Canadian Hematology Today

Toronto Lymphoma Conference 2023

Toronto, ON
November 3, 2023

Event Summary & Evaluation Report

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In this report...

Abbreviations

ABVD	Doxorubicin, bleomycin, vinblastine, and dacarbazine
AlloSCT	Allogeneic stem cell transplant
ALK	Anaplastic lymphoma kinase
ASCO	American Society of Clinical Oncology
ASCT	Autologous stem cell transplant
ASH	American Society of Hematology
AVEPC	Doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide
Axi-cel	Axicabtagene ciloleuce
BEACOPP	Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone
BiTE	Bispecific T-cell engager
BR	Bendamustine plus rituximab
BrECADD	Brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone
Brexu-cel	Brexucabtagene autoleucel
BTKi	Bruton tyrosine kinase inhibitor
BV	Brentuximab vedotin
BV-AVD	Brentuximab vedotin and doxorubicin, vinblastine, and dacarbazine
BV-CHP	Brentuximab vedotin and cyclophosphamide, doxorubicin, and prednisolone
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisolone
CAR-T	Chimeric antigen receptor T-cell
CHL	Classical Hodgkin lymphoma
CLL	Chronic lymphocytic leukemia
CMR	Complete metabolic response
CRS	Cytokine release syndrome
DDGP	Cisplatin, dexamethasone, gemcitabine, and pegaspargase
DLBCL	Diffuse large B-cell lymphoma
eBEACOPP	Escalated BEACOPP
ECOG	Eastern Cooperative Oncology Group
FCR	Fludarabine, cyclophosphamide, and rituximab
GALEN	Obinutuzumab and lenalidomide
GDP	Gemcitabine, dexamethasone, and cisplatin
GVD	Gemcitabine, vinorelbine, and doxorubicin
IPI	International Prognostic Index
IPS	International Prognostic Score
Liso-cel	Lisocabtagene maraleucel
MCL	Mantle-cell lymphoma
mPFS	Median progression-free survival
MRD	Minimal residual disease
N-AVD	Nivolumab and doxorubicin, vinblastine, and dacarbazine
NOS	Not otherwise specified
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
PMR	Partial metabolic response
POD24	Progression of disease within 24 months
Pola	Polatuzumab vedotin
Pola-R-CHP	Polatuzumab vedotin with rituximab, cyclophosphamide, doxorubicin, and prednisone
PTCL	Peripheral T-cell lymphoma
R2	Lenalidomide and rituximab
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone
R-CVP	Rituximab, cyclophosphamide, and vincristine sulfate
R-EPOCH	Rituximab, etoposide phosphate, prednisone, vincristine sulfate (Oncovin), cyclophosphamide, and doxorubicin hydrochloride
R-GDP	Rituximab, gemcitabine, dexamethasone and cisplatin
R-ICE	Rituximab, ifosfamide, carboplatin, and etoposide phosphate
R/R	Relapse/refractory
SMILE	Dexamethasone, methotrexate, ifosfamide, l-asparaginase, and etoposide
SWOG	SouthWest Oncology Group
SUV	Standardized uptake values
Tisa-cel	Tisagenlecleucel

Learning Objectives

Drs. Kuruvilla and Anglin welcomed participants to the conference and thanked the sponsors for the opportunity to learn how research and the approvals of new agents are changing the treatment landscape in Canadian hematology.

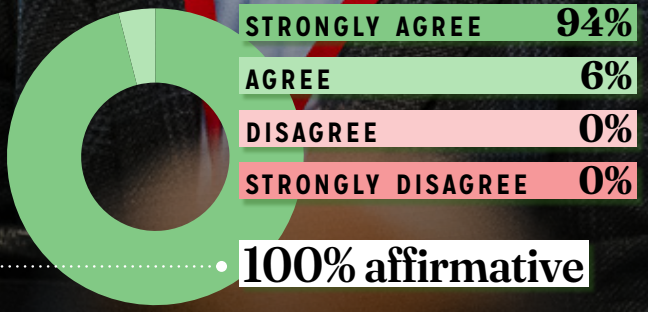
The objectives of the conference were to:

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

Attendee Feedback

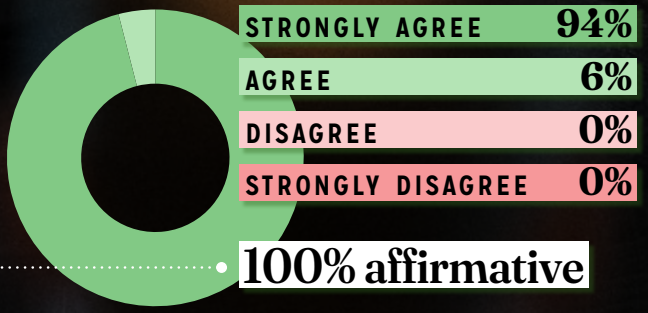
The topics covered provided a a comprehensive discussion of lymphoproliferative disease.

Clinician feedback survey prompt



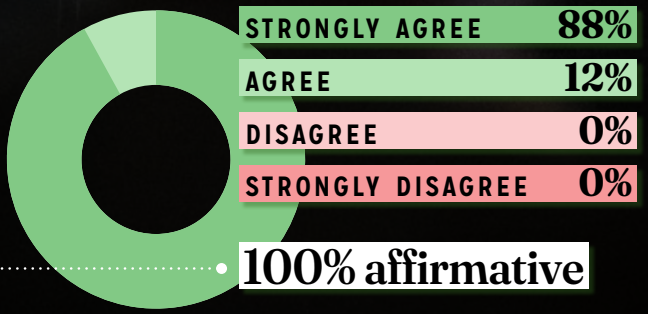
Presentations were appropriate for my level and provided new information or perspectives.

Clinician feedback survey prompt



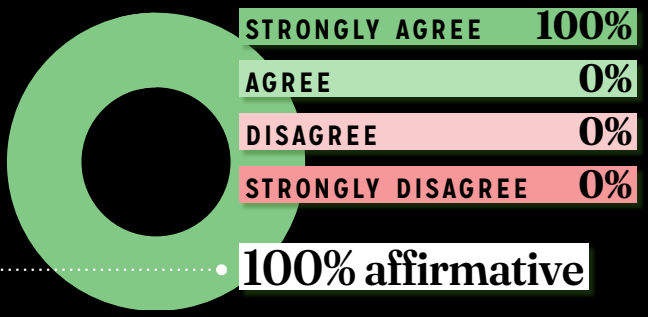
The information presented was high-quality, useful, and relevant to my hematology practice.

Clinician feedback survey prompt



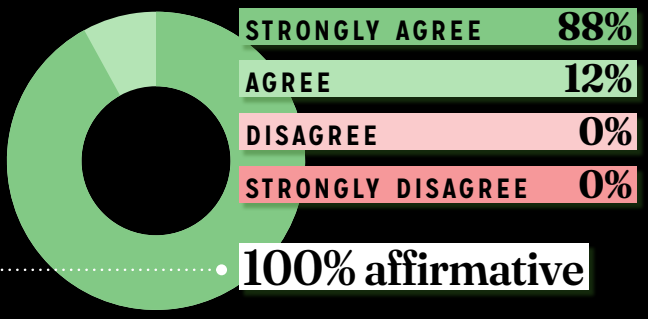
The timing of the agenda (length of lectures, panels, Q&A) was appropriate.

Clinician feedback survey prompt



There were good networking opportunities with colleagues and industry representatives.

Clinician feedback survey prompt



Excellent speakers, important topics, well-organized meeting in a very pleasant setting. I really enjoyed the discussions at the end of each session.

— CLINICIAN FEEDBACK SURVEY

What is the SOC for POD24 FL?

Dr. Dai Chihara

MD Anderson Cancer Center

Dr. Chihara provided an overview of POD24 as an important measure in follicular lymphoma. The OS after POD24 differs by treatment. The five-year OS after progression was 73.5% among patients who had initially received chemo-immunotherapy, compared to 90.9% from rituximab monotherapy and 66.9% from chemotherapy.

In the British Columbia Centre for Lymphoid Cancer analysis of 296 patients from 2013-2018 who received BR, followed by rituximab maintenance, those who experienced POD24 had poor outcomes, with a two-year OS rate of 38%. Even with newer treatments, including R2 and GALEN, POD24 occurs in approximately 10% to 15% of patients.

