Canadian Hematology Today 2025 Symposium on B-cell Malignancies

Event Summary Report

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catalytic health
medical minds meet here

In This Report...

Acronyms

ABVD	ADRIAMYCIN, BLEOMYCIN, VINBLASTINE, AND DACARBAZINE
ASH	AMERICAN SOCIETY OF HEMATOLOGY
BCL2i	BCL2 INHIBITOR
BEAM	CARMUSTINE, ETOPOSIDE, CYTARABINE, AND MELPHALAN
BPd	BELANTAMAB MAFODOTIN, POMALIDOMIDE, AND DEXAMETHASONE
BR	BENDAMUSTINE AND RITUXIMAB
BrECADD	BRENTUXIMAB VEDOTIN, ETOPOSIDE, CYCLOPHOSPHAMIDE, DOXORUBICIN, DACARBAZINE, AND DEXAMETHASONE
Bv-AVD	BRENTUXIMAB VEDOTIN, DOXORUBICIN, VINBLASTINE, AND DACARBAZINE
BVd	BENDAMUSTINE, BORTEZOMIB, AND DEXAMETHASONE
CAR	CHIMERIC ANTIGEN RECEPTOR
CDA	CANADIAN DRUG AGENCY
CHOP	CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE, AND PREDNISONE
cHL	CLASSIC HODGKIN LYMPHOMA
CIRS	CHRONIC INFLAMMATORY RESPONSE SYNDROME
CLL	CHRONIC LYMPHOCYTIC LEUKEMIA
CNS	CENTRAL NERVOUS SYSTEM
CRS	CYTOKINE RELEASE SYNDROME
CTCAE	COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS
ctDNA	CIRCULATING TUMOUR DNA
CVP	CYCLOPHOSPHAMIDE, VINCRISTINE, AND PREDNISONE
D-VRd	DARATUMUMAB, BORTEZOMIB, LENALIDOMIDE, AND DEXAMETHASONE
DLBCL	DIFFUSE LARGE B-CELL LYMPHOMA
DRd	DARATUMUMAB, LENALIDOMIDE, AND DEXAMETHASONE
DVd	DARATUMUMAB, BORTEZOMIB, AND DEXAMETHASONE

Acronyms (cont'd.)

eBEACOPP	ESCALATED BLEOMYCIN, ETOPOSIDE, DOXORUBICIN, CYCLOPHOSPHAMIDE, VINCRISTINE, PROCARBAZINE, AND PREDNISONE
ECOG	EASTERN COOPERATIVE ONCOLOGY GROUP
EHA	EUROPEAN HEMATOLOGY ASSOCIATION
FCR	FLUDARABINE, CYCLOPHOSPHAMIDE, AND RITUXIMAB
FL	FOLLICULAR LYMPHOMA
HSCT	HEMATOPOIETIC STEM CELL TRANSPLANT
ICANS	IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME
ICE	IMMUNE EFFECTOR CELL-ASSOCIATED ENCEPHALOPATHY
ICU	INTENSIVE CARE UNIT
IPI	INTERNATIONAL PROGNOSTIC INDEX
Isa-Rd	ISATUXIMAB, LENALIDOMIDE, AND DEXAMETHASONE
Isa-RVd	ISATUXIMAB, LENALIDOMIDE, BORTEZOMIB, AND DEXAMETHASONE
IsaKd	ISATUXIMAB, CARFILZOMIB, AND DEXAMETHASONE
IsaPd	ISATUXIMAB, POMALIDOMIDE, AND DEXAMETHASONE
IVIG	INTRAVENOUS IMMUNOGLOBULIN
JAMA	JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION
JCO	JOURNAL OF CLINICAL ONCOLOGY
MATRix	METHOTREXATE, CYTARABINE, THIOTEPA, AND RITUXIMAB
MM	MULTIPLE MYELOMA
MRD	MINIMAL RESIDUAL DISEASE
MTR-A	METHOTREXATE, TEMOZOLOMIDE, RITUXIMAB, AND CYTARABINE
MZL	MARGINAL ZONE LYMPHOMA
N-AVD	NIVOLUMAB, DOXORUBICIN, VINBLASTINE, AND DACARBAZINE

Acronyms (cont'd.)

NCCN	NATIONAL COMPREHENSIVE CANCER NETWORK
ORR	OVERALL RESPONSE RATE
OS	OVERALL SURVIVAL
PFS	PROGRESSION-FREE SURVIVAL
PTLD	POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER
PVd	POMALIDOMIDE, BORTEZOMIB, AND DEXAMETHASONE
R-CHOP	RITUXIMAB, CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE, AND PREDNISONE
R/R	RELAPSED/REFRACTORY
R2	RITUXIMAB AND LENALIDOMIDE
RCT	RANDOMIZED CONTROLLED TRIAL
RMPV-A	RITUXIMAB, METHOTREXATE, PROCARBAZINE, VINCRISTINE, AND CYTARABINE
RSV	RESPIRATORY SYNCYTIAL VIRUS
SVd	SELINEXOR, BORTEZOMIB, AND DEXAMETHASONE
TBC	THIOTEPA, BUSULFAN, AND CYCLOPHOSPHAMIDE
TT-BCNU	THIOTEPA AND CARMUSTINE

Thank you to all our sponsors of the 2025 Canadian Hematology Today Symposium on B-cell malignancies.

Welcome and Opening Remarks

DIEGO VILLA, MD, MPH, FRCPC
ISABELLE FLEURY, MD, FRCPC

Dr. Villa and Dr. Fleury welcomed everyone to the 2025 Symposium on B-Cell Malignancies, remarking on the record attendance at the third annual event. They introduced the faculty and sponsors and presented the meeting objectives:

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

DIEGO VILLA, MD, MPH, FRCPC
ISABELLE FLEURY, MD, FRCPC

Sponsored Breakfast Symposium (GSK Canada): Pragmatic Management of Novel Myeloma Treatments

ARLEIGH McCURDY, MD, MHA, FRCPC

Dr. McCurdy discussed the practical management of new bispecific antibodies. She explained that while most patients experience CRS when taking teclistamab, elranatamab or talquetamab, ≥3 CRS events are very rare. With subcutaneous administration, CRS usually occurs the second or third day after bispecific therapy, later than with IV dosing. To mitigate CRS, the dose should be increased gradually over the first 1 to 2 weeks. Dr. McCurdy recommended that treaters consider dose-reducing from cycle seven onwards in patients who have a complete response to teclistamab or elranatamab, to mitigate toxicity risk.

Dr. McCurdy explained that prophylactic tocilizumab remains under study and is currently not routinely recommended. She recommended initiating the following medications before the first full dose, noting that after the CRS risk window, dexamethasone is generally not required.

- Corticosteroid (dexamethasone 16 mg or equivalent)
- Antihistamine (diphenhydramine, 50 mg or equivalent)
- Antipyretics (acetaminophen, 650-1000 mg or equivalent)

Most centres can administer bispecific antibodies in an outpatient setting, but access to inpatient beds and critical care beds during the step-up dosing period is crucial. Dr. Purdy also identified access to neurology consultation, 24/7 availability of tocilizumab, and maintenance of staff training and relevant standard operating procedures as requirements for any centre providing bispecific antibody therapy.

Dr. McCurdy recommended the standard operating procedures created by the UK Myeloma Group on the outpatient administration of bispecific antibodies. She suggested sharing a wallet card for patients that includes contact numbers and provides instructions for emergency departments. She also recommended pre-emptive prescriptions for dexamethasone, as dexamethasone or extra-

Bispecific Antibodies - CRS

	All grade, n/N (%)	Grade 3 or higher, n/N (%)	Median time (range) to onset, any grade	Median duration (range), any grade
BCMA–CD3-targeted				
Teclistamab[5]	119/165 (72·1%)	1/165 (0·6%)	2 days (1–6)	2 days (1–9)
Elranatamab[13,14]	71/123 (57·7%)	0/123 (0%)	2 days (1–9)	2 days (1–19)
Linvoseltamab[15] (200 mg)	51/117 (44%)	1/117 (0·9%)	14·8 h (0–177)	16·5 h (1–144)
ABBV-383[11] (≥40 mg)	71/124 (72·8%)	0/124 (0%)	1 day (1–7)	1 day (1–8)
Alnuctamab[12]	43/78 (55%)	0/78 (0%)	3 days (1–20)	2·5 days (2–10)
GPRC5D–CD3-targeted				
Talquetamab[6] (405 µg/kg)	113/143 (79%)	3/143 (2·1%)	2 days (1–8)	2 days (1–13)
Talquetamab[6] (800 µg/kg)	105/145 (72·4%)	1/45 (0·7%)	2 days (1–8)	2 days (1–29)
Forimtamig[10]	45/57 (78·4%)	1/57 (2·0%)	5 h	2 days
FCRH5–CD3-targeted				
Cevostamab[9]	130/161 (80·7%)	2/161 (1·2%)	NR; onset within 24 h in 113/161 (70%)	NR; resolution within 48 h in 137/161 (85%)

NR=not reported.

Table 2: **Cytokine release syndrome with bispecific antibodies**

strength acetaminophen can effectively treat most adverse events.

Serious ICANS events are very rare with bispecific therapy in myeloma patients, but a mitigation strategy is required. Standard operating procedures should detail the timing of ICE score assessments and neurology assessments. Dr. McCurdy explained that, at her site, patients with grade 1 ICANS are treated with dexamethasone and patients with grade ≥2 ICANS are additionally treated with anakinra.

Dr. McCurdy explained that BCMA-targeted bispecific antibodies are associated with the highest rates of infection, while talquetamab is associated with the lowest rates of infection. To prevent infections, Canadian centres ensure that patients are taking acyclovir and pneumocystis jirovecii pneumonia prophylaxis. Dr. McCurdy strongly recommended IVIG or subcutaneous immunoglobulin for patients on BCMA-targeted bispecific antibodies, based on her centre's experience.

Talquetamab is associated with skin-related adverse events in 70% of patients, which can include a maculopapular or erythematic rash. Skin exfoliation, pruritis, and palmar-plantar erythrodysesthesia syndrome can also occur. Dr. McCurdy explained these off-target effects occur early and resolve over time. Nail changes occur in 60% of patients and can be distressing for patients. Oral symptoms occur in 60% to 70% of patients. Dr. McCurdy recommended discussing side effects with patients before treatment.

