Canadian Hematology Today

2024 Symposium on B-Cell Malignancies

Toronto, ON
April 20, 2024

Event Summary & Evaluation Report

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In this report...

Learning Objectives

Dr. Julie Stakiw welcomed everyone to the 2024 Canadian Hematology Today (CHT) Symposium on B-cell Malignancies and introduced the meeting objectives.

The objectives of the conference were to:

- 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.

Abbreviations

ABVD	Doxorubicin, bleomycin, vinblastine, and dacarbazine
AE	Adverse event
AlloSCT	Allogeneic stem cell transplant
ASCO	American Society of Clinical Oncology
ASCT	Autologous stem cell transplant
ASH	American Society of Hematology
AVD	Doxorubicin, vinblastine, and dacarbazine
Axi-cel	Axicabtagene ciloleucel
BCMA	B-cell maturation antigen
BiTE	Bispecific T-cell engager
BLC2i	BLC2 inhibitor
BR	Bendamustine plus rituximab
Brexu-cel	Brexucabtagene autoleucel
BTKi	Bruton tyrosine kinase inhibitor
BV	Brentuximab vedotin
CADTH	Canadian Agency for Drugs and Technologies in Health
CAR	Chimeric antigen receptor
CHL	Classic Hodgkin lymphoma
CNS	Central nervous system
CR	Complete response
CRS	Cytokine release syndrome
CyBorD	Cyclophosphamide, bortezomib, and dexamethasone
DLBCL	Diffuse large B-cell lymphoma
DRD	Daratumumab, lenalidomide, and dexamethasone
EPOCH	Etoposide phosphate, prednisone, vincristine sulfate, cyclophosphamide, and doxorubicin hydrochloride
FL	Follicular lymphoma
GVHD	Graft versus host disease
HV	Hodgkin variant
ICANS	Immune effector cell-associated neurotoxicity syndrome
INESSS	Institut National d'Excellence en Santé et Services Sociaux
INHL	Indolent non-Hodgkin Lymphoma
IPI	International Prognostic Index
IRC	Independent Review Committee
Isa-KRD	Isatuximab, carfilzomib, lenalidomide, and dexamethasone
ITK	IL-2-inducible T-cell kinase
KRd	Carfilzomib, lenalidomide, and dexamethasone
Liso-cel	Lisocabtagene maraleucel
MCL	Mantle cell lymphoma
mPFS	Median progression-free survival
MRD	Minimal residual disease
MZL	Marginal zone lymphoma
NHL	Non-Hodgkin Lymphoma
NK	Natural-killer cells
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
Pola-R-CHP	Polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone
PR	Partial response
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone
R-DHAP	Rituximab, dexamethasone, cytarabine, and cisplatin
R-GDP	Rituximab, gemcitabine, dexamethasone, and cisplatin
R/R	Relapsed/refractory
R2	Lenalidomide and rituximab
RT	Richter transformation
RVD	Lenalidomide, bortezomib, and dexamethasone
SVD	Selinexor bortezomib, and dexamethasone
Tafa-len	Tafasitamab-lenalidomide
TEAE	Treatment-emergent adverse event
Tisa-cel	Tisagenlecleucel
TTNT	Time to next treatment

Evaluation Summary

Loved the entire day. All the speakers were outstanding. I loved the focus on *what* is funded in Canada.

– CLINICIAN FEEDBACK SURVEY

Great day of talks.
Perfect sized short meeting.

– CLINICIAN FEEDBACK SURVEY

Excellent mix of Canadian and international speakers for a balanced discussion.

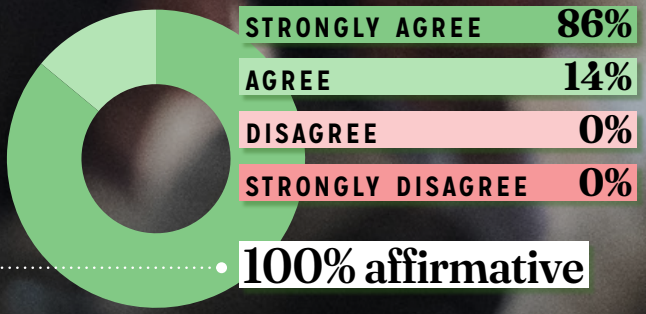
– CLINICIAN FEEDBACK SURVEY

The topics covered provided a comprehensive discussion of B-cell malignancies.

Clinician feedback survey prompt

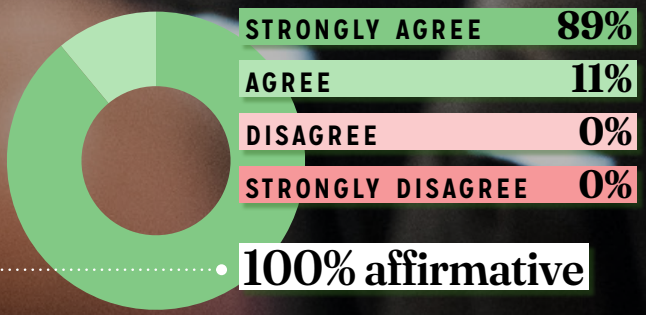
Presentations were appropriate for my level and provided new information or perspectives.

Clinician feedback survey prompt



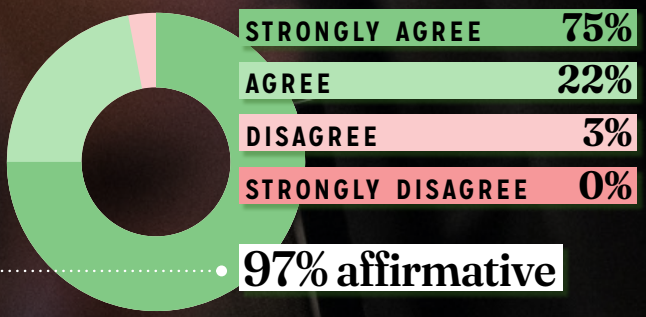
The information presented was high-quality, useful, and relevant to my hematology practice.

Clinician feedback survey prompt



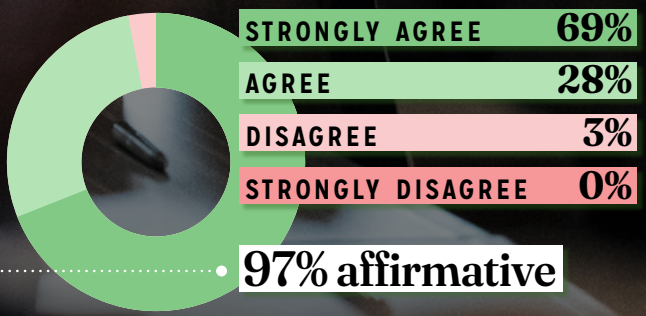
The timing of the agenda (length of lectures, panels, Q&A) was appropriate.

Clinician feedback survey prompt



There were good networking opportunities with colleagues and industry representatives.

