Canadian Hematology Today

Canadian Hematology Today 2026 Symposium on B-cell Malignancies

Event Summary

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In This Report

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Acronyms

AEs	ADVERSE EVENTS
ALL	ACUTE LYMPHOBLASTIC LEUKEMIA
AML	ACUTE MYELOID LEUKEMIA
APL	ACUTE PROMYELOCYTIC LEUKEMIA
AS-PCR	ALLELE-SPECIFIC POLYMERASE CHAIN REACTION
ASCT	AUTOLOGOUS STEM CELL TRANSPLANTATION
ASH	AMERICAN SOCIETY OF HEMATOLOGY
BCMA	B-CELL MATURATION ANTIGEN
BPd	BELANTAMAB MAFODOTIN, POMALIDOMIDE, AND DEXAMETHASONE
BR	BENDAMUSTINE AND RITUXIMAB
BTK	BRUTON TYROSINE KINASE
CAR	CHIMERIC ANTIGEN RECEPTOR
CIBMTR	CENTER FOR INTERNATIONAL BLOOD AND MARROW TRANSPLANT RESEARCH
CLL	CHRONIC LYMPHOCYTIC LEUKEMIA
CMRG	CANADIAN MYELOMA RESEARCH GROUP
CR	COMPLETE RESPONSE
CRS	CYTOKINE RELEASE SYNDROME
CVP	CYCLOPHOSPHAMIDE, VINCRISTINE, AND PREDNISONE
ddPCR	DROPLET DIGITAL POLYMERASE CHAIN REACTION
DKRd	DARATUMUMAB, CARFILZOMIB, LENALIDOMIDE, AND DEXAMETHASONE
DLBCL	DIFFUSE LARGE B-CELL LYMPHOMA
DPd	DARATUMUMAB, POMALIDOMIDE, AND DEXAMETHASONE
DRd	DARATUMUMAB, LENALIDOMIDE, AND DEXAMETHASONE
DVd	DARATUMUMAB, BORTEZOMIB, AND DEXAMETHASONE
DVRd	DARATUMUMAB, BORTEZOMIB, LENALIDOMIDE, AND DEXAMETHASONE

Acronyms Continued

EBV	EPSTEIN-BARR VIRUS
ECOG	EASTERN COOPERATIVE ONCOLOGY GROUP
EFS	EVENT-FREE SURVIVAL
FDA	U.S. FOOD AND DRUG ADMINISTRATION
FCR	FLUDARABINE, CYCLOPHOSPHAMIDE, AND RITUXIMAB
FL	FOLLICULAR LYMPHOMA
GemOx	GEMCITABINE AND OXALIPLATIN
HCT-CI	HEMATOPOIETIC CELL TRANSPLANTATION–COMORBIDITY INDEX
ICE	IMMUNE EFFECTOR CELL-ASSOCIATED ENCEPHALOPATHY
ICANS	IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME
IgM	IMMUNOGLOBULIN M
IMiD	IMMUNOMODULATORY DRUG
IsaRVd	ISATUXIMAB, LENALIDOMIDE, BORTEZOMIB, AND DEXAMETHASONE
IWCLL	INTERNATIONAL WORKSHOP ON CHRONIC LYMPHOCYTIC LEUKEMIA
MCL	MANTLE CELL LYMPHOMA
MRD	MEASURABLE RESIDUAL DISEASE
MZL	MARGINAL ZONE LYMPHOMA
NCCN	NATIONAL COMPREHENSIVE CANCER NETWORK
NGS	NEXT-GENERATION SEQUENCING
NHL	NON-HODGKIN LYMPHOMA
ORR	OVERALL RESPONSE RATE
OS	OVERALL SURVIVAL
PCR	POLYMERASE CHAIN REACTION
PET	POSITRON EMISSION TOMOGRAPHY
PFS	PROGRESSION-FREE SURVIVAL
P-gp	P-GLYCOPROTEIN

Acronyms Continued

POD24	PROGRESSION OF DISEASE WITHIN 24 MONTHS
PR	PARTIAL RESPONSE
PVd	POMALIDOMIDE, BORTEZOMIB, AND DEXAMETHASONE
qPCR	QUANTITATIVE POLYMERASE CHAIN REACTION
R2	RITUXIMAB AND LENALIDOMIDE
R-GemOx	RITUXIMAB, GEMCITABINE, AND OXALIPLATIN
RNA	RIBONUCLEIC ACID
SVd	SELINEXOR, BORTEZOMIB, AND DEXAMETHASONE
TP53	TUMOR PROTEIN P53
VGPR	VERY GOOD PARTIAL RESPONSE

Objectives

- Provide current and high-quality information on the latest developments in the management of B-cell malignancies
- Create collegial learning opportunities that enable clinicians to incorporate real-world learnings into their practice
- Foster discussions that allow for the sharing of knowledge and experience among delegates and representatives
- Respond to emerging professional needs for specific and in-depth information on newly available and forthcoming therapies for B-cell malignancies in the Canadian market

Keynote: The Evolution of CAR T-cell Therapy in Canada

DR. MICHAEL CHU

The clinical impact of CAR T-cell therapy has been most pronounced in B-cell malignancies, where landmark trials in lymphoma and acute leukemia demonstrated that approximately half of heavily pretreated patients, who would otherwise be expected to die within months, achieved long-term remission. While similar efficacy has been observed in multiple myeloma, long-term follow-up indicates that these remissions may be less durable.

Dr. Chu highlighted that next-generation CAR T-cell strategies are being developed to enhance efficacy, access, and safety. Beyond oncology, CAR T-cell approaches are also being explored in autoimmune diseases and viral-specific T-cells show promise in the treatment of specific viruses, particularly EBV.

Contrasting CAR T-cell therapy with bispecific antibodies, Dr. Chu explained that while both approaches engage T cells, they differ substantially in delivery, cost, and therapeutic intent. CAR T-cell therapy is currently viewed as potentially curative but is limited by manufacturing complexity, upfront cost, and toxicity. In contrast, bispecific antibodies are off-the-shelf and more appropriate for older patients, but are generally associated with continuous treatment and less definitive long-term remission. When bispecific therapy is introduced in earlier lines, however, responses are much more durable, as indicated by the STARGLO trial.

Focusing on real-world barriers to CAR T-cell therapy, particularly within the Canadian healthcare system, Dr. Chu highlighted that only a subset of eligible patients ultimately receive CAR T-cell therapy. The ability to travel to a CAR T centre is a key access barrier. In response, decentralized, point-of-care manufacturing models aim to reduce vein-to-vein time and improve accessibility. The C3i Centre in Montreal is a contract, development and manufacturing organization designed around cell therapy with a strong focus on manipulated allografts. The BioCanRx and CLIC groups are the first to conduct a point-of-care CAR T-cell study in Canada with CD19-directed CAR T-cell therapy in lymphoma. The Alberta Cellular and Immunotherapy centre has now treated approximately 90 patients with CD19-directed CAR T-cell therapy in a true point-of-care format.

Discussing his experience launching the ACIT001/EXC002 study, Dr. Chu highlighted that a Canadian point-of-care CAR T-cell program requires a robust lab, administrative support, funding, and clinical support.

KEY IMPLEMENTATION STEPS

LAB	ADMIN	FUNDING	CLINICAL
CliniMACS Prodigy or similar closed bioreactor system	Motivated leadership telling middle managers to help with approvals	Foundation support to provide initial seed money for infrastructure development	Flexible and keen staff willing to adapt SOP's and develop new pathways
Operations manager, 2 experienced technicians (min), quality assurance coordinator	Translational research experience; flexible IP and corporate lawyers	Health authority covering clinical care (in-kind) but initially as grant	Interdisciplinary/interfacility teams willing to assist with new therapies and side effects
QA process mapped out; mycoplasma	University sponsorship of IIT studies	Translational projects (various grants)	

The study is assessing the safety and efficacy of point-of-care CAR T-cell therapy in patients with multiply relapsed aggressive NHL and ALL. The study has accrued 27 patients. Manufacturing success rates were high. There were two manufacturing failures including one in a patient on ruxolitinib and one in a patient with transformed DLBCL who had recently completed bendamustine. The median production time was 10 days and the median vein to vein time was 14 days. The production budget was less than $100,000 per patient. For the NHL cohort (18 patients), 72% achieved a CR, 11% had a partial response, and 17% had progressive disease. In the ALL cohort (8 patients) 100% achieved a CR. An independent economist calculated provincial cost savings of more than $400,000/patient (Shafey et al. 2025). Recognizing the benefit of point-of-care cell therapy, Health Canada has created the Advanced Therapeutic Pathway, which can provide a pathway to an indication with a robust phase 2 clinical trial. The development of provincial hubs can also help to overcome the economic barriers to CAR T-cell innovation and improve geographical access.

How Do BTK Inhibitors Work and How Do They Differ From Each Other?

Sponsored Breakfast Symposium (Eli Lilly)

DR. GIORGIO MINOTTI

There are four clinically approved BTK inhibitors: ibrutinib, acalabrutinib, zanubrutinib (covalent BTK inhibitors) and pirtobrutinib (a noncovalent BTK inhibitor). Covalent BTK inhibitors function by forming an irreversible bond with the cysteine residue at position 481 within the kinase domain. This mechanism results in effective suppression of BTK signalling; however, plasma concentrations decline rapidly within 24 hours, creating a cyclical pattern in which BTK is repeatedly inhibited and then resynthesized. During periods of lower drug concentration, levels may fall below the threshold required for optimal kinase inhibition, allowing for partial recovery of BTK activity.