Practical tips for managing skin side effects include prophylactic emollients, such as urea 10% cream, and regular sunscreen. For rash, Dr. McCurdy recommended the early use of low-potency topical steroids, which can be escalated to medium-potency steroids. For nails, soaks, topical steroids, emollients, vitamin E oil, and triamcinolone 0.025% are options, but Dr. McCurdy explained these treatments are often unsuccessful. For dry mouth, Dr. McCurdy recommended hydration, gum, and sulphate-free toothpaste. For dysgeusia, Dr. McCurdy recommended nutritional supplements, if needed, as well as oral rinses and liquid steroids. Dose reduction seems to be the most effective therapy for oral symptoms.

Dr. McCurdy discussed the management of belantamab mafodotin, noting that while infections are much less of a concern with the therapy, ocular toxicities occur. Most patients treated with belantamab mafodotin will experience some degree of keratopathy and approximately 18% of patients experience decreased visual acuity, according to a study published in *Ophthalmology* in 2020. Very few patients discontinue medication due to ocular toxicity. Dr. McCurdy recommended dose reductions if corneal adverse events emerge. She added that patients on belantamab mafodotin who experience ocular side effects should see an eye care specialist prior to each dose.

Keynote Presentation: Assessment of Adverse Events in Hematological Malignancies

GITA THANARAJASINGAM, MD

Dr. Thanarajasingam highlighted the drawbacks of current toxicity reporting requirements, including that reporting doesn't account for the time profile of adverse events (including onset and duration) not patient-reported outcomes. She called for improved, patient-reported data capturing tolerability, noting that tolerability is difficult to measure, as it is variable among different patients. For example, a small degree of peripheral neuropathy may be life-altering for some patients, but not others.

To improve toxicity assessments in trials, Dr. Thanarajasingam recommended the Toxicity over Time method, a standardized package of statistical tools that provide a more comprehensive longitudinal toxicity analysis. The approach uncovers aspects of toxicity that are clinically relevant and missed in traditional analyses. For example, the Toxicity over Time approach applied to the CALGB 50401 (Alliance) trial demonstrated that fatigue improves over time with lenalidomide therapy; however, neutropenia worsens over time. This is useful information to share with patients.

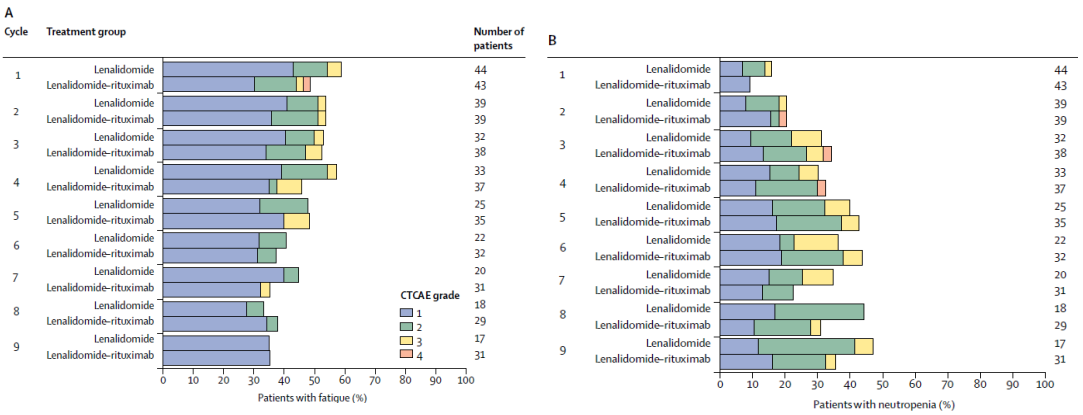
Research shows that clinicians underestimate the incidence of symptomatic adverse events. Dr. Thanarajasingam suggested the PRO-CTCAE™, the validated patient-reported outcomes version of the CTCAE. Investigators select the adverse events that are most relevant to the drug under study and patients answer queries about the frequency, the severity, and, importantly, how these adverse events affect their quality of life.

Dr. Thanarajasingam pointed to several research collaborations focused on improving tolerability evaluation and communication in North America. She expanded on the Lancet Haematology Adverse Events Commission, an international collaborative that involves patient advocates, clinical investigators, clinicians, international regulators and others to define priority areas for improving adverse event assessment in hematology globally. The Commission is launching the first part of a journal series at EHA 2025.

Longitudinal Toxicity over Time (ToxT) analysis to evaluate tolerability: a case study of lenalidomide in the CALGB 50401 (Alliance) trial

Gita Thanarajasingam, John P Leonard, Thomas E Witzig, Thomas M Habermann, Kristie A Blum, Nancy L Bartlett, Christopher R Flowers, Brandelyn N Pitcher, Sin-Ho Jung, Pamela J Atherton, Angelina Tan, Paul J Novotny, Amylou C Dueck

Lancet Haematol 2020; 7: e490–97



FATIGUE OVER TIME

NEUTROPENIA OVER TIME

GITA THANARAJASINGAM, MD

Evaluating physical function during and after treatment is also a very important part of understanding tolerability and the patient experience. Physical function can be assessed with patient-reported outcomes, clinician-reported performance outcomes such as a 6-minute walk test, and novel digital health technologies such as wearable sensors.

Integrating 4 Measures to Assess Physical Function in Patients with Cancer (IN4M) is an ongoing study assessing patients with lymphoma and breast cancer after the initiation of first-line chemotherapy. Physical function was evaluated through multiple validated instruments, including ECOG performance status, a 6-minute walk test, wearable fitness trackers, and patient-reported outcomes. The study found that completion rates for electronic patient-reported outcomes were high, with more than 80% of patients completing the surveys. Approximately half of the patients demonstrated high compliance with wearables. The authors of the study recommend that triallists include at least one physical function assessment modality, tailored for the clinical trial treatment and patient population.

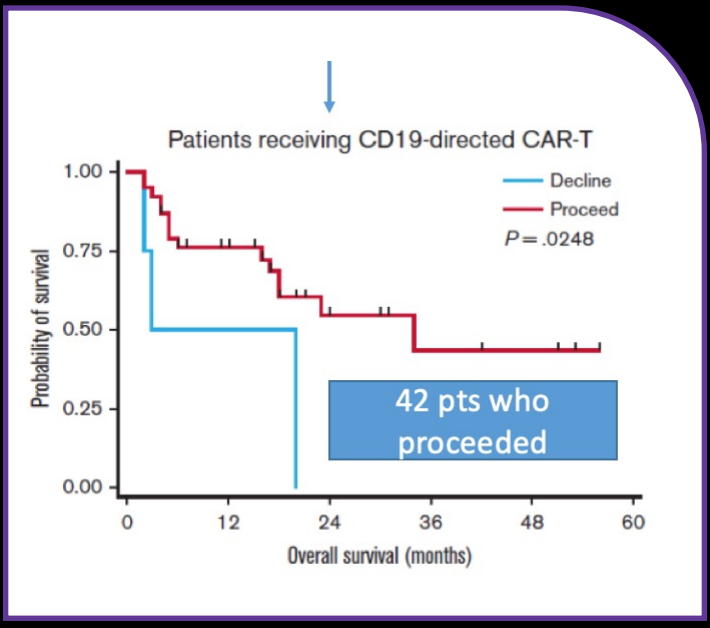
In conclusion, Dr. Thanarajasingam explained that patient-reported outcomes can help to guide optimal rather than maximally tolerated dose selection. Patient-reported outcomes can also guide physicians to better understand what symptoms to ask about and when to ask patients about these symptoms. Better data on physical function will allow physicians to intervene earlier and tailor treatments to prevent long-term loss of function.

Geriatric Assessment of CAR T-cell Therapy

ANCA PRICA, MD

Appropriate patient selection for CAR T-cell therapy is imperative. Not only is the therapy expensive, involving significant logistical challenges and caregiver burdens, published data shows that up to 30% of referred patients don't proceed to infusion. Data gathered by Dr. Sita Bhella at the Princess Margaret Cancer Centre showed that out of 263 patients referred for CAR T-cell therapy before November 2023, 70 patients did not receive the therapy; 14 patients were deemed ineligible at intake, and 56 patients did not proceed to infusion due to product, patient, and/or disease factors.

The risk of CRS and ICANS as well as the longer-term effects of CAR T-cell therapy, including infections and secondary malignancies, also necessitate careful patient selection. A 5-year real-world study published in *JCO* in 2024 showed that non-relapse mortality accounted for 16% of deaths within 5 years of axi-cel therapy. Data from the UK revealed that, out of 119 patients with R/R mantle cell lymphoma, 83 made it to infusion and there was a 24-month cumulative incidence of non-relapse mortality of 25%. The 24-month non-relapse mortality rate was significantly higher in patients over 65. The study also found that 27% of patients were admitted to the ICU, and the rate of grade 3-4 CRS was 11% while the rate of grade 3-4 ICANS was 22%.



In R/R large B-cell lymphoma, high serum lactate dehydrogenase, comorbidities, high metabolic tumour volume, and increased inflammatory markers are predictors of poor outcomes with CAR T-cell therapy. A Severe4 Comorbidity Index (the presence of a CIRS grade 3 or higher comorbidity in either the respiratory, upper GI, renal, or hepatic systems) is associated with shorter PFS and OS as well as almost three times the risk of severe CRS. An analysis of the Phase 2 ALYCANTE trial revealed that 10% of transplant-ineligible patients experienced grade 3-4 CRS and 20% had grade 3/4 ICANS. In addition, 37.5% of patients had prolonged cytopenia and 5% of patients died from infection.

The PILOT trial of liso-cel as second-line therapy in adults with R/R large B-cell lymphoma followed 74 patients who underwent apheresis, with a median age of 74. Dr. Prica highlighted that 26% of patients had an ECOG performance score of 2. Ultimately, 61 patients were infused. The median PFS was 9 months, and the OS was not reached at 17 months. Toxicity outcomes were better with liso-cel, compared to axi-cel; 7% of patients had grade ≥3 infections and 15% of patients required ICU care while grade ≥3 CRS occurred in 2% of patients.

