DOI:
10.1111/bjh.17882

Document Version
Peer reviewed version

Richter Transformation of Chronic Lymphocytic Leukaemia: A British Society for Haematology Good Practice Paper

Writing group: on behalf of the Haemato-Oncology Task Force of the British Society for Haematology

Toby A. Eyre[1], John C. Riches[2], Piers E.M. Patten[3,4], Renata Walewska[5], Helen Marr[6], George Follows[7], Peter Hillmen[8,9] & Anna H. Schuh[1,10]

1. Department of Haematology, Cancer and Haematology Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom.
2. Centre for Haemato-Oncology, Barts Cancer Institute, Queen Mary University of London, London, United Kingdom.
3. Comprehensive Cancer Centre, School of Cancer and Pharmaceutical Sciences, King's College London, London, United Kingdom.
4. Department of Haematology, King's College Hospital, London, United Kingdom.
5. Department of Haematology, University Hospitals Dorset, Bournemouth, United Kingdom.
6. Northern Centre for Cancer Care, Newcastle upon Tyne Hospitals NHS Trust, United Kingdom.
7. Department of Haematology, Addenbrookes, Cambridge, United Kingdom.
8. St. James's Institute of Oncology, Leeds, United Kingdom.
9. Leeds Institute of Cancer and Pathology, University of Leeds, Leeds, United Kingdom.
10. Department of Oncology, University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom.

Correspondence: BSH Administrator, British Society for Haematology, 100 White Lion Street, London, N1 9PF, UK. E-mail: bshguidelines@b-s-h.org.uk

Methodology

This Good Practice Paper was compiled according to the BSH process at https://b-s-h.org.uk/media/16732/bsh-guidance-development-process-dec-5-18.pdf and represents best practice in both teaching and district hospitals in the UK. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org.

Literature review details

Recommendations included a systematic review of published English language literature from publication of previous British Society for Haematology (BSH) Management of Chronic Lymphocytic Leukaemia Guidelines 2012) up to 03/2021. In addition, there are some additional pertinent references and a consensus of expert opinion where no published data are available. PubMed, MEDLINE, EMBASE, Cochrane databases and Web of Science were searched using the preliminary search terms; chronic lymphocytic leukaemia OR CLL AND Richter's transformation OR Richter's syndrome OR transformed/developed/progressed to aggressive lymphoma/high-grade lymphoma/DLBCL/Hodgkin lymphoma. Systematic reviews, including guidelines from other countries, prospective clinical trials, observational studies i.e., cohort or case–control studies, expert reviews and opinions and case series were considered and reviewed as appropriate.

Review of the manuscript

Review of the manuscript was performed by the BSH Guidelines Committee, Haemato-oncology Task Force, Haemato-oncology sounding board of BSH.

WORD COUNT 2478

Introduction and Epidemiology

Richter transformation (RT) is the development of an aggressive lymphoma arising on the background of chronic lymphocytic leukaemia (CLL) (1). RT is uncommon, challenging to treat, very distinct from *de novo* DLBCL and requires specific guidance. RT occurs in 2-10% of CLL patients, usually during the disease course rather than at presentation, representing a transformation rate of 0.5–1% per CLL patient per year (2–5). RT should be suspected when a CLL patient with develops ≥1 new "B symptoms", asymmetric, rapidly progressive lymphadenopathy, or a sudden lactate dehydrogenase (LDH) rise. RT presents as diffuse large B-cell lymphoma (DLBCL-RT) in ~90%, but can present as Hodgkin lymphoma (HL-RT; ~10%) or rarely as histiocytic/dendritic cell sarcoma or other forms of lymphoma (<1%)(6). An important consideration is whether RT is clonally derived-from or unrelated-to the original CLL, as these two states have distinct clinical and pathological characteristics. Strictly speaking, RT refers to clonally-related cases with Richter syndrome encompassing all, but since the clonal origin is often unknown, the term RT includes all cases. Clonally-related RT has an aggressive course, higher rates of treatment resistance and *TP53* aberrations compared with clonally unrelated disease, where outcomes are more akin to de novo DLBCL. A clonal relationship is more common in DLBCL-RT (70-80% of cases), compared with HL-RT where it is seen in 30-40% (5). Genetic clonality studies (i.e. sequencing analysis of immunoglobulin heavy chain variable region (IgVH) genes) are not currently routinely performed in practice at most institutions.

