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Richter Transformation in the Canadian Landscape: Clinical Perspectives and Emerging Trends

Jean-Nicolas Champagne, MD, FRCPC
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Introduction

Over the past decade, the treatment landscape for chronic lymphocytic leukemia (CLL) and its lymphoma counterpart, small lymphocytic lymphoma (SLL), has evolved significantly. The shift from chemoimmunotherapy (CIT) to the increased use of targeted agents, such as Bruton's tyrosine kinase inhibitors (BTKi) and B-cell lymphoma 2 inhibitors (BCL2i), has led to marked improvements in patient outcomes.[1] Despite these advancements, some patients still experience disease transformation to a more aggressive histology known as Richter Transformation (RT), and the clinical outcomes with this histology remain dismal, with median overall survival (OS) typically shorter than one year.[2,3] Therefore, RT represents a significant unmet need for patients with CLL/SLL. This review describes recent advances in the understanding and management of RT within the Canadian landscape, focusing on transformation to diffuse large B-cell lymphoma (DLBCL).

Epidemiology and Clinical Presentation

Originally described by Maurice Richter in 1964,[4] RT is a rare and unpredictable event, occurring in approximately 4% of patients with CLL/SLL, both in clinical trials with CIT[2] and in landmark trials with targeted agents.[5,6] However, a recent observational study reported a lower incidence of RT in patients diagnosed with CLL during the targeted therapy era. This reduction is hypothesized to be due to either decreased exposure to CIT, thereby avoiding the selection of early subclones prone to chemotherapy-induced mutational processes, or a protective effect of targeted agents suppressing the culprit subclone susceptible to cause transformation.[7] RT is suspected in patients with CLL/SLL who experience rapid disease progression and/or new onset constitutional symptoms, often with elevated lactate dehydrogenase (LDH), hypercalcemia, and/or extranodal involvement.[8] These worrisome findings should raise concern for disease transformation to a more aggressive histology and prompt investigations, including a positron emission tomography (PET) scan and a biopsy of the most fluorodeoxyglucose (FDG)-active lesion if amenable. In the CIT era, a threshold standard uptake value (SUV) of 10 has been recognized as both sensitive and specific to properly identify patients with RT.[9] Unfortunately, this threshold may be less reliable in the era of novel agents as it has been shown to have reduced sensitivity and specificity for patients on BTKis.[10]

Pathology and Biology

Most patients with histology-confirmed RT undergo transformation to DLBCL, which requires confirmation of sheets of large B cells by immunohistochemistry for accurate diagnosis. However, a subset may develop the Hodgkin variant of RT or exhibit pro-lymphocytic progression of CLL, previously termed B-cell prolymphocytic leukemia, which is no longer recognized as a separate entity by the most recent update of the World Health Organization Classification of Haematolymphoid Tumours.[11] As the underlying histology of RT will dictate treatment decisions, it is essential to confirm the transformation subtype at diagnosis. While DLBCL is the most common form of RT, patients with prolymphocytic progression are typically treated with CLL-directed therapies, and those with Hodgkin lymphoma are treated accordingly, often with a more favourable prognosis.[12] It is also important to interpret large B cells identified in pathology reports with caution, as cases of

"pseudo-transformation" have been observed following short interruptions of BTKi therapy, with complete resolution upon reinstating therapy, suggesting it does not represent true transformation.[13] In cases where a biopsy is not feasible, patients with a clinical diagnosis of transformation have similarly poor outcomes.[14]

In recent years, improved insights have been gained into the biology of RT, owing in part to new large-scale multi-omic analyses of paired CLL and RT samples, largely of DLBCL histology.[15] RT is now understood to arise through subclonal evolution, with recent studies demonstrating early seeding of the subclone responsible for RT even decades before clinical transformation.[16] Certain genetic features of the underlying CLL have a higher risk of development of RT, including unmutated immunoglobulin status, *TP53* and *CDKN2A/B* loss, activating *NOTCH1* mutations, *MYC* amplification, and certain B cell receptor (BCR) stereotypes, specifically subset #8.[15] In addition, increased programmed cell death protein 1 (PD-1) expression has been observed in clonally related Richter cells, which is generally not observed in *de novo* DLBCL, leading to interest in PD-1 blockade as a therapeutic target.[17,18] Overall, this deeper understanding of the biological mechanisms driving RT is shaping the development of new therapeutic approaches and guiding the design of clinical trials utilizing novel treatment strategies.

Prognosis

RT is associated with a dismal prognosis, and several factors are recognized as influencing patient outcomes. The Richter Prognostic Score, developed in the CIT era, assigns one point for each of the following features: Eastern Cooperative Oncology Group (ECOG) performance status ≥2, LDH >1.5 times the upper limit of normal, thrombocytopenia <100 × 10^9/L, tumour size >5 cm, and ≥2 prior lines of CLL-directed therapy. Patients with low (0-1 factor), intermediate-low (2 factors), intermediate-high (3 factors), and high (4-5 factors) scores have a reported median OS of 13, 11, 4, and 1 months, respectively.[19] As more epidemiologic studies emerge, it is recognized that any prior CLL therapy is a poor prognostic factor, both in the CIT and novel agent era, even without prior chemotherapy exposure.[20]

Another key prognostic factor in RT is the clonal relationship between DLBCL and the underlying CLL. Clonally unrelated DLBCL accounts for approximately 20% of RT and tends to have more favourable outcomes, resembling those with *de novo* DLBCL.[21,22] Clonality can be determined by sequencing the immunoglobulin heavy-chain variable region gene in both the aggressive disease and underlying CLL, with identical sequences indicating clonally-related disease. Given that clonality is a strong predictor of outcomes and testing is becoming increasingly available in Canada, we strongly recommend performing this analysis at the time of RT diagnosis to guide management decisions. Lastly, the presence of a *TP53* mutation not only increases the risk of RT but is also a well-recognized predictor of poor outcomes in RT.[21,23]

Management

The standard treatment for RT remains largely similar to that of de novo DLBCL, involving multi-agent CIT with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Response rates range from 60-70%; however, the duration of response is short, with a reported median progression-free survival (PFS) of only 10 months.[24] Consolidation strategies with reduced intensity allogeneic hematopoietic stem cell transplant are proposed in eligible patients, particularly when the RT is clonally related to the underlying CLL/SLL. While prospective trials are lacking, retrospective studies have demonstrated long-term remissions, with 30% of patients remaining progression-free 3 years following allogeneic hematopoietic stem cell transplant.[25] As a result, transplantation is often considered in first remission.[8] Despite this recommendation, real-world studies demonstrate that transplant is only pursued in a minority of patients. Canadian data from Puckrin *et al*. found that among 99 patients with RT in Alberta, 20% were treated with the intent to undergo a transplant, and of those, 25% successfully underwent allotransplant, representing only 5% of the total RT population.[26] Currently, many alternative treatment strategies are being explored to overcome the poor prognosis of RT, including the incorporation of novel targeted agents into treatment protocols. Selected studies are summarized in **Table 1**.

BTKi and BCL2i have been trialled for RT with demonstrated clinical activity; however, these therapies are not durable as single agents. A phase I/II trial of acalabrutinib monotherapy

Class of Therapy	Design	Previously Treated CLL/SLL	Previously Treated RT	ORR (CR), %	Outcome, Months	Reference
R-CHOP n=15	Phase II	Median prior lines: 2 (range 0-4)	n/a	67 (7)	mPFS, 10 mOS, 24	[24]
Venetoclax Addition						
VR-EPOCH n=27	Phase II	78% Median prior lines: 1 (range 0-7)	7%	62 (50)	mPFS, 10.1 mOS, 19.6	[32]
VR-CHOP n=27	Phase II	100% Median prior lines: 1 (range 1-9)	15%	68 (48)	mPFS, 7.2 mOS, 19.5	[33]
VR-CHOP n=13	Retrospective	69% Median prior lines: 1 (range 0-5)	23%	54 (46)	mPFS, 14.9 mOS, NR	[34]
Bruton Tyrosine Kinase Inhibitors						
Acalabrutinib n=25	Phase I/II	56% Median prior lines: 1 (IQR 0-2)	56%	40 (8)	mPFS, 3.2 mDOR, 6.2	ACE-CL-001[27]
Zanubrutinib n=13	Phase I/II	92% Median prior lines: 1 (range 0-5)	85% Median 1 (range 0-3)	62 (15)	mPFS, 17.3 mOS, 29.3	[29]
Pirtobrutinib n=82	Phase I/II	Median prior lines: 2 (range 0-13)	100%	50 (13)	mDOR, 7.4 mOS, 12.5	BRUIN[31]
PD-1 blockade						
Pembrolizumab n=23* *2 with HL variant	Phase II	n/a	100% Median 3 (range 1-6)	4 (0) *excluding HL variant	mPFS, 1.6 mOS, 3.8	KEYNOTE-170[35]
Novel agent combinations						
Tislelizumab-zanubrutinib n=59* *48 analyzed	Phase II	n/a	21%	58 (19)	mDOR, NR at 13.9; follow-up mPFS, 10 12-month OS: 75%	RT1[36]
Atezolizumab, venetoclax, obinutuzumab n=28	Phase II	71% Median prior lines: 1 (range 0-3)	0%	68 (36)	12-month PFS: 43% 12-month OS: 64%	MOLTO[37]

Class of Therapy	Design	Previously Treated CLL/SLL	Previously Treated RT	ORR (CR), %	Outcome, Months	Reference
Bispecific antibodies CD20xCD3						
Epcoritamab n=10	Phase Ib/II	n/a	40%	60 (50)	n/a	[40]
Glofitamab n=11	Phase II	n/a	Median 3 (range 1-4)	64 (46)	n/a	[41]
Mosunetuzumab n=20	Phase II	n/a	Median 2.5 (range 1-10)	40 (20)	n/a	[42]
Chimeric antigen receptor (CAR)-T cell therapy						
CAR-T (axi, tisa, liso-cel) n=69	Retrospective	Median 4 prior lines of therapy for CLL and/or RT (range 1-15)		63 (46)	mPFS, 4.7 2-year PFS: 29% mDOR, 27.6 mOS, 8.5	[46]

Table 1. Selected clinical trials for the treatment of Richter transformation; *courtesy of Alina S. Gerrie, MD, MPH, FRCPC and Jean-Nicolas Champagne, MD, FRCPC*

Abbreviations: CLL: chronic lymphocytic leukemia; **pts:** patients; **CR:** complete response rate; **HL:** Hodgkin lymphoma; **IQR:** interquartile range; **mDOR:** median duration of response; **mOS:** median overall survival; **mPFS:** median progression-free survival; **n:** number; **n/a:** not available; **NR:** not reached; **ORR:** overall response rate; **R-CHOP:** rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; **RT:** Richter transformation; **VR-EPOCH:** venetoclax, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin.

demonstrated some degree of B cell receptor dependence in RT, with an overall response rate (ORR) of 40%, but a short duration of response (DOR) of only 6.2 months.[27] The addition of acalabrutinib to R-CHOP vs. R-CHOP alone is currently under study in the STELLAR trial, which will be the first reported randomized controlled trial conducted solely in RT.[28] Zanubrutinib has been studied as monotherapy for RT, with an ORR of 62% and favourable PFS and OS of 17 and 29 months, respectively, although only 13 patients were included in the monotherapy arm.[29] As many patients with CLL have previously been treated with covalent BTKi's, there is growing interest in non-covalent BKTis for the treatment of RT, given their effectiveness in settings of BTKi resistance. Both nemtabrutinib and pirtobrutinib are active in RT, the latter demonstrating response rates of approximately 50% and more durable responses up to 7.4 months in a dedicated RT cohort in the phase I/II BRUIN trial.[30,31]

In a multicentre phase II study, venetoclax was added to dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (VR-EPOCH) using an accelerated ramp-up in cycle 2. This combination yielded the highest response rates seen thus far in prospective trials in RT, with an ORR of 62%, and 50% of patients achieving a complete response (CR), resulting in a median PFS and OS of 10.1 and 19.6 months, respectively.[32] Eight patients successfully proceeded to consolidative allogeneic hematopoietic stem cell transplant. However, this increase in effectiveness was observed at the expense of significant toxicity, which primarily consisted of cytopenias and infections. This led to a de-escalation of the CIT backbone in an additional cohort with R-CHOP in combination with venetoclax (VR-CHOP), whereby venetoclax was given in an accelerated inpatient ramp-up in cycle 2 over 5 days, followed by 400 mg daily on days 1-10 of each cycle.[33] Among 25 evaluable patients, the ORR was 68% with a CR rate of 48%, and median PFS and OS of 7.2 and 19.5 months, respectively, as well as decreased toxicity, including less neutropenia, compared

to VR-EPOCH (36% vs. 65%).[33] A multicentre retrospective study of venetoclax-based regimens for RT treatment demonstrated more favourable outcomes of VR-CHOP over venetoclax with BTKi or in combination with more intensive CIT regimens, with all venetoclax-based regimens having improved outcomes compared to historical controls.[34] In this indication, venetoclax currently remains off-label; however, it may be accessible in the context of underlying CLL.

Given the high expression of PD-1 on RT cells, PD-1 blockade has been evaluated in RT, primarily in the relapsed/refractory setting.[17] Unfortunately, this yielded poor response rates when used as monotherapy,[35] but prompted trials using combination regimens, including tislelizumab-zanubrutinib in both first-line and relapsed RT[36] and, more recently, the MOLTO trial assessed atezolizumab, venetoclax, and obinutuzumab in first-line RT.[37] Both trials led to excellent ORRs, with CR rates approaching 20-35%, and durable responses of approximately 1 year. Tislelizumab-zanubrutinib led to a median PFS of 10 months and 12-month OS of 75%, while the MOLTO regimen led to 12-month PFS and OS of 43% and 64%, respectively. Both regimens show promise as first-line treatment options for RT and could potentially replace standard R-CHOP therapy depending on the outcomes with longer-term follow-up. Other emerging treatment options for RT include receptor tyrosine kinase-like orphan receptor 1 (ROR1)-targeting therapy and BTK degraders, which have shown encouraging results in relapsed or refractory B-cell malignancies including CLL/SLL and RT.[38,39]

Finally, T cell-directed therapies such as bispecific T cell engager antibodies[40-42] and anti-CD19 chimeric antigen receptor (CAR)-T cell therapies[43,44] demonstrate promising activity in the relapsed/refractory setting for RT. The data for bispecific antibodies, primarily CD20/CD3-targeting agents, is sparse, with only a small number of patients enrolled and limited follow-up. Nonetheless, response rates appear similar to those reported in large B-cell lymphoma trials, with CR rates of 40% and ongoing responses for those achieving CR. CAR-T response rates and long-term outcomes in CLL have been generally poor compared to large B-cell lymphoma, hypothetically due to T cell dysfunction or a potentially "cold" tumour microenvironment reported in CLL,[45] leading to less enthusiasm for this therapy in this setting than in DLBCL. Moreover, patients with RT were excluded from landmark prospective CAR-T trials for DLBCL. Fortunately, there is emerging real-world data for both axicabtagene ciloleucel (axi-cel) and lisocabtagene maraleucel (liso-cel) demonstrating encouraging results in patients with RT.[43,46,47] For patients who received prior CLL/SLL and/or RT-directed therapy, the ORR ranged from 60 to 75%, with 2-year PFS of approximately 30%. For patients who achieved a CR (~50%), the median duration of response was just over 2 years. High non-relapse mortality remains a concern in this patient population, reported in up to 13% of patients at 12 months, and is mainly due to infections.[46] Given that clonally-unrelated RT shares biological characteristics and prognosis with *de novo* DLBCL, the possibility of offering CAR-T cell therapy as the standard of care for clonally-unrelated DLBCL in the relapsed/refractory setting remains open for consideration.

Based on the encouraging trials listed above and in **Table 1**, a personalized treatment approach is recommended, considering disease characteristics, patient comorbidities, fitness, preferences, as well as cost, healthcare resource utilization, and drug access to guide treatment decisions. Given the relative rarity of RT, most studies are non-randomized, have diverse inclusion criteria, and evaluate different lines of therapy, making cross-trial comparisons challenging. Although randomized controlled trials are underway to compare different first-line treatment strategies, their results will take years to emerge. Taking into account these caveats and focusing on the treatment landscape in Canada, we propose a risk-stratified treatment algorithm illustrated in **Figure 1**. This approach incorporates available and emerging data, including select off-label or unfunded regimens, to address limitations in the current treatment options.

Future Perspectives

The significant unmet need for RT has driven extensive efforts to improve therapy over the past decade. Advances in the understanding of RT biology have provided a strong rationale for integrating novel agents into the therapeutic landscape. However, integrating these agents into high-intensity regimens has also led to increased toxicity. It is important to recognize that patients with RT in the era of novel CLL/SLL therapies are often older and have poorer functional status, limiting their ability to tolerate more intensive therapy.[14] Therefore, clinical trials must refine patient inclusion criteria and therapeutic escalation

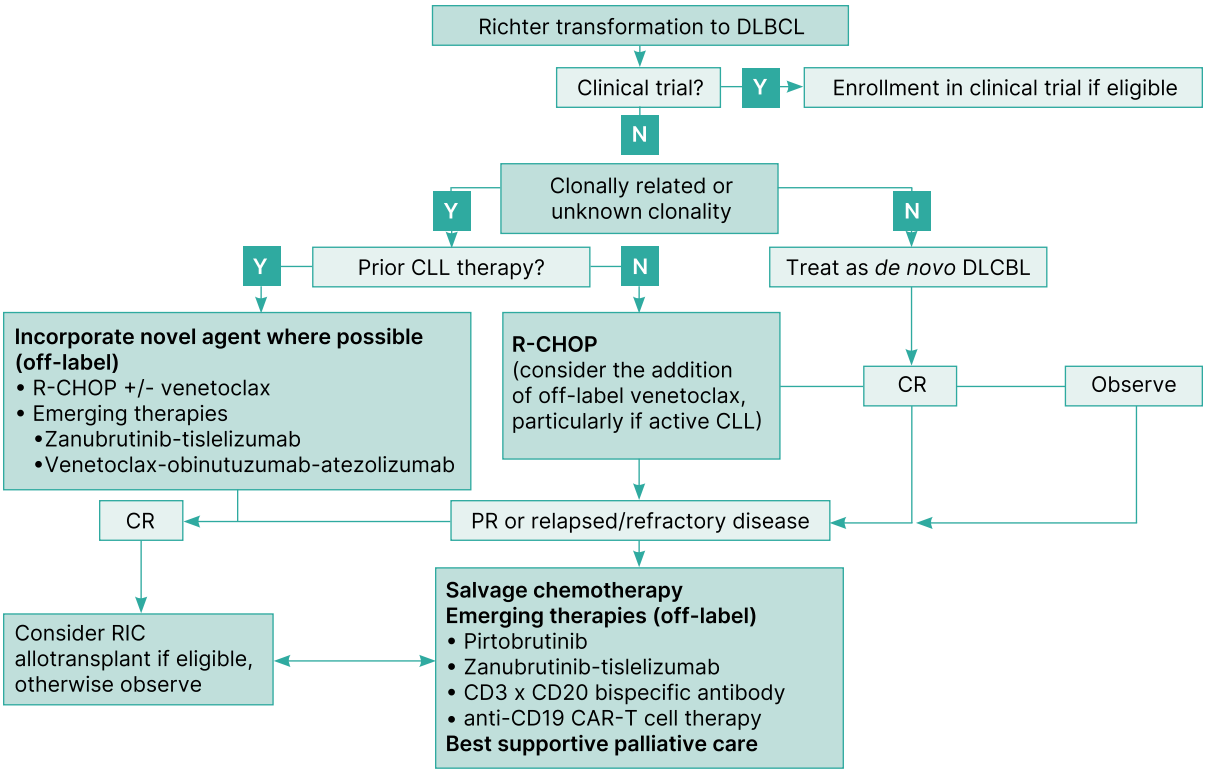

Figure 1. Proposed treatment algorithm for treatment of Richter Transformation (DLBCL) in 2025; *courtesy of Alina S. Gerrie, MD, MPH, FRCPC and Jean-Nicolas Champagne, MD, FRCPC*

Abbreviations: CAR: chimeric antigen receptor; **CLL:** chronic lymphocytic leukemia; **CR:** complete response; **DLBCL:** diffuse large B-cell lymphoma; **PR:** partial response; **R-CHOP:** rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; **RIC:** reduced intensity conditioning.

should be carefully evaluated to balance efficacy with tolerability.

Beyond therapeutics, several key areas warrant further exploration, including early identification of patients at risk of RT and potential preventative strategies to suppress the culprit clone before clinical transformation occurs. As discussed, a subclonal population from which RT arises may be identified decades before true transformation. Identifying high-risk patients could enable closer monitoring for early signs of RT and open the door for CLL-directed interventions aimed at reducing the likelihood of transformation.

Lastly, drug access remains a challenge in the Canadian healthcare system. While new therapies show encouraging results, most are based on single-arm arm studies, with a lack of robust randomized data. In addition, patients with RT are often - perhaps justifiably - excluded from large clinical trials of aggressive B-cell lymphomas, making access to novel therapies challenging. Given RT's devastating impact on the lifetime of a patient with CLL, clinicians in Canada must advocate for improved access to these therapies. It is essential to highlight to regulatory authorities that rare diseases like RT are frequently overlooked in conventional trial designs, yet strong clinical rationale may justify using certain treatments in the absence of large-scale randomized evidence. In addition, we must collaborate to design rational clinical trials for RT treatment within Canada for improved access to novel therapies for our patients.

Conclusion

Despite the challenges that RT presents, advancements in the understanding of its biology and the development of novel therapeutic strategies are driving significant progress in the field. Emerging targeted therapies, improved risk stratification, and ongoing clinical trials are refining treatment paradigms and expanding options for patients. With sustained research

efforts, collaborative clinical trial initiatives, and innovative therapeutic strategies, the future of RT management is evolving toward more personalized and effective treatments, offering greater promise for improved patient outcomes.

