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EDITORS WELCOME

Dear Canadian Hematology Community,

We can't wait to see all of you at ASH 2022 in New Orleans! It has been a tremendous inaugural year for this journal. Thanks to all our authors, advertising partners and, most of all, to our readers who have provided tremendous feedback and encouragement about both the quality of the journal and its place in helping to spread practical knowledge about the Canadian approach to hematological disease.

Our current issue highlights some fascinating topics from our authors including a Canadian perspective on who should get a treatment-free trial and how, as well as a wonderful review on emerging therapies for the treatment of PTCL. Other content in this issue includes an article on hereditary hematologic malignancies, the evolving treatment landscape of higher-risk MDS and the management of follicular lymphoma beyond chemotherapy.

We hope you find these articles illuminating and we thank you for your continued readership. Feel free to share our registration link at canadianhematologytoday.com with your peers so that, they too, can subscribe to future issues!

And, of course, at this time of the year, we want to take an opportunity to wish all of you and your families a wonderful and peaceful holiday season.

Be safe and see you in 2023!

Best wishes,

Peter Anglin, MD *Laurie H. Sehn, MD* *Julie Stakiw, MD* *Darrell White, MD*

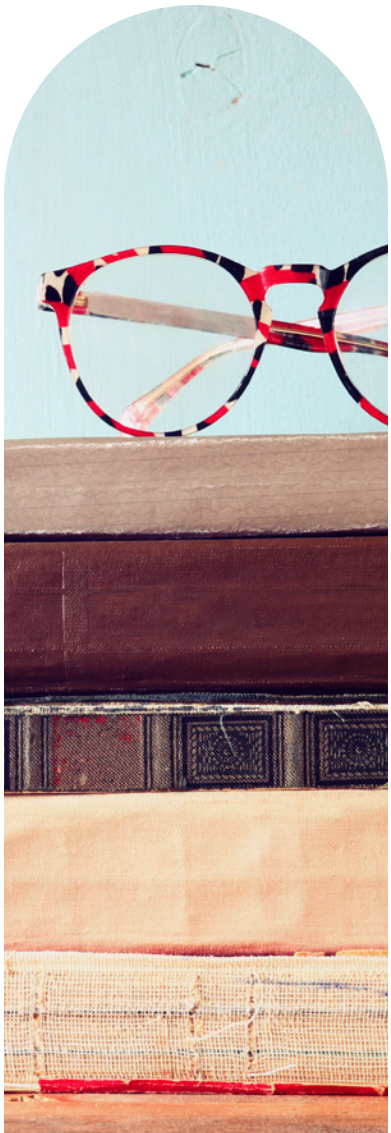

TABLE OF CONTENTS

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Medical minds gather here.

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ABOUT THE AUTHOR

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Dr. Kridel is a lymphoma specialist at the Princess Margaret Cancer Centre in Toronto, having previously completed his medical training in Europe (Switzerland) and Canada (Vancouver). His research focuses on the delineation of distinct patient populations based on integrative genomic profiling of tumour biopsies, aiming to identify vulnerabilities that will lead to biology-adjusted therapeutic approaches. In addition, his research group explores means to overcome treatment resistance through functional genomic approaches.

MOVING BEYOND CHEMOTHERAPY IN THE MANAGEMENT OF FOLLICULAR LYMPHOMA

Introduction

Follicular lymphoma (FL) is the most common indolent lymphoma. It is estimated that approximately 2,000 Canadians are newly diagnosed with FL each year; however, this is an underestimation of the disease burden due to the indolent nature of FL. Indeed, the life expectancy for most patients can be measured in decades, with slow but constant improvement in survival estimates having been achieved over time.

Traditionally, FL has been considered a chemo-sensitive disease and, for the last 15 years, antibodies targeting the CD20 surface epitope on B cells have become a compelling adjunct to induce long-lasting remission in the frontline setting.[1] Outcomes are favourable for most patients; a long-term follow-up from the seminal PRIMA trial showed that the median progression-free survival (PFS) was 10.5 years in patients treated with immunochemotherapy as part of an initial induction regimen followed by rituximab maintenance, as compared with just over 4 years in the control arm (initial induction regimen followed by observation).[2] In terms of chemotherapy backbone, bendamustine has established itself as the preferred standard in Canada and induces durable response in the majority of patients.[3]

This article will focus on patients with high-tumour burden disease in need of treatment, as opposed to patients with limited-stage disease who may benefit from localized radiation or patients with advanced-stage with low-tumour burden disease who may benefit from observation or single agent rituximab.

Reasons to Move Beyond Chemotherapy

The phrase "chemotherapy-free" has gained popularity in recent years to connote a new, modern era of treating FL. It is important to note that the term chemotherapy-free does not equate with an absence of side effects as novel therapeutics can have their own set of adverse effects. In addition, these therapies should not be viewed as "natural," given that they are either chemical probes or highly engineered immune therapies that do not exist as such in the natural world.

There exist multiple reasons to move beyond chemotherapy. Approximately 20% of patients experience early progression after immunochemotherapy and are at increased risk of lymphoma-related mortality.[4] Especially with bendamustine-based treatment, the majority of progression events are due to histological transformation.[5] Preventing early progression and/or transformation should be an important goal with the use of novel therapies.

Secondly, FL tends to become less chemo-sensitive with each successive round of recurrence, and treatment guidelines are not well defined in cases of relapse.[6]

Thirdly, chemotherapy is undoubtedly associated with both acute and long-term toxicity. For example, the GALLIUM trial demonstrated that obinutuzumab significantly prolonged progression-free survival (PFS) in previously untreated patients with follicular lymphoma relative to rituximab (R) when combined with cyclophosphamide (C), doxorubicin, vincristine (V), and prednisone (P; CHOP); CVP; or bendamustine. However, an unexpected risk of fatal adverse events associated with the use of bendamustine was observed which may reflect a difference in baseline patient risk profile.[7] The use of bendamustine and rituximab has also become more controversial in the last two years as the double hit of impairing both humoral and cellular immunity puts patients at risk of severe COVID-19.[8]

Lastly, but importantly, chemotherapy is associated with long-term complications including an increased risk of cardiovascular events and secondary cancers, and, more generally, premature aging.[9] Accordingly, there are compelling reasons to study novel therapeutic agents that may improve outcomes for FL patients. The results from selected trials in relapsed/refractory (R/R) FL are summarized in **Table 1**.

Chemotherapy Alternatives

The most studied chemo-free regimen in both the front-line and relapsed setting is the combination of rituximab with lenalidomide (R2). The latter is a targeted agent that leads to the degradation of the Ikaros and Aiolos lymphoid transcription factors.[10] Despite its selective mode of action on the molecular level, lenalidomide has pleiotropic effects including both direct anti-tumour and also immune-modulating effects.

Therapeutic agent	Phase	N	ORR (%)	CRR (%)	Median PFS (months)
Immunomodulator-based					
Lenalidomide + rituximab (R2) vs. placebo + rituximab[13]	III	147 vs. 148	80% vs. 55%	35% vs. 20%	39 vs. 14
PI3K inhibition					
Idelalisib[16]	II	72	56%	17%	11
Duvelisib[17]	II	83	42%	1%	10*
Umbralisib[20]	IIb	117	45%	5%	11
Copanlisib[18]	II	104	59%	20%	13#
Copanlisib + rituximab vs. placebo + rituximab[19]	III	184 vs. 91	85% vs. 54%	37% vs. 21%	22 vs. 19
BTK inhibition					
Ibrutinib[34]	II	110	21%	11%	5
Epigenetic					
Tazemetostat[24]	II	99	69% (*EZH2*^{mut}) 35% (*EZH2*^{wt})	13% (*EZH2*^{mut}) 4% (*EZH2*^{wt})	14 (*EZH2*^{mut}) 11 (*EZH2*^{wt})
BCL2 antagonist					
Venetoclax[14]	I	29	38%	14%	11
mTOR inhibitors					
Everolimus[35]	II	23	61%	not reported	7*
Temsirolimus[36]	II	39	54%	26%	13
Checkpoint inhibitor					
Nivolumab[37]	II	92	4%	1%	2
Bispecific antibodies					
Mosunetuzumab[28]	I	65	69%	51%	12*
Glofitamab[29]	I	44	71%	48%	12
Epcoritamab[30]	I	11	82%	45%	not reported
Odronextamab[31]	I	40	78%	63%	17&
CAR T-cell therapy					
Axicabtagene ciloleucel[38]	II	86$	94%	79%	not reached
Tisagenlecleucel[39]	II	94^	86%	69%	not reached
CD47 blockade					
Magrolimab (previously referred to as 5F9)[33]	Ib/II	28	66%**	24%**	not reported

Table 1: *Results from selected trials of novel therapies in relapsed/refractory FL*

N, number; ORR, overall response rates; CRR, complete response rate; PFS, progression-free survival; mut, mutated; wt, wild-type. The column with patient numbers specifically refers to FL patients. It is important to note that patient populations may vary between the trials and direct comparisons can be misleading. Only controlled trials can answer the question of head-to-head efficacy.

**, these PFS results include patients with small lymphocytic lymphoma and marginal zone lymphoma; #, these PFS results include patients with small lymphocytic lymphoma, marginal zone lymphoma and lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia; &, PFS refers to patients having received odronextamab doses of 5 mg or higher; $, evaluable for activity (out of 127 follicular lymphoma patients enrolled); ^, efficacy set (out of 98 patients enrolled); **, combined outcomes for 28 patients with follicular lymphoma and 1 patient with marginal zone lymphoma.*

A seminal phase III trial (RELEVANCE) compared the R2 regimen to immunochemotherapy (rituximab plus chemotherapy) in over 1,000 patients.[11] While this study was designed as a superiority trial, the primary endpoints of complete response (CR) at 120 weeks and progression-free survival were ultimately similar in both groups of patients. Study results demonstrated rates of confirmed or unconfirmed complete response at 120 weeks to be 48% in the rituximab–lenalidomide group and 53% in the rituximab–chemotherapy group (P=0.13). The interim 3-year rate of progression-free survival as measured both by independent review committee and as assessed by the investigator was 77% and 78%, respectively. Immunochemotherapy led to a higher rate of neutropenia and febrile neutropenia, while R2 was associated with a higher rate of skin rashes. Thus, overall, R2 can be considered a non-superior alternative to immunochemotherapy; unfortunately, it is not reimbursed in Canada.

A more recent phase II trial (GALEN) studied lenalidomide in combination with obinutuzumab and found that oral lenalidomide plus obinutuzumab was well tolerated and effective in patients with R/R FL.[12] While obinutuzumab may be more effective than rituximab for many indolent lymphomas, including FL, a direct comparison with obinutuzumab-chemotherapy is needed to draw conclusions as to the relative efficacy of an obinutuzumab-lenalidomide combination.

R2 is also a useful regimen in the relapsed setting where it has been studied in comparison with single-agent rituximab in a phase III trial (AUGMENT).[13] R2 was found to be superior, with a median duration of response of 39.4 months, as compared to 11.4 months with rituximab monotherapy. Unfortunately, R2 is also not typically reimbursed in Canada in the relapsed setting.

Given that the t(14;18) translocation, leading to upregulation of anti-apoptotic BCL2, is found in ~85% of all FL cases, it is appealing to hypothesize that BCL2 degradation may have therapeutic benefits in FL akin to those seen in chronic and acute leukemias. Unfortunately, the response rate to venetoclax was lower than expected in a phase I trial of 106 patients with relapsed or refractory NHL receiving venetoclax once-daily until progressive disease or unacceptable toxicity, with only 38% of FL patients responding, and a median PFS of 11 months.[14] In the CONTRALTO study, a chemo-free regimen with venetoclax and rituximab led to a complete response in only 17% of patients with relapsed/refractory FL, and the addition of venetoclax to bendamustine and rituximab was associated with a high rate of grade 3/4 adverse events.[15] It is possible, however, that judicious combination with other targeted therapies may improve upon these results.

FL usurps signaling pathways from normal B cells and their inhibition has been studied, for example by targeting the PI3K pathway using idelalisib,[16] duvelisib,[17] copanlisib[18,19] or umbralisib,[20] with response rates ranging between 42-59% and median PFS between 10-13 months.[21] While the respective side effect profiles of these agents differ, some of the side effects, such as hepatotoxicity, colitis and pneumonitis, can be severe, which has dampened the enthusiasm for this class of agents. Clinicians should note that no PI3K molecule is currently funded for FL in Canada.

Pathogenetic Approach to Therapy

The genetic basis of FL is characterized by mutations in epigenetic modifiers, (i.e. enzymes that catalyze the post-translational modification of histones) resulting in aberrant transcriptional programs. Historically, FL was among the first types of cancer in which mutations of epigenetic modifiers were described.[22] The mutations affecting enhancer of zeste homolog 2 (*EZH2*) are seen in ~20-25% of FL cases and result in gain-of-function of its methyltransferase activity.[23] Consequently, EZH2 has rapidly emerged as a target for pharmacological inhibition.

The most robust data available are for tazemetostat therapy, with response rates of 69% and 35%, and median PFS of 13.8 versus 11.1 months in *EZH2*-mutated and *EZH2*-wildtype FL, respectively.[24] While the PFS results observed in this study may be perceived as underwhelming relative to other treatment regimens, the approach of inhibiting EZH2 has some clear advantages. First of all, tazemetostat is generally well-tolerated, which is important for the quality of life of our patients and is also important because it may portend safe combination with other therapeutic agents. Secondly, *EZH2* mutations represent the first predictive biomarker for FL, allowing identification of those patients with the highest probability of clinical benefit.

Immunocentric Approach to Therapy

FL cells grow in a cellular ecosystem in which they closely interact with their microenvironment, relying on cues from immune and stromal cells to grow, evade immune escape and induce a tumour-promoting microenvironment.[25] FL cells can be conceptually thought of as parasitic colonizers of the germinal centre. Accordingly, the therapeutic disruption of these tumour-immune interactions should reduce the growth of FL.

Unfortunately, the response rate to immune checkpoint inhibition has proven to be very low.[26] This lower clinical response does not mean that immune responses cannot have therapeutic effects. For example, in situ vaccination with a TLR9 agonist, combined with low-dose radiation has been shown to lead to tumour responses in non-treated sites, suggesting that strengthening the immune surveillance through antigen-specific immune responses may be beneficial.[27]

However, the most promising advances in the FL field come from the development of immune therapies that are based on recognition of B-cell epitopes, coupled with activation of T cells in the immediate vicinity of malignant cells. The efficacy of at least 4 different CD20×CD3 bispecific antibodies (mosunetuzumab,[28] glofitamab,[29] epcoritamab[30] and odronextamab[31]) has been reported in early phase trials, with promising CR rates of 69-82%.[32] Longer follow-up of these studies is required in order to fully determine the durability of response. The toxicity profiles of these agents include cytokine release syndrome (CRS), that is often low-grade and mostly confined to the period of treatment initiation, and thus can be mitigated by an appropriate titration schedule.

Chimeric antigen receptor-modified T cells (CAR T-cells) have similarly been studied in R/R FL, with high rates of CR (79% with axicabtagene ciloleucel in the ZUMA-5 trial and 69% with tisagenlecleucel in the ELARA trial) and median PFS results of 18 and 12 months, respectively.[32] These therapies are not currently funded in Canada for FL patients.

Beyond immune therapies that ultimately rely on T cells for anti-tumour effects, blocking the "do-not-eat-me" signals produced by FL cells has been shown to enhance the phagocytic function of macrophages. An early phase trial showed a response rate of 66% and CR rate of 24% in patients with relapsed/refractory indolent lymphomas.[33]

These results highlight the potential of novel immune therapies to induce high response rates in R/R FL, with emerging data providing answers with regards to the durability of these responses.

