Canadian Hematology Today 2025 Toronto Lymphoma Conference

Event Summary

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In This Report

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Acronyms

AAAAI	AMERICAN ACADEMY OF ALLERGY, ASTHMA & IMMUNOLOGY
ABVD	DOXORUBICIN, BLEOMYCIN, VINBLASTINE, AND DACARBAZINE
ALLoSCT	ALLOGENEIC STEM CELL TRANSPLANTATION
ASCO	AMERICAN SOCIETY OF CLINICAL ONCOLOGY
ASCT	AUTOLOGOUS STEM CELL TRANSPLANT
ASH	AMERICAN SOCIETY OF HEMATOLOGY
AVD	DOXORUBICIN, VINBLASTINE, AND DACARBAZINE
Axi-cel	AXICABTAGENE CILOLEUCEL
BEACOPP	BLEOMYCIN, ETOPOSIDE, DOXORUBICIN, CYCLOPHOSPHAMIDE, VINCRISTINE, PROCARBAZINE, AND PREDNISONE
BPd	BELANTAMAB MAFODOTIN, POMALIDOMIDE, AND DEXAMETHASONE
BR	BENDAMUSTINE AND RITUXIMAB
BTK	BRUTON TYROSINE KINASE
BV	BRENTUXIMAB VEDOTIN
BV-AVD	BRENTUXIMAB VEDOTIN, DOXORUBICIN, VINBLASTINE, AND DACARBAZINE
BVd	BELANTAMAB MAFODOTIN, BORTEZOMIB, DEXAMETHASONE
CAR T	CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY
cHL	CLASSICAL HODGKIN LYMPHOMA
CLL	CHRONIC LYMPHOCYTIC LEUKEMIA
CNS	CENTRAL NERVOUS SYSTEM
CR	COMPLETE RESPONSE
CRS	CYTOKINE RELEASE SYNDROME
CyBorD	CYCLOPHOSPHAMIDE, BORTEZOMIB, DEXAMETHASONE
DA-EPOCH-R	DOSE-ADJUSTED ETOPOSIDE, PREDNISONE, VINCRISTINE, CYCLOPHOSPHAMIDE, DOXORUBICIN, AND RITUXIMAB

Acronyms con't

DLBCL	DIFFUSE LARGE B-CELL LYMPHOMA
DRd	DARATUMUMAB, LENALIDOMIDE, AND DEXAMETHASONE
DVd	DARATUMUMAB, BORTEZOMIB, AND DEXAMETHASONE
DVRd	DARATUMUMAB, BORTEZOMIB, LENALIDOMIDE, AND DEXAMETHASONE
EHA	EUROPEAN HEMATOLOGY ASSOCIATION
EMA	EUROPEAN MEDICINES AGENCY
FL	FOLLICULAR LYMPHOMA
GemOx	GEMCITABINE AND OXALIPLATIN
ICANS	IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME
IdelaR	IDELALISIB AND RITUXIMAB
IgG	IMMUNOGLOBULIN G
IsaVRd	ISATUXIMAB, BORTEZOMIB, LENALIDOMIDE, AND DEXAMETHASONE
IVIG	INTRAVENOUS IMMUNOGLOBULIN
JCO	JOURNAL OF CLINICAL ONCOLOGY
Kd	CARFILZOMIB AND DEXAMETHASONE
LDH	LACTATE DEHYDROGENASE
Liso-cel	LISOCABTAGENE MARALEUCEL
MCL	MANTLE CELL LYMPHOMA
MIPI	MANTLE CELL LYMPHOMA INTERNATIONAL PROGNOSTIC INDEX
MM	MULTIPLE MYELOMA
NCCN	NATIONAL COMPREHENSIVE CANCER NETWORK
ORR	OVERALL RESPONSE RATE
OS	OVERALL SURVIVAL
PET	POSITRON EMISSION TOMOGRAPHY

Acronyms con't

PFS	PROGRESSION-FREE SURVIVAL
PMBCL	PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA
POD24	PROGRESSION OF DISEASE WITHIN 24 MONTHS
PVd	POMALIDOMIDE, BORTEZOMIB, AND DEXAMETHASONE
R-ACVBP	RITUXIMAB, DOXORUBICIN, CYCLOPHOSPHAMIDE, VINDESINE, BLEOMYCIN, AND PREDNISONE
R-CHOP	RITUXIMAB, CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE, AND PREDNISONE
R-GemOx	RITUXIMAB, GEMCITABINE, AND OXALIPLATIN
R/R	RELAPSED/REFRACTORY
R2	RITUXIMAB AND LENALIDOMIDE
RT	RADIATION THERAPY
SCIG	SUBCUTANEOUS IMMUNOGLOBULIN
SLL	SMALL LYMPHOCYTIC LYMPHOMA
Tisa-cel	TISAGENLECLEUCEL
Vd	BORTEZOMIB AND DEXAMETHASONE
XVd	SELINEXOR, BORTEZOMIB, AND DEXAMETHASONE

Welcome and Opening Remarks

DR. PETER ANGLIN

Dr. Peter Anglin welcomed everyone to the meeting and introduced the meeting objectives:

- Provide current and high-quality information on the latest developments in the management of lymphoproliferative disease
- Create collegial learning opportunities to enable clinicians to share real-world experience and to directly apply new insights to their practice
- Foster discussions that allow for the sharing of knowledge and experience among delegates and industry representatives
- Respond to emerging professional needs for specific and in-depth information on the latest therapies for lymphoproliferative disease in the Canadian market

DR. PETER ANGLIN

Strategic Sequencing in Early Relapsed/ Refractory Multiple Myeloma: Integrating Established and Novel Agents in 2025

(Sponsored Breakfast Symposium, FORUS Therapeutics)

DR. DARRELL WHITE

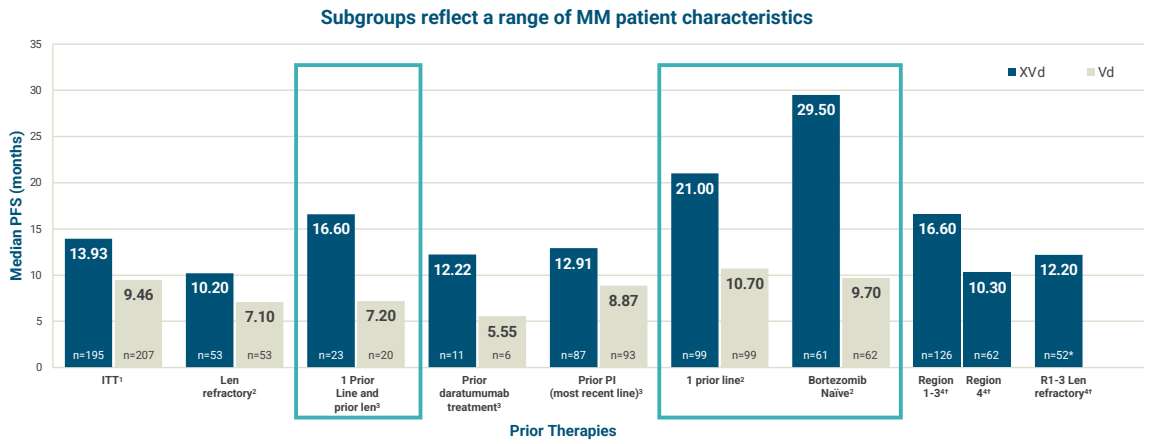
Before discussing R/R MM, Dr. White shared recent data demonstrating impressive treatment advances in the frontline setting. For transplant-eligible patients, DVRd, available in Canada, is now projected to have a median PFS of 17 years, based on modelling from PERSEUS data. For transplant-ineligible patients, IsaVRd also offers an important survival benefit, compared to previous therapies.

In the second-line setting, optimizing sequencing strategies in the early R/R MM setting has become increasingly complex with emerging therapies and novel combinations. Almost all patients are lenalidomide-refractory and many patients have already been exposed to anti-CD38 therapy. Most patients are, however, bortezomib-sensitive at first relapse. The currently funded options for these lenalidomide-refractory, bortezomib-sensitive patients in Canada are Kd and XVd (and PVd in Ontario). Belantamab mafodotin, combined with bortezomib or pomalidomide, is also currently available on a compassionate basis in the second-line setting and beyond.