Diagnostics

Histopathological assessment remains the gold standard to confirm the diagnosis of RT. DLBCL-RT is characterised by the presence of large neoplastic B cells with either centroblastic (60-80% of cases) or immunoblastic (20-40% of cases) morphology. Currently, DLBCL-RT is distinguished from "accelerated" CLL with expanded confluent proliferation centres as the management of the entities is distinct(7). Adherence to two key World Health Organisation diagnostic criteria is critical: (i) DLBCL-RT is typified by the presence of sheets of large B-lymphoid cells with a nuclear size equal to or exceeding that of normal macrophage nuclei or more than twice the size of a normal lymphocyte; and (ii) these cells must show a diffuse

growth pattern, and not be present in small foci throughout the neoplasm (1). These criteria can be subjective, and review of adequate biopsy specimen by at least two independent pathologists is desirable (7). However, these are subjective criteria, and there is increasing evidence from genetic studies that poor risk CLL, accelerated CLL and RS are part of a continuum that is driven by underlying genomic instability.

Most DLBCL-RT (80%) are classified as activated B-cell type with 20% germinal centre B-cell-like. Many studies have conclusively demonstrated that RT is genetically distinct from *de novo* DLBCL. *TP53* aberrations are seen in ~60%, with alterations in *MYC* (40%), *CDKN2A* (30%) and *NOTCH1* (30%) also common. Mutations of ≥1 of these genes are present in 90% (8–10). *NOTCH1* mutations are associated with “subset 8” of the B-cell receptor (BCR) in CLL patients, which exhibits autonomous BCR signalling and responsiveness to multiple auto-antigens and other micro-environmental immune stimuli, and higher rates of RT(11). A recent study of paired samples from peripheral blood CLL and tissue RT phases that combined whole genome sequencing and RNAseq identified defects in the DNA damage response (DDR) as the most discriminative feature in RT. Furthermore, pathway-based clonal deconvolution analysis showed that genes in the MAPK and DDR pathways also demonstrated highest clonal expansion probability. Together, these data point towards disruption of signalling and DDR as dominant drivers of transformation (10).

In contrast, HL-RT is characterised by the presence of CD30+/CD15+/CD20- classical Reed-Sternberg cells on a background of small T-cells, histiocytes, eosinophils and plasma cells (12). Most HL-RT are clonally-unrelated and Epstein-Barr virus (EBV)-positive, representing *de novo*, EBV-driven lymphoma. Little data exist regarding the genetic hallmarks of HL-RT. Susceptibility to infections is well recognised in CLL patients and can occur in early-stage disease. Therefore, it is important to consider infections that may mimic RT presentation, especially EBV or cytomegalovirus, in the differential diagnosis.

Role of Positron emission tomography

Using an SUVmax cut-off >5, positron emission tomography **(**PET) detected RT with a high sensitivity (91%) but low specificity (50%) in a retrospective study of 37

patients previously treated with chemotherapy +/- immunotherapy (13). This study demonstrated a high negative predictive value (NPV) (97%) for RT using this cut-off. The same SUVmax cut-off was applied to 332 patients, of whom 95 had histologically-proven RT(14). Sensitivity and NPV for RT detection were 88% and 92% respectively. However, positive predictive value (PPV) (47%) and specificity (38%) remained low: of the 332 patients, 117 were diagnosed with histologically aggressive CLL without RT and 72% of these cases had SUVmax >5. Using an SUVmax cut-off of >10 improved specificity (95%) with high sensitivity maintained (91%) in a study of 240 patients(15).

The sensitivity and specificity of a SUVmax cut-off >10 may be diminished with targeted inhibitors. In a *post hoc* analysis of a phase II study of venetoclax in BCR inhibitor-exposed patients, the sensitivity of SUVmax cut-off >10 for detecting RT was 71%, with a specificity of only 50%. Fourteen of 19 patients with SUVmax >10 had CLL with no RT(16). Furthermore, in a Mayo study of BCRi-exposed patients, an SUVmax >5 again demonstrated high sensitivity of 96% but low specificity(17). PPV of an SUVmax >5 or >10 remained low at 51% and 67% respectively.

Taken together, histological confirmation remains essential to establish RT. PET may help target the biopsy site to the area with highest ^{18}F-fludeoxyglucose (^{18}F-FDG) uptake and is valuable in excluding RT without biopsy when SUVmax is <5.

Prognostication

Two prognostic score systems predict overall survival (OS). First, a clinical RT score was derived from a multivariate analysis of 130 patients who received chemotherapy or chemoimmunotherapy. Five factors independently correlated with shorter survival: performance status >1, LDH >1.5 x upper limit of normal, platelets <100 × 10^9/l, tumour bulk >5cm, and >1 prior therapy (18). When stratified into four groups according to these factors, median OS ranged from 0.33-1.12 years. The score has been validated in other series (2,19).