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References

1. Muthiah C, Narra R, Atallah E, Juan W, Szabo A, Guru Murthy GS. Evaluating population-level outcomes in Chronic Lymphocytic leukemia in the era of novel therapies using the SEER registry. Leukemia Research. 2024;140:107496.
2. 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(1):169-76.
3. Walker SK, Harrop S, Di Ciaccio P, Lewis KL, Boles R, Tedjaseputra A, et al. Real World Data on the Outcomes of Richter's Transformation of Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma in the Australian Population: An Australasian Lymphoma Alliance Study. Blood. 2021;138:1455.
4. Lortholary P, Boiron M, Ripault P, Levy JP, Manus A, Bernard J. [CHRONIC LYMPHOID LEUKEMIA SECONDARILY ASSOCIATED WITH A MALIGNANT RETICULOPATHY: RICHTER'S SYNDROME]. Nouv Rev Fr Hematol. 1964;4:621-44.
5. Ahn IE, Farooqui MZH, Tian X, Valdez J, Sun C, Soto S, et al. Depth and durability of response to ibrutinib in CLL: 5-year follow-up of a phase 2 study. Blood. 2018;131(21):2357-66.
6. Byrd JC, Hillmen P, Ghia P, Kater AP, Chanan-Khan A, Furman RR, et al. Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial. Journal of Clinical Oncology. 2021;39(31):3441-52.
7. Hampel PJ, Rabe KG, Wang Y, Hwang SR, Kenderian SS, Muchtar E, et al. Incidence of Richter transformation of chronic lymphocytic leukemia/small lymphocytic lymphoma in the targeted therapy era. Leukemia. 2025;39(2):503-7.
8. Ryan CE, Davids MS. Practical Management of Richter Transformation in 2023 and Beyond. American Society of Clinical Oncology Educational Book. 2023(43):e390804.
9. 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. Leukemia & Lymphoma. 2016;57(6):1474-7.
10. 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(11):2258-64.
11. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IBdO, Berti E, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022;36(7):1720-48.
12. Zhu K, Jamroz A, Huang S, Villa D, Freeman CL, Scott DW, et al. Outcomes of Hodgkin variant Richter transformation in chronic lymphocytic leukaemia and small lymphocytic lymphoma in British Columbia. Br J Haematol. 2022;198(4):684-92.
13. Barnea Slonim L, Ma S, Behdad A, Chen Q. Pseudo-Richter transformation of chronic lymphocytic leukaemia/small lymphocytic lymphoma following ibrutinib interruption: a diagnostic pitfall. Br J Haematol. 2020;191(1):e22-e5.
14. Champagne J-N, Huang S, Ramadan R, Venner CP, Ramadan K, Sehn LH, et al. Richter Transformation (RT) in Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL): A Comparison of Two Eras. Blood. 2024;144(Supplement 1):5095-.
15. Parry EM, ten Hacken E, Wu CJ. Richter syndrome: novel insights into the biology of transformation. Blood. 2023;142(1):11-22.
16. Nadeu F, Royo R, Massoni-Badosa R, Playa-Albinyana H, Garcia-Torre B, Duran-Ferrer M, et al. Detection of early seeding of Richter transformation in chronic lymphocytic leukemia. Nature medicine. 2022;28(8):1662-71.
17. He R, Ding W, Viswanatha DS, Chen D, Shi M, Van Dyke D, et al. PD-1 Expression in Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) and Large B-cell Richter Transformation (DLBCL-RT): A Characteristic Feature of DLBCL-RT and Potential Surrogate Marker for Clonal Relatedness. The American Journal of Surgical Pathology. 2018;42(7):843-54.
18. Behdad A, Griffin B, Chen Y-H, Ma S, Kelemen K, Lu X, et al. PD-1 is highly expressed by neoplastic B-cells in Richter transformation. British Journal of Haematology. 2019;185(2):370-3.
19. 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. Journal of Clinical Oncology. 2006;24(15):2343-51.
20. Kittai AS, Huang Y, Miller S, Allan JN, Bhat SA, Bond DA, et al. Outcomes of Patients with Richter Transformation without Prior Chemoimmunotherapy for CLL/SLL: An International Multicenter Retrospective Study. Blood. 2023;142(Supplement 1):497-.
21. 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(12):3391-401.
22. Mao Z, Quintanilla-Martinez L, Raffeld M, Richter M, Krugmann J, Burek C, et al. IgVH Mutational Status and Clonality Analysis of Richter's Transformation: Diffuse Large B-cell Lymphoma and Hodgkin Lymphoma in

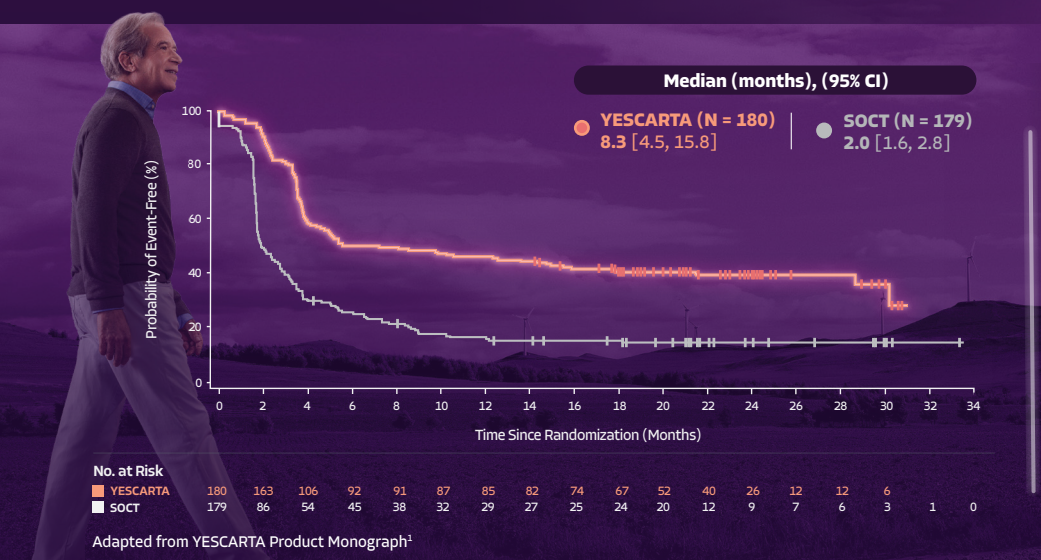
Association With B-cell Chronic Lymphocytic Leukemia (B-CLL) Represent 2 Different Pathways of Disease Evolution. The American Journal of Surgical Pathology. 2007;31(10):1605-14.
23. Negara I, Tomuleasa C, Buruiana S, Efremov DG. Molecular Subtypes and the Role of TP53 in Diffuse Large B-Cell Lymphoma and Richter Syndrome. Cancers. 2024;16(12):2170.
24. 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. American Journal of Hematology. 2014;89(12):E239-E43.
25. Guièze R, Eikema DJ, Koster L, Schetelig J, Sengeloev H, Passweg J, et al. Allogeneic hematopoietic stem-cell transplantation for patients with Richter transformation: a retrospective study on behalf of the Chronic Malignancies Working Party of the EBMT. Bone Marrow Transplant. 2024;59(7):950-6.
26. Puckrin R, Owen C, Fontaine A, Peters A, Stewart D, Shafey M. Allogeneic hematopoietic cell transplantation for Richter transformation of chronic lymphocytic leukemia: an intention-to-transplant analysis. Bone Marrow Transplantation. 2023;58(7):817-9.
27. Eyre TA, Schuh A, Wierda WG, Brown JR, Ghia P, Pagel JM, et al. Acalabrutinib monotherapy for treatment of chronic lymphocytic leukaemia (ACE-CL-001): analysis of the Richter transformation cohort of an open-label, single-arm, phase 1-2 study. Lancet Haematol. 2021;8(12):e912-e21.
28. 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(1):471.
29. Tam C, Munoz J, Cull G, Opat S, Allewelt H, Zhang X, et al. Zanubrutinib, Alone and in Combination With Tislelizumab, for the Treatment of Richter Transformation of Chronic Lymphocytic Leukemia. Hemasphere. 2023;7(4):e870.
30. Woyach J, Stephens DM, Flinn IW, Bhat SA, Savage RE, Chai F, et al. Final results of phase 1, dose escalation study evaluating ARQ 531 in patients with relapsed or refractory B-cell lymphoid malignancies. Blood. 2019;134:4298.
31. Wierda WG, Shah NN, Cheah CY, Lewis D, Hoffmann MS, Coombs CC, et al. Pirtobrutinib, a highly selective, non-covalent (reversible) BTK inhibitor in patients with B-cell malignancies: analysis of the Richter transformation subgroup from the multicentre, open-label, phase 1/2 BRUIN study. Lancet Haematol. 2024;11(9):e682-e92.
32. Davids MS, Rogers KA, Tyekucheva S, Wang Z, Pazienza S, Renner SK, et al. Venetoclax plus dose-adjusted R-EPOCH for Richter syndrome. Blood. 2022;139(5):686-9.
33. Davids MS, Rogers KA, Jain N, Tyekucheva S, Ren Y, Carey C, et al. Initial results of a multicenter phase 2 study of venetoclax in combination with R-CHOP (VR-CHOP) for patients with Richter Syndrome. Hematol Oncol. 2023;41(S2):466-8.
34. Hampel PJ, Swaminathan M, Rogers KA, Parry EM, Burger JA, Davids MS, et al. A multicenter study of venetoclax-based treatment for patients with Richter transformation of chronic lymphocytic leukemia. Blood Adv. 2024;8(10):2342-50.
35. Armand P, Murawski N, Molin D, Zain J, Eichhorst B, Gulbas Z, et al. Pembrolizumab in relapsed or refractory Richter syndrome. Br j haematol. 2020;190(2):e117-e20.
36. Al-Sawaf O, Ligtvoet R, Robrecht S, Stumpf J, Fink A-M, Tausch E, et al. Tislelizumab plus zanubrutinib for Richter transformation: the phase 2 RT1 trial. Nat Med. 2024;30(1):240-8.
37. Tedeschi A, Frustaci AM, Condoluci A, Coscia M, Chiarle R, Zinzani PL, et al. Atezolizumab, venetoclax, and obinutuzumab combination in Richter transformation diffuse large B-cell lymphoma (MOLTO): a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2024;25(10):1298-309.
38. Thompson MC, Parrondo RD, Frustaci AM, Allan JN, Ghia P, Mocanu I, et al. Preliminary Efficacy and Safety of the Bruton Tyrosine Kinase Degrader BGB-16673 in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Results from the Phase 1 CaDAnCe-101 Study. Blood. 2024;144(Supplement 1):885-.
39. Spurgeon SE, Mei M, Barr PM, Barrientos JC, de Vos S, Furman RR, et al. Waveline-001: Updated Results from a Phase 1 Dose Escalation and Cohort Expansion Study of Zilovertamab Vedotin (MK-2140) in Non-Hodgkin Lymphoma. Blood. 2022;140(Supplement 1):6640-1.
40. Kater AP, Ye JC, Sandoval-Sus J, Bellido M, Christensen JH, Mato AR, et al. Subcutaneous Epcoritamab in Patients with Richter's Syndrome: Early Results from Phase 1b/2 Trial (EPCORE CLL-1). Blood. 2022;140(Supplement 1):850-1.
41. Carlo-Stella C, Hutchings M, Offner F, Mulvihill E, Relf J, Byrne B, et al. Glofitamab monotherapy induces durable complete remissions and has a manageable safety profile in patients with Richter's transformation. Hematol Oncol. 2023;41(S2):63-5.
42. Cheah CY, Assouline S, Baker R, Bartlett NL, El-Sharkawi D, Giri P, et al. Mosunetuzumab Monotherapy Demonstrates Activity and a Manageable Safety Profile in Patients with Relapsed or Refractory Richter's Transformation. Blood. 2023;142(Supplement 1):614-.
43. Winter AM, Bharadwaj S, Herrera AF, Iragavarapu C, Mirza S, Palomba ML, et al. Real-world outcomes of lisocabtagene maraleucel (liso-cel) in patients (pt) with Richter transformation (RT) from the Center for International Blood and Marrow Transplant Research (CIBMTR). J Clin Oncol. 2024;42(16_suppl):7010-.
44. 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 Advances. 2020;4(19):4648-52.
45. Todorovic Z, Todorovic D, Markovic V, Ladjevac N, Zdravkovic N, Djurdjevic P, et al. CAR T Cell Therapy for Chronic Lymphocytic Leukemia: Successes and Shortcomings. Curr Oncol. 2022;29(5):3647-57.
46. Kittai AS, Bond D, Huang Y, Bhat SA, Blyth E, Byrd JC, et al. Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy for Richter Transformation: An International, Multicenter, Retrospective Study. J Clin Oncol. 2024;42(17):2071-9.
47. Nadiminti KV, Ahn KW, Patel DJ, Lian Q, Pasquini MC, Hamadani M, et al. CD19-Directed CAR-T Therapy for Richter Transformation: A CIBMTR Analysis. Transplantation and Cellular Therapy. 2025;31(2):S207-S8.

In an open-label study in adult patients with primary refractory or relapsed within 12 months large B-cell lymphoma (R/R LBCL) after 1 line of chemoimmunotherapy*

Pr YESCARTA® (axicabtagene ciloleucel) Suspension for IV infusion

YESCARTA DEMONSTRATED statistically significant improvement in EVENT-FREE SURVIVAL (EFS†) vs STANDARD OF CARE TREATMENT (SOCT)‡

(HR: 0.40 [95% CI: 0.31, 0.51; p<0.0001], primary endpoint[1,2§])



Adapted from YESCARTA Product Monograph[1]

Demonstrated significantly SUPERIOR OVERALL SURVIVAL (OS) vs SOCT (HR: 0.73 [95% CI: 0.54, 0.98; p=0.017§‖], secondary endpoint)[1]

55% OF YESCARTA PATIENTS WERE ALIVE AT 4 YEARS

vs

46% OF PATIENTS RECEIVING SOCT[1]

YESCARTA® (axicabtagene ciloleucel) is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) or high-grade B-cell lymphoma (HGBL) that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy.

#1 DELIVERED CAR T THERAPY IN CANADA TO TREATMENT CENTRES[4¶]

Scan the code to refer your patients to the nearest authorized treatment centre

Most Serious Warnings and Precautions:

Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving YESCARTA. Delay YESCARTA treatment if a patient has active uncontrolled infection or inflammatory disorders, active graft-versus-host disease (GVHD) or unresolved serious adverse reactions from prior therapies. Monitor for CRS after treatment with YESCARTA. Provide supportive care, tocilizumab, or tocilizumab and corticosteroids, as needed.

Neurologic adverse reactions, including fatal or life-threatening reactions, occurred in patients receiving YESCARTA, including concurrently with CRS or independently of CRS. Monitor for neurologic adverse reactions after treatment with YESCARTA. Provide supportive care, tocilizumab (if with concurrent CRS), or corticosteroids, as needed.

YESCARTA should be administered by experienced health professionals at specialized treatment centres.

Other Relevant Warnings and Precautions:

- YESCARTA should be administered at a specialized healthcare/clinical facility with personnel trained in handling and administering YESCARTA and in the management of patients treated with YESCARTA, including monitoring and managing CRS and neurotoxicity. The facility should have immediate access to appropriate emergency equipment and intensive care unit.
- For autologous use only. Under no circumstances should it be administered to other patients.
- Before infusion, the patient's identity must match the patient identifiers on the YESCARTA cassette.
- Safety and efficacy have not been established in patients with central nervous system (CNS) lymphoma.
- Patients should not donate blood, organs, tissues and cells for transplantation.
- Patients should receive life-long monitoring for secondary malignancies.
- Driving, operating machinery, and other hazardous occupations or activities should be avoided in the 8 weeks following YESCARTA infusion.
- Risk of tumour lysis syndrome (TLS).
- Risk of B-cell aplasia and hypogammaglobulinemia.
- Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during YESCARTA treatment, and until immune recovery following treatment with YESCARTA.
- Allergic reactions may occur with YESCARTA infusion. Serious hypersensitivity reactions including anaphylaxis, may be due to dimethyl sulfoxide (DMSO) or residual gentamicin in YESCARTA.
- Risk of prolonged cytopenias.
- Risk of severe or life-threatening infections. Should not be administered to patients with clinically significant active infections.
- Risk of febrile neutropenia.
- Risk of life-threatening and fatal opportunistic infections including disseminated fungal infections and viral reactivation in immunosuppressed patients.
- Risk of reactivation of hepatitis B virus (HBV), human polyomavirus 2 (JC virus; the cause of progressive multifocal leukoencephalopathy [PML]) and human herpesvirus 6 (HHV-6).
- Patients must be monitored at least daily for 7 days at the specialized healthcare/clinical facility following infusion for signs and symptoms of CRS and neurologic adverse reactions.
- CRS and neurologic adverse reactions can occur more than 7 days after the infusion. Instruct patients to remain within proximity of the specialized healthcare/clinical facility for at least 4 weeks following infusion. Educate patients and their caregivers for signs and symptoms of CRS and neurologic adverse reactions. Advise patients and their caregivers to immediately contact the designated health professional if CRS or neurologic adverse reactions are suspected.
- YESCARTA is not recommended for women who are pregnant, and pregnancy after YESCARTA infusion should be discussed with the treating physician. Sexually active females of reproductive potential should have a pregnancy test prior to starting treatment and should use effective contraception (methods that result in less than 1% pregnancy rates) after YESCARTA administration. Sexually active males who have received YESCARTA should use a condom during intercourse with females of reproductive potential or pregnant women. See the Product Monographs for fludarabine and cyclophosphamide for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy. There are insufficient data to provide a recommendation concerning duration of contraception following treatment with YESCARTA.
- Precaution should be exercised for breastfeeding.
- No data in patients < 18 years old are available to Health Canada: therefore, Health Canada has not authorized an indication for pediatric use.
- No dose adjustment required in patients ≥ 65 years of age.

For More Information:

Please consult the product monograph at www.gilead.ca/pdf/ca/YESCARTA_pm_english.pdf for important information relating to adverse reactions, interactions, and dosing which has not been discussed in this piece. The product monograph is also available by calling Gilead Sciences Canada, Inc. at 1-866-207-4267.

CAR T = chimeric antigen receptor T cell therapy; CI = confidence interval; HR = hazard ratio.

* Multicentre, open-label trial comparing YESCARTA (N = 180) to SOCT (N = 179) in adults with LBCL (predominantly diffuse large B-cell lymphoma [DLBCL] or high-grade B-cell lymphoma [HGBL]) that was refractory to, or relapsed within 12 months following first-line rituximab and anthracycline-based chemotherapy. Refractory disease was defined as a lack of complete response to first-line therapy (rituximab and anthracycline-based chemotherapy). Relapsed disease was defined as biopsy-proven disease relapse occurring within 12 months following first-line therapy. Following lymphodepleting chemotherapy, YESCARTA was administered as a single IV infusion at a target dose of 2 x 10^6 CAR-positive viable T cells/kg (max. dose 2 x 10^8 cells).

† Event-free survival was defined as the time from randomization to the earliest date of disease progression according to the Lugano classification, the commencement of new therapy for lymphoma, death from any cause, or best response of stable disease up to and including the response on day 150 assessment after randomization according to an independent review committee.

‡ SOCT was defined as two or three cycles of investigator-selected, protocol-specified chemoimmunotherapy followed by high-dose chemotherapy and autologous stem-cell transplantation (HDT-ASCT) in patients who had a complete or partial response.

§ P-values obtained from the stratified log-rank test or the stratified CMH test were one-sided. The stratification factors were response to first-line therapy (primary refractory, vs relapse within 6 months of first-line therapy vs relapse within > 6 but ≤ 12 months) and second-line age-adjusted International Prognostic Index (0 to 1 vs 2 to 3).

‖ P-value was compared with the one-sided efficacy boundary 0.0249 for the primary OS analysis.

¶ Comparative clinical significance is unknown.

References: 1. YESCARTA® Product Monograph. Gilead Sciences Canada, Inc. May 17, 2024. **2.** Locke FL, et al. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. *N Engl J Med* 2022;386:640-54. **3.** Westin JR, et al. Survival with axicabtagene ciloleucel in large B-cell lymphoma. *N Engl J Med* 2023;389:148-57. **4.** Data on File. IQVIA.

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Dr Chathuri Abeyakoon has recently completed a clinical research fellowship in Lymphoma, Myeloma and Autologous Stem Cell Transplantation at the Princess Margaret Cancer Centre. Prior to her Fellowship in Canada, she completed Hematology training in Australia and is a Fellow of both the Royal Australasian College of Physicians and Royal College of Pathologists Australasia. She has now returned to Melbourne, Australia to continue her career as a Clinician Investigator. Her interest lies in optimizing treatment outcomes with novel and targeted agents in aggressive lymphomas.

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Central Nervous System Relapse of Aggressive B-cell Lymphoma: Insights Into Current Treatment Approaches

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Introduction

Central nervous system (CNS) relapse of lymphoma, also known as relapse with secondary CNS lymphoma (SCNSL), is a rare but devastating complication that confers poor survival outcomes and treatment decision challenges. Diffuse large B-cell lymphoma (DLBCL) accounts for most cases with an incidence of 4-6% and commonly occurs within 1 year of diagnosis (median of 5 months). However, CNS relapse is also seen in the context of other aggressive B-cell lymphoma histological subtypes, such as Burkitt lymphoma and mantle cell lymphoma, with an incidence of 20% and 4%, respectively.[1] Identifying patients at risk of CNS relapse has been limited by the low sensitivity of diagnostic variables and scores. More recently, the use of CNS prophylaxis with high-dose methotrexate (HD-MTX) in DLBCL has also been challenged.[2] CNS involvement can be parenchymal (40-50%), leptomeningeal (30-40%), or both (10-15%).[3] Clinical presentation can occur with a range of neurological symptoms depending on the location of CNS involvement (e.g. motor deficits, symptoms related to increased intracranial pressure, cognitive/personality changes, visual disturbance) together with possible systemic symptoms in the presence of concurrent systemic disease involvement. For ease of making treatment decisions and understanding various approaches to management, SCNSL can be divided into 3 distinct clinical scenarios: 1) treatment-naïve-SCNSL, in which CNS involvement of lymphoma occurs concurrently with systemic disease at diagnosis; 2) relapsed isolated-SCNSL, in which relapse of previously treated systemic disease occurs isolated to the CNS; and 3) relapsed concurrent-SCNSL, in which relapse of previously treated systemic disease occurs both within the CNS and systemically.

This review will focus on treatment approaches for SCNSL in the relapsed setting, both relapsed isolated-SCNSL and relapsed concurrent-SCNSL, confined to DLBCL.

Treatment Goals and Historical Benchmarks

Treatment of SCNSL should address both the CNS and systemic components, as patients usually have concomitant systemic disease or develop systemic disease shortly thereafter. Given its rarity and frequent exclusion of patients in broader clinical trials, randomized Phase 3 data are unavailable. Only Phase 2 prospective single-arm studies, retrospective data, and expert opinion pieces are available to guide treatment decisions. Poor penetration of the blood-brain barrier by chemoimmunotherapy, poor performance status, and impaired neurocognitive function add complexity to the management of patients, resulting in inferior survival outcomes. A benchmark to compare current treatment outcomes to in the rituximab era in SCNSL is an international retrospective analysis, which predominantly included patients with relapsed SCNSL. This study reported a median overall survival (OS) of 3.9 months (95% confidence interval [CI]: 3.3-4.9) and a 2-year OS of 20% (95% CI: 15-25) for the entire study population. Even for patients treated with intensive regimens, the median OS was only 7.5 months (95% CI: 6-10.3).[4]

Prospective Trials for Patients With SCNSL Involvement in the context of DLBCL

Four prospective single-arm Phase 2 trials have been conducted to date in the context of SCNSL: NCT01148173, SCNSL1, HOVON 80 and IELSG42 (MARIETTA)[5-8] **(Table 1)**. The IELSG42 trial, the largest and most recently published trial of the 4, included 75 patients with treatment naive-SCNSL, relapsed isolated-SCNSL, and relapsed concurrent-SCNSL up to the age of 70 years (median 58 years, range 23-70) with an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) <3. Patients received 3 cycles of MATRix (rituximab, methotrexate, cytarabine, thiotepa) followed by 3 cycles of R-ICE (rituximab, ifosfamide, carboplatin, etoposide) with intrathecal chemotherapy in each cycle. Patients with stable or progressive disease (SD/PD) during MATRix were switched to R-ICE, and those having SD/PD on R-ICE were transitioned to receive whole-

	NCT01148173 Korfel *et al.* 2013[5]	SCNSL1 Ferreri *et al.* 2015[6]	HOVON Doorduijn *et al.* 2016[7]	IELSG42 Ferreri *et al.* 2021[8]
Countries	**Germany**	**Italy**	**Netherlands**	**Italy, United Kingdom, Netherlands, Sweden**
N	30	38	36	75
Median age, years (range)	58 (29-65)	59 (36-70)	57 (23-65)	58 (23-70)
ECOG PS >2 (%)	0 (0%)	6 (16%)	0 (0%)	8 (11%)
Disease at trial registration **TN-SCNSL** **RI-SCNSL** **RC-SCNSL**	 0 (0%) 24 (80%) 6 (20%)	 16 (42%) 15 (39%) 7 (18%)	 0 (0%) 16 (44%) 20 (56%)	 32 (43%) 15 (20%) 28 (37%)
Induction treatment → consolidation (% completed)	HD-MTX/IFO followed by HD-ARAC/TT (with IT) → ASCT (80%)	R-MTX-ARAC followed by R-HDS (with IT) → ASCT (53%)	R-DHAP-HDMTX (with IT rituximab) → ASCT (42%)	MATRix/R-ICE (with IT) → ASCT (49%)
Pre-ASCT ORR (CR)	67% (23%)	63% (61%)	53% (22%)	65% (39%)
PFS (transplanted)	2-year 49% (58%)	5-year 40% (63%)	2-year 14%	2-year 46% (83%)
OS (transplanted)	2-year 63% (68%)	5-year 41% (68%)	2-year 22%	2-year 46% (83%)
TRM	3%	10%	8%	5%

Table 1. Prospective Phase 2 clinical trials for SCNSL; *courtesy of Anca Prica, MD, MSc and Chathuri Abeyakoon, MBBS*

