Canadian Hematology Today 2025 Rising Stars Conference

Event Summary

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In This Report

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Acronyms

ABVD	DOXORUBICIN, BLEOMYCIN, VINBLASTINE, DACARBAZINE
AML	ACUTE MYELOID LEUKEMIA
ASCO	AMERICAN SOCIETY OF CLINICAL ONCOLOGY
ASH	AMERICAN SOCIETY OF HEMATOLOGY
BEACOPP	BLEOMYCIN, ETOPOSIDE, DOXORUBICIN, CYCLOPHOSPHAMIDE, VINCRISTINE, PROCARBAZINE, PREDNISONE
BrECADD	BRENTUXIMAB VEDOTIN, ETOPOSIDE, CYCLOPHOSPHAMIDE, DOXORUBICIN, DACARBAZINE, DEXAMETHASONE
BV-AVD	BRENTUXIMAB VEDOTIN, DOXORUBICIN, VINBLASTINE, DACARBAZINE
CAR	CHIMERIC ANTIGEN RECEPTOR
CDA	CANCER DRUG AGENCY
cHL	CLASSICAL HODGKIN LYMPHOMA
CLL	CHRONIC LYMPHOCYTIC LEUKEMIA
CR	COMPLETE RESPONSE
CRS	CYTOKINE RELEASE SYNDROME
DPd	DARATUMUMAB, POMALIDOMIDE, DEXAMETHASONE
DPT	DIPHTHERIA, PERTUSSIS, TETANUS
DVd	DARATUMUMAB, BORTEZOMIB, DEXAMETHASONE
EHA	EUROPEAN HEMATOLOGY ASSOCIATION
ELN	EUROPEAN LEUKEMIANET
EMA	EUROPEAN MEDICINES AGENCY
ET	ESSENTIAL THROMBOCYTHEMIA
FDA	FOOD AND DRUG ADMINISTRATION
GCSF	GRANULOCYTE COLONY-STIMULATING FACTOR
HPV	HUMAN PAPILLOMAVIRUS
ICANS	IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME

Acronyms con't

IEC-HS	IMMUNE EFFECTOR CELL-ASSOCIATED HEMOPHAGOCYTIC SYNDROME
IgG	IMMUNOGLOBULIN G
IMiD	IMMUNOMODULATORY DRUG
IPI	INTERNATIONAL PROGNOSTIC INDEX
IVIG	INTRAVENOUS IMMUNOGLOBULIN
MM	MULTIPLE MYELOMA
MPN	MYELOPROLIFERATIVE NEOPLASM
MRD	MINIMAL RESIDUAL DISEASE
ORR	OVERALL RESPONSE RATE
OS	OVERALL SURVIVAL
PFS	PROGRESSION-FREE SURVIVAL
PV	POLYCYTHEMIA VERA
R-CHP	RITUXIMAB, CYCLOPHOSPHAMIDE, DOXORUBICIN, PREDNISONE
RCHOP	RITUXIMAB, CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE, PREDNISONE
R/R	RELAPSED/REFRACTORY
RSV	RESPIRATORY SYNCYTIAL VIRUS
SCIG	SUBCUTANEOUS IMMUNOGLOBULIN
ULN	UPPER LIMIT OF NORMAL
VZV	VARICELLA-ZOSTER VIRUS

Medical minds meet here.

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Welcome and Opening Remarks

DR. ALISSA VISRAM

Alissa welcomed everyone to the meeting and introduced the meeting objectives:

- Provide current perspectives and disease management insights for early-in-practice clinicians
- 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
- Respond to emerging professional needs for specific and in-depth information on the latest therapies for hematologic disease in the Canadian market

Bispecific Antibody Therapy: Practical Management in 2025

DR. RICHARD LEBLANC

There are three Health Canada-approved bispecific antibodies: elranatamab and teclistamab, which target B-cell maturation antigen (BCMA), and talquetamab, which targets GPRC5D. Linvoseltamab was approved by the FDA and EMA this year. Teclistamab is the only bispecific antibody that is publicly reimbursed in Canada.

The MAJESTEC-1 trial evaluating the efficacy and safety of teclistamab followed patients with a median of five prior lines of therapy and poor prognostic factors (17% of study participants had extramedullary disease and 26% had a high-risk cytogenetic profile at baseline; 78% were triple-class refractory). Results presented at ASCO 2024 demonstrated the ORR was 63% after a median follow-up of 30 months, with 43% of patients achieving a CR or better. The median PFS was 11.4 months, and the median OS was 22.2 months.

Summarizing the safety results, Dr. LeBlanc noted that the CRS rate in MAJESTEC-1 was 72%. One patient who had concurrent pneumonia developed grade 3 CRS. Headache occurred in 8.5% of patients and 3% of patients developed ICANS, all of which were grade 1 or 2 and resolved with therapy. Infections were frequent. Dr. LeBlanc noted that the rate of grade 3 infections for patients on bispecific antibodies is 3% per month.

The clinical management of grade 1 CRS occurring in patients taking teclistamab typically involves a watch-and-wait approach. Dr. LeBlanc said he routinely provides a single dose of tocilizumab at the time of diagnosis, although this is not an established practice across Canada. Tocilizumab should always be administered, however, in the case of a sustained fever. For grade 2 CRS, tocilizumab should be administered every 8 hours; dexamethasone may be needed if there is no improvement within 24 hours after the initiation of tocilizumab.

For the treatment of grade 1 and 2 ICANS that is concurrent with CRS, the standard CRS approach is followed. Non-sedating seizure prophylaxis should be considered for grade 1 ICANS and is recommended for grade 2 ICANS. Close monitoring is recommended for grade 2 CRS, and a neurology consultation should be considered. When ICANS occurs non-concurrently with CRS, dexamethasone therapy is typically adequate.

Noting infection is a major concern with bispecific therapy, Dr. LeBlanc shared the International Myeloma Working Group (IMWG) consensus guidelines on prophylactic management.

INFECTIONS – BASED ON IMWG CONSENSUS

	Agents	Timing	Additional comments and recommendations
Antiviral: **- VZV** **- Hepatitis B** **- CMV**	- Acyclovir or valacyclovir - Entecavir (if at risk of reactivation) - CMV PCR at start and if positive consider monitoring; local guidelines	Throughout treatment	Continue for 3 months off treatment or until CD4 cell count >200/μL
Pneumocystis Jirovecii	Trimethoprim/sulfamethoxazole, pentamidine or atovaquone	Throughout treatment	Continue until CD4 cell count >200/μL
Antibacterial	Local guidelines or quinolone	Neutropenia (consider adding G-CSF ideally not during the first cycle)	Bacterial infection highest in first few cycles during neutropenia or if prolonged steroids needed
Antifungal	Local guidelines or azole	Neutropenia (consider adding G-CSF ideally not during the first cycle)	Consider during prolonged neutropenia or steroid use
Polymicrobial	IVIg or s.c Ig	For IgG level <4 g/L	Hypogammaglobulinemia expected throughout treatment; continue even off therapy for IgG 4 g/L

He noted that antibacterial and antifungal prophylaxis are rarely needed, but quinolone antibiotics and antifungal prophylaxis should be used for patients with grade 4 neutropenia that lasts 7 days or more (prophylaxis can be discontinued when neutropenia resolves). In contrast to the IMWG guidelines, a 2025 paper by Banerjee et al in *Blood Advances* encourages the use of IgG at the time of initiation of a bispecific antibody.