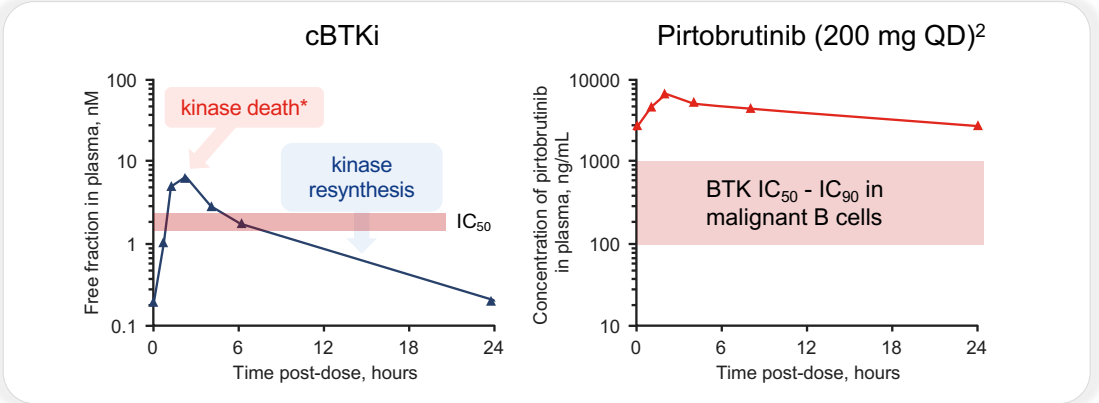
In contrast, pirtobrutinib, the first-in-class non-covalent BTK inhibitor, engages with the cysteine 481 residue for less than two hours. While this might suggest weaker inhibition, Dr. Minotti stressed that this interpretation is inaccurate. Instead, the efficacy of non-covalent inhibitors is driven by their pharmacokinetic profile, characterized by higher sustained plasma concentrations and a longer half-life of approximately 18–19 hours. These properties enable continuous reoccupation of the BTK active site, resulting in persistent, high-level inhibition of the kinase. Dr. Minotti discouraged the use of the term "reversible" BTK inhibitors, instead advocating for descriptions such as "persistent" inhibition.

The structural basis of non-covalent inhibition further supports its potency. Pirtobrutinib forms a complex network of interactions within the kinase active site. Combined with sustained drug exposure, this results in persistent tonic occupation and inhibition of the kinase. Clinically, this activity is reflected in the fact that pirtobrutinib debulks lymph nodes as effectively as ibrutinib (Advani et al. 2013; Mato et al. 2023)

An important clinical implication of this mechanism relates to resistance. Mutations at the cysteine 481 site are a well-established cause of resistance to covalent BTK inhibitors. Because pirtobrutinib does not rely on this binding site, it retains activity in the presence of these mutations. Dr. Minotti noted that pirtobrutinib has demonstrated the ability to eradicate BTK C481-mutated clones.

Safety considerations also differ between the two classes. Covalent BTK inhibitors are associated with cardiovascular toxicities, including atrial fibrillation,

Pirtobrutinib pharmacokinetics are different and…
more cooperative with MOA



*Irreversibly inhibited.
cBTKi, covalent Bruton's tyrosine kinase inhibitor; PK, pharmacokinetics; QD, once daily.
Author's conceptualization of 1. Tam CS, et al. Blood Cancer J. 2023;13(1):141. 2. Mato AR, et al. Lancet. 2021;397(10277):892-901.
VV-Canada Medical-US-DEL-0538

hypertension, and bleeding, which are thought to result from off-target inhibition of other kinases that share similar cysteine residues. In contrast, pirtobrutinib exhibits greater selectivity for BTK at clinically achievable concentrations, minimizing off-target effects. Clinical trial data suggest lower rates of cardiovascular AEs with pirtobrutinib, even in heavily pretreated populations previously exposed to covalent inhibitors. In conclusion, Dr. Minotti emphasized that covalent and non-covalent BTK inhibitors represent complementary therapeutic approaches with distinct mechanistic and pharmacologic profiles.

MRD Primer

DR. SEAN YOUNG

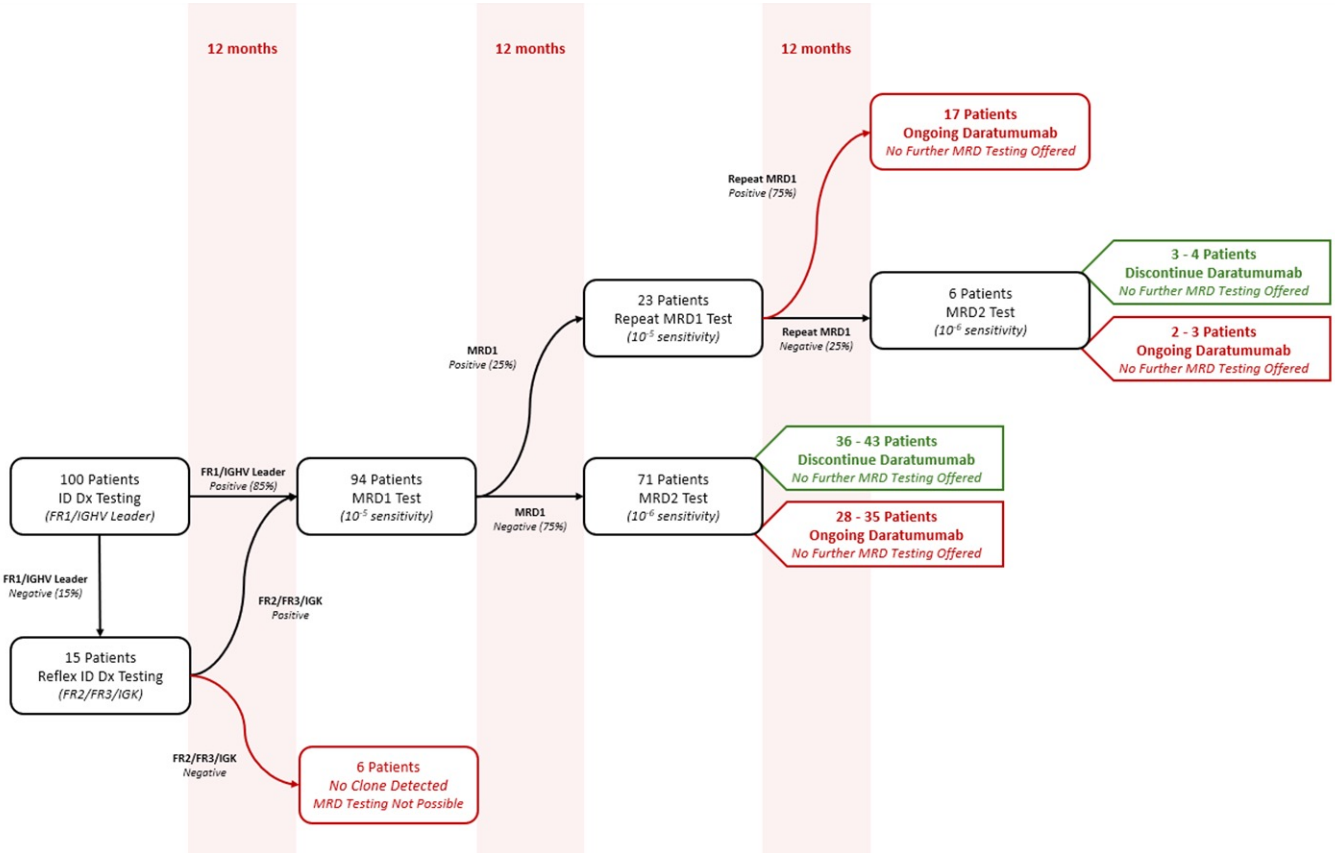
Dr. Young defined MRD as the method-agnostic measurement of the persistence of disease below the threshold of conventional assessment. For solid tumours, MRD can be measured with periodic PET, CT, or MRI scans or ctDNA (NGS/ddPCR). In hematology, methods to measure MRD include post-consolidation marrow examination (microscopy); periodic flow cytometry; molecular MRD in CML and APL and, more recently, AML (NPM1, inv16, t(8;21)). In multiple myeloma, NGS is the gold standard method to assess MRD.

A central theme of the presentation was the importance of selecting an appropriate biomarker for MRD assessment. An ideal biomarker must be stable over time and consistently present throughout the disease course. He also emphasized that biomarkers must be detectable using the chosen assay and that assay limitations can significantly affect interpretation.

While earlier approaches such as PCR-based clonality assays, including BIOMED-2, lack sensitivity, NGS has transformed MRD assessment, increasing the sensitivity limit to ≥ 10^{-6}. NGS-based assays enable the precise bioinformatic calculation of clonal cell frequency, while digital readouts reduce interpretation subjectivity.