Dosing frequency, monitoring and hospitalization requirements are important treatment considerations, as are financial implications, including work disruption and out-of-pocket costs. In addition, patients are increasingly aware that anti-BCMA therapy may affect future options, especially CAR T therapy.

The BOSTON trial, a phase 3, global, randomized trial, compared Vd to XVd. Non-responding patients in the Vd arm could move to the treatment arm, which is important to consider when assessing results. While XVd was superior to Vd in all patient subgroups, the PFS benefit was more pronounced in patients who were bortezomib-naïve and patients who only had one prior line of therapy, including lenalidomide.

BOSTON: consistent PFS benefit across subgroups[1-4]



Limitations of subgroup analyses: These subgroup analyses were exploratory in nature, not included in the study objectives, and do not control for type 1 error. These subgroup analyses were not powered or adjusted for multiplicity to assess PFS across these prespecified subgroups.

1.Grosicki S, et al. Lancet. 2020;396(10262):1563-1573; 2. Mateos MV et al. Eur J Haematol. 2024;1–11; 3. Data on File Karyopharm Therapeutics. 2021; 4 Spencer A et al. EHA 2024, Abstract 1993; *as defined by IMWG criteria

†Regions 1-3 included Canada, US, Australia, Austria, Belgium, France, Germany, Israel, Italy, Spain, UK. Czech Republic, Greece, Hungary, Poland. Region 4 included Bulgaria, India, Romania, Russian Federation, Serbia, Ukraine

Discussing the safety results, Dr. White highlighted that 40% of patients experienced grade 3 or 4 thrombocytopenia and 5% of these patients experienced grade ≥3 bleeding. Frequent non-hematologic side effects in the treatment arm included nausea, diarrhea, fatigue, and decreased appetite. The adverse events responded well to antiemetics and dose-reduction. Dr. White recommended the prophylactic use of antiemetics, noting that once-weekly palonosetron and netupitant works well in his experience. While the on-label dose for XVd is 100 mg, Dr. White recommended starting with a maximum dose of 80 mg.

Dr. White then discussed belantamab mafodotin combinations, including BPd and BVd. The DREAMM-7 trial demonstrated a median PFS of 36.6 months for BVd compared to 13.4 months in the DVd arm. The DREAMM-8 trial comparing BPd versus PVd showed a median PFS difference of 32.6 months versus 12.5 months, respectively. The PFS for lenalidomide-refractory patients in the BPd treatment arm was 24 months, compared to 9.2 months in the control arm.

The ALGONQUIN trial assessing belantamab mafodotin in patients with a median of three prior lines (89% were refractory to lenalidomide) demonstrated a PFS rate of 43% at 24 months. Ocular toxicity occurred in more than half of the patients in the trial, while thrombocytopenia occurred in a third of patients.

Patients who previously responded well to DRd can be treated with XVd or BPd in the R/R setting. The latter therapy offers a longer PFS but may limit future options. Dr. White noted patients who are refractory to anti-BCMA therapy currently cannot access a second anti-BCMA therapy, although patients may be eligible for an additional anti-BCMA treatment if belantamab mafodotin is stopped before they become refractory.

In conclusion, Dr. White emphasized that XVd results for lenalidomide- and daratumumab-refractory patients are impressive, without limiting future line therapy. In addition, preclinical data suggests selinexor may potentiate T-cell function which may be important prior to T-cell receptor therapy.

CAR T-cell Therapy and Bispecifics in Multiple Myeloma in 2025: Who, When, and Where

DR. CHRISTINE CHEN

Dr. Chen began by discussing the "optimal" CAR T and bispecific antibody patient. The CARTITUDE-1 and CARTITUDE-4 studies demonstrated that patients who are not triple-class refractory, patients without high-risk cytogenetics, and patients with a low-tumour burden (achieved through effective bridging therapy) are much more likely to respond to bridging to CAR T therapy.

Toxicity is an important factor as well. A high tumour burden is associated with high peak CAR T cells in the blood, severe CRS, and neurotoxicity. Mitigation strategies include debulking with effective bridging and preemptive dexamethasone.

While age and renal impairment can affect treatment efficacy and toxicity in MM, fortunately, neither renal impairment nor increased age alone appear to impair efficacy nor increase the toxicity of CAR T therapy in MM. Frailty is, however, associated with increased risk of toxicity and a shorter PFS. Baseline cytopenia also increases hematologic toxicity risk.

Many inequities exist when it comes to the "optimal" CAR T patient. Dr. Chen highlighted that patients who live in an urban centre close to an academic CAR T site, have caregiving support and financial resources, and are medically motivated are more likely to benefit from CAR T therapy. More work is necessary to increase supports and improve equity.

While trial data demonstrates median PFS for CAR T therapy is approximately 3 years, compared to less than 1 year with teclistamab, Dr. Chen emphasized that CAR T trials select patients with a slower disease progression.

Dr. Chen noted that teclistamab is the only funded bispecific therapy for MM patients in Canada. The MAGESTEC-1 trial, which included a high proportion (76%) of triple-class refractory patients, demonstrated an ORR of 63%. Responses were durable in many patients. A 2023 update on patients who switched to biweekly dosing showed that they had sustained remission, with a median duration of response of 20.5 months from the date of the switch. Noting inferior outcomes in patients with active infection and high tumor burden, Dr. Chen recommended debulking patients with high tumor burden in advance of teclistamab treatment using high-dose cyclophosphamide or another therapy.

A comparison between studies published in *Blood* in 2024 and presented at ASCO in 2022 suggest patients treated with CAR T therapy ahead of bispecific therapy have superior PFS outcomes, compared to patients treated with bispecific therapy followed by CAR T. The rationale for this sequence includes that continued bispecific antibody exposure leads to exhausted T cells. A paper published in *Nature* in 2023 showed target-antigen loss to be much more common post-bispecific antibodies (up to 40%) compared to post-CAR T (4%). However, bispecific therapy, rather than CAR T therapy, may be the optimal choice for patients with a rapid pace of disease and no effective bridging options, lymphopenia, very frail/elderly patients, patients with comorbid conditions such as pre-existing Parkinson's disease and patients who are unable or unwilling to relocate to a CAR T centre .

While CAR T remains confined to academic, urban centres, due to the need for close monitoring and intensive care and consultative services, there is growing community experience with bispecific therapy. The decentralization of bispecific therapy is possible as CRS is short-lived and neurotoxicity is much less common.

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Amyloid in 2025: Treatment and Management Considerations

DR. VICTOR ZEPEDA

Amyloidosis is a rare systemic disorder characterized by the misfolding of aberrant precursor proteins, leading to amyloid fibril formation. Fibrils are deposited in various organs and progressively affect the function of organs.

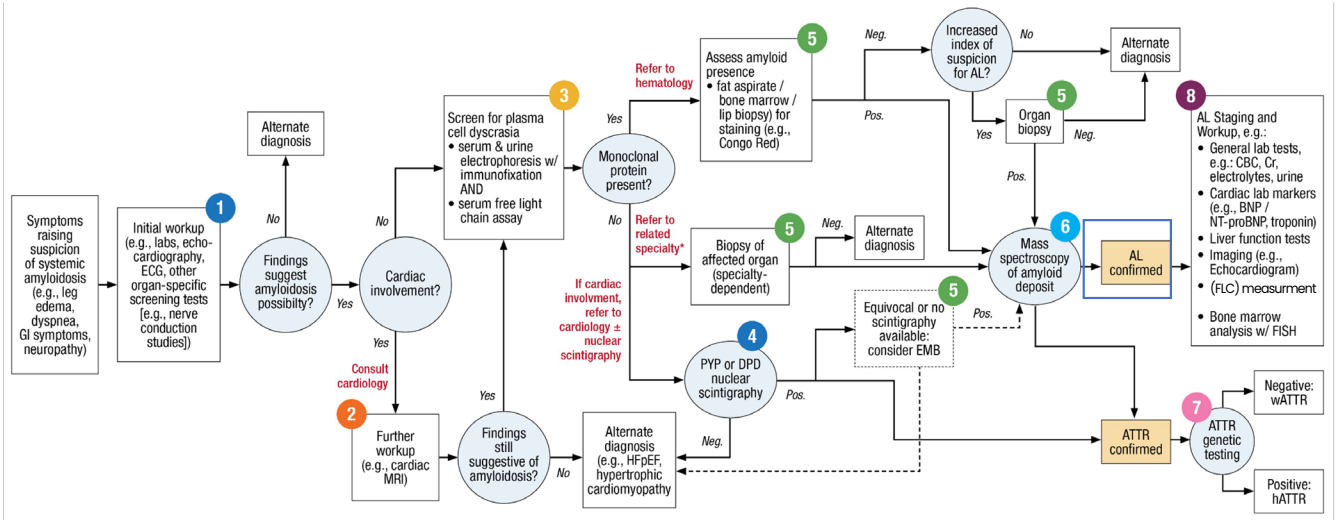
Localized amyloidosis, involving amyloid deposits at the site of production, is not typically associated with monoclonal protein in serum or urine and accounts for approximately 7% of cases. Systemic or light chain amyloidosis, whereby amyloid fibrils accumulate throughout tissues and multiple organs, accounts for approximately 93% of cases.