How should treaters assess patient frailty and functional status? Dr. Prica emphasized that ECOG performance status is highly predictive of OS after CAR T-cell therapy, with poor outcomes concentrated among patients with an ECOG of 2 or more. Data from Princess Margaret Hospital presented at ASH in 2023 additionally showed that Clinical Frailty Scores above 3 and high Vulnerable Elders Survey-13 scores were predictive for poor PFS and OS. Cancer cachexia in the 3 months prior to CAR T-cell therapy that results in a BMI reduction of more than 5% also correlates with poor outcomes.

Dr. Prica described a geriatric assessment-guided multidisciplinary clinic in Chicago that employed physical function tests, functional status, nutrition assessments, cognition assessments, and biomarkers. Patients received nonbinding, summary

recommendations to proceed, defer, or decline CAR T-cell therapy. The outcomes for patients who received the 'decline' recommendation were far worse compared to patients who were recommended to proceed to CAR T-cell therapy.

CAR T-cell therapy optimization for older patients can include peri-CAR T-cell therapy rehab, nutritional support, comorbidity management, proactive CRS/ICANS management that minimizes steroids, aggressive infection management with IVIG or subcutaneous immunoglobulin and antibiotics. Dr. Prica stressed, however, that for frail patients, other treatments would be more beneficial than CAR T-cell therapy.

BiTEs in DLBCL: Are We Ready for First/Second-Line Use?

TYCEL PHILIPS, MD

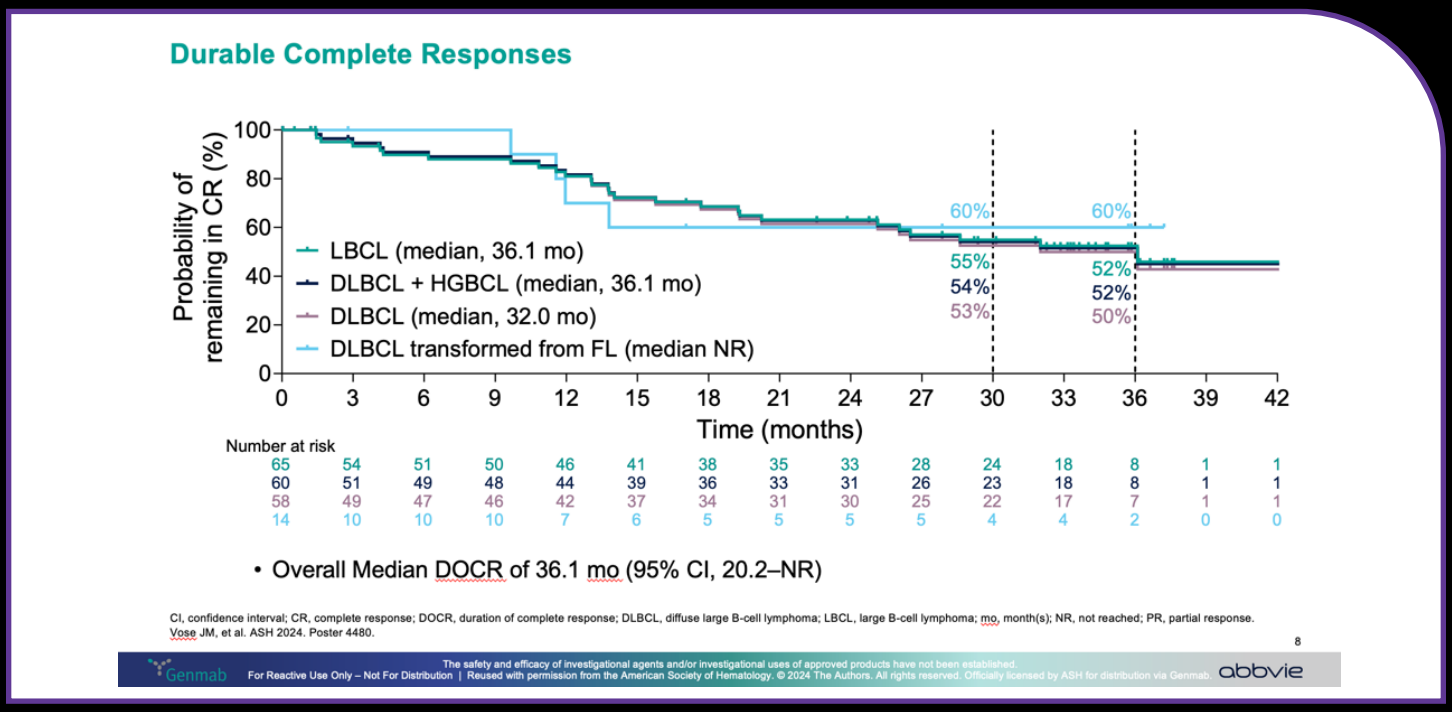
In the U.S., two bispecific antibodies, epcoritamab and glofitamab, are approved for DLBCL in the third-line setting. Epcoritamab is a subcutaneous medication and should be administered in conjunction with acyclovir and trimethoprim-sulfamethoxazole, especially during the early, step-up dosing phase. The therapy is administered until progressive disease or unacceptable toxicity. Dr. Philips shared the results of epcoritamab therapy in heavily pretreated DLBCL, highlighting the long response durations among responders. Longer term data is needed, however, to determine the curative potential of epcoritamab, as well as long-term infection rates.

Glofitamab is a finite therapy, administered following obinutuzumab pretreatment in DLBCL patients in the third-line setting. Dr. Phillips highlighted the impressive duration of response, given that the treatment stops at approximately 8 months.

There is ongoing debate about whether bispecific antibodies should be administered before or after CAR T-cell therapy in DLBCL. Dr. Phillips noted that only approximately 25% of patients eligible for CAR T-cell therapy receive the therapy. While there is concern that treatment with bispecific therapy could reduce the efficacy of CAR T-cell therapy in melanoma. Dr. Phillips pointed to real-world data from Spain and France suggesting this concern does not apply to lymphoma.

Discussing the use of bispecific antibodies in the second-line setting, Dr. Phillips presented data from the STARGLO and LOTIS -7 Phase 1b trials, suggesting that glofitamab combined with a cytotoxic agent may be more effective than glofitamab alone, and chemotherapy seems to mitigate the risk of CRS associated with bispecific antibodies. Dr. Phillips noted that combinations could be used as a bridge to CAR T-cell therapy or as a treatment option for patients who are ineligible for CAR T-cell therapy.

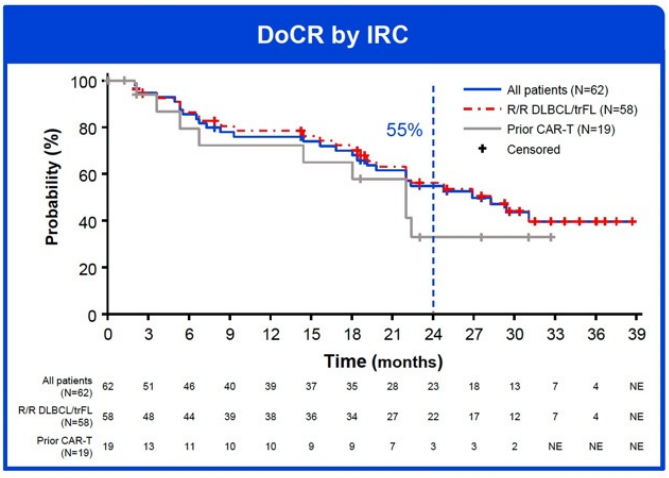
In the frontline DLBCL setting, ongoing research is exploring the use of odronextamab, epcoritamab, and glofitamab in combination with chemotherapy or chemoimmunotherapy. Safety data from the EPCORE NHL-2 trial shows rates of CRS that are, concerningly, similar to those seen in the third-line setting with bispecific antibody therapy. However, data from Phase 2 trials suggests that starting



with chemotherapy to reduce disease burden before introducing bispecific antibodies can improve safety without compromising efficacy. For example, introducing glofitamab after two cycles of R-CHOP resulted in no grade 3 CRS events and very few grade 2 CRS events. However, Phase 3 data is necessary to confirm the optimal approach.

In summary, Dr. Phillips expects bispecific antibodies will be moving into the first- and second-line treatment settings in DLBCL, due to their safety and efficacy in combination with other therapies. Given the benefits of earlier bispecific therapy in DLBCL are expected to be incremental, the costs and logistics of administering these medications will likely be important factors in clinician and payer decision-making.

	All patients (N=155)*	R/R DLBCL/ trFL (N=132)[1†‡]	Prior CAR-T (N=52)[†]
ORR, n (%) [95% CI]	80 (52) [43.5–59.7]	74 (56) [47.2–64.7]	26 (50) [35.8–64.2]
CR rate, n (%) [95% CI]	62 (40) [32.2–48.2]	58 (44) [35.3–52.8]	19 (37) [23.6–51.0]
Median DoCR, months (95% CI)	26.9 (19.8–NR)	28.3 (19.8–NR)	22.0 (6.7–NR)
24-month DoCR, % (95% CI)	55.0 (41.1–68.8)	56.2 (41.9–70.4)	33.1 (7.2–59.0)
Median CR follow-up, months (range)	29.6 (0–39)	29.6 (0–39)	23.0 (0–33)
Ongoing CRs, n/N (%)	34/62 (55)	32/58 (55)	10/19 (53)



- Median time on study: 32.1 months (range: 0–43)

With 32 months median follow-up, glofitamab showed high response rates

Management of Primary CNS Lymphoma

PROF. CHRIS FOX, MBCHB, FRCP, FRCPATH, PHD

Primary CNS lymphoma accounts for approximately 5% of all primary brain tumours. The median age of diagnosis is 67 to 70, based on cohort analyses from Europe. Unselected, population-based data from the UK demonstrates that socio-economic deprivation and comorbidities are significantly correlated with poor OS in primary CNS lymphoma.