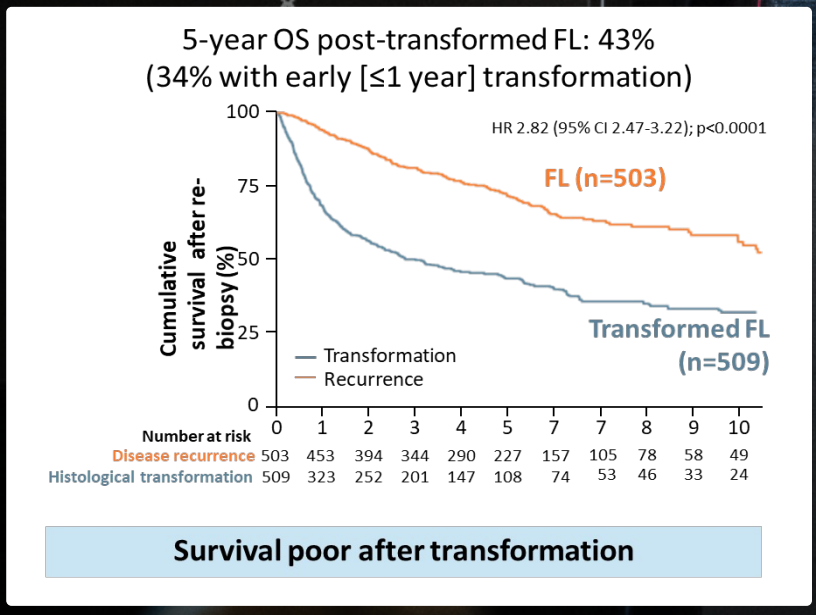
Predicting POD24 requires identifying high-risk patients at the time of diagnosis. The m7-Follicular Lymphoma International Prognostic Index (m7-FLIPI), is the most validated biomarker for predicting POD24, but its accuracy rate is only 75% at the time of diagnosis. Transformation is an important predictor of outcomes in follicular lymphoma patients who experience POD24. There is significantly lower rates of OS following progression in patients who had transformed relapse versus those with non-transformed relapse. This underscores the importance of biopsy every time patients with follicular lymphoma experience progression.

Regarding treatment options, a real-world evidence trial involving eight U.S. academic centers identified 196 patients experiencing POD24 between 2002 to 2019. The outcomes of post-POD24 therapy did not demonstrate a preferred treatment approach, and the OS was very poor.

Two studies have explored the potential impact of ASCT in these high-risk patients. A study led by Dr. Carla Casulo found a moderate OS benefit of ASCT in patients with POD24, but only if the transplant occurred within a year post-progression. The German Low Grade Lymphoma Study Group also found ASCT improved outcomes, while the PRIMA trial found ASCT improved outcomes in those with transformed disease, but not those with relapse. In the current era of CAR-T therapy, Dr. Chihara said he does not refer patients with POD24 for transplant.

The ZUMA-5 trial, studying axi-cel therapy in the third-line setting and beyond showed good activity in POD24 follicular lymphoma. Three-year progression-free survival was 59% in 63 patients with POD24. Bispecific medications are also promising. A Lancet Oncology paper demonstrated an ORR of 83% and complete response rate of 55% with mosunetuzumab, and outcomes were not significantly different between patients with and without POD24. Epcoritamab, in combination with R2 has also shown impressive response, with an ORR of 100% and a complete response rate of 86% in patients with POD24 in the second-line setting. Long-term follow up is needed to see the full potential of this combination.

While bispecific medications and CAR-T therapy are likely to change the trajectory for this high-risk patient population, there is currently no current standard treatment approach. Ongoing, randomized phase III studies are poised to resolve this lack of clarity, and the role of T-cell engaging treatment in POD24 patients.



Survival poor after transformation

BiTEs and CAR-Ts in R/R Follicular Lymphoma

Dr. Ronan Foley
McMaster University

Follicular lymphoma is a highly heterogeneous disease, with an average age at diagnosis of 65. It is a relapsing and remitting disease, characterized by recurrent disease progressions, shorter remission periods, reduced response rates, and decreased survival with each treatment course. The unmet need is currently in the third-line setting, where new treatments are emerging.

First-line therapy includes radiation for limited and localized disease; BR, followed by rituximab maintenance for most patients, and rituximab monotherapy in elderly and frail patients. In the second-line, obinutuzumab in combination with CHOP is used; R-GDP is another option. Autografts can be appropriate for fit patients and BR may be appropriate for patients who had a long remission after the first treatment. In the third-line, options are limited to autologous and allogeneic stem-cell treatment and chemoimmunotherapy options including R-GDP, R-ICE, R-CHOP, BR, R-CVP. R2 doesn't have approval in Canada, but is supported by strong data in the third-line setting.

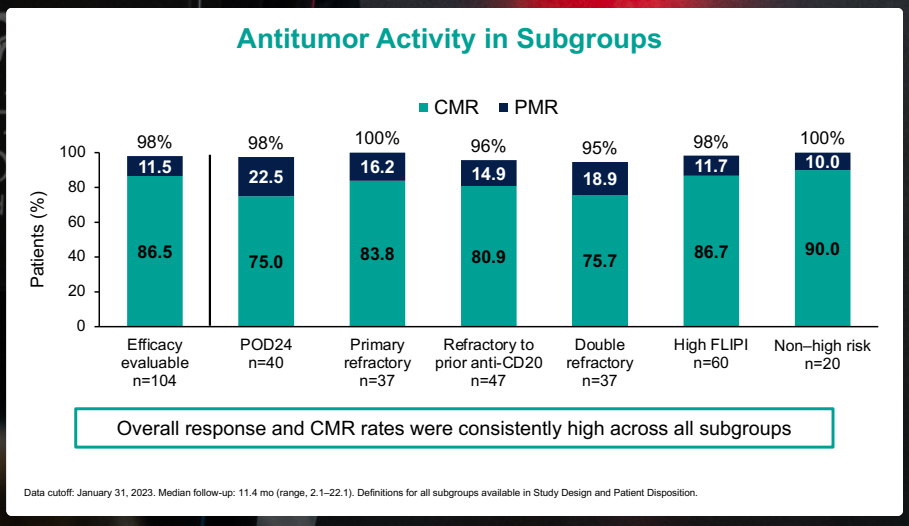
CAR-T therapies are also being considered for advanced follicular lymphoma. The ELARA trial evaluated tisa-cel in follicular lymphoma patients with two or more prior lines of therapy and no evidence of transformation, no active central nervous system involvement and no prior-CD19 therapy. The ORR at 29 months was 86% and the CR was 68%. No deaths were attributed to the drug, and CRS was 48%, with zero patients experiencing grade 3 CRS.

The Zuma-5 trial of axi-cel therapy followed a similar group of R/R follicular lymphoma patients, but also included a cohort with marginal zone lymphoma. Response rates were remarkable over a 23-month period, with 80% of follicular lymphoma patients achieving a complete response. CRS occurred in 78% of patients, with 6% of these experiencing grade 3 CRS. Grade 3 or 4 neurologic events occurred in 19% of patients. Dr. Foley underlined the importance of using prophylaxis to prevent neurologic events in those with concerning serum biomarkers.

Patient selection is extremely important in CAR-T therapy, and should be reserved for patients with an ECOG performance status scale of 0-2, adequate vital organ function and clinically stable cardiac, renal, and pulmonary reserve co-morbidities, and no active uncontrolled infection or prior autoimmune disease.

Noting the danger of the 60-day lead-up before CAR-T infusion, Dr. Foley showed the data for BiTE therapy in R/R follicular lymphoma. In a study of 90 patients, mosunetuzumab demonstrated a 60% CR rate, with 48% achieving PFS at 24 months. Among those who achieved a CR at eight cycles, 77% achieved PFS at 24 months. CRS was manageable, with grade 3 and 4 CRS occurring at 1%.