At Maisonneuve-Rosemont Hospital, bispecific antibodies are administered on an outpatient basis. Patients must stay within 60 minutes of the hospital and have 24/7 caregiving support for the first 10 days of treatment. Patients must demonstrate an ability to connect virtually with the clinic and are contacted twice daily by a nurse and once by a doctor for the first 10 days. All patients are provided with dexamethasone and instructed to take 10 mg in the case of fever, abnormal vital signs or neurological symptoms. Prophylactic tocilizumab is administered before the first step-up dose. In 28 patients treated on an outpatient basis at Maisonneuve-Rosemont Hospital, the ORR was 71% and the rate of CRS was 2%.

Dr. LeBlanc highlighted that ongoing trials suggest that, in the future, bispecific antibodies will be used earlier and in combination. For example, the MAJESTEC-3 trial of teclistamab and daratumumab demonstrated improved OS in comparison with DPd or DVd.

CAR T-cell Therapy Long-term Toxicity Management in 2025

DR. CHRISTINE CHEN

Dr. Chen discussed the long-term management of toxicities following CAR T-cell therapy, emphasizing that as outcomes improve, attention must shift toward survivorship. She noted that the ZUMA-1 trial demonstrated a 5-year OS rate above 40%, suggesting the possibility of cure.

Real-world data from nine centres involving 475 patients found no new CRS and only one ICANS event beyond day 14. Although CRS and ICANS are rare after the acute phase, Dr. Chen highlighted the importance of recognizing IEC-HS, a delayed hyperinflammatory complication. This syndrome, which resembles CRS, may present months later and typically manifests with new or worsening cytopenia, transaminitis, coagulopathy with low fibrinogen, and marked hyperferritinemia (with ferritin levels at least 2X ULN). She recommended ferritin and fibrinogen screening for any patient with suspected IEC-HS, emphasizing that early treatment is very important.

Late-onset neurologic effects are another concern, particularly with the B-cell maturation antigen (BCMA)-targeted cilta-cel therapy. Parkinsonian movement disorders, cranial nerve palsies, and peripheral neuropathies may appear several months up to a year after infusion. Dr. Chen noted that patients with high disease burden and high peak absolute lymphocyte counts during the first month are at greater risk. At her hospital, patients' lymphocyte counts are monitored between 7 to 14 days post CAR T-cell infusion and patients whose counts rise above 3 X 10^3/uL receive pre-emptive dexamethasone.

Prolonged neurocognitive and psychiatric dysfunction, which can last for many months and even years, is also common. Patient-reported data from MD Anderson shows that between 1 to 3 months post CAR T-cell therapy, 15% of patients reported disturbed sleep and 23% of patients reported problems with concentration.

Cytopenia is one of the most frequent late effects of CAR T-cell therapy. The ZUMA-1 trial demonstrated 11% of patients had grade ≥3 neutropenia and 7% had grade ≥3 thrombocytopenia at day 90. Dr. Chen described three neutrophil recovery patterns: a rapid-recovery group, a biphasic group with a second decline at 4 to 6 weeks, and an aplastic group with prolonged neutropenia that typically lasts until the third month post-CAR T-cell therapy. The aplastic phenotype is particularly worrisome, as patients in this group are often resistant to GCSF therapy and prone to severe infections. The aplastic pattern is linked to inferior survival. The CAR-HEMATOTOX score can help to identify those at risk of an aplastic pattern.

Dr. Chen shared the infection prophylaxis approach at her hospital:

INFECTION PROPHYLAXIS

Type	Medication	Start and Duration
Viral	**Valacyclovir** 500 mg PO BID Alternative: **Acyclovir** 400mg PO BID	Start at time of lymphodepleting chemotherapy, and continue for one year
Bacterial	**Ciprofloxacin** 500 mg PO BID Alternative: **Levofloxacin** 500 mg PO daily	Start on Day 0 and continue until ANC greater than 1.0
Fungal	**Fluconazole** 400 mg PO daily	Start on Day 0, and continue until ANC greater than 1
Pneumocystis Jiroveci Pneumonia (PJP)	**Septra** DS 1 tablet (800 mg/160 mg) PO on M,W,F Alternatives if Septra intolerant: • **Atovaquone** suspension 1500 mg =10 ml PO daily (if Septra allergy) • **Pentamidine** 300mg inhaled once monthly	Start at time of lymphodepleting chemotherapy (with fludarabine), and continue for one year. During acute CAR T period, may hold temporarily and resume at Day 30. Consider for longer use if on continued steroid therapy or prolonged neutropenia
Toxoplasmosis	**Septra** DS 1 tablet (800 mg/160 mg) PO daily (note the schedule change from PJP prophylaxis) Alternative: **Atovaquone** 1500mg (10mL) PO daily (if Septra allergy)	Start at time of lymphodepleting chemotherapy and continue for at least one year.

May extend beyond 1 year until CD4 >200 and revaccinated

Quick to stop (effects on gut microbiome) and toxicities (mental health, tendinopathies)

Consider mold coverage (vori or pozaconazole) if heavy steroids or prolonged neutropenia