The second prognostic system (5) used Eastern Cooperative Oncology Group performance status, achievement of complete remission (CR) with induction therapy and *TP53* status. Median OS was 8 and 25 months respectively for high and

intermediate risk patients respectively but the 5-year OS was 70% for low-risk patients. This study established that clonally-unrelated RT is clinically and biologically distinct from clonally-related RT and is characterised by a survival akin to *de novo* DLBCL (median OS 62.5 vs 14.2 months; p=0.017).

For those with proven RT, ^{18}F-FDG uptake by PET scan may add prognostic information. An SUVmax >10 was significantly associated with worse OS in a retrospective study (6 versus 21 months for SUVmax <10, p=0.015), and patients with advanced stage had poorer OS than limited stage (5.1 versus 13.8 months, p=0.04) (20).

The prognostic significance of number of prior treatment lines has been demonstrated in the targeted inhibitor era. Median OS was improved in patients with no prior treatment compared to those previously treated for CLL (46.3 months versus 7.8 months)(17). Similar findings were observed in a recent Spanish cohort (21) and in the CHOP-OR trial (22). Clonal relatedness of the underlying CLL and DLBCL-RT is a strong prognostic differentiator (5).

Recommendations

1. **All patients with a clinical suspicion of transformed CLL and an SUVmax >5 should undergo PET-targeted biopsy of the most safely accessible 18F-FDG avid site (1B)**
2. **A surgical excisional or incisional biopsy is strongly recommended to establish the diagnosis (1B). Where this is not possible, a core needle biopsy is an alternative (2B)**
3. **Patients should have viral serology for human immunodeficiency virus, hepatitis B and hepatitis C, EBV and CMV (1C)**
4. **Consider a bone marrow aspiration and biopsy in RT cases to assess CLL/RT infiltration with unexplained pancytopenia. (2C)**
5. ***TP53* mutation and 17p deletion analysis should be performed (1B)**
6. **If available and analysis is possible, include IgHV rearrangement analysis (genetic sequencing) of CLL and RT tissue to establish relatedness of the clone (2B)**

7. **Ensure specialist haemato-pathology review, clinico-pathological correlation and multi-disciplinary review when considering RT diagnosis (1B)**

Treatment approach

Patients with RT commonly present in the context of pre-treated CLL and immunosuppression, and given the typical demographics of the CLL population, patients are often older with coexisting comorbidities (23). Treatment have historically involved multi-agent cytotoxic chemotherapy, more recently in combination with an anti-CD20 monoclonal antibody. Although intensive regimens including hyper-fractionated alkylator-based therapy(24,25), platinum and purine analogue-based therapy(26–28) have been studied in small phase II trials, toxicity and low efficacy have limited their broad applicability. CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) alongside an anti-CD20 antibody form the largest and most contemporary data from prospective phase II trials (29,30). Outcomes generally remain disappointing with overall response rates (ORR) between 40-60% and a median progression-free survival (mPFS) between 6-10 months. Given the known activity in other aggressive non-Hodgkin lymphoma, dose-adjusted EPOCH-R (etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, rituximab) has also been investigated in a 46 patient single centre retrospective series(31), however the mPFS was only 3.5 months and toxicity was high (30% died without progression or response).

Median OS for RT cohorts studied is ~8-12 months, although potentially lower still in those patients progressing with RT following targeted inhibitor treatment for CLL (32,33). Given these limited survival outcomes, younger and fitter patients should be considered for consolidation strategies such as autologous (autoSCT) or allogeneic stem-cell transplantation (alloSCT). European Society for Blood and Marrow Transplantation (EBMT) data (34) (n=59) suggest that the selected patient population who received an alloSCT (n=25, 72% reduced-intensity conditioning (RIC)) or autoSCT (n=34, mostly chemo-sensitive disease) had an improved long-term survival, with outcomes better in patients with chemo-sensitive disease. Relapses were more common following autoSCT (3-year cumulative incidence of relapse 43%) whilst non-relapse mortality (3-year 26%) and chronic graft-versus-host

disease were more prevalent post-alloSCT. Long-term OS was broadly equivalent with either approach (3-year OS 36-59%). Whilst numbers in this historical series were low, SCT consolidation remains a reasonable approach in otherwise fit patients with chemo-sensitive disease.

There is no strong evidence to guide the management of patients with disease sites associated with high risk of CNS disease or those in whom anthracycline-based therapy is unsuitable.