Abbreviations: ARAC/TT: cytarabine, thiotepa, high-dose methotrexate; **ASCT:** autologous stem cell transplantation; **CR:** complete remission; **ECOG PS:** Eastern Cooperative Oncology Group Performance Status; **HDMTX/IFO:** methotrexate, ifosfamide; **MATRix/RICE:** methotrexate, cytarabine, thiotepa, rituximab/rituximab, ifosfamide, cisplatin, etoposide; **IT:** intra-thecal (methotrexate, cytarabine, hydrocortisone or liposomal cytarabine); **N:** number; **ORR:** overall response rate; **OS:** overall survival; **PFS:** progression-free survival; **RC-SCNSL:** relapsed concomitant-secondary central nervous system lymphoma; **R-DHAP-HDMTX:** rituximab, dexamethasone, cisplatin, cytarabine, high-dose methotrexate; **R-HDS:** rituximab, cyclophosphamide, cytarabine, etoposide; **RI-SCNSL:** relapsed isolated-secondary central nervous system lymphoma; **R-MTX-ARAC:** rituximab, high-dose methotrexate, cytarabine; **TN-SCNSL:** treatment-naïve secondary central nervous system lymphoma; **TRM:** treatment-related mortality.

brain radiotherapy (WBRT). Patients achieving a complete or partial response (CR/PR) were consolidated with a carmustine/thiotepa-based (BCNU/TT) autologous stem cell transplanted (ASCT). The most commonly involved CNS site was the brain parenchyma (n = 43, 45%), followed by involvement of parenchyma and cerebrospinal fluid (CSF) or meninges (n = 13, 17%), parenchyma and eyes (n = 10, 13%), and CSF or meninges (n = 8, 11%). After a median follow-up of 29 months, 1-year progression-free survival (PFS) was 58%, and 2-year OS was 46%. Only approximately 50% of patients demonstrated chemosensitivity and were able to eventually undergo the intended ASCT, which resulted in a superior 1-year PFS of 100% and a 2-year OS of 83%. Relapses on this MARIETTA chemotherapy approach were noted to be very aggressive, with a median survival post-relapse of only 1 month. The need for WBRT on trial was 17%, and none of the 4 patients who received WBRT to control PD responded, and all died within 9 months. A CR to 2 courses of MATRix was a strong favourable prognostic factor in multivariable analysis. Regarding safety, 71% of the planned MATRix-RICE courses were delivered, with high rates of grade 3-4 hematological toxicity (35-60%), 30% grade 3-4 infections, and 5% treatment-related mortality.[8]

The other 3 aforementioned prospective Phase 2 trials comprised smaller cohorts of patients (n = 30-38) and included heterogeneous patient populations with variation in upper age limit, ECOG PS, and intensive induction regimens, as shown in **Table 1**, making comparisons between trials difficult. However, overall, only about 50% of patients were able to proceed to the intended consolidation ASCT.[5-7]

Retrospective Evidence for Treatment Regimens in SCNSL in DLBCL

MR-CHOP-like regimens (high dose methotrexate [HD-MTX], rituximab, cyclophosphamide, vincristine, doxorubicin, prednisolone) are also frequently used based on small retrospective studies that demonstrated overall response rates (ORR) of 66-88% and CR rates of 57-68%, with ASCT consolidation commonly associated with improved survival outcomes.[9-12] A collaborative retrospective study of the Australasian Lymphoma Alliance identified survival differences based on treatment, with a conservative treatment group (treated with HD-MTX and systemic therapy) having a 2-year PFS of 28% versus 50% in an intensive treatment group (treated with both HD-MTX and cytarabine with systemic chemotherapy) (p=0.027).[12]

Role of Consolidation ASCT in SCNSL

The efficacy and favourable benefits of ASCT consolidation in first remission, and the reduced long-term neurocognitive effects compared with WBRT, are well established in the management of primary CNS lymphoma (PCNSL).[13] Furthermore, thiotepa-based conditioning has superseded non-thiotepa-based regimens due to superior bioavailability and reduced relapse rates in PCNSL.[13-15] Extrapolating from PCNSL evidence, thiotepa-based conditioning is increasingly incorporated into the management of SCNSL, demonstrating favourable outcomes. In the Phase 2 trials described above **(Table 1)**, those able to proceed with ASCT appear to have more durable responses than responses in the entire study cohort in 3 out of 4 prospective trials. The 2-year OS was 83% versus 46% in the IELSG42 trial, and 68% versus 63% in the NCT01148173 trial, while the 5-year OS was 68% + 11% versus 41% + 8% in the SCNSL1 trial.[5,6,8] In contrast, the 2-year PFS and OS were notably inferior in the HOVON 80 trial at 14% and 22%, which was postulated to be at least partly due to the absence of incorporating thiotepa to the ASCT conditioning regimen, further highlighting its importance.[7] However, in the absence of randomized controlled trials, small patient numbers, patient selection bias, differences in disease biology, and other unknown confounders likely affect interpretation results in favour of ASCT, highlighting favourable disease biology and patient characteristics possibly driving improved outcomes.

The other evidence in support of ASCT comes from retrospective data with a 3-year OS of approximately 40-60%.[16-19] A study assessing outcomes specifically with thiotepa-based conditioning included 134 patients (treatment naive-SCNSL 39%, relapsed isolated-SCNSL 46%, relapsed concurrent-SCNSL 15%) and 17 patients between 71-77 years of age. With a median follow-up of 47 months, the 3-year OS and PFS rates were 71.6% and 61.1%, respectively. The majority (79%) of relapses occurred within 2 years of ASCT. Patients with a PR on pre-ASCT assessment had similar outcomes to those who had achieved a CR. Multivariable analysis of relapsed concurrent-SCNSL showed that age and 2 or more prior lines of therapy were significant

	PUBLICATIONS		ABSTRACTS					
	Alsouqi *et al.*[28] 2024 US	Epperla *et al.*[29] 2023 US	Ahmed *et al.*[30] 2024 CIBMTR	Alderuccio *et al.*[20] 2024 US, UK, Canada	Hashimi *et al.*[31] 2024 CIBMTR	Luttwak *et al.*[32] 2024 US & Israel	Saidy *et al.*[33] 2023 EBMT	Ahmed *et al.*[34] 2023 US
N	113 (86 pts with active CNS disease)	61	36	105 (compared with n=167 that received TT-ASCT	144 (39 pts with active CNS disease)	49 (n=44 SCNSL, n=5 PCNSL)	88 (n=78 SCNSL, n=10 PCNSL)	90 (68 pts with active CNS disease)
Median age, years (range)	62 (51-70)	56 (18-62)	62 (30-83)	62 (52-70)	61 (23-83)	61 (49-71)	63 (32-80)	61.5 (28-82)
CAR-T cell product	Axi-cel 39%, Tisa-cel 20%, Liso-cel 41%	Axi-cel 49%, Tisa-cel 31%, Liso-cel 18%	Liso-cel 100%	Not reported	Axi-cel 60%, Tisa-cel 33%, Liso-cel 6%	Axi-cel 31%, Tisa-cel 29%, Liso-cel 24% POC CAR-T 16%	Axi-cel 56% Tisa-cel 44%	Axi-cel 42%, Tisa-cel 41%, Liso-cel 14%
CNS involvement location	Paren n=35, lepto n=33, both n=18	Not reported	Paren n=30, lepto n=6	Paren 41%, lepto 33.3%, both 15.2%	Paren n=89, lepto n=40, both n=15	Paren n=22, lepto n=18, both n=8	Not reported	Paren n=24, lepto n=30, both n=17 none n=22
Bridging therapy	RT n=19, systemic therapy with BTKi n=24	Not reported	81%	Not reported	56% (systemic therapy 48%, IT/intra-ocular 5%, RT 3%)	RT n=13, HD-MTX n=15, IT n=12, BTKi n=10	Not reported	31%
CRS (>G3)	With CNS disease vs. without CNS disease 73% (5%) vs. 82% (0%)	70% (16%)	64% (8%)	Not reported	75% (12%)	45% (>G3)	Not reported	79% (3.3%)
ICANS (>G3)	With CNS disease vs. without CNS disease 57% (51%) vs. 52% (43%)	57% (44%)	47% (22%)	Not reported	35% (24%)	41% (>G3)	Not reported	61% (28.8%)
Median follow-up	10.7 months	14.1 months	12 months	13.7 months	24 months	11 months	20.3 months	6 months

	PUBLICATIONS		ABSTRACTS					
	Alsouqi *et al.*[28] 2024 US	**Epperla *et al.*[29] 2023 US**	**Ahmed *et al.*[30] 2024 CIBMTR**	**Alderuccio *et al.*[20] 2024 US, UK, Canada**	**Hashimi *et al.*[31] 2024 CIBMTR**	**Luttwak *et al.*[32] 2024 US & Israel**	**Saidy *et al.*[33] 2023 EBMT**	**Ahmed *et al.*[34] 2023 US**
ORR (CR)	With CNS disease vs. without CNS disease 77% (56%) vs. 72% (68%)	68% (57%)	64% (53%)	Not reported	Not reported	65% (58%)	Not reported	75% (62%) at 1 month within CNS 80% (70%) at 1 month for systemic disease
PFS	12-month with CNS disease vs. without CNS disease 17% vs. 53%	6-month 35% (median 3.3 months)	1-year 36%	Median CAR-T 9.2 months vs. TT-ASCT 34.1 months	2-year 21%	1-year 34% (median lepto 4.7 months vs. paren 19 months)	2-year 32%	2-year 16%
OS	12-month with CNS disease vs. without CNS disease 39% vs. 77%	6-month 59% (median 7.6 months)	1-year 39%	Median CAR-T 21.9 months vs. TT-ASCT 105.3 months	2-year 34%	1-year 57% (median lepto 8.6 months vs paren 19 months)	2-year 47%	2-year 31%

Table 2. Reported retrospective cohorts (including >20 patients) of CAR-T cell therapy in SCNSL; *courtesy of Anca Prica, MD, MSc and Chathuri Abeyakoon, MBBS*

Abbreviations: BTKi: Bruton's tyrosine kinase inhibitor; **CAR-T cell:** chimeric antigen receptor T cell; **CIBMTR:** Centre for Blood and Marrow Transplant Research; **CNS:** central nervous system; **CR:** complete remission; **CRS:** cytokine release syndrome; **EBMT:** European Group for Blood and Marrow Transplantation; **HD-MTX:** high-dose methotrexate; **ICANS:** immune effector cell therapy associated neurotoxicity; **IT:** intra-thecal; **lepto:** leptomeningeal; **N:** number; **ORR:** overall response rate; **OS:** overall survival; **paren:** parenchymal; **PFS:** progression-free survival; **POC:** point of care; **PCNSL:** primary central nervous system lymphoma; **pts:** patients; **RT:** radiotherapy; **SCNSL:** secondary central nervous system lymphoma; **TT-ASCT:** thiotepa conditioning autologous stem cell transplantation; **UK:** United Kingdom; **US:** United States.

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1. OJJAARA Product Monograph. GlaxoSmithKline Inc.

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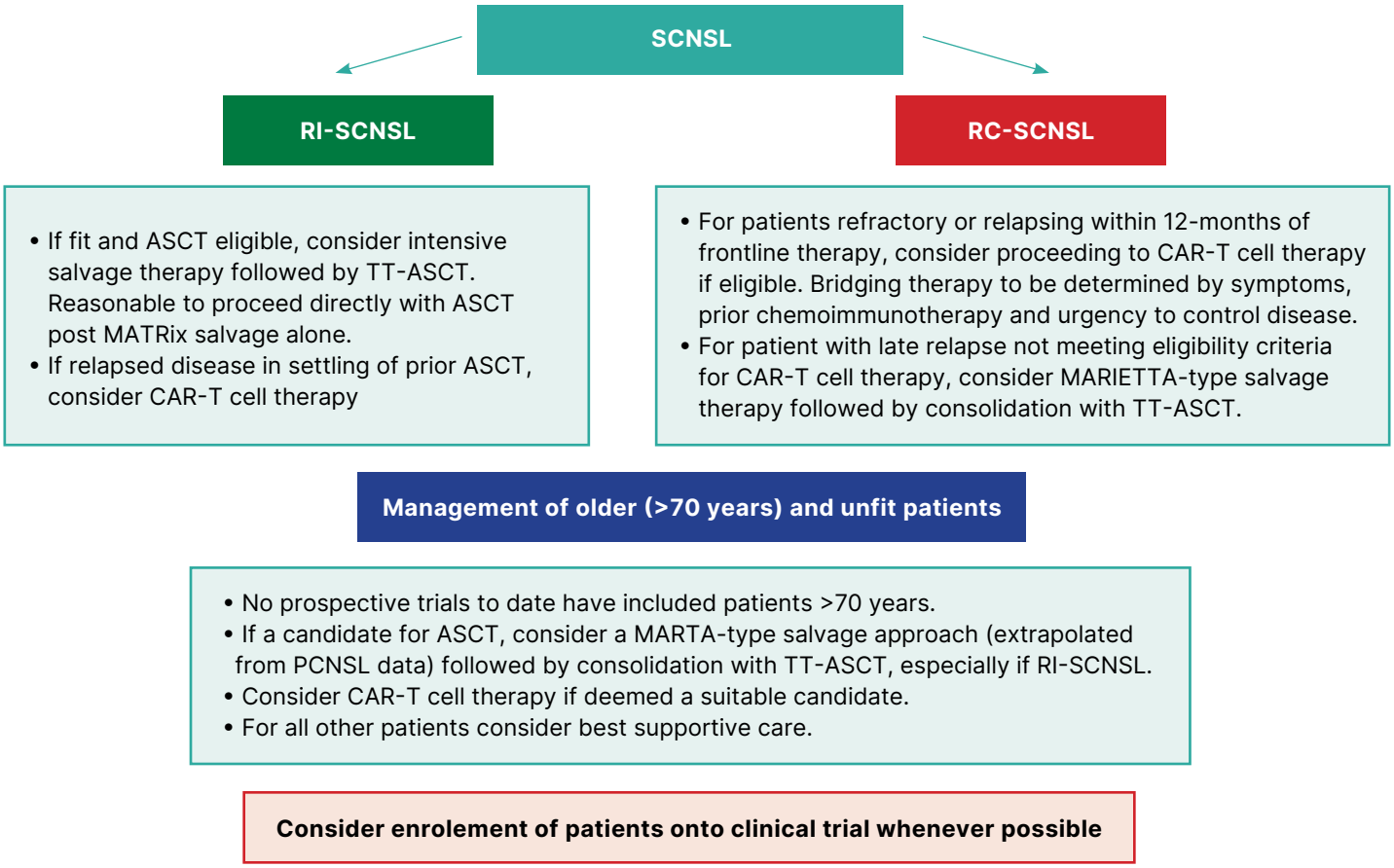

Figure 1. Recommendations for management of SCNSL; *courtesy of Anca Prica, MD, MSc and Chathuri Abeyakoon, MBBS*

Abbreviations: ASCT: autologous stem cell transplantation; **CAR-T cell therapy:** chimeric antigen receptor T cell therapy; **MATRix:** methotrexate, cytarabine, thiotepa, rituximab; **PCNSL:** primary central nervous system lymphoma; **RC-SCNSL:** relapsed concomitant-secondary central nervous system lymphoma; **RI-SCNSL:** relapsed isolated-secondary central nervous system lymphoma; **SCNSL:** secondary central nervous system lymphoma; **TT-ASCT:** **t**hiotepa-based ASCT.

predictors for inferior PFS and inferior OS. The 100-day non-relapse mortality was 3%, and the cumulative incidence rate at 1 and 3-years was 8.4%. Importantly, only 44% of patients with relapsed SCNSL presented within 1 year of diagnosis, while this typically is expected to be approximately 90%, which may suggest a noteworthy favourable selection bias in this analysis.[18]

The largest retrospective dataset to date was recently presented at the 66th American Society of Hematology annual meeting in 2024, which included 1,197 patients and demonstrated improved PFS and OS in those consolidated with a thiotepa-based ASCT compared to chimeric antigen receptor (CAR)-T cell therapy. However, a caveat of this study is the patient selection, as patients included in the CAR-T cell therapy cohort were older, had more *MYC* and *BCL 2* rearrangement, more leptomeningeal disease, and more relapsed concurrent-SCNSL, which are all factors considered associated with poorer outcomes.[20]

CAR-T Cell Therapy for SCNSL

CD19-directed CAR-T cell therapy has transformed the management of relapsed/refractory DLBCL and was shown to result in durable remissions in approximately 30-40% of patients, improving the median OS of approximately 6 months as achieved by available prior therapies.[21-23] However, of the 3 pivotal prospective Phase 2 trials that investigated the efficacy of CAR-T cell

therapy after ≥3 lines of therapy and the three pivotal Phase 3 trials that investigated the efficacy of CAR-T cell therapy in comparison to ASCT as second-line therapy in refractory disease, only the lisocabtagene maraleucel (liso-cel) trials TRANSCEND NHL001 and TRANSFORM included patients with SCNSL, albeit only 7 and 4 patients, respectively.[21, 22,24-27] As such, the majority of evidence for CAR-T cell therapy in this context is derived from retrospective data from registries, such as the Centre for Blood and Marrow Transplant Research (CIBMTR) and European Group for Blood and Marrow Transplantation (EBMT), and consortiums of academic centres.[20,28-34]

The largest reported analysis included 113 patients and compared CAR-T cell outcomes in patients who had active (defined as the presence of CNS disease at the last assessment prior to CAR-T cell infusion) versus inactive CNS disease and demonstrated inferior outcomes in the former group, with a median PFS of 2.9 months versus 14 months, respectively. Involvement of both leptomeningeal and parenchymal disease portended worse response rates within the CNS and patients with leptomeningeal involvement tended to lose their CR by 3 months.[28] Overall, retrospective evidence suggests a reasonable ORR of approximately 60-75%, but generally short durability of responses with 2-year PFS of only 20-30%. Data suggest inferior PFS in patients with active CNS disease proceeding to CAR-T cell therapy. However, more recently the CIBMTR trial reported more encouraging SCNSL outcomes with liso-cel in 57 patients (n=39 with SCNSL at the time of infusion), indicating potential efficacy even for patients with active CNS disease. In this study, the median PFS was 6.9 months (95% CI: 4.4-9.2) in all patients compared to 5.8 months (95% CI: 2.3-8.4) in patients with active CNS disease. Additionally, a more favourable response was observed in patients achieving CR within the CNS compartment prior to CAR-T cell infusion.[30] However, it is important to note that no uniform definition of active CNS disease has been utilized or described across analyses, including description of responses achieved post-bridging therapy, challenging the interpretation of these results. Additionally, leptomeningeal involvement in comparison to the absence of leptomeningeal involvement, has been associated with inferior OS (median 8.6 months versus 19 months) and PFS (median 4.7 months versus 19 months).[32] A recent small case series demonstrated the feasibility of bridging radiation without excess neurotoxicity; however, larger series and prospective validation of these results are needed.[35]

Management Approach

Approach to Relapsed Isolated-SCNSL

As demonstrated in several case series, patients with relapsed intolerant-SCNSL appear to have more favourable outcomes than those with relapsed concurrent-SCNSL. In fit patients <70 years, intensive salvage therapy should be offered. The most robust data comes from the MARIETTA trial, where ORR of 67% was achieved with two cycles of MATRix, and since relapse is isolated to the CNS, it is reasonable to proceed directly to a consolidative thiotepa-based ASCT with MATRix induction alone if a response is achieved. Based on current available data, consolidation with thiotepa-based ASCT for responding disease appears to be the preferred option with more robust, favourable outcome data available than CAR-T cell therapy, while we await more mature data. However, CAR-T cell therapy is accessible in Canada for patients with relapsed isolated-SCNSL as second-line treatment (axi-cel) if CNS disease relapse is within 12-months of frontline therapy or as third-line therapy (axi-cel and tisa-cel) for later relapses. For patients who have relapsed after a prior ASCT, proceeding with CAR-T cell therapy should be considered.

Approach to Relapsed Concurrent-SCNSL

Patients with relapsed concurrent-SCNSL have the poorest outcomes, with a 3-year PFS of 40% versus 62.7% in treatment naive-SCNSL and 67.7% in relapsed isolated-SCNSL. In patients with SCNSL at the time of primary refractory disease or at the time of relapse within 12 months since completing front-line therapy, it is reasonable to consider CAR-T cell therapy, if control of CNS disease can be achieved. Although a direct comparison of CAR-T cell products is not available, the toxicity-efficacy profile seems most favourable with liso-cel for CNS disease, as per the most recent data presented by the CIBMTR. Although we currently do not have access to liso-cel in the Canadian landscape, this may be the preferred product when it becomes available. Holding/bridging therapy needs to be individualized, based on prior chemoimmunotherapy exposure, symptoms, and urgency to control disease, and may include radiation. Similar to relapsed isolated-SCNSL,

in Canada, CAR-T cell therapy is accessible for patients with relapsed concomitant-SCNSL as second-line or as third-line therapy. Treated SCNSL with both active or persistent disease (defined as recent neurological signs/symptoms, positive imaging results or positive CSF and inactive CNS disease) are eligible. Although attainment of a complete response within the CNS compartment is not currently mandatory, limited evidence with variable definitions does suggest inferior survival outcomes for those patients going into CAR-T cell infusion with active disease. An alternative strategy, or in patients with late relapse of relapsed concurrent-SCNSL, salvage treatment, such as a MARIETTA protocol with the aim to consolidate with a thiotepa-based ASCT, can be considered.

Approach to Management of Older Patients

Importantly, there are no prospective data for patients >70 years of age in relapsed SCNSL and the optimal treatment pathway is yet to be defined. The MATRix regimen is associated with increased toxicity, especially from infectious complications, and worse outcomes have been observed in patients >70 years. Extrapolating from the MARTA trial, which was performed in primary CNS lymphoma and demonstrated favourable responses (12-month PFS of 58.8% [95% CI: 44.1-70.9], salvage therapy with rituximab, HD-MTX, and cytarabine could be considered for patients >70 years with relapsed isolated-SCNL who are fit for consolidation ASCT, and dose reduction of cytarabine should be considered to improve tolerability, based on expert opinions. If deemed an appropriate candidate, CAR-T cell therapy can also be considered, especially in relapsed concurrent-SCNSL. For patients unfit for ASCT or CAR-T cell therapy, outcomes remain dismal and best supportive care may be appropriate.

Conclusions

Relapse of SCNSL remains a challenging complication and an area of unmet need, especially in elderly patients. Emerging data strengthens the benefit of thiotepa-based ASCT consolidation, especially in relapsed isolated-SCNSL following a MARIETTA-salvage regimen. Based on retrospective evidence, CAR-T cell therapy also appears to be efficacious and safe. However, the durability of remissions remains disappointing, especially for patients with active CNS and leptomeningeal disease at the time of infusion. Improved bridging or novel maintenance strategies pre/post-CAR-T cell therapy and management strategies for unfit elderly patients are urgently needed, and we encourage enrolment of all patients into clinical trials whenever possible.