Epcoritamab is another BiTE option, which is subcutaneously administered. The EPCORE NHL-2 trial assessed epcoritamab in combination with R2, to test the potential for the immunomodulatory properties of lenalidomide increasing the therapeutic potential of epcoritamab. The safety data showed 46% experienced grade 1 or 2 CRS, and 2% experienced grade 3 CRS. The timing of CRS was predictable, at the first full dose of CRS, and all CRS resolved. The response rates were remarkable, with a 98% ORR, with impressive results across subgroups. Dr. Foley noted the results are based on 12 month follow-up, so more time is needed to demonstrate success.



Dr. Foley concluded that the capacity of centers and patient preference of treatment location will play a role in the decision between BiTE and CAR-T therapies. He expects that approximately 80% of patients will be best suited for BiTE treatment, while 20% will go on to CAR-T therapies. With repeated BiTE and CAR-T therapies, it will be important to monitor cytopenia, B cell aplasia, and T-cell fitness over the long-term.

Panel Discussion

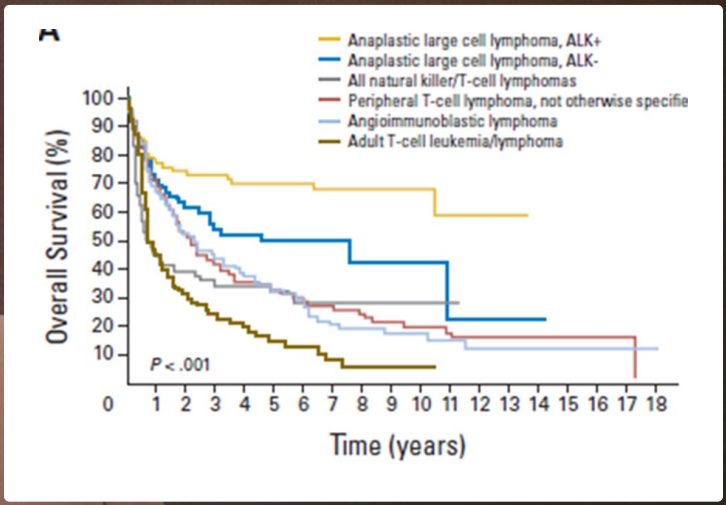
Dr. Dai Chihara, Dr. Ronan Foley
Moderator: Dr. Peter Anglin

- Dr. Anglin asked Dr. Chihara how he treats follicular lymphoma patients who relapse a year after primary therapy with BR?
- Dr. Chihara said he uses R2, so long as there is no transformation. Anglin noted that R2 is not currently used in Canada. (Dr. Anglin has used it in one patient).
- Dr. Anglin asked Dr. Chihara how he utilizes PET scanning in a progressing patient?
- Dr. Chihara said he doesn't trust SUV, based on Dr. Julia Trotman's study showing this is not necessarily predictive of transformation. PET-CT can, however, guide the physician on where to do the biopsy. He doesn't treat patients as having transformed disease based on SUV alone; however, if patients are symptomatic with high lactate dehydrogenase, he will sometimes use anthracycline-based treatments in these cases, even without confirming transformation.
- Dr. Lunning noted that many institutions catch POD24 progression based on surveillance imaging, while others observe POD24 based on symptoms alone. He questioned whether the latter have worsened outcomes than the former.
- Dr. Chihara said that question while important, is difficult to answer, given that there is significant heterogeneity across practice sites regarding scan frequency.
- Dr. Svodboda asked if there is any effort to study the biology of tumors in follicular lymphoma with next-generation sequencing?
- Dr. Chihara noted Dr. Michael Green published data last year in Cancer Discovery, looking at the immune signature subtypes. While BR remains the gold standard, further understanding of the genetic subtypes could help physicians identify patients who may have better outcomes on alternatives to BR.
- Dr. Siddiqui asked why R2 is not used in Canada?
- Dr. Anglin explained that there are many access barriers, despite the fact that rituximab and lenalidomide are generic. Dr. Foley added that the manufacturer never took the drug to Health Canada for approval.
- Dr. Anglin asked about access to cellular therapies in follicular lymphoma. Dr. Foley said he expects CAR-T therapy to be available for follicular lymphoma in 24 months. Ideally, BiTEs will be available in the same period.
- Dr. Anglin asked about compassionate access to epcoritamab and mosunetuzumab. Dr. Banerji noted that there is compassionate access in Canada for B-cell malignancies for epcoritamab.

Overview of the Treatment of PTCL-NOS

Dr. Matthew Lunning
University of Nebraska Medical Center

Dr. Lunning provided an overview of the subtypes of PTCL, noting that PTCL NOS and angioimmunoblastic lymphoma are the most prevalent. There are efforts to delineate PTCL NOS based on GATA3 and TBX21 gene expression. ALK+ anaplastic large cell lymphoma has the best prognosis. However, regardless of the subtype, OS at one year is poor.



Dr. Lunning highlighted the importance of checking patients' HTLV1 status, because adult T-cell leukemia/lymphoma patients require a different treatment approach, compared to the other subtypes.

A randomized trial of BV-CHP versus CHOP in PTCL included 75% of patients with anaplastic large cell lymphoma, ALK-. It found five-year PFS rates were 51% for BV-CHP versus 43% with CHOP, and five-year OS rates were 71% and 61% respectively. Dr. Lunning said he prefers BV-CHP for PTCL-NOS, as BV seems to be more powerful than vincristine.

The median OS of PTCL is 6 months. Chemotherapy is often ineffective against primary or refractory PTCL, no matter the regimen. Novel agents can, however, provide benefit. Much of the progression occurs in drug breaks, and Dr. Lunning recommended adjunctive strategies to keep patients on therapy.

Cellular therapies are emerging in PTCL, with data presented at ICML showing an ORR of 70% and complete response rate of 30% in small trials of CAR-T therapies in PTCL patients. He noted, however, that the window to initiate CAR-T therapy is often only a few months in these patients.

Agent	MOA	Response	Median DOR
APPROVED IN USA			
Romidepsin	HDACi	ORR: 38% CR: 18%	8.9 months
		ORR: 25% CR: 18%	17 months
Belinostat	HDACi	ORR: 26% CR: 11%	13.6 months
Pralatrexate	DHFRi	ORR:29% CR: 10%	10 months
Brentuximab	CD30 ADC	ALCL: ORR: 86% CR: 57%	25.6 months
		PTCL/AITL: ORR: 41% CR: 24%	7.6 months
APPROVED OUTSIDE USA			
Chidamide	HDACi	ORR: 29% CR:14%	9.9 months
Forodesine	PNPI	ORR: 24% CR: 10%	10 months

Management of Rare PTCL Subtypes

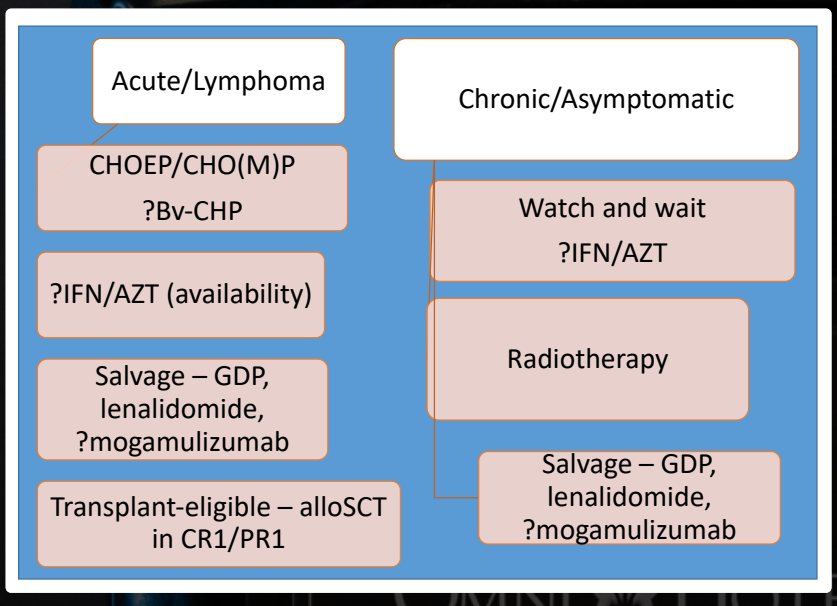
Dr. Anca Prica

Princess Margaret Cancer Centre

Dr. Prica focused her talk on HTLV-1 adult T-cell leukemia/lymphoma, extranodal natural killer T-cell lymphoma, aggressive natural killer T-cell leukemia, and hepatosplenic T-cell lymphoma.