Symptoms raising suspicion of light chain amyloidosis include leg edema, dyspnea, GI symptoms, and neuropathy. Cardiac and kidney involvement are frequently identified, occurring in 70% and 60% of patients with amyloidosis, respectively. The journey to diagnosis is not straightforward, as the affected organs and symptoms vary widely. In Canada, the frequency of light chain amyloidosis is about 9 to 12 per million.

As 30% of patients die within 1 year of diagnosis, early diagnosis is crucial. Dr. Zepeda noted that the combination of fat pad aspiration and bone marrow examination demonstrate a sensitivity for light chain amyloidosis of approximately 90%. Mass spectrometry is required to confirm AL amyloidosis. If no monoclonal protein is present and pyrophosphate imaging results in a grade of 2 or 3, transthyretin amyloidosis is confirmed.

Treatment for AL amyloidosis includes anti-plasma cell therapy. In addition, nutritional support, fluid retention and neuropathy management, and anti-microbial prophylaxis are important aspects of care. ASCT can increase survival in carefully selected patients, based on biomarkers of cardiac involvement and clonal burden. Dr. Zepeda explained that while all AL amyloidosis patients receive induction chemotherapy, only 10% to 20% of patients ultimately proceed to ASCT. In a Mayo Clinic study, 30% of AL amyloidosis patients treated with high-dose chemotherapy followed by transplant survived beyond 20 years. CAR T therapy is also

REVIEW: Amyloidosis is difficult to diagnose



Adapted from Jimenez-Zepeda et al 2023

AL, light chain; ATTR, transthyretin amyloidosis; BNP, brain natriuretic peptide; CBC, complete blood count; DPD, [99mTc]-3,3-diphosphono-1,2-propanodicarboxylic acid; ECG, electrocardiogram; EMB, endomyocardial biopsy; FISH, fluorescence in situ hybridization; FLC, free light chain; GI, gastrointestinal; HFpEF, heart failure with preserved ejection fraction; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PYP, technetium pyrophosphate.

Jimenez-Zepeda V, et al. *Clin Lymphoma Myeloma Leuk.* 2023;23(3):194-202.

being evaluated in the treatment of amyloidosis.

The ANDROMEDA trial demonstrated that the addition of daratumumab to CyBorD significantly improved outcomes. At over 60 months of follow-up, 59.2% of patients in the daratumumab-CyBorD arm met the PFS without major organ deterioration criteria, compared to 19.2% of patients in the CyBorD arm.

Novel therapies including birtamimab and anti-fibrillar antibodies produce high hematologic responses. However, the durability of these responses has yet to be established.

Emerging Therapies in Chronic Lymphocytic Leukemia: Non-covalent BTK Inhibitors, Cellular Therapy, and T-cell Therapies

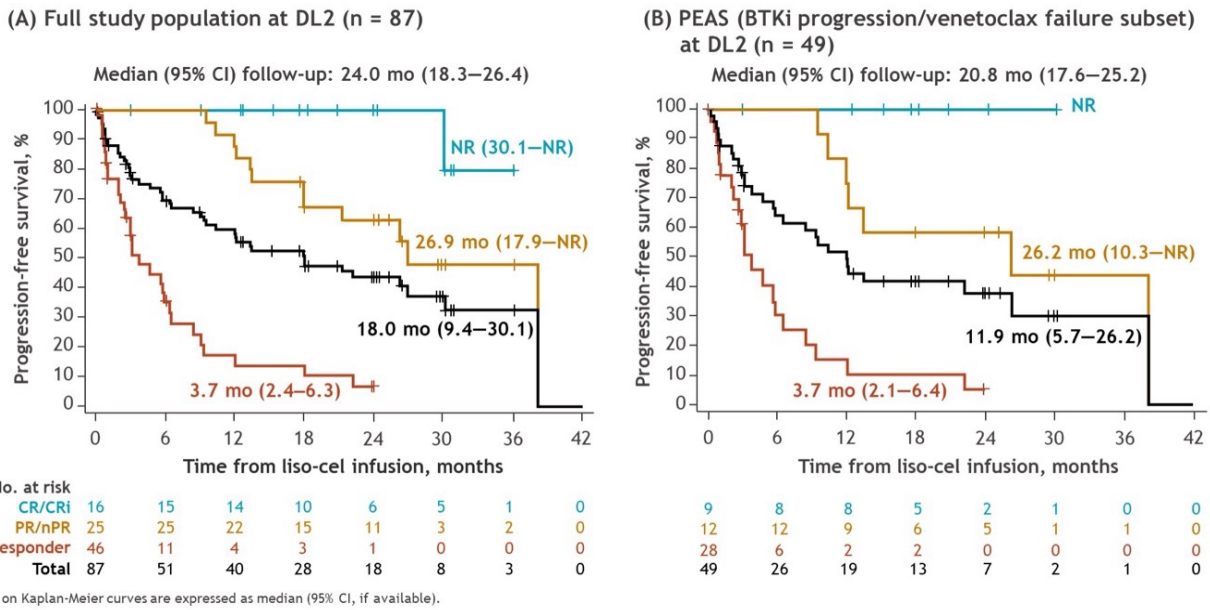
DR. MATTHEW DAVIDS

R/R CLL poses a significant challenge, despite first-line ibrutinib showing OS rates similar to the general population. Treating R/R CLL is particularly difficult for younger patients and those with high-risk cytogenetics, who urgently need new therapeutic options. Dr. White outlined that the prognosis for double-class refractory patients is dismal; an Australian study published in 2021 found a median OS of just 5 months among 165 such patients treated between 2011 and 2020.

Fortunately, noncovalent BTK inhibitors, including pirtobrutinib and nemtabrutinib, can overcome resistance to covalent BTK inhibitors and improve outcomes in R/R CLL. Pirtobrutinib is a highly selective noncovalent BTK inhibitor that is similarly active against BTK wild-type versus patients with the C481X mutation. The therapy is well-tolerated, with low rates of cardiovascular toxicity. In the phase 1/2 BRUIN clinical trial, the median PFS was 19.6 months in the overall study population, and 23 months in BCL2-inhibitor naïve patients previously treated with a covalent BTK inhibitor.

The BRUIN CLL-321, recently published in *JCO*, randomized patients previously treated with covalent BTK inhibitor therapy to pirtobrutinib monotherapy or investigator's choice of BR or IdelaR. Most patients had unmutated IGHV (93% in the pirtobrutinib arm) and more than half of patients had a TP53 aberration. BTK resistance mutations were reported in 37% of patients in the treatment arm. More than 70% of patients stopped covalent BTK inhibitor therapy due to disease progression. Pirtobrutinib demonstrated a median PFS of about 14 months, which was superior to the control arm. While there was no OS difference, most patients crossed over to the pirtobrutinib arm.

Progression-free survival



Data on Kaplan-Meier curves are expressed as median (95% CI, if available).

Data is accumulating for pirtobrutinib combined with other therapies, including venetoclax and rituximab. The BRUIN-322 study is ongoing, assessing pirtobrutinib, venetoclax, and rituximab versus venetoclax and rituximab.

Nemtabrutinib is in late-stage development. The BELLWAVE-001 study has reported ORR rates of 40% to 60% across the three treatment cohorts. Overall median PFS has not been reached; however, in the cohort of patients with a known C481 BTK resistance mutation, the median PFS is approximately 16 months. Notable adverse effects include dysgeusia, which is typically mild and tolerant, as well as hypertension, which occur in 11% of patients. Overall, nemtabrutinib was well-tolerated.