Conclusion

In summary, the role of chemo-free treatment options for FL patients is rapidly evolving, with an increasing number of novel therapies being investigated in clinical trials, as monotherapy or as part of combination treatments. Simultaneously, our understanding of the pathobiological underpinnings of FL is expanding at a fast pace. Ideally, predictive biomarkers will facilitate decision-making in the future, beyond the current individualized decision-making criteria involving factors such as frailty or comorbidities. While the cost of approved novel therapies will likely be significant, a cost-effective approach to FL treatment can be rationalized through the prioritization of the most effective therapy for a given patient, ultimately improving patient outcomes. However, to fully evaluate the relative efficacy of novel therapies, comparative clinical trials are urgently needed.

References

1. *Marcus R, Imrie K, Solal-Celigny P, et al. Phase III Study of R-CVP Compared With Cyclophosphamide, Vincristine, and Prednisone Alone in Patients With Previously Untreated Advanced Follicular Lymphoma. J. Clin. Oncol. 2008;26(28):4579–4586.*
2. *Bachy E, Seymour JF, Feugier P, et al. Sustained Progression-Free Survival Benefit of Rituximab Maintenance in Patients With Follicular Lymphoma: Long-Term Results of the PRIMA Study. J. Clin. Oncol. 2019;37(31):JCO.19.01073.*
3. *Kuruvilla J, Assouline S, Hodgson D, et al. A Canadian evidence-based guideline for the first-line treatment of follicular lymphoma: Joint consensus of the lymphoma Canada scientific advisory board. Clin. Lymphoma, Myeloma Leuk. 2015;15(2):59–74.*
4. *Mozessohn L, Cheung MC, Crump M, et al. Chemoimmunotherapy resistant follicular lymphoma: predictors of resistance, association with transformation and prognosis. Leuk. Lymphoma. 2014;55(11):2502–7.*
5. *Freeman CL, Kridel R, Moccia AA, et al. Early progression after BR is associated with high risk of transformation in advanced stage follicular lymphoma. Blood. 2019;134(9):blood.2019000258.*
6. *Batlevi CL, Sha F, Alperovich A, et al. Follicular lymphoma in the modern era: survival, treatment outcomes, and identification of high-risk subgroups. Blood Cancer J. 2020;10(7):.*
7. *Hiddemann W, Barbui AM, Canales MA, et al. Immunochemotherapy With Obinutuzumab or Rituximab for Previously Untreated Follicular Lymphoma in the GALLIUM Study: Influence of Chemotherapy on Efficacy and Safety. J. Clin. Oncol. 2018;JCO2017768960.*
8. *Lamure S, Duléry R, Di Blasi R, et al. Determinants of outcome in Covid-19 hospitalized patients with lymphoma: A retrospective multicentric cohort study. EClinicalMedicine. 2020;27:.*
9. *Cupit-Link MC, Kirkland JL, Ness KK, et al. Biology of premature ageing in survivors of cancer. ESMO Open. 2017;2(5):1–8.*
10. *Krönke J, Udeshi ND, Narla A, et al. Lenalidomide causes selective degradation of IKZF1 and IKZF3 in multiple myeloma cells. Science. 2014;343(6168):301–5.*
11. *Morschhauser F, Fowler NH, Feugier P, et al. Rituximab plus Lenalidomide in Advanced Untreated Follicular Lymphoma. N. Engl. J. Med. 2018;379(10):934–947.*
12. *Morschhauser F, Salles G, Le Gouill S, et al. An open-label, phase Ib study of obinutuzumab plus lenalidomide in relapsed/refractory follicular B-cell lymphoma. Blood. 2018;132(14):blood-2018-05-853499.*
13. *Leonard JP, Trneny M, Izutsu K, et al. AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma. J. Clin. Oncol. 2019;37(14):1188–1199.*
14. *Davids MS, Roberts AW, Seymour JF, et al. Phase I First-in-Human Study of Venetoclax in Patients With Relapsed or Refractory Non-Hodgkin Lymphoma. J. Clin. Oncol. 2017;35(8):826–833.*
15. *Zinzani PL, Flinn IW, Yuen SLS, et al. Venetoclax-rituximab with or without bendamustine vs bendamustine-rituximab in relapsed/refractory follicular lymphoma. Blood. 2020;136(23):2628–2637.*
16. *Wagner-Johnston ND, Schuster SJ, deVos S, et al. Outcomes of patients with up to 6 years of follow-up from a phase 2 study of idelalisib for relapsed indolent lymphomas. Leuk. Lymphoma. 2021;62(5):1077–1087.*
17. *Flinn IW, Miller CB, Ardeshna KM, et al. DYNAMO: A Phase II study of duvelisib (IPI-145) in patients with refractory indolent non-hodgkin lymphoma. J. Clin. Oncol. 2019;37(11):912–922.*
18. *Dreyling M, Santoro A, Mollica L, et al. Long-term safety and efficacy of the PI3K inhibitor copanlisib in patients with relapsed or refractory indolent lymphoma: 2-year follow-up of the CHRONOS-1 study. Am. J. Hematol. 2020;95(4):362–371.*
19. *Matasar MJ, Capra M, Özcan M, et al. Copanlisib plus rituximab versus placebo plus rituximab in patients with relapsed indolent non-Hodgkin lymphoma (CHRONOS-3): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2021;22(5):678–689.*
20. *Fowler NH, Samaniego F, Jurczak W, et al. Umbralisib, a dual PI3Kδ/CK1ε inhibitor in patients with relapsed or refractory indolent lymphoma. J. Clin. Oncol. 2021;39(15):1609–1618.*
21. *Phillips TJ, Michot JM, Ribrag V. Can Next-Generation PI3K Inhibitors Unlock the Full Potential of the Class in Patients With B-Cell Lymphoma? Clin. Lymphoma, Myeloma Leuk. 2021;21(1):8-20.e3.*
22. *Morin RD, Johnson NA, Severson TM, et al. Somatic mutations altering EZH2 (Tyr641) in follicular and diffuse large B-cell lymphomas of germinal-center origin. Nat. Genet. 2010;42(2):181–5.*
23. *Yap DB, Chu J, Berg T, et al. Somatic mutations at EZH2 Y641 act dominantly through a mechanism of selectively altered PRC2 catalytic activity, to increase H3K27 trimethylation. Blood. 2011;117(8):2451–9.*
24. *Morschhauser F, Tilly H, Chaidos A, et al. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. Lancet Oncol. 2020;21(11):1433–1442.*
25. *Lackraj T, Goswami R, Kridel R. Pathogenesis of follicular lymphoma. Best Pract. Res. Clin. Haematol. 2018;31(1):2–14.*
26. *Lesokhin AM, Ansell SM, Armand P, et al. Nivolumab in patients with relapsed or refractory hematologic malignancy: Preliminary results of a phase ib study. J. Clin. Oncol. 2016;34(23):2698–2704.*
27. *Frank MJ, Reagan PM, Bartlett NL, et al. In Situ Vaccination with a TLR9 Agonist and Local Low-Dose Radiation Induces Systemic Responses in Untreated Indolent Lymphoma. Cancer Discov. 2018;8(10):1258–1269.*
28. *Budde LE, Assouline S, Sehn LH, et al. Single-Agent Mosunetuzumab Shows Durable Complete Responses in Patients with Relapsed or Refractory B-Cell Lymphomas: Phase I Dose-Escalation Study. J. Clin. Oncol. 2022;40(5):481–491.*
29. *Hutchings M, Morschhauser F, Iacoboni G, et al. Glofitamab, a Novel, Bivalent CD20-targeting t-cell-engaging bispecific antibody, induces durable complete remissions in relapsed or refractory B-Cell Lymphoma: A phase i trial. J. Clin. Oncol. 2021;39(18):1959–1970.*
30. *Hutchings M, Mous R, Clausen MR, et al. Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study. Lancet. 2021;398(10306):1157–1169.*
31. *Bannerji R, Arnason JE, Advani RH, et al. Odronextamab, a human CD20×CD3 bispecific antibody in patients with CD20-positive B-cell malignancies (ELM-1): results from the relapsed or refractory non-Hodgkin lymphoma cohort in a single-arm, multicentre, phase 1 trial. Lancet Haematol. 2022;9(5):e327–e339.*
32. *Qualls D, Salles G. Prospects in the management of patients with follicular lymphoma beyond first-line therapy. Haematologica. 2022;107(1):19–34.*
33. *Advani R, Bartlett NL, Smith SM, et al. The First-in-Class Anti-CD47 Antibody HU5F9-G4 + Rituximab Induces Durable Responses in Relapsed/Refractory DLBCL and Indolent Lymphoma: Interim Phase 1B/2 Results. Hematol. Oncol. 2019;37:89–90.*
34. *Gopal AK, Schuster SJ, Fowler NH, et al. Ibrutinib as treatment for patients with relapsed/refractory follicular lymphoma: Results from the open-label, multicenter, phase II DAWN study. J. Clin. Oncol. 2018;36(23):2405–2412.*
35. *Bennani NN, LaPlant BR, Ansell SM, et al. Efficacy of the oral mTORC1 inhibitor everolimus in relapsed or refractory indolent lymphoma. Am. J. Hematol. 2017;92(5):448–453.*
36. *Smith SM, Van Besien K, Karrison T, et al. Temsirolimus has activity in non-mantle cell non-Hodgkin's lymphoma subtypes: The University of Chicago phase II consortium. J. Clin. Oncol. 2010;28(31):4740–4746.*
37. *Armand P, Janssens A, Gritti G, et al. Efficacy and safety results from CheckMate 140, a phase 2 study of nivolumab for relapsed/refractory follicular lymphoma. Blood. 2021;137(5):637–645.*
38. *Jacobson CA, Chavez JC, Sehgal AR, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. Lancet. Oncol. 2022;23(1):91–103.*
39. *Fowler NH, Dickinson M, Dreyling M, et al. Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. Nat. Med. 2022;28(2):325–332.*

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HEREDITARY HEMATOLOGIC MALIGNANCIES: A CANADIAN PERSPECTIVE

Introduction
When a patient is newly diagnosed with a malignancy, two common questions are often asked: 1) why did I get this cancer and 2) are my children or other family members at risk? In the case of hematologic malignancies, the standard response has been that the cause is unknown and family members are not at increased risk. However, hereditary predisposition to hematologic malignancies, especially myeloid malignancies, is becoming increasingly recognized, necessitating a change to this dogma.[1] Hereditary hematologic malignancies are not as rare as previously believed, with an ever-increasing number of predisposition genes and alleles being discovered. Since the initial discovery of familial platelet disorder with associated myeloid malignancy (FPDMM) due to deleterious germline variants in *RUNX1* in 1999,[2] the list of predisposition genes, such as *CEBPA, DDX41, ETV6, GATA2*, and others continues to grow.[3–6]

What are Hereditary Hematologic Malignancies?
Hereditary hematologic malignancy is a heterogenous term used to describe a hematologic malignancy that arises in the setting of a deleterious (pathogenic or likely pathogenic) germline variant. These predisposing variants can be inherited or can occur *de novo*, as is the case for the majority of GATA2 deficiency syndrome variants.[6] To date, predisposition alleles have been identified in over 40 different genes, resulting in a variety of predisposition syndromes **(Table 1)**.[1] Most germline predisposition syndromes are autosomal dominant (e.g. *ANKRD26, DDX41, RUNX1, TP53*, and many others), however others are autosomal recessive in their inheritance (e.g. *SBDS* and *FANCA*). Phenotype and penetrance vary depending on the particular gene as well as the individual variant involved. Some predisposition variants, like those in *CEBPA*, predispose to myeloid malignancies only, whereas others, like those in *RUNX1*, predispose to both myeloid and lymphoid malignancies as well as a pre-existing platelet disorder, and those in *TP53* predispose to both myeloid and lymphoid malignancies as well as numerous solid tumours.[1] Hereditary hematologic malignancies can be broken down into categories based on the predominant type(s) of hematologic malignancy to which they predispose as well as by the presence or absence of other features such as thrombocytopenia and/or platelet dysfunction, solid organ dysfunction, or additional predisposition to solid tumours **(Table 1)**.

Why is Recognition of Hereditary Hematologic Malignancies Important?
Knowledge of hereditary hematologic malignancies is becoming more commonplace and their importance is underscored by the incorporation of germline predisposition to myeloid neoplasms in the 2016 WHO update on myeloid neoplasms as well as the 2022 ELN Acute Myeloid Leukemia (AML) recommendations.[7,8] Within the 2022 ELN AML recommendations, "germline predisposition" is now included as a qualifier for the diagnostic classification of AML and related neoplasms.[7]

Recognition and identification of a predisposing germline variant has important implications for patients as well as their family members. The penetrance varies depending on the gene involved, but for some, such as 5' *CEBPA* variants, it is nearly 100% for development of AML.[3] For these and other germline predisposed patients, the risk of relapse after chemotherapy alone is high and an allogeneic hematopoietic stem cell transplant (HSCT) is recommended, but donor selection must be approached carefully.[9] Most predisposition variants are

Gene(s)	Inheritance	Predisposition to:
Myeloid neoplasms with germline predisposition without pre-existing platelet disorder or organ dysfunction		
CEBPA	AD	AML
DDX41	AD	Most common: MDS, AML Less common: MPNs, lymphoid neoplasms
Myeloid neoplasms with germline predisposition and pre-existing platelet disorders		
RUNX1	AD	Life-long mild/moderate thrombocytopenia and qualitative platelet defects Most common: MDS, AML, T-cell ALL Less common: HCL, CMML, B-cell malignancies
ANKRD26	AD	Thrombocytopenia and variety of platelet function defects MDS, AML, other myeloid neoplasms
ETV6	AD	Life-long thrombocytopenia ALL > myeloid malignancies
Myeloid neoplasms with germline predisposition and potential organ dysfunction		
GATA2	AD	GATA2 deficiency syndrome Lymphedema, immunodeficiencies, warts, NTM infections, pulmonary alveolar proteinosis, and many other phenotypes. MDS, AML (often with monosomy 7 and/or trisomy 8)
ELANE, GFI1 CSF3R, HAX1, G6PC3	AD, AR	Severe congenital neutropenia BMF, MDS, AML
SDBS, DNAJC21, EFL1, SRP54	AR	Shwachman-Diamond Syndrome BMF, MDS, AML, ALL
FANCA – FANCW	AR	Fanconi anemia BMF, MDS, AML
ACD, CTC1, DKC1, RTEL1, TERC, TERT, TINF2, NHP2, NOP10, PARN, WRAP53	AD, AR, X-linked	Telomere biology disorders BMF, mucocutaneous triad, pulmonary fibrosis, liver cirrhosis, squamous cell carcinoma, MDS, AML
SAMD9, SAMD9L	AD	MIRAGE syndrome, Ataxia-Pancytopenia syndrome BMF, MDS, non-syndromic monosomy 7
CBL, KRAS, NRAS, PTPN11	AD	Noonan syndrome or Noonan syndrome-like JMML, AML
NF1	AD	Neurofibromatosis 1 JMML, AML
Multiple myeloma with germline predisposition		
ARID1A, DIS3, POT1, TNFRSF13B, USP45	AD	MM, lymphoid neoplasms
Hodgkin lymphoma with germline predisposition		
DICER1, NPAT, POT1	AD	HL, other lymphoid neoplasms
Germline predisposition causing multiple cancer types including hematologic malignancies		
CHEK2	AD	Clonal hematopoiesis, myeloid neoplasms, lymphoid neoplasms, solid tumours
RECQL4	AR	Aplastic anemia, myeloid neoplasms, lymphoid neoplasms, solid tumours
BRCA1, BRCA2	AD	Hereditary breast and ovarian cancer syndrome Myeloid and lymphoid neoplasms, solid tumours
MLH1, MSH2, MSH6, PMS2	AD, AR	Lynch Syndrome Myeloid and lymphoid neoplasms, solid tumours
NBN	AR	Nijmegen Breakage Syndrome Aplastic anemia, lymphoid neoplasms (ALL > lymphoma), solid tumours
TP53	AD	Li-Fraumeni syndrome Myeloid and lymphoid neoplasms, numerous solid tumours
WAS	X-linked	Wiskott-Aldrich Syndrome Microthrombocytopenia, lymphoma, myeloid neoplasms, solid tumours (glioma, acoustic neuroma, testicular carcinoma)

***Table 1**. List of genes for which deleterious variants predispose to hematologic malignancies*

Myeloid neoplasm classifications are adapted from the 2022 European Leukemia Net AML recommendations.[7] ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; BMF, bone marrow failure; CMML, chronic myelomonocytic leukemia; HCL, hairy cell leukemia; HL, Hodgkin lymphoma; JMML, juvenile myelomonocytic leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; NTM, nontuberculous mycobacteria.