R-CHOP (rituximab-CHOP) is curative in a minority of RT patients receiving the regimen for front-line RT treatment. Previously CLL-treatment naïve, *TP53*-intact patients who achieve a complete metabolic response following R-CHOP may have a similar long-term PFS to *de novo* DLBCL (5,17,21). As such, it may be reasonable to observe these patients without consolidation therapy. Patients with *TP53* aberrations or those who develop RT having previously received CLL-directed treatment have a poor outcome with R-CHOP alone, although this remains the standard of care and provides at least initial disease control for most patients. There are currently no novel targeted therapies specifically licensed for RT.

Optimum treatment for HL-RT is less clear with no prospective trial evidence available. Multi-agent chemotherapy is often used, with documented outcomes with ABVD (adriamycin, bleomycin, vinblastine and dacarbazine), CHOP (+/-R) and hybrid regimens from small series (12,35,36). Outcomes for 94 patients in a recent multicentre, retrospective series found a 2-year OS of 72% (37). Sixty-two patients who received ABVD had a median OS of 13.2 years. This series did not support the use of consolidation SCT in HL-RT, with survival outcomes equivalent.

Recommendations

- **Due to the poor outcome of most RT patients with standard therapy, all patients should be offered clinical trials when available (2B)**
- **Offer R-CHOP in patients considered appropriate for anthracycline-based treatment (1B)**

- **Consider consolidation in first remission with either autologous or allogeneic stem-cell transplantation in fit patients typically <70 years old (2B)**
- **Consider observation following R-CHOP for *TP53*-intact, previously treatment-naïve patients across all ages obtaining a complete metabolic remission (2B)**
- **Consider ABVD in anthracycline-fit patients developing HL-RT (2B)**
- **Autologous or allogeneic stem-cell transplantation in first remission is not typically considered in HL-RT (2B)**

Relapsed, Refractory (R/R) RT

Although the management of R/R RT patients may differ depending on previous therapy, co-morbidities and fitness, the outcome is generally poor for all patients. Patients who relapse following cellular therapy or who are not fit for this modality should be offered clinical trials or palliative care. Others should be considered for second line intensive chemotherapy followed by alloSCT although it is recognised the response rates to second line chemotherapy remain limited.

Investigational approaches

In light of the poor outcomes described, ongoing clinical and translational research remain critical for progress in RT management. Recent retrospective and phase I/II studies suggest that inhibitors targeting Bruton tyrosine kinase (BTK) (ibrutinib, acalabrutinib, pirtobrutinib)(38–42), B-cell lymphoma-2 (BCL2) (venetoclax)(43) and the Programmed death-1-Programmed death-ligand-1 (PD1-PDL1) axis - which is upregulated in RT - (nivolumab, pembrolizumab)(44,45) result in an ORR between ~20-50% as monotherapy or in combination. All series are small, heterogenous, subject to selection bias and challenging to cross-compare. Unfortunately, the most responses seen in these trials are not durable. Prospective trials with combination strategies using novel-novel combinations (e.g. BTK/mTOR dual inhibition plus immunomodulation(46)) and targeted inhibitors combined with anthracycline-based immunochemotherapy are ongoing(47,48). Which strategy will provide the optimum benefit for patients remains unclear. Future selection of novel agents to be tested could be based on targeting the molecular events driving transformation, in particular impaired DDR.

CAR T-cell Therapy

Chimeric antigen receptor-modified T-cell (CAR-T) therapy directed against CD19-positive B-cell malignancies have shown promising results in patients with relapsed or refractory (R/R) DLBCL, leading to international approval of three anti-CD19 CAR-T products (49–51). Owing in part to concerns related to CLL-induced immune T-cell exhaustion, patients with RT were excluded from the pivotal trials of axicabtagene ciloleucel (Axi-cel) and tisagenlecleucel (Tisagen). As a result, there remains an open question about the benefit RT patients may gain from this approach. Recent, small and heterogeneous (each <10 patients) series(52,53) suggest encouraging efficacy, although toxicities observed in larger R/R DLBCL data sets, including immune effector cell–associated neurotoxicity syndrome and cytokine release syndrome, were seen. Detailed response analysis of the CLL versus RT disease components are currently lacking in available data and are necessary in future CAR-T efficacy evaluation. At the time of writing, CAR T-cells are funded through the Cancer Drugs Fund for DLBCL patients who have failed ≥2 treatment lines. Patients with a background of CLL (i.e. regarded as having RT) are considered on a case-by-case basis via the UK national panel and must fulfil all other eligibility criteria. Specifically, the ≥2 lines of prior treatment must be regarded as standard DLBCL regimens e.g., R-CHOP, R-GemOx.