Dr. Young underscored the importance of standardization and consistency in MRD testing. He highlighted that results can vary significantly between laboratories due to discrepancies in assay platforms (ddPCR versus qPCR) or denominators (BCR::ABL1/GENE-A versus BCR::ABL1/GENE-B). Dr. Young strongly advised that MRD monitoring for an individual patient should be conducted

MM MRD TESTING IN BC (TEMM)



consistently by the same laboratory.

Regarding DNA versus RNA MRD testing, Dr. Young discouraged the widespread use of RNA testing, as RNA is unstable and measurements are based on the relative expression of BCR::ABL1. The advantage, however, is that sensitivity is high with RNA testing, as every cell expresses many copies of BCR::ABL1 RNA and only one copy of BCR::ABL1 DNA.

Dr. Young additionally highlighted that MRD testing should be affordable. He emphasized the inherent trade-offs between assay sensitivity, cost, and practicality, noting that highly sensitive techniques such as NGS may not be feasible for frequent monitoring, whereas lower-cost methods such as flow cytometry may be more suitable for routine use.

Finally, Dr. Young highlighted the importance of a stable, consistently present biomarker. For example, peripheral blood sampling can lead to discordant results when disease is limited to the bone marrow. Other scenarios in which misleading results can occur include pediatric ALL cases in which positive cells in the myeloid lineage lead to an MRD-positive result. For this reason, qPCR should be performed in conjunction with either flow cytometry or NGS in ALL. In summary, Dr. Young highlighted that pitfalls and complexities in MRD testing reinforce the need to interpret MRD results within the broader clinical context and, where necessary, to corroborate findings.

Sequencing in Myeloma in 2026: The Canadian Algorithm

DR. STEVEN SHIH

Dr. Shih provided an overview of the evolving treatment landscape in multiple myeloma, emphasizing both the significant advances in frontline therapy and the growing complexity of managing relapsed disease. He noted that an increasing proportion of patients present with lenalidomide- and daratumumab-refractory disease at first relapse.

Concerningly, a subset of patients are refractory after quadruplet therapy, effectively rendering them triple-class refractory at an early stage. These patients represent a significant unmet need, with poor outcomes and limited treatment options.

Data suggest that 13% to 16% of patients do not achieve a VGPR to DVRd induction (Joseph et al. 2024; Kaufman et al.) Predictors of this failure to achieve a VGPR include t(11;14) and del(17p) mutations.

Dr. Shih highlighted efforts to redefine "functional high-risk" disease in the context of more effective frontline therapies. Using real-world and clinical trial datasets, early relapse within 3 years of initial therapy (DKRd and DVRd) has been proposed as a clinically meaningful threshold, associated with a median OS of 2 years (Costa et al. 2025). Importantly, the same analysis suggests that patients who can access T-cell redirecting therapies, including CAR T-cell therapy or bispecific antibodies, may achieve improved outcomes compared to those treated with conventional regimens, although these analyses are subject to selection bias.

While cilta-cel therapy is not reimbursed in multiple myeloma, due to failed negotiations, teclistamab is now funded in the fourth line. Belantamab mafodotin is available for patients in the second-line setting and beyond through a compassionate program, but this program is expected to close to new patients in July 2026. At this time, there will be no BCMA-targeting agent or T-cell redirecting therapy available until the fourth line. SVd will remain helpful in this setting and will not preclude BCMA-targeting agents in the future. For triple-class refractory patients, talquetamab,

Outcomes of available 2L+ conventional therapy for Lenalidomide-refractory RRMM

Regimens	Pivotal trial	Prior lines	Overall cohort mPFS (months)	Len-refractory subgroup mPFS (months)
IsaKd*	IKEMA	2 (1-4)	35.7	15.7*
IsaPd**	ICARIA-MM	3 (2-4)	11.6 (94% len-refractory)**	
DVd	CASTOR	2 (1-9)	16.7	7.8
Kd	ENDEAVOR	2 (1-3)	18.7	8.6
KCd	GEM-KyCyDex [MCRN-003/MYX.1]	1 (1-3) [(1-3)]	19.1 [17.2]	18.4***
PVd	OPTIMISMM	2 (1-3)	11.2 (only 1 prior line: 20.7)	(Only 1 prior line: 17.8)
SVd	BOSTON	2 (1-3)	13.2 (only 1 prior line: 21.0)	10.2 (only 1 prior line: 16.6)
SPd	STOMP	3 (1-10)	10.4	12.2 (pom-naïve)

*AENEID (retrospective observational): IsaKd as second line in RRMM in patients who had ASCT and len maintenance. Median PFS 24.4 months.
**Multicentre French study: IsaPd as second line in RRM, len-refractory. Median PFS 22.4 months.
***Post hoc analysis showed addition of cyclophosphamide beneficial for lenalidomide refractory subgroup

cevostamab and CELMoDs are being investigated. Similarly, there are several other BCMA-targeting agents or combinations that are being actively investigated in early line relapse, including bispecific, trispecific, and CAR T-cell therapies. However, only 38% of high-risk patients are fit enough to be eligible for a clinical trial.

Dr. Shih presented the results of options in the second line and beyond for patients who are lenalidomide-refractory. After daratumumab, outcomes with carfilzomib and pomalidomide regimens after are inferior, with median PFS of 4 to 5 months. The BOSTON trial signals that SVd may be beneficial after daratumumab use, but the small sample size makes it challenging to definitively draw conclusions.

In addition to efficacy, factors such as toxicity, logistical burden, need for caregiver support, and impact on quality of life are critical considerations, particularly in an older and often frail patient population. There is no single optimal treatment algorithm, and decisions must be individualized based on patient characteristics, disease biology, and access to therapy.

Discussing sequencing, Dr. Shih shared real-world data showing inferior responses patients who had prior BCMA-targeting therapy before teclistamab. He referred to criteria from Alberta Health Services and Cancer Care Ontario suggesting patients can receive teclistamab after belantamab mafodotin as long as they are not refractory. In the real-world, patients are receiving belantamab mafodotin at 8- to 12-week intervals, rather than 4-week intervals. Dr. Shih suggested that patients who receive belantamab mafodotin every 9 or more weeks may be eligible for teclistamab.

Concluding with potential future strategies, Dr. Shih presented investigations of combination therapies with bispecific antibodies, with the goal of achieving deeper, more durable responses. Trispecific combinations are also being explored. Dr. Shih encouraged attendees to contact academic centres early to discuss clinical trial options for patients, noting that the therapeutic landscape in myeloma continues to rapidly evolve.

Rolling out an Outpatient Bispecific Program

DR. JEAN-SEBASTIEN CLAVEAU

Dr. Claveau provided an overview of bispecific antibodies in relapsed and refractory multiple myeloma, the second-most prevalent hematologic cancer. Bispecific antibodies are currently approved for patients with relapsed or refractory multiple myeloma who have prior exposure to a proteasome inhibitor, an IMiD, and an anti-CD38 antibody; have received ≥3 prior lines of therapy; and have an ECOG performance status of 0-1.

Clinical trial data from studies such as MajesTEC-1 (evaluating teclistamab) and MagnetisMM (evaluating elranatamab) demonstrate meaningful activity in heavily pretreated populations, with median PFS ranging from approximately 11 to over 24.6 months, respectively.

Discussing safety, Dr. Claveau highlighted that CRS is the most common early AE with bispecific therapy, occurring in approximately 60% to 70% of patients in clinical trials, although the majority of cases are grade 1 or 2. Prophylactic tocilizumab, administered approximately 1 hour before the first dose, has been demonstrated to reduce CRS rates to 10%. Dr. Claveau noted that CRS generally occurs within 24 to 48 hours of dosing during the step-up phase. Symptoms typically include fever, with less frequent occurrences of hypotension or hypoxemia. Management strategies for grade 1 CRS (whereby fever is the only presenting symptom) include dexamethasone or tocilizumab. Although the two are equally effective, dexamethasone is ideal for managing CRS in the outpatient setting.

Neurotoxicity is less common, occurring in approximately 3% to 4% of patients in clinical trials, and is typically manageable with dexamethasone. Dr. Claveau highlighted the importance of structured monitoring using tools such as the ICE score to detect early neurologic changes. Prophylactic tocilizumab has not been shown to significantly affect neurotoxicity rates.

While not included in the product monograph, tumour pain is an anecdotally reported symptom of bispecific antibodies. This acute and difficult-to-control pain typically occurs after the second

Results to Date

	N = 48 (teclistamab)
ORR – no/total no (%)	34/48 (70%)
All grade CRS – no (%)	5 (10%)
grade ≥2§	1 (2%)
All grade ICANS – no (%)	2 (4%)
grade ≥2§	0 (0)
Admission – no (%)	7 (15)
	*1 for CRS and sepsis

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dose. In some patients, dexamethasone (10-20 mg PO/IV q6h) works well to relieve this symptom. IV opioids may also be required. Dr. Claveau noted that patients who receive prophylactic tocilizumab seem to have a higher risk of developing tumour pain, but the underlying cause of the pain is unclear.

Dr. Claveau then turned to the practical challenges of delivering bispecific therapy within the constraints of the Canadian healthcare system. He described the development of an outpatient virtual care model at his centre. Patients selected for this approach must meet specific criteria, including residing within 1 hour of the hospital, the ability to travel independently, absence of active infection or cognitive impairment, and the availability of a caregiver. After screening, patients meet with a nurse who educates the patient on what to expect with outpatient bispecific therapy and instructs the patient on how to use loaned equipment, including blood pressure, temperature, and blood-oxygen monitors.