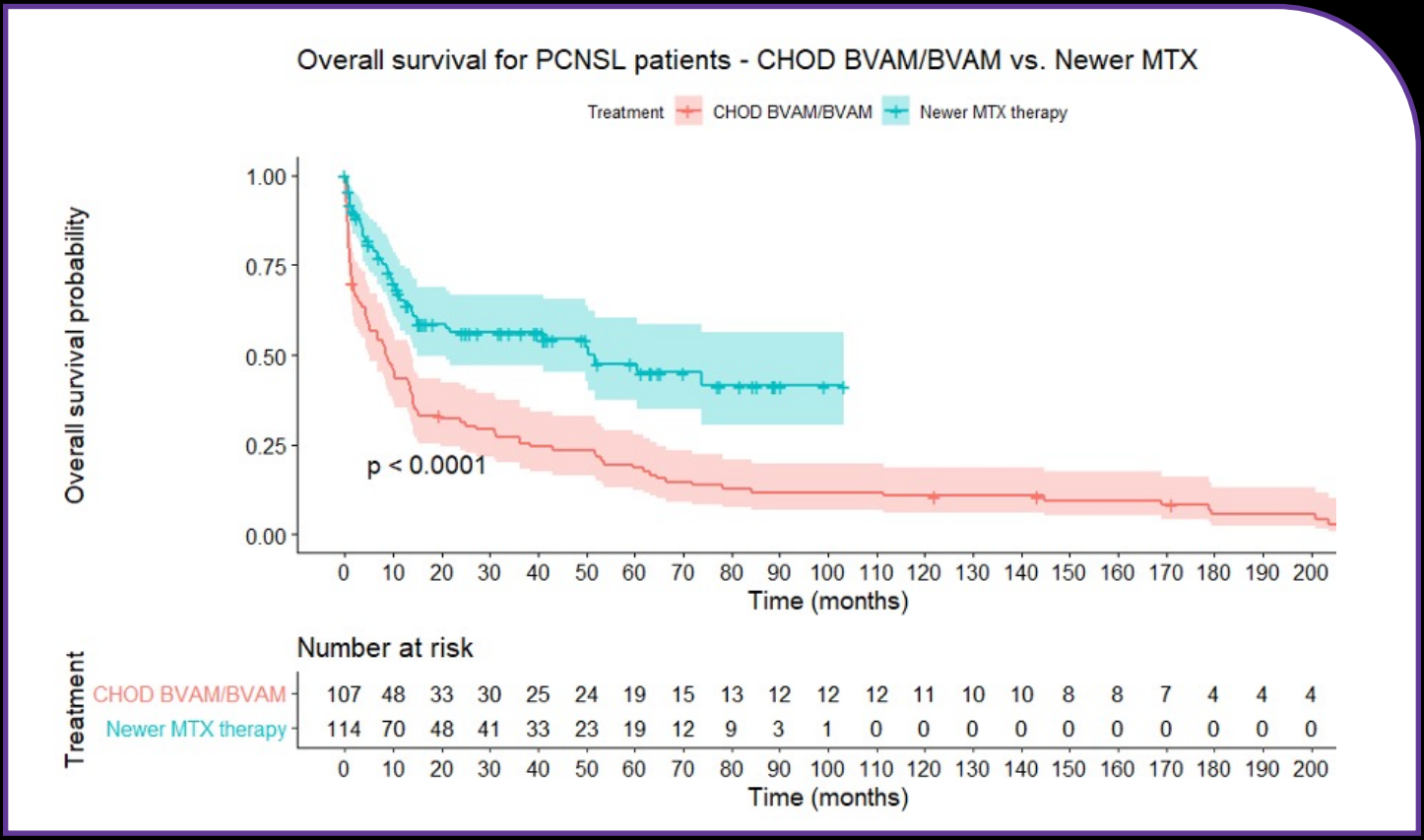
Almost all patients with primary CNS lymphoma present with neurocognitive dysfunction. Dr. Fox highlighted that primary CNS lymphoma is a whole-brain disease. Even in patients with unifocal lesions on MRIs, post-mortem studies show lesions throughout the brain.

Data from the East Midlands Region in the UK shows OS has improved from 1982-2010 (red) and 2011-2020 (blue), which is likely due to earlier diagnoses, improved supportive care, and, importantly, increased uptake of CNS-directed high-dose therapy.

There is no international consensus on the optimal induction regimen for primary CNS lymphoma; while MATRix is most common, RMPV-A and MTR-A are also used. The complete response rates are similar across the regimens.

The two-phase treatment approach for primary CNS lymphoma is well established internationally, consisting of a methotrexate-based immunochemotherapy, followed by ASCT or whole-brain radiation therapy. However, about a third of patients experience early treatment failure and don't proceed to ASCT or radiation therapy. Dr. Fox recommended ASCT versus conventional-dose whole-brain radiation based on the IELSG32 study, which found improved neurocognitive measures in the ASCT consolidation group, compared to the whole-brain radiotherapy arm.

Two RCTs strongly favour myeloablative chemotherapy versus conventional-dose



PROF. CHRIS FOX, MBCHB, FRCP, FRCPATH, PHD

chemotherapy, including the ALLIANCE 55101 trial and the IELSG43 trial presented at ICML 2023.

There is no prospective data to guide the optimal conditioning regimen for ASCT, however, retrospective analysis published in *JAMA Oncology* in 2021 suggested BEAM is associated with inferior PFS and OS, when compared to TBC and TT-BCNU. Dr. Fox noted that thiotepa is a small molecule that has very high brain penetration in animal studies.

Returning to the challenge of early treatment failure in the two-stage treatment of primary CNS lymphoma, Dr. Fox described the OptiMATE Phase 3 study, which enrolled patients 70 years and above with an ECOG performance status of 0 to 2 and patients aged 65 to 69 years above with an ECOG performance status of 0-3. The study is comparing a cycle of R-MTX followed by two cycles of MATRix, to the standard four cycles of MATRix induction regimen. The hope is that the age-adapted induction regimen would increase the proportion of patients proceeding to ASCT and also improve OS.

Dr. Fox emphasized that age and performance status are the only reliable prognostic factors in CNS lymphoma. While the older brain is more vulnerable to treatment toxicities, neurocognitive improvements can occur in older patients in remission 1 year or more after consolidation therapy. This is important to communicate to patients and families. Dr. Fox recommended a low threshold for deescalating the thiotepa dose in patients in their 70s, as well as patients in their late 60s with comorbidities. Dr. Fox presented results from the MARTA trial, which used an abbreviated, age-adapted induction regimen in older patients with a median age of 72 years. A 2024 *Lancet Hematology* publication showed 1-year OS rates of 63%. However, non-relapse mortality was high, and possibly related to the use of full-dose cytarabine in the trial.

Finally, Dr. Fox presented his PRiZM+ study of zanubrutinib monotherapy and combination therapy, explaining that seven of 23 patients were consented by a legal representative. At the 1-year mark, the ORR was 50% in the zanubrutinib monotherapy in the high-risk R/R primary CNS lymphoma cohort; with complete response rates of 35% by central review.

Dr. Fox expressed hope that future primary CNS lymphoma research can better elucidate the disease biology, improve risk stratification, and incorporate advanced technologies, including ctDNA, in treatment.

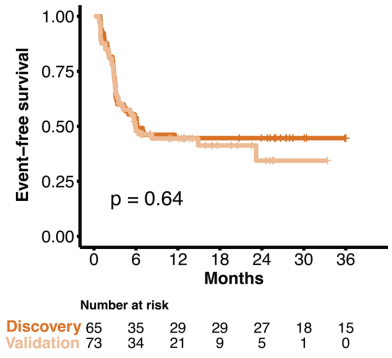
Liquid Biopsy in DLBCL Where Are We in 2025?

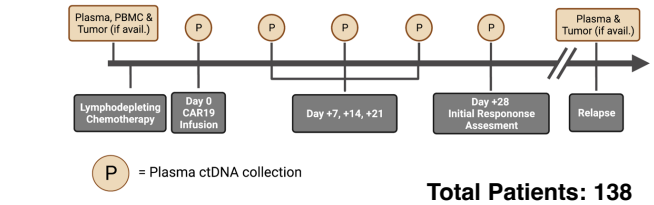
ASH ALIZADEH, MD, PHD

Dr. Alizadeh presented a study published in *Cancer Cell* in 2023 that analyzed 719 samples from 138 patients and showed that ctDNA levels before the start of therapy strongly correlated with known measures of disease burden. There was very wide variation of the disease burden as measured by ctDNA within the same Ann Arbor stage and similar IPI score and tumour volumes. Stratifying 118 treatment-naive patients into a high ctDNA versus low ctNA threshold at baseline demonstrated that high ctDNA is associated with a 2.5 increased risk of disease progression in frontline DLBCL.

Dr. Alizadeh showed that baseline ctDNA levels can independently predict outcomes in large cell lymphomas. In addition, early ctDNA responses after one to two cycles can more strongly predict treatment failure than baseline ctDNA levels. Several trials, including the Phase 2 ALPHA3 trial in frontline DLBCL, are using this strategy to escalate or deescalate frontline therapy.