Clinician feedback survey prompt



BeiGene Sponsored Breakfast Symposium

Recent Therapeutic Advancements in Relapsed Refractory FL: Application of New Clinical Data

Dr. Laurie Sehn
BC Cancer Centre

Dr. Sarit Assouline
Jewish General Hospital

Dr. Sehn provided a high-level overview of the potential treatment options in R/R FL, with a focus on new advances in treatment. FL accounts for 20%–30% of all NHL cases in Canada. Chemoimmunotherapy is the most frequently used regimen for symptomatic, advanced-stage, first-line therapy. In recent years, BR has become the preferred regimen in the Canadian first-line setting because of its better long-term disease control and favorable toxicity profile, compared to R-CHOP. However, about 20% of patients with FL have more treatment-resistant disease, and propensity toward transformation and poorer outcomes. In addition, chemoimmunotherapy works less well for all patients over time. Novel therapies could be valuable for the high-risk group, as well as in overcoming inevitable resistance for the majority of FL patients.

Options beyond first-line therapy include retreatment with an anti-CD20-based chemoimmunotherapy, R2 (which is not currently approved in Canada), and other novel targeted and immune-based therapies. Despite the enthusiasm about the use of BTKis in lymphoma, due to the recognition that the B-cell receptor pathway is an important driver of pathogenesis for FL, the initial trials of ibrutinib monotherapy were disappointing, with the DAWN trial revealing an ORR of 21% and mPFS of 4.6 months. A randomized phase 2 trial investigating the addition of ibrutinib to rituximab also showed little added benefit. There is limited data on acalabrutinib as monotherapy in FL. A study led by Dr. Paolo Strati published in *Blood* in 2022 found little difference in response rates between patients receiving acalabrutinib and rituximab or rituximab alone. Combining acalabrutinib with R2 seems to show more promise, and this combination is being investigated in ongoing trials.

The next-generation BTKi zanubrutinib has also been evaluated in FL. In a 2022 *Blood Advances* study that included 36 patients with R/R FL, the combination of zanubrutinib and obinutuzumab resulted in a 72% ORR and 39% CR rate. The success of zanubrutinib could be related to its favourable pharmacokinetic profile, which provides constant exposure above the 50% inhibitory concentration. In addition, zanubrutinib is more specific than ibrutinib, and spares ITK, which has been associated with better outcomes in FL.

Dr. Assouline presented the results of the ROSEWOOD trial, a randomized, phase 2 study in patients with FL, who had at least two prior lines of treatment. Patients were randomized to either zanubrutinib and obinutuzumab or obinutuzumab alone. In the combination arm, the duration of zanubrutinib exposure was 12 months and in the obinutuzumab-alone arm, treatment duration was 6.5 months. The ORR was 69% for the combination, compared to 46% for obinutuzumab. The CR rate was 39.3% in the combination arm, and 19.4% in the obinutuzumab monotherapy group. The mPFS was 28 months versus 10.4 months, respectively. Adverse events, including non-hematologic TEAEs, were similar across both groups, although pyrexia and infusion-related reactions were greater in the obinutuzumab alone arm and selected grade ≥3 nonhematologic TEAEs, including pneumonia and COVID-19, were higher in the combination arm.

The favourable risk-benefit profile of the combination, compared to obinutuzumab alone, has led to a phase 3 study of zanubrutinib plus obinutuzumab in patients who previously received at least one line of systemic therapy. The combination has been approved by Health Canada and is available through a special access program in Quebec.

Q&A: What are your thoughts on the role of alloSCT in R/R FL?

Dr. Sehn said she considers this only in extremely rare cases and couldn't recall referring a patient with R/R FL for alloSCT in recent years. Many patients with R/R FL are older and the toxicity is difficult to justify even for younger patients, when novel transplants are on the horizon.

Q&A: Why were there more infusion-related reactions with obinutuzumab monotherapy, compared to the combination therapy, in the ROSEWOOD study?

Dr. Assouline said that zanubrutinib and obinutuzumab were initiated at the same time; perhaps zanubrutinib has a dampening effect.

Management of Relapsed/Refractory Mantle Cell Lymphoma

Dr. Diego Villa
BC Cancer Centre

Dr. Villa began by highlighting the unmet need for innovation in MCL treatment, noting that MCL is a heterogeneous disease with variable outcomes. Despite advances in recent decades, median overall survival is only 6.7 years in the era of bendamustine and other novel agents.

In the R/R MCL setting, currently available options include covalent BTKis, brexu-cel, alloSCT, chemotherapy with or without rituximab, BCL2is, proteasome inhibitors, and lenalidomide. Future options may include non-covalent BTKis, zilovertamab vedotin and bispecific antibodies.

All three covalent BTKis are approved in Canada. However, there are no head-to-head comparisons of these therapies in MCL. The ibrutinib experience shows that these agents are most effective when used in the second-line setting, compared to use in subsequent lines of therapy. Second-generation BTKis (acalabrutinib and zanubrutinib) have lower rates of AEs, particularly cardiovascular-related AEs.

Dr. Villa presented the results of the SYMPATICO trial, a multinational, randomized, double-blind, placebo-controlled, phase 3 study that compared ibrutinib and placebo with ibrutinib and venetoclax in patients who received one to five prior therapies for MCL. Ibrutinib was given continuously and venetoclax was administered for a 24-month period. Approximately 29% of patients in the study had a TP53 mutation, and this was similar across both groups. Results showed a nearly 10-month improvement in PFS in the combination arm, compared to the monotherapy arm. The effect continues after the 24-month discontinuation of venetoclax. No cardiovascular signals were noted with the combination, though longer term data is needed.

Moving on to CAR T-cell therapy, Dr. Villa highlighted that CAR T-cell therapy is associated with excellent long-term outcomes in MCL. The 3-year follow up of the ZUMA-2 trial showed prolonged PFS in patients who experienced a CR. It remains unknown if CAR T-cell therapy can be curative. Reassuringly, data from the US Lymphoma CAR T-cell consortium show similar results have been achieved with brexu-cel in the real-world setting. Health Canada has approved brexu-cel for the treatment of adult patients with relapsed or refractory MCL after two or more lines of systemic therapy, including a BTKi.

Non-covalent BTKis are also being evaluated in the treatment of R/R MCL. The BRUIN trial highlighted the possibility of overcoming BTKi resistance by using a non-covalent BTKi (pirtobrutinib), which inhibits BTKi differently than covalent BTKis. The ongoing BRUIN MCL-321 trial will inform whether non-covalent BTKis have a role earlier in therapy, potentially in the first-line setting.

To guide treatment decisions on when to use CAR T-cell therapy and consider novel agents, Dr. Villa presented a 2024 treatment algorithm he published with colleagues in *Leukemia & Lymphoma*. He emphasized that patients treated with a BTKi first line need CAR T-cell consolidation in the second-line setting. Options after CAR T-cell therapy include non-covalent BTKis, alloSCT, novel agents including bispecifics and zilovertamab vedotin, as well as retreatment with R-chemotherapy, lenalidomide, and bortezomib.

Q&A: What is your perspective on the possibility of assessing patients' biological risk to determine first-line treatments in MCL?

Dr. Villa noted that up until recently, MCL has been treated in a one-size-fits-all way. As it is a less common B-cell malignancy, trials have enrolled all comers and treatment outcome advancements lag behind other conditions, such as CLL, where patients are stratified to different treatments based on whether they have del(17p) and/or TP53 mutations. He expects that the treatment algorithm for MCL will change in the near future, however, pointing out the European MCL Network's trial looking specifically at starting CAR T-cell therapy in the first line for high-risk patients.