Adult T-cell leukemia/lymphoma is one of the most fatal lymphoid malignancies, with a five-year OS of less than 20%. About 10 to 20 million people have HTLV1 worldwide, which causes adult T-cell leukemia/lymphoma in 1-4% of patients.

Dr. Prica explained that chemotherapy remains the main treatment approach for adult T-cell leukemia/lymphoma. Methotrexate may be added for patients with central nervous system presentation. BV-CHP is approved on a case-by-case basis. Interferon and azidothymidine are supported by data, but challenging to access.



For refractory patients, GDP or lenalidomide can provide benefit, and mogamulizumab may be available on a compassionate basis. The goal with treatment is remission, so that the patient can proceed to alloSCT.

Chronic and asymptomatic adult T cell leukemia/lymphoma is more rare, with treatments including a watch-and-wait approach; interferon and azidothymidine, if accessible and radiotherapy (for patients with cutaneous presentations).

Experiences from Japan show that approximately one third of patients who get alloSCT have a longer period of remission, and outcomes are especially improved among those who access alloSCT within 100 days of diagnosis. Donor availability is, however, is much lower in North America, compared to the Japanese context. There are several new treatment options on the horizon. Dr. Prica highlighted valemetostat, which was demonstrated to have an ORR of 48% in adult T cell leukemia/lymphoma.

Another subtype, NK/T-cell lymphoma, is more prevalent in China, Japan, Korea, and Southeast Asia, as well as Mexico, Central America, and South America. This subtype is almost exclusively extranodal, and usually limited to the nose and nasopharynx. The treatment protocol used at Dr. Prica's center since 2011 is radiation therapy and cisplatin plus chemotherapy. Approximately one quarter of patients experience early failure and poor outcomes, while the remainder achieve OS rates above 80%. Other approaches include chemotherapy followed by radiation as well as radiation between chemotherapy cycles.

For aggressive natural killer T-cell leukemia, a new regimen of DDGP improved PFS and OS, compared to SMILE. These results could be driven by a higher proportion of patients completing all cycles of the DDGP regimen, compared to the SMILE regimen.

When chemotherapy fails, PD1/PDL1 inhibitors may be accessible on a case-by-case basis, and demonstrate ORR rates ranging from 31% to 68% in small studies.

Hepatosplenic T-cell lymphoma occurs in less than 5% of all PTCL cases, with slightly over 200 cases reported in the literature. Outcomes with standard anthracycline-containing induction regimens, such as CHOP, have been disappointing, with a median OS of 13 months. However, none of the other approaches have been successful. As with the other subtypes, complete response is the goal, so that the patient can proceed to alloSCT.

Panel Discussion

Dr. Matthew Lunning, Dr. Anca Prica
Moderator: Dr. John Kuruvilla

- Dr. Kuruvilla asked about clinically important biomarkers, beyond CD30 expression percentages?
- Dr. Lunning said that for anaplastic large cell lymphoma, he will request TP63 as well as and DUSP22 testing. For patients who have ALK- lymphoma and DUSP22 expression, he will look at the IPS, and may accordingly defer consolidative autologous transplant in such patients.
- Dr. Kuruvilla agreed that the lesson is that there is no-one-size-fits-all approach, and CHOP is not always appropriate for everyone.
- Dr. Kuruvilla asked about the applicability of non-CHOP regimens for PTCL.
- Dr. Prica said that giving DDGP, and then radiation, and then returning to chemotherapy may be more feasible for some centers. In some of the regimens, pegasparaginase makes a difference, particularly for advanced stage natural killer T-cell lymphoma and Cancer Care Ontario is funding a single injection given every three weeks.
- Dr. Lunning added the caveat that pegasparaginase has a thrombosis and fatty liver disease risk. Dr. Prica agreed, noting she ensures patients are followed by nurse practitioners who have experience with this therapy.
- Dr. Foley also questioned if pathologists are picking up the follicular helper T-cell phenotype.
- Dr. Lunning said other markers, such as CD10 and PD1, can help to differentiate the TFH phenotype diagnosis.
- Dr. Crump asked why lenalidomide hasn't been added to T-cell lymphoma regimens?
- Dr. Prica said she anecdotally hasn't had great responses with lenalidomide in PTCL patients, but it would be reasonable to add to CHOP, based on data in adult T-cell lymphoma.
- Dr. Lunning said he uses lenalidomide and romidepsin, in certain angioimmunoblastic T-cell lymphoma patients.

Evolving Primary Therapy Approaches in DLBCL

Dr. Jason Westin
MD Anderson Cancer Center

Dr. Westin explained that DLBCL is the most common lymphoid malignancy, with a median age at diagnosis of 64. The distinct signalling pathways of the ACB or GCB subtypes has been known for more than 20 years, but is not used in clinical decisions as testing is not widely available.

Studies show that more intensive therapy is better for those with the double-hit subtype (high-grade MYC and BCL2 rearrangements). Data from the MD Anderson Cancer Center from 2014 shows that patients with double-hit lymphoma do better on R-EPOCH, compared to R-CHOP.

In general, however, the addition of other agents to R-CHOP have shown little improvement, nor have alternative chemotherapy regimens outperformed R-CHOP overall. There may be benefit in some subgroups, however. A presentation at the most recent ASH meeting of a five-year update from the ReMoDL-B trial showed BR-CHOP led to a significant improvement in OS in molecular high-grade DLBCL patients, compared to R-CHOP. Dr. Westin does not recommend using BR-CHOP off-label due to the toxicity of bortezomib, and noted the subgroup was relatively small. However, these findings suggest that future treatment regimens could be targeted according to molecular subtype.

Similarly, an age subgroup analysis in the Phoenix trial showed ibrutinib and R-CHOP resulted in better outcomes in a small subset of younger patients. The Phoenix trial also demonstrated high efficacy of ibrutinib in patients with the MCD and N1 subtypes of DLBCL. If it were possible to identify people with these molecular subtypes, it may be possible to achieve high cure rates with targeted therapy in the first line.

The POLARIX trial, a large randomized controlled study comparing Pola-R-CHP and R-CHO, demonstrated a relatively small benefit with Pola-R-CHP. The 24-month PFS was 76.7%, versus 70.2% with R-CHOP. The toxicities between the two groups were similar. However, a cost-effectiveness analysis showed a dramatic cost increase if Pola-R-CHP were to be incorporated into the first-line setting, despite the cost savings of preventing some CAR-T therapy in the second-line setting for some patients. Pola-R-CHP showed the strongest benefit in patients with ABC subtype DLBCL. This data, combined with similar findings in earlier studies, suggest Pola-R-CHP could be used in the frontline setting for those with ABC subtype DLBCL.

Another new approach could be to deescalate therapy. The FLYER study of 588 patients with stage I/II aggressive B-cell lymphoma showed four cycles were as effective as six cycles.

Regarding novel treatments, Zuma-12 looked at axi-cel therapy in a high-risk frontline patient population, with poor responses to two cycles of chemotherapy. The CR rate was nearly 80% and the ORR almost 90%.

Dr. Westin highlighted his team's study of rituximab, lenalidomide, and ibrutinib in patients with newly diagnosed large B-cell lymphoma, followed by six cycles of R-CHOP. The CR at the end of the therapy was 94.5%. Two year-results show PFS of 91.3%.

Dr. Westin summarized that while R-CHOP remains the best option for many patients with DLBCL, R-CHP-Pola and R-EPOCH may be preferred in some subgroups. New approaches are exploring the role of BTKis and bispecific antibodies in combination with R-CHOP therapy.

What is new in CAR-T for DLBCL?

Dr. Jakub Svoboda
University of Pennsylvania

Dr. Svoboda provided an overview of the current CAR-T therapies, and their approved indications. He noted that in Canada, axi-cel and tisa-cel are approved in the third line and beyond for DLBCL, and second-line indications may be available in the near future.

A one-time infusion of CAR-T therapy can cure DLBCL in some patients, as evidenced by the five-year follow up of the ZUMA-1 trial. Toxicity of CAR-T therapy is manageable, with CRS rates ranging from 43% in the TRANSCEND trial to 93% in the ZUMA-1 trial. This demonstrates the improvements in managing and mitigating the risks of CAR-T therapy, through earlier use of tocilizumab and other agents.