Study Cohort (Stanford University)





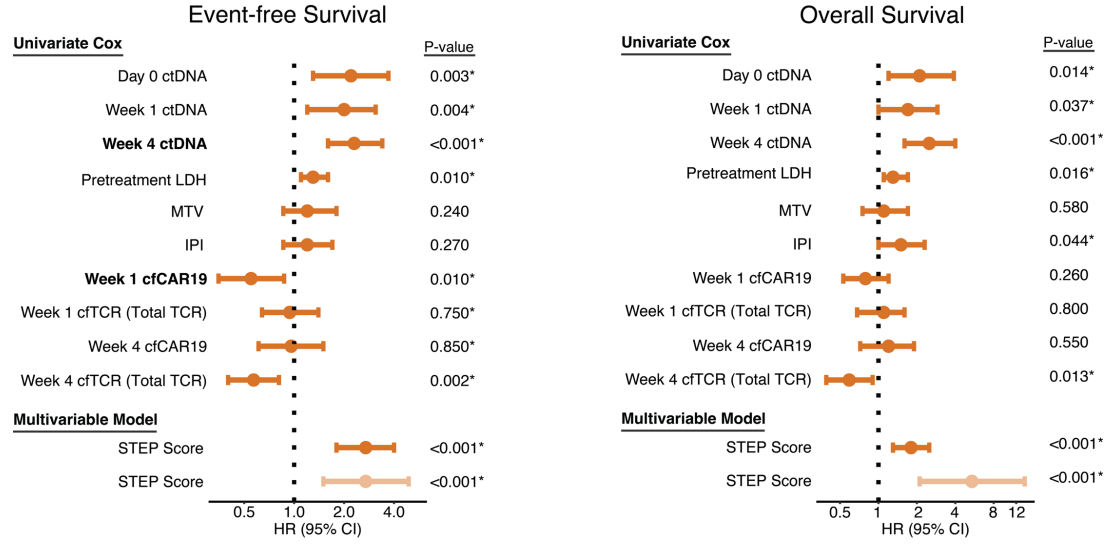
Total Patients: 138
Total Samples: 719

Sworder et al. *Cancer Cell* 2023

	CAR19 Discovery Cohort (N=65)	CAR19 Validation Cohort (N=73)
Outcome		
Ongoing Response	29 (45%)	31 (42%)
Progression	36 (55%)	42 (58%)
Follow-up (Median, 95% CI)	36.9 (30.4 - 40.8)	14.0 (12.5 – 17.6)
Age	58 (49-68)	63 (58-72)
Sex		
Female	22 (34%)	37 (51%)
Male	43 (66%)	36 (49%)
Histology		
DLBCL	35 (54%)	37 (51%)
HGBCL	9 (14%)	11 (15%)
PMBCL	3 (4.6%)	3 (4.1%)
TFL	18 (28%)	21 (29%)
THRLBCL	0 (0%)	1 (1.4%)
Prior Lines of Therapy		
0-1	0 (0%)	0 (0%)
2	27 (42%)	25 (34%)
3	18 (28%)	22 (30%)
4	15 (23%)	18 (25%)
5 or more	5 (7.7%)	8 (11%)
Prior Auto SCT	13 (20%)	19 (26%)

DLBCL, diffuse large B-cell lymphoma; HGBCL, high grade B-cell lymphoma; PMBCL, primary mediastinal B-cell lymphoma; TFL, transformed follicular lymphoma; THRLBCL, T-cell histiocyte rich large B-cell lymphoma; SCT, stem cell transplantation

What are the strongest tumor-intrinsic & extrinsic determinants of CAR19 outcomes?



STEP Score:
Week 4 ctDNA & Week 1 cfCAR19

Discovery Cohort
Validation Cohort

Management of PTLD in 2025

SUHEIL ALBERT ATALLAH-YUNES, MD

PTLD is a complex, heterogenous group of lymphoproliferative disorders that occur after solid organ transplant or HSCT. The cornerstone approach to CD20-positive PTLD is to reduce immunosuppression, most commonly by decreasing calcineurin inhibitors by 50% and discontinuing antimetabolite agents. This should only be done when feasible, upon careful discussion with the transplant team. Dr. Atallah-Yunes recommended close follow-up and monitoring of graft function, with restaging in 14 days.

If immunosuppression is not feasible or patients fail immunosuppression, Dr. Atallah-Yunes recommended rituximab induction (4 doses of 375 mg/m^2), followed by restaging. Patients in complete remission can proceed to consolidation with four doses of rituximab, spaced 3 weeks apart. Patients who are not in complete remission should receive further rituximab therapy or R-CHOP. Most patients require R-CHOP but a small subset of patients who achieve partial responses with induction rituximab and have an IPI score of 0 to 2 may be able to achieve a complete response with four additional rituximab doses. The risk-stratified approach is based on prospective Phase 2 studies conducted by the German PTLD study group and European PTLD Network. The risk-stratified approach with escalation to R-CHOP when necessary yielded 70% complete response rates, a median OS of 6.6 years, and treatment-related mortality of 8%.

CD20-negative B-cell PTLD is most often treated with CHOP. However, off-label brentuximab vedotin is an option for patients unfit for chemotherapy.

The risk-stratified sequential treatment approach may not be suitable for all patients. Patients with high disease burden, graft compromise, and significant lymphoma-related symptoms may require frontline R-CHOP chemoimmunotherapy. EBV-negative PTLD is treated with R-CHOP, given immunosuppressive medications have already reduced by the time this PTLD occurs. Radiotherapy can be considered in localized disease, following treatment guidelines of DLBCL. Finally, Dr. Atallah-Yunes emphasized reducing immunosuppression is not feasible in HSCT-PTLD due to risk of graft versus host disease. These patients should receive frontline rituximab.

There is far less data to guide the treatment of R/R PTLD. Treatment options include high-dose chemotherapy followed by ASCT, CD19/CD20-directed therapy, and adoptive cell therapy.

The largest retrospective study of ASCT in PTLD included 21 patients, most of whom had monomorphic DLBCL PTLD. The 3-year PFS was 62%, and the 3-year OS was 61%. Concerningly, the 100-day non-relapse mortality rate was 14%.

Adoptive cell therapy with EBV-directed cytotoxic lymphocytes is more promising. Tabelecleucel is an off-the-shelf allogeneic EBV-directed cytotoxic lymphocyte therapy that has been approved in Europe. The Phase 3 ALLELE study, presented at the 2024 ASH meeting, included 75 patients, 49 patients who had a solid organ transplant, and 26 patients who had HSCT. Most (87%) patients had received rituximab therapy, while 47% of patients received chemotherapy. The ORR was 50% and was similar in solid organ transplant and HSCT patients. The median OS was 18.4 months, and the median duration of response was 23 months. There were no fatal treatment-emergent adverse events and no CRS, ICANS, or bone marrow/graft rejections in the trial. Dr. Atallah-Yunes suggested this therapy could be beneficial in patients who do poorly on R-CHOP after failing rituximab, as well as thoracic organ transplant patients, and patients with CNS disease.

There is a growing use of CAR T-cell therapy in PTLD, but this requires a careful discussion on when to reduce the immunosuppression and when to resume immunosuppression after CAR T-cell therapy. A real-world study of 22 patients and systemic review and meta-analysis involving 35 patients found that 33% to 36% of patients stopped all immunosuppressive medications prior to CAR T-cell infusion, and the ORR was 64% to 69%. The real-world data demonstrated a 2-year PFS of 35% and a 2-year OS of 58%. Most patients experienced ICANS and CRS, while graft rejection occurred in 14% of patients.

Non-DLBCL monomorphic PTLD and cHL-like PTLD are rare and typically have delayed onset. These subtypes are treated similarly to DLBCL and cHL immunocompetent patients, with the exception of plasmacytoma-like PTLD and early-stage cHL-PTLD, in which reducing immunosuppression may be attempted prior to chemoimmunotherapy.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Sponsored Lunch Symposium (Eli Lilly Canada)—Unlocking the Future: Treatment and Outcome of Double-Exposed CLL

INHYE AHN, MD

CLL is the most common adult leukemia. There is no current consensus on how to define double-refractory CLL. A case series published in *Blood Advances* in 2025 described double-refractory patients as patients with progressive disease during active treatment with a BTKi and a BCL2i, given sequentially or in combination, and double-exposed patients as those who stopped either or both BTKi/BCL2i due to reasons other than progressive disease. The median OS in the double-refractory population was poor, at 2.2 years, while the median OS was not reached in the double-exposed population after 4 years of follow-up. The double-refractory group had a higher proportion of high-risk markers, including TP53 aberrations, unmutated IGHV, and BTK mutations.

Treatment options for double-refractory CLL patients include pirtobrutinib, liso-cel, and allogeneic stem cell transplant. The BRUIN CLL-321 study, presented at last year's ASH meeting, enrolled 238 patients who were previously treated with a covalent BTKi, and randomized patients to pirtobrutinib monotherapy or to the investigator's choice of idelalisib and rituximab or bendamustine and rituximab. Most of the patients enrolled had unmutated IGHV, and about half of the patients had a TP53 aberration. The pirtobrutinib arm included more patients with complex karyotypes, with 72% of patients having three or more aberrations, compared to 60% in the comparator arm. All patients were previously treated with a covalent BTKi (largely ibrutinib), and approximately half were exposed to BCL2i. Approximately 72% of patients in the study were refractory to covalent BTKi therapy.

The median PFS in the pirtobrutinib arm was 14 months, compared to 9 months in the comparator arm. Due to the high rate of crossover (76%), there was no OS difference between the arms. As CLL patients can have progressive disease without disease-related symptoms, the time to next treatment or death indicator is clinically meaningful. In the trial, the median time to next treatment or death was 24 months in the pirtobrutinib arm, compared to 11 months in the control arm. With the exception of pneumonia, the side effect profile favoured pirtobrutinib, as rates of neutropenia, cardiovascular events, and other toxicities were lower in the pirtobrutinib arm.

Regarding novel therapy for double-refractory and double-exposed CLL, Dr. Ahn shared information from two trials of BTK degraders in development (NX-5948 and BGB-16673), which were presented at ASH 2024. Nearly all the patients in both trials had been exposed to a covalent BTKi, and approximately 60% to 80% of the patients had been double-exposed; 78% to 90% stopped BTKi therapy due to progressive disease. With limited follow-up of 4 and 10 months, initial ORRs were over 75% in both studies.

Immune-directed therapy can also work in double-exposed/refractory CLL. However, the ORR in the TRANSCEND CLL 004 study was relatively low, with 20% of patients achieving complete responses. Alternatively, a dose-optimizing cohort of 17 patients from the EPCORE CLL-1 study of epcoritamab, presented at ASH 2024, found that step-up dosing resulted in no high-grade CRS events, and 0% ICANS events.


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What's the new standard for first-line Hodgkin Lymphoma?

ANN LACASCE, MD, MMSC

Hodgkin lymphoma primarily affects adolescents and young adults, with most patients diagnosed in their 20s and 30s. To set the stage for early-stage Hodgkin lymphoma, Dr. LaCasce discussed the incorporation of novel agents in advanced-stage Hodgkin lymphoma. She compared the landmark study of N-AVD versus Bv-AVD, published in *NEJM* in 2024, with the HD21 study of eBEACOPP vs BrECADD, published in Lancet Oncology in 2024. Dr. LaCasce noted that the N-AVD study had a higher-risk population, with more patients with stage 4 disease and higher IPI scores. N-AVD was superior to Bv-AVD, with a 2-year PFS of 92% versus 83%. With longer follow-up, the 4-year PFS rate was 94% in the BrECADD arm, versus 91% with eBEACOPP.