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autosomal dominant and since the preferred donors for HSCT are matched-related donors, there is high risk of giving back the same predisposing variant if the related donor's germline status is unknown. Devastating complications including graft failure, donor-derived leukemia, and leukemia development in the donor following stem cell mobilization have all been reported when donors who carry deleterious germline variants have been used for HSCT.[10–12] It is therefore recommended to test potential related donors and to avoid their use as a hematopoietic stem cell donor if they carry the same predisposition variant.[1,9]

The identification of deleterious variants in genes associated with thrombocytopenia such as *ANKRD26*, *ETV6*, and *RUNX1* are important as these patients often get misdiagnosed as having immune thrombocytopenia. Without proper recognition, these patients may be subject to unhelpful and potentially harmful immunosuppressive therapies. In the case of other genes, such as *TERT* and *TERC*, deleterious variants are associated with organ dysfunction, most notably pulmonary fibrosis, and solid tumours in addition to hematologic malignancies. The identification of such variants enables informed treatment decisions, screening for occult organ dysfunction, and solid tumour screening.[13]

For hereditary hematologic malignancy patients being considered for HSCT, careful assessment for gene-specific organ dysfunction is important in order to better evaluate and mitigate the risk of severe transplant-associated morbidity or mortality. For example, GATA2 deficiency syndrome patients are at high risk of atypical mycobacterial infections and antimicrobial prophylaxis with a macrolide is recommended.[14] Although evidence-based guidelines for each individual predisposition gene do not exist, expert opinion recommendations suggest using standard preparative regimens for myelodysplastic syndrome (MDS)/AML patients with germline variants not associated with bone marrow failure or severe organ dysfunction. For those with germline variants in bone marrow failure or telomere biology disorder genes, a fludarabine-based reduced intensity conditioning regimen similar to that used for Fanconi anemia patients is recommended to avoid excessive toxicity and poor survival observed with fully myeloablative conditioning.[13,15]

Surveillance for asymptomatic carriers of a hereditary hematologic malignancy predisposition variant is based upon expert opinion recommendations and includes universal recommendations as well as gene/syndrome-specific recommendations.[13] Individual gene-specific surveillance recommendations for carriers with and without hematologic malignancies are beyond the scope of this article and readers are referred to previously published reviews.[13,16–19] Universal screening recommendations for those currently without hematologic malignancies include a CBC with differential every 6-12 months, HLA typing at baseline, and a bone marrow biopsy and aspirate including cytogenetics and molecular if any abnormalities on the CBC develop, such as new cytopenia(s) or macrocytosis. Some experts advocate for a bone marrow biopsy and aspirate to be conducted at baseline, however this remains controversial for patients with no hematologic abnormalities.

How Common are Hereditary Hematologic Malignancies?

Among patients between the ages of 18-40 years, a deleterious germline variant was found in 19% of those with MDS/AML and 15% with aplastic anemia.[20] *DDX41* is the most frequently germline-mutated gene among adults with myeloid neoplasms. Studies examining unselected, unrelated adults with MDS/AML have found 2-6% harboured a germline predisposing variant in *DDX41*.[21,22] These patients often did not have a family history of hematologic malignancy and the median age at diagnosis was 68-69 years, similar to that of sporadic MDS/AML. In a recent CIBMTR study, 7% of all MDS patients (ages 11-71 years) undergoing related HSCT were found to have a deleterious germline variant.[23] Therefore, older age at diagnosis and lack of family history cannot be used to exclude the possibility of an underlying germline predisposition.

As shown in **Table 1**, several genes have also been found to predispose to lymphoid neoplasms and/or plasma cell dyscrasias, including many that also predispose to a variety of solid tumours.[1,24,25] However, in comparison to myeloid neoplasms there are much fewer data available on germline predisposition to lymphoid neoplasms and this is an area of active research.

Who and How to Test for Hereditary Hematologic Malignancies?

Germline predisposition should be considered as a possibility for all patients with hematologic malignancies given the relatively high frequency of occurrence. **Figure 1** depicts an approach for selection and testing of suspected hereditary hematologic malignancy patients. Suggestive features can include: a personal history of multiple malignancies, long standing cytopenias and/or bleeding diatheses, family history of hematologic malignancy and/or younger than average age onset of solid tumours within two generations of the patient, physical phenotype consistent with a known germline predisposition syndrome, and/or the identification of a potential germline variant on tumour-based molecular testing. In addition to testing those with suggestive features, given the high frequency of predisposition variants in patients with MDS of all ages undergoing HSCT as well as those with AA, MDS, and AML under the age of 40 years, routine germline testing at the time of diagnosis for these patients should be considered.

For patients with myeloid or lymphoid neoplasms with bone marrow or peripheral blood involvement, DNA derived from cultured skin fibroblasts should be obtained as the gold standard to eliminate possible malignant cell contamination. A 3 mm punch skin biopsy is easily performed and sufficient for this purpose. Culturing of the skin fibroblasts can be conducted at most Canadian cytogenetics laboratories. Hair follicles are an alternative source of germline DNA; however,

DNA yield is often low. Clinical testing is typically performed using next-generation sequencing (NGS) platforms. Knowledge of the panel used for testing is important to ensure it is sufficiently comprehensive in terms of the genes captured and the ability to detect single nucleotide variants as well as copy number variants, which are often not detected by standard NGS-based assays. Results of genetic testing and genetic counseling (both pre- and post-testing) should be provided by personnel with expertise and dedicated training in this field.

In order to learn more about existing predisposition syndromes and to uncover new syndromes, all patients with suspected hereditary hematologic malignancy should be offered participation in research, where available. Unfortunately, clinical germline genetic testing is not currently available at most major academic centres within Canada. However, testing options do exist via shipment to commercial labs or to a limited number of academic laboratories, such as the IWK Clinical Genomics Laboratory in Halifax, which have validated clinical germline testing panels for hematologic malignancies.

Conclusions and Future Directions

Hereditary hematologic malignancies are more common than previously appreciated and may be accompanied by unique phenotypic characteristics and cancer risks. The identification of patients harbouring these germline predisposing variants is vital to ensure optimal care, to reduce risk of relapse, to institute screening for possible associated solid tumors or organ dysfunction, and to avoid unnecessary treatments or interventions. As these predisposition syndromes gain increasing attention and have begun to be incorporated in major diagnostic and management guidelines, there will be an increasing demand for clinical germline testing. As Canadian hematologists, we need to collaborate with and encourage our local molecular laboratories and/or genetics centres to incorporate germline testing for hereditary hematologic malignancies for optimal patient care.

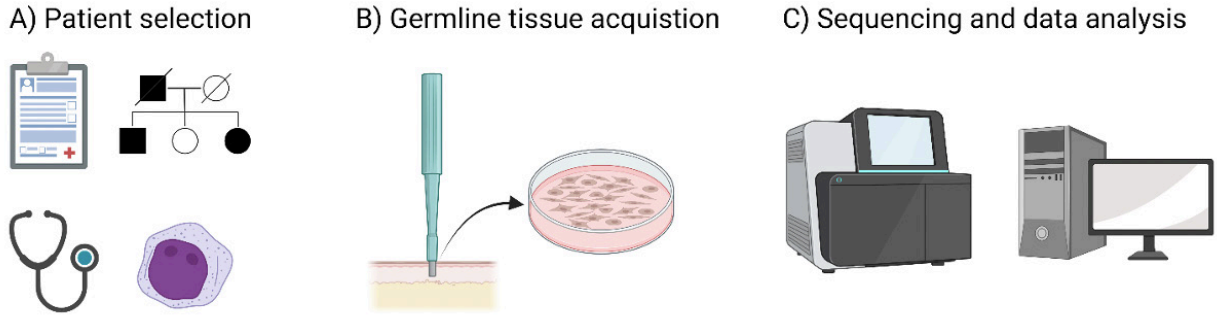

Figure 1. *Approach for selection and testing of patients with suspected hereditary hematologic malignancy. A) Suspicious features that would prompt recommendations for germline genetic testing and pre-test counseling include: a personal history of multiple malignancies; long standing cytopenias and/or bleeding diatheses; a diagnosis of aplastic anemia, myelodysplastic syndrome, or acute myeloid leukemia under the age of 40 years; a diagnosis of myelodysplastic syndrome and plans to undergo allogeneic hematopoietic stem cell transplant; a family history of hematologic malignancy and/or younger than average age of onset of solid tumours within two generations of the patient; physical phenotype consistent with a known germline predisposition syndrome; and/or the identification of a potential germline variant on tumour-based molecular testing. B) For patients that decide to undergo testing, the recommended source for germline DNA is cultured skin fibroblasts, which can easily be obtained with a 3mm punch biopsy. C) Next-generation sequencing is performed on the germline DNA, variants are analyzed and classified according to their pathogenicity,[26] and a clinical report is generated. A comprehensive testing panel with capabilities to call single nucleotide variants and copy number variants is recommended.*

References

1. *Trottier AM, Godley LA. Inherited predisposition to haematopoietic malignancies: overcoming barriers and exploring opportunities. Br J Haematol. 2021;194(4):663-676. doi:10.1111/BJH.17247*
2. *Song W-J, Sullivan MG, Legare RD, et al. Haploinsufficiency of CBFA2 causes familial thrombocytopenia with propensity to develop acute myelogenous leukaemia. Nat Genet. 1999;23:166-175. Accessed November 12, 2017. http://www.nature.com.ezproxy.lib.ucalgary.ca/articles/ng1099_166.pdf*
3. *Tawana K, Wang J, Renneville A, et al. Disease evolution and outcomes in familial AML with germline CEBPA mutations. Blood. 2015;126(10):1214-1223. doi:10.1182/blood-2015-05-647172*
4. *Polprasert C, Schulze I, Sekeres MA, et al. Inherited and Somatic Defects in DDX41 in Myeloid Neoplasms. Cancer Cell. 2015;27(5):658-670. doi:10.1016/j.ccell.2015.03.017*
5. *Zhang MY, Churpek JE, Keel SB, et al. Germline ETV6 mutations in familial thrombocytopenia and hematologic malignancy. Nat Genet. 2015;47(2):180-185. doi:10.1038/ng.3177*
6. *Wlodarski MW, Collin M, Horwitz MS. GATA2 deficiency and related myeloid neoplasms. Semin Hematol. 2017;54(2):81-86. doi:10.1053/j.seminhematol.2017.05.002*
7. *Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and Management of AML in Adults: 2022 ELN Recommendations from an International Expert Panel. Blood. Published online July 7, 2022. doi:10.1182/BLOOD.2022016867/485817/DIAGNOSIS-AND-MANAGEMENT-OF-AML-IN-ADULTS-2022-ELN*
8. *Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391-2405. doi:10.1182/blood-2016-03-643544*
9. *Trottier AM, Bannon S, Bashir Q, Carraway HE, Hofmann I, Godley LA. When should transplant physicians think about familial blood cancers? Adv Cell Gene Ther. 2019;2(4). doi:10.1002/acg2.68*
10. *Rojek K, Nickels E, Neistadt B, et al. Identifying Inherited and Acquired Genetic Factors Involved in Poor Stem Cell Mobilization and Donor-Derived Malignancy. Biol Blood Marrow Transplant. 2016;22(11):2100-2103. doi:10.1016/J.BBMT.2016.08.002*
11. *Buijs A, Poddighe P, Wijk R van, et al. A novel CBFA2 single-nucleotide mutation in familial platelet disorder with propensity to develop myeloid malignancies. Blood. 2001;98(9):2856-2858. doi:10.1182/BLOOD.V98.9.2856*
12. *Hertenstein B, Hambach L, Bacigalupo A, et al. Development of leukemia in donor cells after allogeneic stem cell transplantation--a survey of the European Group for Blood and Marrow Transplantation (EBMT). Haematologica. 2005;90(7):969-975. Accessed February 10, 2019. http://www.ncbi.nlm.nih.gov/pubmed/15996934*
13. *University of Chicago Hematopoietic Malignancies Cancer Risk Team TU of CHMCR. How I diagnose and manage individuals at risk for inherited myeloid malignancies. Blood. 2016;128(14):1800-1813. doi:10.1182/blood-2016-05-670240*
14. *Spinner MA, Sanchez LA, Hsu AP, et al. GATA2 deficiency: a protean disorder of hematopoiesis, lymphatics, and immunity. Blood. 2014;123(6):809-821. doi:10.1182/blood-2013-07-515528*
15. *Agarwal S. Evaluation and Management of Hematopoietic Failure in Dyskeratosis Congenita. Hematol Oncol Clin North Am. 2018;32(4):669-685. doi:10.1016/j.hoc.2018.04.003*
16. *Savage SA, Niewisch MR. Dyskeratosis Congenita and Related Telomere Biology Disorders. Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews® [Internet]. Published online March 31, 2022. Accessed August 16, 2022. https://www.ncbi.nlm.nih.gov/books/NBK22301/*
17. *Deuitch N, Broadbridge E, Cunningham L, Liu P. RUNX1 Familial Platelet Disorder with Associated Myeloid Malignancies. Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews® [Internet]. Published online May 6, 2021. Accessed August 16, 2022. https://www.ncbi.nlm.nih.gov/books/NBK568319/*
18. *Churpek JE, Smith-Simmer K. DDX41-Associated Familial Myelodysplastic Syndrome and Acute Myeloid Leukemia. GeneReviews® [Internet]. Published online October 28, 2021. Accessed August 16, 2022. https://www.ncbi.nlm.nih.gov/books/NBK574843/*
19. *Godley LA, Shimamura A. Genetic predisposition to hematologic malignancies: management and surveillance. Blood. 2017;130(4):424-432. doi:10.1182/BLOOD-2017-02-735290*
20. *Feurstein S, Churpek JE, Walsh T, et al. Germline variants drive myelodysplastic syndrome in young adults. Leukemia. 2021;35(8):2439. doi:10.1038/S41375-021-01137-0*
21. *Sébert M, Passet M, Raimbault A, et al. Germline DDX41 mutations define a significant entity within adult MDS/AML patients. Blood. 2019;134(17):1441-1444. doi:10.1182/BLOOD.2019000909*
22. *Wan Z, Han B. Clinical features of DDX41 mutation-related diseases: a systematic review with individual patient data. Ther Adv Hematol. 2021;12. doi:10.1177/20406207211032433*
23. *Feurstein SK, Trottier AM, Estrada-Merly N, et al. Germline predisposition variants occur in myelodysplastic syndrome patients of all ages. Blood. Published online August 18, 2022. doi:10.1182/BLOOD.2022015790*
24. *Srivastava A, Giangiobbe S, Kumar A, et al. Identification of Familial Hodgkin Lymphoma Predisposing Genes Using Whole Genome Sequencing. Front Bioeng Biotechnol. 2020;8:179. doi:10.3389/FBIOE.2020.00179/BIBTEX*
25. *Pertesi M, Went M, Hansson M, Hemminki K, Houlston R, Nilsson B. Genetic predisposition for multiple myeloma. Leukemia. 2020;34(3):697-708. doi:10.1038/S41375-019-0703-6*
26. *Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424. doi:10.1038/GIM.2015.30*

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THE EVOLVING TREATMENT LANDSCAPE OF HIGHER-RISK MDS

Introduction
Myelodysplastic neoplasms (MDS) are a group of clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis, cytopenia, and morphologic dysplasia.[1] Most cases of MDS are de novo, and a minority are post cytotoxic therapy About 30% of the cases will eventually progress to acute myeloid leukemia (AML), with a higher incidence among the higher-risk MDS group. MDS is a rare disorder with an overall incidence of 3.7-4.8/100,000; the rate increases with age.[2,3]

Diagnosis and risk stratification
Bone marrow examination is needed to confirm the diagnosis of MDS after exclusion of other causes of cytopenia and morphological changes. Cytogenetics and molecular genetics are used to refine the diagnosis and risk stratification, which affects the management plan.[4]

Different risk stratification approaches can be used for MDS patients. The most commonly used is the International Prognostic Scoring System (IPSS), which uses three variables—blast percentages, cytogenetics, and the number of cytopenia—to define 4 risk categories—low, intermediate 1, intermediate 2, and high risk.[5] **(Tables 1 & 2)** The Revised International Prognostic Scoring System (IPSS-R) also considers degree of cytopenia in addition to blast percentages and cytogenetics, creating 5 risk categories: very low, low, intermediate, high, and very high.[6] **(Tables 3 & 4)**

Patients may be divided into lower-risk MDS (low and intermediate 1 on the IPSS and up to 3.5 in score on the IPSS-R) and higher-risk MDS (intermediate 2 and high on the IPSS or above 3.5 on the IPSS-R).