Recommendations

- **Consider early introduction of palliative care support in heavily pre-treated patients with CLL and co-morbidities who develop DLBCL-RT on a targeted inhibitor (2B)**
- **Consider clinical trial enrolment in patients with relapsed RT (2B).**
- **Consider CAR-T in RT patients who have received ≥2 prior DLBCL standard-of-care treatments including R-CHOP (2C)**

Acknowledgements

The BSH Haemato-Oncology task force members at the time of writing this guideline were Professor Guy Pratt (Chair), Dr Nilima Parry-Jones (Secretary), Dr Simon Stern, Dr Shireen Kassam, Dr Matthew Cullen, Dr Alastair Whiteway, Dr Oliver Miles, Dr Elspeth Payne, Dr Toby A. Eyre. The authors would like to thank them, the

BSH sounding board, and the BSH guidelines committee for their support in preparing this Good Practice Paper.

Declaration of Interests

The BSH paid the expenses incurred during the writing of this Good Practice Paper. All authors have made a declaration of interests to the BSH and Task Force Chairs which may be viewed on request. TAE has received financial reimbursement, advisory board and / or research funding from Roche, Gilead/KITE, Takeda, Janssen, Abbvie, Beigene, Incyte, Loxo Oncology, Secura Bio and AstraZeneca. RW has received financial reimbursement, advisory board and / or research funding from Abbvie, Janssen, AstraZeneca, and Secura Bio. PH has received financial reimbursement, advisory board and / or research funding from Janssen, Abbvie, Roche, AstraZeneca, Sobi, Beigene, Pharmacyclics, and Gilead Sciences. HM has received financial reimbursement, advisory board and / or research funding from Abbvie, Takeda, Roche and AstraZeneca. PEMP has received financial reimbursement, advisory board and / or research funding from Roche, Gilead, Abbvie, Astra Zeneca, Janssen and Novartis. GF has received financial reimbursement, advisory board and / or research funding from Roche, Abbvie, Janssen, AstraZeneca, Karyopharm, BMS, Takeda, and Centessa Pharmaceuticals. The following members of the writing group: JCR, have no conflicts of interest to declare.

Review Process

Members of the writing group will inform the writing group Chair if any new evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be reviewed regularly by the relevant Task Force and the literature search will be re-run every three years to search systematically for any new evidence that may have been missed. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BSH guidelines website (https://b-s-h.org.uk/guidelines/).

Disclaimer

While the advice and information in this Good Practice Paper is believed to be true and accurate at the time of going to press, neither the authors, the BSH nor the publishers accept any legal responsibility for the content of this Good Practice Paper.

Author Contribution

All authors reviewed the literature and contributed to the drafting and editing of this manuscript. TAE co-ordinated, wrote and edited the Good Practice Paper and was responsible for the final submission.

References

1. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France. *World Heal Organ Classification Tumours Haematop Lymphoid Tissue.* 2017.
2. Parikh S a, Rabe KG, Call TG, Zent CS, Habermann TM, Ding W, et al. Diffuse large B-cell lymphoma (Richter syndrome) in patients with chronic lymphocytic leukaemia (CLL): a cohort study of newly diagnosed patients. *Br J Haematol.* 2013;**162**:774–82.
3. Parikh SA, Shanafelt TD. Risk Factors for Richter Syndrome in Chronic Lymphocytic Leukemia. *Curr Hematol Malig Rep.* 2014;**9**:294–9.
4. Al-Sawaf O, Robrecht S, Bahlo J, Fink AM, Cramer P, v Tresckow J, et al. Richter transformation in chronic lymphocytic leukemia (CLL)—a pooled analysis of German CLL Study Group (GCLLSG) front line treatment trials. *Leukemia*. 2021;**35**:169-76.
5. Rossi D, Spina V, Deambrogi C, Rasi S, Laurenti L, Stamatopoulos K, et al. The genetics of Richter syndrome reveals disease heterogeneity and predicts survival after transformation. *Blood*. 2011;**117**:3391–401.
6. Petrackova A, Turcsanyi P, Papajik T, Kriegova E. Revisiting Richter transformation in the era of novel CLL agents. *Blood Rev.* 2021;100824.
7. Soilleux EJ, Wotherspoon A, Eyre TA, Clifford R, Cabes M, Schuh AH. Diagnostic dilemmas of high-grade transformation (Richter's syndrome) of chronic lymphocytic leukaemia: results of the phase II National Cancer Research Institute CHOP-OR clinical trial specialist haemato-pathology central review. *Histopathology*. 2016;**69**:1066–76.
8. Chigrinova E, Rinaldi A, Kwee I, Rossi D, Rancoita PM V, Strefford JC, et al. Two main genetic pathways lead to the transformation of chronic lymphocytic leukemia to Richter syndrome. *Blood*. 2013;**122**:2673–82.
9. Fabbri G, Khiabanian H, Holmes AB, Wang J, Messina M, Mullighan CG, et al. Genetic lesions associated with chronic lymphocytic leukemia transformation to Richter syndrome. *J Exp Med*. 2013;**210**:2273–88.
10. Klintman J, Appleby N, Stamatopoulos B, Ridout K, Eyre TA, Robbe P, et al. Genomic and transcriptomic correlates of Richter transformation in chronic lymphocytic leukemia. Blood. 2021;**137:**2800–16.