Patients over 60 were not included in the BrECADD study, due to the toxicity of eBEACOPP. The 2-year PFS for patients over 60 in the N-AVD arm was 88% versus 65% in the BV-AVD arm. For patients between the ages of 12-17, N-AVD resulted in a 2-year PFS was 95%, versus 83% in the comparator arm.

Longer-term follow-up will reveal the durability of the N-AVD regimen, with a Phase 1 study published in *Blood* in 2025 of brentuximab vedotin, nivolumab, doxorubicin, and dacarbazine demonstrating a risk of relapse after 12 months.

Toxicities were higher in the BrECADD arm, with 24% of patients requiring red blood cell transfusions and 21% requiring platelet transfusion; compared to 6% and 1% in the N-AVD arm. In addition, 28% of patients had febrile neutropenia in the BrECADD arm, compared to 6% in the N-AVD arm. However, 11% of patients discontinued nivolumab due to immune toxicity. Long-term, BrECADD is expected to be more harmful to fertility and more myelotoxic, especially for patients who require six cycles of therapy, but long-term data on nivolumab is lacking.

In early-stage Hodgkin lymphoma, the goal is to reduce the risk of recurrence while limiting late toxicity, including cardiovascular toxicities and secondary malignancies. Late effects with radiotherapy include secondary cancer, especially breast cancer before age 30, as well as cardiovascular disease, especially with the coadministration of doxorubicin. Nevertheless, Dr. LaCasce pointed out that these late effects may be significantly diminished with newer radiotherapy techniques and lower doses of radiotherapy.

Dr. LaCasce explained that the current standard of care is ABVD chemotherapy, with a PET-adapted/individualized use of radiotherapy. Among favourable EORTC-risk, PET-negative patients, the EORTC H10 study demonstrated a 10-year PFS of 99% in those who received three cycles of ABVD and involved node radiotherapy, compared to 85% among patients randomized to four cycles of ABVD. In the unfavourable EORTC-risk group, the PFS difference was not significant, with a 10-year PFS rate of 91% among those randomized to four cycles of ABVD and involved node radiotherapy and 87% among those who received six cycles of ABVD.

The ambitious AHOD 2131 study is assessing the impact of incorporating brentuximab and nivolumab in early-stage disease, with the goal of determining which patients will benefit from regimens containing these novel agents. Dr. LaCasce stated that the future of Hodgkin lymphoma is individualized therapy, with the possibility of determining Hodgkin lymphoma subgroups based on ctDNA, and targeting treatment to immunophenotype and patient preference. In addition, ctDNA, combined with biomarkers and PET responses could be used to deescalate therapy to reduce toxicity.


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Guidelines for CLL Survivorship

ALESSANDRA FERRAJOLI, MD

The survival of CLL has improved tremendously. The 5-year survival for CLL in 2022 was 94%, which compares to 88.5% from 2014 to 2020 and 65% in 1975. With a median age of diagnosis of 72, CLL patients have many comorbidities. CLL accounts for 46% of deaths in CLL patients, with the combination of other cancers, comorbidities, and infections more commonly causing mortality. The disease can cause significant morbidity, due to hypogammaglobulinemia, autoimmune phenomena, exaggerated responses to arthropod attacks, suboptimal responses to vaccinations, and an increased rate of other primary malignancies.

Dr. Ferrajoli described the approach of the Survivorship Clinic for CLL patients at MD Anderson Cancer Center. Given CLL patients have double the risk of other cancers, cancer screening is imperative. In addition to following the United States Preventative Services Task Force screening recommendations for breast, cervical, colorectal, and lung cancer, the Survivorship Clinic recommends an annual skin exam, and a prostate-specific antigen test, with or without a digital rectal exam annually for patients aged 50 to 69, and for high-risk patients aged 45 to 69. Dr. Ferrajoli noted that in CLL patients, breast and colorectal cancers are associated with reduced cancer-specific OS, and skin cancers have an increased risk of recurrence, metastasis, and death. A study by the MD Anderson Cancer Centre showed that the risk of other cancers was as common in CLL patients requiring therapy as watch-and-wait CLL patients. A University of Rochester study published in 2018 found that 3.8% of 407 CLL patients developed melanoma and CLL patients had six times the risk of invasive melanoma, compared to the general population. A 2019 study published in *Leukemia & Lymphoma* reported a similar melanoma rate in CLL patients. The Swedish Family Cancer Database suggests this increased risk is bidirectional, with a 1.5, 3- and 7-fold increased risk of CLL in patients with melanoma, squamous cell cancer, and Merkel cell cancer respectively.

In addition to cancer screening, Dr. Ferrajoli encouraged those who manage CLL to ensure patients receive recommended immunizations, including pneumococcal, influenza, COVID-19, herpes zoster, and RSV vaccinations, as early as possible before treatment, and to vaccinate family members. CLL patients may require pneumococcal, herpes zoster and RSV vaccinations at an earlier age. Live zoster vaccines should be avoided in CLL patients. Dr. Ferrajoli presented data showing that vaccine responses were much more robust in CLL patients in the earlier stages of diseases, and before CLL therapy.

To prevent bacterial infections in CLL patients, the NCCN guidelines recommend patients with IgG levels <500 mg/dL receive monthly IVIG 0.3–0.5 g/kg or subcutaneous immunoglobulin weekly at equivalent doses.

An MD Anderson study published in the European Journal of Haemotology in 2023 showed that lifestyle modifications can significantly improve fatigue and weight gain in CLL patients. Patients with obesity and diabetes may particularly benefit from participation in exercise interventions, as the study demonstrated lower rates of CD4+ T-cells that express both human leucocyte antigen-DR and PD-1 in these patients after 4 months of follow-up.


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Management of CLL patients with del(17p)

ALINA GERRIE, MD, MPH, FRCPC

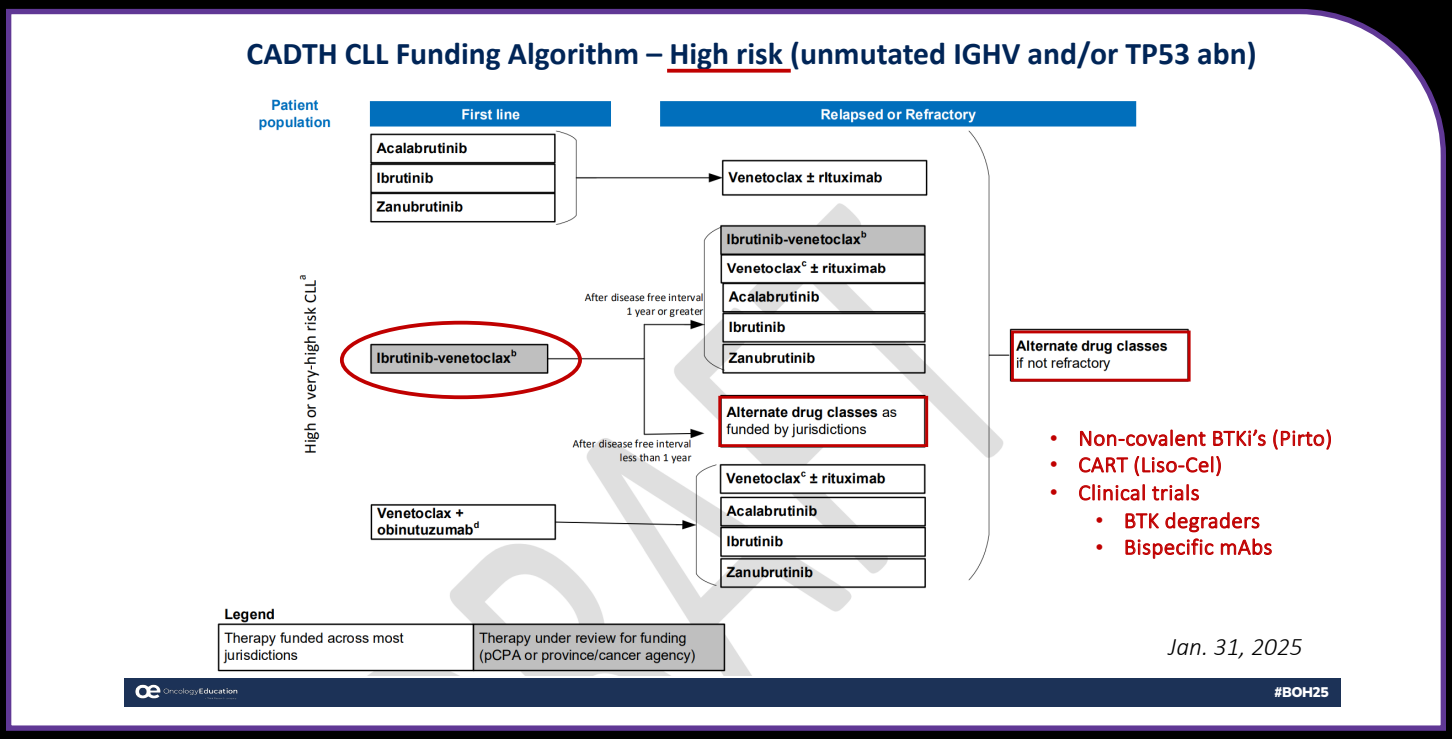
The del(17p) mutation is found in 3% to 8% of CLL cases at diagnosis and up to 30% of patients at relapse. The 2025 CDA CLL funding algorithm recommends BTKi therapy, ibrutinib-venetoclax or venetoclax and obinutuzumab in the frontline setting for patients with unmutated IGHV and/or *TP53* aberrations.