Molecular International Prognostic Scoring System (IPSS-M): Given the widespread availability of next-generation sequencing (NGS) as a diagnostic tool, researchers have investigated the utility of somatic gene mutations for risk stratification of MDS.[7] Diagnostic samples from 2,957 patients with less than 20% blasts and a white blood cell count below 13 X 10^9/L were profiled for mutations in 152 driver genes (discovery cohort). This was validated in an independent external cohort of 754 Japanese patients.

Candidate target risk variables included hematologic parameters (blood counts and blasts), cytogenetics, IPSS-R category, and both the type and number of mutations in 31 genes, resulting in 6 risk categories: very low, low, moderate-low, moderate-high, high and very high. The IPSS-M model improved prognostic discrimination across all clinical end points, restratifying 46% of patients as compared to the IPSS-R risk categories.[7]

Current and novel therapies
Goals of therapy: The goals of therapy for higher-risk MDS include altering the disease's natural history by delaying transformation to acute myeloid leukemia and prolongation of overall survival.[8]

Patients are usually divided into non-transplant candidates or transplant candidates based on several factors, including age, performance status, and co-morbidities, which are

	Score				
	0	0.5	1	1.5	2.0
Medullary blasts, %	0-4	5-10	-	11-20	21-29
Number of cytopenias*	0-1	2-3	-	-	-
Cytogenetic risk group†	Low	Intermediate	High	-	-

Table 1: *International Prognostic Scoring System (IPSS)[5]*
*† Low risk = normal karyotype, 5q,-20q -Y; intermediate risk = all other aberrations; High risk = complex karyotype (≥3 anomalies), chromosome 7 anomalies. * Platelets <100 000/μL; hemoglobin <10 g/dL, absolute neutrophil count <1 800/μL.*

Score	Risk Groups
0	Low risk
0.5-1	Intermediate risk 1
1.5-2	Intermediate risk 2
≥2.5	High risk

Table 2*: IPSS prognostic risk categories[5]*

	Score						
	0	0.5	1	1.5	2	3	4
Cytogenic group*	Very good	-	Good	-	Intermediate	Poor	Very Poor
Medullary blasts, %	≤2	-	>2 to <5	-	5-10	>10	-
Hemoglobin	≥10	-	8 to <10	<8	-	-	-
Platelets	≥100	50 to <100	<50	-	-	-	-
ANC	≥0.8	<0.8	-	-	-	-	-

Table 3: *Revised International Prognostic Scoring System (IPSS-R)[6]*
*ANC, absoulte neutrophil count. * Very good = del(11q), -Y;good = normal karyotype, del(20q), del(5q), del(12p), double including del(5q); intermediate = +8, del(7q), i(17q), +19, any other single or double independent clone, poor = -7 inv(3)/t(3q), double including -7/del(7q), complex: abnormalities; very poor = complex >3 abnormalitites.*

Score	Risk Groups	Median Survival, y	Median time to 25% evolution, y
0-1.5	Very low risk	8.8	Not reached
1.5-3	Low	5.3	10.8
>3-4.5	Intermediate	3.0	3.2
4.5-6	High	1.6	1.4
>6	Very High	0.8	0.73

Table 4: *IPSS-R prognostic risk categories[6]*

usually determined by individual institutional' policy. Treatments for non-transplant candidates usually involve hypomethylating agents (HMA) until disease progression or intolerance. For transplant candidate patients, hypomethylating agents are usually used as a bridge to allogeneic stem cell transplant.[9]

otherwise rapidly degrades decitabine in the gut and liver. A fixed-dose combination (oral tablet cedazuridine 100mg and decitabine 35mg) was used in the phase 3 ASCERTAIN trial for patients with higher-risk MDS, CMML and AML 20-30% blasts.[12] Patients were randomized to receive oral decitabine versus intravenous decitabine. The primary end point of this trial was mean

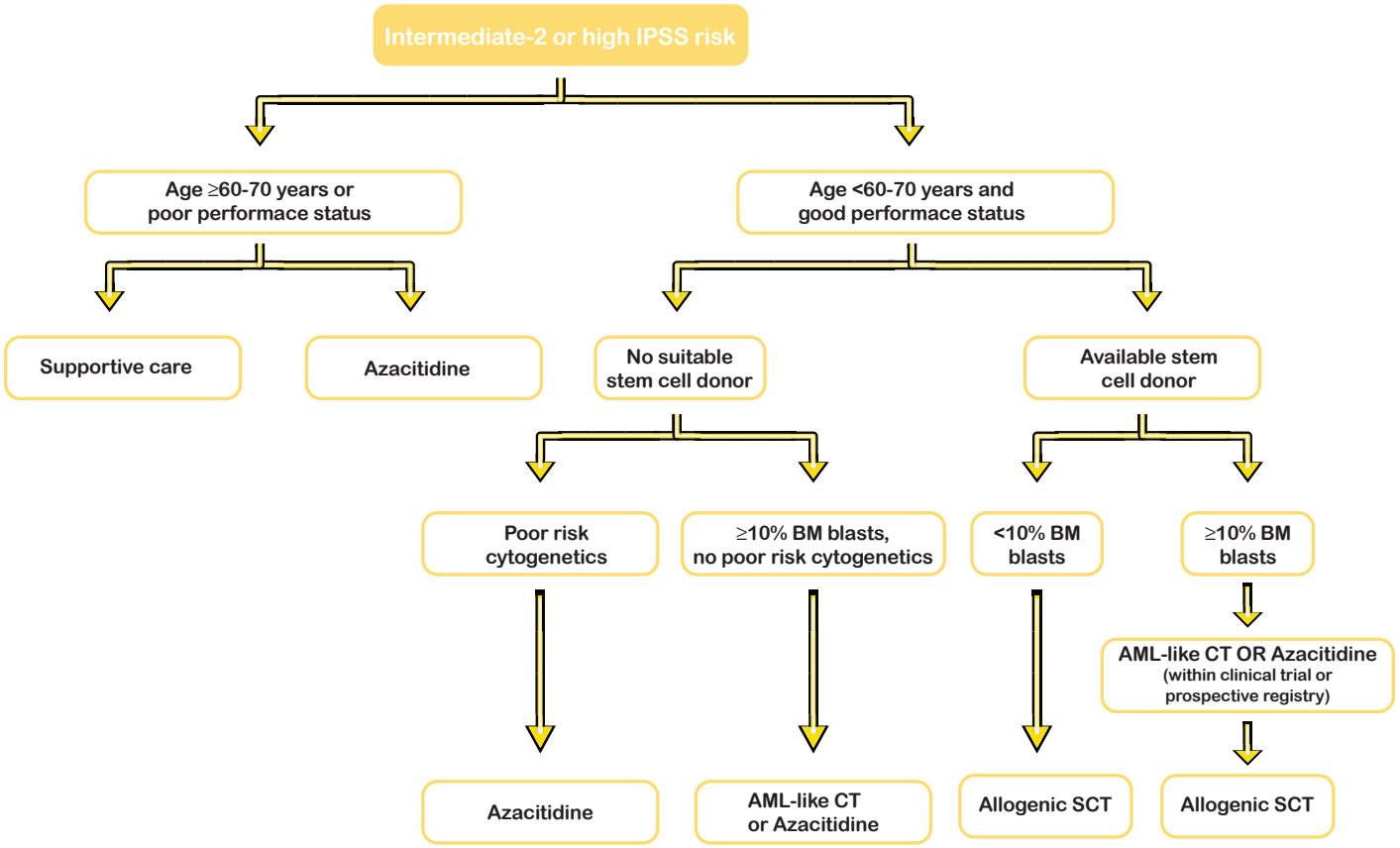

Figure 1. *Therapeutic algorithm for adult patients with primary MDS and intermediate-2 or high IPSS score. CT, chemotherapy; Adapted from Malcovati et al.*[10]

Available options for treatment

Azacitidine is currently the standard of care for higher-risk MDS and is used as monotherapy at the standard dose of 75 mg/m^2 daily for 7 days every 4 weeks until disease progression or intolerance. The AZA-001 phase 3 trial compared azacitidine to conventional care regimens, including intensive chemotherapy, low dose cytarabine, and best supportive care.[11] The study showed that azacitidine significantly improved outcomes versus conventional care regimens, with an overall response rate (ORR) of 29% and a complete response (CR) rate of 17%, as compared to 12% and 8% respectively in the conventional care group. After a median follow-up of 21.1 months, median overall survival was 24.5 months for the azacitidine group versus 15.0 months for the conventional care group (hazard ratio 0.58; 95% CI 0.43-0.77; stratified log-rank p=0.0001).[11]

Oral decitabine (Cedazuridine/Decitabine): When given in combination, cedazuridine enables the efficient oral bioavailability of decitabine. Cedazuridine is a novel, potent and safe inhibitor of cytidine deaminase, which

decitabine systemic exposure of oral/IV 5-day area under curve from time 0 to last measurable concentration. The trial demonstrated that oral cedazuridine/decitabine (100/35 mg) produced a similar systemic decitabine exposure, DNA demethylation, and safety vs decitabine 20 mg/m^2 IV in the first 2 cycles, with similar efficacy. Results also showed an objective response rate of 64% (65 patients), with CR or marrow CR (mCR) with hematological improvement in 26% of patients.[12]

Intensive chemotherapy: Intensive chemotherapy is a reasonable option for younger patients without unfavorable cytogenetics. It can yield a high complete response rate of 45 to 60%.[13,14]

Induction chemotherapy versus HMA in specific patients with higher-risk MDS: In a retrospective study, patients with higher-risk MDS and nucleophosmin (*NPM1*) mutations with more than 10 blasts treated with chemotherapy had higher complete response rates (90% vs 28%, P = .004), longer median progression-free survival

(not reached vs 7.5 months, P = .023), and overall survival (not reached vs 16 months, P = .047) as compared with patients receiving HMA or lenalidomide.[15] According to the new 2022 WHO classification, those patients are now considered acute myeloid leukemia cases.[16]

Allogeneic hematopoietic stem cell transplant (HSCT) is the only curative approach for higher-risk MDS. A patient's disease risk can be considered based on the IPSS or IPSS-R and the presence of underlying comorbidities may be graded according to the HCT Comorbidity Index (HCT-CI) which will help determine HSCT eligibility. Generally speaking, fit patients within higher-risk categories and those with lower-risk, with profound cytopenias, or high transfusion burden are candidates for HSCT. A retrospective analysis compared reduced-intensity SCT to HMA or best supportive care in patients aged 50-75 with intermediate 2 or high-risk de novo MDS.[17] The cohort was divided based on the availability of a matched donor within 90 days of study registration. The donor arm showed significant improvement versus the no-donor arm, with leukemia-free survival of 35.8% vs 20.6% and overall survival rate of 47.9% vs 26.6% at 3 years.[17]

Allogeneic stem cell transplant outcomes are affected by genetic mutations as well as the patient's risk profile. For example, research has demonstrated that *TP53* mutations confer poor outcomes in the range of 15-20% survival rates, even with HSCT.[18]

Investigational therapies

Different targeted therapies are emerging for the treatment of MDS.

1- *Venetoclax plus Azacitidine:* Abnormal overexpression of BCL-2 has been found in patients with higher-risk MDS. Venetoclax is a highly selective, orally bioavailable small-molecule BCL-2 inhibitor. Azacitidine treatment indirectly increases sensitivity to BCL-2 inhibition in higher-risk MDS by modifying the relative levels of BCL-2 family members, thus increasing sensitivity to BCL-2 inhibition by Venetoclax.[19]

A phase 1b dose escalation study of venetoclax plus azacitidine in treatment-naïve patients with higher-risk MDS showed a combined CR and mCR rate of 77%, with a median time to mCR of 0.9 months and a median time to CR of 2.6 months.[20] In addition, molecular responses were noted in patients who achieved CR or marrow CR. Venetoclax was used only for 14 days in addition to the standard doses of azacitidine until disease progression or intolerance.[20]

The phase 3 VERONA trial, a randomized, double-blind, phase 3 study of patients with treatment-naïve HR-MDS, comparing venetoclax plus azacitidine to azacitidine alone is currently ongoing.[21]

In July 2021, the FDA granted breakthrough therapy designation to the combination of venetoclax plus azacitidine as a potential systemic therapy for patients with treatment-naive higher-risk MDS.

2- *Magrolimab plus Azacitidine:* Magrolimab is a first-in-class anti-CD47 macrophage immune checkpoint inhibitor that promotes tumor cell elimination via phagocytosis. It has been observed to have synergistic effects in combination with azacitidine both in vitro and in-vivo.[22]

A phase 1b study showed an overall response rate to magrolimab plus azacytidine of 91% with a CR rate of 42%, with high response in patients with MDS and TP53 mutations, with an overall response rate of 75% and a CR rate of 42%.[23]

3- *Pevonedistat plus Azacitidine:* Pevonedistat is a first-in-class, selective inhibitor of NEDD8-activating enzyme, that causes cancer cell death by disrupting protein homeostasis. The phase 3 PANTHER trial randomized patients with higher-risk MDS, CMML or AML with 20-30% blasts to receive upfront treatment with a combination of pevonedistat plus azacitidine versus azacitidine alone. This trial did not meet the primary endpoint of event-free survival; however, in a post-hoc analysis, median overall survival(OS) for patients receiving >3 cycles was 23.8 vs 20.6 months (P = 0.021) and for >6 cycles was 27.1 vs 22.5 months (P = 0.008).[24]

4- *Sabatolimab plus Azacitidine:* Sabatolimab is a humanized IgG4 antibody targeting T-cell immunoglobulin and mucin domain-3 (TIM-3), a co-inhibitory receptor involved in regulating adaptive and innate immune responses. TIM-3 is highly expressed on immune cells in MDS and leukemic blasts and not on healthy cells. The combination with azacitidine showed promising antileukemic activity with an overall response rate of 64.7% and combined CR and mCR of 41.2%.[25]

Sabatolimab showed a high and durable response in patients with TP53, with an overall response rate of 71.4% and a median duration of response of 21.5 months.[26]

This combination received FDA Fast Track designation for the treatment of high-risk MDS in May of 2021.