If cytopenic at Day 30, use atovaquone or inhaled pentamidine

We monitor Igs and CD4/CD19 by flow in blood every 3 months

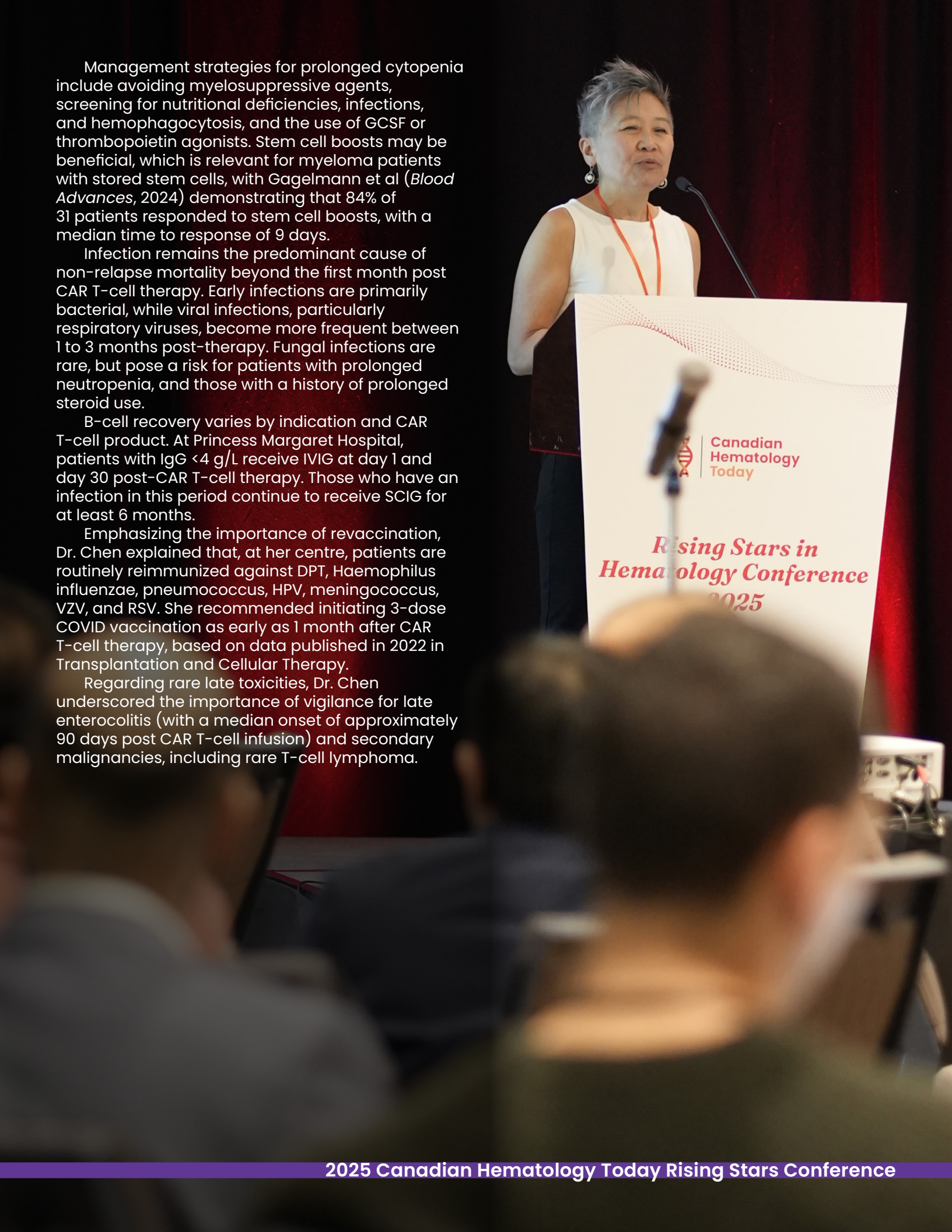
Management strategies for prolonged cytopenia include avoiding myelosuppressive agents, screening for nutritional deficiencies, infections, and hemophagocytosis, and the use of GCSF or thrombopoietin agonists. Stem cell boosts may be beneficial, which is relevant for myeloma patients with stored stem cells, with Gagelmann et al (*Blood Advances*, 2024) demonstrating that 84% of 31 patients responded to stem cell boosts, with a median time to response of 9 days.

Infection remains the predominant cause of non-relapse mortality beyond the first month post CAR T-cell therapy. Early infections are primarily bacterial, while viral infections, particularly respiratory viruses, become more frequent between 1 to 3 months post-therapy. Fungal infections are rare, but pose a risk for patients with prolonged neutropenia, and those with a history of prolonged steroid use.

B-cell recovery varies by indication and CAR T-cell product. At Princess Margaret Hospital, patients with IgG <4 g/L receive IVIG at day 1 and day 30 post-CAR T-cell therapy. Those who have an infection in this period continue to receive SCIG for at least 6 months.

Emphasizing the importance of revaccination, Dr. Chen explained that, at her centre, patients are routinely reimmunized against DPT, Haemophilus influenzae, pneumococcus, HPV, meningococcus, VZV, and RSV. She recommended initiating 3-dose COVID vaccination as early as 1 month after CAR T-cell therapy, based on data published in 2022 in Transplantation and Cellular Therapy.

Regarding rare late toxicities, Dr. Chen underscored the importance of vigilance for late enterocolitis (with a median onset of approximately 90 days post CAR T-cell infusion) and secondary malignancies, including rare T-cell lymphoma.



Sequencing in Relapsed/Refractory Multiple Myeloma in 2025

DR. IRWINDEEP SANDHU

Dr. Sandhu presented version 8 of the CDA algorithm, noting a key change from previous algorithms: treatment options for patients resistant to anti-CD38, IMiD, and proteasome inhibitor therapy are now under review for provincial funding. Increasingly, patients may also be resistant to anti-B-cell maturation antigen (BCMA) therapy.

Emphasizing the importance of considering previous therapies in sequencing, Dr. Sandhu said patients should be considered resistant if progression occurred within 60 days of a previous agent's use. If a therapy was discontinued due to toxicity rather than resistance, retreatment at a lower dose in combination with a novel agent may provide benefit. However, from a practical standpoint, a previously used agent, such as bortezomib or pomalidomide, may not be feasible due to reimbursement limitations.

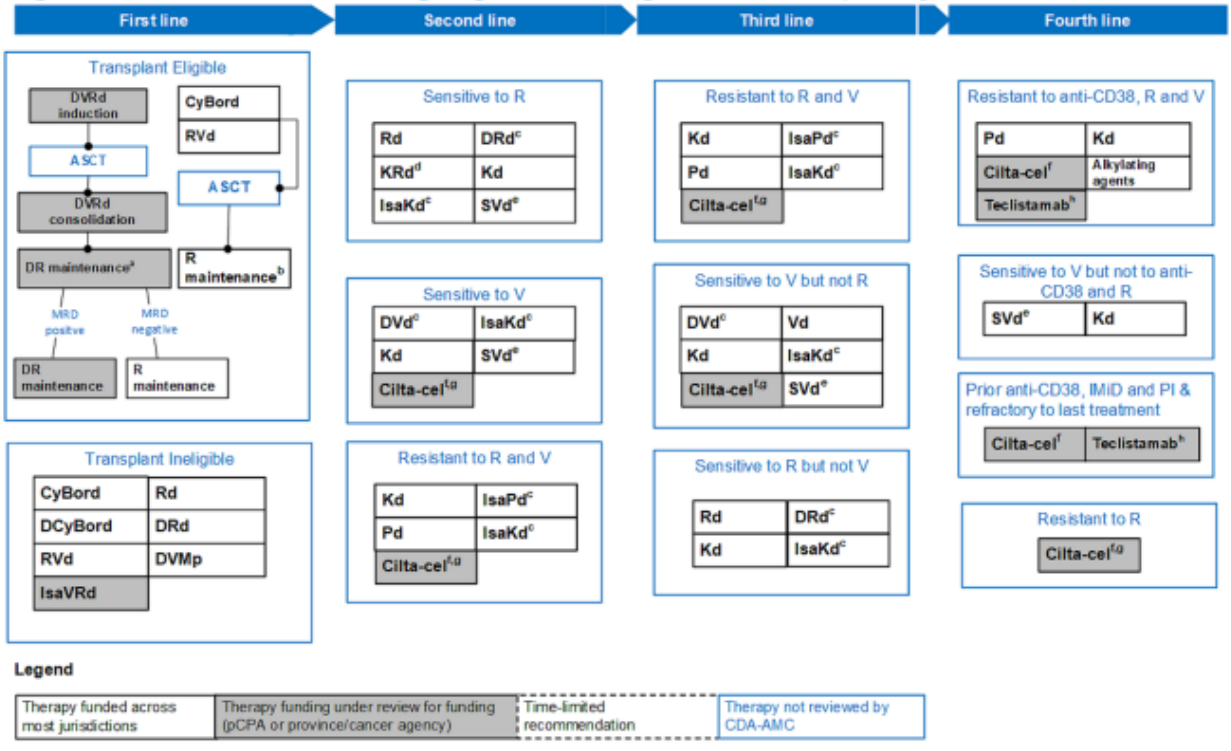
Another key consideration is the patient's most recent line of therapy. Dr. Sandhu advised against repeating a drug class within a 6-month period. He also recommended considering alternating the therapeutic backbone between an IMiD and proteasome inhibitor. If a patient has not been exposed to an anti-CD38 monoclonal antibody, Dr. Sandhu encouraged the early introduction of this therapy in the R/R setting.