Long-term results from the Alliance A041202 trial show that treatment with ibrutinib significantly improved PFS compared to chemoimmunotherapy and appears to overcome the risk of *TP53* aberrations. Long-term follow-up of 34 patients with del(17p) show a 6-year PFS rate of 61% and a 6-year OS rate of 79% for first-line ibrutinib therapy, which is impressive considering that in 2020, the OS for CLL patients with del(17p) was 2.7 years. Other pooled analyses of clinical trials show very similar outcomes for frontline BTKi monotherapy in CLL patients. Real-world outcomes are inferior to clinical trial outcomes, however. The US Flatiron database published in 2022 found a time to next treatment of approximately 4 years among patients with del(17p) treated with first-line ibrutinib therapy.

Similarly, 6-year follow-up from the ELEVATE-TN trial found no significant difference in acalabrutinib-treated patients with or without *TP53* aberrations. In the relapse setting, among high-risk CLL patients, the ALPINE trial showed an improvement in survival with zanubrutinib compared to ibrutinib.

Discussing time-limited therapy options, Dr. Gerrie presented the CLL14 trial results, which revealed that patients with *TP53* aberrations had inferior outcomes on venetoclax and obinutuzumab, compared to patients without *TP53* aberrations. Patients with TP53 aberrations had a median PFS of approximately 4.5 years on this time-limited combination. While physicians generally prefer BTKi monotherapy for patients who have TP53 aberrations, due to the improved PFS, Dr. Gerrie said it can be reasonable to start patients who prefer time-limited therapy on venetoclax and obinutuzumab and then move to BTKi therapy at disease progression.

Discussing ibrutinib-venetoclax, which will soon be funded in Canada, Dr. Gerrie presented the results of the CAPTIVATE Phase 2 trial in patients over 70 years. The 3-year PFS among patients with



ALINA GERRIE, MD, MPH, FRCPC

TP53 aberrations was 81%, compared to 91% among patients without TP53 mutations. This combination could be considered for high-risk CLL patients, although Dr. Gerrie pointed out there is no long-term data with which to compare this combination against BTKi monotherapy.

Another possible future option for patients with del(17p) therapy is acalabrutinib, venetoclax, and obinutuzumab. A Phase 2 trial from the Dana Farber Cancer Institute evaluating this combination showed 3-year PFS rates of approximately 75% in patients with *TP53* aberrations.

In the relapse setting, a study published in Blood Advances in 2024 found that the median PFS in predominantly relapsed patients was 28 months with venetoclax monotherapy. However, in that study, only 11% of patients had prior B-cell receptor inhibitors. A small Phase 3b study of venetoclax monotherapy for R/R CLL, published in Lancet Oncology in 2024, found a median PFS of 21 months among patients with del(17p) who had prior B-cell receptor inhibitor therapy. Data from another small study, the MURANO trial, demonstrated a median PFS of 37.4 months among patients with *TP53* aberrations on venetoclax with rituximab.

Allogenic stem cell transplant remains a consideration for young, fit patients. Despite the high risk of non-relapse mortality (30% to 40%), it is the only potential curative strategy for high-risk CLL. Future treatment for high-risk CLL may include BTK degraders, ROR1-targeted therapies, dual covalent and non-covalent BTKi therapy, and CAR T-cell therapy.

Management of POD24 in FL and MZL

KELLY DAVISON, MD

While there is no universal definition of POD24, the term is commonly used to describe patients who progress, transform, or relapse within 24 months of the initiation of chemoimmunotherapy.

About 20% of patients with FL will experience POD24 events after initial R-CHOP chemoimmunotherapy. The National LymphoCare Prospective Observational Study found 5-year OS rates of approximately 50% in POD24 FL patients, versus 90% for those without POD24. Several other studies have demonstrated similarly inferior survival outcomes in FL patients with POD24.

For patients who receive BR in the frontline setting, POD24 rates seem to be lower, with a 2019 study published in *Blood Advances* finding POD24 rates of 13% of patients on BR and rituximab maintenance. However, for patients who do experience POD24 on this therapy, survival outcomes are poor, with 2-year OS survival rates of 38%. About 76% of patients with POD24 in this study had histologic transformation.

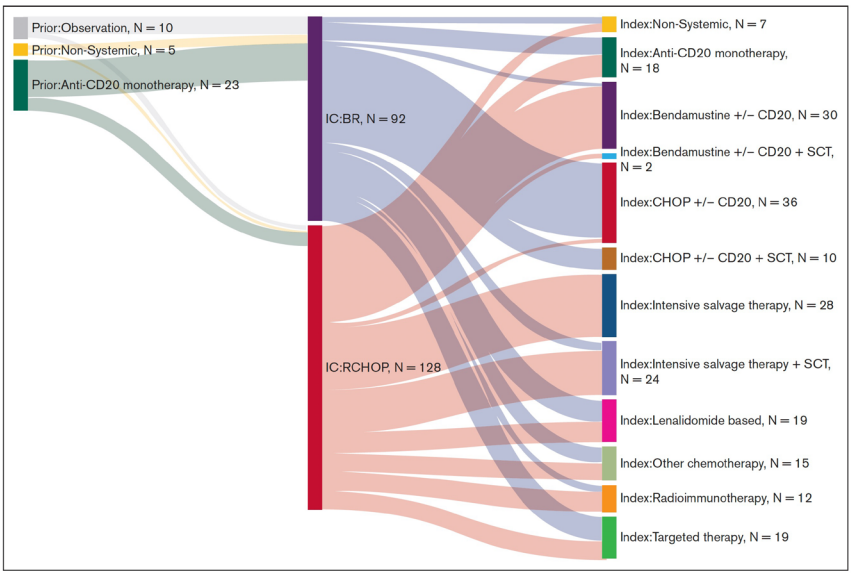
The GALLIUM study evaluated frontline obinutuzumab, plus CHOP, CVP, or bendamustine, compared to rituximab-based chemoimmunotherapy and found POD24 rates of 12% for patients taking obinutuzumab, versus 19% among patients in the rituximab-based chemoimmunotherapy arm. Among patients who received obinutuzumab and bendamustine, the POD24 rate was 7%. Dr. Davison pointed out, however, that obinutuzumab is rarely used, even in jurisdictions where it's available, due to high rates of grade 5 adverse events.

Various risk models have been developed to predict POD24, including models that utilize clinical information, as well as those that incorporate genetic testing. However, none of these tools have been accurate enough for use in the clinical setting. Future prediction tools could include tumour microenvironment biomarkers, imaging biomarkers, and post-induction response assessments, such as MRD testing by ctDNA methods.

There is no established standard of care for FL POD24 patients, though centres usually retreat with chemoimmunotherapy with or without ASCT. A 2025 study in *Blood Advances* followed 220 POD24 FL patients over two decades and identified 12 different

Patterns of care in POD24 FL

- N = 220
- Median age = 58
- Median EFS 9.8 mos
- 5-yr OS 71%
- No treatment category stood out as best
- 16% HSCT at index therapy



Day. Blood Adv. 2025;9:1013

second-line regimens. None of the treatments were clearly superior, though the numbers in each treatment group were very small. Only 16% of patients received HSCT.

Several retrospective studies suggest ASCT may prolong survival in second-line FL patients. However, few studies specifically follow POD24 patients. A study led by Dr. Puckrin in Calgary, published in *Haematology* in 2023, included 162 patients with R/R FL who underwent ASCT between 1992 and 2020. More than half met the definition of POD24. The 12-year time-to-progression was 50% for POD24 patients, versus 67% for non-POD24 patients, suggesting the possibility of a cure with early ASCT in POD24 patients.

The German low grade lymphoma study group trials demonstrated 5-year PFS rates of 51% in FL POD24 patients who received ASCT versus 19% in patients who received other second-line therapy. Dr. Davison highlighted that in these trials, POD24 outcomes with ASCT appeared comparable to the non-POD24 R/R population.

Novel therapies can overcome the negative prognostic impact of POD24 status. The AUGMENT trial demonstrated superior PFS and OS of R2 compared to rituximab monotherapy and similar responses between POD24 and non-POD24 patients in the combination arm. The INMIND trial also demonstrated similar outcomes with tafasitamab and R2 in POD24 versus non-POD24 FL or MZL patients, with a median PFS of 19 months versus 24 months respectively. In the third-line setting, the ZUMA-5 trial and Phase 2 study of mosunetuzumab monotherapy in R/R FL both demonstrate similar efficacy in both POD24 and non-POD24 patients.

The Canadian Myeloma Algorithm in 2025—An Update

ARLEIGH MCCURDY, MD, MHA, FRCPC

Dr. McCurdy reviewed the current Canadian myeloma treatment algorithm and discussed the pivotal updates in 2025. She explained that for transplant-eligible patients in the first-line setting, the current standard of care in Canada is RVd, followed by ASCT; CyBord is no longer the standard of care.

The DETERMINATION trial, updated in NEJM in 2022, demonstrated a median PFS of 67.5 months in patients treated with RVd followed by ASCT, compared to 46 months in the RVd-alone arm. A Canadian retrospective database study of 1,300 patients evaluated CyBord, followed by ASCT and lenalidomide maintenance and demonstrated a median PFS of 58 months.

Looking to the future for transplant-eligible patients, the PERSEUS study assessed D-VRd versus RVd and reported 48-month PFS rates of 84% versus 68%. D-VRd outperformed RVd across all subgroups. The GMMG-HD7 trial demonstrated improved survival in patients treated with Isa-RVd versus RVd. However, Dr. McCurdy pointed out that patients who achieve MRD-negativity on RVd had superior outcomes to patients who remained MRD-positive after Isa-RVd, illustrating that disease biology remains paramount.