5- *CPX-351 as first-line treatment for higher-risk MDS:* CPX-351 is a liposomal formulation of daunorubicin and cytarabine at a fixed 1:5 ratio that has shown synergistic activity, preferential uptake by leukemic cells, and prolonged delivery with a longer half-life than traditional chemotherapy. The Groupe Francophone des Myélodysplasies (GFM) carried out a phase 2 trial of CPX-351 in higher-risk MDS patients. Treatment included an induction phase and up to 4 cycles of consolidation with the option of allogeneic stem cell transplant after 1-4 cycles. The study included 31 patients; overall response

rate was 87% with a combined CR/Cri of 65% and mCR rate of 28%. Twenty-two patients (94%) proceeded to allogeneic stem cell transplants.[27]

Approaches to MDS patients who failed HMA: Patients who fail or relapse post-azacitidine therapy have a very poor prognosis, with median overall survival from a few months up to 1 year. Allogeneic stem cell transplant patients post HMA failure has a better median overall survival than other conventional or investigational therapies.[28]

There is no widely agreed upon standard of care for most patients who fail HMA therapy. However, newer targeted therapies for patients with certain genetic mutations, such as *IDH-1/2, BCL-2, CD47, NPM1, TP53, or FLT3*, may provide benefit.

Conclusions

MDS continues to pose a diagnostic and therapeutic challenge. Risk stratification for better assessment of prognosis and to guide therapy is essential and should be performed at diagnosis. Hypomethylating agents continue to represent first-line therapy for higher-risk MDS patients. Several ongoing frontline trials exploring combination therapies suggest synergies with HMA. There is no consensus approach to the management of patients who relapse or have refractory higher-risk MDS after HMA failure; however, several novel agents are being investigated. Participation in clinical trials is highly encouraged for higher-risk MDS patients.

References:

1. *Khoury J.D., Solary E., Abla O, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia 2022; 36, 1703–1719*
2. *Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2016, National Cancer Institute. Based on November 2018 SEER data submission, posted to the SEER web site, April 2019.*
3. *Zeidan AM, Shallis R, Wang R, et al. Blood Rev. 2019;34:1-15.*
4. *Valent P, Orazi A, Steensma D, et al. Oncotarget. 2017 Sep 26; 8 (43): 73483-73500.*
5. *Greenberg P, Cox C, LeBeau M et al. International Scoring System for evaluating prognosis in myelodysplastic syndromes. Blood 1997;89:2079-2088.*
6. *Greenberg P, Tuechler H, Schanz J et al. Revised International Prognostic Scoring System for Myelodysplastic Syndromes. Blood 2012;120 9120 (12):2454; 2465.*
7. *Bernard E, Tuechler H, Greenberg PL, et al. Molecular International Prognosis Scoring system for myelodysplastic syndromes. Blood. 2021;138 (supplement 1):61.*
8. *Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood. 2006 Jul 15;108(2):419-25.*
9. *Steensma DP. Myelodysplastic syndromes current treatment algorithm 2018. Blood Cancer J. 2018 May 24;8(5):47.*
10. *Malcovati L, Hellström-Lindberg E, Bowen D, Adès L, et al. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. Blood. 2013 Oct 24;122(17):2943-64.*
11. *Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol. 2009 Mar;10(3):223-32.*
12. *Garcia-Manero G, McCloskey J, Griffiths EA, et al. Pharmacokinetic exposure equivalence and preliminary efficacy and safety from a randomized cross over phase 3 study (ASCERTAIN study) of an oral hypomethylating agent ASTX727 (cedazuridine/decitabine) compared to IV decitabine [ASH abstract 846]. Blood. 2019;134(suppl 1).*
13. *Kantarjian H, O'Brien S, Cortes J, et al. Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: predictive prognostic models for outcome. Cancer. 2006 Mar 1;106(5):1090-8.*
14. *Knipp S, Hildebrand B, Kündgen A, et al. Intensive chemotherapy is not recommended for patients aged >60 years who have myelodysplastic syndromes or acute myeloid leukemia with high-risk karyotypes. Cancer. 2007 Jul 15;110(2):345-52.*
15. *Montalban-Bravo, Kanagal-Shamanna R, Sasaki K, et al. NPM1 mutations define a specific subgroup of MDS and MDS/MPN patients with favorable outcomes with intensive chemotherapy. Blood Adv. 2019; 3 (6): 922–933.*
16. *Khoury, J.D., Solary, E., Abla, O. et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. 2022; 36, 1703–1719*
17. *Nakamura R, Saber W, Martens M, et al. A Multi-Center Biologic Assignment Trial Comparing Reduced Intensity Allogeneic Hematopoietic Cell Transplantation to Hypomethylating Therapy or Best Supportive Care in Patients Aged 50-75 with Advanced Myelodysplastic Syndrome: Blood and Marrow Transplant Clinical Trials Network Study 1102. Blood. 2020; 136 (Supplement 1):75; 19-21.*
18. *Lindsley R, Saber W, Mar B et al. Prognostic Mutations in Myelodysplastic Syndrome after Stem Cell Transplantation. N Engl J Med. 2017; 376:536-547.*
19. *Stomper, J., Rotondo, J.C., Greve, G. et al. Hypomethylating agents (HMA) for the treatment of acute myeloid leukemia and myelodysplastic syndromes: mechanisms of resistance and novel HMA-based therapies. Leukemia 2021; 35, 1873-1889.*
20. *Garcia JS, Wei AH, Jacoby MA, et al. Molecular Responses Are Observed across Mutational Spectrum in Treatment-Naïve Higher-Risk Myelodysplastic Syndrome Patients Treated with Venetoclax Plus Azacitidine. Blood 2021; 138 (Supplement 1):241.*
21. *Zeidan AM, Garcia JS, Fenaux P, et al. Phase 3 VERONA study of venetoclax with azacitidine to assess change in complete remission and overall survival in treatment-naïve higher-risk myelodysplastic syndromes. J Clin Oncol. 2021, 39:15 Suppl.*
22. *Feng D et al. Combination treatment with 5F9 and azacitidine enhances phagocytic elimination of acute myeloid leukemia. Blood. 2018;132(Suppl 1):2729.*
23. *Sallman DA, Al Malki M, Asch AS, etal. Tolerability and efficacy of the first-in-class anti-CD47 antibody magrolimab combined with azacitidine in MDS and AML patients: Phase Ib results. J Clin Oncol. 2020;38 (Supplement 15) 7507.*
24. *Sekeres M, Girshova L, Doronin V et al. Pevonedistat (PEV) + Azacitidine (AZA) Versus AZA Alone As First-Line Treatment for Patients with Higher-Risk Myelodysplastic Syndromes (MDS)/Chronic Myelomonocytic Leukemia (CMML) or Acute Myeloid Leukemia (AML) with 20-30% Marrow Blasts: The Randomized Phase 3 PANTHER Trial. Blood. 2021 ; 138 (Supplement 1):242.*
25. *Brunner AM, Esteve J, Porkka K, et al. Efficacy and Safety of Sabatolimab (MBG453) in Combination with Hypomethylating Agents (HMAs) in Patients (Pts) with Very High/High-Risk Myelodysplastic Syndrome (vHR/HR-MDS) and Acute Myeloid Leukemia (AML): Final Analysis from a Phase Ib Study. Blood. 2021; 138 (supplement1):244.*
26. *Garcia-Manero G, Wei A, Porkka K et al. MDS-420: Sabatolimab Plus Hypomethylating Agents (HMAs) in Patients with High-/Very High-risk Myelodysplastic Syndrome (HR/vHR-MDS) and Newly Diagnosed Acute Myeloid Leukemia (ND-AML): Subgroup Analysis of a Phase 1 Study. Clinical Lymphoma, Myeloma and Leukemia. 2021; Volume 21, Supplement 1: S350.*
27. *Peterlin P, Turlure P, Chevallier P, et al. CPX 351 As First Line Treatment in Higher Risk MDS, a Phase II Trial By the GFM. Blood 2021; 138 (Supplement 1): 243.*
28. *Prébet T, Gore SD, Esterni B, et al. Outcome of high-risk myelodysplastic syndrome after azacitidine treatment failure. J Clin Oncol. 2011 Aug 20;29(24):3322-7.*

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- **VENCLEXTA is only available through specialty pharmacies and/or retail oncology pharmacies that are part of AbbVie's managed distribution program.**
- **Tumour lysis syndrome (TLS)**
  - Weekly dosage ramp-up over a period of 5 weeks with CLL, with blood chemistry monitoring on each dose ramp-up is required.
  - Patients must receive prophylaxis for TLS, including hydration and anti-hyperuricemics prior to initiating treatment.
  - In patients with CLL, concomitant use of strong CYP3A inhibitors at initiation and during ramp-up phase is contraindicated.
- **Serious infections that may lead to hospitalization or death.**

Other relevant warnings and precautions:
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- Monitor patients more frequently for signs of VENCLEXTA toxicities.
- Neutropenia; dose interruption/reduction recommended for severe neutropenia; prophylactic use of growth factors (e.g. G-CSF) may be considered.
- Immunization using live vaccines should be avoided during treatment and thereafter until B-cell recovery.
- Monitor for signs of infection and have their complete blood counts monitored throughout treatment.
- Recommended dose not determined for patients with severe renal impairment (CrCl <30 mL/min) or on dialysis.
- Females of reproductive potential: test to exclude pregnancy before treatment; use of effective contraceptives during treatment and for at least 30 days after last dose.
- Male fertility may be compromised.
- Avoid use during pregnancy.
- Breastfeeding should be discontinued.
- No overall difference in effectiveness and safety observed in patients ≥65 years of age compared to younger patients. In the combination study (MURANO), patients ≥65 years of age experienced higher incidences of diarrhea, peripheral oedema, dizziness, blood creatinine increased, constipation, pyrexia and fall than those <65 years of age.
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Please refer to the study parameters[†§] and reference list at: **meddocs.ca/CA-VENC-210030.html**.

* V: VENCLEXTA.
‡ The median follow-up at the time of analysis was 28 months (range: 0 to 36 months).
¶ The median follow-up at the time of primary analysis was 24.8 months (range: 0.3 to 37.4 months) in the VENCLEXTA + rituximab arm and 22.1 months (range: 0 to 33.8 months) in the bendamustine + rituximab arm (data cut-off date May 8, 2017).

CLL: chronic lymphocytic leukemia; PFS: progression-free survival; HR: hazard ratio; CI: confidence interval; R/R: relapsed/refractory; IRC: independent review committee; ITT: intention-to-treat; G-CSF: granulocyte-colony stimulating factor; CrCl: creatinine clearance.

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CHRONIC MYELOID LEUKEMIA: WHO SHOULD GET A TREATMENT-FREE TRIAL AND HOW?

Introduction

Treatment with a BCR::ABL1 targeted tyrosine kinase inhibitor (TKI) has afforded a near-normal life expectancy for most patients with chronic myelogenous leukemia (CML).[1-3] Approximately half of CML patients achieve a deep molecular response with TKI therapy and can discontinue treatment. In these patients, the CML can remain in prolonged remission, and patients can experience an improvement in quality of life.[4]

The European Leukemia Network (ELN)[5] and the National Comprehensive Cancer Network (NCCN)[6] provide the most up-to-date frameworks for treatment-free trials (TFTs), reflecting best practices from over 13 clinical trials published since the concept first entered the CML vernacular around 2010.[7] Provincial guidelines also exist, such as those published in Quebec by the Groupe Québécois de Recherche en LMC-NMP (the Chronic Myeloid Leukemia and Myeloproliferative Neoplasms Quebec Research Group).

The discontinuation of therapy for patients with CML in deep remission marks a potential shift from the management of CML as a chronic illness to the potential for a curative approach to CML. However, for now, only 50% of eligible patients have undergone successful TFT; optimal patient selection and monitoring is required to ensure the best outcomes with such a management strategy.

Patient selection

In 2022, almost all patients with CML are candidates for one of several available TKIs, including the first generation TKI, imatinib; second generation TKIs, such as dasatinib, nilotinib, and bosutinib; and third generation TKIs, such as ponatinib and asciminib. These therapies are approved in Canada either in the first line or beyond and can all produce a molecular response level of at least MR4, (a BCR::ABL1 transcript level of <0.01% on the International Scale [IS]) the minimum value required for consideration of a TFT **(Figure 1)**.

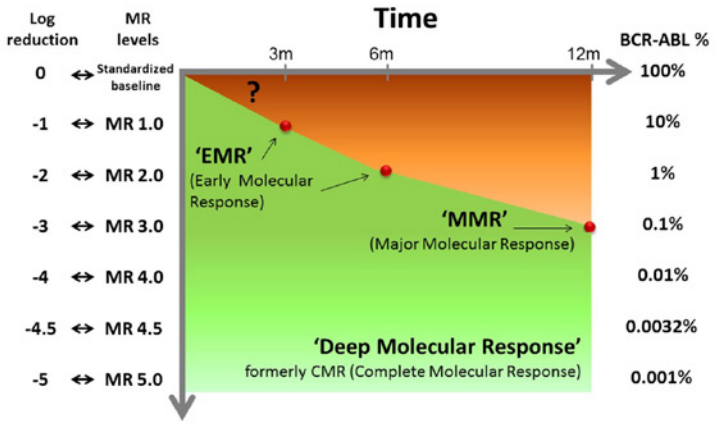

Figure 1. *The bar for molecular response in CML; adapted from Baccarani et al, 2014*

To be eligible for therapy discontinuation, patients must achieve sustained MR4 or better for at least 18 to 24 months (with measurements at least 6 months apart) and must have received TKI therapy for at least 3 years Based on EURO-SKI, the largest TKI discontinuation study in CML, the optimal duration of TKI therapy is about 5 years.[8] The duration and depth of molecular response may impact the success of a TFT.[8-11]

In addition, the patient's CML must have a measurable or typical transcript according to the results of the assay being used (98% of patients have a measurable transcript). The presence of an

atypical transcript can be assessed at the time of diagnosis if the real-time quantitative PCR (RT-qPCR) run along with cytogenetics shows a BCR::ABL1 transcript level of <MR2 (<1% IS) while the cytogenetics clearly demonstrate the presence of the Philadelphia chromosome. Being able to quantify the BCR::ABL1 ensures that the patient indeed has achieved deep remission and that a relapse can be identified early during the TFT.

Eligible patients must also be available and willing to undergo regular, frequent monitoring after stopping their TKI therapy. Since the depth of molecular response is strongly associated with compliance,[12] patients who are candidates for a TFT tend to have a history of good compliance with drug therapy and medical visits.

Choice of TKI prior to TFT

The possibility of a TFT should be discussed with all newly diagnosed patients as it may impact the choice of first-line therapy. Second generation TKIs given in the first-line setting are associated with a 10% to 20% higher deep MR4 rate than imatinib,[13-15] and thus potentially offer a greater chance at therapy discontinuation. However, the evidence shows that there is no noticeable difference in the overall success rate of TFTs based on the choice of initial TKI.[4,16,17] In selecting a first-line therapy, it is essential to first ensure that the chosen TKI will result in the best tolerability and long-term compliance, as the primary goal in treating CML remains a durable clinical response and the subsequent impact on survival.