BTK degraders are a novel therapy targeting the mutations in BTK that drive resistance in CLL. A phase 1 study of catadegbrutinib included many patients who were triple-class refractory (post-noncovalent BTK inhibitor). The ORR was 85% and the 12-month PFS was 77%, as reported at EHA this year. Similarly, a phase 1/2 study of bexobrutideg has demonstrated an ORR of 81%.

Outlining CAR T therapy in CLL, Dr. Davids presented the ZUMA-8 study of brexucel in R/R CLL. Objective responses were observed in seven patients (47%), including one patient with CR (7%). However, toxicity rates were high, as patients requiring CAR T for CLL are older with comorbidities. CRS rates were 80% (7% grade 4) and neurologic events occurred in 73% of patients (20% grade 3). The rates of T-cell expansion were very low. Dr. Davids explained that as CLL is immunosuppressive, CAR T is unlikely to be effective in a CLL patient with bulky disease.

The TRANSCEND study of liso-cel demonstrated an ORR of 43% of the patients responded, and a CR rate of 18%. Responses were very durable among the patients who achieved CR, although the median PFS in the overall study population was 18 months and 11.9 months in the patients who were double-refractory.

Bispecific antibodies are also showing early promise, with a study presented at ASH demonstrating that epcoritamab led to CR rates of approximately 40% in a small R/R CLL population.

Approaches to Relapsed/Refractory Diffuse Large B-Cell Lymphoma

DR. NANCY BARTLETT

Dr. Bartlett began by outlining CAR T therapy in DLBCL. In the third-line setting and beyond, 25% to 35% of patients survive without relapse. Real-world evidence demonstrates CR rates of 64%, 60% and 45% with axi-cel, liso-cel and, tisa-cel respectively. Five-year data demonstrates that approximately 50% of CRs are durable. When comparing CAR T outcomes to other treatments, it is important to consider that patients undergoing for CAR T must meet strict eligibility criteria.

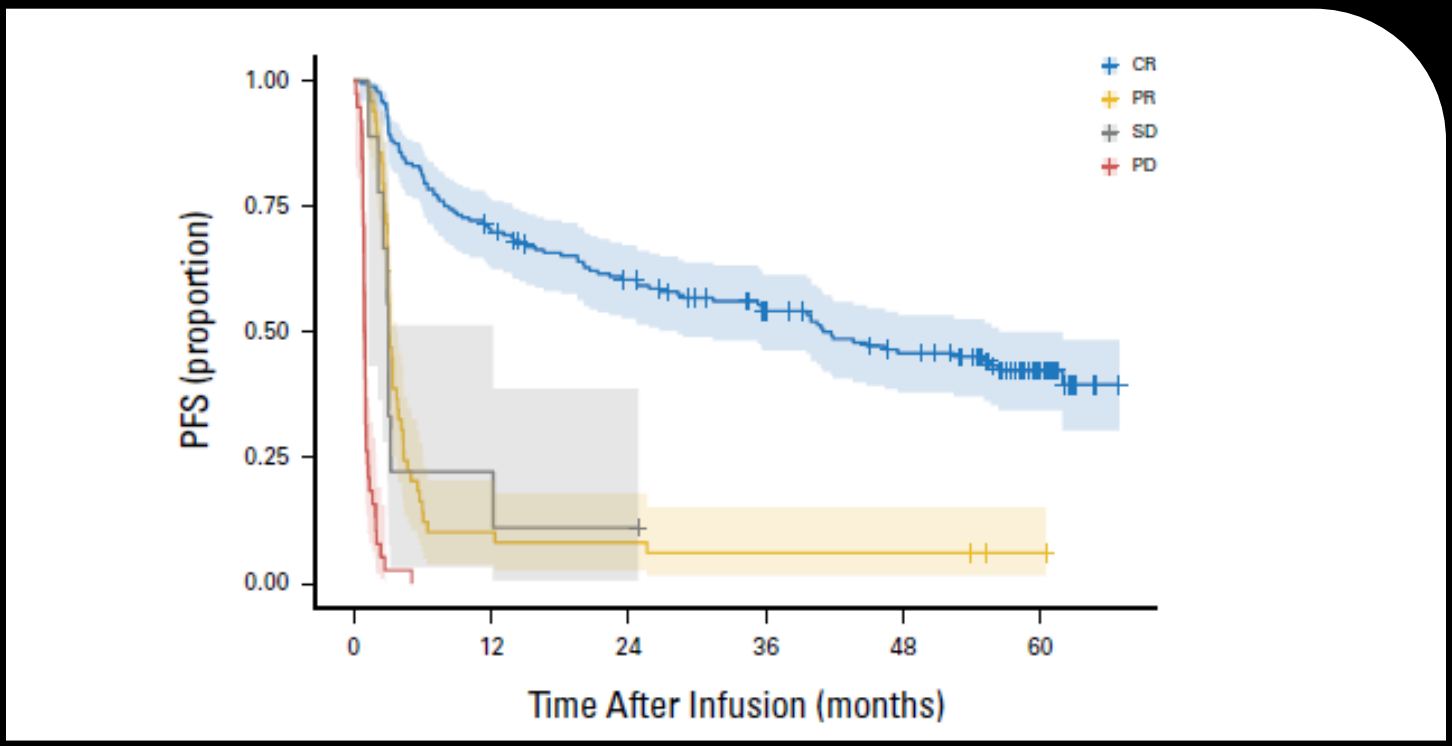
Real-world evidence published in *JCO* in 2024 demonstrates that partial responses after CAR T are not durable, necessitating the need to rapidly move to subsequent therapy in patients with partial responses.

In the second-line setting, CAR T therapy has shown a modest OS advantage over ASCT, with 3-year OS rates of 63% among patients treated with liso-cel compared to 52% for those treated with ASCT. Ultimately, however, the majority of patients will require a subsequent therapy. The 4-year PFS rate for axi-cel in the seond-line is 42%.

Outcomes post-CAR T in secondary CNS lymphoma are dismal, however. A large multicentre retrospective study of patients with CNS, two-thirds of who also had systemic disease, showed a 1-year PFS rate of 16% and no difference based on the CAR T product type.

Liso-cel shows the most favourable toxicity. Liso-cel demonstrates lower rates of grade ≥3 neurotoxicity (4% in second line; 10% in third line), compared to axi-cel (21% in second line and 32% in third line). Grade ≥3 infections occur in approximately 12% of patients treated with liso-cel in the second line compared with 15% in the third-line. (Infection rates among patients treated with axi-cel were 14% and 28% respectively). Real-world evidence demonstrates a non-relapse mortality of 7% with liso-cel, and higher rates in clinical trials.

Bispecific antibodies also represent both promise and challenges. In the third-line setting and beyond, 40% of patients achieved a CR in trials for epcoritamab and glofitamab, and approximately half of CRs appear durable at 2 to 3 years. Similar to CAR T therapy, PRs are not durable with bispecific antibodies.



Bispecific antibody therapy trials in DLBCL show modestly higher rates of grade ≥3 CRS, and neurotoxicity, compared to the FL setting. Grade ≥3 CRS rates were reported at 3% and 4% in the epcoritamab and glofitamab trials respectively, while grade ≥3 ICANS occurred at 3% and <1% among patients treated with epcoritamab and glofitamab. Dr. Bartlett cautioned that grade ≥3 infection rates were high, and many infections occurred after 6 months of treatment.

Combining bispecific antibodies and chemotherapy can improve outcomes in R/R DLBCL. While the FDA determined that results from the STARGLO trial were not applicable to the U.S. population, the combination of glofitamab and GemOx was added to the NCCN guidelines and most insurers fund the combination. The phase 1/ 2 trial of epcoritamab and GemOx demonstrated very similar results to the glofitamab combination, with 12-month PFS rates of 63% among patients with one prior line of therapy and 33% among those treated with two or more prior lines of therapy.

A phase 3 study of mosunetuzumab and polatuzumab demonstrated CR rates of 51% in the treatment arm, compared to 24% among patients treated with R-GemOx. CRS rates were lower with the therapy, compared to the other two bispecific antibodies. The glofitamab and polatuzumab combination has shown similar promise in R/R DLBCL. Additional follow-up is needed to show whether bispecific antibody combinations could be as effective as CAR T therapy, with lower toxicity rates.