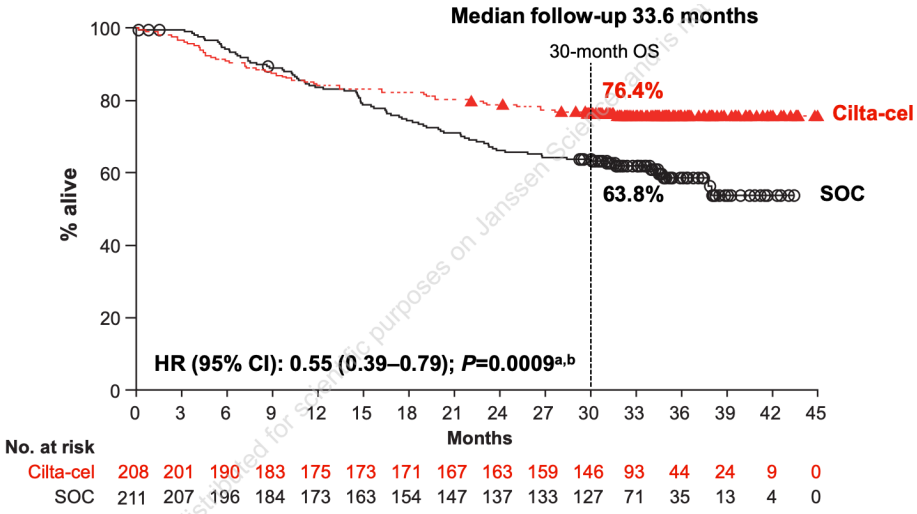
Other possible future options in transplant-eligible newly diagnosed MM patients include CAR T-cell therapy and bispecific antibodies.

In the transplant-ineligible population, the current frontline standard of care is DRd. The most recent update of the MAIA trial, published in *Leukemia* in 2025, showed the median PFS of DRd surpassed 5 years in newly diagnosed, transplant-ineligible patients. The study also demonstrated an OS benefit.

A potential future option for transplant-ineligible MM in the frontline is Isa-RVd. The BENEFIT trial evaluated Isa-RVd versus Isa-Rd in transplant-ineligible patients. At 18 months, 47% of patients were MRD-negative in the Isa-RVd arm versus 24% in the Isa-Rd arm.

In R/R MM, the standard of care is DRd for patients who are lenalidomide- and daratumumab-naïve, however, this is very rare. For patients who are lenalidomide-refractory, the standard of care is IsaKd or IsaPd, depending on fitness. For patients who are refractory to lenalidomide and CD38-targeted therapy, Dr. McCurdy recommended treatment with

CARTITUDE-4 OS



First CAR-T to demonstrate overall survival benefit in multiple myeloma

ARLEIGH MCCURDY, MD, MHA, FRCPC

SVd, based on results from the BOSTON trial.

CAR T-cell therapy may be a future treatment option, with the CARTITUDE-4 trial in lenalidomide-refractory patients showing the median PFS was not reached at 30 months, which is impressive in the R/R MM setting. The DREAMM-7 trial, evaluating DVd versus BVd, also demonstrated impressive results, with a median PFS of 37 months in the BVd arm, compared to 13 months in the DVd arm. The DREAMM-8 trial, published in *NEJM* 2024, found a hazard ratio for disease progression or death of 0.52 when comparing BPd versus PVd in a more refractory population than the DREAMM-7 trial.

Fourth-line patients have had very few options, with a median OS of 13 months, according to a *BCJ* 2023 publication. BCMA-targeted therapies offer hope, however. Dr. McCurdy pointed to the CARTITUDE-1 trial, which demonstrated a median PFS of 35 months; the median OS was not reached at 36 months of follow-up.

Sequencing for CAR T-cell and bispecifics for MM in 2025

GUIDO LANCMAN, MD

To set the stage for the discussion of CAR T-cell and bispecific therapies, Dr. Lancman compared the efficacy of these therapies with pomalidomide, carfilzomib, daratumumab, selinexor, and belantamab mafodotin monotherapy.

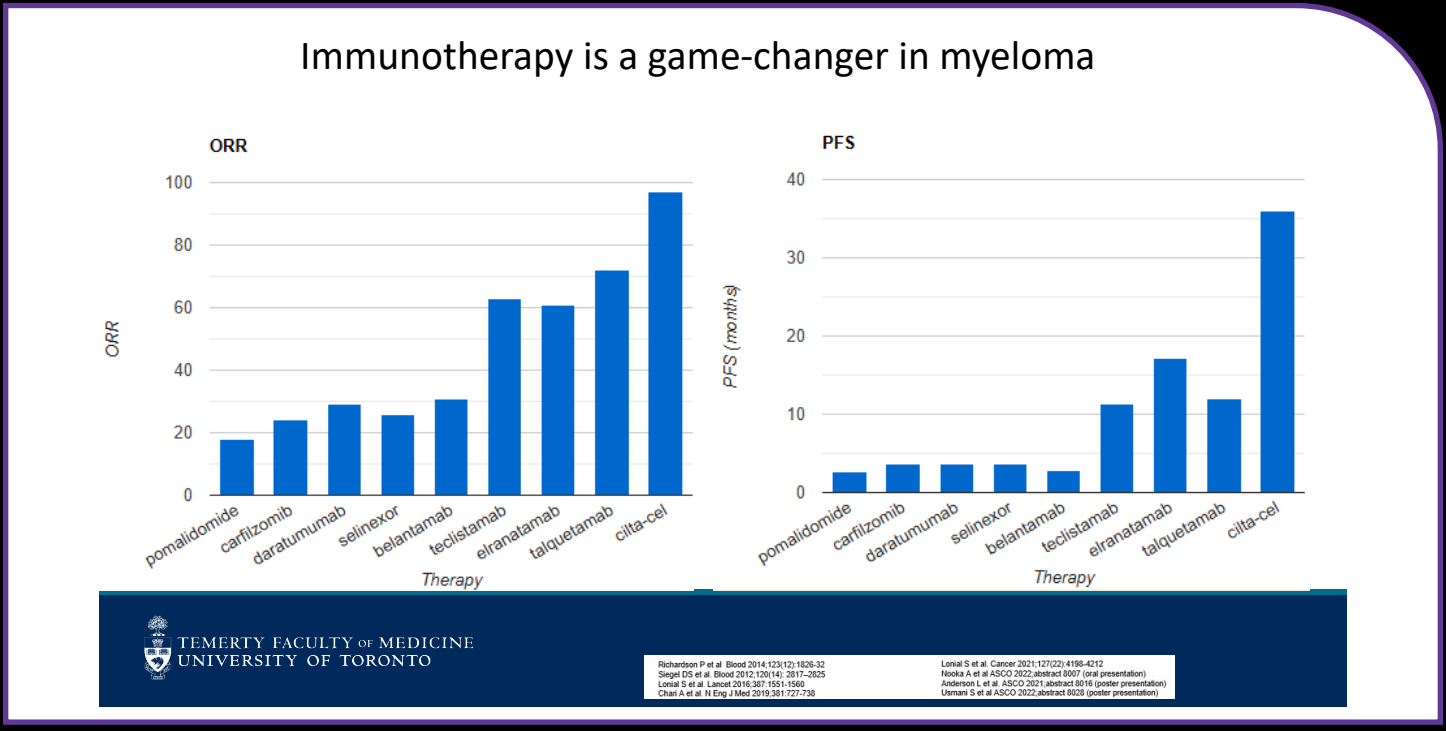
The CDA will currently not fund cilta-cel after BCMA-directed therapy or any other prior CAR T-cell therapy. Bispecific antibodies can be used after CAR T-cell therapy, for those who are not refractory to the latter. Data on optimal sequencing is low-quality, considering that a patient who receives two immunotherapies could be sequenced in 30 different possible ways.

Dr. Lancman noted that a BCMA-targeted bispecific antibody after BCMA-targeted CAR T-cell therapy is an acceptable option, given that studies examining teclistamab or elranatamab after CAR T-cell therapy show ORRs between 33% to 63%.

However, studies show excellent response rates in patients who receive GPRC5d-targeted CAR T-cell or bispecific therapy after BCMA-targeted CAR T-cell therapy, ranging from an ORR of 71% with talquetamab monotherapy to 100% with OriCAR-017 (in a study of only five patients).

Based on a small study of 11 patients, the ORR with cevostamab after BCMA CAR T-cell therapy also appears to be robust, with an ORR of 73% and complete response rates of 27%.

However, prior belantamab mafodotin seems to affect efficacy of subsequent anti-BCMA CAR T-cell therapy, with ORRs of 62% and 68% with cilta-cel and ide-cel, respectively. The median duration of response was 11.5 months with cilta-cel and 7 months with ide-cel in previously belantamab mafodotin-treated patients. Trials of anti- BCMA bispecific antibodies after belantamab mafodotin reveal ORRs of anywhere from 40% to 75%. The data is not clear-cut, because many studies include both patients who stopped belantamab mafodotin after progression as well as patients who discontinued belantamab mafodotin due to toxicity. Switching targets after belantamab mafodotin is a safer strategy, with an ORR of 75% among patients taking talquetamab after belantamab mafodotin, and an ORR of 60% among patients who initiate cevostamab after belantamab mafodotin.



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Based on very small studies, sequencing an anti-BCMA bispecific antibody before BCMA-targeted CAR T-cell therapy seems to be detrimental. The ORR was 57% and the median duration of response was only 8.2 months in a study of seven patients treated with cilta-cel after a BCMA-targeted bispecific antibody. However, starting with a BCMA bispecific antibody and then treating with a GPRC5d-targeted bispecific antibody leads to excellent ORRs, ranging from 58% with talquetamab monotherapy to 83% with talquetamab, daratumumab, and pomalidomide. The 12-month PFS rate was 74% with the talquetamab, daratumumab, and pomalidomide combination among patients previously treated with a BCMA bispecific antibody.

Limited data supports any BCMA- or FcRH5-targeted therapy after GPRC5d-targeted bispecific therapy, such as talquetamab. BCMA-targeted CAR T-cell therapy leads to ORRs of approximately 80% after GPRC5d-targeted bispecific therapy. BCMA-targeted bispecific therapy after GPRC5d-targeted therapy resulted in an ORR of 58% in 19 patients.

Dr. Lancman summarized that although optimal sequencing data is very limited, patients can successfully receive multiple immunotherapies. Among the BCMA-targeted therapies, the preferred order is CAR T-cell therapy, followed by bispecific antibodies, followed by an antibody-drug conjugate. Switching targets is a highly successful strategy, regardless of the order or modality. Finally, when switching from a bispecific antibody therapy to another bispecific antibody, a practical consideration is that patients are unlikely to respond to a different bispecific if high-tumour burden is the reason for the poor response to the initial bispecific therapy. However, treatment with another bispecific antibody can be successful in patients who had a long response to a bispecific antibody before relapse.

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