survival; OS — overall survival; R-CHOP — rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-EPOCH — rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin

**Table II.** Ongoing clinical trials for Richter's transformation (RT) treatment

| Study | ClinicalTrials.gov Identifier | Investigated drugs |
|---|---|---|
| Phase II Study of Venetoclax in Combination With Dose-adjusted EPOCH-R or R-CHOP for Patients With Richter's Syndrome | NCT03054896 | Venetoclax + EPOCH-R<br>Venetoclax + R-CHOP |
| Trial of CHOP-R Therapy, With or Without Acalabrutinib, in Patients With Newly Diagnosed Richter's Syndrome (STELLAR) | NCT03899337 | Acalabrutinib + R-CHOP<br>R-CHOP |
| Study to Evaluate the Efficacy and Safety of Obinutuzumab, Ibrutinib, and Venetoclax in Patients With Richter's Syndrome | NCT04939363 | Obinutuzumab + ibrutinib + venetoclax |
| Polatuzumab Vedotin in Combination With Chemotherapy in Subjects With Richter's Transformation | NCT04679012 | Polatuzumab vedotin + EPOCH-R |
| Safety and Efficacy Study of Epcoritamab in Subjects With Relapsed/Refractory Chronic Lymphocytic Leukemia and Richter's Syndrome | NCT04623541 | Epcoritamab + venetoclax<br>Epcoritamab + lenalidomide<br>Epcoritamab + R-CHOP |
| Duvelisib and Venetoclax in Relapsed or Refractory CLL or SLL or RS | NCT03534323 | Duvelisib<br>Venetoclax |
| Phase II Study of Glofitamab as Monotherapy or in Combination With Polatuzumab Vedotin or Atezolizumab in Richter's Transformation | NCT06043674 | Glofitamab<br>Glofitamab + polatuzumab vedotin<br>Glofitamab + atezolizumab |
| R-EPOCH in Combination With Ibrutinib for Patients With Classical RT of CLL | NCT04992377 | Ibrutinib + EPOCH-R |

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**Table II (cont.).** Ongoing clinical trials for Richter's transformation (RT) treatment

| Study | ClinicalTrials.gov Identifier | Investigated drugs |
|---|---|---|
| Atezolizumab, Obinutuzumab, and Venetoclax in Treating Patients With Chronic Lymphocytic Leukemia, Small Lymphocytic Lymphoma, or Relapsed or Refractory Richter's Syndrome | NCT02846623 | Atezolizumab<br>Obinutuzumab<br>Venetoclax |
| Ipilimumab, Ibrutinib, and Nivolumab for the Treatment of Chronic Lymphocytic Leukemia and Richter's Transformation | NCT04781855 | Ibrutinib<br>Ipilimumab<br>Nivolumab |
| Copanlisib and Nivolumab in Treating Patients With Richter's Transformation or Transformed Indolent Non-Hodgkin Lymphoma | NCT03884998 | Copanlisib<br>Nivolumab |
| ObinutuzuMab AtezOlizumab and VenetocLax in RichTer transfOrmation | NCT04082897 | Obinutuzumab<br>Atezolizumab<br>Venetoclax |
| Time-limited Triplet Combination of Pirtobrutinib, Venetoclax, and Obinutuzumab for Patients With Treatment-naïve Chronic Lymphocytic Leukemia (CLL) or Richter's Transformation (RT) | NCT05536349 | Pirtobrutinib<br>Obinutuzumab<br>Venetoclax |
| Study of Zilovertamab Vedotin (MK-2140) as Monotherapy and in Combination in Participants With Aggressive and Indolent B-cell Malignancies (MK--2140-006) | NCT05458297 | Zilovertamab vedotin<br>Nemtabrutinib |
| Study of Brexucabtagene Autoleucel in Adults With Rare B-cell Malignancies | NCT05537766 | Brexucabtagene autoleucel |
| (CHANT) Real World Study of Duvelisib in the Treatment of Non-Hodgkin's Lymphoma (NHL) | NCT05923502 | Duvelisib |
| Lisocabtagene Maraleucel, Nivolumab and Ibrutinib for the Treatment of Richter's Transformation | NCT05672173 | Ibrutinib<br>Lisocabtagene maraleucel<br>Nivolumab |
| Acalabrutinib, Venetoclax and Durvalumab for the Treatment of Richter's Transformation From Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma | NCT05388006 | Acalabrutinib<br>Durvalumab<br>Venetoclax |
| Zanubrutinib and Lisocabtagene Maraleucel for the Treatment of Richter's Syndrome | NCT05873712 | Lisocabtagene maraleucel<br>Zanubrutinib |
| Phase I/II study evaluating safety and efficacy of palbociclib in combination with immunochemotherapy R-CHOP in patients with Richter's transformation (PALIMRI) | | R-CHOP<br>Palbocyclib |