Dr. Sandhu also underscored the importance of preserving T-cell health to optimize future CAR T-cell manufacturing, even though cilta-cel is not yet funded for R/R MM patients. At his centre, hematologists have observed inferior responses to bispecific antibody therapy after carfilzomib, and often primary refractoriness, although this association has not been evaluated in the literature.

Tumour burden is another factor to consider in

PROVISIONAL FUNDING ALGORITHM

Figure 1: Provisional Funding Algorithm Diagram for Multiple Myeloma



DR. IRWINDEEP SANDHU

sequencing, as bispecific and CAR T-cell therapies may not be as effective and can be more toxic in patients with a high tumour burden.

Access considerations should also influence sequencing decisions, as MM patients may only have access to one B-cell maturation antigen (BCMA)-targeted agent. While not mentioned on the CDA algorithm, frailty assessment and cytogenetic findings (particularly t(11;14)) can also be decisive treatment factors. Phase 3 data indicate BCL2 inhibitors may offer superior efficacy in patients with the t(11;14) mutation.

Dr. Sandhu concluded by stressing that the treatment approach in R/R MM should be tailored to each individual patient. R/R MM patients have had very variable treatment journeys, dependent on which approved and clinical trial options were available to them at the time of their diagnoses and subsequent relapses. Although most patients are now initiated on quadruplet regimens, it is also possible that R/R MM patients may have been treated solely with lenalidomide and dexamethasone. R/R MM patients may be proteasome inhibitor-sensitive in the second line and possibly even in the third-line setting.

In summary, Dr. Sandhu encouraged his colleagues to consider the patient's previous treatment path, anticipated access to future options, province-specific funding and emerging phase 2/3 data when planning next steps.

2025 Canadian Hematology Today Rising Stars Conference

Approach to Hodgkin's Lymphoma in 2025

DR. MARY-MARGARET KEATING

Hodgkin lymphoma predominantly affects young adults, placing considerations of long-term infertility, secondary malignancies, and other late effects at the forefront. Fortunately, recent years have brought major advances in the management of Hodgkin lymphoma, with improved efficacy and reduced toxicity.

Beginning with late-stage Hodgkin lymphoma, Dr. Keating presented the ECHELON-1 trial, a landmark phase 3 trial that enrolled patients with stage III-IV cHL to evaluate BV-AVD versus ABVD. The BV-AVD regimen resulted in superior 6-year PFS rates (82% versus 75%) and OS (94% versus 89%). The BV-AVD regimen was associated with higher rates of neuropathy and neutropenia while the ABVD cohort had higher rates of pulmonary toxicity. Dr. Keating noted that the BV-AVD regimen is currently funded in Canada for advanced stage cHL.

More recently, the S1826 study compared nivolumab-AVD with BV-AVD in stage III to IV Hodgkin lymphoma. The 2-year PFS for nivolumab-AVD was 92%, compared to 83% in the BV-AVD arm. The nivolumab-based regimen demonstrated favorable tolerability, with less neuropathy and febrile neutropenia, and an 8% rate of immune-related toxicities, which were managed with standard steroids. Nivolumab-AVD represents a new benchmark for the treatment of Hodgkin lymphoma, though it is not yet funded in Canada.

The German HD21 PET-adapted study of BrECADD versus escalated BEACOPP is another recent example of the continued trend toward improved tolerability and preserved efficacy. Following approximately 1,500 patients between ages 18 and 60 with stage IIb-IV disease, the trial demonstrated a 3-year PFS of 94.9% for BrECADD versus 92.3% with escalated BEACOPP. Dr. Keating highlighted the replacement of procarbazine in the BEACOPP regimen with dacarbazine in the BrECADD regimen, explaining procarbazine can lead to early menopause and infertility. While the PFS was the highest reported in advanced stage PFS to date, the treatment-related morbidity was 42% for BrECADD versus 59% for escalated BEACOPP.

Comparing nivolumab-AVD and BrECADD, Dr. Keating summarized that nivolumab-AVD, which was studied in older, comorbid patients, demonstrated slightly lower PFS rates with a better overall safety profile. A benefit of BrECADD is that the treatment duration is 12 to 18 weeks, compared to 24 weeks with nivolumab-AVD. Dr. Keating pointed out that an additional 3 months off of therapy can be especially appealing to young people who may be attending university or planning to start their careers or grow their families.

In Canada, ABVD is currently the therapy of choice for most stage III Hodgkin lymphoma patients. BV-AVD is widely funded for stage IV

THE MESSY MIDDLE: MAKING THE CALL

2, 3 or 4 ABVD ? With or without RT ? ±bleo de-esclation

Clinical Realities	Trade-offs & Philosophy
• Multiple large, RCTs with varied eligibility & PET response criteria • iPET guiding RT and chemo length • All modern strategies → 5-yr PFS > 90 %	• Omission of RT → small (~5 %) PFS penalty but ↓ acute + late toxicity • Practice patterns differ by center, philosophy, and patient preference

ⓘ Every combination (2–4 ABVD, ±RT) works well, the challenge is deciding whose toxicity risk justifies which trade-off

Discussion of RT with multidisciplinary team and patient looking at patient specific short and long term effects

patients but is likely to be replaced in the near future by nivolumab-AVD, due to its excellent tolerability across all subgroups. BrECADD is funded in some Canadian centres, under cost-neutral initiatives, and is expected to replace escalated BEACOPP. For patients older than 60 years, bleomycin toxicity is a major concern, as the available data suggests treatment-related mortality may approach 30% and dose reductions or discontinuations occur in 40% of patients. While sequential BV-AVD and BV-dacarbazine or BV monotherapy are options for older patients, nivolumab-AVD will greatly improve toxicity and efficacy in older patients. Nivolumab-AVD resulted in a 1-year PFS rate of 93% in patients older than 60 years, compared to a 64% 1-year PFS rate with BV-AVD.