CAR T and Bispecifics in 2025 in Relapsed/Refractory Follicular Lymphoma: Who, When, and Where

DR. GILLES SALLES

One of the main concerns with FL is the risk of histologic transformation. More than one-third of progressions are observed during the first year after treatment. Dr. Salles emphasized the importance of obtaining a new biopsy before determining the treatment course for R/R FL to rule out transformation.

Results from recent clinical trials of bispecific antibodies are encouraging in the treatment of R/R FL. A trial evaluating mosunetuzumab, published in *Lancet Oncology* in 2022, demonstrated an ORR of approximately 80% and a CR rate of 60%. About half of patients experienced CRS, which was largely grade 1 or 2 in severity and most often occurred after the third step-up dose. The median duration of response was 35.9 months in the overall study population, and the duration of CR did not differ based on POD24 status nor age.

Serious infections occurred primarily within the first four cycles of therapy. Data suggest full recovery of B-cell and immunoglobulin levels may take approximately 2 years among patients who achieve a CR, especially in heavily pre-treated patients.

The NHL-1 study of epcoritamab showed similar efficacy and safety results, with an ORR of 80% and a CR rate of 63%; results were consistent in patients with POD24. The NHL-2 Arm 2 study comparing epcoritamab with R2 also produced impressive response rates. Results presented at ASH in 2024 revealed an ORR of 96% and a CR of 87% in a phase 1/2 trial. At 2 years, duration of CR rates remain very high. The CR rates for mosunetuzumab, odronextamab, and epcoritamab are 60%, 73% and 67% respectively, based on non-head-to-head clinical trials.

Outlining CAR T therapy in R/R FL, Dr. Salles noted that cross-trial efficacy comparisons of CAR T therapies are not useful, due to differing patient populations. However, tisa-cel and liso-cel demonstrate much lower rates of severe CRS and ICANS compared to axi-cel.

Long-term follow-up data show responses are very durable, and CAR T therapy could be curable in the FL setting. The ELARA trial of tisa-cel demonstrated less favourable results in patients with bulky disease, highlighting the importance of bridging in these patients.

The TRANSCEND-FL study found that liso-cell led to an impressive CR rate of 96% in the second- and third-line settings, and 96% in the fourth-line setting and beyond. However, patients who received bendamustine within 12 months prior to CAR T therapy appeared to respond less well, with CR rates of 75% among eight patients.

While CAR T therapy offers a "one-and-done" treatment with very high CR rates, a prolonged duration of CR, and a possibility of a cure, logistics are a challenge, and rates of CRS, ICANS, and prolonged cytopenia are higher than with bispecific antibodies. Dr. Salles argued patient preference should be a major consideration of treatment choice in R/R FL.

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Optimizing Care for Dual-Exposed Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Canadian Insights and Strategies

(Sponsored Lunch Symposium, Eli Lilly Canada)

DR. ROBERT PUCKRIN

While novel therapies have transformed the treatment of CLL/SLL, outcomes are poor for CLL patients who are double-exposed or double-refractory to BTK inhibitor and BCL2 inhibitor therapy.

Patients who are double-refractory tend to have higher risk disease with frequent TP53 aberrations and frequent BTK resistance mutations. They typically require treatment urgently and have a higher risk of developing Richter transformation. Dr. Puckrin recommended assessing double-exposed/refractory patients for signs of transformation, including rapidly growing lymph nodes or hypercalcemia and high LDH levels, and ordering a PET scan and biopsy if indicated.

For patients who stopped a BTK inhibitor due to intolerance, rather than progression, monitoring is an option as is retreatment with another covalent BTK inhibitor. Among patients who stopped one or more covalent BTK inhibitors for intolerance, only 10% to 17% discontinued acalabrutinib, zanubrutinib, or pirtobrutinib due to adverse events.

For patients who have relapsed at later time points after time-limited therapy, the CAPTIVATE trial showed that retreatment is a promising strategy, with high responses and no BTK or PLCγ2 mutations identified in patients retreated with ibrutinib or ibrutinib and venetoclax.

For double-refractory CLL/SLL in Canada, current treatment options include IdelaR, which demonstrates a response rate of approximately 50%

Prognosis of double-refractory versus double-exposed CLL/SLL

	Double-refractory (n=30)	Double-exposed (n=65)
Median prior lines of therapy	4	3
TP53 aberration	73%	46%
BTK mutations	59%	27%
Required subsequent therapy	97%	26%
Richter transformation	30%	6%
Median time to next treatment or death	0.6 months	Not reached
2-year overall survival rate	53%	76%

VV-Canada Medical-US-DEL-0419

Blood Adv 2025;9(11):2808

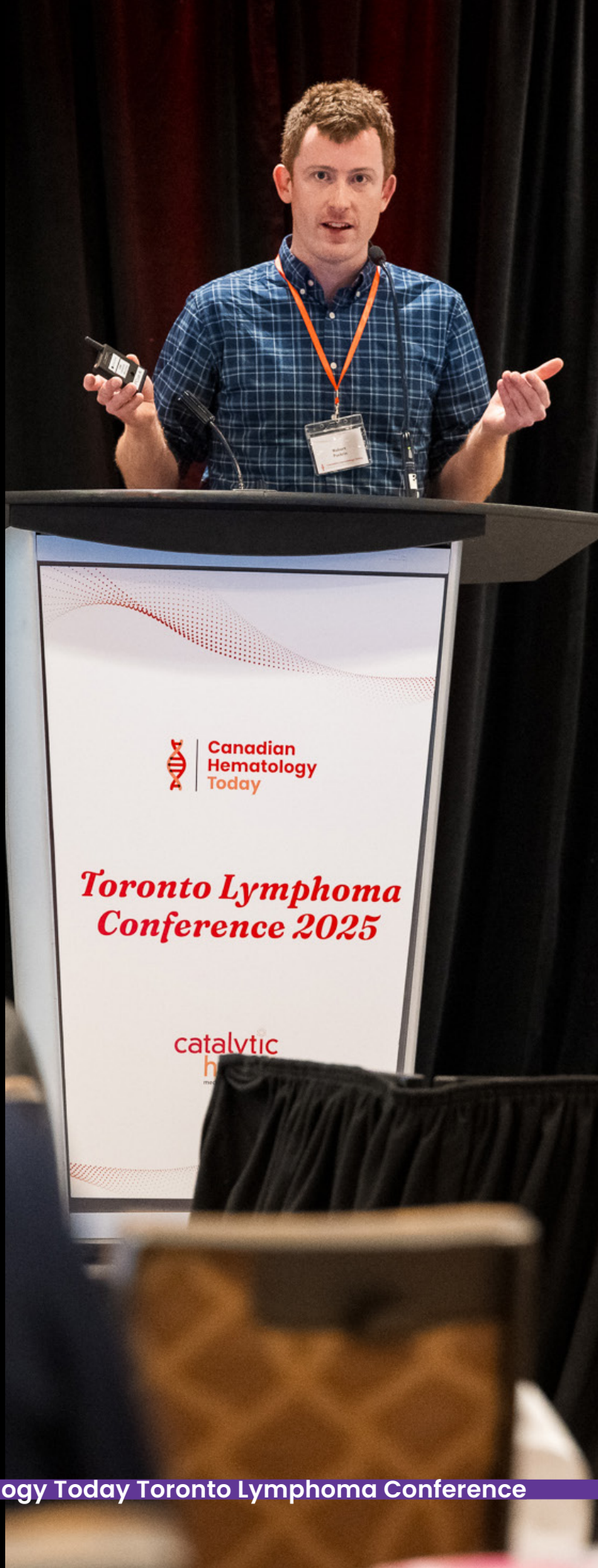
and a median PFS of 5 to 8 months. The targeted therapy is associated with high infection rates, but can be used as a short-term strategy, such as a bridge to a clinical trial.

AlloSCT can have curative potential in R/R CLL, but comes with serious risks including graft versus host disease, infections, and non-relapse mortality. AlloSCT is appropriate for younger, fit, and medically motivated patients with short durations of remission. However, it is important to initiate alloSCT while patients continue to respond to their last available line of therapy. AlloSCT is associated with a 2-year PFS rate of 63%, OS rate 81%, and non-relapse mortality of 13% in the era of novel agents, including among double-exposed cases. Dr. Puckrin recommended maximizing both novel drug classes, as well as pirtobrutinib, before proceeding to AlloSCT.