11. Rossi D, Spina V, Cerri M, Rasi S, Deambrogi C, De Paoli L, et al. Stereotyped B-cell receptor is an independent risk factor of chronic lymphocytic leukemia transformation to Richter syndrome. *Clin Cancer Res.* 2009;**15**:4415–22.
12. Bockorny B, Codreanu I, Dasanu C a. Hodgkin lymphoma as Richter transformation in chronic lymphocytic leukaemia: a retrospective analysis of world literature. *Br J Haematol*. 2012;**156**:50–66.
13. Bruzzi JF, Macapinlac H, Tsimberidou AM, Truong MT, Keating MJ, Marom EM, et al. Detection of Richter's transformation of chronic lymphocytic leukemia by PET/CT. *J Nucl Med*. 2006;**47**:1267–73.
14. Falchi L, Keating MJ, Marom EM, Truong MT, Schlette EJ, Sargent RL, et al. Correlation between FDG/PET, histology, characteristics, and survival in 332 patients with chronic lymphoid leukemia. *Blood*. 2014;**123**:2783–90.
15. Michallet A-S, Sesques P, Rabe KG, Itti E, Tordot J, Tychyj-Pinel C, et al. An 18F-FDG-PET maximum standardized uptake value > 10 represents a novel valid marker for discerning Richter's Syndrome. *Leuk Lymphoma*. 2016;**57**:1474–7.
16. Mato AR, Wierda WG, Davids MS, Cheson BD, Coutre SE, Choi M, et al. Utility of positron emission tomography-computed tomography in patients with chronic lymphocytic leukemia following B-cell receptor pathway inhibitor therapy. Haematologica. 2019;**104**:2258–64.
17. Wang Y, Tschautscher MA, Rabe KG, Call TG, Leis JF, Kenderian SS, et al. Clinical characteristics and outcomes of Richter transformation: Experience of 204 patients from a single center. *Haematologica*. 2020;**105**:765-73.
18. Tsimberidou A-M, O'Brien S, Khouri I, Giles FJ, Kantarjian HM, Champlin R, et al. Clinical outcomes and prognostic factors in patients with Richter's syndrome treated with chemotherapy or chemoimmunotherapy with or without stem-cell transplantation. *J Clin Oncol.* 2006;**24**:2343–51.
19. Tadmor T, Shvidel L, Bairey O, Goldschmidt N, Ruchlemer R, Fineman R, et al. Richter's transformation to diffuse large B-cell lymphoma: a retrospective study reporting clinical data, outcome, and the benefit of adding rituximab to chemotherapy, from the Israeli CLL Study Group. *Am J Hematol*. 2014;**89**:218-22.
20. Falchi L, Keating MJ, Marom EM, Truong MT, Schlette EJ, Sargent RL, et al. Correlation between FDG/PET, histology, characteristics, and survival in 332 patients with chronic lymphoid leukemia. *Blood*. 2014;**123**:2783–90.