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References

1. Alderuccio JP, Nayak L, Cwynarski K. How I treat secondary CNS involvement by aggressive lymphomas. Blood. 2023;142(21):1771-83.
2. Lewis KL, Jakobsen LH, Villa D, Smedby KE, Savage KJ, Eyre TA, et al. High-Dose Methotrexate as CNS Prophylaxis in High-Risk Aggressive B-Cell Lymphoma. J Clin Oncol. 2023;41(35):5376-87.
3. Bobillo S, Khwaja J, Ferreri AJM, Cwynarski K. Prevention and management of secondary central nervous system lymphoma. Haematologica. 2023;108(3):673-89.
4. El-Galaly TC, Cheah CY, Bendtsen MD, Nowakowski GS, Kansara R, Savage KJ, et al. Treatment strategies, outcomes and prognostic factors in 291 patients with secondary CNS involvement by diffuse large B-cell lymphoma. Eur J Cancer. 2018;93:57-68.
5. Korfel A, Elter T, Thiel E, Hanel M, Mohle R, Schroers R, et al. Phase II study of central nervous system (CNS)-directed chemotherapy including high-dose chemotherapy with autologous stem cell transplantation for CNS relapse of aggressive lymphomas. Haematologica. 2013;98(3):364-70.
6. Ferreri AJ, Donadoni G, Cabras MG, Patti C, Mian M, Zambello R, et al. High Doses of Antimetabolites Followed by High-Dose Sequential Chemoimmunotherapy and Autologous Stem-Cell Transplantation in Patients With Systemic B-Cell Lymphoma and Secondary CNS Involvement: Final Results of a Multicenter Phase II Trial. J Clin Oncol. 2015;33(33):3903-10.
7. Doorduijn JK, van Imhoff GW, van der Holt B, Schouten HC, Schaafsma MR, MacKenzie MA, et al. Treatment of secondary central nervous system lymphoma with intrathecal rituximab, high-dose methotrexate, and R-DHAP followed by autologous stem cell transplantation: results of the HOVON 80 phase 2 study. Hematol Oncol. 2017;35(4):497-503.
8. Ferreri AJM, Doorduijn JK, Re A, Cabras MG, Smith J, Ilariucci F, et al. MATRix-RICE therapy and autologous haematopoietic stem-cell transplantation

in diffuse large B-cell lymphoma with secondary CNS involvement (MARIETTA): an international, single-arm, phase 2 trial. Lancet Haematol. 2021;8(2):e110-e21.
9. Damaj G, Ivanoff S, Coso D, Ysaebert L, Choquet S, Houillier C, et al. Concomitant systemic and central nervous system non-Hodgkin lymphoma: the role of consolidation in terms of high dose therapy and autologous stem cell transplantation. A 60-case retrospective study from LYSA and the LOC network. Haematologica. 2015;100(9):1199-206.
10. Nijland M, Jansen A, Doorduijn JK, Enting RH, Bromberg JEC, Kluin-Nelemans HC. Treatment of initial parenchymal central nervous system involvement in systemic aggressive B-cell lymphoma. Leuk Lymphoma. 2017;58(9):1-6.
11. Fleming M, Huang Y, Dotson E, Bond DA, Reneau J, Epperla N, et al. Feasibility of high-dose methotrexate administered on day 1 of (R)CHOP in aggressive non-Hodgkin lymphomas. Blood Advances. 2022;6(2):460-72.
12. Wight JC, Yue M, Keane C, Johnston A, Linton K, Chin C, et al. Outcomes of synchronous systemic and central nervous system (CNS) involvement of diffuse large B-cell lymphoma are dictated by the CNS disease: a collaborative study of the Australasian Lymphoma Alliance. Br J Haematol. 2019;187(2):174-84.
13. Ferreri AJM, Cwynarski K, Pulczynski E, Fox CP, Schorb E, Celico C, et al. Long-term efficacy, safety and neurotolerability of MATRix regimen followed by autologous transplant in primary CNS lymphoma: 7-year results of the IELSG32 randomized trial. Leukemia. 2022;36(7):1870-8.
14. Kasenda B, Schorb E, Fritsch K, Finke J, Illerhaus G. Prognosis after high-dose chemotherapy followed by autologous stem-cell transplantation as first-line treatment in primary CNS lymphoma--a long-term follow-up study. Ann Oncol. 2012;23(10):2670-5.
15. Scordo M, Wang TP, Ahn KW, Chen Y, Ahmed S, Awan FT, et al. Outcomes Associated With Thiotepa-Based Conditioning in Patients With Primary Central Nervous System Lymphoma After Autologous Hematopoietic Cell Transplant. JAMA Oncol. 2021;7(7):993-1003.
16. Akin S, Hosing C, Khouri I, Ahmed S, Alousi A, Fowler N, et al. Autologous stem cell transplantation for large B-cell lymphoma with secondary central nervous system involvement. Blood Adv. 2022;6(7):2267-74.
17. Maziarz RT, Wang Z, Zhang MJ, Bolwell BJ, Chen AI, Fenske TS, et al. Autologous haematopoietic cell transplantation for non-Hodgkin lymphoma with secondary CNS involvement. Br J Haematol. 2013;162(5):648-56.
18. Khwaja J, Kirkwood AA, Isbell LK, Steffanoni S, Goradia H, Pospiech L, et al. International multicenter retrospective analysis of thiotepa-based autologous stem cell transplantation for secondary central nervous system lymphoma. Haematologica. 2023;108(3):882-8.
19. Bromberg JE, Doorduijn JK, Illerhaus G, Jahnke K, Korfel A, Fischer L, et al. Central nervous system recurrence of systemic lymphoma in the era of stem cell transplantation--an International Primary Central Nervous System Lymphoma Study Group project. Haematologica. 2013;98(5):808-13.
20. Alderuccio JP, Khwaja J, Han S, Ghione P, Nizamuddin IA, Saha A, et al. Prognostication and Treatment-Related Outcomes in Secondary Central Nervous System Involvement of Large B-Cell Lymphoma (SCNSL): Evidence from a Large International Cohort. Blood. 2024;144(Supplement 1):571-.
21. Locke FL, Miklos DB, Jacobson CA, Perales MA, Kersten MJ, Oluwole OO, et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. N Engl J Med. 2022;386(7):640-54.
22. Abramson JS, Solomon SR, Arnason J, Johnston PB, Glass B, Bachanova V, et al. Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study. Blood. 2023;141(14):1675-84.
23. Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. 2017;130(16):1800-8.
24. Neelapu SS, Jacobson CA, Ghobadi A, Miklos DB, Lekakis LJ, Oluwole OO, et al. Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma. Blood. 2023;141(19):2307-15.
25. 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(1):45-56.
26. Abramson JS, Palomba ML, Gordon LI, Lunning M, Wang M, Arnason J, et al. Two-year follow-up of lisocabtagene maraleucel in relapsed or refractory large B-cell lymphoma in TRANSCEND NHL 001. Blood. 2024;143(5):404-16.
27. Bishop MR, Dickinson M, Purtill D, Barba P, Santoro A, Hamad N, et al. Second-Line Tisagenlecleucel or Standard Care in Aggressive B-Cell Lymphoma. N Engl J Med. 2022;386(7):629-39.
28. Alsouqi A, Ahmed G, Wang J, Cassanello G, Szabo A, Rojek AE, et al. Chimeric antigen receptor T-cell therapy in secondary central nervous system lymphoma: A multicenter analysis. Am J Hematol. 2024;99(8):1624-7.
29. Epperla N, Feng L, Shah NN, Fitzgerald L, Shah H, Stephens DM, et al. Outcomes of patients with secondary central nervous system lymphoma following CAR T-cell therapy: a multicenter cohort study. J Hematol Oncol. 2023;16(1):111.
30. Ahmed S, Kallam A, Frigault M, Hunter BD, Patel SS, Bernasconi D, et al. Real-World (RW) Outcomes of Lisocabtagene Maraleucel (liso-cel) in Patients (pts) with Relapsed or Refractory (R/R) Large B-Cell Lymphoma (LBCL) and Secondary Central Nervous System (sCNS) Involvement from the Center for International Blood and Marrow Transplant Research (CIBMTR) Registry. Blood. 2024;144(Supplement 1):472-.
31. Hashmi H, Epperla N, Ahn K, Allbee-Johnson M, Mercadal S, Lee CJ, et al. Outcomes of Large B-Cell Lymphoma (LBCL) Patients with Secondary Central Nervous System Involvement Following Chimeric Antigen Receptor T-Cell Therapy: A CIBMTR Analysis. Transplantation and Cellular Therapy, Official Publication of the American Society for Transplantation and Cellular Therapy.

2024;30(2):S42.
32. Luttwak E, Cassanello G, Brown S, Devlin SM, Imber BS, Ip A, et al. CAR T-Cell Therapy for DLBCL with CNS Involvement: Overall Safe and Effective with Limited Efficacy in Patients with Leptomeningeal Disease. Blood. 2024;144(Supplement 1):4509-.
33. Ossami Saidy A, Fuhrmann S, Peczynski C, Boumendil A, Michel E, Galimard J-E, et al. Efficacy of CD19-Directed CAR T Cell Therapy in Patients with Primary or Secondary CNS Lymphoma - an Analysis of the EBMT Lymphoma WP and the Gocart Coalition. Blood. 2023;142(Supplement 1):1031-.
34. Ahmed G, Alsouqi A, Szabo A, Rojek AE, Riedell PA, Awan FT, et al. Chimeric Antigen Receptor T-Cell (CAR-T) Therapy in Secondary Central Nervous System Large B-Cell Lymphoma (SCNSL): A Multicenter Retrospective Analysis. Blood. 2023;142(Supplement 1):3088-.
35. Cederquist GY, Schefflein J, Devlin SM, Shah GL, Shouval R, Hubbeling H, et al. CNS bridging radiotherapy achieves rapid cytoreduction before CAR T-cell therapy for aggressive B-cell lymphomas. Blood Advances. 2024;8(19):5192-9.

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Front-line Treatment of B-cell Acute Lymphoblastic Leukemia in Canada: Current Strategies and Evolving Paradigms

Curtis Marcoux, MD

Introduction

The treatment landscape for adults with B-cell acute lymphoblastic leukemia (B-ALL) has evolved considerably, with pediatric-inspired regimens, targeted therapies, and measurable residual disease (MRD)-guided approaches improving outcomes. However, treatment strategies in the clinic remain highly variable due to heterogeneity in prospective trials, a lack of randomized comparative data, and the continued evolution of therapies—particularly with the increasing use of targeted agents and immunotherapies in the front-line setting. The absence of national standardization further contributes to variability in clinical practice.

This review provides an overview of current front-line treatment strategies for B-ALL in Canada, highlighting key therapeutic approaches and recent advancements in optimizing care.

Front-line Treatment of *BCR::ABL1*-negative B-ALL

Multiple cooperative groups have developed front-line protocols for *BCR::ABL1*-negative B-ALL based on age, fitness, and prognostic factors.[1] However, the lack of randomized comparisons and significant heterogeneity among protocols have led to global variability, including differences among Canadian centres, without a standardized approach.

Early retrospective analyses showed superior outcomes in adolescents and young adults (AYA) treated with pediatric versus adult regimens,[2,3] prompting prospective trials to evaluate the feasibility of pediatric regimens in adults.[4-10] Although no cooperative group trials have directly randomized patients to pediatric or adult regimens, data favour pediatric-based approaches,[11,12] which are now preferred for AYA patients at experienced centres. However, age cut-offs for 'young adults' vary widely across trials and clinical practice.

Despite becoming standard at many centres in Canada and globally, pediatric regimens present unique challenges.

Pediatric regimens are complex, incorporating multiple phases and, in some cases, risk-adapted therapy. Beyond induction, regimens are designed for outpatient administration, requiring robust clinic and day hospital infrastructure for frequent patient visits. Unlike conventional adult regimens (e.g., hyperCVAD; hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), pediatric approaches emphasize non-myelosuppressive agents such as asparaginase, glucocorticoids, and vincristine, alongside intensive early central nervous system (CNS) prophylaxis.[4,5,9] Derived from Berlin-Frankfurt-Münster (BFM) protocols, these regimens include extended induction, consolidation, delayed intensification, and prolonged maintenance. In contrast, adult-based protocols rely more on myelosuppressive agents like cyclophosphamide, cytarabine, and anthracyclines, with later and less frequent CNS prophylaxis.[13] Historically, adult regimens have also incorporated allogeneic hematopoietic stem cell transplantation (allo-HSCT) in first remission (CR1) as an intensification strategy in those at high risk of relapse. While pediatric-inspired regimens improve outcomes in AYA patients, they increase risks such as hepatotoxicity, pancreatitis, and avascular necrosis, primarily linked to asparaginase.[12] Nevertheless, the benefit-to-toxicity ratio remains favourable. CNS-directed therapy remains essential in all ALL treatment regimens.

In Canada, modified versions of the Dana-Farber Cancer Institute (DFCI) pediatric-like regimen[5] and, less commonly, the CALGB 10403 regimen[4] are the most frequently used for AYA patients. For older adults (>50–60 years), no

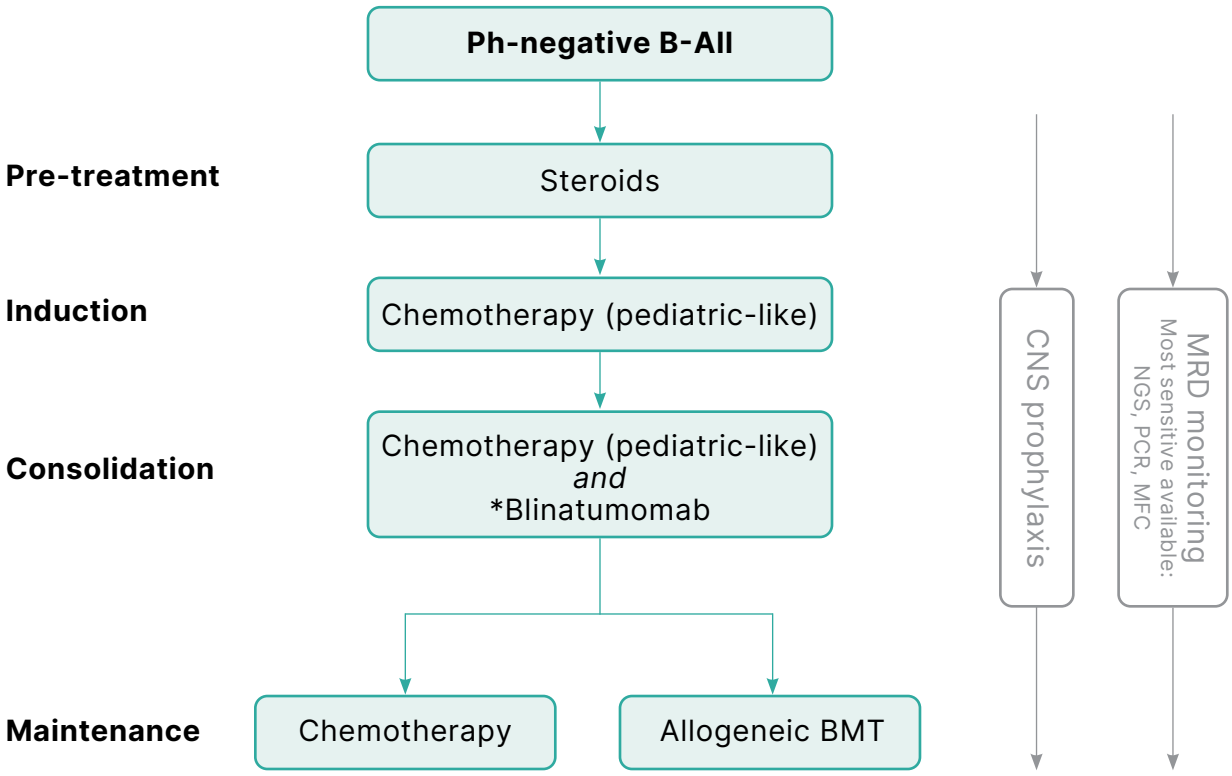

Figure 1. How I Treat *BCR::ABL1*-negative B-ALL; *courtesy of Curtis Marcoux, MD*

Abbreviations: BMT: bone marrow transplantation; **CNS:** central nervous system; **MFC:** multiparametric flow cytometry; **MRD:** measurable residual disease; **NGS:** next-generation sequencing; **PCR:** polymerase chain reaction.

* If available

standardized approach exists across Canadian centres. Some experienced centres use age-adjusted DFCI-based protocols, supported by data from the Princess Margaret Cancer Centre, where Philadelphia chromosome (Ph)-negative ALL patients aged 60–79 years had a 5-year overall survival (OS) of 40%.[14] Age-adjusted hyperCVAD is another acceptable approach.[15] In elderly patients (>75 years) or those with significant comorbidities or reduced fitness, palliative strategies—such as steroids, vincristine, intrathecal therapy, and maintenance with mercaptopurine and methotrexate—are often employed.

Blinatumomab, a bispecific CD19-CD3 T-cell engager, has demonstrated safety and efficacy in treating MRD ($\geq 10^{-3}$)[16] and relapsed/refractory (R/R) BCR::ABL1-negative B-ALL,[17] prompting interest in its use as consolidation in front-line therapy for MRD-negative patients. The ECOG-ACRIN 1910 trial, a randomized phase 3 study in patients aged 30–70 years, compared 4 cycles of blinatumomab plus consolidation chemotherapy to chemotherapy alone in those achieving MRD-negative remission (<0.01%) after induction and intensification.[18] Blinatumomab significantly improved 3-year relapse-free survival (RFS) (80% vs. 64%) and OS (85% vs. 68%) over chemotherapy alone and has since become the standard of care as part of consolidation therapy in *BCR::ABL1*-negative B-ALL, regardless of MRD status, where available.

Blinatumomab is currently under reimbursement review by the Canadian Drug Agency for use in adult *BCR::ABL1*-negative B-ALL as consolidation in the frontline with multiphase chemotherapy. While not yet publicly funded, a patient assistance program is available in Canada to support access regardless of MRD status.

The Canadian Leukemia Study Group (CLSG) recently developed the CLSG ALL 1 protocol,

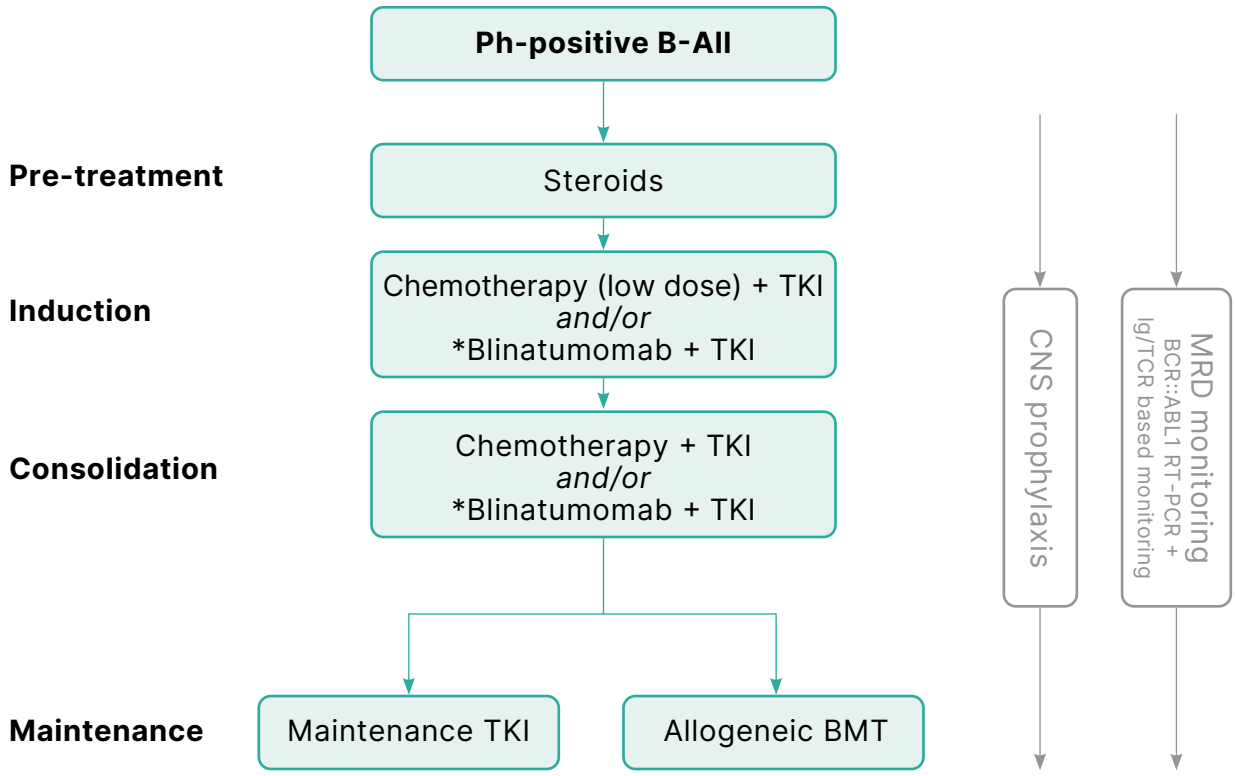

Figure 2. How I Treat *BCR::ABL1*-positive B-ALL; *courtesy of Curtis Marcoux, MD*

Abbreviations: BMT: bone marrow transplantation; **CNS:** central nervous system; **Ig/TCR:** immunoglobulin/T cell receptor; **MRD:** measurable residual disease; **RT-PCR:** reverse-transcription polymerase chain reaction; **TKI:** tyrosine kinase inhibitor.

* If available

integrating blinatumomab into consolidation based on a modified Princess Margaret-DFCI regimen. CLSG ALL 1 includes four MRD-independent cycles of post-induction blinatumomab and aims to reduce chemotherapy exposure, steroid use, and overall treatment duration. Key modifications include reducing intensification to seven cycles across all age groups, eliminating methotrexate from intensification, and shortening maintenance to 18 cycles. Regular MRD assessments are recommended to validate the CLSG ALL 1 approach, clarify the role of transplant, and inform future treatment refinements. My approach to the upfront treatment of *BCR::ABL1*-negative ALL is shown in **Figure 1**.

Front-line Treatment of *BCR::ABL1*-positive B-ALL

Ph-positive B-ALL, the most common genetic subtype of B-ALL, occurs in 25%–30% of cases, with incidence increasing with age.[19] It arises from the t(9;22) translocation, resulting in BCR-ABL1 oncoprotein expression and constitutive kinase activation. Previously associated with poor survival, the introduction of tyrosine kinase inhibitors (TKIs) and sensitive MRD monitoring has markedly improved outcomes.

BCR::ABL1-positive ALL exhibits reduced chemosensitivity with remissions often being short-lived even in patients achieving a complete response (CR).[20,21] Historically, allo-HSCT was recommended for all eligible patients with suitable donors, though long-term survival rates remained low.[22,23] The introduction of TKIs has transformed treatment, with imatinib combined with low-dose chemotherapy inducing CR rates exceeding 95%, reducing induction-related mortality, and achieving survival outcomes comparable to standard induction therapy.[24,25] Second-generation TKIs (e.g. dasatinib, nilotinib) have further improved efficacy and proven safe in combination with chemotherapy.[26-30] Though indirect comparisons suggest these agents may be superior to imatinib, no front-line randomized trials have established a definitive standard. The only randomized data come from a pediatric study (median age 7.8 years), where dasatinib combined with intensive chemotherapy significantly improved 4-year event-free survival (EFS; 71.0% vs. 48.9%) and OS (88.4% vs. 69.2%) while reducing the 4-year cumulative risk of isolated CNS relapse (2.7% vs. 8.4%) compared to imatinib.[31]

The acquisition of the T315I mutation is a key mechanism of relapse in patients treated with first- and second-generation TKIs, driving interest in the front-line use of ponatinib, a third-generation TKI with activity against *ABL1* mutations including T315I.[32-34] The recent PhALLCON trial randomized newly diagnosed patients with Ph+ ALL to ponatinib versus imatinib with reduced-intensity chemotherapy, demonstrating significantly higher MRD-negative CR (≤0.01% BCR::ABL1) rates with ponatinib (34.4% vs. 16.7%) and a trend toward improved EFS.[35] Long-term survival data are awaited to determine whether these findings translate into a survival benefit. Based on current evidence, second- or third-generation TKIs are preferred for front-line therapy, though imatinib remains a reasonable option where access to newer agents is limited. Finally, dual *BCR::ABL1* inhibition with asciminib—an allosteric *BCR::ABL1* inhibitor targeting a distinct site from ATP-competitive TKIs—and dasatinib has shown promise in a phase 1 study. However, further research is needed to determine the safety and efficacy of dual TKI therapy relative to current standard treatments.[36]

Given the success of blinatumomab in MRD eradication[16] and treatment of low-level disease in R/R B-ALL,[37] there was interest in evaluating its role as a consolidation therapy in *BCR::ABL1*-positive B-ALL. The GIMEMA LAL2116 (D-ALBA) study evaluated dasatinib and prednisone induction followed by 2 to 5 cycles of blinatumomab consolidation in newly diagnosed Ph-positive B-ALL.[38] Nearly all patients (98%) achieved complete hematologic response after chemotherapy-free induction, with 29% achieving molecular remission (MR), defined as undetectable or non-quantifiable *BCR::ABL1*. MR rates increased to 60% and over 80% after 2 and 4 cycles of blinatumomab, respectively. Similarly, ponatinib, when used either concurrently[39,40] or sequentially[41] with blinatumomab, has demonstrated safety and efficacy, leading to high rates of deep molecular responses. While CNS prophylaxis is a standard component of ALL therapy, particular attention is needed in chemotherapy-free regimens, as CNS relapse remains a common pattern of disease recurrence. Further, patients with the IKZF1Plus genotype (*IKZF1* deletion alongside deletions in *CDKN2A/B* and/or *PAX5*) remain at high risk of relapse.[40] Notably, blinatumomab is not currently available in Canada outside of clinical trials for front-line *BCR::ABL1*-positive ALL. My approach to

the upfront treatment of *BCR::ABL1*-positive ALL is shown in **Figure 2**.