At the Abramson Cancer Center at the University of Pennsylvania, Dr. Svoboda explained that 41BB CAR-T cells are administered in an outpatient facility, with nurse practitioner monitoring. Data found 30% of those patients were admitted to the hospital within 28 days, showing 70% of outpatients did not require hospitalization. Retrospective data comparing fludarabine/cyclophosphamide and bendamustine as a lymphodepleting agent show the latter could reduce infections as well as CRS and neurotoxicity syndromes of any grade.

CAR-T therapy is especially effective in the second-line setting. Randomized trials presented at ASH 2021, comparing CAR-T therapy in the second-line to the standard of care, showed that mPFS among those randomized to CAR-T therapy was approximately 15 months, compared to 4 to 6 months in the standard of care cohorts. In the U.S., the aim is to proceed to CAR-T in the second-line setting for patients who relapse within a year of frontline treatment.

Patient selection of CAR-T therapy is more important in the context of new treatment options, such as bispecific medications. Patients with a high metabolic tumor volume and two or more extranodal sites have poor outcomes from CAR-T therapy, with PFS probability below 20% at six months. Comparatively, patients who have neither of these factors have a PFS probability of 75% nearly 1 year post-treatment. Circulating tumor DNA shortly after infusion also shows promise as a prognostic tool, and, in the future, could guide physicians to move more quickly to subsequent therapies in high-risk patients.

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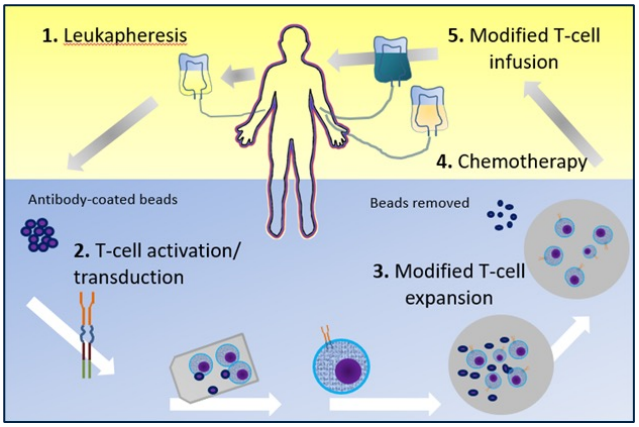
Outcomes for those who progress after CAR-T are poor. An analysis by Dr. Roberta Di Blasi published in 2022 in Blood found a median OS of 5.2 months in patients who progressed after CAR-T. A study at the University of Pennsylvania and a multi-site SWOG trial is underway exploring whether bispecific antibodies at one-month post-CAR-T therapy could improve outcomes among partial responders with stable disease. Changing the target of CAR-T therapy could also show benefit, as evidenced by preliminary data from trials of CD20- and CD22-targeting therapies as well as the combination of CD19- and CD20-targeting CAR T-cell therapies in various types of lymphoma.

Additional improvements may be found in expedite the manufacturing time of CAR-T cells and fourth-generation CAR-T therapy, which is engineered to secrete transgenic cytokine, potentially adding immune-modulating benefit.

CHIMERIC ANTIGEN RECEPTOR T CELLS IN LYMPHOMAS

AUTOLOGOUS CELL PRODUCTS



FDA APPROVED PRODUCTS AND INDICATIONS

Axi-cel	•**2017: ≥3L LBCL** •2021: ≥3L FL •**2022: 2L high risk LBCL**
Tisa-cel	•**2018: ≥3L LBCL** •2022: ≥3L FL
Liso-cel	•**2021: ≥3L LBCL** •**2022: 2L high risk LBLC**
Brexu-cel	•2021: r/r MCL

Bispecific Antibodies in RR-DLBCL

Dr. Krish Patel

Swedish First Hill Hospital, Seattle, WA

Dr. Patel explained that cellular therapy, while transformative, remains out of reach for many patients, due to disease progression, social barriers, and limitations in manufacturing. Even in the ideal setting of clinical CAR-T trials, about 15% do not go on to CAR-T therapy. This number is likely much higher in the real-world setting. CAR-T therapy cures approximately 30% to 40% of patients, showing the great demand for post-CAR-T options.

Bispecific antibodies are currently used when CAR-T therapy is not feasible, and more commonly, in the third-line setting beyond post-CAR-T therapy failure. Dr. Patel explained CAR-T therapy may be not feasible due to a lack of market access, a lack of transportation/caregiving support, or in the case of very aggressive disease and comorbidities.

Ten-year follow up studies of blinatumomab suggest the possibility of a functional cure with bispecific antibodies, but it remains unknown for which patients modern bispecific medications may be curative therapies.

Glofitimab, approved in Canada for DLBCL in the third-line setting, has been studied in an expansion cohort of patients with large-cell lymphoma who had at least two prior lines of therapy. In the cohort, 60% of patients were in the third-line-plus setting, 33% had prior CAR-T therapy and 85% were refractory to prior therapy. Results demonstrated an ORR of 61% and a CR rate of 39%.

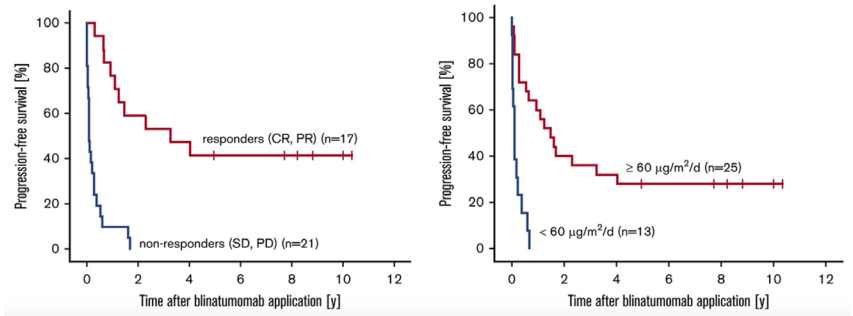
The median OS for glofitimab of 11.5 months compares to the data from DESCAR-T registry, showing progression in post-CAR-T cell therapy patients of 2 to 6 months. Data for patients with an early complete response is encouraging, with an OS rate of 80% at 18 months. CRS with Glofitimab occurred in 63% of patients, with very few patients experiencing grade 3 (2.6%) or grade 4 CRS (1.3%).

Epcoritimab is also approved in the U.S. for third-line-plus CLL. It was administered until progression or toxicity in a high-risk population. The ORR in this cohort was 63%, and the mPFS was 4.4 months. As with glofitimab, most of the benefit is driven by patients achieving complete responses. CRS occurred in 50% of patients, with most CRS events occurring with the first full dose.

Dr. Patel highlighted that bispecific therapies have similar ORR and CR rates across agents, but most patients would prefer fixed duration treatment. Given the early CRs in most cases, further research should elucidate the subset of patients who truly benefit from prolonged therapy, and those who would benefit from a shorter duration of therapy.

How should we think about BsAb: Curative Potential?

- MT103-104 phase 1 Blina study→10 yr f/u



Majority were R/R FL, but MCL/DLBCL also

Median 3 prior lines

Median treatment duration 51 days (range 1-87) or ~ 1 8 week cycles

Small #s but for patients with CR/PR (45%), ~40% w/o disease progression >4 yrs from treatment
~20% long term non-progressors

Panel Discussion

Dr. Jason Westin, Dr. Jakub Svoboda, Dr. Krish Patel
Moderator: Dr Peter Anglin

- Dr. Prica asked about the infectious complications in BiTEs, including fungal infections and COVID. She inquired about possible prophylactic strategies.
- Dr. Patel said his institution's approach has been to use antimicrobial prophylaxis, similar to that used in the post-cellular therapy setting. He underlined the importance of intravenous immunoglobulin in patients who have a history of recurring infections, especially sinus and pulmonary infections.
- Dr. Westin said infections and neutropenia suggest fixed duration strategies are most appropriate for DLBCL.
- Dr. Crump asked about the approach for patients presenting with central nervous system relapse, in the context of data showing patients with extranodal refractory DLBCL do poorly on CAR-T therapy.
- Dr. Svoboda said that most clinical trials allowed patients with a history of CNS involvement, as long as they were controlled. Dr. Westin added if patients responded to bridging therapy, his approach is to proceed with CAR-T therapy in patients with CNS involvement. He recommended liso-cel, due to better data. However, due to manufacturing challenges, he has used axi-cel in patients with CNS involvement, and there have been no issues with cerebral edema. Dr. Patel added that recent research suggests CAR-T therapy outcomes for patients with CNS involvement appear to be similar to those without CNS involvement.
- Dr. Chihara asked whether the panellists were concerned about repeatedly targeting the same CD19 or CD20 antigen, and whether the expression level of the antigens changes treatment decisions.
- Dr. Svoboda said that CD20 expression is important for bispecific medications, however, for CAR-T therapy, CD19 expression testing isn't required, outside of clinical trials.