Frontline therapy of FL in Canada: Moving beyond BR + maintenance

Dr. Laurie Sehn
BC Cancer Centre

Dr. Sehn introduced her talk by describing the challenges in the treatment of FL. Though FL is responsive to many treatments, it remains incurable. While most patients have a prolonged survival, about 20% of patients exhibit a propensity to transformation or treatment resistance. The genetics of FL is highly variable from patient to patient, and it is therefore currently not feasible to use genetic differentiators to select different treatments. Transformation is the singular biggest threat to the overall survival of FL, and the risk of transformation is approximately 3% per year.

On the positive side, outcomes for FL have dramatically improved over recent decades. In 1986, the 10-year OS rate was 54%. By 2015, the 10-year OS rate reached approximately 80%, largely due to the advent of chemoimmunotherapy.

About 20% of patients with FL have localized disease that can be successfully treated with radiation therapy. Around 35% present with advanced stage asymptomatic FL and can be treated with a 'watch and wait' approach, or rituximab therapy. For the 45% who present with symptomatic advanced stage FL, anyone suited to receive chemoimmunotherapy currently receives this therapy in the first-line setting, with or without maintenance. Chemoimmunotherapy has moved from R-CHOP to BR, due to better tolerability and improved, long-term PFS data. Dr. Sehn highlighted that the PRIMA trial, conducted before the availability of BR, showed the rituximab maintenance improved mPFS (10.5 yrs vs. 4.1 yrs) in the group randomized to receive no maintenance therapy. Noting that maintenance therapy is less commonly offered in the era of COVID-19, due to concerns about immunosuppression, Dr. Sehn said she still offers maintenance therapy as an option, noting the advantage of delaying subsequent-line options until better R/R treatment options are available.

Fatal adverse events remain a concern with chemoimmunotherapy, driving efforts for novel treatment options. Ongoing randomized trials in the frontline FL setting are focused on bispecific antibodies, including mosunetuzumab and epcoritamab, based on their efficacy in R/R FL. A study led by Dr. Franck Morschhauser reported impressive results for mosunetuzumab and lenalidomide in the frontline setting, with a CR rate approaching 90%. Early data presented at ASH 2023 on epcoritamab and R2 in untreated FL also showed strong efficacy. Dr. Sehn added the caveat that an observational study published in *Blood* in 2023 showed lower CD20 levels in samples taken upon progression in patients who have been exposed to mosunetuzumab. With the bar being set so high for both chemoimmunotherapy and bispecific therapy in FL, Dr. Sehn highlighted that patient preferences will likely be a key treatment decision-making factor.

Q&A: How would you treat someone with FL who has an unrelated, coincident second tumor?

Dr. Sehn underlined the importance of collaborating with colleagues to determine which cancer posed the largest threat. She added there is wariness about rituximab maintenance therapy for many reasons, and in this case, the patient's immune system could be important in containing or preventing risk of relapse of a secondary cancer.

Update on the Use of CAR-T in iNHL

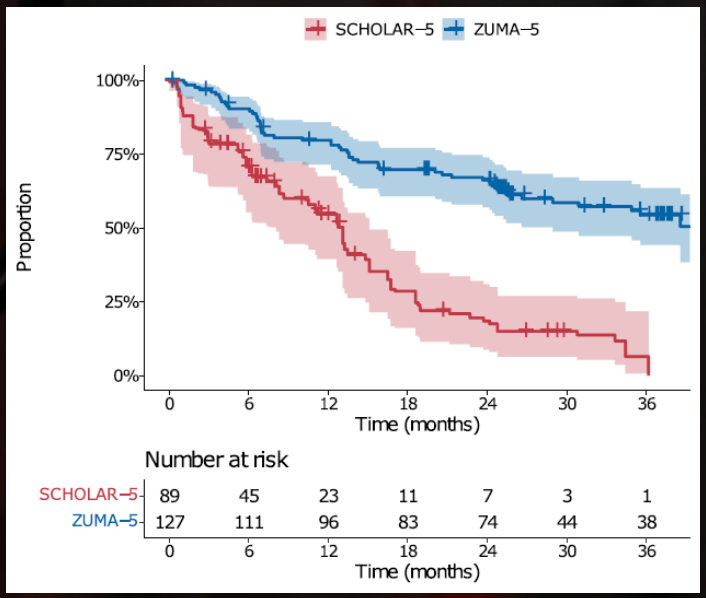
Dr. Paolo Strati

MD Anderson Cancer Center

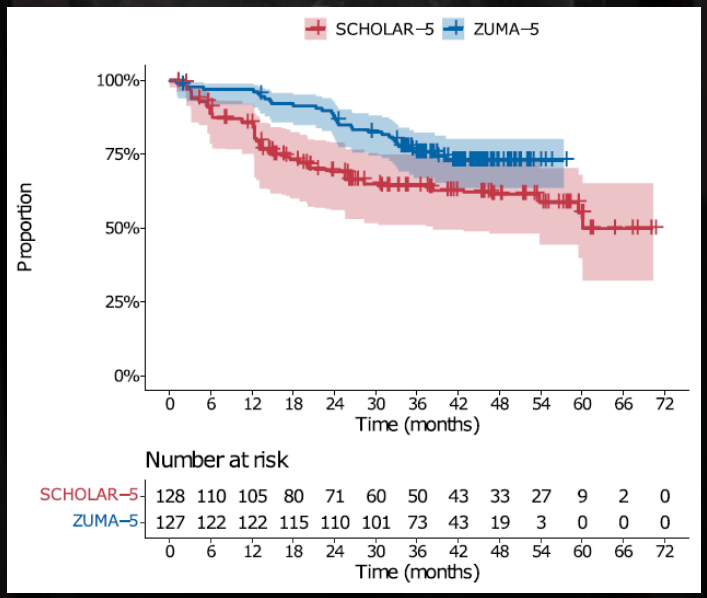
Dr. Strati began with an overview of the ZUMA-5 trial. He noted the median age in the trial was 60, while the median age of patients with R/R FL is significantly higher, and the vast majority of those enrolled in the trial were Caucasian. Only 31% previously took lenalidomide, while in the real world, R2 is currently the most commonly utilized second-line regimen in North America. Results of the ZUMA-5 trial showed that 94% of patients responded to axi-cel and 79% had a CR. Among patients with MZL, the CR rate was 65%; mPFS was not met for patients with FL, with 3 years of follow up, and was 12 months for patients with MZL. Presenting safety data, Dr. Strati highlighted that 96% of patients with MZL had a grade 3 or higher AE, compared to 85% of patients with FL. Grade 3 to 4 cytopenia rates were 34%. Though the sample size was small, Dr. Strati questioned whether MZL patients had higher doses of axi-cel, due to lower efficacy, which led to higher AEs.

Comparing ZUMA-5 to real-world outcomes in FL, evaluated in SCHOLAR-5, axi-cel was associated with better PFS and OS rates at 3 years.

Progression-free survival (≥ 3 LoT)



Overall survival (≥ 3 LoT)



ZUMA-5 vs SCHOLAR-5 at 3 years.
Ghione P et al, *Clin Lymphoma Myeloma Leuk*, 2024.
Slide courtesy of Dr. Paolo Strati.