CLL — chronic lymphocytic leukemia; R-CHOP — rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-EPOCH — rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin

It is worth mentioning that HSCT as a consolidation therapy in RT has been available only to a selected group of younger, fit, and chemosensitive patients [31]. Only four of the 204 patients proceeded to allo-HSCT in one large single-institution publication of biopsy-proven RT, underlying the unmet need for effective induction therapies and the rarity of transplant-eligible RT patients [13]. A retrospective analysis by the European Group for Blood and Marrow Transplantation (EBMT) centers included 59 patients with RT (n = 34, auto-HSCT; n = 25, allo-HSCT). In 18 allo-HSCT recipients (72%), reduced-intensity conditioning (RIC) was used. The 3-year estimates of the probabilities of OS and relapse-free survival (RFS) and the cumulative incidences of relapse and non-relapse mortality were 36%, 27%, 47%, and 26% for allo-HSCT and 59%, 45%, 43%, and 12% for auto-HSCT. RIC was associated with superior RFS after allo-HSCT in multivariate analysis. In this study, again, the results for the auto-HSCT group appear better compared to the allo-HSCT group. Although autografted and allografted patients were comparable

with regards to sex, age, and time from RT diagnosis to transplantation, significantly more allografted patients had chemotherapy-resistant disease at transplantation, and had received more than two lines of chemotherapy since their diagnosis of CLL [32].

## BTKi and BCL inhibitors

The limited efficacy obtained with conventional treatments for DLBCL-RT has prompted the investigation of novel therapies, including targeted inhibitors of Bruton's tyrosine kinase (BTKi) and BCL2. However, the outcomes of monotherapy treatment with novel agents have been reported in only small series and describe short PFS [31].

In a phase I study of venetoclax as monotherapy, a cohort of seven patients with RT was included. 3/7 (43%) achieved a response, suggesting some biological activity of the drug in this disease, although these responses were mostly relatively short-lived [33].

In a retrospective series of four RT patients treated with ibrutinib, three achieved a response, but median treatment duration was only 6.1 months [34]. Similar outcomes were observed with acalabrutinib. In a phase I/II study, a cohort of 25 patients was included. The overall response rate was 40% (8% CR), but the median PFS was short, reaching only 3.2 months [35]. More favorable results were reported with zanubrutinib in monotherapy. In a recently published study, 13 RT patients received zanubrutinib. The majority of them received CHOP/R-CHOP as their first-line treatment for RT. The ORR was 62%, and the median PFS and OS were favorable at 17.3 months and 29.3 months, respectively (Table I) [36].

Similar results may be observed in treatment with noncovalent BTK inhibitors such as pirtobrutinib and nemtabrutinib. In the phase I/II BRUIN study with pirtobrutinib in monotherapy, a cohort of 82 RT patients was included, with efficacy data available for 75 patients to date including 68 who had received prior RT treatment. The ORR was 52%, with a CR rate of 10%, an ORR of 47% in patients who received a prior covalent BTKi and an ORR of 50% in RT patients who had received prior RT-directed therapy. Median OS was 13.1 months, even though the patients were relatively heavily pretreated, with a median of four lines of previous CLL and two lines of RT therapy. Despite these encouraging response rates, the median PFS was short at 3.7 months (Table I) [11, 37]. The results for six RT patients treated with nemtabrutinib were reported in the BELLWAVE-001 study, with an encouraging ORR of 50% (three patients achieved a PR) [38].