In most discontinuation trials, results have shown that patients were not refractory to any prior TKI (defined as a loss of response or failure to achieve at least a complete cytogenetic response [MR2, or 1% IS]). Non-TKI refractory patients who switch due to intolerance or to achieve deeper response have a similar TFT success rate as those stopping after a first-line therapy.[18-20] However, among first line imatinib-resistant patients who switched to dasatinib or nilotinib to achieve a deeper molecular response, the rates of TFT success have been shown to be lower.[19-21] Accordingly, the ELN and NCCN favour non-refractory patients for TFTs.

Ultimately, approximately 50% to 60% of patients will be eligible for a TFT when the criteria for discontinuation are met **(Figure 2)**.

Molecular monitoring

The assay used to measure molecular response prior to the TFT must have a sensitivity of at least 1/10,000, and the copy number of the control gene should be provided for each molecular response assessment to ensure that an adequate quantity of RNA was evaluated in generating the result. Ideally, the molecular assay should use the International Scale (IS) to ensure validity against an international standard and consistency across different laboratories. In addition, the turnaround time for molecular results should be no longer than 4 weeks to allow for a timely assessment n in case of a rising PCR value.

Once a patient starts the TFT, they must undergo molecular monitoring every 4-8 weeks during the first year. Thereafter,

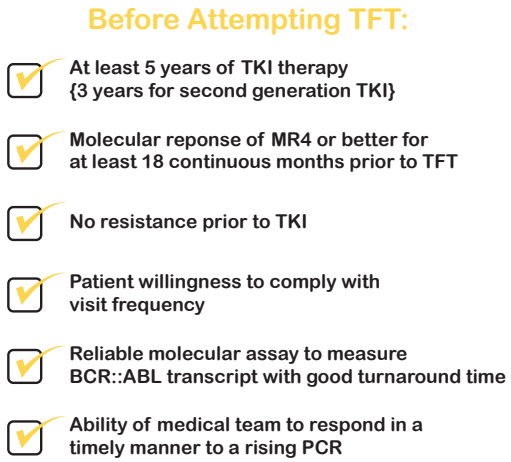

Figure 2. *Criteria for TFT eligibility; courtesy of Sarit Assouline, MD*

monitoring can be done every 12 weeks. The goal is to maintain a minimum major molecular response (MR3, <0.1% IS). Most losses of molecular response during TFTs typically occur within the first 6 to 12 months of the discontinuation of TKI therapy, but there can be late losses, which reinforces the need for long-term monitoring. The molecular patterns following the initiation of a TFT can vary, as shown in **Figure 3**.

There is rarely loss of cytogenetic or hematological remission during TFTs. The risk of such outcomes is mitigated by close patient follow-up during the TFT period. Most patients (95%) who lose MR3 regain at least MR3 when either the original or a new TKI is re-initiated. Episodes of blast crisis, the transformation of CML from the chronic phase to the blast phase, during TFTs have been reported, raising some concerns, but more research is needed to determine the rate of transformation and the surrounding circumstances.

While frequent molecular monitoring is essential, clinic visits need not be as frequent if the treating team is able to follow and communicate molecular results in a timely manner.

Clinical Scenarios for TFT consideration

When criteria for discontinuation are met, a patient should be offered a TFT because of the potential long-term adverse effects associated with chronic TKI treatment. Interestingly, many patients do not choose a TFT, citing the security of taking a medication to control their disease, the absence of bothersome adverse effects, and the risk of relapse associated with discontinuation. Patients who choose to discontinue therapy have reported doing so because of persistent or recurrent side effects, concerns about long-term toxicity, the impact on quality of life of taking medication, and the cost of their therapy.[22]

While men who wish to conceive need not discontinue therapy, TKI therapy is unsafe for the developing fetus. For women wishing to become pregnant, a TFT appears to be the best option but given that only 50% of patients qualify for a TFT and that only 50% have a successful TFT outcome, this option may be unachievable for many. For patients planning to become pregnant, the safest option is surrogacy, but pregnancy following TKI therapy can be safe once MR3 levels or better have been

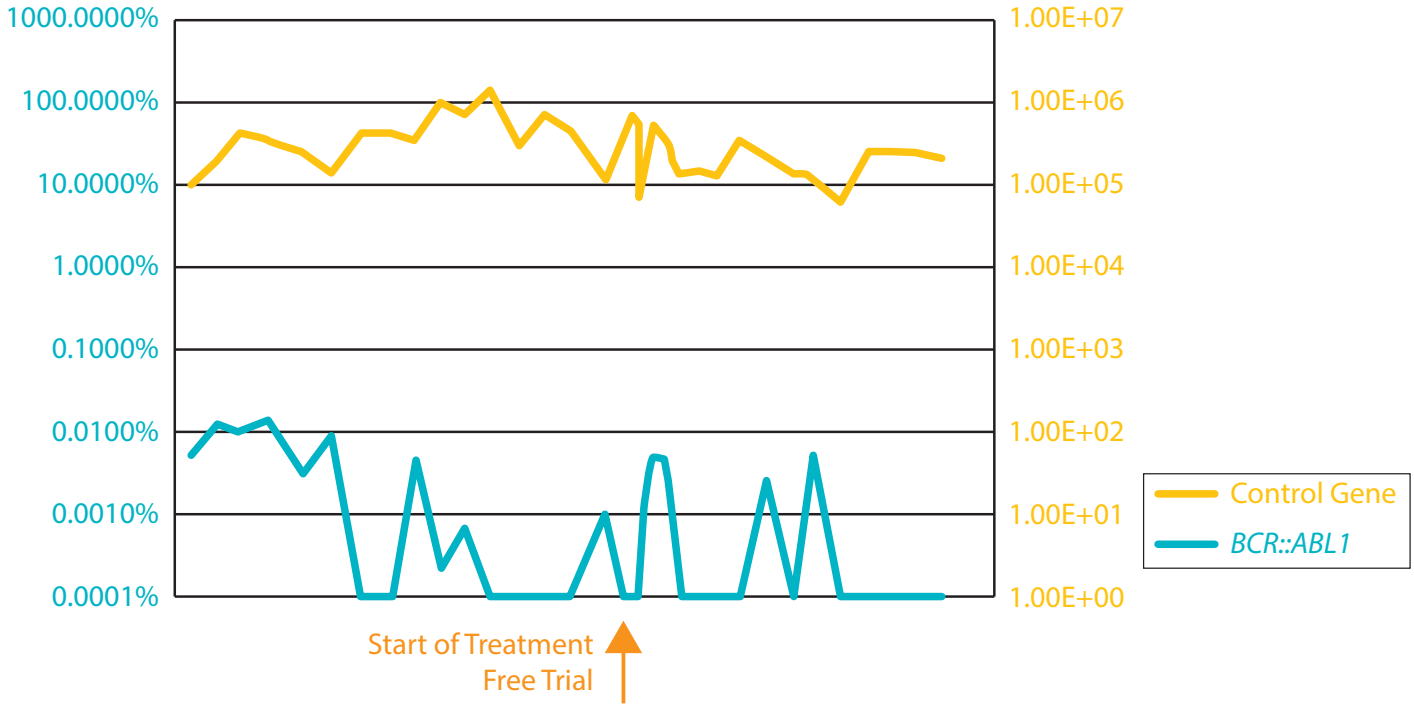

Figure 3. *Sample molecular patterns following initiation of TFT; courtesy of Sarit Assouline, MD*

achieved and the pregnancy is planned at least after 2 years of TKI therapy, when the risk of disease transformation to blast crisis is significantly reduced.[23] Furthermore, there are anecdotal reports that nilotinib and imatinib can be administered safely during the later stages of pregnancy, but this is not recommended in the respective product monographs.[23]

Some patients may discontinue TKI therapy without consulting their treating physician, often based on information gleaned from sources outside the clinic. It is therefore important to counsel patients that the best outcomes are achieved in close collaboration with their healthcare team.

TKI withdrawal syndrome

Among patients who attempt a TFT, 20% to 30% may experience withdrawal syndrome which typically manifests as musculoskeletal and peri-articular pain. TKI withdrawal syndrome usually appears within weeks to months after discontinuing therapy and may take months to resolve. Symptoms can be managed with acetaminophen, non-steroidal anti-inflammatories and glucocorticosteroids, if needed.[24] Patients should be reassured that the withdrawal symptoms will eventually resolve or improve. There are reports of patients resuming TKI therapy due to the symptoms of withdrawal. Notwithstanding those affected by TKI withdrawal syndrome, most patients report an improvement in pain when stopping TKI therapy.[4]

Second TFTs

Second TKI discontinuation attempts are less successful, measured at about a 20% success rate, with even lower rates among patients who have a rapid loss of MR3 levels during a first TFT attempt[25]. As such, a second TFT is not yet recommended by the ELN and NCCN. If considering a second TFT for the sake of diminishing TKI toxicity, better options may include switching TKIs or dose reductions to optimize tolerance.

Improving the TFT success rate

Ongoing studies are currently underway to examine of the combination of imatinib and asciminib, a third generation TKI targeting the myristoyl pocket of ABL. These studies are promising, and early results suggest that the combination of ATP binding TKI and asciminib is more effective than either agent alone[26].

Conclusion

TFTs have become part of routine practice in the treatment of CML in the last several years, owing to robust data and revised management guidelines. For Canadian patients with CML, a TFT should be considered from the time of diagnosis and throughout the course of treatment. When performed correctly, a TFT can be a very positive experience for both the patient and medical team alike.

References:

1. *Hoglund M, Sandin F, Hellstrom K, et al. Tyrosine kinase inhibitor usage, treatment outcome, and prognostic scores in CML: report from the population-based Swedish CML registry. Blood 2013; 122(7): 1284-92.*
2. *Gambacorti-Passerini C, Antolini L, Mahon FX, et al. Multicenter independent assessment of outcomes in chronic myeloid leukemia patients treated with imatinib. Journal of the National Cancer Institute 2011; 103(7): 553-61.*
3. *Hochhaus A, Larson RA, Guilhot F, et al. Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia. N Engl J Med 2017; 376(10): 917-27.*
4. *Atallah E, Schiffer CA, Radich JP, et al. Assessment of Outcomes After Stopping Tyrosine Kinase Inhibitors Among Patients With Chronic Myeloid Leukemia: A Nonrandomized Clinical Trial. JAMA Oncology 2021; 7(1): 42-50.*
5. *Hochhaus A, Baccarani M, Silver RT, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia 2020; 34(4): 966-84.*
6. *Deininger MW, Shah NP, Altman JK, et al. Chronic Myeloid Leukemia, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2020; 18(10): 1385-415.*
7. *Mahon FX, Rea D, Guilhot J, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. Lancet Oncol 2010; 11(11): 1029-35.*
8. *Saussele S, Richter J, Guilhot J, et al. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial. Lancet Oncol 2018; 19(6): 747-57.*
9. *Mori S, Vagge E, le Coutre P, et al. Age and dPCR can predict relapse in CML patients who discontinued imatinib: the ISAV study. Am J Hematol 2015; 90(10): 910-4.*
10. *Radich JP, Hochhaus A, Masszi T, et al. Treatment-free remission following frontline nilotinib in patients with chronic phase chronic myeloid leukemia: 5-year update of the ENESTfreedom trial. Leukemia 2021; 35(5): 1344-55.*
11. *Nicolini FE, Dulucq S, Boureau L, et al. Evaluation of Residual Disease and TKI Duration Are Critical Predictive Factors for Molecular Recurrence after Stopping Imatinib First-line in Chronic Phase CML Patients. Clinical Cancer Research 2019; 25(22): 6606-13.*
12. *Marin D, Bazeos A, Mahon F-X, et al. Adherence Is the Critical Factor for Achieving Molecular Responses in Patients With Chronic Myeloid Leukemia Who Achieve Complete Cytogenetic Responses on Imatinib. Journal of Clinical Oncology 2010; 28(14): 2381-8.*
13. *Kantarjian HM, Hughes TP, Larson RA, et al. Long-term outcomes with frontline nilotinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase: ENESTnd 10-year analysis. Leukemia 2021; 35(2): 440-53.*
14. *Cortes JE, Saglio G, Kantarjian HM, et al. Final 5-Year Study Results of DASISION: The Dasatinib Versus Imatinib Study in Treatment-Naive Chronic Myeloid Leukemia Patients Trial. J Clin Oncol 2016; 34(20): 2333-40.*
15. *Chuah C, Koh LP, Numbenjapon T, et al. Efficacy and safety of bosutinib versus imatinib for newly diagnosed chronic myeloid leukemia in the Asian subpopulation of the phase 3 BFORE trial. Int J Hematol 2021; 114(1): 65-78.*
16. *Shah NP, García-Gutiérrez V, Jiménez-Velasco A, et al. Dasatinib discontinuation in patients with chronic-phase chronic myeloid leukemia and stable deep molecular response: the DASFREE study. Leukemia Lymphoma 2020; 61(3): 650-9.*
17. *Giles FJ, Masszi T, Casares MTG, et al. Treatment-free remission (TFR) following frontline (1L) nilotinib (NIL) in patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP): 192-week data from the ENESTfreedom study. Journal of Clinical Oncology 2019; 37(15_suppl): 7013-.*
18. *Rea D, Rousselot P, Guilhot Fo, et al. Discontinuation of Second Generation (2G) Tyrosine Kinase Inhibitors (TKI) in Chronic Phase (CP)-Chronic Myeloid Leukemia (CML) Patients with Stable Undetectable BCR-ABL Transcripts. Blood 2012; 120(21): 916-.*
19. *Shah NP, Garcia-Gutierrez V, Jimenez-Velasco A, et al. Dasatinib discontinuation in patients with chronic-phase chronic myeloid leukemia and stable deep molecular response: the DASFREE study. Leuk Lymphoma 2020; 61(3): 650-9.*
20. *Hughes TP, Boquimpani CM, Takahashi N, et al. Treatment-Free Remission in Patients with Chronic Myeloid Leukemia in Chronic Phase According to Reasons for Switching from Imatinib to Nilotinib: Subgroup Analysis from ENESTop. Blood 2016; 128(22): 792-.*
21. *Okada M, Imagawa J, Tanaka H, et al. Final 3-year Results of the Dasatinib Discontinuation Trial in Patients With Chronic Myeloid Leukemia Who Received Dasatinib as a Second-line Treatment. Clin Lymphoma Myeloma Leuk 2018; 18(5): 353-60 e1.*
22. *Flynn KE, Myers JM, D'Souza A, Schiffer CA, Thompson JE, Atallah E. Exploring Patient Decision Making Regarding Discontinuation of Tyrosine Kinase Inhibitors for Chronic Myeloid Leukemia. Oncologist 2019; 24(9): 1253-8.*
23. *Abruzzese E, Mauro M, Apperley J, Chelysheva E. Tyrosine kinase inhibitors and pregnancy in chronic myeloid leukemia: opinion, evidence, and recommendations. Therapeutic advances in hematology 2020; 11: 2040620720966120.*
24. *Richter J, Söderlund S, Lübking A, et al. Musculoskeletal Pain in Patients With Chronic Myeloid Leukemia After Discontinuation of Imatinib: A Tyrosine Kinase Inhibitor Withdrawal Syndrome? Journal of Clinical Oncology 2014; 32(25): 2821-3.*
25. *Dulucq S, Astrugue C, Etienne G, Mahon F-X, Benard A. Risk of molecular recurrence after tyrosine kinase inhibitor discontinuation in chronic myeloid leukaemia patients: a systematic review of literature with a meta-analysis of studies over the last ten years. British Journal of Haematology 2020; 189(3): 452-68.*
26. *Eide CA, Zabriskie MS, Savage Stevens SL, et al. Combining the Allosteric Inhibitor Asciminib with Ponatinib Suppresses Emergence of and Restores Efficacy against Highly Resistant BCR-ABL1 Mutants. Cancer Cell 2019; 36(4): 431-43 e5.*

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EVOLVING STRATEGIES IN T-CELL LYMPHOMA

Background
Peripheral T-cell lymphomas (PTCL) are derived from post-thymic, mature T-cells and represent a clinically and biologically heterogeneous group of diseases. A common feature of the majority of PTCLs is a poor prognosis compared to their aggressive B-cell counterparts. Additionally, due to the rarity of the disease, the optimal therapy remains unknown. A large proportion of patients present with multiple poor risk factors as per the International Prognostic Index (IPI) and are rarely cured.[1-3] The one exception is ALK positive anaplastic large cell lymphoma (ALCL), a group of diseases that has a much more favourable prognosis; however, those patients with ALCL and multiple IPI factors have a similar poor prognosis.[4] CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CHOP-like chemotherapy has been the mainstay of therapy for aggressive lymphomas, including PTCLs. However, response rates for most PTCLs are inferior to those observed in aggressive B-cell lymphomas and relapses are frequent. In a meta-analysis of 31 studies of patients with PTCL treated with anthracycline based chemotherapy (n=2912), excluding ALCL cases, the estimated 5- year overall survival (OS) was only 36.6%.[5] The German High Grade Non-Hodgkin Lymphoma Group (DSHNHL) retrospectively evaluated the outcome of 289 PTCL patients included in phase II and III trials and reported that the addition of etoposide in young patients (≤ 60 years of age) with a normal lactate dehydrogenase (≤ upper value of normal) improved event-free survival (EFS) but not OS. However, the benefit appeared to be mainly in patients with ALK-pos ALCL (p=.012) with only a trend to improved 3 year event-free survival (EFS) observed in the other common PTCL subtypes (p=.057).[6] Importantly for patients above the age of 60, the addition of etoposide conferred no benefit.