The structured virtual care pathway includes multiple daily nursing assessments (3 video calls and 1 phone call), remote monitoring of vital signs using connected devices, and real-time alerts for abnormalities such as fever. Step-up dosing occurs in the first week, and all patients receive prophylactic tocilizumab. Dr. Claveau shared the results of 48 patients treated with teclistamab using this outpatient approach (see chart). Dr. Claveau highlighted that out of five patients who developed CRS, four patients received dexamethasone at home, and one patient required tocilizumab. Neurotoxicity rates were consistent with published data, and hospital admissions were largely unrelated to treatment-related toxicities.

Outpatient administration was associated with reduced costs compared to inpatient care, with estimated savings of $10,000 to $15,000 per patient. Patient and caregiver feedback was also highly positive – while 36% of patients reported anxiety about virtual bispecific therapy at the beginning of the process; at completion, 91% of patients said they would be willing to participate in the virtual care unit again. Dr. Claveau emphasized that the virtual care model offers a scalable approach to expanding access, but requires appropriate patient selection criteria, ongoing nurse training, and multidisciplinary coordination.

CLL in 2026: The U.S. Experience

DR. JOHN ALLAN

Dr. Allan provided an overview of contemporary CLL management in the United States, noting that broader access to therapies and flexibility within U.S. guidelines allows clinicians to tailor treatment based on disease biology, patient characteristics, and emerging subgroup data.

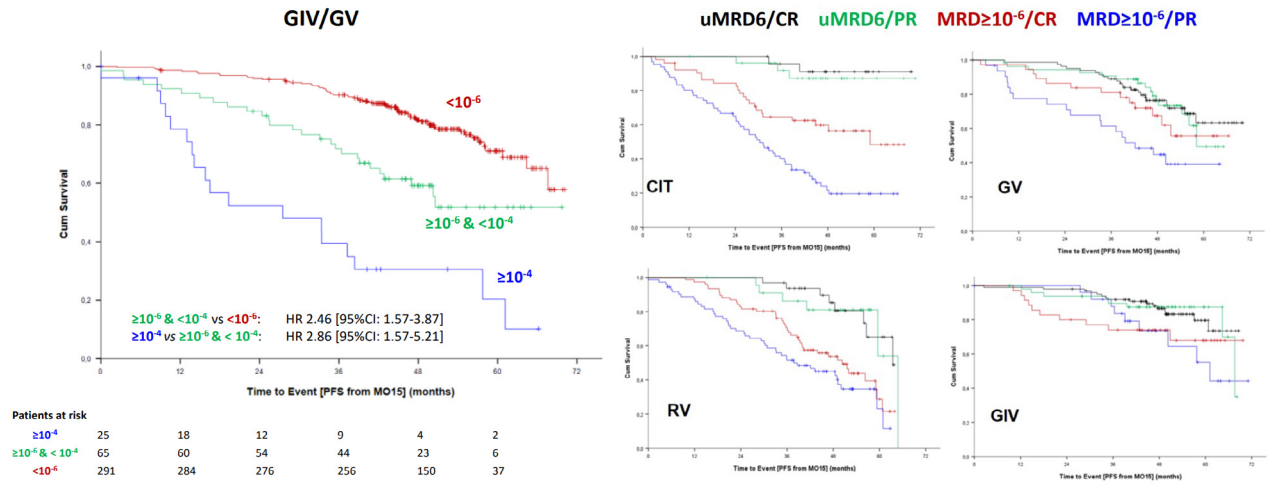
Current guideline-endorsed frontline options include both continuous BTK inhibitor therapy and fixed-duration regimens, which include BCL2 inhibitor and anti-CD20 monoclonal antibody regimens, BTK inhibitor-venetoclax combinations (acalabruitinib-venetoclax is the only currently FDA-approved combination), and, increasingly, the incorporation of triplet regimens consisting of a BCL2 inhibitor, BTK inhibitor, and obinutuzumab. Continuous BTK inhibitor therapy remains a foundational strategy, associated with median PFS rates of approximately 9 years. However, concerns regarding long-term toxicity, adherence, and cost have driven interest in time-limited therapies.

Fixed-duration regimens offer the advantage of treatment cessation after approximately 1 year, reducing cumulative toxicity and cost. However, these regimens are not curative, with a median PFS of approximately 6 years. MRD-negative status is a very important predictor of long-term outcomes. Dr. Allan also highlighted that patients with low-risk, IGHV-mutated disease often achieve durable remissions with venetoclax-based doublets alone, with long-term PFS exceeding 80% in some cohorts. In contrast, patients with higher-risk features, including unmutated IGHV or del(17p) mutations, have inferior outcomes and may benefit from treatment intensification.

Data from CLL13 demonstrate that adding a BTK inhibitor to venetoclax-obinutuzumab increases MRD negativity rates and may lead to improved PFS over time, particularly in higher-risk subgroups. Patients with uMRD6 or better (regardless of whether they had a PR or CR) saw dramatically better results than patients who had MRD ≥10^-6 (Furstenau, IWCLL 2025). Due to the increased toxicity, including higher rates of infections and cytopenias with triplet regimens, Dr. Allan recommended triplet regimens for patients with unmutated IGHV disease.

For patients with TP53 aberrations, while

Depth of Remission is Important and MRD A Better Predictor than Response



Furstenau IWCLL 2025

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continuous BTK inhibitor therapy remains effective in this population, fixed-duration regimens are associated with shorter remissions, with the median PFS in the CAPTIVATE study (ibrutinib and venetoclax) shown to be approximately 4 years. Triplet therapy (acalabrutinib, venetoclax, and obinutuzumab) is associated with better 4-year PFS rates, of 88% in patients with del(17p) or TP53 mutations or complex karyotypes. In a small study, maintenance ibrutinib therapy in patients with MRD-negative remission post-ibrutinib and venetoclax led to remarkable 4-year PFS rates of 95% in high-risk patients (Allan, 2023).

Dr. Allan also addressed the emerging role of non-covalent BTK inhibitors, particularly pirtobrutinib. While effective, real-world and trial data suggest relatively modest PFS of approximately 13 to 14 months in patients progressing on prior BTK inhibitors. Patients intolerant to prior BTK inhibitors appear to derive greater benefit than those with true progression, highlighting that venetoclax-based first-line approaches may lead to better outcomes on subsequent pirtobrutinib.

In the first-line setting, pirtobrutinib has demonstrated a PFS advantage against BR and trending OS improvement, despite the crossover design. Dr. Allan remarked that, in comparison, no covalent BTK inhibitor has shown an OS benefit against BR in first-line settings. Early data suggest pirtobrutinib-based regimens may achieve very high MRD negativity rates, exceeding those seen with current doublet or triplet therapies, although toxicity rates are higher. As new agents and combinations emerge, optimizing sequencing and balancing efficacy with toxicity will remain central challenges in the evolving CLL treatment landscape.

Sequencing With Intent: Making Every Line of Therapy Matter in the Real World

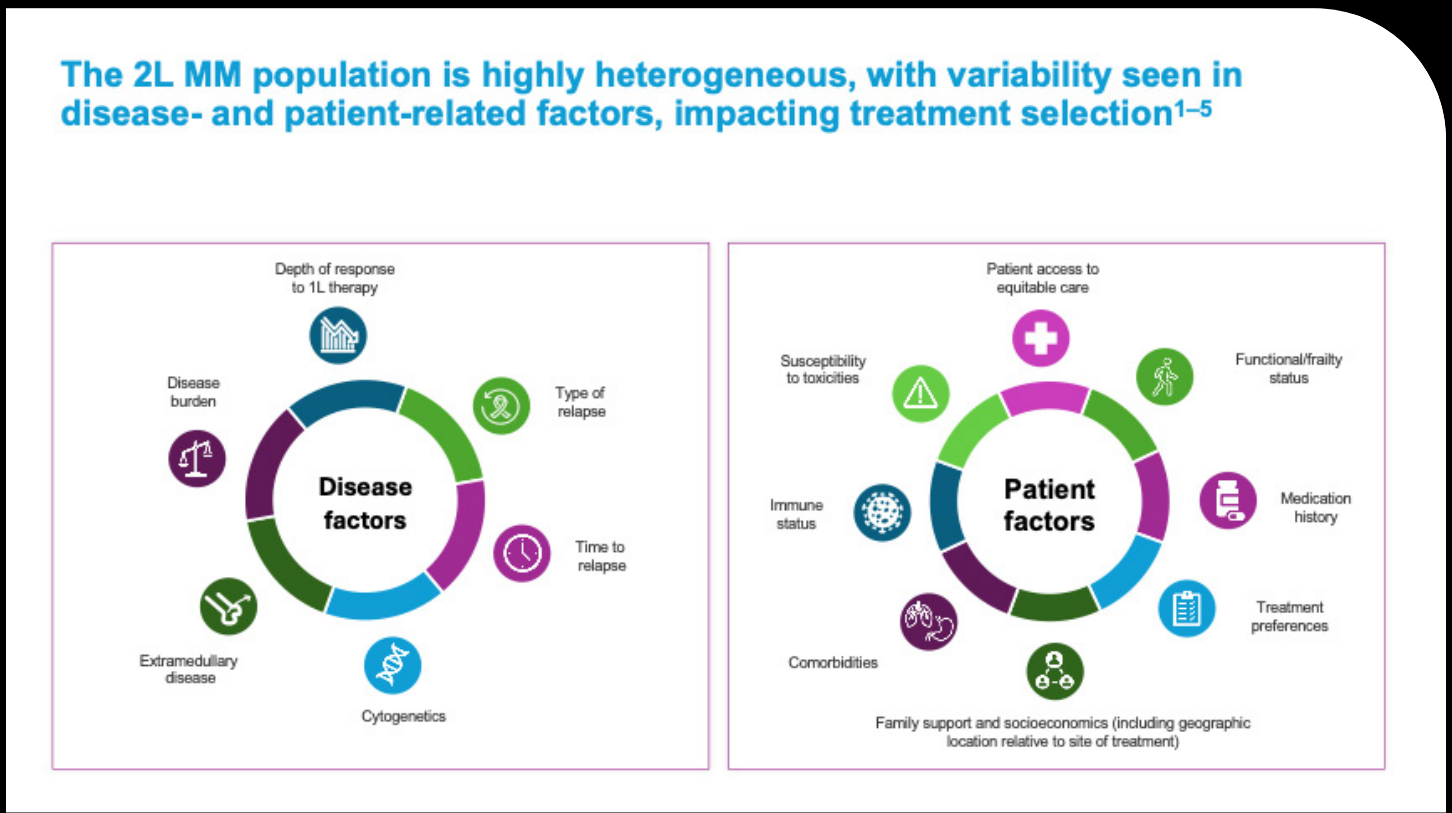
Sponsored Lunch Symposium (GSK)