Additional Considerations: CNS Prophylaxis

There is a paucity of data on CNS-directed therapy in adult ALL, leading to variability in clinical practice. The first lumbar puncture (LP) is typically performed at the time of the first scheduled intrathecal (IT) chemotherapy unless neurological symptoms warrant earlier evaluation. Whether LP should be delayed until circulating blasts clear remains debated due to the theoretical risk of CSF contamination.

Adult ALL regimens include CNS-penetrating systemic agents (e.g., dexamethasone, pegaspargase, methotrexate, 6-mercaptopurine, cytarabine, dasatinib) alongside IT chemotherapy for prophylaxis. Standard regimens for CNS-negative patients historically include 8–12 IT treatments, but with the incorporation of immunotherapies (e.g., blinatumomab) and reduced-intensity chemotherapy, CNS prophylaxis has become increasingly important. Modern regimens now incorporate upwards of 15 IT treatments. Adherence to established treatment protocols for CNS-directed prophylaxis is essential to ensure adequate protection against CNS relapse. Notably, most adult protocols do not include radiotherapy for patients without CNS involvement at diagnosis.

Indications for Transplant in First Complete Remission

Allo-HSCT remains a critical therapeutic strategy for high-risk ALL, particularly when standard chemotherapy alone is unlikely to provide durable disease control.[42] Advances in targeted therapies and MRD-driven treatment strategies have improved survival rates, and indications for allo-HSCT in first complete remission (CR1) continue to evolve, balancing the risk of relapse against transplant-related morbidity and mortality.

BCR::ABL1-negative B-ALL

Among Ph-negative B-ALL subtypes, Ph-like, *KMT2A*-rearranged (*KMT2A*-r) ALL and those with complex karyotype remain particularly challenging due to high relapse rates and poor responses to conventional chemotherapy. Ph-like ALL, defined by a gene expression profile similar to Ph-positive ALL but lacking *BCR::ABL1*,[43,44] is associated with inferior survival outcomes with chemotherapy alone. However, routine identification of Ph-like ALL remains limited in many centres due to the lack of widely available, standardized diagnostic assays. Data from GIMEMA,[45,46] MD Anderson,[43] and City of Hope[47] suggest that allo-HSSCT improves outcomes, particularly in MRD-positive patients, with post-transplant survival rates comparable to other Ph-negative subtypes. Further, a recent U.S. multicentre study found that, despite higher induction failure in Ph-like ALL, progression-free survival (PFS) and OS after allo-HCT in CR1 were similar to other Ph-negative subtypes.[48]

Similarly, *KMT2A*-r ALL has historically carried a poor prognosis, though data from MD Anderson[49] and the GRAALL[50] support the benefit of allo-HSCT in this subgroup. However, emerging evidence suggests that a subset of *KMT2A*-r patients with early MRD-negativity and favourable molecular features may achieve durable remissions without transplant.[51] Complex karyotype (≥5 abnormalities) and low hypodiploidy (30–39 chromosomes)[52] are both high-risk cytogenetic abnormalities and should prompt early referral for allo-HSCT.

As targeted therapies,[53,54] immunotherapies,[18] and refined MRD-based risk stratification[55] continue to advance, the role of allo-HSCT in these subtypes may evolve. For now, it remains a key consideration for eligible patients in CR1.

BCR::ABL1-positive B-ALL

The role of allo-HSCT in *BCR::ABL1*-positive ALL has evolved significantly. Before the introduction of TKIs, transplant was the standard of care for all eligible patients, supported by donor versus no-donor analyses demonstrating superior outcomes.[20,23] In the TKI era, studies have continued to support the benefit of consolidative allo-HSCT with first or second-generation TKIs;[29,56-58] however, these studies did not routinely incorporate MRD-guided risk stratification into transplant decisions.

Recent evidence suggests that patients achieving early, deep remissions with TKI-based therapy may safely forgo allo-HSCT. Prospective trials of imatinib-[24] and nilotinib-based[59] regimens found no survival advantage for transplant in MRD-negative patients. Similarly, a U.S. multicentre study reported no OS benefit for allo-HSCT in patients achieving complete molecular remission (CMR) within 90 days of diagnosis, as higher non-relapse mortality (NRM) offset lower relapse rates in those undergoing transplant.[60] Although

not yet routinely available in Canada for front-line therapy, ponatinib has shown efficacy in inducing deep and durable remissions without allo-HSCT. A single-centre study of ponatinib and hyperCVAD reported CMR rates exceeding 80%,[32] with only 23% of patients undergoing allo-HSCT in CR1 and a 6-year OS of 87% in those not transplanted.[32,61]

The necessity of transplant is further challenged by the emergence of highly effective low-intensity or chemotherapy-free regimens incorporating blinatumomab. The GIMEMA LAL2116 (D-ALBA) trial, which combined dasatinib with blinatumomab, reported a 98% CR rate, with the majority achieving MRD-negative remissions.[38,62] Sustained remissions were observed in nearly all MRD-negative patients without transplant, whereas MRD-positive patients undergoing allo-HSCT experienced low transplant-related mortality. Ponatinib combined with blinatumomab may further improve these outcomes, as an MD Anderson study of concurrent ponatinib and blinatumomab reported next-generation sequencing (NGS)-MRD negativity in 98% of patients, with only 3% requiring transplant and a 3-year OS of 91%.[39,40] An interim analysis of the GIMEMA ALL2820 trial, a follow-up to LAL2116 in which dasatinib was replaced with ponatinib, demonstrated similarly impressive results.[41] Although the median follow-up was just over 6 months, the estimated 12-month disease-free survival and OS were 95.6% and 94.9%, respectively. Transplant allocation was based on the presence of the *IKZF1*plus genotype and MRD persistence, with only 12% of patients undergoing allo-HSCT. The GRAAPH-2024 study (NCT06860269) aims to clarify the role of transplant by randomizing patients in CMR after treatment with ponatinib, blinatumomab, and low-intensity chemotherapy to either allo-HSCT or continued TKI-based therapy.

Measurable Residual Disease

MRD is a key predictor of relapse and a critical determinant in transplant decisions for both Ph-negative and Ph-positive ALL, often outweighing traditional clinical and genetic risk factors.[63-66] Across multiple risk stratification models, MRD is the most consistent factor guiding allo-HCT in CR1,[67] with transplant offering a survival advantage in MRD-positive patients.[68,69] The necessity of allo-HSCT in MRD-negative high-risk patients remains uncertain, particular when highly sensitive methods of MRD detection (NGS-MRD) are used. In BCR-ABL1-positive ALL, reverse transcription-polymerase chain reaction (RT-PCR) for *BCR::ABL1*, though widely used, is less sensitive and correlates poorly with immunoglobulin (Ig)/ T cell receptor (TCR) PCR and NGS-based MRD.[70,71] NGS-MRD can identify patients with a "CML-like" profile, where residual *BCR::ABL1* transcripts do not necessarily indicate active disease.[71] Given the limited access to NGS-MRD in Canada, the most sensitive assay available should be used for *BCR::ABL1*-negative ALL, while in *BCR::ABL1*-positive ALL, quantitative PCR for both p190 and p210 ABL1 transcripts, ideally alongside Ig/TCR-based assays, is recommended to guide transplant decisions. Ongoing evaluation of MRD dynamics and treatment-specific thresholds remains crucial as front-line therapies evolve.

Conclusion

Despite significant advances in B-ALL treatment, challenges persist, particularly the absence of standardized guidelines and disparities in access to novel agents such as blinatumomab and ponatinib. The expanding role of targeted and immunotherapies, including chimeric antigen receptor (CAR)-T cell therapies and next-generation TKIs, is reshaping treatment paradigms and necessitating a reassessment of transplant indications. Moving forward, harmonizing treatment strategies and refining risk-adapted approaches will be crucial to optimizing outcomes across diverse clinical settings.

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References

1. Gökbuget N, Boissel N, Chiaretti S, Dombret H, Doubek M, Fielding A, et al. Diagnosis, prognostic factors, and assessment of ALL in adults: 2024 ELN recommendations from a European expert panel. Blood. 2024;143(19):1891-902.
2. Stock W, La M, Sanford B, Bloomfield CD, Vardiman JW, Gaynon P, et al. What determines the outcomes for adolescents and young adults with acute lymphoblastic leukemia treated on cooperative group protocols? A comparison of Children's Cancer Group and Cancer and Leukemia Group B studies. Blood. 2008;112(5):1646-54.
3. Boissel N, Auclerc MF, Lhéritier V, Perel Y, Thomas X, Leblanc T, et al. Should adolescents with acute lymphoblastic leukemia be treated as old children or young adults? Comparison of the French FRALLE-93 and LALA-94 trials. J Clin Oncol. 2003;21(5):774-80.

4. Stock W, Luger SM, Advani AS, Yin J, Harvey RC, Mullighan CG, et al. A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403. Blood. 2019;133(14):1548-59.
5. DeAngelo DJ, Stevenson KE, Dahlberg SE, Silverman LB, Couban S, Supko JG, et al. Long-term outcome of a pediatric-inspired regimen used for adults aged 18-50 years with newly diagnosed acute lymphoblastic leukemia. Leukemia. 2015;29(3):526-34.
6. Huguet F, Leguay T, Raffoux E, Thomas X, Beldjord K, Delabesse E, et al. Pediatric-inspired therapy in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: the GRAALL-2003 study. J Clin Oncol. 2009;27(6):911-8.
7. Huguet F, Chevret S, Leguay T, Thomas X, Boissel N, Escoffre-Barbe M, et al. Intensified Therapy of Acute Lymphoblastic Leukemia in Adults: Report of the Randomized GRAALL-2005 Clinical Trial. J Clin Oncol. 2018;36(24):2514-23.
8. Ribera JM, Oriol A, Sanz MA, Tormo M, Fernández-Abellán P, del Potro E, et al. Comparison of the results of the treatment of adolescents and young adults with standard-risk acute lymphoblastic leukemia with the Programa Español de Tratamiento en Hematología pediatric-based protocol ALL-96. J Clin Oncol. 2008;26(11):1843-9.
9. Rytting ME, Jabbour EJ, Jorgensen JL, Ravandi F, Franklin AR, Kadia TM, et al. Final results of a single institution experience with a pediatric-based regimen, the augmented Berlin-Frankfurt-Münster, in adolescents and young adults with acute lymphoblastic leukemia, and comparison to the hyper-CVAD regimen. Am J Hematol. 2016;91(8):819-23.
10. Toft N, Birgens H, Abrahamsson J, Griškevičius L, Hallböök H, Heyman M, et al. Results of NOPHO ALL2008 treatment for patients aged 1-45 years with acute lymphoblastic leukemia. Leukemia. 2018;32(3):606-15.
11. Ram R, Wolach O, Vidal L, Gafter-Gvili A, Shpilberg O, Raanani P. Adolescents and young adults with acute lymphoblastic leukemia have a better outcome when treated with pediatric-inspired regimens: systematic review and meta-analysis. Am J Hematol. 2012;87(5):472-8.
12. Siegel SE, Stock W, Johnson RH, Advani A, Muffly L, Douer D, et al. Pediatric-Inspired Treatment Regimens for Adolescents and Young Adults With Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia: A Review. JAMA Oncol. 2018;4(5):725-34.
13. Kantarjian H, Thomas D, O'Brien S, Cortes J, Giles F, Jeha S, et al. Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. Cancer. 2004;101(12):2788-801.
14. Martell MP, Atenafu EG, Minden MD, Schuh AC, Yee KW, Schimmer AD, et al. Treatment of elderly patients with acute lymphoblastic leukaemia using a paediatric-based protocol. Br J Haematol. 2013;163(4):458-64.
15. Rausch CR, Jabbour EJ, Kantarjian HM, Kadia TM. Optimizing the use of the hyperCVAD regimen: Clinical vignettes and practical management. Cancer. 2020;126(6):1152-60.
16. Gökbuget N, Dombret H, Bonifacio M, Reichle A, Graux C, Faul C, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. Blood. 2018;131(14):1522-31.
17. Kantarjian H, Stein A, Gökbuget N, Fielding AK, Schuh AC, Ribera JM, et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. N Engl J Med. 2017;376(9):836-47.
18. Litzow MR, Sun Z, Mattison RJ, Paietta EM, Roberts KG, Zhang Y, et al. Blinatumomab for MRD-Negative Acute Lymphoblastic Leukemia in Adults. N Engl J Med. 2024;391(4):320-33.
19. Secker-Walker LM, Craig JM, Hawkins JM, Hoffbrand AV. Philadelphia positive acute lymphoblastic leukemia in adults: age distribution, BCR breakpoint and prognostic significance. Leukemia. 1991;5(3):196-9.
20. Dombret H, Gabert J, Boiron JM, Rigal-Huguet F, Blaise D, Thomas X, et al. Outcome of treatment in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia--results of the prospective multicenter LALA-94 trial. Blood. 2002;100(7):2357-66.
21. Cytogenetic abnormalities in adult acute lymphoblastic leukemia: correlations with hematologic findings outcome. A Collaborative Study of the Group Français de Cytogénétique Hématologique. Blood. 1996;87(8):3135-42.
22. Gleissner B, Gökbuget N, Bartram CR, Janssen B, Rieder H, Janssen JW, et al. Leading prognostic relevance of the BCR-ABL translocation in adult acute B-lineage lymphoblastic leukemia: a prospective study of the German Multicenter Trial Group and confirmed polymerase chain reaction analysis. Blood. 2002;99(5):1536-43.
23. Fielding AK, Rowe JM, Richards SM, Buck G, Moorman AV, Durrant IJ, et al. Prospective outcome data on 267 unselected adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia confirms superiority of allogeneic transplantation over chemotherapy in the pre-imatinib era: results from the International ALL Trial MRC UKALLXII/ECOG2993. Blood. 2009;113(19):4489-96.
24. Chalandon Y, Thomas X, Hayette S, Cayuela JM, Abbal C, Huguet F, et al. Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia. Blood. 2015;125(24):3711-9.
25. Ottmann OG, Wassmann B, Pfeifer H, Giagounidis A, Stelljes M, Dührsen U, et al. Imatinib compared with chemotherapy as front-line treatment of elderly patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL). Cancer. 2007;109(10):2068-76.
26. Ottmann OG, Pfeifer H, Cayuela J-M, Spiekermann K, Jung W, Beck J, et al. Nilotinib (Tasigna®) and Low Intensity Chemotherapy for First-Line Treatment of Elderly Patients with BCR-ABL1-Positive Acute Lymphoblastic Leukemia: Final Results of a Prospective Multicenter Trial (EWALL-PH02). Blood. 2018;132(Supplement 1):31-.
27. Chalandon Y, Rousselot P, Chevret S, Cayuela JM, Kim R, Huguet F, et al. Nilotinib with or without cytarabine for Philadelphia-positive acute lymphoblastic leukemia. Blood. 2024;143(23):2363-72.
28. Chiaretti S, Ansuinelli M, Vitale A, Elia L, Matarazzo M, Piciocchi A, et al. A multicenter total therapy strategy for de novo adult Philadelphia chromosome positive acute lymphoblastic leukemia patients: final results of the GIMEMA LAL1509 protocol. Haematologica. 2021;106(7):1828-38.
29. Ravandi F, Othus M, O'Brien SM, Forman SJ, Ha CS, Wong JYC, et al. US Intergroup Study of Chemotherapy Plus Dasatinib and Allogeneic Stem Cell Transplant in Philadelphia Chromosome Positive ALL. Blood Adv. 2016;1(3):250-9.
30. Ravandi F, O'Brien SM, Cortes JE, Thomas DM, Garris R, Faderl S, et al. Long-term follow-up of a phase 2 study of chemotherapy plus dasatinib for the initial treatment of patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Cancer. 2015;121(23):4158-64.
31. Shen S, Chen X, Cai J, Yu J, Gao J, Hu S, et al. Effect of Dasatinib vs Imatinib in the Treatment of Pediatric Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: A Randomized Clinical Trial. JAMA Oncol. 2020;6(3):358-66.
32. Kantarjian H, Short NJ, Jain N, Sasaki K, Huang X, Haddad FG, et al. Frontline combination of ponatinib and hyper-CVAD in Philadelphia chromosome-positive acute lymphoblastic leukemia: 80-months follow-up results. Am J Hematol. 2023;98(3):493-501.
33. Ribera JM, García-Calduch O, Ribera J, Montesinos P, Cano-Ferri I, Martínez P, et al. Ponatinib, chemotherapy, and transplant in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood Adv. 2022;6(18):5395-402.
34. Martinelli G, Papayannidis C, Piciocchi A, Robustelli V, Soverini S, Terragna C, et al. INCB84344-201: Ponatinib and steroids in frontline therapy for unfit patients with Ph+ acute lymphoblastic leukemia. Blood Adv. 2022;6(6):1742-53.
35. Jabbour E, Kantarjian HM, Aldoss I, Montesinos P, Leonard JT, Gómez-Almaguer D, et al. Ponatinib vs Imatinib in Frontline Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: A Randomized Clinical Trial. Jama. 2024;331(21):1814-23.
36. Luskin MR, Murakami MA, Keating J, Flamand Y, Winer ES, Garcia JS, et al. Asciminib plus dasatinib and prednisone for Philadelphia chromosome-positive acute leukemia. Blood. 2025;145(6):577-89.
37. Martinelli G, Boissel N, Chevallier P, Ottmann O, Gökbuget N, Topp MS, et al. Complete Hematologic and Molecular Response in Adult Patients With Relapsed/Refractory Philadelphia Chromosome-Positive B-Precursor Acute Lymphoblastic Leukemia Following Treatment With Blinatumomab: Results From a Phase II, Single-Arm, Multicenter Study. J Clin Oncol. 2017;35(16):1795-802.
38. Foà R, Bassan R, Vitale A, Elia L, Piciocchi A, Puzzolo MC, et al. Dasatinib-Blinatumomab for Ph-Positive Acute Lymphoblastic Leukemia in Adults. N Engl J Med. 2020;383(17):1613-23.

39. Jabbour E, Short NJ, Jain N, Huang X, Montalban-Bravo G, Banerjee P, et al. Ponatinib and blinatumomab for Philadelphia chromosome-positive acute lymphoblastic leukaemia: a US, single-centre, single-arm, phase 2 trial. Lancet Haematol. 2023;10(1):e24-e34.
40. Kantarjian H, Short NJ, Haddad FG, Jain N, Huang X, Montalban-Bravo G, et al. Results of the Simultaneous Combination of Ponatinib and Blinatumomab in Philadelphia Chromosome-Positive ALL. J Clin Oncol. 2024;42(36):4246-51.
41. Chiaretti S, Leoncin M, Elia L, Soddu S, Piciocchi A, Matarazzo M, et al. Efficacy and Toxicity of Frontline Ponatinib Plus Blinatumomab for Adult Ph+ ALL Patients of All Ages. Intermediate Analysis of the Gimema ALL2820. Blood. 2024;144(Supplement 1):835-.
42. Marcoux C, Kebriaei P. Transplant in ALL: who, when, and how? Hematology Am Soc Hematol Educ Program. 2024;2024(1):93-101.
43. Jain N, Roberts KG, Jabbour E, Patel K, Eterovic AK, Chen K, et al. Ph-like acute lymphoblastic leukemia: a high-risk subtype in adults. Blood. 2017;129(5):572-81.
44. Roberts KG, Gu Z, Payne-Turner D, McCastlain K, Harvey RC, Chen IM, et al. High Frequency and Poor Outcome of Philadelphia Chromosome-Like Acute Lymphoblastic Leukemia in Adults. J Clin Oncol. 2017;35(4):394-401.
45. Chiaretti S, Messina M, Della Starza I, Piciocchi A, Cafforio L, Cavalli M, et al. Philadelphia-like acute lymphoblastic leukemia is associated with minimal residual disease persistence and poor outcome. First report of the minimal residual disease-oriented GIMEMA LAL1913. Haematologica. 2021;106(6):1559-68.
46. Koller P, Saliba RM, Ledesma C, Rondon G, Popat U, Alousi A, et al. Outcomes in patients with CRLF2 overexpressed acute lymphoblastic leukemia after allogeneic hematopoietic cell transplantation. Bone Marrow Transplant. 2021;56(7):1746-9.
47. Aldoss I, Yang D, Tomasian V, Mokhtari S, Jackson R, Gu Z, et al. Outcomes of allogeneic hematopoietic cell transplantation in adults with fusions associated with Ph-like ALL. Blood Adv. 2022;6(17):4936-48.
48. Rahman ZA, Othman T, Saliba RM, Vanegas YAM, Mohty R, Ledesma C, et al. A Multicenter Analysis of Allogeneic Transplant Outcomes in Adults with Philadelphia-Like B-Cell Acute Lymphoblastic Leukemia in First Complete Remission. Transplant Cell Ther. 2024;30(12):1197-205.
49. Richard-Carpentier G, Kantarjian HM, Tang G, Yin CC, Khoury JD, Issa GC, et al. Outcomes of acute lymphoblastic leukemia with KMT2A (MLL) rearrangement: the MD Anderson experience. Blood Adv. 2021;5(23):5415-9.
50. Lafage-Pochitaloff M, Baranger L, Hunault M, Cuccuini W, Lefebvre C, Bidet A, et al. Impact of cytogenetic abnormalities in adults with Ph-negative B-cell precursor acute lymphoblastic leukemia. Blood. 2017;130(16):1832-44.
51. Kim R, Bergugnat H, Pastoret C, Pasquier F, Raffoux E, Larcher L, et al. Genetic alterations and MRD refine risk assessment for KMT2A-rearranged B-cell precursor ALL in adults: a GRAALL study. Blood. 2023;142(21):1806-17.
52. Moorman AV, Barretta E, Butler ER, Ward EJ, Twentyman K, Kirkwood AA, et al. Prognostic impact of chromosomal abnormalities and copy number alterations in adult B-cell precursor acute lymphoblastic leukaemia: a UKALL14 study. Leukemia. 2022;36(3):625-36.
53. Jabbour E, Searle E, Abdul-Hay M, Abedin S, Aldoss I, Alfonso Piérola A, et al. A First-in-Human Phase 1 Study of the Menin-KMT2A (MLL1) Inhibitor JNJ-75276617 in Adult Patients with Relapsed/Refractory Acute Leukemia Harboring KMT2A or NPM1 Alterations. Blood. 2023;142:57.
54. Aldoss I, Issa GC, Thirman M, DiPersio J, Arellano M, Blachly JS, et al. Revumenib Monotherapy in Patients with Relapsed/Refractory KMT2Ar Acute Leukemia: Topline Efficacy and Safety Results from the Pivotal Augment-101 Phase 2 Study. Blood. 2023;142(Supplement 2):LBA-5-LBA-.
55. Burmeister T, Ströh AS, Kehden B, Trautmann H, Meyer C, Marschalek R, et al. Measurable residual disease quantification in adult patients with KMT2A-rearranged acute lymphoblastic leukemia. Leukemia. 2024;38(7):1600-3.
56. Chalandon Y, Thomas X, Hayette S, Cayuela JM, Abbal C, Huguet F, et al. Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia. Blood. 2015;125(24):3711-9.
57. Kim DY, Joo YD, Lim SN, Kim SD, Lee JH, Lee JH, et al. Nilotinib combined with multiagent chemotherapy for newly diagnosed Philadelphia-positive acute lymphoblastic leukemia. Blood. 2015;126(6):746-56.
58. Wieduwilt MJ, Yin J, Wetzler M, Uy GL, Powell BL, Kolitz JE, et al. Dasatinib and dexamethasone followed by hematopoietic cell transplantation for adults with Ph-positive ALL. Blood Adv. 2021;5(22):4691-700.
59. Kim DY, Joo YD, Lim SN, Kim SD, Lee JH, Lee JH, et al. Nilotinib combined with multiagent chemotherapy for newly diagnosed Philadelphia-positive acute lymphoblastic leukemia. Blood. 2015;126(6):746-56.
60. Ghobadi A, Slade M, Kantarjian H, Alvarenga J, Aldoss I, Mohammed KA, et al. The role of allogeneic transplant for adult Ph+ ALL in CR1 with complete molecular remission: a retrospective analysis. Blood. 2022;140(20):2101-12.
61. Jabbour E, Short NJ, Ravandi F, Huang X, Daver N, DiNardo CD, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: long-term follow-up of a single-centre, phase 2 study. Lancet Haematol. 2018;5(12):e618-e27.
62. Foà R, Bassan R, Elia L, Piciocchi A, Soddu S, Messina M, et al. Long-Term Results of the Dasatinib-Blinatumomab Protocol for Adult Philadelphia-Positive ALL. J Clin Oncol. 2024;42(8):881-5.
63. Borowitz MJ, Devidas M, Hunger SP, Bowman WP, Carroll AJ, Carroll WL, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. Blood. 2008;111(12):5477-85.
64. Bassan R, Brüggemann M, Radcliffe HS, Hartfield E, Kreuzbauer G, Wetten S. A systematic literature review and meta-analysis of minimal residual disease as a prognostic indicator in adult B-cell acute lymphoblastic leukemia. Haematologica. 2019;104(10):2028-39.
65. Berry DA, Zhou S, Higley H, Mukundan L, Fu S, Reaman GH, et al. Association of Minimal Residual Disease With Clinical Outcome in Pediatric and Adult Acute Lymphoblastic Leukemia: A Meta-analysis. JAMA Oncol. 2017;3(7):e170580.
66. Ribera JM, Oriol A, Morgades M, Montesinos P, Sarrà J, González-Campos J, et al. Treatment of high-risk Philadelphia chromosome-negative acute lymphoblastic leukemia in adolescents and adults according to early cytologic response and minimal residual disease after consolidation assessed by flow cytometry: final results of the PETHEMA ALL-AR-03 trial. J Clin Oncol. 2014;32(15):1595-604.
67. Giebel S, Marks DI, Boissel N, Baron F, Chiaretti S, Ciceri F, et al. Hematopoietic stem cell transplantation for adults with Philadelphia chromosome-negative acute lymphoblastic leukemia in first remission: a position statement of the European Working Group for Adult Acute Lymphoblastic Leukemia (EWALL) and the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant. 2019;54(6):798-809.
68. Gökbuget N, Kneba M, Raff T, Trautmann H, Bartram CR, Arnold R, et al. Adult patients with acute lymphoblastic leukemia and molecular failure display a poor prognosis and are candidates for stem cell transplantation and targeted therapies. Blood. 2012;120(9):1868-76.
69. Dhédin N, Huynh A, Maury S, Tabrizi R, Beldjord K, Asnafi V, et al. Role of allogeneic stem cell transplantation in adult patients with Ph-negative acute lymphoblastic leukemia. Blood. 2015;125(16):2486-96; quiz 586.
70. Cazzaniga G, De Lorenzo P, Alten J, Röttgers S, Hancock J, Saha V, et al. Predictive value of minimal residual disease in Philadelphia-chromosome-positive acute lymphoblastic leukemia treated with imatinib in the European intergroup study of post-induction treatment of Philadelphia-chromosome-positive acute lymphoblastic leukemia, based on immunoglobulin/T-cell receptor and BCR/ABL1 methodologies. Haematologica. 2018;103(1):107-15.
71. Short NJ, Jabbour E, Macaron W, Ravandi F, Jain N, Kanagal-Shamanna R, et al. Ultrasensitive NGS MRD assessment in Ph+ ALL: Prognostic impact and correlation with RT-PCR for BCR::ABL1. Am J Hematol. 2023;98(8):1196-203.