In early-stage disease, Dr. Keating emphasized that two to four cycles of ABVD, with or without radiation therapy, is generally highly effective. When to omit bleomycin and radiotherapy depends on practice-specific approaches and patient preferences regarding short-term versus long-term toxicities. The phase 3 HD16 trial in early favourable cHL demonstrated the omission of radiotherapy in patients who were PET-negative after two cycles of ABVD led to lower PFS (86% versus 93%) but had no impact on OS. The HD17 trial in early unfavorable disease showed omitting bleomycin and radiotherapy in patients led to non-inferior outcomes in patients who were PET-negative after two cycles of ABVD, with markedly lower pulmonary toxicity.

Updates on the Management of Myeloproliferative Neoplasm in 2025

DR. VIKAS GUPTA

Dr. Gupta outlined interferon therapy in Canada, new options to treat anemia associated with myelofibrosis, and emerging investigational *CALR*-directed therapies. He noted that the primary goal of therapy in PV and ET is to mitigate the risk of cardiac complications, including myocardial infarction and stroke.

Ropeginterferon's potential disease-modifying activity distinguishes it from older cytoreductive therapies like hydroxyurea. The pivotal PROUD-PV study compared ropeginterferon with hydroxyurea in patients with PV. While short-term hematologic responses were similar, longer-term follow-up showed sustained reductions in Janus kinase (JAK) allele burden with ropeginterferon. The SURPASS-ET phase 3 study tested ropeginterferon in ET patients who were intolerant or resistant to hydroxyurea. The mean JAK2 allele burden reduced from 33.7% to 25.3% over 12 months in the ropeginterferon arm versus no reduction in the anagrelide arm. ET-related major thrombotic and cardiovascular events were significantly lower in the treatment arm, compared to the control arm. The primary endpoint of response defined by the modified ELN response criteria was achieved in 43% of patients in the ropeginterferon arm, compared to 6.0% in the anagrelide arm. These data may support future regulatory submissions for ropeginterferon in ET.

Dr. Gupta highlighted that while the starting dose for ropeginterferon is 100 mcg in the product monograph, the ECLIPSE-PV and EXCEED-ET trials are investigating an alternative regimen that starts with 250 mcg and reaches 500 mcg by the third dose. Dr. Gupta stated that he frequently starts with the 250 mcg dose in his clinical practice.

Three JAK inhibitors (ruxolitinib, fedratinib, and momelotinib) are approved by Health Canada, with approval expected soon for pacritinib. In pivotal trials, all JAK inhibitors similarly improved spleen size and symptoms. The SIMPLIFY-1 head-to-head trial comparing ruxolitinib and momelotinib demonstrated a similar spleen volume response with a somewhat inferior symptom response in the momelotinib arm. Dr. Gupta highlighted, however,

JAK Inhibitors and Cytopenias in JAKi-naïve patients

Grade 3/4 Hematological Toxicity in Selected JAK Inhibitor Therapy Trials

Trial	Study Arm	Grade 3/4 Anemia (%)	Grade 3/4 Thrombocytopenia (%)	Grade 3/4 Neutropenia (%)
COMFORT-1[1]	Ruxolitinib	45.2	12.9	7.1
	Placebo	19.2	1.3	2.0
JAKARTA[2]	Fedratinib[a]	43	17	8
	Placebo	25	9	4
PERSIST-1[3]	Pacritinib	Gr 3 15, Gr 4 2	Gr 3 5, Gr 4 14	Gr 3 -, Gr 4 2
	BAT	Gr 3 12, Gr 4 3	Gr 3 9, Gr 4 3	Gr 3 -, Gr 4 <1
SIMPLIFY1[4]	Momelotinib	5.6	7.0	2.8
	Ruxolitinib	23.1	4.6	4.6

*Data are not from head-to-head trials and are not comparable across trials.
[a]400 mg once daily dose.
BAT, best available therapy; JAK, Janus kinase.
1. Vertovsek S, et al. *N Engl J Med*. 2012;366(9):799-807; 2. Pardanani A, et al. *JAMA Oncol*. 2015;1(5):643-651. 3. Mesa R, et al. *Lancet Haematol*. 2017;4(5):e225-e236;
4. Mesa RA, et al. *J Clin Oncol*. 2017;35(34):3844.

that across the four JAK inhibitor trials, rates of grade 3 and 4 anemia were lowest in the momelotinib arm in the SIMPLIFY-1 trial (5.6% compared to 23% in the ruxolitinib arm). This benefit stems from momelotinib's dual inhibition of JAK1/JAK2 and ACVR1, which reduces hepcidin levels and improves iron availability. The SIMPLIFY-2 trial demonstrated favourable transfusion independence rates at week 24 (43% versus 21%) in patients treated with momelotinib, compared to ruxolitinib.

For anemia unresponsive to epoetin alfa, luspatercept has demonstrated encouraging results. The phase 3 INDEPENDENCE trial enrolled transfusion-dependent myelofibrosis patients treated with a JAK2 inhibitor for 32 weeks. The trial did not meet its primary endpoint of transfusion independence, but it showed numerically and clinically meaningful improvements in transfusion independence favouring luspatercept. The ODYSSEY clinical trial at Princess Margaret is exploring combination therapy with momelotinib and luspatercept to target both early and late stages of erythropoiesis, potentially yielding synergistic benefits for severe anemia.

Immunotherapy clinical trials in Calreticulin (CALR)-mutated MPN represent an exciting area of research. Approaches under investigation include monoclonal antibodies and bispecific T-cell engagers. Preliminary data presented this year at EHA showed that INCA33989 induced rapid normalization of platelet counts in CALR-mutated patients with high-risk ET or myelofibrosis, even at low doses. Among patients who received 400 mg to 2,500 mg of the investigational therapy, 82% achieved a CR. Molecular responses were impressive, with 47% achieving over 20% best reduction in CALR variant allele fraction. Such molecular remissions have not been observed with existing ET therapies, offering hope that MPNs could one day be curable. Dr. Gupta concluded with the prediction that MPNs will be treated very differently in the next 5 years.