The ELARA trial evaluated tisa-cel in 97 patients with FL. Once again, the median age was lower than the real-world demographics for FL, and the vast majority were immunotherapy naïve. The CR rate was above 70% and ORR was approximately 90%. Toxicities were lower with tisa-cel, compared to axi-cel, with 48.5% of patients experiencing CRS of any grade and 3% of patients experiencing a grade 3 AE. Grade 3 to 4 cytopenia rates were 17%. With 2 years of follow up, mPFS and OS have not yet been reached. A 2023 analysis from Dr. Nathan Fowler revealed that the PFS was not different among patients who received tisa-cel as outpatients, compared to those who received the CAR T-cell therapy as inpatients, and the cost of inpatient administration was seven times higher, compared to outpatient administration.

Liso-cel was evaluated as second-line therapy for 23 patients and as third-line therapy for 107 patients in the TRANSCEND trial. Liso-cel is expected to be approved in the U.S. this summer, and it could be approved in the second-line setting for patients with high-risk FL, while axi-cel and tisa-cel were approved in the third line. Baseline characteristics were similar in the TRANSCEND trial, compared to the ELARA and ZUMA-5 trials. In the third-line setting, 94% of patients achieved a CR, compared to 96% in the second-line setting. The mPFS has not been reached after 18 months of follow up. Regarding safety, rates of CRS were high, at 58%, though these were mostly low-grade CRS events and only one patient had grade 3 CRS. Grade 3 to 4 cytopenia rates were 22%.

Dr. Strati highlighted the key differences between the trials, including that ZUMA-5 included MZL patients, ELARA allowed bendamustine as a lymphodepleting agent instead of fludarabine and cyclophosphamide, and the TRANSCEND trial included patients who received CAR T-cell infusion in the second-line setting. A matching-adjusted indirect comparison between ZUMA-5 and ELARA published in Leukemia & Lymphoma in 2024 revealed similar rates of efficacy but higher rates of toxicity with axi-cel, compared to liso-cel.

Despite the availability of CAR T-cell agents, there is limited use of CAR T-cell therapy in FL, mainly because patients with FL are largely older and frail and because bispecifics are an available alternative. A matching-adjusted indirect comparison led by Dr. Francesc Bosch from 2023 suggests that CAR T-cell agents could be more effective than bispecifics in FL, but more data is needed.

Immunotherapy in HL: Role in 1L and treatment for R/R disease

Dr. Reid Merryman
Dana-Farber Cancer Institute

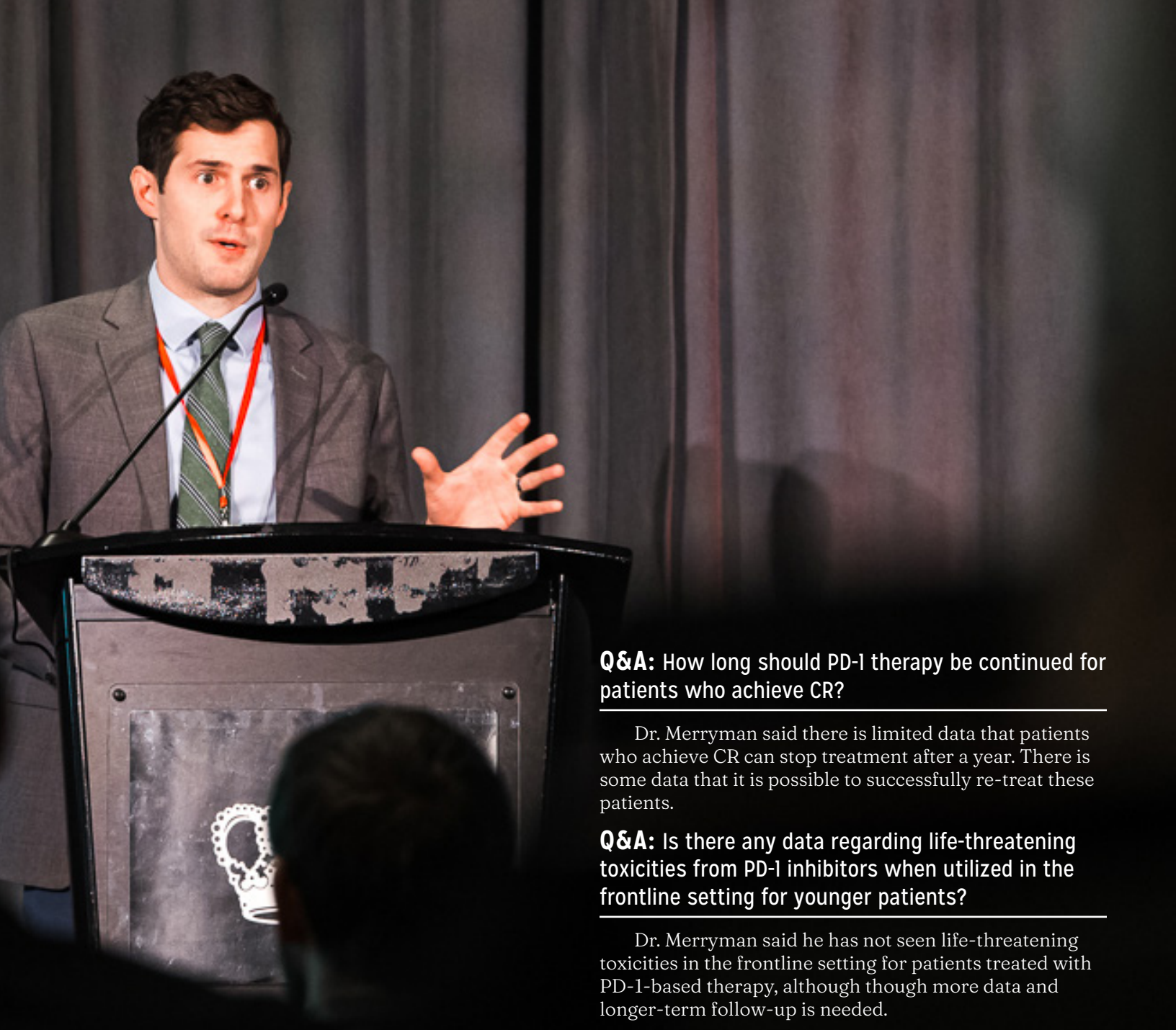
PD-1 inhibitors, nivolumab and pembrolizumab, have shown impressive efficacy and relatively low toxicity in R/R CHL. However, there are no randomized trials comparing second-line treatment regimens. With the caveat that phase 2 study comparisons are limited, preliminary data suggests a PD-1 inhibitor with traditional salvage chemotherapy is the best treatment regimen for optimizing the complete metabolic response rate. Patients who underwent PD-1-based salvage therapy followed by ASCT have particularly good outcomes.

To support the idea that PD-1 inhibitors can resensitize patients to chemotherapy, Dr. Merryman presented retrospective data from two studies that showed the average duration of response to chemotherapy after PD-1 inhibitor treatment was longer than the average response to chemotherapy before PD-1 inhibitor treatment. In a multi-center study, Dr. Merryman and colleagues followed a high-risk group of 78 patients who underwent PD-1 inhibitor therapy and had at least three lines of therapy before ASCT, with most having undergone at least four lines of therapy. At 18 months, PFS was 81%, which is impressive when compared to historical data of patients undergoing transplant after two lines of therapy. The analysis stratified patients based on whether they were refractory to one, two, three, or all lines of therapy before PD-1 inhibitors and all subsets had good outcomes. Those patients who had a longer duration between PD-1 inhibitor therapy and ASCT, and those who did not respond to PD-1-based treatments had poorer outcomes.