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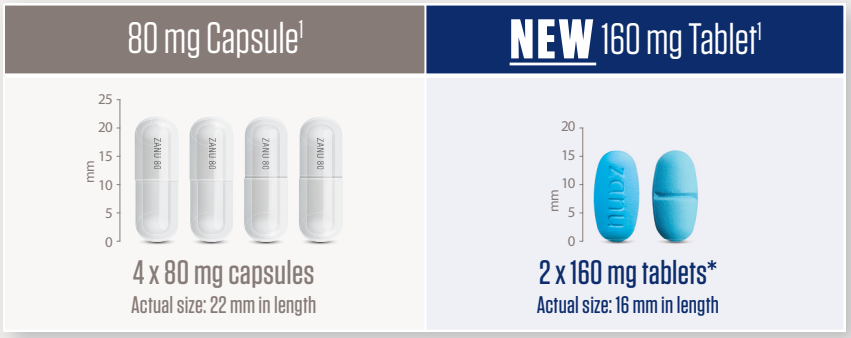

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Hemophagocytic Lymphohistiocytosis and Other Cytokine Storm Syndromes in Adults

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare and highly fatal syndrome of pathological immune activation leading to excessive inflammation, hypercytokinemia, and multi-organ failure.[1,2] HLH is broadly divided into primary HLH, driven mainly by genetic defects in cytotoxicity[3,4] and secondary HLH, a heterogeneous group of disorders with similar clinical and laboratory features to primary HLH, but characterized by hyperinflammation rather than defective cytotoxicity.[5] Primary HLH occurs nearly exclusively in children. Most adult HLH is secondary, often in the context of immunomodulatory therapy, infection, malignancy, autoimmune/autoinflammatory diseases, or immunodeficiency.

HLH falls under the umbrella concept of cytokine storm syndrome (CSS).[6] In 2020, the coronavirus disease 2019 (COVID-19) pandemic greatly amplified clinical interest and research in CSS,[6-8] and specifically the concept of a maladaptive immune response to infection.[9,10] Early on, COVID-19-CSS was compared to HLH.[11,12] However, HLH is mainly driven by the interferon-γ (IFN-γ)-chemokine ligand 9 (CXCL-9) axis, resulting in profound T cell and macrophage activation, and is characterized by very high ferritin and soluble CD25 (sCD25, synonymous with the alpha chain of the soluble interleukin (IL)-2 receptor), often with only modestly elevated C-reactive protein (CRP). In contrast, COVID-19-CSS is characterized by defective type I/type III interferon responses leading to excessive IL-6 signaling and very high CRP, which can be ameliorated by IL-6 inhibition.[13,14]

The increased interest in CSS spurred by COVID-19 has coincided with significant recent advances in our understanding of other CSS, such as thrombocytopenia, anasarca, fever/(reticulin) fibrosis, organomegaly, renal dysfunction (TAFRO) syndrome (typically associated with idiopathic multicentric Castleman disease, iMCD-TAFRO) and severe or catastrophic Still's disease. This review will provide practical guidance for clinicians in diagnosing adult HLH, differentiating it from TAFRO syndrome and Still's disease. Specifically, in section 3 and Table 2, we propose a heuristic (problem-solving strategy or shortcut) to decrease cognitive load when faced with an acutely ill patient with evolving CSS, with a focus on simple and readily available inflammatory markers (CRP, ferritin, sCD25). This heuristic can help clinicians make diagnostic and therapeutic decisions in real time.

Diagnosis of HLH

Diagnosis of HLH is challenging because initial symptoms are often nonspecific, yet prompt recognition is critical due to the rapidly progressive nature and high mortality of the disease. Clinicians should suspect HLH in patients with fever, unexplained cytopenias, hyperferritinemia, hepatosplenomegaly, liver enzyme elevation, coagulopathy, and neurologic findings, particularly in patients with predisposing conditions such as underlying lymphoproliferative disorder, autoimmune disorder, or viral infection. Diagnostic criteria and tools are summarized in **Table 1.**

The most widely used diagnostic criteria were derived from the HLH-2004 study, which was based on the observation of 369 pediatric patients, most of whom had primary HLH.[15] However, there are some limitations in applying these criteria to adults; for example, ferritin >500 µg/L is very nonspecific in adults,[16,17] and tests of cytotoxic function, such as natural killer (NK) cell activity or perforin expression by flow cytometry are rarely helpful in secondary

	HLH-2004[15]	HScore[19]	MS Score[21]
Primary Use	Pediatric HLH diagnosis	Adult HLH, predictive probability	MAS in autoimmune conditions
Key Features	Diagnosis requires presence of ≥5 of 8 criteria	Points-based score based on 9 variables	Weighted equation based on 7 variables
Ferritin	≥500 µg/L	>2,000 µg/L (weighted)	Yes
sCD25	>2400 IU/mL	Not used	Not used
LDH	Not used	Yes, Elevated (no cutoff specified)	Not used
Triglycerides	≥265 mg/dL	>132 mg/dL (weighted)	Not used
Cytopenias	Yes, ≥2 lineages	Hemoglobin <9 g/dL or platelets <100k	Yes, platelet count only
Hemophagocytosis	Yes	Yes	Not used
NK Cell Activity	Yes, decreased or absent	Not used	Not used
Fibrinogen	Yes, ≤150 mg/dL	Yes, ≤250 mg/dL	Yes
AST	Not used	Yes, >30 U/L	Not used
Hepatosplenomegaly	Yes	Yes	Not used
Fever	Yes, ≥38.5°C	Yes, ≥38.4°C	Not used
Threshold for Diagnosis	≥5 of 8 criteria	Score ≥169 (~80% HLH probability)	Score ≥-2.1 is suggestive of MAS in pediatrics and ≥-1.74 in adults
Advantages	Standardized, globally recognized	Quantitative, accommodates adults	Specific to autoimmune-associated MAS
Limitations	Not designed for adult patients; focused on cytotoxicity defects (NK function, genetic tests) rather than hyperinflammatory defects	Lack of markers of immune activation make it difficult to distinguish physiologic from pathologic immune activation	Limited applicability outside of pediatric JIA/Still's

Table 1. Diagnostic criteria and tools for HLH; *courtesy of Marian Goubran, MD and Luke Chen, MD, FRCPC, MMEd*

Abbreviations: AST: aspartate aminotransferase; **HLH:** hemophagocytic lymphohistiocytosis; **JIA:** juvenile idiopathic arthritis; **LDH:** lactate dehydrogenase; **MAS:** macrophage activation syndrome; **NK:** natural killer; **sCD25:** soluble CD25.

Typical ranges	CRP (<3.1 mg/L)	Ferritin (<300 µg/L)	sCD25* (<846 IU/mL)	Key pathology findings
HLH*	10-100 mg/L	>>3,000 µg /mL	>3,000 IU/mL	Hemophagocytosis (typically in bone marrow)
COVID-19 CSS	>100 mg/L	<3,000 µg /mL	<3,000 IU/mL	Vasculopathic changes, such as thickened, reactive endothelium in the skin[64] and intussusceptive angiogenesis in pulmonary vessels[65]
TAFRO	>>50 mg/L	<3,000 µg /mL	<3,000 IU/mL	Castleman changes in lymph node Vasculopathy is common[66] Hemophagocytes may be seen in bone marrow or tissue
Severe Still's disease	>100 mg/L	>3,000 µg /mL	<3,000 IU/mL	Skin: dyskeratotic/necrotic keratinocytes in superficial layers and vacuolar interface change [37]

Table 2. Typical inflammatory biomarker patterns and key pathology findings in four cytokine storm syndromes: a heuristic*[31,32]; *courtesy of Marian Goubran, MD and Luke Chen, MD, FRCPC, MMEd*

Abbreviations: COVID-19 CSS: coronavirus disease 2019 cytokine storm syndrome; **CRP:** C-reactive protein; **HLH:** hemophagocytic lymphohistiocytosis; **sCD25:** soluble CD25.

*Heuristic: problem solving method to decrease cognitive load.
**the authors use the "rule of 3,000" for diagnosing HLH – in most cases of adult HLH, ferritin is >3,000 µg/L and sCD25 is >3,000 IU/mL.

HLH.[18] A partial answer to this problem was the development of the HScore, which was designed to use widely available clinical and laboratory parameters to diagnose secondary HLH.[19] An HScore greater than 169 has a sensitivity of 93% and specificity of 86%, accurately classifies 90% of patients, and has similar utility to HLH-2004 in adults.[20] While the wide applicability of the HScore is one of its strengths, the deliberate omission of specialized tests of immune activation, such as sCD25 and cytokine/chemokine levels, also limits the ability of HScore to answer the practical question: "Does this patient have pathological immune activation (as opposed to a physiological response to infection, acute illness, liver disease, blood transfusion, etc.) as the explanation for their condition?"

HLH can often be triggered by an underlying autoimmune or autoinflammatory disorder (sometimes referred to as macrophage activation syndrome [MAS] in that context), and it can be challenging to distinguish between HLH and flare of pre-existing diseases such as lupus or juvenile idiopathic arthritis juvenile idiopathic arthritis (JIA)/Still's disease. Therefore, the MS score was developed based on pediatric patients to distinguish between patients with a flare of juvenile idiopathic arthritis and those with MAS/HLH. This score utilizes a weighted equation to calculate a score. A score of -2.1 or higher was shown to have 85% sensitivity and 95% specificity in distinguishing JIA from MAS.[21] A subsequent analysis in adult patients with Still's disease suggested a cutoff of ≥-1.74 for adult patients, which yielded a sensitivity of 93.5% and a specificity of 92.6% in diagnosing MAS.[22,23] We include the MS Score as an illustration of the evolving approach to diagnosing HLH; other specialized diagnostic criteria also exist for JIA, Still's disease, malignancies (most notably the

activation (e.g. IL-18, CXCL9) and cytotoxicity (NK function, perforin, and CD107a) must be sent out to the few centres that offer clinically validated tests (such as those in Toronto, Cincinnati, or the Mayo Clinic). This means the results are often not readily available for urgent therapeutic decisions. One exception is sCD25, for which the test is available in many centres. An important caveat for interpreting sCD25 is that the HLH-2004 cutoff of >2,400 IU/mL is based on the functional assay, whereas many labs utilize an enzyme-linked immunosorbent assay, which reports results in pg/mL. Unfortunately, there is no reliable conversion factor from pg/mL to IU/mL;[29] some labs suggest that 20,000 pg/mL is approximately the same as 2,400 IU/mL, but this can vary greatly depending on the laboratory and reagents used.

Considering these limitations in laboratory assessment of immune activation/hyperinflammation, we suggest a heuristic summarized in Table 2. The typical pattern for HLH includes very high ferritin and sCD25 levels (typically well over 3,000 µg/L and 3,000 IU/mL, respectively) and a modestly elevated CRP (often <100 mg/L).[30,31] In contrast, both Still's disease and TAFRO syndrome are driven largely by IL-1 (and its helper cytokine, IL-18) and IL-6 and, thus, have markedly elevated CRP levels that are often well over 100 mg/L. Further, both syndromes are characterized by low or modestly elevated sCD25, and Still's disease is well known to cause hyperferritinemia, albeit to a lesser degree than HLH.[31,32]

Still's disease is an autoinflammatory disease formerly called JIA in children and Still's disease in adults, while now both pediatric and adult cases fall under the umbrella term of Still's disease.[28,33] Like HLH, patients with Still's disease present with fever, hyperferritinemia, liver dysfunction, and organomegaly. Still's disease is typically more indolent than HLH but a subset of patients with Still's disease can present with a particularly severe illness known as catastrophic adult-onset Still's disease. These patients can be particularly challenging to distinguish from HLH.[34] CRP and sCD25 levels can help distinguish these two conditions: CRP levels >130 mg/L and sCD25 levels <3,900 IU/mL are more suggestive of Still's disease and differentiate between HLH and Still's with a sensitivity of 91% and specificity of 93%.[32] Additionally, tissue biopsy can be helpful in these patients. Importantly, hemophagocytosis in the bone marrow, liver, lymph node, and other tissues is nonspecific and can be observed in any type of CSS **(Figure 1A)**.[35,36] In Still's disease, particularly in patients with a persistent cutaneous eruption (more so than the more classic evanescent pink rash), skin biopsies may reveal dyskeratosis, apoptotic keratinocytes in the superficial epidermis and cornified layer, and vacuolar interface change. These histological findings are highly specific for Still's disease in the correct clinical context **(Figure 1B)**.[37]

TAFRO can also mimic HLH. In most cases, TAFRO is idiopathic (human herpesvirus-8 negative) multicentric Castleman's disease (iMCD-TAFRO), but TAFRO without lymphadenopathy or iMCD has been described as well.[38,39] TAFRO syndrome, first described in 2010, is a condition characterized by thrombocytopenia, anasarca (edema, pleural effusion, and ascites), fever, reticulin myelofibrosis (or renal insufficiency), and organomegaly (hepatosplenomegaly and lymphadenopathy).[40] Hemophagocytosis is often a feature of bone marrow, liver and other tissue biopsies in TAFRO **(Figure 1C)**. TAFRO is primarily driven by IL-6 and is, therefore, associated with more marked elevations in CRP than are typically seen in HLH [38], while hyperferritinemia is typically more modest in TAFRO. Anasarca is considered an obligatory feature of TAFRO. When diagnosing HLH, Still's disease, or TAFRO, tissue biopsy is crucial for TAFRO. Patients with lymphadenopathy (which is often small volume in TAFRO, <3 cm in short axis and modestly fludeoxyglucose-positron emission tomography avid) require urgent biopsy, which should be excisional whenever possible. iMCD-TAFRO is a clinicopathological diagnosis, and therefore, communication between clinician and pathologist is crucial. Often, the changes associated with MCD, such as regressed/atrophic germinal centers, expanded mantle zones with "onion skin" appearance, polyclonal plasmacytosis, prominent follicular dendritic cells, and hypervascularity, can be read as "reactive" or non-diagnostic if the pathologist is not aware that iMCD is in the clinical differential diagnosis **(Figure 1D)**.[27]

Management of HLH

Well-designed prospective clinical trials are lacking for CSS. The overall mortality for adult HLH is high, upward of 40% in most centres, and patients over 65 years and/or with critical illness have a very guarded prognosis. The HLH-94 study is the largest prospective study previously performed for HLH treatment, in which

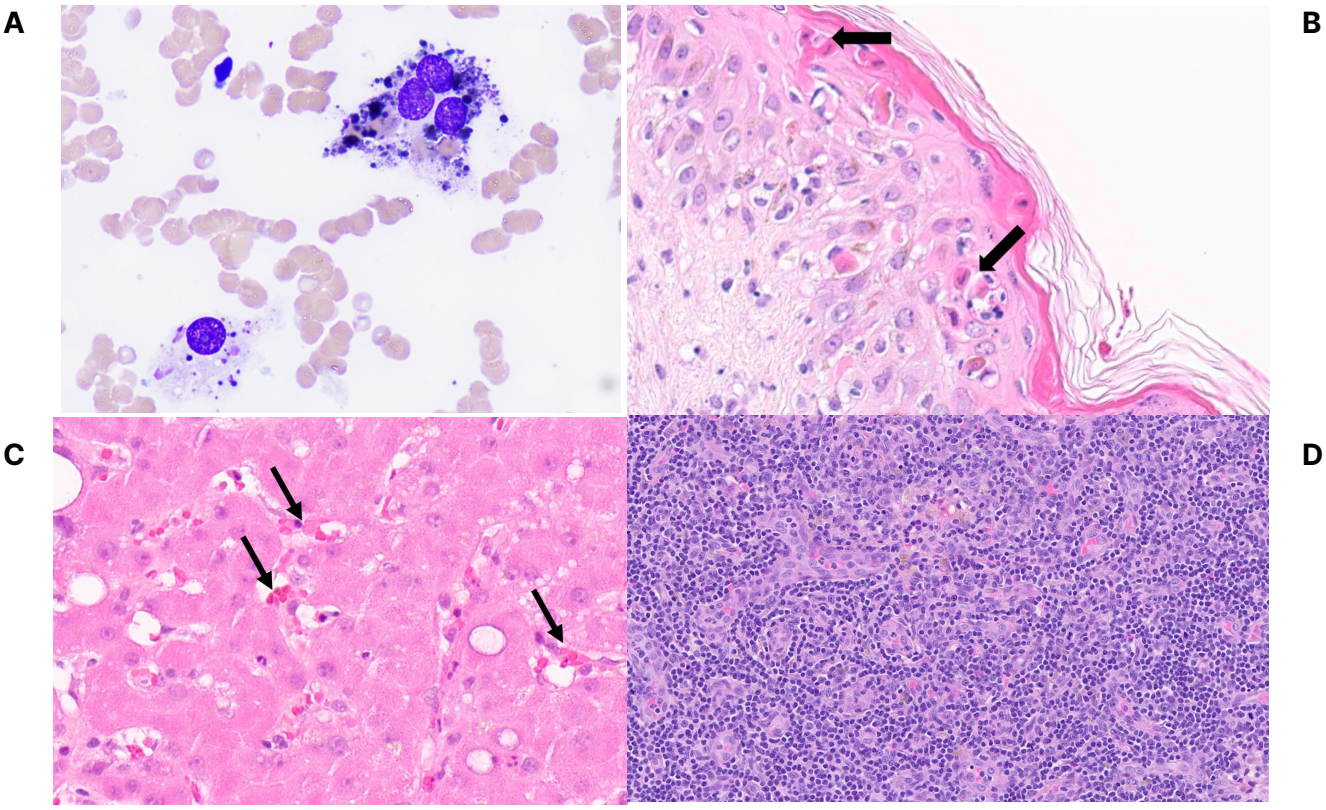

Figure 1. (A) Macrophages exhibiting haemophagocytic activity in the bone marrow of a 12-year-old girl with nodular lymphocyte-predominant Hodgkin lymphoma; *courtesy of Dr. Audi Setiadi, BC Children's Hospital*; (B) Dyskeratotic keratinocytes in the upper epidermis and cornified layer (arrows) of a 23-year-old female; characteristic of the persistent skin eruption in adult-onset Still's Disease; *courtesy of Dr. Sylvia Pasternak, Dalhousie University*; (C) Haematoxylin and eosin-stained core needle biopsy of liver showing reactive haemophagocytosis by sinusoidal Kupffer cells (arrows) in a 46-year-old man with iMCD-TAFRO; 400× magnification; *courtesy of Dr. Daniel Owen, Vancouver General Hospital*; (D) Lymph node showing hypervascular changes in a 22-year-old male with iMCD-TAFRO; *courtesy of Dr. Amrah Pirzada, Memorial University of Newfoundland*

optimized hyperinflammatory index), and critical illness.[24,25]

When approaching a patient with suspected HLH, in addition to a thorough history and physical examination, we order ferritin, sCD25, and CRP, and typically perform a bone marrow biopsy to look for specific causes such as lymphoma and infectious granulomas, as well as to examine for hemophagocytosis **(Figure 1)**. Infections, such as human immunodeficiency virus status, anaplasmosis (Atlantic Canada), Dengue fever, and tuberculosis should be assessed. We typically order Epstein-Barr virus (EBV) and cytomegalovirus viral loads (determined by PCR test). EBV is an important and distinctive cause of HLH associated with worse prognosis and, rarely, chronic active EBV.[26]

Distinguishing HLH from Other Cytokine Storm Syndromes

Identifying and accurately diagnosing patients with cytokine storm syndromes is a challenge for clinicians, particularly as these patients are often evaluated in the context of a busy inpatient consult service. While COVID-19-CSS is easily recognized because patients have an acute COVID-19 infection, HLH can be challenging to differentiate from other inflammatory syndromes, particularly severe Still's disease and iMCD-TAFRO. Diagnostic guidelines recommend measurement of cytokines such as IL-6 for iMCD,[27] and IL-18 for Still's disease,[28] but these are more helpful in theory than in practice for most clinicians. Many of the specialized tests of immune

249 pediatric patients with HLH were treated with etoposide-based therapies. This study showed significant improvement in overall survival to >50%, in a previously almost universally fatal disease.[41] While etoposide and corticosteroid-based therapy remain the standard for adults with secondary HLH,[42,43] new therapeutic tools are emerging.