DR. PHILIP KURUVILLA

DR. SUZANNE TRUDEL

Dr. Kuruvilla highlighted that the widespread use of quadruplet regimens incorporating proteasome inhibitors, immunomodulatory drugs, and anti-CD38 antibodies, are making relapse treatment decisions complex. In the frontline setting, the NCCN guidelines recommend DVRd or IsaRVd for transplant-eligible patients, and the same combinations, or DRd for transplant-ineligible patients. Dr. Kuruvilla emphasized that lenalidomide-refractory disease, in particular, is associated with poor outcomes. Historically, the PFS rates for patients who are lenalidomide- and bortezomib-refractory have been demonstrated to be less than 6 months (Hartley-Brown, 2024; Bondili et al. 2021, and Takakuwa et al. 2021). Similarly, retreatment with anti-CD38 antibodies in previously exposed patients yields limited benefit.

In this context, Dr. Kuruvilla stressed the importance of individualized treatment selection, incorporating both disease-related factors, such as prior response, cytogenetic risk, and timing of relapse, and patient-related considerations, including fitness, comorbidities, treatment goals, and access to therapy. He also drew attention to attrition rates. In CMRG data from academic settings, 7% of transplant-eligible patients do not proceed to second-line therapy, compared to 19% of transplant-ineligible patients. After the third line, these numbers are 23% and 40% respectively. This reinforces the importance of optimizing therapy earlier in the disease course rather than deferring more effective treatments to later lines.



Dr. Trudel then focused on emerging BCMA-targeted therapies to address unmet needs in the relapse setting. She outlined three principal BCMA-targeting approaches: antibody drug conjugates, CAR T-cell therapies, and bispecific antibodies. In the DREAMM-7 trial, the combination of belantamab mafodotin with bortezomib and dexamethasone demonstrated a marked improvement in PFS compared with standard therapy, with median PFS exceeding 36 months versus approximately 13 months in the DVd arm. Long-term follow-up data demonstrate an OS benefit, an uncommon finding in myeloma trials. Similarly, the DREAMM-8 trial, evaluating BPd in lenalidomide-exposed patients, showed a median PFS of over 32 months, with consistent benefit observed in lenalidomide-refractory subgroups.

Dr. Trudel also addressed the safety profile of belantamab mafodotin, particularly ocular toxicity. Keratopathy, characterized by corneal epithelial changes, is a class effect of antibody drug conjugates targeting BCMA and may present with blurred vision, reduced visual acuity, and dry eye. However, this toxicity is generally manageable with dose delays and monitoring. The AE was reversible in approximately 90% of patients in the DREAMM trials.

Another BCMA-targeted modality, cilta-cel, has demonstrated high response rates and durable remissions in both early and later relapse settings, with the CARTITUDE-4 trial showing significant improvements in PFS and OS compared with standard-of-care regimens. At the 30-month mark, 59.4% of patients remained progression-free in the cilta-cel arm, compared to 25.7% in the standard of care (DPd or PVd) arm. However, access remains limited, and patient selection is critical, as some patients may not reach infusion due to rapid disease progression. Bispecific antibodies, such as teclistamab, offer an alternative off-the-shelf approach and demonstrate meaningful response rates and durable remissions in triple-class-exposed populations.

Dr. Trudel emphasized that the timing of BCMA-targeted therapy is a critical consideration. Data from multiple studies suggest that earlier use of these agents may result in improved outcomes compared with reserving them for later lines, with PFS benefits maintained against control arms that were rescued with anti-CD38 or BCMA-directed therapies.

2026 Canadian Hematology Today Symposium on B-cell Malignancies

Precision Treatment Pathways in CLL: Optimizing CLL Outcomes with Finite-Duration and Continuous BTKi Approaches

Sponsored Lunch Symposium (Astra Zeneca)

DR. EMILY TOMASULO

Dr. Tomasulo reviewed current Canadian CLL treatment guidelines, which stratify patients primarily based on fitness, as well as the presence of high-risk genomic features, particularly del(17p) and TP53 mutations. Fit, younger patients with mutated IGHV disease may still be considered for chemoimmunotherapy, although there is an increasing shift toward targeted therapies in this group, particularly continuous BTK inhibitor therapy. For patients with unmutated IGHV disease, options include both continuous BTK inhibitor therapy or venetoclax-obinutuzumab.

In older, FCR-ineligible patients, both fixed and continuous targeted regimens have Category 1 recommendations, regardless of mutational status, while chemoimmunotherapy may be considered for patients with IGHV-mutated disease (Category 2A recommendation). Acalabrutinib and venetoclax is under review for funding for those with and without high-risk cytogenetic markers.

Summarizing data for continuous BTK inhibitor therapy, the time on therapy is consistently 72 to 74 months across trials evaluating ibrutinib, acalabrutinib and zanubrutinib. However, second-generation BTK inhibitors are associated with lower rates of cardiovascular toxicity compared with first-generation agents. While cross-trial comparisons are not conclusive, acalabrutinib demonstrated lower rates of bleeding than zanubrutinib (5.6% versus 52%) as well as lower rates of hypertension (11.2% versus 20%). Dr. Tomasulo said that she monitors patients' blood pressure before choosing

Frontline Treatment Plan in the Preferential Population Is Guided by Patient and CLL Factors

Continuous BTKi-Based

- Higher-risk CLL
  - Higher risk cytogenetics
  - *IGHV* unmutated
- Option for all-oral therapy
- Minimal TLS risk
  - High disease bulk
  - Concerns: adherence with lab ramp-up
- Lower risk of myelosuppression

Finite-Duration AV or IV

- *IGHV* unmutated
- Fit patient
- Option for all-oral therapy
- Monitoring for:
  - Cytopenias
  - Infection
  - Hemorrhage
- Noting more data needed on:
  - Higher risk cytogenetics
  - Patients with CVD
  - Comparison to VO

Finite-Duration VO

- Lower-risk CLL
  - Normal / intermediate cytogenetics
  - *IGHV* mutated
- At risk for CV events:
  - Arrhythmias
  - Uncontrolled HTN
  - Severe CAD
- At risk for hemorrhage
  - DAPT, therapeutic anticoagulation

a therapy, so that she can optimize blood pressure ahead of BTK inhibitor therapy and select acalabrutinib for patients with hypertension.

Discussing fixed-duration regimens, Dr. Tomasulo highlighted that higher MRD rates in BTK inhibitor combinations may be due to the fact that ibrutinib inhibits P-gp, which can lead to a higher concentration of venetoclax. This may also explain the higher rate of infection seen in ibrutinib and venetoclax trials, compared to acalabrutinib and venetoclax. Dr. Tomasulo shared data from the CLL17 trial, which demonstrated that fixed-duration venetoclax-based regimens are non-inferior to continuous BTK inhibition at early follow-up. However, longer-term data are needed, as divergence in PFS curves may emerge over time, particularly in higher-risk populations.

When choosing between highly effective fixed and continuous options, Dr. Tomasulo recommended considering fitness, comorbidities, neutropenia risk (including other immunosuppressive medications), renal function, tolerance to prior treatments, patient preferences and the ability to travel and adhere to complex treatment protocols. Important disease-related factors include del(17p)/TP53 mutation status, IGHV mutation status, disease burden, and prior treatment response.

Through a poll, the audience indicated that the top three factors determining treatment are del(17p) mutational status, comorbidities, and logistical considerations. Dr. Tomasulo agreed with the audience, while adding that patient preference may weigh more heavily than any other factor.