Chronic Lymphocytic Leukemia Management in 2025 (Frontline vs Relapse)

DR. CAROLYN OWEN

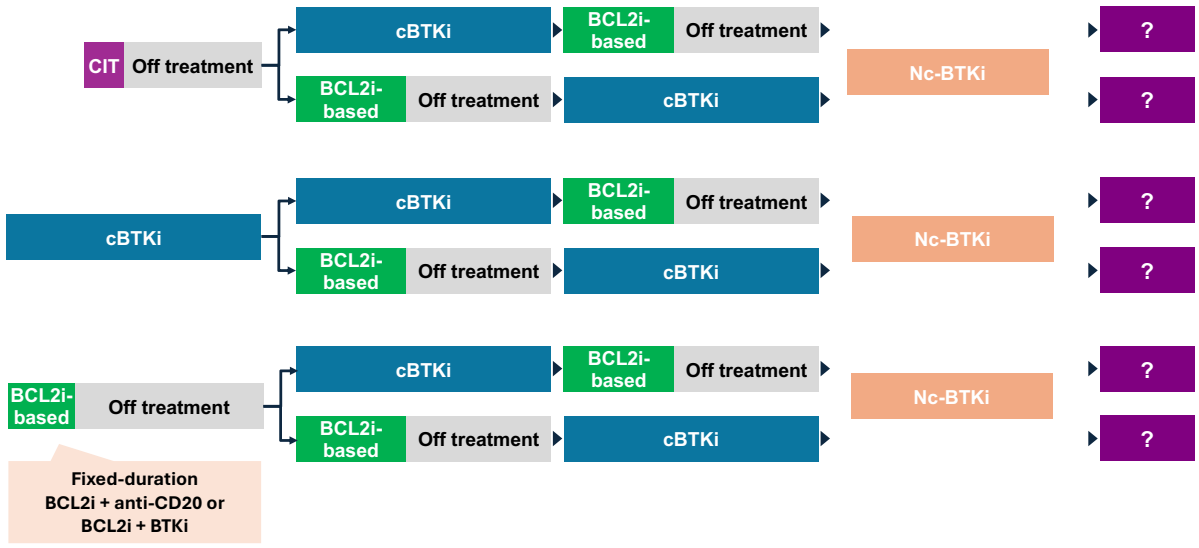
Dr. Owen presented a flow chart of treatment sequencing options in CLL. While a variety of therapeutic options are available in CLL, there is no clear evidence guiding the best treatment pathway.

Discussing Bruton's tyrosine kinase (BTK) inhibitor therapy in the frontline setting, Dr. Owen explained that although ibrutinib is associated with atrial fibrillation, myalgias, and other toxicities, many patients don't experience side effects with BTK inhibitor therapy. The therapy also leads to excellent disease control with a follow-up of the RESONATE-2 study showing disease progression occurred in only 13% of patients with unmutated *IGHV* at 9 years of follow-up. The greatest relative benefit from BTK inhibitors occurs in patients with unmutated *IGHV*, who typically have poorer outcomes with other treatments.

The fixed-duration venetoclax and obinutuzumab combination yields deep remissions, with a 5-year PFS of 63% in "unfit" CLL patients (CLL14) and significantly improved PFS compared to chemoimmunotherapy in young patients (CLL13). While outcomes are relatively inferior for patients with unmutated *IGHV* and *TP53* aberrations, Dr. Owen pointed out that the median time to next treatment or death was 85 months in patients with unmutated *IGHV* and 57 months in patients with *TP53* aberrations. It is therefore appropriate to offer time-limited therapy to unmutated *IGHV* patients. While most hematologists recommend continuous *BTK* inhibitor therapy for patients with *TP53* aberrations (the ALLIANCE study showed no difference in outcomes with ibrutinib for patients with and without *TP53* aberrations), Dr. Owen stressed that venetoclax and obinutuzumab can be appropriate for *TP53*-mutated patients who have significant cardiovascular morbidity or strongly prefer the fixed-duration therapy.

A more recent development is the fixed-duration, all-oral combination therapy of ibrutinib plus venetoclax, which is now funded across Canada. The GLOW trial demonstrated the combination's strong efficacy but reported a small number of fatal cardiac events related to ibrutinib. Dr. Owen said that she favours venetoclax and obinutuzumab over ibrutinib plus venetoclax for this reason and also

TREATMENT SEQUENCING OPTIONS IN CLL



because obinutuzumab is only funded in the first-line setting in many Canadian jurisdictions. Noting that it is not clear if ibrutinib and venetoclax is more beneficial than venetoclax and obinutuzumab in patients with unmutated *IGHV* (based on 2-year follow-up data presented by Niemann et al at ASH in 2022), Dr. Owen explained treatment choice is often influenced by patient factors, including caregiving support, and patient preferences.

Once acalabrutinib and venetoclax is available, the combination is expected to be favoured over venetoclax and obinutuzumab. The AMPLIFY study of acalabrutinib plus venetoclax showed no cardiac deaths, and an OS benefit with the novel combination compared to chemoimmunotherapy (94% versus 86% OS with a median follow-up of 40 months).

For R/R disease, the treatment landscape is equally complex. While older studies of ibrutinib and of venetoclax-rituximab enrolled heavily pretreated, chemo-exposed patients, most current CLL patients have never received chemotherapy. It is unclear how the currently funded therapies for R/R CLL apply to the current patient population. Typically, physicians treat patients who were exposed to fixed-duration therapy in the frontline with either BTK inhibitor therapy, or, in the case of a very long first remission, venetoclax and rituximab. Those exposed to covalent BTK inhibitor in the first line are typically treated with venetoclax and rituximab or indefinite venetoclax.

By contrast, the BRUIN-321 study is relevant to today's R/R CLL population. Noting that pirtobrutinib was just-approved in Canada for patients exposed to a BTK inhibitor therapy and venetoclax, Dr. Owen explained the BRUIN CLL-321 study enrolled patients previously treated with a covalent BTK inhibitor (approximately half of patients were also previously treated with venetoclax). Although median PFS was modest, Dr. Owen highlighted that the median time to next treatment or death was 24 months in the heavily pretreated population.