Janus Kinase (JAK) inhibition with ruxolitinib has shown promise as an adjunctive therapy in HLH.[44-46] Several cytokines implicated in HLH, such as IL-2, IL-6, and IFN-γ, rely on JAK-dependent signalling pathways. Ruxolitinib has been examined as salvage therapy and is increasingly used as a first-line therapy as well for lower-risk patients, such as those with autoimmune/autoinflammatory HLH.[47-49] Our practice is to treat patients initially with dexamethasone and etoposide (often a lower dose of 75 mg/m^2) and then transition them to ruxolitinib-based therapy where possible to decrease exposure to corticosteroid and chemotherapy toxicity.

Emapalumab is a human monoclonal antibody directed against IFN-γ. It was initially studied in patients with primary HLH with relapsed/refractory disease, and response rates were greater than 60%, and overall survival was 70% at 12 months.[4] These results have also been confirmed in real-world data, in which response rates and overall survival rates were found to be comparable.[50] Studies in adults are limited, but small studies of patients with secondary HLH suggest a positive response.[51] Access to emapalumab is challenging in the Canadian context.

Other agents used to treat HLH include anakinra, an IL-1 antagonist, which may be particularly effective in patients with MAS.[52-54] IL-6 blockade with tocilizumab gained recognition in the era of the COVID-19 pandemic, where it demonstrated improved outcomes in patients with COVID-19-CSS. Small retrospective studies in HLH have also demonstrated a modest benefit in critically ill patients.[55-57] Nivolumab, an immune checkpoint inhibitor initially designed for cancer treatment, has been successfully used in patients with HLH secondary to EBV infection.[58,59]

In contrast, patients with severe Still's disease are typically treated with glucocorticoids initially. Those who are not responsive to steroids or have more severe disease can often benefit from either IL-1 or IL-6 blockade. In our experience, for severe Still's disease, rapid initiation of anakinra or tocilizumab is crucial for preventing end-organ damage and reducing toxicity from corticosteroids.[28,60,61]

The first-line treatment for iMCD-TAFRO is IL-6 inhibition with siltuximab (11 mg/kg intravenously [IV]) or tocilizumab (8 mg/kg, up to 800 mg, IV). Corticosteroids can be used as adjunctive therapy but should be tapered off quickly to minimize toxicity. Other agents that can be used for patients with relapsed or refractory disease include inhibitors of mammalian target of rapamycin, such as sirolimus, IL-1 antagonists, such as anakinra, tumour necrosis factor (TNF) inhibitors, such as adalimumab, thalidomide, and cytotoxic chemotherapy, such as lymphoma-based protocols.[39,62,63]

Conclusion

Clinicians must be able to differentiate HLH from disease mimickers, including disease entities such as Still's disease and the TAFRO variant of multicentric Castleman's disease. Simple inflammatory biomarkers (CRP, ferritin, sCD25), and histological findings from bone marrow, lymph node, and skin biopsies can be combined with clinical findings to arrive at a rapid working diagnosis. While etoposide-based therapies have classically been the mainstay of treatment, emerging therapies, including JAK inhibition and blockade of specific cytokines (IL-1, IL-6, IFN-γ, TNF), have an increasing role in treating patients.

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References

1. Hayden A, Park S, Giustini D, Lee AY, Chen LY. Hemophagocytic syndromes (HPSs) including hemophagocytic lymphohistiocytosis (HLH) in adults: A systematic scoping review. Blood Rev. 2016;30(6):411-20.
2. Setiadi A, Zoref-Lorenz A, Lee CY, Jordan MB, Chen LYC. Malignancy-associated haemophagocytic lymphohistiocytosis. The Lancet. 2022;9(3):e217-e27.
3. Jordan MB, Hildeman D, Kappler J, Marrack P. An animal model of hemophagocytic lymphohistiocytosis (HLH): CD8+ T cells and interferon gamma are essential for the disorder. Blood. 2004;104(3):735-43.

4. Locatelli F, Jordan MB, Allen C, Cesaro S, Rizzari C, Rao A, et al. Emapalumab in Children with Primary Hemophagocytic Lymphohistiocytosis. N Engl J Med. 2020;382(19):1811-22.
5. Carvelli J, Piperoglou C, Farnarier C, Vely F, Mazodier K, Audonnet S, et al. Functional and genetic testing in adults with HLH reveals an inflammatory profile rather than a cytotoxicity defect. Blood. 2020;136(5):542-52.
6. Fajgenbaum David C, June Carl H. Cytokine Storm. New England Journal of Medicine. 2020;383(23):2255-73.
7. England JT, Abdulla A, Biggs CM, Lee AYY, Hay KA, Hoiland RL, et al. Weathering the COVID-19 storm: Lessons from hematologic cytokine syndromes. Blood Rev. 2021;45:100707.
8. Cron RQ, Goyal G, Chatham WW. Cytokine Storm Syndrome. Annual Review of Medicine. 2023;74(1):321-37.
9. Chen LYC, Quach TTT. COVID-19 cytokine storm syndrome: a threshold concept. The Lancet Microbe. 2021;2(2):e49-e50.
10. Zhang Q, Bastard P, Bolze A, Jouanguy E, Zhang S-Y, Effort CHG, et al. Life-Threatening COVID-19: Defective Interferons Unleash Excessive Inflammation. Med (New York, NY). 2020;1(1):14-20.
11. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-4.
12. Lucas C, Wong P, Klein J, Castro TBR, Silva J, Sundaram M, et al. Longitudinal analyses reveal immunological misfiring in severe COVID-19. Nature. 2020.
13. Chen LYC, Hoiland RL, Stukas S, Wellington CL, Sekhon MS. Confronting the controversy: interleukin-6 and the COVID-19 cytokine storm syndrome. The European Respiratory Journal. 2020;56(4):2003006.
14. Stukas S, Goshua G, Kinkade A, Grey R, Mah G, Biggs CM, et al. Reduced fixed dose tocilizumab 400 mg IV compared to weight-based dosing in critically ill patients with COVID-19: A before-after cohort study. Lancet Reg Health Am. 2022;11:100228.
15. Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48(2):124-31.
16. Chen LYC, Hayden A, Mattman A. Extreme hyperferritinaemia, soluble interleukin-2 receptor, and haemophagocytic lymphohistiocytosis. Br J Haematol. 2019;185(3):605-6.
17. Rubin TS, Zhang K, Gifford C, Lane A, Choo S, Bleesing JJ, et al. Perforin and CD107a testing is superior to NK cell function testing for screening patients for genetic HLH. Blood. 2017;129(22):2993-9.
18. Fatma A, Raida BS, Mourad C, Ikram D, Zouheir B, Henda E. Performances of the H-score and the HLH-2004 score in the positive diagnosis of secondary hemophagocytic lymphohistiocytosis. Curr Res Transl Med. 2023;72(2):103430.
19. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol. 2014;66(9):2613-20.
20. Bilston L, Croden J, Taparia M, Karkhaneh M, Grossman J, Sun HL. Validation of the HScore and the HLH-2004 diagnostic criteria for the diagnosis of hemophagocytic lymphohistiocytosis in a multicenter cohort. Eur J Haematol. 2022;109(2):129-37.
21. Minoia F, Bovis F, Davì S, Horne A, Fischbach M, Frosch M, et al. Development and initial validation of the MS score for diagnosis of macrophage activation syndrome in systemic juvenile idiopathic arthritis. Ann Rheum Dis. 2019;78(10):1357-62.
22. Yao H, Wang Y, Wang Z, Zhao J, Deng X, Zhang Z, et al. The performance of the diagnostic scoring system or criteria for macrophage activation syndrome in systemic juvenile idiopathic arthritis for adult-onset Still's disease. A multicentre case-control study in China. Clin Exp Rheumatol. 2021;39 Suppl 132(5):129-34.
23. Zhang L, Yang X, Li TF, Liu X, Liu S. Comparison of MS score and HScore for the diagnosis of adult-onset Still's disease-associated macrophage activation syndrome. Ann Rheum Dis. 81. England2022. p. e99.
24. Zoref-Lorenz A, Murakami J, Hofstetter L, Iyer S, Alotaibi AS, Mohamed SF, et al. An improved index for diagnosis and mortality prediction in malignancy-associated hemophagocytic lymphohistiocytosis. Blood. 2022;139(7):1098-110.
25. Knaak C, Nyvlt P, Schuster FS, Spies C, Heeren P, Schenk T, et al. Hemophagocytic lymphohistiocytosis in critically ill patients: diagnostic reliability of HLH-2004 criteria and HScore. Critical Care. 2020;24(1):244.
26. Goubran M, McGinnis E, Stubbins RJ, Nicolson H, Pourshahnazari P, Belga S, et al. A young woman with persistent sore throat, Epstein-Barr virus, lymphadenopathy, and aberrant CD4 + CD7- T-cells. Am J Hematol. 2023;98(5):824-9.
27. Fajgenbaum DC, Uldrick TS, Bagg A, Frank D, Wu D, Srkalovic G, et al. International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. Blood. 2017;129(12):1646-57.
28. Fautrel B, Mitrovic S, De Matteis A, Bindoli S, Antón J, Belot A, et al. EULAR/PReS recommendations for the diagnosis and management of Still's disease, comprising systemic juvenile idiopathic arthritis and adult-onset Still's disease. Annals of the Rheumatic Diseases. 2024:ard-2024-225851.
29. Martin BA. Just in time: mal-HLH in Sweden, 1997 to 2018. Blood. 2024;143(3):187-8.
30. Hayden A, Lin M, Park S, Pudek M, Schneider M, Jordan MB, et al. Soluble interleukin-2 receptor is a sensitive diagnostic test in adult HLH. Blood advances. 2017;1(26):2529-34.
31. Goubran M, Spaner C, Stukas S, Zoref-Lorenz A, Shojania K, Beckett M, et al. The role of C-reactive protein and ferritin in the diagnosis of HLH, adult-onset still's disease, and COVID-19 cytokine storm. Scientific reports. 2024;14(1):31306.
32. Beckett M, Spaner C, Goubran M, Wade J, Avina-Zubieta JA, Setiadi A, et al. CRP and sCD25 help distinguish between adult-onset Still's disease and HLH. Eur J Haematol. 2024.
33. Ruscitti P, Cantarini L, Nigrovic PA, McGonagle D, Giacomelli R. Recent advances and evolving concepts in Still's disease. Nat Rev Rheumatol. 2024.

34. Wahbi A, Tessoulin B, Bretonnière C, Boileau J, Carpentier D, Decaux O, et al. Catastrophic adult-onset Still's disease as a distinct life-threatening clinical subset: case–control study with dimension reduction analysis. Arthritis research & therapy. 2021;23(1):1-10.
35. Abdelhay A, Mahmoud AA, Al Ali O, Hashem A, Orakzai A, Jamshed S. Epidemiology, characteristics, and outcomes of adult haemophagocytic lymphohistiocytosis in the USA, 2006–19: a national, retrospective cohort study. eClinicalMedicine. 2023;62.
36. Chandra H, Chandra S, Kaushik R, Bhat N, Shrivastava V. Hemophagocytosis on bone marrow aspirate cytology: single center experience in north himalayan region of India. Ann Med Health Sci Res. 2014;4(5):692-6.
37. Chong DHY, Pasternak S, Taylor T, Armstrong S, Purdy K, Chen LYC. Skin biopsy findings of dyskeratotic keratinocytes and vacuolar interface change in a patient with Still's disease. The Lancet. 2024;404(10467):e6.
38. Iwaki N, Fajgenbaum DC, Nabel CS, Gion Y, Kondo E, Kawano M, et al. Clinicopathologic analysis of TAFRO syndrome demonstrates a distinct subtype of HHV-8-negative multicentric Castleman disease. Am J Hematol. 2016;91(2):220-6.
39. Nishimura Y, Fajgenbaum DC, Pierson SK, Iwaki N, Nishikori A, Kawano M, et al. Validated international definition of the thrombocytopenia, anasarca, fever, reticulin fibrosis, renal insufficiency, and organomegaly clinical subtype (TAFRO) of idiopathic multicentric Castleman disease. Am J Hematol. 2021;96(10):1241-52.
40. Takai K, Nikkuni K, Shibuya H, Hashidate H. [Thrombocytopenia with mild bone marrow fibrosis accompanied by fever, pleural effusion, ascites and hepatosplenomegaly]. Rinsho Ketsueki. 2010;51(5):320-5.
41. Henter JI, Aricò M, Egeler RM, Elinder G, Favara BE, Filipovich AH, et al. HLH-94: a treatment protocol for hemophagocytic lymphohistiocytosis. HLH study Group of the Histiocyte Society. Med Pediatr Oncol. 1997;28(5):342-7.
42. Ehl S, Astigarraga I, von Bahr Greenwood T, Hines M, Horne A, Ishii E, et al. Recommendations for the Use of Etoposide-Based Therapy and Bone Marrow Transplantation for the Treatment of HLH: Consensus Statements by the HLH Steering Committee of the Histiocyte Society. The journal of allergy and clinical immunology. 2018;6(5):1508-17.
43. La Rosée P, Horne A, Hines M, von Bahr Greenwood T, Machowicz R, Berliner N, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood. 2019;133(23):2465-77.
44. Keenan C, Nichols KE, Albeituni S. Use of the JAK Inhibitor Ruxolitinib in the Treatment of Hemophagocytic Lymphohistiocytosis. Front Immunol. 2021;12:614704.
45. Wang J, Zhang R, Wu X, Li F, Yang H, Liu L, et al. Ruxolitinib-combined doxorubicin-etoposide-methylprednisolone regimen as a salvage therapy for refractory/relapsed haemophagocytic lymphohistiocytosis: a single-arm, multicentre, phase 2 trial. Br J Haematol. 2021;193(4):761-8.
46. Zhou L, Liu Y, Wen Z, Yang S, Li M, Zhu Q, et al. Ruxolitinib combined with doxorubicin, etoposide, and dexamethasone for the treatment of the lymphoma-associated hemophagocytic syndrome. J Cancer Res Clin Oncol. 2020;146(11):3063-74.
47. Zhao L, Yang H, Qu WY, Lu YJ, Feng Z. Case report: Ruxolitinib plus dexamethasone as first-line therapy in haemophagocytic lymphohistiocytosis. Front Oncol. 2023;13:1054175.
48. Wang J, Wang Y, Wu L, Wang X, Jin Z, Gao Z, et al. Ruxolitinib for refractory/relapsed hemophagocytic lymphohistiocytosis. Haematologica. 2020;105(5):e210-e2.
49. Merrill SA, Spaner C, Chen LYC. Goodbye etoposide? Taking the leap to ruxolitinib in haemophagocytic lymphohistiocytosis. Br J Haematol. 2024.
50. Chandrakasan S, Jordan MB, Baker A, Behrens EM, Bhatla D, Chien M, et al. Real-world treatment patterns and outcomes in patients with primary hemophagocytic lymphohistiocytosis treated with emapalumab. Blood advances. 2024;8(9):2248-58.
51. Chandrakasan S, Allen CE, Bhatla D, Carter J, Chien M, Cooper R, et al. Emapalumab Treatment in Patients With Rheumatologic Disease-Associated Hemophagocytic Lymphohistiocytosis in the United States: A Retrospective Medical Chart Review Study. Arthritis Rheumatol. 2024.
52. Lee BJ. Improved survival outcomes with anakinra over etoposide-based therapies for the management of adults with hemophagocytic lymphohistiocytosis: a retrospective multicenter research network study. Ther Adv Hematol. 2024;15:20406207241245517.
53. Naymagon L. Anakinra for the treatment of adult secondary HLH: a retrospective experience. Int J Hematol. 2022;116(6):947-55.
54. Rajasekaran S, Kruse K, Kovey K, Davis AT, Hassan NE, Ndika AN, et al. Therapeutic role of anakinra, an interleukin-1 receptor antagonist, in the management of secondary hemophagocytic lymphohistiocytosis/sepsis/multiple organ dysfunction/macrophage activating syndrome in critically ill children*. Pediatr Crit Care Med. 2014;15(5):401-8.
55. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397(10285):1637-45.
56. Kim JY, Kim M, Park JK, Lee EB, Park JW, Hong J. Limited efficacy of tocilizumab in adult patients with secondary hemophagocytic lymphohistiocytosis: a retrospective cohort study. Orphanet Journal of Rare Diseases. 2022;17(1):363.
57. Dufranc E, Del Bello A, Belliere J, Kamar N, Faguer S, group Ts. IL6-R blocking with tocilizumab in critically ill patients with hemophagocytic syndrome. Crit Care. 24. England2020. p. 166.
58. Liu P, Pan X, Chen C, Niu T, Shuai X, Wang J, et al. Nivolumab treatment of relapsed/refractory Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis in adults. Blood. 2020;135(11):826-33.
59. Sun J, Luo P, Guo Y, He Y, Wang C. Clinical Features, Treatment, and Outcomes of Nivolumab-Induced Hemophagocytic Lymphohistiocytosis. J Immunother. 2024.

60. Bindoli S, De Matteis A, Mitrovic S, Fautrel B, Carmona L, De Benedetti F. Efficacy and safety of therapies for Still's disease and macrophage activation syndrome (MAS): a systematic review informing the EULAR/PReS guidelines for the management of Still's disease. Annals of the Rheumatic Diseases. 2024;83(12):1731-47.
61. Leavis HL, van Daele PLA, Mulders-Manders C, Michels R, Rutgers A, Legger E, et al. Management of adult-onset Still's disease: evidence- and consensus-based recommendations by experts. Rheumatology. 2023;63(6):1656-63.
62. Fajgenbaum DC, Langan RA, Japp AS, Partridge HL, Pierson SK, Singh A, et al. Identifying and targeting pathogenic PI3K/AKT/mTOR signaling in IL-6-blockade-refractory idiopathic multicentric Castleman disease. J Clin Invest. 2019;129(10):4451-63.
63. Mumau M, Irvine A, Ma C, Pierson SK, Shaw B, Gonzalez MV, et al. A Translational Approach to Identifying and Targeting TNF Signaling in Idiopathic Multicentric Castleman Disease. Blood. 2023;142:3921.
64. Domizio JD, Gulen MF, Saidoune F, Thacker VV, Yatim A, Sharma K, et al. The cGAS-STING pathway drives type I IFN immunopathology in COVID-19. Nature. 2022;603(7899):145-51.
65. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med. 2020;383(2):120-8.
66. Campbell CM, Owen DR, Montazeripouragha A, McCormick I, Fajgenbaum DC, Chen LYC. Idiopathic multicentric Castleman disease with arteriolar endotheliopathy and secondary haemophagocytosis. The Lancet Haematology. 2022;9(7):e546.

First bispecific antibody indicated in the treatment of the triple-class exposed patients with R/R MM[1,2*]

TECVAYLI® has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization.[1]

TECVAYLI® (teclistamab injection) is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received ≥3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.[1]

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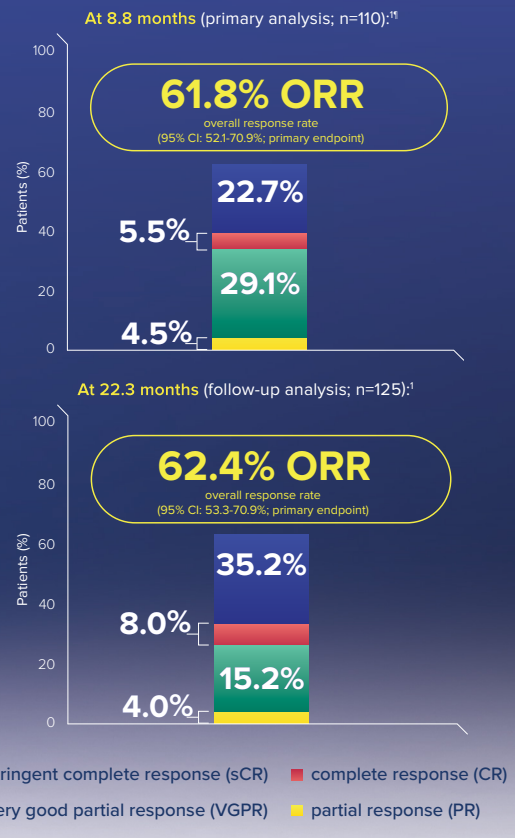
Efficacy profile investigated in the open-label MajesTEC-1 trial:[1¶§]



Adapted from TECVAYLI® Product Monograph[1]

Clinical use:

Pediatrics (<18 years of age): not authorized for pediatric use.

Most serious warnings and precautions:

Cytokine release syndrome (CRS): can occur in patients receiving TECVAYLI®, including life-threatening or fatal reactions. Initiate treatment with TECVAYLI® step-up dosing schedule to reduce the risk of CRS. Monitor patients for signs or symptoms of CRS. Withhold TECVAYLI® until CRS resolves, provide supportive care and treatment as needed, or permanently discontinue based on severity.

Serious or life-threatening neurologic toxicities: can occur following treatment with TECVAYLI®, including immune effector cell-associated neurotoxicity syndrome (ICANS). The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. Monitor patients for signs or symptoms of neurologic toxicity, including ICANS, during treatment. Withhold TECVAYLI® until neurologic toxicity resolves or permanently discontinue based on severity.

Other relevant warnings and precautions:

- Driving and operating machinery during and for 48 hours after completion of TECVAYLI® step-up dosing schedule and in the event of new onset of any neurological symptoms
- Hypogammaglobulinemia
- Neutropenia and febrile neutropenia
- Severe, life-threatening, or fatal infections
- New/reactivated viral or opportunistic infections
- Progressive multifocal leukoencephalopathy (PML), which can be fatal
- Hepatitis B virus reactivation
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- Neurologic toxicities
- Live viral vaccines are not recommended
- Not recommended for women who are pregnant or breastfeeding
- Patients should use effective contraception

For more information:

Please consult the Product Monograph at innovativemedicine.jnj.com/canada/our-medicines for important information relating to contraindications, adverse reactions, drug interactions, and dosing/administration that has not been discussed in this piece.

The Product Monograph is also available by calling 1-800-567-3331.

R/R MM=relapsed/refractory multiple myeloma; CD38=cluster of differentiation 38; CI=confidence interval; CRS=cytokine release syndrome; HBV=hepatitis B virus; IRC=Independent Review Committee; IMWG=International Myeloma Working Group; PML=progressive multifocal leukoencephalopathy; PR=partial response; Q2W=every 2 weeks; SC=subcutaneous; sCR=stringent CR; CR=complete response; VGPR=very good PR.

* Comparative clinical significance unknown.

† Phase 1/2, single arm, open-label, multicentre study in adults with R/R MM who had received ≥3 prior therapies, including a proteasome inhibitor, immunomodulatory agent and anti-CD38 monoclonal antibody. Patients received initial step-up doses of 0.06 mg/kg and 0.3 mg/kg administered SC, followed by 1.5 mg/kg SC once-weekly thereafter until disease progression or unacceptable toxicity. Patients who had a CR or better for ≥6 months were eligible to reduce dosing frequency to 1.5 mg/kg SC Q2W until disease progression or unacceptable toxicity. Efficacy population treated at the pivotal study dose in Phase 2 had a median duration of follow-up of 8.8 months at the primary analysis.

‡ ORR was a composite of sCR + CR + VGPR + PR as determined by the IRC assessment using IMWG 2016 criteria.

§ Follow-up analysis included 15 additional patients since the primary analysis.

¶ Efficacy population treated at the pivotal dose in Phase 2.

References: 1. TECVAYLI® (teclistamab injection) Product Monograph. Janssen Inc. August 29, 2024. **2.** Data on file, Janssen Inc.