Dr. Merryman showed a pooled analysis involving 5 US academic centers of almost 1,000 patients with Hodgkin lymphoma who underwent ASCT between 2010 and 2022. At a median follow up of 2 years, patients who received PD-1-based salvage therapy had significantly improved outcomes, with a 2-year PFS of 93%, versus 72% to 74% for patients who received BV- or chemotherapy-based salvage therapies. Both PD-1 regimens, with and without BV, had similarly good outcomes. Based on this data, Dr. Merryman now selects a PD-1 inhibitor salvage regimen for his patients.

	N	Refractory pts	CMR	PFS (all pts)	PFS (ASCT cohort)	Median f/u	Citations
ICE	105	46%	33%*	56% (4 yrs)	63% (4 yrs)	84 mo	Moskowitz, *BJH*, 2010
BV + Benda	55	50%	74%	63% (2 yrs)	70% (2 yrs)	21 mo	LaCasce, *BJH*, 2020
BV + Nivo	93	42%	67%	77% (3 yrs)	91% (3 yrs)	34 mo	Advani, *Blood 2021*
Nivo +/- ICE	37	44%	91%	72% (2 yrs)	94% (2 yrs)	31 mo	Mei, *Blood*, 2022
Pembro + ICE	42	43%	87%	87% (2 yrs)	NR	24 mo	Bryan, *JAMA Onc*, 2023
Pembro + GVD	68	41%	93%	96% (2.5 yrs)	96% (2.5 yrs)	30 mo	Moskowitz, *Hemasphere*, 2022

Second-line treatment regimens.
Slide courtesy of Dr. Reid Merryman.



Concerning the use of PD-1 inhibitors in the first-line setting, the randomized phase 3 SWOG S1826 trial compared nivolumab and AVD with BV and AVD. The 1-year PFS rate for nivolumab-AVD was 94%, compared to 86% for BV-AVD. Assessing safety data, Dr. Merryman noted that higher rates of neutropenia and leukopenia in the nivolumab arm didn't translate into higher rates of infections. Nivolumab-AVD also showed benefit over BV-AVD in elderly patients. Dr. Merryman said that Nivolumab-AVD is now his preferred regimen for both younger and older patients.

Q&A: How long should PD-1 therapy be continued for patients who achieve CR?

Dr. Merryman said there is limited data that patients who achieve CR can stop treatment after a year. There is some data that it is possible to successfully re-treat these patients.

Q&A: Is there any data regarding life-threatening toxicities from PD-1 inhibitors when utilized in the frontline setting for younger patients?

Dr. Merryman said he has not seen life-threatening toxicities in the frontline setting for patients treated with PD-1-based therapy, although though more data and longer-term follow-up is needed.

Q&A: What is the safety of PD-1 inhibitors before alloSCT?

Emerging research suggests patients who receive PD-1 inhibitors before alloSCT seem to have higher rates of immune-related adverse events with alloSCT. While there are higher rates of acute and chronic GVHD, there is also better disease control among patients who received PD-1 inhibitors before transplant. An individualized treatment approach balancing the two concerns is key. Most physicians attempt to wait 6 weeks between PD-1 inhibitor treatment and alloSCT.

Incyte Biosciences Sponsored Lunch Symposium

The Evolving Landscape of R/R DLBCL: Navigating the Treatment Options

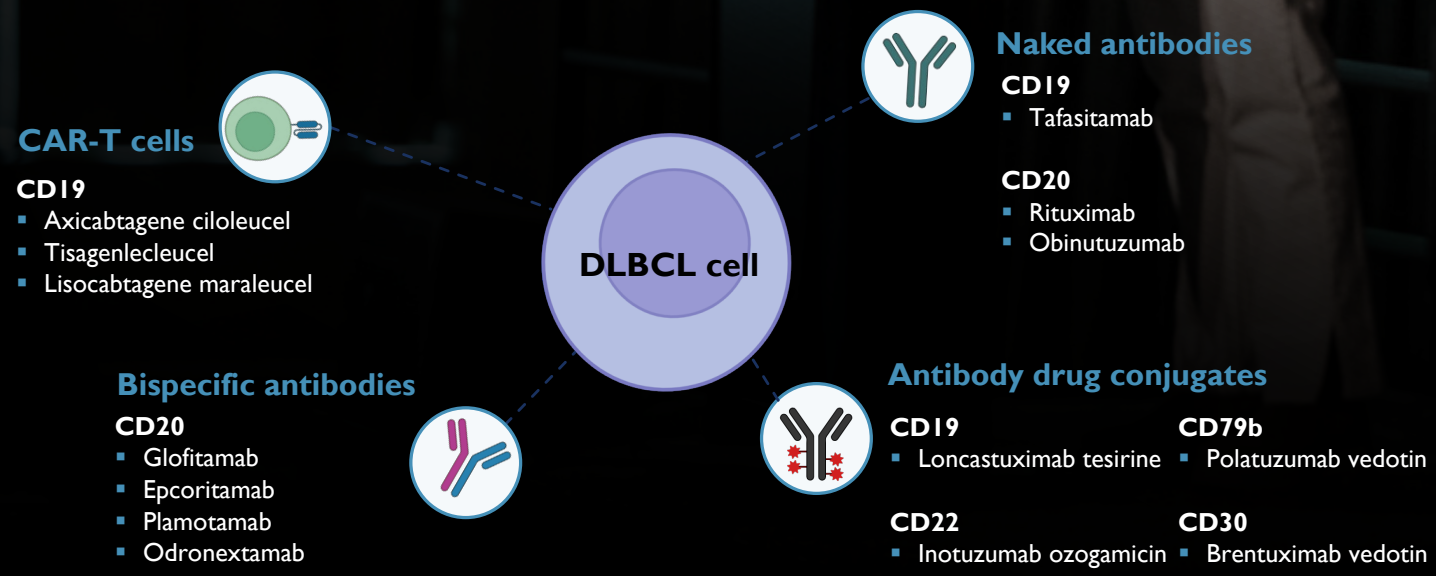
Dr. Isabelle Fleury
Hôpital Maisonneuve-Rosemont

Dr. Mary-Margaret Keating
Dalhousie University

Dr. Fleury reviewed that DLBCL is the most common NHL, representing 30% to 40% of all cases. Most patients are diagnosed with advanced stage NHL, and the median age at diagnosis is in the mid 60s. Frontline treatment considers patients' fitness and comorbidities, cardiac function, disease stage, IPI, MYC and BCL2 rearrangements and CNS involvement. In Canada, frontline treatment is predominantly R-CHOP. Other alternative frontline therapies for patients with high grade lymphoma and/or double hit lymphoma include dose-adjusted EPOCH-R, the Magrath protocol, and Pola-R-CHP. There is no randomized data showing that these therapies are superior to R-CHOP, however.

About 15 to 25% of patients with DLBCL are primary refractory to treatment, while 20% to 30% relapse after frontline therapy and 50% to 60% are cured. Early relapse is associated with poor prognosis.

Treatment selection for R/R DLCBL depends on patient characteristics, including preference for fixed or indefinite treatment, whether patients are ASCT- or CAR T-cell therapy-eligible, and whether patients are in the primary refractory or relapse category.