Several studies have investigated the efficacy of novel agents in RT with a combination of standard immunochemotherapy, which is hypothesized to show more encouraging outcomes than single-agent efficacy. Promising results were achieved with venetoclax in combination with dose-adjusted R-EPOCH, albeit in a small, select cohort. In a group of 26 patients, 20 received venetoclax and immunochemotherapy. The ORR was 62% (50% CR), median PFS 10.1 months, and median OS 19.6 months (Table I). Eight patients successfully proceeded to allo-HSCT, while 11 remained on venetoclax monotherapy maintenance at the end of the study. It is noteworthy that although only two patients in this study received prior RT treatment, and the cohort comprised relatively young and fit patients (median age 63), 52% (14/26) had prior novel agent therapy for CLL [39]. These encouraging results have prompted an extension of the study with a total of 67 patients enrolled (NCT03054896) (Table II). Immunochemotherapy was de-intensified from dose-adjusted R-EPOCH to R-CHOP due to excess toxicity (cytopenias and infections). Forty patients received R-CHOP-venetoclax, and the initial results of the first 27 patients (presented at the ICML 2023) showed ORR of 68% and CR of 48% [40, 41].

A real-world analysis from the Mayo Clinic and MD Andreson has led to further validation that venetoclax has synergistic properties with R-CHOP. In 55 patients evaluated with RT, 10 received venetoclax in combination with R-CHOP (ORR of 60%, CR of 50%); 20 received venetoclax in combination with chemoimmunotherapy (ORR of 50%, CR of 40%); 20 received venetoclax in combination with a BTKi and anti-CD20 antibody (ORR of 40%, CR of 30%); three received venetoclax in combination with "varied-based regimens" (ORR/CR not reported); and two received venetoclax monotherapy (ORR/CR not reported) [40, 42, 43]. Venetoclax is now being investigated in a range of combination strategies in ongoing clinical trials (NCT05388006, NCT02846623, NCT04939363) (Table II).

Additionally, the ongoing first-line STELLAR trial is a randomized study exploring the combination of acalabrutinib and R-CHOP versus R-CHOP alone in RT. This is the first, and currently only, randomized clinical trial globally in RT [44, 40].

## Phosphoinositide 3-kinase inhibition

The treatment of RT is currently being investigated with another class of targeted agents: phosphoinositide 3-kinase inhibitors (PI3Kis). Limited data is available for PI3Kis as monotherapy. Idelalisib was tested in four patients with ibrutinib-resistant RT and demonstrated a 75% ORR, but with a response duration of only 6.4 months [45]. The combination of duvelisib plus venetoclax is now being tested in an ongoing phase I/II trial for relapsed and refractory CLL (R/R CLL) and RT [46]. The rationale for this combination is based on preclinical data demonstrating that PI3K enhances the dependence of CLL cells on BCL-2 for their survival [47]. Eight RT patients have been evaluated with this combination, and four responded to the treatment, with two achieving CR. Two patients underwent cellular therapy (allo-HSCT and chimeric antigen receptor T-cell) [46].