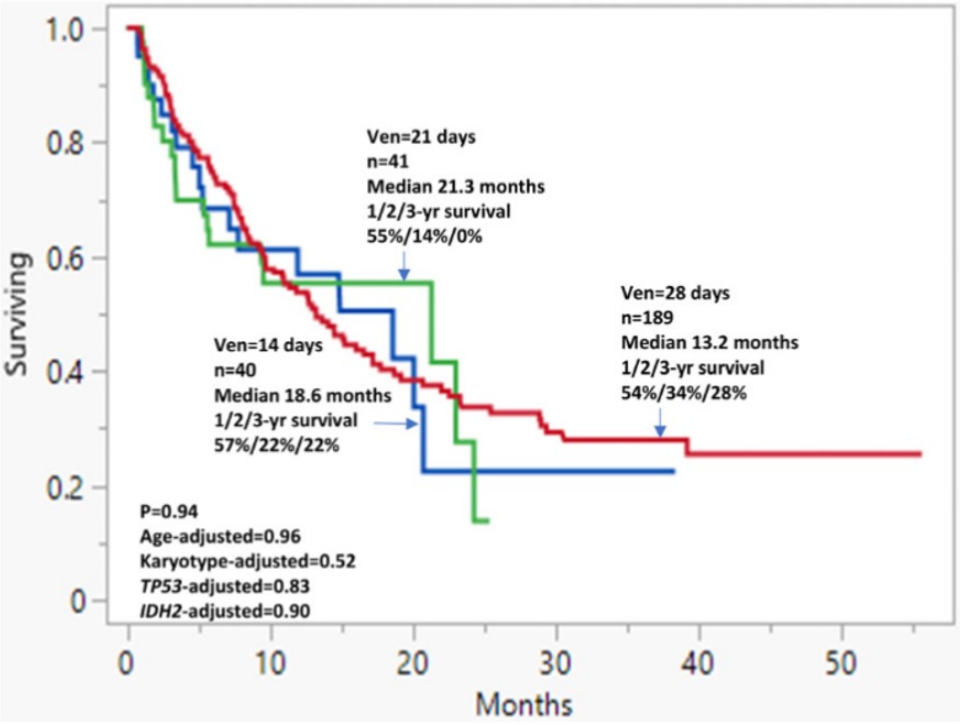
In ongoing trials, BTK degraders have shown impressive responses in patients resistant to both covalent and non-covalent BTK inhibitors. Dr. Owen concluded by noting that, thanks to treatment advances, many patients with CLL can expect near-normal life expectancy, marking a dramatic transformation from the chemotherapy era.

Non-intensive Acute Myeloid Leukemia Therapy: Frontline and First Relapse

DR. KAREN YEE

Frontline lower-intensity therapy for AML can include monotherapy, but most frequently involves venetoclax-based combination therapy. Azacitidine and low-dose cytarabine have limited efficacy and are used infrequently, in patients who are too frail for combination therapy.

Venetoclax and azacitidine are widely prescribed in Canada for treatment-naïve patients. The VIALE-A trial demonstrated improved OS with the combination, compared to placebo and azacitidine. The CR rate for the combination was 67%, versus 29% in the control arm. Responses were durable, with an 18-month duration of CR in the treatment arm, compared to 11 months in the placebo and azacitidine arm. The regimen is, however, associated with high rates of thrombocytopenia and febrile neutropenia. Importantly, long-term follow-up from VIALE-A demonstrates that dose reductions and extended dosing intervals of venetoclax do not appear to impact OS. Additionally, a retrospective study published in 2025 by Willekens et al compared a 7-day course of venetoclax in combination with hypomethylating agents for AML, repeated every 28 days, versus the standard 28-day venetoclax cycle. While the time to response was delayed in patients who received 7-day venetoclax, the



Randomized phase 2 trial of 28-day versus 14-day schedule of VEN + AZA in newly diagnosed AML patients ≥ 60 years (sub-study of the Beat AML Master Trial (NCT03013998))

ORR, durations of response, and OS were similar across both dosing groups. Surprisingly, there was no reduction in the percentage of patients who developed febrile neutropenia. Similarly, a retrospective study by Karrar et al, published in 2024, found no significant differences in OS nor safety events in patients who received 14-day, 21-day or 28-day venetoclax cycles. An ongoing randomized phase 2 trial is comparing 14-day versus 28-day venetoclax regimens.

More recently, Health Canada approved ivosidenib and azacitidine for the treatment of newly diagnosed AML patients with *IDH1* mutations who are not eligible to receive intensive induction chemotherapy. Despite no head-to-head comparisons between ivosidenib and azacitidine versus venetoclax and azacitidine, many physicians opt for the ivosidenib-based regimen for patients with *IDH1* mutations, due to lower rates of neutropenia and thrombocytopenia.

TP53-mutated AML continues to pose a major therapeutic challenge. Recent evidence demonstrates increased remission rates with venetoclax and azacitidine, versus azacitidine alone, in patients with *TP53*-mutated AML, but no improvement in OS. Dr. Yee identified a role for venetoclax for *TP53*-mutated AML patients who are expected to proceed to transplant.

For relapsed or refractory AML, outcomes remain poor. After venetoclax-based therapy failure, several groups, including MD Anderson, have demonstrated that survival is typically under 3 months. Gilteritinib is a lower-intensity therapy approved by Health Canada for patients with R/R AML and a confirmed *FLT3* mutation. The ADMIRAL study showed gilteritinib monotherapy improved OS (1-year OS rates were 36.6% with gilteritinib versus 19.2% with salvage chemotherapy; 3-year OS rates were 15.8% and 10.4%). However, patients previously exposed to other *FLT3* inhibitors have inferior outcomes with gilteritinib, and outcomes are especially poor with gilteritinib in patients who are venetoclax-refractory.

Venetoclax-based combinations are increasingly used off-label as lower-intensity salvage regimens after frontline intensive chemotherapy failure. Retrospective comparisons suggest similar remission rates and transplant eligibility as with intensive salvage regimens but with lower toxicity. Randomized trials are needed to define the optimal approach; in the meantime, Dr. Yee noted that many centres are treating first AML relapses with venetoclax-based therapy.

Relapsed Aggressive B-cell Lymphoma: A 2025 Overview

DR. MICHAEL CHU

With the recognition that not all aggressive B-cell lymphomas carry the same risk, the field is moving toward a more individualized approach to prognosis and therapy. Dr. Chu predicted that, in the next 5 to 10 years, other tools will be added to the IPI to assess risk, including pathologic metrics, functional tumour burden, and MRD testing. AI is likely to play a major role in determining the risk of various clinical, molecular, and tumor factors as well as determining individual therapeutic paths based on each patient's unique combination of risk factors.

Major institutions, including MD Anderson, are developing automated tools to calculate metabolic tumour volume, which could provide a more precise alternative to traditional Deauville scoring, once validated in clinical trials. In addition, ctDNA as a measure of MRD could be used to assess treatment response and potentially detect relapse earlier than radiographic or clinical evaluation. The challenge is that clonoSEQ is very expensive, costing about the same as a PET scan. Dr. Chu opined the use of ctDNA, and mutational analyses may depend on individual lab infrastructure and funding.

Transitioning to treatment, Dr. Chu shared data demonstrating inferior survival outcomes of patients with ABC subtypes, prompting efforts to improve frontline therapy. The POLARIX trial, which evaluated R-CHP plus polatuzumab vedotin versus RCHOP, achieved a notable improvement in 2-year PFS in the non-GCB population (84% versus 60% with RCHOP). While not yet funded in Canada, Pola-R-CHP is expected to become the new standard of care for this subgroup.