Management of Relapsed/Refractory Waldenström Macroglobulinemia

DR. JORGE CASTILLO

Dr. Castillo provided a comprehensive overview of Waldenström macroglobulinemia focusing on the diagnostic framework, the heterogeneity of clinical presentation, and evolving treatment strategies in the relapsed and refractory setting. The diagnostic criteria for Waldenström macroglobulinemia include the presence of three criteria:

1. IgM monoclonal protein in serum protein electrophoresis and immunofixation
2. Lymphoplasmacytic lymphoma in the bone marrow
3. *MYD88 L265P* mutation by AS-PCR or NGS

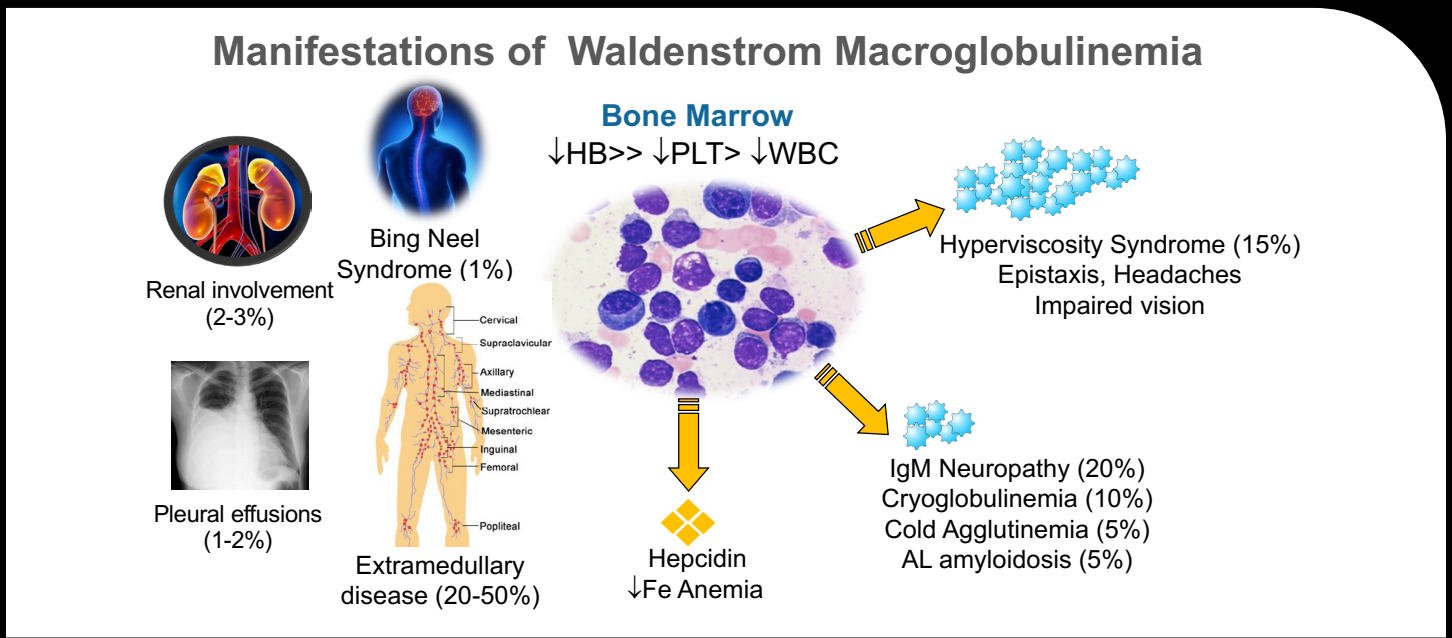
A critical management principle is that not all patients require immediate treatment. Treatments are not curative, and involve toxicities. Data from longitudinal cohorts show that only approximately 30% of patients require treatment within 2 years, and up to 20% may remain untreated for over a decade. Given the median age at diagnosis of approximately 70 years, many patients may never require therapy.

The clinical manifestations of Waldenström's are highly heterogeneous, contributing to the complexity of management. While anemia is the most common presenting feature, the disease can involve neuropathy, extramedullary disease, hyperviscosity syndrome and more. Dr. Castillo noted that he may see 15 different patients in a day with 15 very different clinical presentations of Waldenström's, underscoring the need for individualized treatment decisions.

In the frontline setting, treatment options include rituximab-based chemoimmunotherapy and covalent BTK inhibitors, both of which demonstrate high response rates. Overall response rates typically range from 80% to 100%, with major response rates (≥50% IgM reduction) of approximately 70% to 90%, and PFS extending several years. However, the absence of robust randomized comparative data limits the ability to definitively select one treatment approach over another.

As a result, treatment decisions are guided by toxicity profiles, route of administration, genomic features, and patient preference. Dr. Castillo noted that practice patterns vary significantly across centres, reflecting differences in familiarity and comfort with these regimens.

In the relapsed setting, covalent BTK inhibitors, such as ibrutinib and zanubrutinib, have demonstrated rapid and durable responses. There is less evidence to assess chemoimmunotherapy in the second-line setting, when following BTK inhibitors, but emerging data suggests the sequencing is similarly effective. Maintenance therapy was commonly recommended in the



past, however, a study published in 2019 found no difference between patients treated with or without maintenance rituximab after chemoimmunotherapy (Rummel et al. 2019). Dr. Castillo added that he occasionally prescribes maintenance therapy for a small group of patients who require deep responses, due to renal disease or other factors.

In the second-line, Dr. Castillo presented research showing that BTK inhibitors are cytomodulating, rather than cytotoxic, and therefore therapy should continue to progression. Patients typically relapse within a few months if BTK inhibitor therapy is stopped (Treon et al. 2015, 2021). The ASPEN study compared zanubrutinib versus ibrutinib in first- and second-line Waldenström's patients, with 80% of patients categorized as relapsed/refractory. Due to its favourable safety profile, zanubrutinib was approved for Waldenström's in 2021 and is the standard BTK inhibitor used in the U.S.

In later relapses, treatment options become more limited, and outcomes are less durable. Emerging data supports the use of venetoclax monotherapy, which has demonstrated a median PFS of approximately 3 years. Importantly, retreatment with venetoclax provides additional clinical benefit, including the reinduction of VGPR in some patients. Based on limited data in small numbers of patients, Dr. Castillo's treatment approach in the third line is to administer venetoclax at 400 mg/day indefinitely.

Non-covalent BTK inhibitors, such as pirtobrutinib, represent another important option in later lines of therapy, particularly for patients resistant to covalent BTK inhibitors. However, pirtobrutinib's effect appears limited, with a median PFS of approximately 18 to 24 months and worse outcomes in patients with resistance to covalent BTK inhibitors. Emerging data suggests that CXCR4 mutations may be associated with reduced benefit of pirtobrutinib, while TP53 alterations may confer inferior responses to venetoclax.

Early-phase data combining venetoclax with non-covalent BTK inhibitors have demonstrated promising activity, including CR rates of 11%, a notable finding in Waldenström's, where deep responses are relatively uncommon. Other novel therapies showing early signs of efficacy in heavily pretreated populations include BTK degraders, which could overcome resistance mechanisms; antibody-drug conjugates targeting CD19; and bispecific antibodies.

2026 Canadian Hematology Today Symposium on B-cell Malignancies

High-Risk MCL

DR. KAMI MADDOCKS

Dr. Maddocks explained that "high-risk" MCL is defined by a constellation of clinical, biological, and molecular features. Historically, risk stratification has relied on clinical tools such as the MCL International Prognostic Index, which incorporates age, performance status, lactate dehydrogenase, and leukocyte count. Increasingly, biological risk factors are recognized as more clinically meaningful. These include aggressive histologic variants (blastoid and pleomorphic), high proliferative index (Ki-67 ≥30%, with ≥50% defining an ultra–high-risk subgroup), and genomic features such as complex karyotype and TP53 abnormalities.

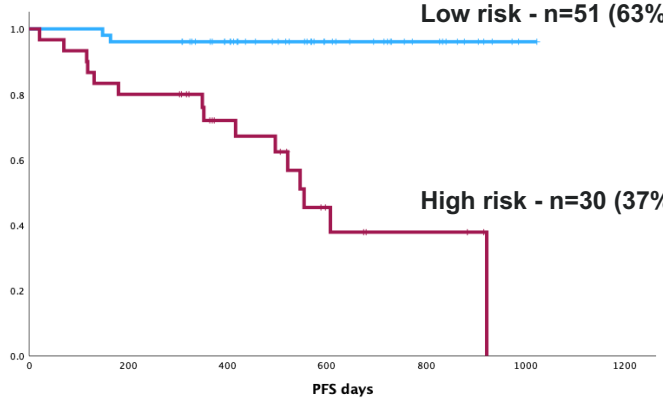
Treatment advances have improved outcomes in MCL overall, particularly with the incorporation of BTK inhibitors. In younger, fit patients eligible for intensive therapy, the TRIANGLE study demonstrated that adding ibrutinib to standard induction and maintenance significantly improved failure-free survival and OS. Notably, the study also suggested that ASCT may not be necessary when BTK inhibitors are incorporated. In high-risk subgroups, outcomes were also improved with BTK inhibitor-containing regimens. Given that transplant entails increased toxicity, Dr. Maddocks said her current approach is not to recommend ASCT in high-risk MCL patients.