## PD-1 blockade

The evidence of programmed death-1 (PD-1) expression and its ligands in the tumor microenvironment are promising biomarkers to select RT patients for PD-1 blockade. In nine RT cases, pembrolizumab, a humanized PD–1––blocking antibody, exhibited selective efficacy. In heavily pretreated RT patients, most of whom had received prior anthracycline-containing chemotherapy and/or ibrutinib, pembrolizumab was associated with an ORR of 44% and an OS of 10.7 months (Table I). Clinically durable responses were observed in RT patients who experienced progression after prior ibrutinib. It is worth mentioning that pembrolizumab demonstrated clinical activity in patients with RT, while no clear activity was observed for patients with relapsed CLL. Subsequently, some patients who responded to the treatment developed thrombocytopenia as a result of progressive CLL. Thrombocytopenia improved with the addition of a PI3K inhibitor (idelalisib), suggesting combination therapy to treat the underlying CLL. Another important observation resulting from this investigation was that PD-1/PD-L1 expression was associated with earlier ibrutinib treatment [48]. However, in the KEYNOTE-170 study, in 23 patients treated with pembrolizumab, the ORR was 13% with a median OS of 3.8 months and a median PFS of 1.6 months. Moreover, two of the three patients who responded had classical Hodgkin lymphoma histology, rather than DLBCL. It is difficult to compare the differing results between these two studies since the latter did not report prognostic RT variables, nor did it report PD-1 expression [42, 49].

More favorable outcomes have been achieved when checkpoint inhibitors were combined with other targeted agents to enhance the antitumor effect and additionally control the underlying CLL clone. Jain et al. investigated a combination of ibrutinib and nivolumab in patients with RT and CLL. In a group of 24 RT patients, ORR was 42%, with 34% CR. The median OS was 13 months, with an even higher rate of 24.1 months in patients treatment-naïve for RT (Table I) [50]. In the CLL-RT1 trial, a combination of zanubrutinib and a PD-1 inhibitor (tislelizumab) is being investigated. In preliminary results of seven patients, three have achieved a response (one CR and two PR) with a median PFS and OS of 2.9 months and 15.4 months, respectively. The group consists of 52 patients and the final results are eagerly awaited [51]. Copanlisib plus nivolumab has been investigated in a phase I study, showing an acceptable toxicity profile with an ORR of 29% and a CR of 14% [52]. Another investigational strategy including the combination of pembrolizumab, umbralisib (a PI3Ki) and ublituximab (a type I CD20 antibody) has shown promising initial results, with an ORR of 50% in four relapsed/refractory RT patients with ongoing remissions of 7+ months [42, 53].

Impressive results were recently reported in the MOLTO trial evaluating the activity and safety of a combination of atezolizumab (humanized monoclonal antibody blocking PD-L1), venetoclax and obinutuzumab in untreated DLBCL--RT. Twenty-eight patients were enrolled and the observed ORR was 67.9%, with a 28.6% CR rate. After a median follow-up of 11.6 months, 57.9% of patients are in continuous remission (eight on active therapy, two received allo-HSCT, and one discontinued therapy due to secondary myelodysplastic syndrome), and in six cases remission has been for ≥24 months. Median PFS was 16.2 months, and median OS was 31.6 months (Table I) [54]. There is also an ongoing trial with durvalumab (humanized monoclonal antibody blocking PD-L1), acalabrutinib and venetoclax (NCT05388006) (Table II).

## CAR-T therapy

The promising results of chimeric antigen receptor T-cell (CAR-T) therapy in *de novo* DLBCL have prompted studies in RT. However, there is a lack of prospective data on the utility of CAR-T in RT specifically. One of the first small studies suggested a lack of response to CAR T-cell therapy or a non-sustained response in the context of RT [55, 56].

However, in a single-center phase II trial in Israel, 4/6 patients with DLBCL-RT achieved CR. At a median follow-up of 5.5 months, all patients were alive, and two underwent allo-HSCT [57].