Discussing investigational and emerging therapies, Dr. Puckrin noted that non-covalent BTK inhibitors are the most promising treatment class for double-refractory disease. Pirtobrutinib has demonstrated not only superior efficacy, but also improved tolerability, compared to IdelaR. The phase 1/2 and 3 trials for pirtobrutinib enrolled heavily pretreated patients, most of whom were resistant to a BTK inhibitor and about half of whom were also exposed to a BCL2 inhibitor. In these trials, the response rates ranged from 65% to 82%, with similar efficacy in the double-exposed as in the BCL2-naïve population. The median PFS ranged from 11 to 17 months for the double-exposed patients, and the median time to next treatment was approximately 20 months for the double-exposed patients. These are encouraging results, considering the convenience and tolerability of the oral drug, which is currently available through compassionate access. Pirtobrutinib is an ideal treatment option both for older and unfit patients as well as younger and fit patients as a bridge to transplant.

BTK degraders are also showing high response rates in double- and even triple-exposed populations. For example, BGB-16673 achieved an ORR of 91% in 42 patients with double-exposed CLL/SLL in the phase I CaDAnCe-101 trial.

CAR T therapy may not work as well in CLL due to T-cell dysfunction, however CAR T trials reveal some patients achieve very durable responses. In the TRANSCEND CLL trial, liso-cel resulted in an ORR of 44% and a CR rate 20% in 50 patients with mostly double-refractory CLL/SLL. CAR T may be an appealing alternative to transplant for R/R CLL patients who can tolerate the toxicities associated with the therapy. Promising early data for bispecific antibodies in double-exposed cohorts suggests this therapy may be a more feasible and well-tolerated option for patients in Canada.



Primary Therapy for Mantle Cell Lymphoma in 2025

DR. JOHN KURUVILLA

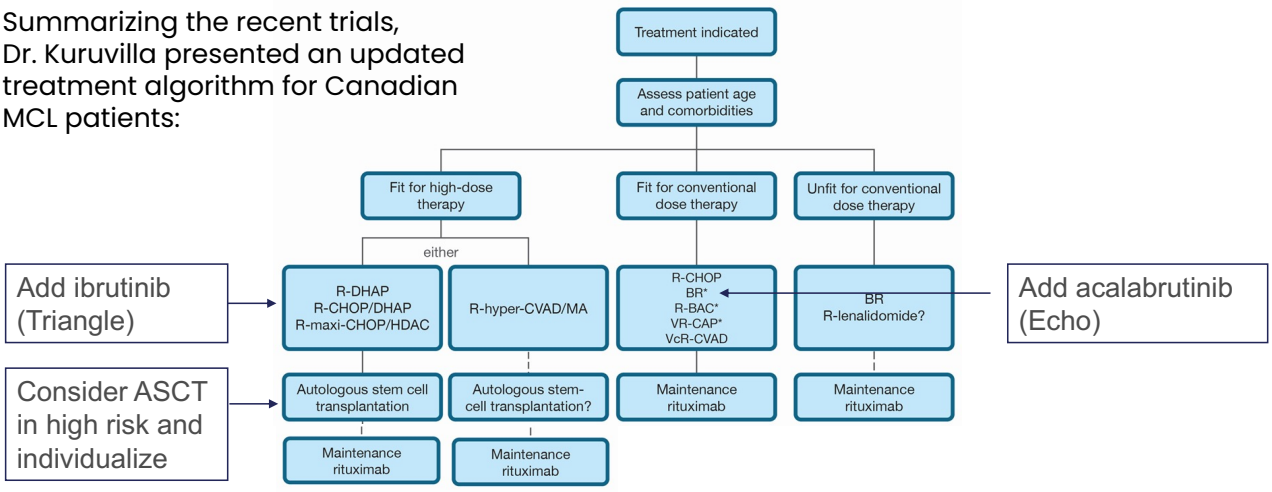
There has been a rapid evolution in the treatment landscape for MCL in recent years, as BTK inhibitors have moved from the R/R setting into frontline therapy. While the SHINE trial found there was no OS benefit and increased infection-related toxicity with the addition of ibrutinib to BR in older MCL patients, the phase 3 ECHO trial, published in *JCO* this year, demonstrated improvement with BTK inhibitor therapy in the frontline. The ECHO trial evaluated BR with or without acalabrutinib in older MCL patients and demonstrated a median PFS improvement of 17 months with the addition of the newer BTK inhibitor. Approximately 27% of patients were ≥75 years old, 13% of patients had blastoid/pleomorphic histology and most patients had an intermediate or high-risk MIPI score. The rates of treatment-emergent adverse events and deaths did not differ across the study and control arms. While cardiac adverse events were similar across both arms, grade ≥3 infections were 41% in the treatment arm, compared to 34% in the control arm. The ECHO study raises the question of whether a treat-to-progression approach is appropriate for BTK inhibitor therapy frontline setting.

In younger, transplant-eligible populations, the TRIANGLE study established a 12% improvement in failure-free survival with the addition of ibrutinib to conventional chemotherapy, with or without transplantation. The trial raises the question of the role of transplantation in the era of BTK inhibition, as there was no OS benefit with the addition of transplant to frontline BTK inhibitor therapy. However, subgroup analyses point toward a possible benefit with continued transplant among high-risk patients (high Ki-67 score, blastoid morphology, or high P53 expression). This benefit should be balanced with toxicity considerations. Dr. Kuruvilla noted that 54% of patients who received ibrutinib and ASCT developed ≥grade 3 blood and lymphatic system disorders, compared to 28% in the chemotherapy and ibrutinib arm and 23% in the chemotherapy and transplant arm. The infection rate was also significantly higher in the transplant and ibrutinib arm, compared to the other two treatment groups. Toxicities were higher in older patients.

Emerging data from the ECOG-ACRIN/BMT-CTN study suggest that MRD negativity after induction may help identify patients who can safely omit

SUMMARY: Evolving frontline treatment of MCL (in Canada)

Summarizing the recent trials, Dr. Kuruvilla presented an updated treatment algorithm for Canadian MCL patients:



transplantation without compromising OS or PFS. However, longer follow-up is needed, as 3-year data may not demonstrate the longer-term benefit of transplant. Early data also suggests the benefit of transplant for patients who are MRD-positive. The challenge in Canada is that MRD-guided strategies are limited by assay availability (the clonoSEQ assay is not yet available in Canada).

Chemotherapy-free combinations, including venetoclax-R2, ibrutinib-R and acalabrutinib-venetoclax-rituximab, are showing encouraging results, but Dr. Kuruvilla cautioned the studies are small phase 1/2 studies that may be skewed by selection biases. In the ENRICH trial, ibrutinib plus rituximab was superior to R-CHOP in previously untreated older MCL patients. However, a subgroup analysis suggested ibrutinib-rituximab may not provide benefit compared to standard BR therapy.

Overall, frontline BTK inhibitor therapy has demonstrated both efficacy and safety across age groups, while transplant should be used more selectively and limited to high-risk disease.

Management of the Limited Stage Hodgkin Lymphoma Patient in 2025

DR. MICHAEL CRUMP

Dr. Crump presented data from his centre showing that the outcomes post-transplant were poor in the chemotherapy era, with a median OS of 23 months. However, recent data show that BV, nivolumab, and pembrolizumab resulted in 5-year survival rates of 41%, 71%, and 71%, respectively, in heavily pretreated and transplanted patients. These successes provide a rationale for moving novel agents into earlier lines of therapy.