Ongoing trials continue to explore targeted combinations for non-GCB DLBCL, including those involving lenalidomide, acalabrutinib, and tafasitamab. PET-adapted early consolidation may also improve outcomes in R/R aggressive B-cell

Risk factors	High-risk features	Survival	References
Clinical factors	IPI = 3; high-intermediate	5-y OS (43%-67%)	10,13
	IPI = 4, 5; high risk	5-y OS (26%-53.9%)	10,13
	R-IPI = 3 (3-5 risk factors)	4-y OS (55%-60.9%)	11,13
	NCCN-IPI = 6-8; high risk	5-y OS (33%-49%)	12,13
Biological factors	COO = ABC subtype	5-y OS (35%-56%)	14,15
	COO = type 3 unclassifiable	5-y OS (39%-62%)	14,15
	DEL	5-y OS (30%-40%)	16-18
	DHL/THL	2-y OS (38%-82%)	19-22
	DHTsig$^+$	5-y TTP 57%	23
Biological factors: molecular taxonomy	MCD/C5/MYD88	5-y OS (26%-60%)	24-26
	N1	5-y OS (27%-40%)	24,27
	A53/C2	5-y OS 63% (33%-100%)	24-26
	BN2/C1/NOTCH2	5-y OS 67% (38%-100%)	24-27
	EZB DHTsig$^+$ MYC$^+$	5-y OS (40%-48%)	24-27
Radiomics prognostic factors: baseline and dynamic	ΔSUVmax < 66% at iPET2	2-y OS 54.2%	28
	High TMTV > 328 cm^3 and ΔSUVmax < 66% at iPET2	2-y OS 37.1%	28
	ECOG-PS ≥ 2 and TMTV > 220 cm^3	4-y OS (41%-61%)	29
	High-risk IMIPI	3-y OS 51.5%	30
	High-risk clinical PET model	2-y PFS 48.6%	31
ctDNA: baseline and dynamic	No EMR	2-y EFS 50%	32
	No MMR	2-y EFS 46%	32

lymphoma. The phase 2 ZUMA-12 trial evaluated the early use of axicel in patients with Deauville scores of 4 or 5 after two cycles of RCHOP. Remarkably, for this high-risk population, the ORR was 89% (including a 78% rate of CR) with a 3-year PFS of approximately 75%.

Bispecific antibodies represent an important step forward in therapy for aggressive B-cell lymphoma. Epcoritamab (subcutaneous) and glofitamab (intravenous, preceded by obinutuzumab) are currently available for R/R DLBCL. Dr. Chu emphasized there is no clear evidence supporting the superiority of either bispecific antibody; a retrospective analysis comparing efficacy and safety outcomes could be helpful.

CAR T-cell therapy offers a potential cure but carries significant acute toxicity. The choice between CAR T-cell and bispecific therapy depends heavily on patient age, fitness, and treatment goals. Future therapy may also factor into decision-making. Based on patients who underwent CAR T-cell therapy after glofitamab (STARGLO) and epcoritamab (EPCORE NHL-2), CAR T-cell therapy can be an effective option after bispecific therapy. Dr. Chu noted that a larger study, using correlative data on patients' T-cell health, is necessary to confirm the best sequencing of CAR T-cell and bispecific therapies.

While improving efficacy, recent advances in therapy for R/R aggressive B-cell lymphoma come with new challenges, particularly infection risk. Infection remains the leading cause of non-relapse mortality after CAR T-cell therapy, underscoring the need for vigilant infection monitoring and prophylaxis.

Panel Discussion

Are new-to-practice physicians ready to be a community hematologist after post-graduate year 5? Related to this, do community hematologists tend to subspecialize or does community hematology remain general?

Dr. Keating: I spent the first 5 years of my career as a community hematologist in Dartmouth because of my partner was working in Halifax. While my main focus was benign hematology, I also worked one day a week at the QEII Cancer Centre, where I cared for lymphoma patients and was involved in clinical trials. I think my story shows that you can change from academic to community hematology – you don't have to stay in one box.

Dr. Chen: Academia and community lines are increasingly becoming blurred. For example, Dr. Anglin runs clinical trials and administers bispecific therapies at a community hospital. As a community hematologist, you need to be prepared for your practice to evolve. You may be providing complex cell therapies in the future, for instance. As you become more senior, you will be able to collaborate with your peers to shape the direction of your institution.

Dr. Gupta: Community hospital programs are getting bigger. For example, many community hospitals are caring for acute leukemia patients, either independently or under a shared care model. Princess Margaret Hospital offers short-term, 6-month fellowships for community hematologists who want to adopt a subspecialty practice.

Dr. Chu: I think fellowships can be helpful for both community and academic positions because malignant hematology is so varied, with many different subtypes and unique scenarios. The fellowship is when you start seeing your 'weird or wonderful' cases. In my view, the mentorship and support of a fellowship is a helpful transition to independent practice.

Dr. LeBlanc: After my fellowship, I focused my practice on medical oncology but about five years in, I changed my mind, and I transitioned to focus on myeloma. It's important to know that you can change your mind. Still, I think it's a helpful thought exercise to think about where you want to be in 15-20 years. You may see yourself practising in the community but develop a field of expertise in a specific area, for instance. In Quebec, there are many short-term hematology fellowships, in areas like acute leukemia, lymphoma, and MPN.

What advice do you have for a community hematologist who is interested in clinical trials?

Dr. Anglin: We have an active clinical trials program at the Stronach Cancer Center in Newmarket. A successful clinical trial program in the community requires both an administrative and clinical champion to explain how clinical trials benefit patients and boost the hospital's reputation. For residents seeking positions, it's important to join a centre with clear leadership and institutional commitment. You can sense that commitment during an interview, as well as through visiting the centre and meeting the team.

What are the questions you should ask during job interviews? What are the aspects that are up for negotiation?

Dr. Chu: In the academic setting, protected time for research versus clinical work is typically negotiable. It is often in your benefit to leverage other offers in negotiations. Regarding protected time, it's important to keep in mind that if you have more protected time, more academic output will be expected of you. You can also expect your academic ideas and research interests to shift with more time and experience. Therefore, I suggest starting with less protected time for research and expanding that organically over time.

Dr. Chen: I think the most important questions are the ones you ask yourself. These questions include: Do I want to be a clinician investigator? Do I like teaching? What clinical area am I interested in? What is my focus within a clinical area? Everyone's attested to the fact those answers can change, but you need to start with a plan. As for the questions you want to pose to hiring institutions, I would suggest asking about how your interests will fit in with your potential colleagues. For instance, if you're the fifth person who wants to be a clinician investigator in the area of newly diagnosed large B-cell lymphoma, there won't be much space for you to maneuver. You want to know that infrastructure and resources will be available to you, but you also want to be bringing something to the centre as well. You don't want to be redundant.

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