The Shifting Sands of Primary Treatment of Advanced CHL

Dr. Ann LaCasce
Dana-Farber Cancer Institute

Systemic therapies for CHL include ABVD, a regimen that has been used effectively for many years and does not cause infertility, nor stem-cell toxicity. Bleomycin can lead to lung toxicity in older patients, and those with renal dysfunction. PET-adapted delivery can mitigate these risks, by reducing the number of cycles. BEACOPP shows a PFS benefit over ABVD, but does impact fertility and cause stem-cell damage. BV has demonstrated high response rates, with CR rates of about 30%, in highly refractory patients. The main toxicity is peripheral neuropathy. Finally, the PD1 inhibitors are associated with high ORR, but are not expected to achieve long term disease control as a single agent. PD1 inhibitors are well-tolerated by most patients, but serious toxicities can occur.

The current management of advanced stage Hodgkin lymphoma in the U.S. is BV-AVD, while the approach in Europe is PET-adapted eBEACOPP. A 2022 study in NEJM showed impressive outcomes with BV and AVEPC and radiotherapy. Dr. LaCasce provided an overview of the trial outcomes and associated toxicities for each regimen:

Outcomes and toxicity

BV-AVD	EscBEACOPP	BV-AVEPC + RT
6 yr PFS: 82%	5 yr PFS: 91%	3 yr PFS: 92%
Neuropathy	Risk of infertility Stem cell damage (MDS/AML)	RT related side effects
Connors et al. NEJM 2017	Borchmann et al. Lancet Onc 2017	Castellino et al. NEJM 2022

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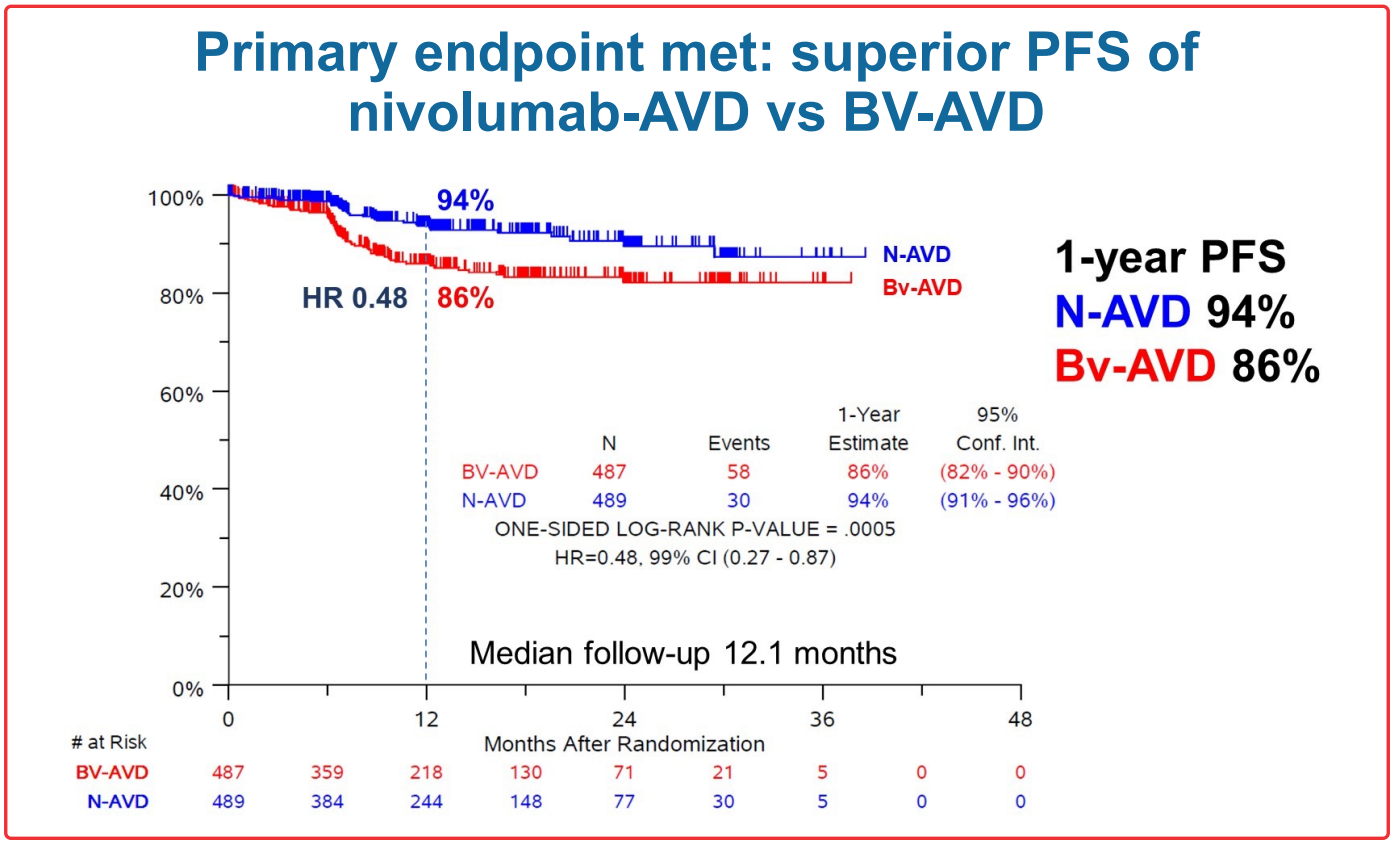
An important study presented by Dr. Alex Herrera at ASCO randomized patients 12 years and older with stage 3 and 4 CHL to either BV-AVD or N-AVD. The cohort was a young patient population, with a median age of 26.5. The IPS was high in about a third of patients and a third had bulky disease. At one-year, PFS was 94% for N-AVD, versus 86% for BV-AVD. Febrile neutropenia rates were similar across both regimens; thyroid dysfunction was 10% with N-AVD, versus 1% with BV-AVD. Peripheral sensory neuropathy was almost two times higher among patients who received BV-AVD. Of those who received N-AVD, the discontinuation rate was 11%, compared to 22% of patients discontinuing BV-AVD. For older patients, data from small subsets show that the hazard ratio (0.25) significantly benefits N-AVD.

A small, phase II study of BV with nivolumab, doxorubicin, and dacarbazine in 57 patients with advanced stage Hodgkin lymphoma was presented at the ASH meeting last year, demonstrating a 12-month PFS of 94%. Longer-term follow up is necessary to show whether this regimen is superior to N-AVD.

Despite new regimens, chemotherapy is still required in the treatment of Hodgkin lymphoma, especially in elderly patients with advanced stage disease. Given the expense of new regimens and the long-term remission success of BV-AVD in many patients, there is opportunity to use circulating tumor DNA to select patients who may do well with less therapy. Dynamic risk-adapted imaging approaches and tumor metabolic volumes may aid in identifying patients who need intensive therapy.

Overall, quality of life and financial burden will be important considerations in CHL treatment decisions.



Changing direction in the treatment of relapsed and refractory Hodgkin lymphoma

Dr. Michael Crump
Princess Margaret Cancer Centre

Dr. Crump described the three phases of intensive therapy for R/R Hodgkin lymphoma, from salvage therapy to high-dose chemotherapy to post-remission strategies, highlighting the lack of randomized comparisons of high-dose regimens in Hodgkin lymphoma. Outcomes are excellent for R/R patients who achieve a CR, but poor for those who don't achieve a CR on high-dose chemotherapy.