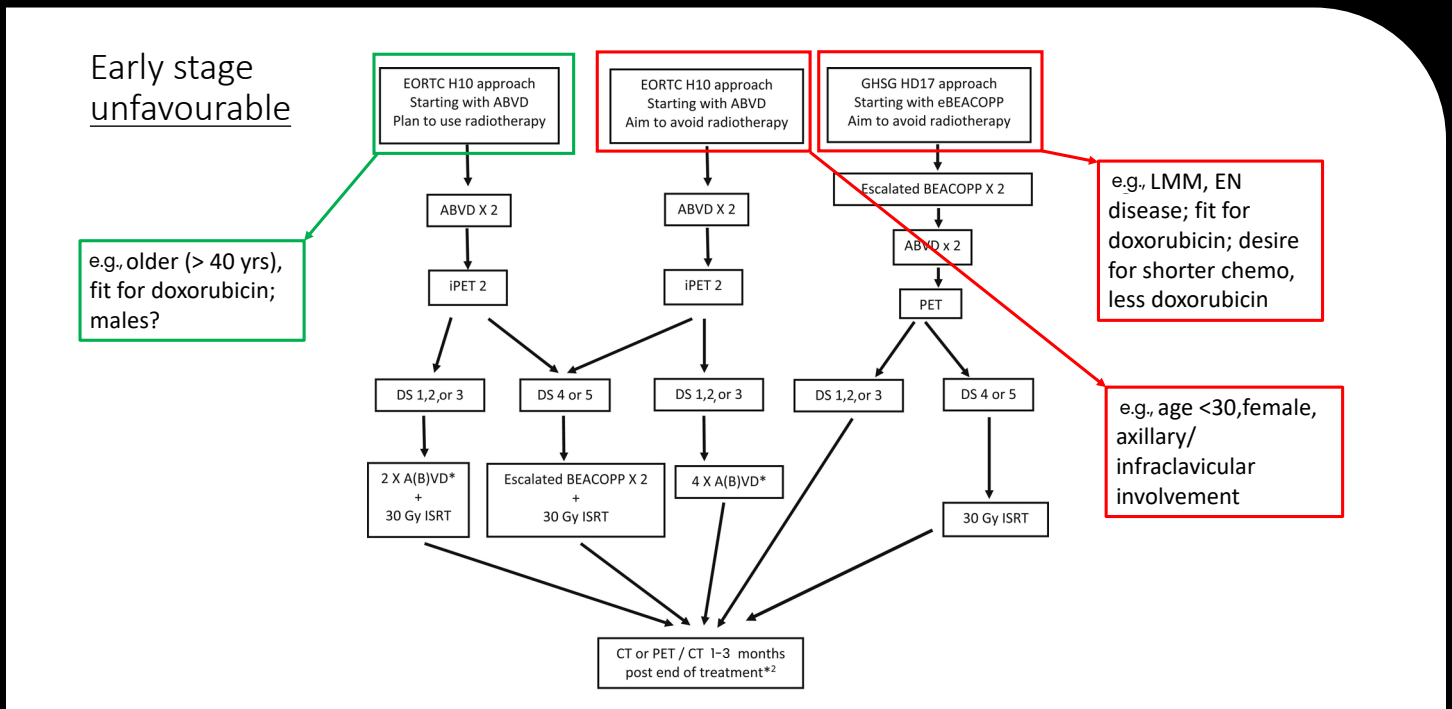
PET-guided therapy is important to frontline management, allowing treatment de-escalation in patients achieving PET-negativity. Dr. Crump emphasized all patients at his centre receive PET-guided therapy, but this doesn't occur at all centres in Canada.

Discussing the risk of breast cancer in patients undergoing cHL therapy, Dr. Crump presented a study published in *JCO* in 2024 that demonstrated doxorubicin-based chemotherapy is associated with an increased risk of breast cancer, with a dose-mediated effect, including among patients who do not receive radiation. However, an Ontario study presented at ASH 2024, was unable to replicate this data. That study showed increased breast cancer risk in cHL survivors with chest radiotherapy, but no difference in breast cancer risk across low- and high-dose doxorubicin groups. Longer follow-up data may be needed to show a deleterious effect of doxorubicin.

Lessons from PET-adapted early-stage cHL trials, including the EORTC H10 and GHSG HD16 studies, include that the omission of radiation in patients responding to two cycles ABVD chemotherapy results in inferior PFS compared to combined modality therapy. In the GHSG HD16 study, the 5-year PFS rate was 85.9% in the PET-guided arm versus 92.8% in the combined modality arm.

However, the GHSG HD16 study found that, in early-stage unfavourable disease, the omission of radiotherapy in patients with PET-negativity after two cycles of escalated BEACOPP and two cycles of ABVD did not negatively affect PFS outcomes, suggesting radiotherapy can be avoided in this patient population.

Turning to novel frontline therapies, Dr. Crump reviewed pivotal phase 3 trials evaluating BV and



nivolumab in advanced-stage cHL. In ECHELON1, patients were randomized to brentuximab vedotin and AVD versus ABVD, while SWOG 1826 compared nivolumab and AVD versus BV-AVD. Both reported PFS benefit with the addition of novel therapies. A number of pilot studies have evaluated the addition of BV to AVD in patients with limited stage Hodgkin lymphoma, both in early unfavourable and early favourable disease.

A Memorial Sloan Kettering study of BV-AVD in predominantly high-risk, bulky cHL demonstrated excellent outcomes, with an 87% PET-negativity rate after four cycles and comparable PFS across radiation subgroups, including patients receiving no radiotherapy. The BREACH trial similarly demonstrated high PET-negativity response rates with BV-AVD (82.3% compared to 75% in the ABVD arm) and PFS improvement. Neutropenia rates were similar across both arms, however, peripheral neuropathy was higher in the BV-AVD arm.

Similarly, the GHSG NIVAHL study found durable CRs with nivolumab and AVD, whether administered together or sequentially and minimal toxicity, including a 15% rate of hypothyroidism and no cardiac events above grade 1. There were no toxicity differences between sequential and concomitant therapies. Looking ahead, biomarkers such as circulating tumour DNA and baseline total metabolic tumour volume may further refine risk-adapted therapy.

Primary Mediastinal Large B-cell Lymphoma

DR. KIERON DUNLEAVY

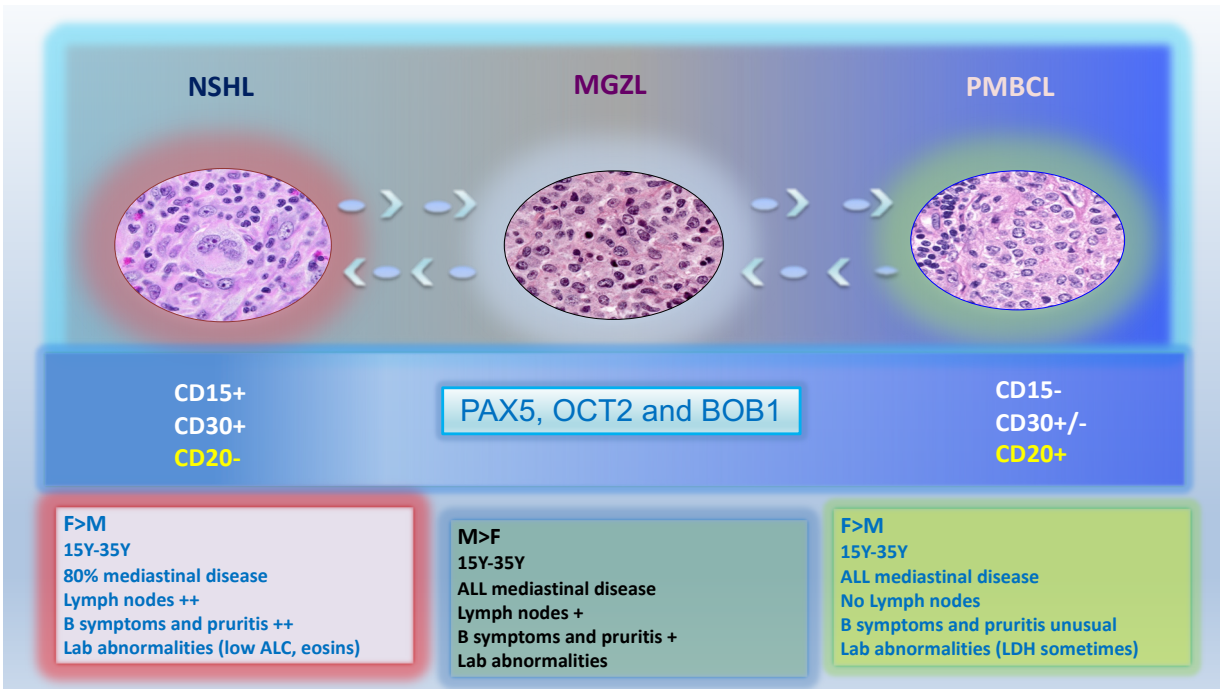
PMBCL is more common in females than males, and is most commonly diagnosed between ages 15 to 35. Due to similar pathological features, the condition can be misdiagnosed as nodular sclerosis Hodgkin lymphoma or mediastinal gray zone lymphoma. Dr. Dunleavy encouraged physicians to carefully consider the clinical presentation when making a diagnosis of PMBCL.