Recently, the ECHELON2 trial reported improved progression-free survival (PFS) and OS with the addition of brentuximab to frontline therapy compared with CHOP alone in CD30+ T-cell lymphomas (75% of which were ALCL)[7] and this regimen has become the standard frontline treatment in many jurisdictions for these lymphomas. Adverse events such as febrile neutropenia and peripheral neuropathy were similar between both groups. Other attempts at improving CHOP with the addition of a novel agent have not been as successful. A phase III randomized controlled trial (RCT) compared romidepsin-CHOP to CHOP alone in 421 untreated PTCL patients demonstrated that this combination did not result in an improved PFS or OS but was associated with more grade 3 or 4 treatment-emergent adverse events (TEAEs) such as thrombocytopenia, neutropenia, anemia and leukopenia.[8] Similarly, the addition of alemtuzumab to CHOP did not improve survival in a cohort of elderly patients due to excessive toxicity.[9]

For patients who do have a complete response to frontline therapy, some centres proceed to consolidation with an autologous stem cell transplant(ASCT). However, there is no randomized data to support this approach,, and thus it has been recommended by experts based mostly on retrospective cohort comparisons or prospective phase II trials.[10.11] A recent Dutch nationwide population-based study identified that in patients age < 65 years of age with advanced-stage ALK- ALCL, AITL, or PTCL (ALCL,

35%; AITL, 21%; and PTCL NOS, 44%, respectively), consolidation with ASCT was associated with an improved OS (78% vs. 45%) compared with patients receiving induction chemotherapy only, including in the subgroup who achieved a complete response (CR) to frontline therapy **(Figure 1)**.[12]

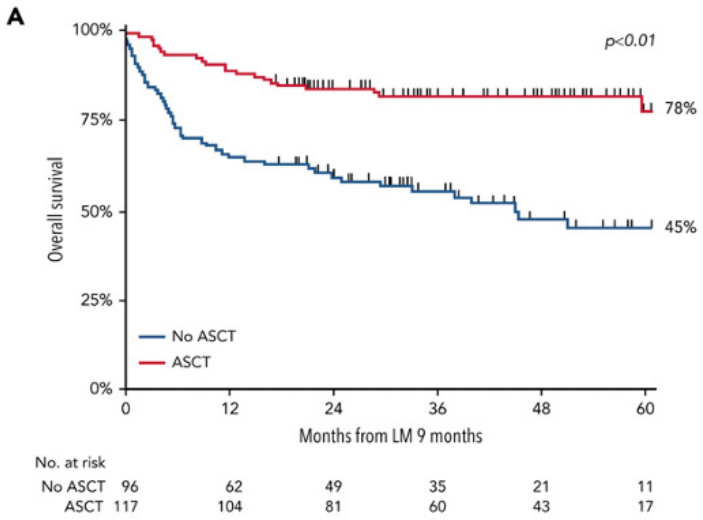

Figure 1. *OS in patients aged <65 years with stage II to IV disease. (A-B) OS in patients with ALCL, AITL, or PTCL NOS treated with or without consolidation with ASCT after chemotherapy in the first-line setting, measured in months after the 9-month landmark (LM) (A); Brink et al, 2022*

Relapsed/Refractory PTCL

Despite the approaches above, many PTCL patients relapse. The present approach to treatment of these patients can be divided into two categories: salvage chemotherapy with the goal of a stem cell transplant (SCT) (autologous or allogeneic) or single agent treatment, including the use of novel agents as part of clinical trials, either with a palliative intent or more rarely, as bridging with the goal of potentially reaching an allogeneic SCT in younger, fit patients. This review will focus on those available single agents beyond chemotherapy with an emphasis on evolving novel therapies.

Histone Deacetylase (HDAC) inhibitors

Mutations in epigenetic regulatory genes are common in AITL and PTCL-NOS, particularly in TET2, DNMT3A, IDH2 and KMT2D.[13] Romidepsin is an HDAC inhibitor derived as a natural product from *Chromobacterium violaceum*. It has been investigated as monotherapy in phase 2 trials of previously treated PTCL patients, at the dose of 14 mg/m^2 on day 1, 8 and 15 of 28 day cycles. One trial of 47 patients of various PTCL subtypes demonstrated an overall response rate (ORR) of 38% with a CR rate of 18 %, and median duration of response (DoR) of 8.9 months.[14] In 2014, other researchers conducted a pivotal phase 2 trial of 130 patients, demonstrating an ORR of 25% (CR/CRu 15%), with a median PFS of 29 months in those patients who achieved a CR/Cru ≥ 12 months.[15] Interestingly in this study, there were long term responders having confirmed/unconfirmed complete response (CR/Cru) who achieved DoR as long as 48 months, and among AITL patients, the median DoR was 38 months. Thus, patients achieving a good response, can stay on romidepsin until progression, with some clinicians decreasing the dosing frequency to every 2 weeks. Pre-clinical and early phase studies have demonstrated synergy between romidepsin and the DNA methyltransferase inhibitor 5-azacytidine (5-aza).[16] A phase 2 trial combining 5-aza
300 mg po daily on days 1 to 14 with romidepsin 14 mg/m^2 on days 8, and 15, and 22 on a 35 day cycle in 25 patients who were treatment naïve or who had R/R PTCL demonstrated an ORR of 61% (CR 48%), and median PFS of 8.0 months. Seventeen patients (68%) had AITL or PTCL of T-follicular helper (tTFH) cell phenotype and the ORR in this subgroup was 80% (CR 67%), with a median PFS of 8.9 months vs. 2.3 months for other PTCL subtypes.[17] The most common observed toxicity was myelosuppression (thrombocytopenia 48%; neutropenia 40%). There is an ongoing study testing this combination (NCT04747236).

Nanatinostat is an HDACi being studied in EBV-positive lymphomas, including AITL and PTCL-NOS. A phase 1b/2 study tested the combination of this drug with valgancyclovir in EBV-positive R/R-lymphoma, including 15 T/NK lymphoma patients. In total 9 of the 15 patients had a response (60%), 4 of whom had a CR.[18] The phase II trial NAVAL-1 testing this combination is currently ongoing (NCT05011058).

Pralatrexate

Pralatrexate is an intravenous anti-folate with high affinity for the reduced folate carrier, resulting in higher internalization and retention in cells than methotrexate. Pralatrexate is approved in Canada for the treatment of R/R-PTCL based on data from the PROPEL trial, a phase 2 international multicenter trial of 109 evaluable patients demonstrating an ORR of 29% (CR 11%), median PFS of 3.5 months and DoR of 10.1 months.[19] Cytopenias and mucositis can be severe, and, as such, patients must be pre-medicated with vitamin B12, folic acid and leucovorin. Pralatrexate has also been studied in combination with romidepsin in a phase 1 trial to determine the dose-limiting toxicities (DLTs), maximum tolerated dose, pharmacokinetic profile, and response rates, and the combination demonstrated an ORR of 71% and CR of 40% (**Figure 2**).The most common grade 3 toxicities included anemia (29%), oral mucositis (14%), thrombocytopenia (14%), and neutropenia (10%). Five grade 4 toxicities were observed, including thrombocytopenia (14%), neutropenia (10%), sepsis (7%), fever (3%), and pneumonia. These toxicities may limit the applicability of this combination in R/R PTCL patients.[20]

Parameter	Number
Total # of Patients (evaluable)	29 (23)
All patients ORR	13/23 (57%)
All patients CR	4/23 (17%)
All patients PR	9/23 (39%)
non-TCL ORR	3/9 (33%)
non-TCL CR	0/9 (0%)
non-TCL PR	3/9 (33%)
T-Cell ORR	10/14 (71%)
T-Cell CR	4/10 (40%)
T-Cell PR	6/10 (60%)

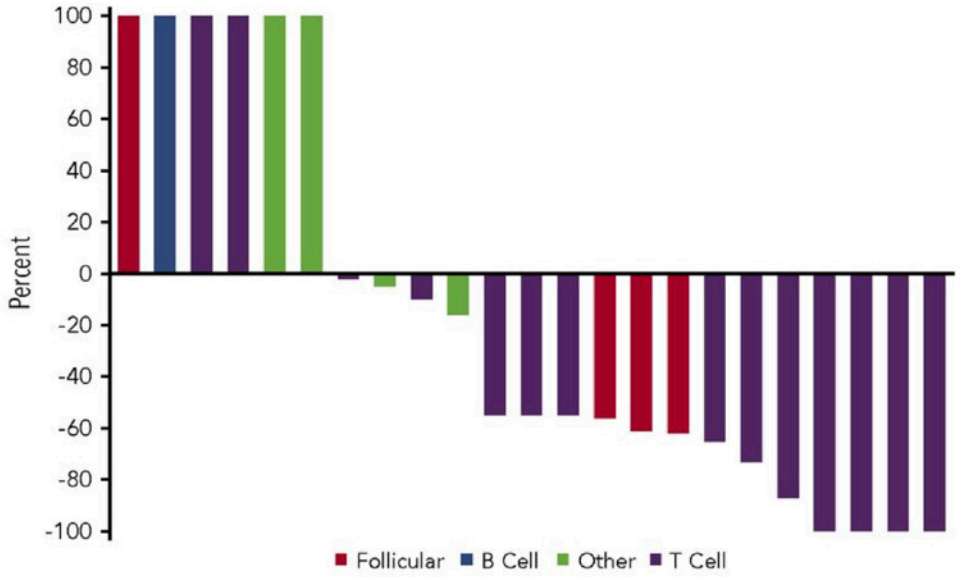

Figure 2. *Summary of response rates across study population for patients treated with romidepsin and pralatrexate. (A) Response rates by disease subtype. (B) Waterfall plot representing the percentage change in tumor growth following treatment depicted by disease subtype. ORR, overall response rate; TCL, T-cell lymphoma; Amengual et al, 2018*

Duvelisib

Duvelisib is an oral dual inhibitor of phosphatidylinositol 3-kinase (PI3K)-δ and PI3K-γ that has been well studied in PTCL patients. It is postulated to inhibit both the proliferation of lymphoma cells through its inhibition of PI3K-γ, as well as M2 tumour-associated macrophages, which leads to increased CD8+ cytotoxic T-cell activation. The phase 2 Primo trial in R/R-PTCL patients has completed enrollment at the expansion dose of 75 mg twice daily for two months, followed by 25 mg twice daily. An interim analysis of the first 78 patients is available and the results are very encouraging: in patients with a median of 3 prior lines of therapy, the ORR is 50% and the CR rate is 32%. Notably, patients with AITL showed a 66.7% ORR with a 47.6% CR rate.[21] Patients did have TEAEs, leading to 18% of patients discontinuing treatment, with the most common grade 3 or greater adverse events being neutropenia (39%), ALT/AST increase (24%/21%)), rash (7.7%), decrease in lymphocyte count (7.7%) and sepsis (6.4%). Recently, a phase I trial combined duvelisib with romidepsin in 64 PTCL patients. Interestingly, the rate of transaminase elevation was much lower in this study of a combination compared with the single agent duvelisib.[22] An ORR of 55% (CR 34%) with a median PFS of 6.9 months in PTCL patients was observed, which is encouraging in this patient population. A similar study combining tenalisib, a highly selective PI3K δ/γ and SIK3 inhibitor with romidepsin in R/R-PTCL and CTCL patients yielded promising results, with an ORR of 75% with a CR of 50% in twelve PTCL patients.[23]

Valemetostat

Valemetostat is an oral dual inhibitor of the histone methyltransferases EZH1 and EZH2, leading to increased gene expression of pro-apoptotic and tumour suppressor genes by altering histone methylation. This mechanism of action is felt to be an important therapeutic approach, given that epigenetic dysregulation is a hallmark of T-cell lymphomas. Early data has demonstrated efficacy in R/R-adult T-cell leukemia/lymphoma[24], and as such a phase 1 trial was undertaken in R/R-PTCL and ATLL. In a cohort of forty-five PTCL patients treated with varying dose regimens, an encouraging ORR rate of 55.6% and CR rate of 24% was observed, with AITL patients, specifically, having an observed ORR rate of 70.6%. Significant side effects included predominantly cytopenias, dysgeusia and alopecia, but overall valemetostat is a well-tolerated treatment option.[25] The dose selected for the phase II evaluation was 200 mg/day, and the ongoing VALENTINE-PTCL01 study is close to completing recruitment in R/R-PTCL (NCT04703192).[26]

Tolinapant

Tolinapant (ASTX660) is a novel oral non-peptidomimetic, small-molecule antagonist of cellular/X-linked inhibitors of apoptosis proteins. In the phase II trial, 98 patients with PTCL (45% PTCL-NOS, 34% AITL) and 51 with cutaneous T-cell lymphoma (CTCL) received tolinapant orally at 180 mg/day on Days 1 to 7, and 15 to 22 of a 28-day cycle. Treatment was well tolerated, with the most common grade ≥3 adverse events in PTCL patients being lipase elevation (15%), rash (8%), and amylase elevation (6%); 2 patients had grade 4 pancreatitis. The ORR for PTCL patients was 22%, including 9 complete responses (CRs) and 13 partial responses (PRs). The median PFS was only 1.8 months with a DoR of 6.5 months. The ORR in CTCL was 28% including 2 CRs and 12 PRs.[27] An ongoing trial combining tolinapant with oral decitabine/cedazuridine in R/R-PTCL is currently enrolling patients [NCT05403450].