Emerging Landscape of salvage options for R/R DLBCL.
Slide courtesy of Dr. Isabelle Fleury & Dr. Mary-Margaret Keating.

The LY12 trial showed that R-GDP and ASCT provides curative potential for many patients. However, only about half of patients go on to transplant. This is where CAR T-cell therapies can bring benefit. Dr. Fleury provided an overview of the strong results for CAR T-cell therapies among ASCT-eligible patients in the ZUMA-7, TRANSFORM and BELINDA trials. In ASCT-ineligible patients in the second-line setting, the PILOT (liso-cel) and ALYCANTE (axi-cel) studies found CR rates of 54% and 82% respectively. In the third-line setting and beyond in ASCT-ineligible patients, CR rates with CAR-T cell therapy range from 39% to 58%, with mPFS ranging from 3 to 6 months.

Dr. Keating reviewed the evidence supporting tafasitamab, a CD-19-targeting immunotherapy, and lenalidomide in R/R DLCBL. Five-year follow-up of the L-MIND phase II study of 81 patients, 19% of whom were primary refractory and 43% refractory to previous-line therapy, found a 57.5% ORR and 41% CR rate. The ORR among patients with two or more prior lines of therapy was 47.5% and the CR rate was 30%. Median duration of response was not reached at 5 years, regardless of the number of previous lines of therapy. Median OS was not reached among patients who had one prior line of treatment. Regarding the safety profile, 64% of patients experienced a grade 3 or higher TEAE; 26 patients stopped study treatment while responding to the combination due to TEAEs.

Tafa-len performs more poorly in the real world. A study by Dr. David Qualls presented at ASH in 2022, found the mPFS for tafa-len was 2.1 months, and OS was 7.3 months. The study followed high-risk patients. Similar numbers (a mPFS of 4.7 months and OS of 8.9 months) were found in a study by Dr. Anna Ruckdeschel evaluating tafa-len in real-world cohorts in Germany and Austria.

In conclusion, the presenters noted that the treatment landscape for DLCBL is improving, and there are benefits and downsides of various strategies. Pola-BR and tafa-len are widely available and the side effects can be managed in all cancer centers. However, Pola-BR shows limited duration of benefit, while tafa-len shows a prolonged duration of response. There is limited data with tafa-len in primary refractory disease and its activity seems to be lower in patients who have received at least 2 lines of therapy.

Advantages of bispecifics include sustained remission, but the high toxicity profile is difficult for smaller cancer centers to manage. Regarding CAR T-cell therapy, the benefits include that it is potentially curative, but it has limited geographical access, and the toxicity profile is high. Many patients do not make it to CAR T-cell therapy due to bridging challenges. Key factors to consider with salvage therapy include patient comorbidities, fitness, and patient preference, lymphoma kinetics, past therapies, and access.

Q&A: Does long-term non-disease-related mortality post-CAR T-cell therapy influence your treatment choice?

Dr. Fleury said that fatal AEs seem to be below 10% in 3-year and 5-year follow-up studies on the use of CAR T-cell in DLBCL, and the rate should reduce over time with better AE management.

Q&A: Do you hesitate to offer patients Pola-BR when considering CAR T-cell in the future?

The presenters said they do avoid bendamustine for these patients. In Halifax, Dr. Keating said her center will frequently use Pola-R for patients who are likely to receive CAR T-cell therapy.

Q&A: Early data suggested that patients with higher levels of NK levels seemed to do better with tafa-len. Would it be possible to select patients for this therapy, based on NK levels?

Dr. Keating said that is interesting point to consider; she is not sure if there is clinical data to provide insight on this question.

Firstline therapy in CLL: BTKi vs BCL2i vs combined therapies

Dr. Sarit Assouline
Jewish General Hospital

Treatment options for frontline CLL in Canada include indefinite options (ibrutinib, acalabrutinib, and zanubrutinib) as well as finite options, including venetoclax-obinutuzumab and ibrutinib-venetoclax, the latter of which has been recommended for funding by CADTH and INESSS, but is not yet reimbursed.

The E1912 study, coordinated by the Eastern Cooperative Oncology Group, and the RESONATE2 study of ibrutinib in CLL demonstrated that about 60% of patients have remained on treatment after a follow up of 5+ years. The ELEVATE TN trial compared acalabrutinib, with or without obinutuzumab, to chlorambucil and obinutuzumab. Six-year follow up data shows the mPFS has not been reached and 62% of patients have not experienced disease progression. The study shows that acalabrutinib is superior to chemoimmunotherapy and among patients with unmutated IGHV CLL, there is a PFS benefit with the addition of obinutuzumab. The SEQUOIA trial demonstrated an estimated 24-month PFS of 85.5% for zanubrutinib and 69.5% for BR.

To determine how to choose between available BTKis, Dr. Assouline presented data showing no difference in PFS between acalabrutinib and ibrutinib in R/R CLL, but a lower incidence of AE with acalabrutinib. In addition, the ALPINE trial, comparing zanubrutinib and ibrutinib, showed zanubrutinib was associated with a better PFS, as well as a lower rate of AEs, including cardiac events. A matching-adjusted indirect comparison analysis of zanubrutinib in the ALPINE trial and acalabrutinib in the ASCEND trial, presented at the International Congress on Hematologic Malignancies in 2024, found zanubrutinib may be associated with a better PFS and potentially overall survival advantage, compared to acalabrutinib. There was no comparison of safety due to differing treatment exposure times.

Dr. Assouline highlighted that BLC2is have the potential to induce MRD-negative disease, allowing for finite therapy. The CLL14 trial showed the combination of venetoclax and obinutuzumab has a PFS benefit over chlorambucil and obinutuzumab. The PFS was significantly lower in patients with unmutated IGHV. Regarding safety data, 52% of patients experienced neutropenia with the venetoclax-obinutuzumab combination, though this was generally not associated with infection and easy to treat.

Moving on to BLC2i and BTKi combination therapy, Dr. Assouline noted that the ibrutinib and venetoclax combination approval in Canada was based on the GLOW randomized phase 3 study, which included patients with newly diagnosed CLL without a TP53 aberration. Results showed ibrutinib and venetoclax reduced the risk of death by 55% versus chlorambucil and obinutuzumab. TTNT also favours ibrutinib and venetoclax, and approximately 75% of patients receiving ibrutinib and venetoclax remained treatment free after 5 years. While serious adverse events were lower overall in the ibrutinib plus venetoclax arm, the cardiac adverse events were higher.

When choosing between a finite or indefinite regimen, Dr. Assouline noted that BTKi therapies afford long-term disease control, especially for high-risk patients, and there is a potentially years-long TTNT with BLC2i-BTKi combination finite therapy. In terms of tolerability, finite therapy results in fewer long term adverse events. Dr. Assouline stressed the importance of considering patient safety when choosing between a fixed or indefinite treatment option, including assessing patients' fitness and cardiovascular risk. Patient preference and molecular characteristics are other important considerations.

Q&A: Will the combination of ibrutinib and venetoclax be used in Canada, considering cardiovascular toxicities?

Dr. Assouline said that for higher-risk, younger patients without cardiovascular risk, the combination could offer a considerable PFS benefit.