21. Abrisqueta P, Delgado J, Alcoceba M, Oliveira AC, Loscertales J, Hernández-Rivas JA, et al. Clinical outcome and prognostic factors of patients with Richter syndrome: real-world study of the Spanish Chronic Lymphocytic Leukemia Study Group (GELLC). *Br J Haematol*. 2020;**190**:854–63.
22. Eyre TA, Clifford R, Roberts C, Boyle L, Francis A, Schuh A, et al. Single arm NCRI phase II study of CHOP in combination with Ofatumumab in induction and maintenance for patients with newly diagnosed Richter's syndrome. *BMC Cancer*. 2015;**15**:52.
23. Eyre TA, Schuh A. An update for Richter syndrome – new directions and developments. *Br J Haematol*. 2017;**178**:508-20.
24. Dabaja BS, O'Brien SM, Kantarjian HM, Cortes JE, Thomas DA, Albitar M, et al. Fractionated cyclophosphamide, vincristine, liposomal daunorubicin (daunoXome), and dexamethasone (hyperCVXD) regimen in Richter's syndrome. Vol. 42, *Leukemia & lymphoma*. 2001;**42**:329-37.
25. Tsimberidou AM, Kantarjian HM, Cortes J, Thomas DA, Faderl S, Garcia-Manero G, et al. Fractionated cyclophosphamide, vincristine, liposomal daunorubicin, and dexamethasone plus rituximab and granulocyte-macrophage-colony stimulating factor (GM-CSF) alternating with methotrexate and cytarabine plus rituximab and GM-CSF in patients with Rich. *Cancer*. 2003;**97**:1711–20.
26. Tsimberidou AM, Wierda WG, Plunkett W, Kurzrock R, O'Brien S, Wen S, et al. Phase I-II study of oxaliplatin, fludarabine, cytarabine, and rituximab combination therapy in patients with Richter's syndrome or fludarabine-refractory chronic lymphocytic leukemia. *Journal of Clinical Oncology*. 2008;**26**:196-203.
27. Tsimberidou AM, Wierda WG, Wen S, Plunkett W, O'Brien S, Kipps TJ, et al. Phase I-II clinical trial of oxaliplatin, fludarabine, cytarabine, and rituximab therapy in aggressive relapsed/refractory chronic lymphocytic leukemia or Richter syndrome. *Clin Lymphoma Myeloma Leuk*. 2013;**13**:568–74.
28. Tsimberidou AM, O'Brien SM, Cortes JE, Faderl S, Andreeff M, Kantarjian HM, et al. Phase II study of fludarabine, cytarabine (Ara-C), cyclophosphamide, cisplatin and GM-CSF (FACPGM) in patients with Richter's syndrome or refractory lymphoproliferative disorders. *Leukemia & lymphoma*. 2002;**43**:767-72.
29. Eyre TA, Clifford R, Bloor A, Boyle L, Roberts C, Cabes M, et al. NCRI phase II study of CHOP in combination with ofatumumab in induction and maintenance in newly diagnosed Richter syndrome. *Br J Haematol*. 2016;**175**:43-54.

30. Langerbeins P, Busch R, Anheier N, Dürig J, Bergmann M, Goebeler M-E, et al. Poor efficacy and tolerability of R-CHOP in relapsed/refractory chronic lymphocytic leukemia and Richter transformation. *Am J Hematol*. 2014;**89**:E239-43.
31. Rogers KA, Huang Y, Ruppert AS, Salem G, Stephens DM, Heerema NA, et al. A single-institution retrospective cohort study of first-line R-EPOCH chemoimmunotherapy for Richter syndrome demonstrating complex chronic lymphocytic leukaemia karyotype as an adverse prognostic factor. *Br J Haematol.* 2018;**180**:259–66.
32. Davids MS, Huang Y, Rogers KA, Stern R, Brown JR, Thompson PA, et al. Richter's syndrome (RS) in patients with chronic lymphocytic leukemia (CLL) on novel agent therapy. *Journal of Clinical Oncology*. 2017;35(15_suppl):7505.
33. Woyach JA, Ruppert AS, Guinn D, Lehman A, Blachly JS, Lozanski A, et al. BTKC481S-Mediated resistance to ibrutinib in chronic lymphocytic leukemia. *Journal of Clinical Oncology*. 2017;**35**:1437-43.
34. Cwynarski K, van Biezen A, de Wreede L, Stilgenbauer S, Bunjes D, Metzner B, et al. Autologous and allogeneic stem-cell transplantation for transformed chronic lymphocytic leukemia (Richter's syndrome): A retrospective analysis from the chronic lymphocytic leukemia subcommittee of the chronic leukemia working party and lymphoma working. *Journal of Clinical Oncology.* 2012;**30**:2211–7.
35. Parikh SA, Habermann TM, Chaffee KG, Call TG, Ding W, Leis JF, et al. Hodgkin transformation of chronic lymphocytic leukemia: Incidence, outcomes, and comparison to de novo Hodgkin lymphoma. *Am J Hematol*. 2015;**90**:334–8.
36. Tsimberidou A-M, O'Brien S, Kantarjian HM, Koller C, Hagemeister FB, Fayad L, et al. Hodgkin transformation of chronic lymphocytic leukemia. *Cancer*. 2006;**107**:1294–302.
37. Stephens DM, Boucher K, Kander E, Parikh SA, Parry EM, Shadman M, et al. Hodgkin lymphoma arising in patients with chronic lymphocytic leukemia: outcomes from a large multi-center collaboration. *Haematologica* 2020 Oct 5; Online ahead of print.
38. Wang M, Shah NN, Alencar AJ, Gerson JN, Patel MR, Fakhri B, et al. LOXO-305, A Next Generation, Highly Selective, Non-Covalent BTK Inhibitor in Previously Treated Mantle Cell Lymphoma, Waldenström's Macroglobulinemia, and Other Non-Hodgkin Lymphomas: Results from the Phase 1/2 BRUIN Study. *Blood*. 2020;136(Supplement 1):8–10.