Chimeric Antigen Receptor (CAR) T-cell Therapy

The development of CAR-T therapy in T-cell lymphomas has been more difficult than in B-cell lymphomas due to a number of challenges. Firstly, CAR-T therapy leads to aplasia of normal lymphocytes it is targeting along with the malignant lymphocytes. Although B-cell aplasia is a manageable side effect of CD19 directed CAR-T cell therapy, T-cell aplasia is less tolerable in the long term, and can lead to life-threatening infections.[28] However, approaches using either transient CAR-T cell expression or persistence, targeting T-cell subsets, or suicide genes, could be used to allow for T-cell immune reconstitution. Secondly, the killing of CAR-expressing cells by each other, known as fratricide, can undermine the generation of CAR-T cell products. Possible solutions include gene editing, knocking out the T-cell receptor on the cell surface, or using NK cells. Circulating tumor cells can contaminate leukapheresis products and be transduced with CARs during manufacturing, and this can be bypassed by using NK cells or allogeneic T-cells. Finally, identifying targets uniquely expressed on malignant but not normal T cells has been challenging. One approach has been to target molecules expressed by a subpopulation of T cells, or which are downregulated when T cells are activated. With this approach, CARs against CD4, CD5, CD7, CD30, CD37, CCR4, and the 2 alleles of the T cell receptor beta chains (TRBC1/TRBC2) have been designed.[28] There are several ongoing early phase clinical trials using both autologous and allogeneic T-cells, as well as NK cells for the potential treatment of T-cell lymphomas.

CTX130 is an investigational allogeneic, CRISPR/Cas9 gene-edited, anti-CD70 CAR-T cell therapy that is being studied in CD70+ R/R T-cell lymphomas. CD70 is a ligand for CD27 with transient expression on activated lymphocytes and is highly expressed in many TCLs. The outcomes of 18 patients (8 with PTCL and 10 with CTCL) were recently presented.[29] Median lymphoma CD70 expression was 90%. Responses occurred in PTCL (80% ORR at dose level > 3) and CTCL (60% ORR at dose level ≥ 3) across disease compartments (skin, blood, organs and lymph nodes). There was no graft versus host disease, and there were no DLTs, no Grade ≥ 3 cytokine release syndrome or immune effector cell-associated neurotoxicity syndrome. However, 80% of patients in the higher cell dose cohorts had grade 1-2 CRS, and 30% grade 1-2 ICANS. Four patients (22%) experienced a Grade ≥3 infection. This study is ongoing.

Conclusions and ongoing work

PTCL patients continue to experience poor outcomes, and despite development of new treatments in the relapsed/refractory setting, many of these newer agents only offer short remissions with a palliative intent. The early data with duvelisib and valemetostat are encouraging and further results are anticipated. However, it is likely that larger gains will be achieved with combination therapies, and the new combinations of romidpesin and duvelisib, as well as romidepsin and 5-aza seem promising. Incorporation of these drugs into earlier lines of therapy, including frontline therapy in non-CD30 positive T-cell lymphomas needs to be explored more meaningfully in order to improve outcomes in these patients. An upfront trial through the North American Lymphoma Intergroup is ongoing, comparing the addition of either duvelisib or 5-aza to CHOEP in patients ≤ 60 years of age to CHOEP alone in untreated CD30 negative T-cell lymphomas (NCT04803201). The development of CAR-T therapy is in earlier development than in B-cell lymphomas, but promising results are emerging. Recent data has confirmed that conducting phase 3 randomized trials is feasible in patients with T-cell lymphomas and will be needed to demonstrate that these therapies may lead to more durable response and improved survival for T-cell lymphoma patients.

References

1. *Savage, K.J.; Chhanabhai, M.; Gascoyne, R.D.; Connors, J.M. Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification. Ann. Oncol. 2004, 15, 1467–1475.*
2. *Vose, J.; Armitage, J.; Weisenburger, D.; Project, I.T.-C.L. International peripheral T-cell and natural killer/T-cell lymphoma study:Pathology findings and clinical outcomes. J. Clin. Oncol. 2008, 26, 4124–4130.*
3. *Weisenburger DD, Savage KJ, Harris NL, Gascoyne RD, Jaffe ES, MacLennan KA, Rüdiger T, Pileri S, Nakamura S, Nathwani B, Campo E, Berger F, Coiffier B, Kim WS, Holte H, Federico M, Au WY, Tobinai K, Armitage JO, Vose JM; International Peripheral T-cell Lymphoma Project. Peripheral T-cell lymphoma, not otherwise specified: a report of 340 cases from the International Peripheral T-cell Lymphoma Project. Blood. 2011 Mar 24;117(12): 3402-8.*
4. *Savage, K.J.; Harris, N.L.; Vose, J.M.; Ullrich, F.; Jaffe, E.S.; Connors, J.M.; Rimsza, L.; Pileri, S.A.; Chhanabhai, M.; Gascoyne, R.D.; et al. ALK-anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: Report from the International Peripheral T-Cell Lymphoma Project. Blood 2008, 111, 5496–5504.*
5. *Abouyabis AN, Shenoy PJ, Sinha R, Flowers CR, Lechowicz MJ. A Systematic Review and Meta-Analysis of Front-line Anthracycline-Based Chemotherapy Regimens for Peripheral T-Cell Lymphoma. ISRN Hematol. 2011;623924 Epub.*
6. *Schmitz N, Trümper L, Ziepert M, Nickelsen M, Ho AD, Metzner B, Peter N, Loeffler M, Rosenwald A, Pfreundschuh M. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood. 2010 Nov 4;116(18):3418-25.*
7. *Horwitz, S.; O'Connor, O.A.; Pro, B.; Illidge, T.; Fanale, M.; Advani, R.; Bartlett, N.L.; Christensen, J.H.; Morschhauser, F.; Domingo-Domenech, E.; et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): A global, double-blind, randomised, phase 3 trial. Lancet 2019, 393, 229–240.*
8. *Bachy, E.; Camus, V.; Thieblemont, C.; Sibon, D.; Casasnovas, R.O.; Ysebaert, L.; Damaj, G.; Guidez, S.; Pica, G.M.; Kim, W.S.; et al. Romidepsin Plus CHOP Versus CHOP in Patients With Previously Untreated Peripheral T-Cell Lymphoma: Results of the Ro-CHOP Phase III Study (Conducted by LYSA). J. Clin. Oncol. 2022, 40, 242–251.*
9. *Wulf, G.G., Altmann, B., Ziepert, M. et al. Alemtuzumab plus CHOP versus CHOP in elderly patients with peripheral T-cell lymphoma: the DSHNHL2006-1B/ACT-2 trial. Leukemia. 2021. 35, 143–155.*
10. *D'Amore, F.; Relander, T.; Lauritzsen, G.F.; Jantunen, E.; Hagberg, H.; Anderson, H.; Holte, H.; Österborg, A.; Merup, M.; Brown, P.; et al. Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. J. Clin. Oncol. 2012, 30, 3093–3099.*
11. *Park SI, Horwitz SM, Foss FM, Pinter-Brown LC, Carson KR, Rosen ST, Pro B, Hsi ED, Federico M, Gisselbrecht C, et al; COMPLETE Investigators. The role of autologous stem cell transplantation in patients with nodal peripheral T-cell lymphomas in first complete remission: Report from COMPLETE, a prospective, multicenter cohort study. Cancer. 2019 May 1;125(9):1507-1517.*
12. *Brink M, Meeuwes FO, van der Poel MWM, Kersten MJ, Wondergem M, Mutsaers PGNJ, Böhmer LH, Woei-A-Jin FJSH, Visser O, Oostvogels R, Jansen PM, Plattel W, Huls GA, Vermaat JSP, Nijland M. Impact of etoposide and ASCT on survival among patients aged <65 years with stage II to IV PTCL: a population-based cohort study. Blood. 2022 Sep 1;140(9):1009-1019.*
13. *Ye, Y.; Ding, N.; Mi, L.; Shi, Y.; Liu, W.; Song, Y.; Shu, S.; Zhu, J. Correlation of mutational landscape and survival outcome of peripheral T-cell lymphomas. Exp. Hematol. Oncol. 2021, 10, 9.*
14. *Piekarz, R.L.; Frye, R.; Prince, H.M.; Kirschbaum, M.H.; Zain, J.; Allen, S.L.; Jaffe, E.S.; Ling, A.; Turner, M.; Peer, C.J.; et al. Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma. Blood 2011, 117, 5827–5834.*
15. *Coiffier, B.; Pro, B.; Prince, H.M.; Foss, F.; Sokol, L.; Greenwood, M.; Caballero, D.; Morschhauser, F.; Wilhelm, M.; Pinter-Brown, L.; et al. Romidepsin for the treatment of relapsed/refractory peripheral T-cell lymphoma: Pivotal study update demonstrates durable responses. J. Hematol. Oncol. 2014, 7, 11.*
16. *O'Connor, O.A.; Falchi, L.; Lue, J.K.; Marchi, E.; Kinahan, C.; Sawas, A.; Deng, C.; Montanari, F.; Amengual, J.E.; Kim, H.A.; et al. Oral 5-azacytidine and romidepsin exhibit marked activity in patients with PTCL: A multicenter phase 1 study. Blood 2019, 134, 1395–1405.*
17. *Falchi, L.; Ma, H.; Klein, S.; Lue, J.K.; Montanari, F.; Marchi, E.; Deng, C.; Kim, H.A.; Rada, A.; Jacob, A.T.; et al. Combined oral 5-azacytidine and romidepsin are highly effective in patients with PTCL: A multicenter phase 2 study. Blood 2021, 137, 2161–2170.*
18. *Haverkos, B.M.; Alpdogan, O.; Baiocchi, R.; Brammer, J.E.; Feldman, T.A.; Capra, M.; Brem, E.A.; Nair, S.M.; Scheinberg, P.; Pereira, J.; et al. Nanatinostat (Nstat) and Valganciclovir (VGCV) in Relapsed/Refractory (R/R) Epstein-Barr Virus-Positive (EBV+) Lymphomas: Final Results from the Phase 1b/2 VT3996-201 Study. Blood 2021, 138 (Suppl. S1), 623.*
19. *O'Connor, O.A.; Pro, B.; Pinter-Brown, L.; Bartlett, N.; Popplewell, L.; Coiffier, B.; Lechowicz, M.J.; Savage, K.J.; Shustov, A.R.; Gisselbrecht, C.; et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: Results from the pivotal PROPEL study. J. Clin. Oncol. 2011, 29, 1182–1189.*
20. *Amengual, J.E.; Lichtenstein, R.; Lue, J.; Sawas, A.; Deng, C.; Lichtenstein, E.; Khan, K.; Atkins, L.; Rada, A.; Kim, H.A.; et al. A phase 1 study of romidepsin- and pralatrexate reveals marked activity in relapsed and refractory T-cell lymphoma. Blood 2018, 131, 397–407.*
21. *Brammer, J.E.; Zinzani, P.L.; Zain, J.; Mead, M.; Casulo, C.; Jacobsen, E.D.; Gritti, G.; Litwak, D.; Cohan, D.; Katz, D.J.; et al. Duvelisib in Patients with Relapsed/Refractory Peripheral T-Cell Lymphoma from the Phase 2 Primo Trial: Results of an Interim Analysis. Blood 2021, 138, 2456.*
22. *Horwitz, S.M., Moskowitz, A.J., Mehta-Shah, N., Jacobsen, E.D., Khodadoust, M.S., Ganesan, N., Drill, E., Hancock, H., Davey, T., Myskowski, P., Maccaro, C., Blouin, W., Schwieterman, J., Cathcart, E., Fang, S., Perez, L., Ryu, S., Galasso, N., Straus, D., Fisher, D.C., Kumar, A., Noy, A., Falchi, L., Dogan, A., Kim, Y.H. and Weinstock, D. The combination of duvelisib and romidepsin (DR) is highly active against relapsed/refractory peripheral T-cell lymphoma with low rates of transaminitis: final results. Hematological Oncology 2021, 39.*
23. *Iyer, S.P.; Huen, A.; Ai,W.Z.; Jagadeesh, D.; Lechowicz, M.J.; Okada, C.; Feldman, T.A.; Sundaram, S.; Alderuccio, J.P.; Reddy, N.; et al. Safety and Efficacy of Tenalisib Given in Combination with Romidepsin in Patients with Relapsed/Refractory T-Cell Lymphoma: Final Results from a Phase I/II Open Label Multi-Center Study. Blood 2021, 138 (Suppl. S1), 1365.*
24. *Izutsu K, Makita S, Nosaka K, Yoshimitsu M, Utsunomiya A, Kusumoto S, Morishima S, Tsukasaki K, Kawamata T, Ono T, Rai S, Katsuya H, Ishikawa J, Yamada H, Kato K, Tachibana M, Kakurai Y, Adachi N, Tobinai K, Yonekura K, Ishitsuka K. An Open-Label, Single-Arm, Phase 2 Trial of Valemetostat in Relapsed or Refractory Adult T-Cell Leukemia/Lymphoma. Blood. 2022 Sep 23. Epub ahead of print.Ishitsuka, K.; Izutsu, K.; Maruyama, D.; Makita, S.; Jacobsen, E.D.; Horwitz, S.; Kusumoto, S.; Allen, P.; Porcu, P.; Imaizumi, Y.; et al. First-in-human study of the ezh1 and ezh2 dual inhibitor valemetostat tosylate (ds-3201b) in patients with relapsed or refractory non-hodgkin lymphomas. Hematol. Oncol. 2021, 39 (Suppl. S2).*
25. *Foss, F.M.; Porcu, P.; Horwitz, S.M.; Izutsu, K.; Ishitsuka, K.; Kato, K.; Jin, J.; Du, Y.; Inoue, A. A Global Phase 2 Study of Valemetostat Tosylate (Valemetostat) in Patients with Relapsed or Refractory (R/R) Peripheral T-Cell Lymphoma (PTCL),Including R/R Adult T-cell Leukemia/Lymphoma (ATL)-Valentine-PTCL01. Blood 2021, 138, 2533.*
26. *Michot, J.-M.; Mehta, A.; Samaniego, F.; Bachy, E.; Zinzani, P. L;. Prica, A. Colins, G. P; Ribrag, V; Wagner-Johnston, N.; El-Sharkawi, D.; et al. PRELIMINARY ANALYSIS OF THE PHASE II STUDY USING TOLINAPANT (ASTX660) MONOTHERAPY IN 98 PERIPHERAL T-CELL LYMPHOMA AND 51 CUTANEOUS T-CELL LYMPHOMA SUBJECTS WITH RELAPSED REFRACTORY DISEASE.. HemaSphere: 2022 – Volume 6 – Issue – p 118-119*
27. *Scarfò I, Frigault MJ, Maus MV. CAR-Based Approaches to Cutaneous T-Cell Lymphoma. Front Oncol. 2019 Apr 16;9:259.*
28. *Iyer, S. P.; Sica, R. A.; Ho, P. J.; Hu, B.; Zain, J.; Prica, A.; Weng, W.-K.; Kim, Y. H.; Khodadoust, M. S.; Palomba, M. L; et al. THE COBALT-LYM STUDY OF CTX130: A PHASE 1 DOSE ESCALATION STUDY OF CD70-TARGETED ALLOGENEIC CRISPR-CAS9–ENGINEERED CAR T CELLS IN PATIENTS WITH RELAPSED/REFRACTORY (R/R) T-CELL MALIGNANCIES. HemaSphere: June 2022 – Volume 6 – Issue – p 163-164*

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* Comparative clinical significance has not been established.

Reference:
1. EVUSHELD Product Monograph. AstraZeneca Canada Inc., April 14, 2022.

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