Management of BTK and BCL2 Inhibitor Refractory CLL

Dr. John Allan
Weill Cornell Medicine

Dr. Allan discussed options for managing patients who are refractory to both BTKi and BCL2i therapy. The BRUIN study included 282 patients with CLL who had prior covalent BTKi therapy, 77% of whom had progressive disease, and 48% of whom had a 17p deletion or a TP53 mutation. Results showed an ORR of 81.6%. The response rates were similar regardless of whether patients had been exposed to a BTKi or both a BTKi and BCL2i therapy. The mPFS in this cohort was 19 months, and 23 months among those who were BCL2i naïve.

At 2 years, safety data demonstrates the emergence of BTKi class effects, including bruising, bleeding, and arthralgia. Approximately 4% of patients had treatment-related AEs leading to pirtobrutinib dose reduction and 2.5% had treatment-related AEs leading to pirtobrutinib discontinuation. Overall, however, pirtobrutinib is very well-tolerated, due to its high degree of selectivity.

Looking at the patients who experience disease progression on pirtobrutinib, 44% had BTK mutations at time of progression, 24% had non-BTK mutations and mutations were not detected in 32% of patients.

BTK degraders offer a potential solution to this resistance. Two main BTK degraders under study include BGB-16673 and NX-5948. Very early data presented at ASH 2023 shows they are effective at degrading BTK at very low doses. Despite expected rates of bleeding (4%) and infection (16%), small studies show the BTK degraders are, overall, well tolerated.

Dr. Allan then provided an overview of CAR T-cell therapy in CLL. In very high risk, double-refractory patients, a 2023 *Lancet* study found an impressive, IRC-assessed CR rate of 80%. Even among people who had partial responses, the mPFS was 26 months. Safety data showed that 9% of patients with double refractory CLL experienced grade 3 CRS, 18% experienced grade 3 neurological events and 1% (1 patient) experienced grade 4 neurological events.

Finally, the EPCORE-CLL-1 trial showed that epcoritamab resulted in a CR rate of 33% in very high-risk, double refractory patients. Of the 12 patients assessed for MRD, 9 had undetectable MRD. The study found a grade 3 CRS rate of 18%, which could be due to the small numbers of patients enrolled in the study. However, no AEs led to discontinuation, and all resolved.

Q&A: Given data on downstream mutation profiles, does it matter whether physicians choose a BCL2i or BTKi, or a combination BCL2i-BTKi in the frontline?

Dr. Allan said that in his own experience using ibrutinib and venetoclax, upon retreatment, approximately 80% of patients respond. He doesn't have an issue offering the two best drugs to frontline patients, so long as patients are on a fixed duration regimen. Emerging data shows the highest risk patient is the del-17p complex karyotype patient, and bringing these patients to an MRD-negative state, and potentially maintaining that MRD-negative state may be important. In the future, mutational status may determine which patients receive MRD-maximizing therapy.

CLL Richter in the Era of Targeted Therapies

Dr. Jean-François Larouche
Centre Hospitalier Universitaire de Québec

Dr. Larouche explained that RT is a phenomenon that is limited to CLL. While 95% to 99% of Richter's transformations occur in DLCBL, 1–5% of RT cases occur in Hodgkin's lymphoma.

The time to transformation is usually between 2 to 4 years. In the chemoimmunotherapy era, an estimated 2% to 10% of patients experience RT, but the real incidence is difficult to define in the absence of clinical trials.

Clinical risk factors for RT include lymph nodes measuring more than 3cm, extranodal lesions, constitutional symptoms, and prior treatment with a combination of purine analogs and alkylating agents. He noted that before the era of BTKis, PET scan had high sensitivity and specificity. Now, the sensitivity is approximately 70% for RT and the specificity is 60%. Molecular risk factors include unmutated immunoglobulin status, NOTCH1 alterations, TP53 alterations, CDKN2A/B loss, BCR subset #8 configuration, and complex karyotype. CLL and RT clones have concordant IGHV D-J rearrangement in 80% of DLBCL-RT and 40% HV-RT. Clonally unrelated RT follows a course which is more similar to the naïve diseases.

There are few clinical trials to guide the treatment of RT; treatment is mostly based on retrospective studies and case reports. There is a difference in the treatment between DLCBL-RT and HV-RT.

Outcomes of DLBCL-RT with standard chemo-immunotherapy are poor, though people with clonally unrelated DLBCL-RT have better outcomes. If it is possible at one's center to determine that a patient has a clonally unrelated DLBCL-RT variant, little available evidence suggests R-CHOP and observation is optimal. This can be appropriate for people DLBCL-RT at the same time of CLL diagnosis. For other patients, evidence suggests alloSCT may be ideal. A 2024 retrospective analysis led by Dr. Romain Guièze of 66 patients with RT from 2008 to 2018 found 42% patients had a CR at the time of transplant. Just under 30% of patients experienced 3-year PFS (39% of those who had a CR achieved a 3-year PFS).

Outcomes in DLBCL-RS with standard CIT

Study and years of patient recruitment	Regimen	n	Median age (years)	Results		
				ORR	CRR	Median OS
Anthracycline-containing regimens						
Langerbeins et al[16] (2003–2008)	R-CHOP	15	69 (N/A)	67%	7%	21 months
Dabaja et al[17] (published 2000)	HyperCVXD	29	61 (36–75)	41%	38%	10 months
Tsimberidou et al[18] (1999–2001)	Rituximab and GM-CSF with alternating hyperCVAD and MTX/cytarabine	30	59 (27–79)	43%	18%	8.5 months
Rogers et al[19] (2006–2014)	R-EPOCH	46	67 (38–83)	39%	N/A	5.9 months

Treatment DLBCL variant.
Thompson P et al. ASH 2022.
Slide courtesy of Dr. Jean-François Larouche.

In terms of BCL2i therapy, the most robust data comes from a phase 2 trial of 26 patients published in *Blood* in 2022, which found a 50% CR rate for DLBCL-RT when venetoclax was combined with dose-adjusted-EPOCH-R2. In the study, 78% of patients had prior CLL treatment and 52% had a complex karyotype.

Regarding BTKi therapy, responses to covalent BTKis are poor in patients with DLBCL-RT. A small cohort with RT in the BRUIN study found that six of eight patients had a partial response to pirtobrutinib, but there is no information available regarding the duration of therapy or PFS for this subset. Checkpoint inhibitors and some bispecific antibodies (mosunetuzumab and blinatumomab) also have had disappointing outcomes in patients with DLBCL-RT, in early, small studies. However, epcoritamab and glofitamab show promise based on abstract presentations in 2022 and 2023.

CAR T-cell therapy is more promising for DLBCL-RT, but the quality of the data remains poor. In a phase 2 trial of axi-cel published in *Blood Advances* in 2020, eight of nine DLCBL-RT patients responded, but the follow-up was short.

With HV-RT, data is even more limited. Patients are usually treated with standard Hodgkin treatment, such as ABVD, and while the outcomes are inferior to de novo HD, these patients generally have better outcomes compared to patients with DLBCL-RT. For R/R HV-RT, expert opinion, based on a very small number of cases, recommends using the same treatments as for R/R de novo Hodgkin's disease, such as pembrolizumab and brentuximab. AlloSCT can also be considered at the time of CR with non-myeloablative chemotherapy.

Despite major progress in CLL in the last 10 years, and improvement in the understanding of the pathology of RT in recent years, there has been no major progress for treatment of Richter transformation with targeted therapies.