A recent study by Kittai et al. reviewed nine high-risk RT patients with a median of four previous lines of treatment. Eight patients received a bridging therapy before axicabtagene ciloleucel (axi-cel) infusion: seven were treated with BTKis and the eighth with rituximab, dexamethasone, cytarabine, and oxaliplatin (R-DHAX). One patient received no bridging therapy. 55.6% of patients achieved CR, and three had PR. At a median follow-up of 6 months, only one patient had progressed, while all the others showed durable responses [58]. Moreover, ibrutinib has been shown to potentially address the immune dysfunction observed in CLL patients. This suggests that BTKis could improve CAR-T cell expansion and enhance its effector function in CLL patients [28, 59, 60]. In comparison, one recent multicenter analysis identified 55 patients who received anti-CD19 CAR-T infusion, mostly axi-cel, of whom c.45% achieved CR, although the OS was only 8.5 months [61]. Some prospective trials are ongoing to evaluate CAR-T's efficacy in RT patients. The ongoing ZUMA-25 trial investigates the role of brexucabtagene-autoleucel (brexu-cel) in relapsed and refractory rare B-cell malignancies (NCT05537766). Lisocabtagene-maraleucel (liso-cel) is being studied in combination with either zanubrutinib (NCT05873712) or with nivolumab and ibrutinib (NCT05672173) (Table II) [28].

Interestingly, one trial featured a novel CAR T-cell construct, ARI-0001 (CART19 product), given to five patients with RT. Four patients responded to the treatment; however, minimal residual disease (MRD) negativity was achieved in

all patients, both in peripheral blood and bone marrow, even those with a PR or stable disease in the lymph nodes. So far in this study, neurotoxicity has not been observed [62].

Another potential alternative therapeutic strategy is the use of chimeric antigen receptor-NK cells (CAR-NK). Initial results for CAR-NK treatment indicate lower toxicity and fewer complications compared to CAR-T treatment. Liu et al. conducted a phase I/II trial using anti-CD19 CAR-NK derived from cord blood, which was administered to 11 heavily pretreated patients with NHL (n = 6) and CLL/RT (n = 5, one patient with RT) (median of four prior lines of therapy). There were no reported cases of cytokine release syndrome or neurotoxicity. Three patients with CLL achieved CR, and one had remission of the RT component (but persistent CLL). At a median follow-up of 13.8 months, two of the three responding CLL patients required additional CLL therapy, as did the RT patient [63].

## Bispecific antibodies

Bispecific T-cell–engaging antibodies (BITes) simultaneously bind to antigens on tumor cells and CD3 subunits on T cells. This simultaneous binding brings tumor cells close to effector T cells, followed by T-cell activation, degranulation and tumor cell elimination [64]. To date, four BITes have been analyzed for clinical efficacy in RT: blinatumomab (CD19/CD3 BITes), glofitamab, epcoritamab and mosunetuzumab (CD20/CD3 BITes). Early data seems promising. In the BLINART trial, blinatumomab was proven to induce a significant CR rate in patients with RT. 39 patients initiated treatment with R-CHOP. After two initial cycles, those patients who did not achieve CR assessed in PET-CT (25/39 patients) went on a course of blinatumomab. ORR was achieved in 46% of patients, and CR in 36% (Table I) [65].

Glofitamab has exhibited favorable activity with frequent and durable CRs and a predictable and manageable safety profile in patients with refractory DLBCL. A phase I study included 10 patients with DLBCL-RT. Six were evaluated for efficacy assessment: 3/6 achieved CR, and 2/6 achieved PR [66].

Similarly, epcoritamab has demonstrated its efficacy in initial results. In the ongoing EPCORE CLL-1 study (NCT04623541), RT patients treated with a maximum one prior line of RT therapy were enrolled. 6/10 patients responded and 50% (5/10) achieved CR (Tables I, II) [67].

In very recently published results of a phase I/II study, mosunetuzumab in monotherapy demonstrated efficacy in 20 patients with relapsed and refractory RT. Patients were treated with at least one line of prior therapy; the median number of treatment lines was 2.5, and 45% had received prior treatment with a BTKi. ORR was 40%, with 20% CR. Two of the patients had CR ongoing for ≥20 months at the data cut-off, and the other two patients had received a subsequent stem-cell transplant [68].