BrECADD is a more recent regimen in R/R Hodgkin lymphoma. Data presented at ICML 2023 showed improvement in toxicity endpoints and slight statistical superiority in efficacy, compared to eBEACOPP. Dr. Crump's centre is working to adopt BrECADD as a standard regimen.

Outcomes of Hodgkin lymphoma are also improving among patients relapsing after ASCT, and this improvement is driven in part by bendamustine and checkpoint inhibitors. An analysis of data from 18 centers, published in Blood Advances in 2023, show median survival is 114 months in R/R Hodgkin lymphoma patients post-ASCT, compared to 27 months in an analysis presented by Dr. Crump from 2008.

Regimens incorporating brentuximab and PD1 inhibitors appear promising but the Phase II data for these agents is subject to selection bias. Long-term follow-up studies of anti-PD1 antibodies in R/R Hodgkin lymphoma show five-year survival estimates of 74% for nivolumab and 71% for pembrolizumab, based on similar patient cohorts. Remarkably, 42% of the responses in the pembrolizumab study lasted more than two years, raising the possibility that newer agents could replace ASCT.

Regarding the monoclonal regimen brentuximab, regimens studied include combining BV with either bendamustine or nivolumab. A small study of BV and bendamustine showed a CR rate of 74%, with 40 of 53 proceeding to ASCT (75%). A multicentre phase 2 study of BV in combination with nivolumab found 91% of patients received ASCT per protocol. The 36-month PFS was 61% in primary refractory patients, and 90% in relapsed patients.

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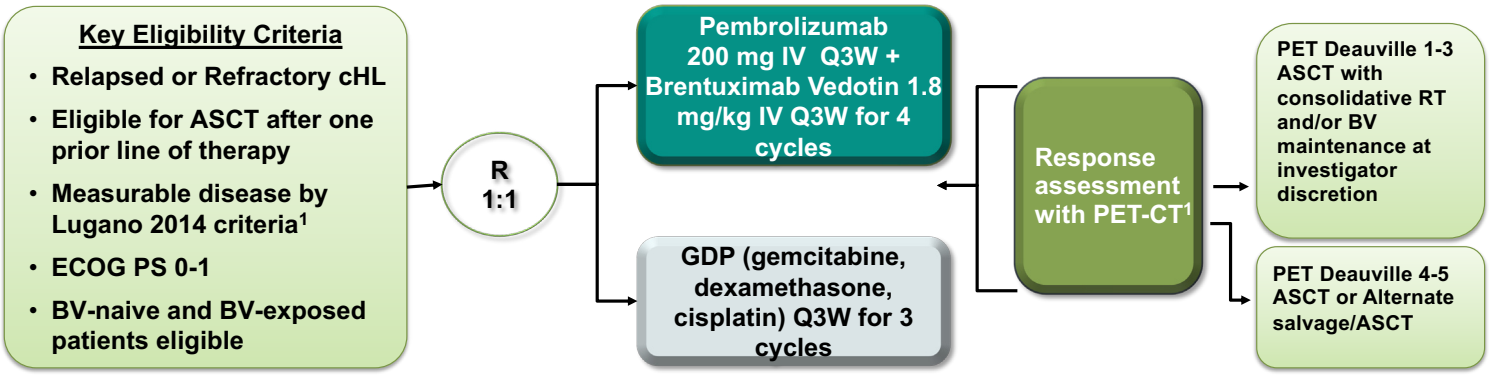
To answer the question of whether brentuximab or PD1 inhibitors should be used first in R/R HL, a randomized trial by Dr. Kuruvilla comparing the two options demonstrated superiority of pembrolizumab in patients refractory after one line of therapy, or after ASCT. Studies comparing brentuximab and PD1 inhibitors in combination with salvage chemotherapy show CR rates of 85-95% in those receiving PD1 inhibitors in addition to salvage chemotherapy, compared to 70%-80% in those receiving brentuximab and salvage chemotherapy.

Dr. Crump underscored the vital need to compare new combinations (bendamustine-brentuximab, nivolumab-brentuximab, and pembrolizumab-GVD) to standard chemotherapy, and presented the following study design for a trial currently recruiting patients:

CCTG HD.11: Randomized Phase 2 Trial of Pembrolizumab + Brentuximab Vedotin or GDP Salvage Therapy in patients pre-ASCT



Stratification Factors

- Prior Brentuximab vedotin and/or PD-1 inhibitor with primary therapy (Y/N)
- Duration of response to prior therapy (Refractory vs. Relapsed < 1 year vs Relapsed > 1 year

Canadian Cancer Trials Group PIs: K Savage, J Kuruvilla

Primary End Point: PET-CR by Lugano 2014 (Deauville 1-3)

Secondary End Points: PFS, EFS, OS, transplantation rate, toxicity and safety, HRQOL,health economics
Exploratory: translational correlatives, PET radiomics, RECIL criteria response

[1]Cheson BD et al. *J Clin Oncol. 2014*

Panel Discussion

Dr. Ann LaCasce; Dr. Michael Crump
Moderator: Dr. John Kuruvilla

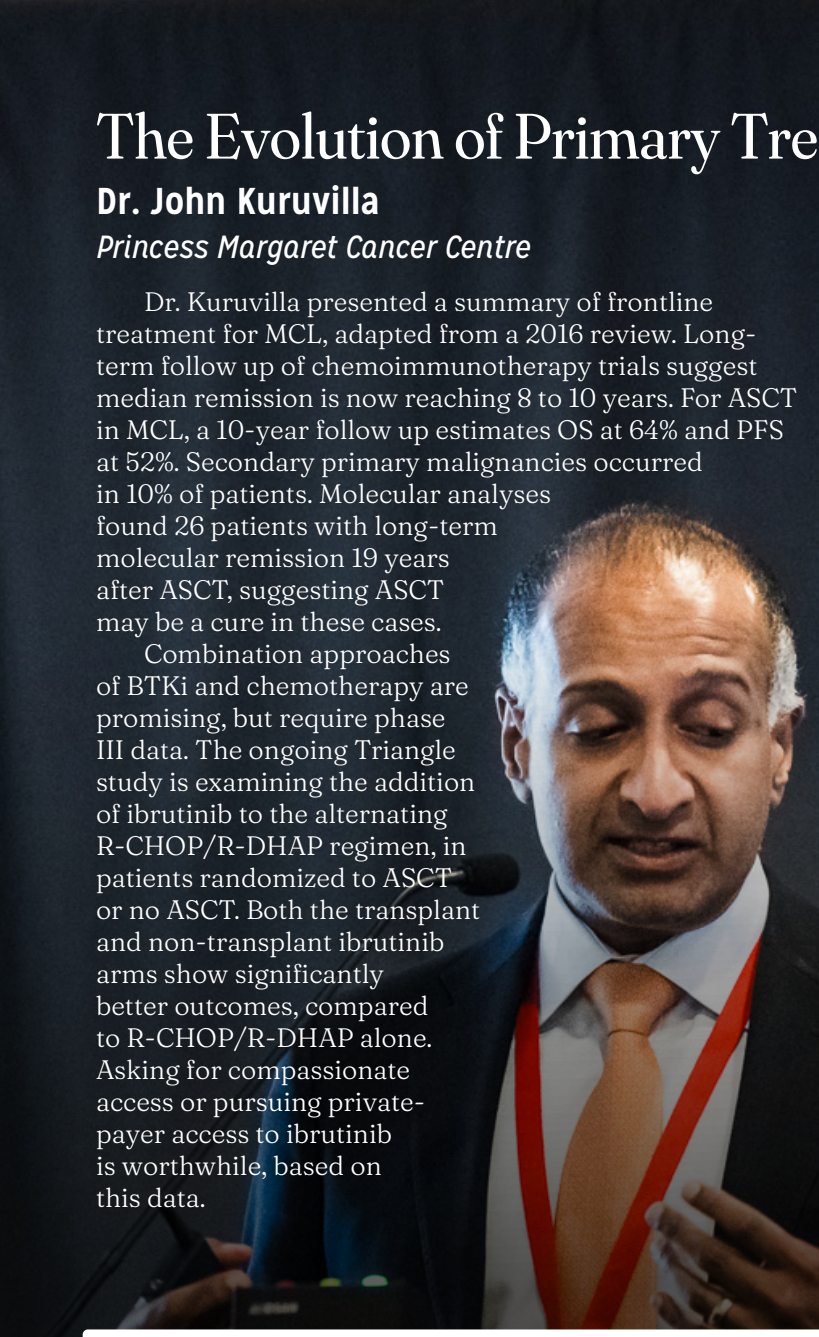
- Dr. Foley asked how to respond if a patient in the ECHELON trial has severe peripheral neuropathy in frontline setting?
- Dr. LaCasce recommending dropping brentuximab and continue AVD. Some argue it is better to dose-reduce or omit vinblastine but there isn't strong data to support either strategy.
- Dr. Crump recommended doing a PET scan, and would consider switching the patient to eBEACOPP if the PET scan was positive. He recommended all patients should undergo a PET scan after two cycles of therapy.
- Dr. Foley asked if a 45-year-old with an IPS of 7 should be initiated on eBEACOPP?
- Dr. LaCasce said this would be reasonable step, adding that N-AVD could be more effective, if accessible.
- Dr. Crump said he would pivot to eBEACOPP. He noted the toxicities are manageable, making the analogy to toxicities with BiTEs and CAR-T therapy.
- Dr. LaCasce asked if Dr. Crump would deescalate patients if they are PET2-negative?
- Dr. Crump said this is a conversation with the patient. He noted young patients often prefer a shorter duration of therapy, despite increased toxicity risk.
- Dr. Siddiqui asked about treating a Hodgkin lymphoma patient who has had prior anthracycline therapy and radiation for a previous cancer?
- Dr. LaCasce said she would try to access liposomal doxorubicin for such a patient.
- Dr. Crump said liposomal doxorubicin is difficult to access, but he often uses dexrazoxane in these cases. Nausea and hematologic toxicity is a concern, but it is effective.
- Dr. Kuruvilla asked whether longer follow up of the SWOG trial comparing N-AVD and BV-AVD might influence the practice in Europe to use eBEACOPP if the PFS stays over 90%?
- Dr. Crump said that he expects Europe to move away from eBEACOPP, but the treatment decision of PD1 inhibitors versus other new agents will depend on the toxicity profile.
- Noting that Dr. Crump said the goal of therapy should be complete metabolic response by PET scan, there was a question about whether interim PET scans are as prognostic as end-of-treatment PET scans?
- Dr. Crump said interim PET scans collected in the ongoing SWOG trial will provide insight as to their predictive value for treatment failure.