CAR T-cell and BiTEs in MM

Dr. Ciara Freeman
Moffitt Cancer Center

Dr. Freeman began by highlighting that recent evidence shows that after four cycles of induction with quadruplet therapy, half of patients are MRD-negative. This is an impressive feat to build upon in the future, with de-escalation for those low-risk patients, and intensification and alternative strategies for high-risk patients. It's estimated that the mPFS after induction, consolidation, and maintenance therapy will be approximately 90 months.

In the second line-setting, in the US, patients who are lenalidomide-refractory now have access to cilta-cel. Emerging data shows a marked improvement in the PFS with cilta-cel in the second-line setting, compared to CAR T-cell therapy in the fourth line setting. Approximately 70% of patients who had received only one prior line of therapy were progression free at 24 months, based on a poster presentation at ASCO in 2023.

In the third-line setting, treatment options include ide-cel for patients with triple class-exposed MM and cilta-cel for patients with lenalidomide-refractory MM. In the third-line setting, the mPFS for ide-cel is 13 months, which was somewhat disappointing. However, this data may improve with better targeting of patients who are likely to derive benefit from ide-cel. Although the general view is that cilta-cel is a more toxic agent than ide-cel, cilta-cel is generally chosen for younger patients with more aggressive disease. It remains to be demonstrated in matched study whether cilta-cel is truly more toxic than ide-cel.

A study based on registry data compared a large cohort of patients above 70 years of age receiving ide-cel with a matched, younger cohort and found that older patients achieved slightly better PFS outcomes. It is unclear if this difference is due to biology that wasn't captured in the registry, but this is a phenomenon recognized with other CAR T-cell studies that researchers are working to understand.

In the fourth-line setting, three bispecific medications are now FDA-approved: elranatamab, teclistamab, and talquetamab. Bispecific agents achieve reasonably similar outcomes, with a range of 60% to 75% ORR, and a CR rate of approximately 30%. The mPFS is approximately 9 to 11 months. All the available bispecifics are administered by subcutaneous infusion, with a ramp-up phase. Elranatamab has the shortest inpatient ramp up, with a 5-day hospital admission. The bispecifics have similar rates of CRS and ICANS is rare. The infection risk with the bispecifics is very high however, with approximately 55% of R/R MM patients experiencing grade 3 or 4 infections with teclistamab. Aggressive pre-treatment with IVIG and monitoring for CMV reactivation will be important with bispecific treatment. Due to high rates of dysguesia and skin-related issues, Dr. Freeman recommended reserving talqeutamab for patients who have loss of BCMA expression or have progressed after BCMA-targeted therapy. A pooled analysis by Dr. Charan Vegivinti revealed a better ORR for CAR T-cell therapy, compared to BiTEs in the treatment of relapsed multiple myeloma and found a better ORR for CAR T-cell therapy (0.86 versus 0.67). In addition, the earlier that CAR T-cell therapy is used, the better and more functional the CAR T-cells will be. Another reason not to start with BiTEs is that continuously administering the product until toxicity or progression exhausts T-cells.

Ongoing trials are evaluating the use of cilta-cel and ide-cel in the frontline therapy. The FDA is expected to approve MRD as an endpoint, based on a petition from the Oncology Drug Advisory Committee, which will ideally lead to an earlier approval of agents.

While CAR T-cell therapy is highly effective in R/R MM, there is still a need to improve CAR T-cells. For those who are not candidates or don't have access to CAR T-cell therapy, BiTEs offer good responses and are easy to administer. Patients want finite therapy, and this can be more cost effective than indefinite therapy.

Q&A: What can CAR T-cell centers expect in terms of demand when CAR T-cell therapy is available for MM patients in Canada?

Dr. Freeman said in the near future, most MM patients will have access to CAR T-cell therapy in the second line. It will be easier to bridge patients to CAR T-cell therapy when they are earlier in the course of disease. There could be an initial hesitancy among providers, however. Dr. Freeman said her institution has worked to scale up capacity to prepare for a widespread uptake of CAR T-cell therapy. It's unclear, however, whether Johnson & Johnson and Legend have the manufacturing capacity to accommodate the influx. For the last 6 to 8 months, she has not had to wait for cilta-cell access for any patient who meets the indication.

Q&A: As CAR T-cell therapy is being evaluated in the first line setting at your center, which eligible patients will you decline for this therapy?

Dr. Freeman said her center has a paradigm for optimizing CAR T-cell therapy in older patients, that includes supervised exercise interventions and a cardiologist consult to manage cardiac comorbidities. She recently provided CAR T-cell therapy for a patient on dialysis. One goal of her center is to generate the data on CAR T-cell therapy in less fit patients. Her center's research has shown that patients with pre-existing cardiac comorbidities are not at an increased risk of a cardiac event, so long as their cardiac conditions are optimally managed. While there are patients for whom CAR T-cell is not suitable, strict age-based and comorbidity-based criteria are becoming less defensible.

The Current and Future Landscape of MM in Canada

Dr. Darrell White
Dalhousie University
Canadian Myeloma Research Group

Dr. White said that in the first-line setting, the majority of centres use RVD as induction to ASCT, followed by R maintenance. A study presented at EHA 2023 showed that 3-year PFS rates were 68% among patients who received RVD as induction, versus 40% among patients who had received CyBorD. For transplant ineligible, there are many possible options, but most receive DRD, outside of clinical trials.

In the near future, D-RVD could replace RVD as induction therapy. The GRIFFIN trial showed that PFS was longer for D-RVD, compared to RVD, with a 55% reduction in the risk of disease progression or death. OS is not yet different, perhaps due to the short-term follow up of the trial. The PERSEUS trial showed a similar reduction in the risk of progression with D-RVD, as well as higher rates of CR and MRD-negativity. Benefits were found in all subgroups except for patients over 65, where the PFS was similar across both trial arms.

Another question being explored is whether an anti-CD38 therapy should be included in the induction phase. A study from Dr. Francesca Gay presented at ASH 2023 showed isatuximab added to KRd induction and consolidation increased MRD negativity rates in each treatment phase in transplant-eligible patients. Rates of MRD negativity after consolidation with Isa-KRd versus KRd were 77% and 67%, respectively.

In transplant-ineligible patients, the MAIA trial demonstrated an efficacy advantage for DRd over Rd, with a mPFS of 62 months compared to 34 months. Frontline CAR T-cell therapy could be a better option, given the toxicity of DRd, however.

In the second-line setting, Dr. White highlighted the common situation in which patients are sensitive to bortezomib, and refractory to lenalidomide and possibly daratumumab. For such patients who are anti-CD38 naïve, Dr. White recommended the consideration of IsaKd or SVd, based on the IKEMA and BOSTON data. If the patient is refractory to both lenalidomide and anti-CD38 therapy, Dr. White recommended considering SVD.

In the third-line setting, patients are likely to be refractory to lenalidomide and anti-CD38 therapy. If they are sensitive to bortezomib, Dr. White recommended considering SVD if not already used, or carfilzomib or bortezomib. For triple-class refractory patients (refractory to lenalidomide, bortezomib and anti-CD38 therapy), Dr. White recommended choosing either carfilzomib or pomalidomide, and using the alternative in the fourth line.

In the fourth-line setting, most patients are likely refractory to either carfilzomib or pomalidomide, or both. Current off-trial options include the compassionate use of teclistamab or elranatamab. Cilta-cel is Health Canada-approved and may also be available soon for these patients.