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TECVAYLI (teclistamab) Injection for subcutaneous use 10 mg/mL and 90 mg/mL
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Diagnosis and Management of Small Lymphocytic Lymphoma (SLL) Versus Chronic Lymphocytic Leukemia (CLL) in 2025

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Introduction

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are recognized as a single disease entity with distinct phenotypic manifestations, characterized by predominant peripheral blood (PB) involvement in CLL and nodal and/or splenic disease in SLL[1-3]. This article explores the historically divergent approaches taken to treat CLL and SLL, highlights recent advances in understanding their shared biology, and advocates for a unified approach to real-world management and clinical trial eligibility for both conditions.

Disease Definitions and Nomenclature

CLL and SLL are both characterized by an abnormal accumulation of clonal mature B lymphocytes aberrantly co-expressing CD5 and CD23.[1] The immunophenotype shared by CLL and SLL is characterized by expression of CD19 and CD5, and dim surface expression of immunoglobulin (Ig)M/IgD, CD20, CD22, and CD79b, while CD23 and CD200 are strongly positive.[2] According to the 2018 International Workshop on CLL (iwCLL) guidelines, CLL is defined by the persistence of ≥5×10^9/L clonal B cells in the PB for ≥3 months or by cytopenias due to bone marrow (BM) infiltration.[1] For patients with <5×10^9/L clonal B cells in the PB, SLL is diagnosed in the presence of lymphadenopathy and/or organomegaly, whereas these are absent in monoclonal B cell lymphocytosis.

Biology of SLL Versus CLL

Few studies have attempted to characterize the molecular features of SLL, but the available data suggest only minor biological differences between SLL and CLL. Moia *et al.* compared the molecular features of PB, lymph node (LN), and circulating tumour DNA (ctDNA) from patients with SLL using multiregional sequencing.[4] Surprisingly, only 22% of representative gene mutations were common in all three compartments, in contrast to diffuse large B-cell lymphoma (DLBCL) and Hodgkin lymphoma, in which ctDNA is more representative of the tumour. Tooze *et al.* compared chemokine receptors expression, DNA single nucleotide polymorphism microarray analysis, and proteomic profiling between CLL and SLL to determine the biological basis of their slightly different clinical presentations.[5] CXC motif chemokine receptor (CXCR)3 and CXCR4, receptors involved in migration and homing, were more strongly expressed in CLL, whereas CD49b, an adhesion molecule, was more strongly expressed in SLL.

Martinez-Trillos *et al.* described a large dataset of 777 patients with CLL and 113 with SLL and compared clinical features and the mutational landscape.[6] When patients with Rai stage 0 and Binet stage A (stage A0) CLL were excluded, the only significantly different biologic features of SLL were higher expression of CD38, CD49d, and trisomy 12, none of which alter clinical management. There was no difference in deletion 17p (del[17p]) between SLL and CLL, in agreement with earlier studies.[3] Gene expression profiles from blood also revealed no differences between CLL and SLL, further supporting their shared underlying biology.

Clinical Presentation of SLL

Similar to CLL, the median age at diagnosis of SLL is approximately 70-75 years.[5-10] Most patients present with lymphadenopathy (>95%), while some exhibit splenomegaly (>25%), low-level PB or BM involvement, or, less commonly, other extranodal organ involvement (5-20%).[7,9] A proportion (5-20%) of patients with SLL appear to have localized disease,[3,6-9] although rigorous evaluation for PB or BM involvement may uncover evidence of disease elsewhere. Constitutional or "B" symptoms are infrequent.[7-9] A subset of patients with SLL may develop a more clinically aggressive presentation consistent with 'accelerated CLL/SLL' or Richter transformation to DLBCL.[7]

Most patients with SLL present with a relatively normal complete blood count, since the presence of ≥5×10^9/L circulating clonal B cell lymphocytes or any cytopenias attributable to bone marrow involvement are classified as CLL.[1] However, lymphocytosis may emerge in the PB over time, as some patients with SLL progress to an overt CLL phenotype or vice versa.[6, 7, 9] Evolution to the leukemic phase does not affect patient outcomes.[6] Of note, older studies reported a higher prevalence of BM involvement (43-92%) or cytopenias (4-15%) among patients with SLL,[3,11] but these were published before the 2018 iwCLL diagnostic criteria for SLL were revised to mandate an "absence of cytopenias caused by a clonal marrow infiltrate".[1]

Diagnostic evaluation of SLL

An LN biopsy is typically required to establish a diagnosis of SLL, but if PB flow cytometry is consistent with a CLL immunophenotype (with <5×10^9/L clonal B cells) and physical exam or imaging reveals enlarged lymph nodes, the diagnosis of SLL can be inferred. Diagnostic imaging is generally not required for the initial staging or response assessment of CLL/SLL in routine clinical practice, but may be performed for clinical trial enrolment, to determine tumour lysis risk prior to venetoclax, or for patients with suspected Richter transformation.[1] Patients with SLL should undergo testing for molecular prognostic markers (e.g. *IGHV* mutation status, *TP53* mutation status, cytogenetics) of PB, LN, and/or BM whenever possible,[12] although this appears to be seldom performed in routine clinical practice.[7] In the absence of sufficient malignant cells in the PB and BM, LN tissue can be used for next-generation sequencing for *TP53* mutation status and fluorescence in situ hybridization for del(17p), with the caveats that fresh or frozen tissue always is preferred over formalin-fixed tissue, due to DNA degradation and that local laboratory capabilities for each test vary.[13]

Treatment Guidelines for SLL

Many patients with SLL are asymptomatic at diagnosis and may initially be managed with active surveillance until the iwCLL criteria for treatment initiation are met.[1] The most common indications for initiating treatment include progressive or symptomatic lymphadenopathy or splenomegaly, refractory immune-mediated cytopenias, or extranodal involvement.[7] Patients with SLL were observed to have a shorter time to first treatment than those with CLL in one study, although this difference did not persist when stage-matched patients with SLL and CLL were compared.[6]

Historically, many patients with SLL were treated using therapeutic approaches developed for follicular lymphoma and other nodal indolent B cell non-Hodgkin lymphomas (iNHL) instead of CLL. This is exemplified by a 2015 Italian Society of Hematology guideline that recommended similar management strategies for SLL, marginal zone lymphoma, and lymphoplasmacytic lymphoma.[14] However, advances in understanding the shared biology of CLL and SLL have led to a growing consensus that patients with SLL should be treated identically to those with CLL. This is reflected in contemporary guidelines from Canada,[15] China,[16] the European Society for Medical Oncology (ESMO),[17], Lymphoma Research Foundation,[18] and the United States National Comprehensive Cancer Network (NCCN),[19] all of which recommend similar treatment approaches for both conditions. However, the treatment of SLL is not explicitly addressed by guidelines published by the British Society for Haematology,[20,21] or the Australasian[22] and Dutch HOVON[23] groups, underscoring the continuing need to clarify and harmonize the management of SLL and CLL between regions.

The sole distinction between CLL and SLL within treatment guidelines pertains to the potential use of radiation therapy for patients with symptomatic localized SLL, which is mentioned as a treatment option in the ESMO and NCCN guidelines, among others.[14,16,17,19] However, data supporting this approach are limited to small

cohorts in the modern era and suggest relatively high relapse rates with this strategy.[24]

Representation of SLL in CLL Clinical Trials

Patients with SLL have unfortunately been excluded from numerous pivotal clinical trials for CLL, including the CLL10, CLL11, CLL13, CLL14, A041202, ELEVATE-TN, ELEVATE-RR, and MURANO trials. Indeed, an analysis of 56 Phase II and III clinical trials cited in the 2024 NCCN guidelines revealed that patients with SLL were explicitly included in only 38% of CLL clinical trials between 1999 and 2020.[25] Paradoxically, patients with SLL were instead enrolled in numerous non-CLL clinical trials dedicated to follicular lymphoma and other indolent B cell lymphomas during this period, including the StiL NHL1 and GADOLIN trials. The inclusion of SLL in CLL clinical trials has varied between classes of therapies, ranging from 0% of clinical trials evaluating chemoimmunotherapy or BCL2 inhibitors to 67% of those focused on Bruton's tyrosine kinase (BTK) inhibitors or BTK and BCL2 inhibitor combinations.[25]

The arbitrary exclusion of patients with SLL from CLL clinical research represents a significant barrier to clinical trial participation and equitable access to innovative cancer therapies. To resolve this dilemma, the 2018 iwCLL guidelines stipulated that "the inclusion of patients with SLL in clinical trials for CLL is encouraged".[1] Reassuringly, the inclusion of patients with SLL among the CLL clinical trials cited in the NCCN guidelines has grown over time, rising from 13% in studies that began enrollment between 1999 and 2012 to 55% in those initiated from 2013 onward.[25] Furthermore, patients with SLL appear to be eligible for 77% of the actively accruing or planned CLL clinical trials registered with ClinicalTrials.gov as of November 2024.[25] Despite these promising improvements in clinical trial design, patients with SLL remain ineligible from several recent or ongoing trials, including the AMPLIFY, CELESTIAL-TNCLL, and CLL17 trials, highlighting the ongoing need to support the inclusion of SLL in CLL clinical research.

Real-world Management of SLL

Management of SLL in clinical practice remains highly variable, reflecting the historical exclusion of patients with SLL from CLL clinical trials and previous inconsistencies in treatment guidelines. A retrospective study of 60 patients with SLL treated in Alberta between 2015 and 2022 found that 55% received suboptimal therapies traditionally used for indolent B cell lymphomas rather than CLL-specific regimens.[7] These included rituximab monotherapy, maintenance rituximab, lower doses of rituximab used for iNHL than for CLL, anthracycline- or platinum-based chemoimmunotherapy, and even autologous stem cell transplantation.[7] Although patients initiating treatment between 2019 and 2022 were more likely to receive therapies consistent with CLL guidelines compared to those treated between 2015 and 2018 (64% versus 28%), some patients with SLL continued to receive chemoimmunotherapy or rituximab monotherapy instead of a publicly funded BTK or BCL2 inhibitors.[7] Similar patterns of divergent treatment practices for SLL have been reported in studies conducted in Europe and the United States.[8-10]

Given the robust clinical trial evidence supporting the superior efficacy and tolerability of novel targeted agents compared to chemoimmunotherapy in CLL, it is likely that patients with SLL would derive similar benefits from CLL-directed treatments rather than regimens traditionally employed for iNHL. Subgroup analyses from the SEQUOIA and HELIOS trials suggest comparable efficacy of BTK inhibitors in both the CLL and SLL populations,[26-28] although definitive conclusions are limited due to the small number of patients with SLL enrolled. Real-world data further support the effectiveness of BTK and BCL2 inhibitors in small cohorts of patients with SLL.[7,9] However, additional clinical trial and real-world evidence is needed to better characterize the risks and benefits of novel CLL therapies in SLL, particularly given the preferential activity of BTK inhibitors in nodal disease, the increased risk of tumour lysis syndrome associated with BCL2 inhibitors in cases of bulky adenopathy, and the uncertain applicability of measurable residual disease directed treatment strategies to patients without overt PB involvement.[25]

Conclusions

SLL and CLL represent the same disease entity but differ slightly in clinical presentation. Distinguishing SLL from CLL is largely academic, as there are shared biological features, frequent evolution from one disease phenotype to the other, similar response rates to treatment, and no discernible differences in outcomes. The

arbitrary distinction between SLL and CLL can have negative consequences for patients, such as exclusion from access to novel therapies in publicly funded healthcare systems and significant emotional distress or confusion when patients are informed they have lymphoma and, subsequently, leukemia. Although many guidelines now state that CLL and SLL should be treated identically, some fail to address SLL explicitly and many clinical trials restrict enrolment to CLL and exclude SLL without justification. Going forward, we recommend that clinical trial sponsors include patients with SLL alongside those with CLL and that expert committees explicitly incorporate SLL into CLL clinical practice guidelines. These measures are essential to ensure equitable access to treatments and optimal care for all patients with CLL/SLL.

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References

1. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood. 2018;131(25):2745-60.
2. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375-90.
3. Santos FP, O'Brien S. Small lymphocytic lymphoma and chronic lymphocytic leukemia: are they the same disease? Cancer J. 2012;18(5):396-403.
4. Moia R, Favini C, Ferri V, Forestieri G, Terzi Di Bergamo L, Schipani M, et al. Multiregional sequencing and circulating tumour DNA analysis provide complementary approaches for comprehensive disease profiling of small lymphocytic lymphoma. Br J Haematol. 2021;195(1):108-12.
5. Tooze JA, Hamzic E, Willis F, Pettengell R. Differences between chronic lymphocytic leukaemia and small lymphocytic lymphoma cells by proteomic profiling and SNP microarray analysis. Cancer Genet. 2017;218-219:20-38.
6. Martínez-Trillos A, Pinyol M, Delgado J, Aymerich M, Rozman M, Baumann T, et al. The mutational landscape of small lymphocytic lymphoma compared to non-early stage chronic lymphocytic leukemia. Leuk Lymphoma. 2018;59(10):2318-26.
7. Puckrin R, Owen C, Stewart D, Peters A. Real-world management of small lymphocytic lymphoma as chronic lymphocytic leukaemia versus an indolent non-Hodgkin lymphoma. Br J Haematol. 2023;202(2):445-8.
8. Olszewski AJ, Shafqat H, Ali S. Disparate survival outcomes after front-line chemoimmunotherapy in older patients with follicular, nodal marginal zone and small lymphocytic lymphoma. Leuk Lymphoma. 2015;56(4):942-50.
9. Cencini E, Calomino N, Sicuranza A, Gozzetti A, Fabbri A, Bocchia M. Are small lymphocytic lymphoma and chronic lymphocytic leukemia the same disease? The unsolved dilemma. J Chemother. 2024;36(6):501-5.
10. Sachanas S, Pangalis GA, Fink AM, Bahlo J, Fischer K, Levidou G, et al. Small Lymphocytic Lymphoma: Analysis of Two Cohorts Including Patients in Clinical Trials of the German Chronic Lymphocytic Leukemia Study Group (GCLLSG) or in "Real-Life" Outside of Clinical Trials. Anticancer Res. 2019;39(5):2591-8.
11. Tsimberidou AM, Wen S, O'Brien S, McLaughlin P, Wierda WG, Ferrajoli A, et al. Assessment of chronic lymphocytic leukemia and small lymphocytic lymphoma by absolute lymphocyte counts in 2,126 patients: 20 years of experience at the University of Texas M.D. Anderson Cancer Center. J Clin Oncol. 2007;25(29):4648-56.
12. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111(12):5446-56.
13. Malcikova J, Tausch E, Rossi D, Sutton LA, Soussi T, Zenz T, et al. ERIC recommendations for TP53 mutation analysis in chronic lymphocytic leukemia-update on methodological approaches and results interpretation. Leukemia. 2018;32(5):1070-80.
14. Tarella C, Arcaini L, Baldini L, Barosi G, Billio A, Marchetti M, et al. Italian Society of Hematology, Italian Society of Experimental Hematology, and Italian Group for Bone Marrow Transplantation guidelines for the management of indolent, nonfollicular B-cell lymphoma (marginal zone, lymphoplasmacytic, and small lymphocytic lymphoma). Clin Lymphoma Myeloma Leuk. 2015;15(2):75-85.
15. Owen C, Banerji V, Johnson N, Gerrie A, Aw A, Chen C, et al. Canadian evidence-based guideline for frontline treatment of chronic lymphocytic leukemia: 2022 update. Leuk Res. 2023;125:107016.
16. Association HCoCM, Association HOCoCA-C, Leukemia CWGfCL. [The guidelines for diagnosis and treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma in China(2022)]. Zhonghua Xue Ye Xue Za Zhi. 2022;43(5):353-8.
17. Eichhorst B, Robak T, Montserrat E, Ghia P, Niemann CU, Kater AP, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021;32(1):23-33.
18. Soumerai JD, Barrientos JC, Ahn IE, Coombs CC, Gladstone DE, Hoffmann MS, et al. Consensus Recommendations from the 2024 Lymphoma Research Foundation Workshop on Treatment Selection and Sequencing in CLL or SLL. Blood Adv. 2024.
19. N. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 1.2025 — October 1, 2024 https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf2024 [
20. Schuh AH, Parry-Jones N, Appleby N, Bloor A, Dearden CE, Fegan C, et al. Guideline for the treatment of chronic lymphocytic leukaemia: A British Society for Haematology Guideline. Br J Haematol. 2018;182(3):344-59.
21. Walewska R, Parry-Jones N, Eyre TA, Follows G, Martinez-Calle N, McCarthy H, et al. Guideline for the treatment of chronic lymphocytic leukaemia. Br J Haematol. 2022;197(5):544-57.
22. Anderson MA, Bennett R, Badoux X, Best G, Chia N, Cochrane T, et al. Chronic lymphocytic leukaemia Australasian consensus practice statement. Intern Med J. 2023;53(9):1678-91.
23. Raa DGT, van der Straten L, van Gelder M, Kersting S, Levin MD, Mous R, et al. Diagnosis, treatment and supportive management of chronic lymphocytic leukemia: recommendations of the Dutch HOVON CLL working group. Leuk Lymphoma. 2022;63(10):2276-89.
24. Burlile JF, Saifi O, Laughlin B, Harmsen WS, Rule WG, Peterson JL, et al. Local Control after Low-Dose Radiation for Two Rare Forms of Indolent Non-Hodgkin Lymphoma. International Journal of Radiation Oncology, Biology, Physics , . 2023;117(2):e459.
25. Puckrin R, Owen C, Peters A. Underrepresentation of Small Lymphocytic Lymphoma in Clinical Trials for Chronic Lymphocytic Leukemia. Eur J Haematol. 2024.
26. Tam CS, Brown JR, Kahl BS, Ghia P, Giannopoulos K, Jurczak W, et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. Lancet Oncol. 2022;23(8):1031-43.
27. Tam CS, Robak T, Ghia P, Kahl BS, Walker P, Janowski W, et al. Zanubrutinib monotherapy for patients with treatment naïve chronic lymphocytic leukemia and 17p deletion. Haematologica. 2021;106(9):2354-63.
28. Chanan-Khan A, Cramer P, Demirkan F, Fraser G, Silva RS, Grosicki S, et al. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. Lancet Oncol. 2016;17(2):200-11.

DARZALEX® daratumumab concentrate for solution for infusion

DARZALEX® SC daratumumab subcutaneous

Consider DARZALEX®/DARZALEX® SC

for your newly diagnosed multiple myeloma (NDMM) patients who are ineligible for autologous stem cell transplant (ASCT)[1,2]*

DARZALEX® (daratumumab for injection) is indicated in combination with lenalidomide and dexamethasone, or with bortezomib, melphalan, and prednisone, for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.[1]

DARZALEX® SC (daratumumab injection) is indicated in combination with lenalidomide and dexamethasone, or with bortezomib, melphalan, and prednisone, for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.[2]

In MAIA, a phase 3, randomized, open-label trial:[1]*†

In combination with lenalidomide and dexamethasone (Rd), DARZALEX® demonstrated:[1]*

Significant improvement in PFS vs. Rd alone at interim analysis after a median follow-up of 28.0 months (primary endpoint)[1]

PFS

- **Instantaneous risk of disease progression or death was reduced by 44%** (HR=0.56; 95% CI: 0.43, 0.73; $p<0.0001$)
  - Number of events: 26.1% (97/368) in the DRd arm vs. 38.8% (143/369) in the Rd arm

In an updated PFS analysis occurring after a **median follow-up of 64 months** (range 0.0 to 77.6 months), **median PFS was 61.9 months** (95% CI: 54.8, NE) in the DRd arm **and 34.4 months** (95% CI: 29.6, 39.2) in the Rd arm.

DARZALEX® IV or SC dosing with the DRd regimen (1 cycle=28 days):

- CYCLES 1–2 (Weeks 1–8) **Once weekly** (**4** doses per cycle)
- CYCLES 3–6 (Weeks 9–24) **Once every 2 weeks** (**2** doses per cycle)‡
- CYCLE 7 onwards until disease progression (Week 25 onwards) **Once every 4 weeks** (**1** dose per cycle)§

Please see the DARZALEX® and DARZALEX® SC Product Monographs for complete dosing and administration instructions.

DARZALEX® safety information

Clinical use:

- No overall differences in effectiveness were observed between elderly (≥65 years of age) and younger patients. Some differences in clinical safety have been identified between elderly and younger subjects.
- DARZALEX® is not authorized for pediatric use.

Most serious warnings and precautions:

Infusion-related reactions: DARZALEX® can cause severe and/or serious infusion-related reactions. Early diagnosis and appropriate management are essential to minimize potential life-threatening complications. Patients should be monitored for signs and symptoms suggestive of immune-mediated adverse reactions.

Other relevant warnings and precautions:

- Patients with hereditary fructose intolerance
- Risk of neutropenia/thrombocytopenia when used in combination with background therapy
- Monitor CBC periodically during DARZALEX® treatment when used in combination with background therapies; monitor patients with neutropenia for signs of infection
- Hypogammaglobulinemia
- Infections
- Risk of hepatitis B virus (HBV) reactivation
- Interference with indirect antiglobulin test (Indirect Coombs test); patient's blood should be typed and screened prior to starting DARZALEX®
- Interference with determination of complete response and of disease progression in some patients with IgG kappa myeloma protein
- Pregnant women or women in their childbearing years
- Breastfeeding
- Hepatic impairment
- Renal impairment
- Risk of fetal harm, the presence and transmission in sperm and blood, and prohibitions against blood and/or sperm donation when used in combination therapy

For more information:

Please consult the Product Monograph at innovativemedicine.jnj.com/canada/our-medicines for important information relating to adverse reactions, drug interactions, and dosing that has not been discussed in this piece.

The Product Monograph is also available by calling 1-800-567-3331.

DARZALEX® SC safety information

Please consult the Product Monograph at innovativemedicine.jnj.com/canada/our-medicines for important information relating to conditions of clinical use, warnings, precautions, adverse reactions, drug interactions, and dosing that has not been discussed in this piece. The Product Monograph is also available by calling 1-800-567-3331.

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SC=subcutaneous; Rd=Revlimid® (lenalidomide) + dexamethasone; PFS=progression-free survival; HR=hazard ratio; CI=confidence interval; DRd=DARZALEX® (daratumumab) + Revlimid® (lenalidomide) + dexamethasone; NE=not estimable; IV=intravenous; IgG=immunoglobulin G; ASCT=autologous stem cell transplant; MM=multiple myeloma.

* MAIA, a phase 3, randomized, open-label study to assess DARZALEX® + Rd (DRd) (n=368) vs. Rd alone (n=369) in patients with newly diagnosed, ASCT-ineligible MM. Patients were randomized 1:1 to receive DARZALEX® 16 mg/kg (IV) on Days 1, 8, 15 and 22 of cycles 1 and 2, on Days 1 and 15 of cycles 3–6, and on Day 1 of cycle 7 and subsequent cycles, plus lenalidomide (25 mg once daily orally on Days 1–21 of repeated 28-day [4-week] cycles) with low-dose oral or intravenous dexamethasone 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years or body mass index [BMI] <18.5), OR lenalidomide and low-dose dexamethasone (Rd) alone. Treatment was continued until disease progression or unacceptable toxicity. The primary efficacy endpoint was PFS based on International Myeloma Working Group (IMWG) criteria.[1]

† The following protocol amendments were made in the updated analysis: Patients in the Rd control group were given the option to receive daratumumab after confirmation of disease progression according to IMWG criteria based on the superiority of DRd over Rd alone with respect to the primary endpoint (progression-free survival) at the second interim analysis. To prioritize the safety of patients during the COVID-19 pandemic and reduce time spent at the study centre, patients in the daratumumab group were given the option to switch from intravenous daratumumab to subcutaneous daratumumab on Day 1 of any cycle at a fixed dose of 1800 mg, administered by manual injection for 3–5 minutes once every 4 weeks.[3]

‡ First dose of the once-every-2-weeks dosing schedule is given at Week 9.

§ First dose of the once-every-4-weeks dosing schedule is given at Week 25.

References: 1. DARZALEX® (daratumumab for injection) Product Monograph. Janssen Inc. April 30, 2024. **2.** DARZALEX® SC (daratumumab injection) Product Monograph. Janssen Inc. November 27, 2024. **3.** Facon T, Kumar SK, Plesner T, *et al*. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol* 2021;22(11):1582–1596.

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