DA-EPOCH-R is widely used as a first-line therapy for PMBCL. Dr. Dunleavy presented three retrospective studies demonstrating the regimen is associated with high event-free survival and OS rates in PMBCL. The multicentre retrospective LYSA study of 313 patients examined three regimens and found that R-ACVBP and R-CHOP-14 demonstrated superior PFS outcomes, compared to R-CHOP-21. A study published in *Blood* in 2021 assessed 159 patients with PMBCL and concluded that patients with Deauville 1-3 scores had excellent outcomes, without radiotherapy, while patients with Deauville 5 scores (72% of whom had radiotherapy) had a poorer prognosis.

The IELSG-37 study, published in 2024 in *JCO*, evaluated the safety of omitting consolidation radiotherapy in PMBCL patients who achieved a complete metabolic response after immunochemotherapy. Researchers assessed 530 patients randomly assigned to either observation or radiotherapy and determined that there was no added advantage of radiotherapy, with both groups showing similar OS rates. A sub-analysis found the R-CHOP-21 regimen yielded an inferior metabolic response compared to more intensive regimens, but this finding should be interpreted cautiously due to small numbers and non-randomization. Similarly, a meta-analysis of observational data published in *Haematologica* in 2024 demonstrated better outcomes in patients who received dose-intensive approaches versus standard chemoimmunotherapy.

Dr. Dunleavy emphasized the need for caution when interpreting end-of-treatment Deauville score results, pointing to a 2018 study in *Haematologica* that found 17 of 18 patients with a Deauville score of 4 and four of eight patients with a Deauville score of 8 did not have treatment failure.

Novel therapies for PMBCL include anti-CD19 CAR T therapy, bispecific T-cell engagers and



immune checkpoint inhibitors. Pembrolizumab was approved for R/R PMBCL after the KEYNOTE-170 trial demonstrated meaningful response rates, with a CR rate of 21% and a 4-year PFS rate of 33%. The CheckMate 436 phase 1/2 study, which included 30 patients with R/R PMBCL, found nivolumab in combination with BV resulted in an ORR of 73% and a 37% CR rate. Demonstrating the real-world effectiveness of axi-cel, Dr. Dunleavy presented a 2021 study of 33 patients treated with axi-cel that showed the 2-year PFS rate for was 64%.

This phase 3 ANHL 1931 trial, assessing the addition of nivolumab in newly diagnosed PMBCL patients, will be important to watch. The study includes molecular testing to evaluate if certain molecular subtypes benefit more from the addition of nivolumab.

While recent studies demonstrate the safety of omitting radiotherapy, Dr. Dunleavy concluded his presentation by emphasizing that radiotherapy can be curative for post-chemoimmunotherapy PMBCL patients with limited disease confined to the mediastinum and within a radiation field.

Secondary Immunodeficiency in Hematologic Malignancy: What to Do?

DR. JEANNIE CALLUM

Dr. Callum explained there are ethical issues with immunoglobulin replacement therapy, including that the therapy costs more than $30,000 per patient and there are controversies surrounding paid plasma donation in the U.S. Much of the immunoglobulin used in Canada is imported from the U.S.

While guidelines on the use of immunoglobulin differ, Dr. Callum recommended the 2022 AAAAI Primary Immunodeficiency and Altered Immune Response Committees guideline, which recommends patients with IgG <150 mg/dL receive a 6 to 12-month immunoglobulin trial, followed by reassessment. Patients with a history recurrent or severe infections who meet additional criteria may also be considered for an immunoglobulin therapy. Patients who don't meet the AAAAI criteria but have a history of recurrent or severe infections should receive prophylactic antibiotic therapy. Approximately 20% of this latter group will ultimately require escalation to immunoglobulin.

In Ontario, immunoglobulin funding is limited to patients who have had a history of infections and serum IgG less than the lower limit on two occasions as well as one of the following:

- One invasive or life-threatening infection in the last 12 months
- Recurrent, severe infections
- Clinically active bronchiectasis confirmed by radiology
- Assessment by an immunologist indicating a significant antibody defect

The data informing the use of immunoglobulin replacement therapy is very limited. The evidence includes three small randomized controlled trials from the 1980s and 1990s, enrolling a total of 262 patients with CLL or MM, as well as small observational studies. A systematic review published in *Blood Advances* in 2023 found that IGRT versus no prophylactic therapy reduced infections but had no effect on all-cause mortality. The PILOT study of the RATIONAL study enrolled patients with an IgG level <4 g/L or an IgG level below the lower limit of the reference range (excluding paraprotein) and a history of recurrent or severe bacterial infections. The study randomized patients 2:1 to antibiotic versus immunoglobulin therapy and enrolled more than 60 patients. The rate of discontinuation was similar across both groups. The data showed severe confirmed infections were numerically less frequent in the antibiotic arm (57% versus 86%), and mortality was lower (2.4% vs. 9.5%).

The TEAMM trial of MM chemotherapy determined that IgG recovered in 60% of patients, none of whom received immunoglobulin replacement therapy, by 12 months. Therefore, it may be reasonable to trial stopping immunoglobulin replacement therapy at 1 year.

Observational data underscore inappropriate immunoglobulin use. In an Australian CLL cohort, 12% received immunoglobulin replacement, with one-quarter maintained on immunoglobulin therapy for over 5 years. Prescriptions quadrupled over 14 years, despite rising infection rates and no survival benefit. A European audit of MM patients found only 24% of immunoglobulin prescriptions met eligibility criteria.

Clinicians can choose between IVIG and SCIG. Weekly SCIG achieves more stable IgG trough levels, though clinical differences in infection rates are minimal. A new monthly SCIG formulation (HyQvia) offers improved convenience with similar safety results. Dr. Callum suggested selecting weekly SCIG versus HyQvia, based on patient preference. Dr. Callum added that dose-adjusting by height and weight is mandatory in Canada, and she strongly recommended the use of an immunoglobulin dose calculator.

Cost is an important consideration. IVIG is thousands of dollars more expensive than SCIG and immunoglobulin replacement therapy costs approximately $30,000 more in total compared to antibiotic prophylactic therapy.

To address the evidence gap, the RATIONAL platform trial will evaluate antibiotics versus immunoglobulin therapy with three randomized arms, as outlined below. This is an important trial to guide the ethical stewardship of immunoglobulin therapy.

RATIONAL-PT

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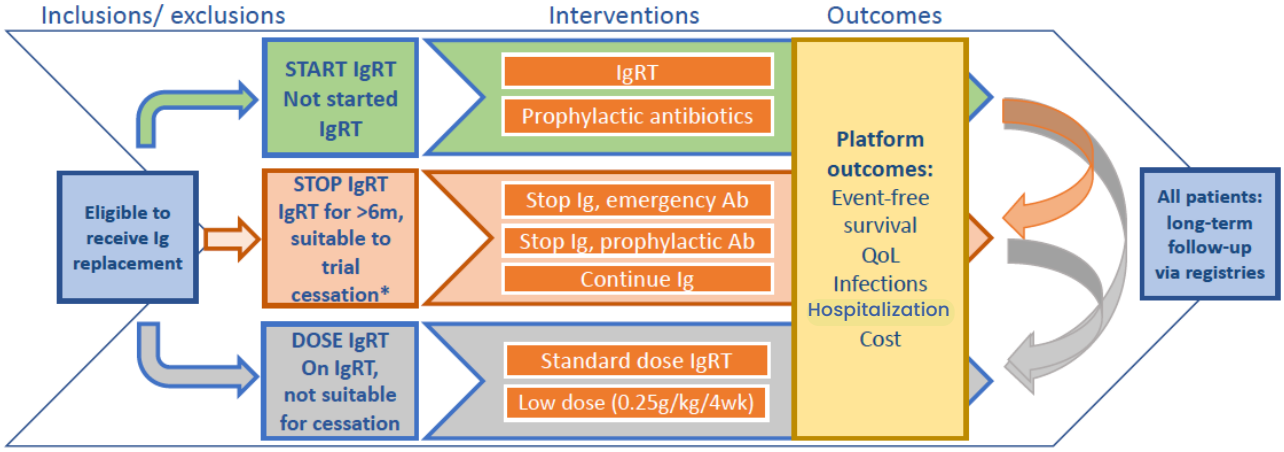

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