39. Hillmen P, Schuh A, Eyre TA, Pagel JM, Brown JR, Ghia P, et al. Acalabrutinib Monotherapy in Patients with Richter Transformation from the Phase 1/2 ACE-CL-001 Clinical Study. *Blood*. 2016;128(22).
40. Tsang M, Shanafelt TD, Call TG, Ding W, Chanan-Khan A, Leis JF, et al. The efficacy of ibrutinib in the treatment of Richter syndrome. *Blood*. 2015;**125**:1676–8.
41. Mato AR, Shah NN, Jurczak W, Cheah CY, Pagel JM, Woyach JA, et al. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. Lancet. 2021;**397**:892–901.
42. Jurczak W, Shah NN, Lamanna N, Eyre TA, Woyach J, Lech-Maranda E, et al. PIRTOBRUTINIB (LOXO-305), A NEXT GENERATION HIGHLY SELECTIVE NON-COVALENT BTK INHIBITOR IN PREVIOUSLY TREATED RICHTER TRANSFORMATION: RESULTS FROM THE PHASE 1/2 BRUIN STUDY. Hematological Oncology. Volume 39. 17 June 2021 https://doi.org/10.1002/hon.41_2880
43. Davids MS, Roberts AW, Seymour JF, Pagel JM, Kahl BS, Wierda WG, et al. Phase i first-in-human study of venetoclax in patients with relapsed or refractory non-hodgkin lymphoma. *Journal of Clinical Oncology*. 2017;**35**:826-33.
44. Jain N, Ferrajoli A, Basu S, Thompson PA, Burger JA, Kadia TM, et al. A Phase II Trial of Nivolumab Combined with Ibrutinib for Patients with Richter Transformation. *Blood*. 2018;132(Suppl 1):296.
45. Ding W, LaPlant BR, Call TG, Parikh SA, Leis JF, He R, et al. Pembrolizumab in patients with CLL and Richter transformation or with relapsed CLL. *Blood*. 2017; **129**:3419-3427.
46. Mato AR, Schuster SJ, Foss FM, Isufi I, Ding W, Brander DM, et al. A Phase Ia/Ib Study Exploring the Synthetic Lethality of the Orally Administered Novel BTK Inhibitor, Dtrmwxhs-12 (DTRM-12), in Combination with Everolimus and Pomalidomide in Patients with Relapsed/Refractory CLL, DLBCL or Other B-Cell Lymphomas. *Blood*. 2019 Nov 13;134(Supplement_1):810.
47. Davids MS, Thompson PA, Rogers KA, Tyekucheva S, Pazienza S, Francoeur K, et al. Initial results of a multicenter phase 2 study of venetoclax in combination with dose-adjusted r-epoch for patients with richter's syndrome (CRC-043). *Hematol Oncol.* 2019;**37**:134-5.
48. Appleby N, Eyre TA, Cabes M, Jackson A, Boucher R, Yates F, et al. The STELLAR trial protocol: A prospective multicentre trial for Richter's syndrome

consisting of a randomised trial investigation CHOP-R with or without acalabrutinib for newly diagnosed RS and a single-arm platform study for evaluation of novel agents in relapsed disease. *BMC Cancer*. 2019;**19**:471.

49. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N Engl J Med*. 2017;**377**:2531-44.

50. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *N Engl J Med*. 2019;**380**:45-56.

51. Abramson JS, Palomba ML, Gordon LI, Lunning MA, Wang M, Arnason J, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet*. 2020;**396**:839–52.

52. Kittai AS, Bond DA, William B, Saad A, Penza S, Efebera Y, et al. Clinical activity of axicabtagene ciloleucel in adult patients with Richter syndrome. *Blood Adv.* 2020;4:4648–52.

53. Benjamini O, Shimoni A, Besser M, Shem-Tov N, Danylesko I, Yerushalmi R, et al. Safety and Efficacy of CD19-CAR T Cells in Richter's Transformation after Targeted Therapy for Chronic Lymphocytic Leukemia. *Blood*. 2020;136(Supplement 1):40.