In older or transplant-ineligible patients, the ECHO study evaluated the addition of acalabrutinib to BR, followed by rituximab maintenance therapy. This combination significantly improved PFS compared with BR alone. Importantly, in biologically high-risk patients, defined by TP53 mutation, high Ki-67, or aggressive histology, the addition of BTK inhibitor-based therapy increased complete metabolic response rates and translated into improved PFS. Dr. Maddocks said she has begun to use the BTK inhibitor-chemoimmunotherapy combination in patients with high-risk disease (but not TP53-mutated disease, discussed below).

The ALTAMIRA trial of acalabrutinib and rituximab in newly diagnosed MCL showed that while patients in the low-risk MCL group had 2-year PFS rates above 90%, patients with high-risk disease had significantly inferior PFS, with 2-year PFS rates ranging from 26% to 37%. Similarly, the ENRICH trial demonstrated that while most patients benefitted from ibrutinib and rituximab versus chemoimmunotherapy, patients with blastoid disease had inferior outcomes on ibrutinib and rituximab.

TP53-mutated MCL represents a particularly high-risk subgroup, with historically poor outcomes regardless of treatment intensity. Median PFS is approximately 1 year, and OS is less than 2 years with conventional chemoimmunotherapy. The BOVen trial evaluated a chemotherapy-free triplet regimen combining zanubrutinib, venetoclax, and obinutuzumab. This small study of 25 patients

R-BTKi not sufficient to overcome high-risk biology (Ki67 >30%, *TP53,* blastoid)



Ki67 > 30%TP53, Blastoid

37% high risk – 24 m PFS 38%
63% low risk – 24 m PFS 96%

TP53 and Blastoid

26% high risk – 24 m PFS 32%
74% low risk – 24 m PFS 91%

demonstrated a marked improvement in outcomes, with 2-year PFS rates of 72% and 2-year OS rates of 76%. Importantly, this trial incorporated an MRD-guided approach, with patients who achieved undetectable MRD negativity able to discontinue therapy. The trial led to incorporation of this regimen into the NCCN guidelines and Dr. Maddocks added that the triplet regimen is her treatment of choice for TP53-mutated disease.

In the relapsed and refractory setting, cellular and immunotherapies have demonstrated promising activity. CD19-directed CAR T-cell therapy has shown high response rates in trials such as ZUMA-2, although real-world data suggest reduced durability in high-risk patients. Results for liso-cel were consistently impressive across high-risk subgroups, but the sample size is small (Wang et al. 2023). Bispecific antibodies have also demonstrated encouraging early efficacy, although patients with high-risk disease features had earlier relapses than patients with low-risk disease. Emerging combinations, such as mosunetuzumab and polatuzumab vedotin, may further improve outcomes.

In the frontline setting, three ongoing trials are evaluating bispecific antibodies for high-risk disease (CARMEN, WINDOW 3 and the phase 2 study of glofitamab, lenalidomide, and venetoclax). Ongoing clinical trials and more standardized approaches to risk stratification will be essential to further refine treatment strategies and improve outcomes in the high-risk MCL population.

2L CAR T-cell Therapy: Which One to Choose?

DR. PATRICK CONNOR JOHNSON

Dr. Johnson provided practical guidance on selecting CAR T-cell therapy in second-line large B-cell lymphoma. The ZUMA-7 study demonstrated significant EFS improvement with axi-cel compared with standard chemoimmunotherapy, with a 3-year EFS exceeding 40% in the axi-cel versus approximately 19% in the control arm. Despite the crossover design, OS favoured axi-cel by approximately 8%. The CRS rate was 92% and 6% experienced ≥3 CRS events; 60% experienced neurologic toxicity, with 20% experiencing grade ≥3 events.

The TRANSFORM trial, evaluating liso-cel in patients with similar baseline characteristics, showed a significant improvement in EFS. Although an OS benefit was not statistically demonstrated, this was likely due to the small study size and the fact that two-thirds of patients in the standard-of-care arm crossed over to receive liso-cel. CRS rates were lower, compared with axi-cel, with grade ≥3 CRS and ICANS events occurring in approximately 1% and 4% of patients, respectively.

Dr. Johnson stressed that age alone should not preclude CAR T-cell therapy, noting that both retrospective and prospective data demonstrate favourable outcomes in older adults, including patients in their 70s and beyond. Comorbidities must be considered, particularly severe cardiac or renal dysfunction, but the small PILOT study, which enrolled 44% of patients with HCT-CI scores ≥3, demonstrated a CR rate of just over 50%. He advocated for early referral to CAR T centres when eligibility is uncertain.

One critical practical factor influencing product selection is often product acquisition time. Differences in manufacturing timelines and "vein-to-vein" time can significantly impact outcomes, particularly for patients with rapidly progressive disease. Axi-cel generally has shorter and more consistent manufacturing timelines compared with liso-cel, which may favour its use in patients with aggressive disease where delays could compromise outcomes.

Closely related to product acquisition time is effective bridging therapy. Dr. Johnson typically uses radiation therapy, followed by polatuzumab and rituximab and chemotherapy. However, polatuzumab and rituximab is becoming less effective as more patients receive polatuzumab in the frontline setting. Dr. Johnson highlighted that adaptive radiotherapy allows the treatment of multiple disease sites in patients who historically may not have been considered candidates for bridging radiation.

Toxicity considerations represent the other major axis of decision-making. For patients with a higher

PILOT: Liso-cel in 2L Transplant Ineligible LBCL

Baseline Characteristics	Liso-cel (N=61)
Median age (range), years	74 (53–84)
ECOG PS of 2, n (%)	16 (26)
HCT-CI total score of ≥3, n (%)	27 (44)
DHL/THL*, n (%)	20 (33)
Bridging therapy†, n (%)	32 (52)

Safety

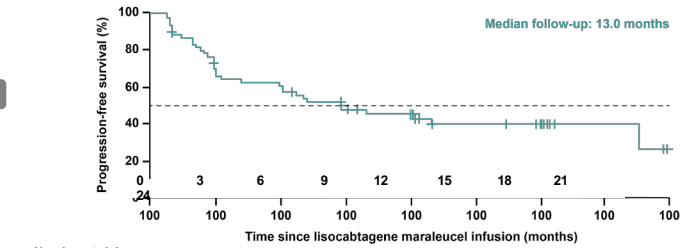
TEAE, n (%)	Grade 3	Grade 4
Thrombocytopenia	4 (7)	8 (13)
Neutropenia	8 (13)	21 (34)
CRS	1 (2)	0
Neurological events	3 (5)	0
	Grade ≥3	
Infections	4 (7)	
Prolonged cytopenia's‡	18 (30)	

Efficacy

Progression-Free Survival

Median PFS, months: 9.03 (95% CI 4.17-NR)

ORR: 80% (95% CI 68-89)
CRR: 54% (95% CI 41-67)



risk of complications—such as older individuals or those with significant comorbidities—liso-cel may be preferred due to its safety profile. The OUTREACH study, a multicentre U.S. study, demonstrated that the outpatient administration of liso-cel resulted in a CR rate of 54% and ORR of 80%, as well as the avoidance of hospitalization in 25% of patients.

Reviewing real-world evidence, Dr. Johnson highlighted that retrospective analyses suggest similar efficacy and safety outcomes to those demonstrated in pivotal trials, including higher rates of CRS and ICANS observed with axi-cel. Importantly, non-relapse mortality and infection rates appear comparable between products. Neutropenic fever was higher with axi-cel, compared with liso-cel. The ABC Consortium comparative real-world analysis demonstrated that patients receiving liso-cel were typically older, and axi-cel had a median acquisition time that was 12 days shorter than liso-cel.

Summarizing the data, Dr. Johnson noted that efficacy appears similar across liso-cel and axi-cel. Therefore, in practice, treatment decisions are often driven by the urgency of disease control versus the need to minimize toxicity, with careful consideration of patient characteristics and institutional capabilities.

2026 Canadian Hematology Today Symposium on B-cell Malignancies

Treatment Sequencing in the Era of Targeted Therapies, Bi-specifics, and CAR T in Large B-Cell Lymphoma

DR. ANCA PRICA

Dr. Prica reviewed data to guide decision-making between bispecific therapies and CAR T-cell therapies in large B-cell lymphoma. Grounding the discussion in real-world outcomes, she cited Ontario data from Dr. Gong and Kuruvilla (2025) showing that the 5-year survival for second-line DLBCL patients was 26%. Only 20% of patients received second-line therapy, 58% of which was curative attempt therapy. The LY12 data, evaluating the effectiveness and safety of gemcitabine-based chemotherapy compared to standard treatment in patients with relapsed or refractory aggressive lymphoma, demonstrated patients who relapsed within 12 months of primary therapy tended to have poorer responses to salvage therapy and were less likely to proceed to ASCT.

CAR T-cells and bispecific antibodies can dramatically improve outcomes. The ALYCANTE and PILOT studies demonstrated reasonable efficacy of CAR T-cell therapy in transplant-ineligible patients. Data from ZUMA-7 shows that older age does not universally preclude CAR T-cell therapy benefit. Dr. Prica also discussed concerns about organ dysfunction constraining eligibility: CIBMTR real-world data indicated that patients not eligible for ZUMA-7, especially due to cardiac impairment and cytopenia, had somewhat poorer EFS and OS rates.