## ROR1-targeting antibody-drug conjugate

The receptor tyrosine kinase-like orphan receptor 1 (ROR1) is a transmembrane oncofetal protein present on the surface of CLL and RT cells, as well as other hematological malignancies, and has recently been investigated as a target of ROR1-antibodies [11, 69, 70]. One potential advantage of this target is that it is not expressed on other hematopoietic cells, including B cells, thus having the potential to be less immunosuppressive [11]. The WAVELINE-001 study investigated the role of zilovertamab vedotin (MK-2140), which is an antibody-drug conjugate comprising a humanized IgG1 monoclonal antibody and the antimicrotubule cytotoxic agent monomethyl auristatin E (MMAE), in patients with relapsed/refractory NHLs. Recently reported results included seven patients with RT, four of whom responded, with a median duration of response of 2.8 months [71].

## Richter treatment algorithm

Recent advancements in the treatment of lymphoid malignancies can also be applied to RT. Upon diagnosis, evaluating patient fitness and comorbidities is crucial to determine whether a patient can tolerate R-CHOP or dose-adjusted EPOCH-R and be considered for allo-HSCT. Currently, based on clinical trials and retrospective analyses, such an approach holds the potential for a cure, or may enable longer OS as the sole immunochemotherapy administration. It should be noted that the role of auto-HSCT in RT treatment diminishes, as it does not allow control of the underlying CLL clone. Nevertheless, only c.10% of RT cases can be treated with such a curative approach. Both prospective and retrospective analyses have indicated that R-CHOP and dose-adjusted EPOCH-R regimens can be well-tolerated and combined with venetoclax to increase the likelihood of achieving deep remission. However, it must be emphasized that the addition of venetoclax is used in an off-label setting in this indication. Furthermore, clinical trials assessing such combinations have predominantly involved younger RT patients, and regimens incorporating venetoclax appear to have yielded the most favorable responses among reported treatment approaches. Treating older patients with RT remains a clinical challenge, as these regimens can be excessively toxic and poorly tolerated.

Clinical trials evaluating combinations of BTK inhibitors with immunochemotherapy or other targeted agents are currently underway, with results eagerly anticipated. However, it is important to underscore that the widespread use of BTK inhibitors in CLL treatment may potentially reduce the effectiveness of such combinations. The alternative use of covalent or non-covalent BTK inhibitors, depending on the patient's treatment history, is likely to carry significant clinical implications when selecting appropriate agents for combinations. Given these considerations, clinical trials investigating the tolerability and effectiveness of compounds