Summarizing challenges with CAR T-cell therapy in the second-line, Dr. Prica highlighted that long-term effects of prolonged immunosuppression/infections, prolonged cytopenias, and secondary malignancies require a lifelong need for monitoring. In addition, geographical and logistical challenges are sizeable. Most importantly, more than 50% of patients who receive CAR T-cell therapy will relapse. Flatiron data from the U.S. (Perales et al. 2025) demonstrate that only 25% of patients eligible for CAR T-cell therapy in the second-line went on to receive the therapy.

Bispecific antibodies will be an increasingly important treatment option for patients who are not candidates for CAR T-cell therapy or who relapse following the therapy. Glofitamab and epcoritamab have demonstrated meaningful activity in heavily pretreated populations. While the median PFS remains below 6 months, patients who achieve a CR have durable responses, with a median DoCR of 29.8 months. Real-world data suggest that outcomes with these bispecific therapies are inferior to those reported in clinical trials, with a median PFS of

Evolving landscape of bispecifics and ADCs in 2L DLBCL

	Bispecific antibodies				ADCs		
	STARGLO[1]	OLYMPIA-4[3]	SUNMO[5]	EPCORE DLBCL-1[7]	POLARGO[8]	LOTIS-5[10]	MK-2140-003[12]
	R/R DLBCL transplant ineligible (N=274)[1,2]	R/R aNHL transplant eligible (N=216)[4]	R/R aNHL transplant ineligible (N=222)[6]	R/R DLBCL transplant ineligible (N=552)	R/R DLBCL transplant ineligible (N=270)[8,9]	R/R DLBCL (N=350)[11]	R/R DLBCL (N=290)
	Glofit + GemOx (8 cycles*) **Glofit mono** (4 cycles*) vs **R-GemOx**[2]	**Odronextamab**† (4 cycles*) vs SoC (**R-ICE or R-DHAP or R-GDP;** 3 cycles*)[4]	**Mosun SC** (8 cycles*) **+ Pola** (six cycles*) vs **R-GemOx** (8 cycles)[6]	**Epcoritamab SC**‡ vs INV choice **chemo** (**R-GemOx**‡ **or BR**†)[§]	**Pola-R-GemOx** (8 cycles*) vs **R-GemOx** (8 cycles*)[9]	**Lonca-R** (8 cycles) vs **R-GemOx** (8 cycles)[11]	**Zilovertamab + R-GemOx** (6 cycles*) vs **R-GemOx** (6 cycles*)
	OS[2]	EFS[4]	ORR and PFS (by IRF)[5,6]	OS	OS[9]	PFS (by IRC)[11]	PFS (by IRC)
	April 2025	May 2027	November 2027	April 2028	Completed November 2024	June 2025	Sep 2027

2.6 months in 245 patients from 21 US centres treated from epcoritamab or glofitamab (46% were primary refractory and 60% were post CAR T-cell therapy). Outcomes were particularly poor in patients with negative CD20 status. Real-world evidence also demonstrates a significantly better benefit of bispecific antibody therapy in patients who had late CAR T-cell therapy failure, compared to those who relapsed early after CAR T-cell therapy.

The STARGLO trial, evaluating glofitamab in combination with GemOx in transplant-ineligible patients, demonstrated a clinically meaningful improvement in PFS of approximately 10 months, compared to R-GemOx. In the second-line cohort, the 36-month OS rate was close to 55%. Grade ≥3 AEs occurred in 78% of patients in the glofitamab arm, compared to 41% of patients in the R-GemOx arm. The median B-cell and immunoglobulin counts remained above the lower limit of normal 18 to 24 months after the end of treatment, which is an important point of discussion with older patients.

Regarding sequencing CAR T-cell therapy and bispecific antibodies, while data remain limited, early analyses suggest that responses to CAR T-cell therapy following bispecific antibody exposure are preserved, and may even be enhanced in some settings. In contrast, responses to bispecific antibodies after CAR T-cell therapy appear more inferior and seem to be influenced by factors such as prior response to CAR T-cell therapy and CD20 expression status.

Dr. Prica summarized that CD19-directed CAR T-cell therapy remains the preferred second-line approach for eligible, fit patients who can travel to a CAR T-cell centre and have relapsed within 12 months since primary treatment. However, for patients who have relapsed beyond 12 months after primary treatment, salvage and ASCT offer good outcomes. Bispecific therapies can be considered for those who have relapsed 6 months or longer after primary therapy and are CD20-positive (biopsies are crucial when considering bispecific therapy). For transplant-ineligible patients with rapidly progressive disease and borderline performance, glofitamab and GemOx offers the potential for long-term remissions, while logistics and toxicity remain important considerations.

Management of Relapsed FL in 2026

DR. CAROLYN OWEN

Unlike many other malignancies, relapsed FL increasingly presents clinicians with a wide range of reasonable therapeutic choices, making individualized decision-making critical. Patient and disease characteristics include age, comorbidities, functional status, prior treatment history, response to earlier lines of therapy, and POD24.

Historically, treatment options in relapsed FL were limited, with most patients receiving repeated courses of chemotherapy, often with diminishing efficacy over time. Rituximab maintenance therapy was first established in the relapsed setting for FL, demonstrating a clear PFS benefit. For patients who relapse within 6 months of a rituximab regimen, the GADOLIN study that demonstrated bendamustine-obinutuzumab, followed by obinutuzumab maintenance, improved PFS and OS versus bendamustine alone in patients with FL or MZL. However, as most FL patients receive bendamustine in the frontline setting, obinutuzumab is typically combined with CHOP or CVP. The AUGMENT study showed that R2 improves PFS and OS versus rituximab monotherapy in relapsed FL. R2 is funded in Canada.

Dr. Owen then reviewed several recent studies evaluating novel combinations built on the R2 backbone. The inMIND trial evaluated the addition of tafasitamab, a CD19-targeted monoclonal antibody, to R2 and demonstrated a clinically meaningful improvement in PFS compared with R2 alone (22.4 months versus 13.9 months). The time to next treatment was not reached in the tafasitamab arm after 28 months of follow-up. While the regimen is generally well tolerated, practical considerations may limit tafasitamab's use, including frequent clinic visits for intravenous infusions, particularly during the early phases of treatment.

The EPCOR FL-1 trial evaluated the addition of the bispecific antibody epcoritamab to R2. Early data from this trial suggest a potentially greater improvement in PFS compared with tafasitamab-based combinations (studies included similar patient populations), although follow-up is short. The estimated 16-month PFS was 85.5% for epcoritamab and R2 and 40.2% for R2, and early follow-up suggests an OS benefit.

The ROSEWOOD study demonstrated improved outcomes with zanubrutinib and obinutuzumab, compared with obinutuzumab monotherapy (median PFS of 22 months versus 10 months). While BTK inhibitors have shown limited activity as single agents in FL, combination approaches may enhance efficacy, although access, toxicity, and cost considerations may limit widespread adoption.

Dr. Owen emphasized that cross-trial comparisons must be interpreted cautiously but noted that all three studies show robust efficacy across similar patient populations. However, R2 and

CROSS-TRIAL COMPARISON – CONSIDER AT YOUR RISK

	LenR + EPCORITAMAB	LenR + TAFASITAMAB	Zanubrutinib + Obin
Median age	60	64	63
Median prior lines of therapy	1	1	3
Proportion R refractory	43%	43%	54%
Proportion POD24	44%	44%	35%
Median PFS	86% at 16 mo	22 mo (65% at 16mo)	22 mo (60% at 16 mo)
Median TTNT	93% at 16 mo	84% at 16 mo	52 mo (75% at 16 mo)
Median OS	95% at 16 mo	>90% at 16 mo	NE at 49 mo (88% at 16mo)

epcoritamab may offer the most benefit.

ASCT remains an important consideration, particularly for younger, fit patients with high-risk disease, including patients with POD24 disease. Long-term follow-up data suggest that ASCT can produce prolonged remissions, with some patients remaining disease-free beyond 15 years.

CAR T-cell therapy is now approved in later lines of therapy for FL and represents another important option, particularly for patients with multiply relapsed disease. Data from Puckrin et al. (2022) suggest ASCT is an effective option for first or second relapse of FL and should be strongly considered for patients with POD24 or younger fit patients who prioritize the potential for a durable remission.

Bispecific antibodies have demonstrated meaningful activity in heavily pretreated patients and offer the advantage of off-the-shelf availability. Data presented at ASH 2023 demonstrated 3-year PFS rates of 43% in relapsed and refractory FL, of whom 52% had POD24 disease. Ongoing studies are evaluating the use of bispecific therapies earlier in the disease course, including in combination with other agents.

Using case-based examples, Dr. Owen highlighted that, for an older relapsed and refractory FL patient, tafasitamab or epcoritamab plus R2 are ideal options, offering better efficacy than R2 alone. Zanubrutinib and obinutuzumab is another efficacious option, but will be challenging to access in Canada. For younger patients, epcoritamab plus R2, ASCT and CAR T-cell therapy are all reasonable options. Emerging data points to bispecific therapy as potentially preferable to CAR T-cell therapy in these patients. For FL patients with POD24, ASCT remains the most evidence-supported option, but emerging data suggest that epcoritamab plus R2 could be equally effective.

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