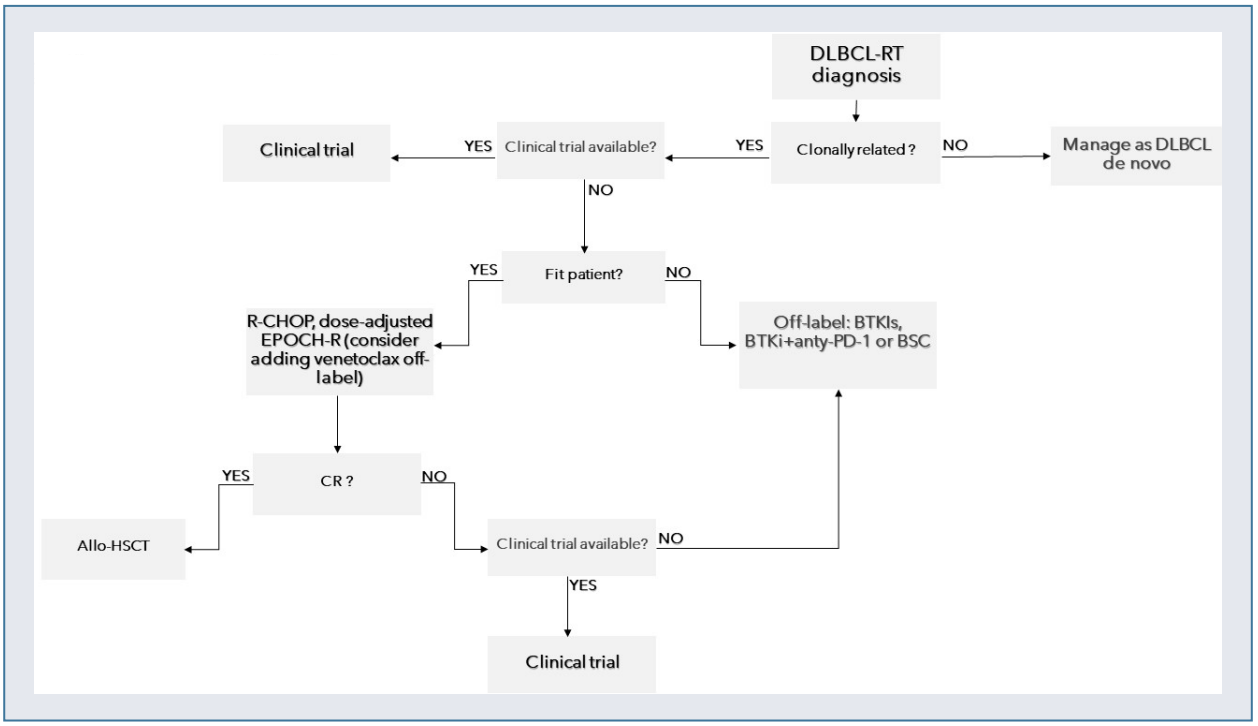


**Figure 1.** Richter treatment algorithm; allo-HSCT — allogeneic hematopoietic stem cell transplantation; anti-PD-1 — anti-programmed death-1; BSC — blood stem cell; BTKI — Bruton's tyrosine kinase inhibitors; CR — complete remission; DLBCL — diffuse large B-cell lymphoma; R-CHOP — rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-EPOCH — rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; RT — Richter's transformation

not extensively used for CLL treatment may identify novel and effective combinations. The blockade of the PD-1/PD-1L axis by atezolizumab, nivolumab, or pembrolizumab appears promising for specific patients. Inhibition of proliferation using cyclin-dependent kinase inhibitors (CDK) has demonstrated efficacy in experimental settings, and the first human trial combining a CDK4/6 inhibitor with R-CHOP is underway (Table II). As previously mentioned, ROR1 may also represent a novel target for RT, and a clinical trial with zilovertamab vedotin is currently underway.

For older patients, treatment with less toxic regimens in clinical trials, such as PD-1/PD-L1 axis inhibitors, bispecific antibodies, CAR-T, or non-chemotherapy-based combinations, appears to hold promise, as demonstrated by recently published clinical trials. Therefore, this specific patient group should be prioritized for clinical trial allocation whenever possible. The RT treatment algorithm is presented in Figure 1.

## Conclusions

Despite significant advances in recent years, DLBCL-RT continues to pose challenges in terms of treatment. Current management strategies still utilize historical treatment approaches with immunochemotherapy, with the potential incorporation of novel agents through participation in clinical trials. However, tight eligibility criteria for clinical trials and a relative lack of available RT-specific trials are, for many patients, insurmountable obstacles.

For patients who are fit, allo-HSCT represents the only proven modality that can provide highly durable remission, with outcomes associated with the depth of response entering the transplant [11]. However, it should be emphasized that due to the clinical context, allo-HSCT can only be performed in 10–15% of patients diagnosed with RT [13, 72].

Many of the ongoing studies are single-arm, with some relying on retrospective data. Prospective studies often have limited sample sizes, and there have been no reported randomized controlled trials yet. Encouraging results observed in small patient cohorts may be influenced by factors such as the absence of clonal correlation evidence between CLL and DLBCL clones, leading to cases that may not truly represent Richter's transformation.

Despite all these challenges, broader advances in targeted therapeutics within the field of hematology are beginning to impact the management of RT. Promising targets include the inhibition of BTK, BCL2, and the PD1-PD-L1 axis, as well as T-cell–activating/engaging therapies. Many of these treatments, along with their combinations, demonstrate good tolerability and acceptable toxicity profiles. However, despite such promising developments, no

specific agents have yet been licensed or reimbursed for RT in the United States or Europe [40].

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