The Evolution of Primary Treatment in MCL

Dr. John Kuruvilla
Princess Margaret Cancer Centre

Dr. Kuruvilla presented a summary of frontline treatment for MCL, adapted from a 2016 review. Long-term follow up of chemoimmunotherapy trials suggest median remission is now reaching 8 to 10 years. For ASCT in MCL, a 10-year follow up estimates OS at 64% and PFS at 52%. Secondary primary malignancies occurred in 10% of patients. Molecular analyses found 26 patients with long-term molecular remission 19 years after ASCT, suggesting ASCT may be a cure in these cases.

Combination approaches of BTKi and chemotherapy are promising, but require phase III data. The ongoing Triangle study is examining the addition of ibrutinib to the alternating R-CHOP/R-DHAP regimen, in patients randomized to ASCT or no ASCT. Both the transplant and non-transplant ibrutinib arms show significantly better outcomes, compared to R-CHOP/R-DHAP alone. Asking for compassionate access or pursuing private-payer access to ibrutinib is worthwhile, based on this data.



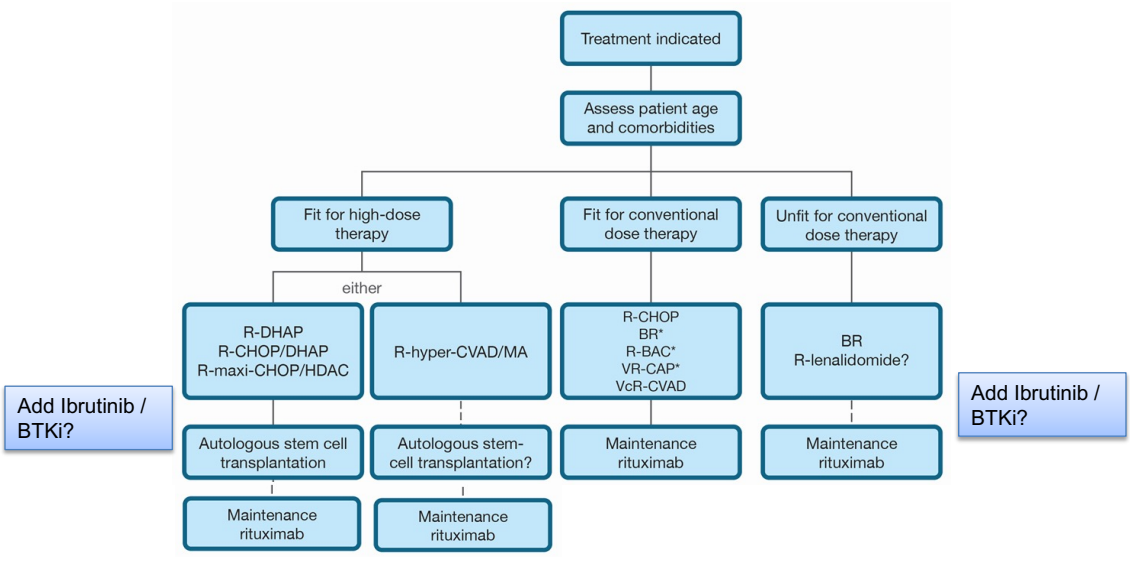
While noting the efficacy data for ASCT in MCL is excellent and supported by multiple trials, Dr. Kuruvilla said the challenge is that the randomized controlled data are based on young, fit patients and may not apply to real-world settings. In the real-world, transplants are being used less frequently, given effective alternatives and the toxicity, complexity, and cost of transplants, especially when novel agents like BTKis are increasingly used ahead of ASCT. For high-risk patients in particular, ASCT may not be the most effective therapy.

While many don't see the SHINE trial of ibrutinib combined with BR and R maintenance as positive, due to the high toxicities, the ongoing ECHO trial investigating BR +/- acalabrutinib in frontline MCL could have a more favorable toxicity profile and a similar PFS benefit. Based on the currently available data, ASCT-eligible patients should still have a transplant, but this recommendation is likely to evolve with further trials.

Furthering this goal of introducing novel agents earlier, with the hope of supplanting ASCT, a trial by the Eastern Cooperative Oncology Group (ECOG) and the American College of Radiology Imaging Network (ACRIN) is following transplant eligible patients and randomizing people who are MRD-negative to a transplant. The study results could answer the question of whether a transplant is necessary in patients who achieve unquestionable remission. Those who don't go on to transplant will receive maintenance rituximab.

Another future pathway may be to combine chemotherapy with novel agents. Studies are testing ibrutinib with BR, as well as lenalidomide and bortezomib. Chemotherapy-free approaches are also on the horizon, including R2; R2 in combination with venetoclax; ibrutinib and rituximab; venetoclax, ibrutinib and obinutuzumab; and other options. Many of these combinations demonstrate two-year PFS rates ranging from 85% to 90%. Longer-term follow-up will illuminate whether these options are comparable to a transplant, especially for younger patients.

Summary: Frontline treatment of MCL is changing?



Positioning Novel Therapy in RR-MCL

Dr. Kami Maddocks
Ohio State University Comprehensive Cancer Center

Dr. Maddocks outlined that BTKis are currently the preferred second line agent for the treatment of MCL. Phase II trials show that 70% to 80% of patients will achieve a response when treated with a BTKi in the R/R setting. While the toxicities in the SHINE trial led ibrutinib to be withdrawn from the U.S. market, second-generation BTKis have a better toxicity profile. Longer-term follow up for zanubrutinib and acalabrutinib shows PFS rates between two and three years. Pooled analyses of zanubrutinib and ibrutinib show that BTKis are more effective in the second-line setting, with statistically significant improvements in OS, compared to later-line usage.

Progression with BTKis is, however, expected, and outcomes following progression are poor, with median OS between four to nine months. Patients treated with acalabrutinib have better outcomes, with median OS after progression approaching two years. This likely reflects the benefit of using BTK inhibitors in earlier lines, as well as improvements in the management of patients who are progressing on a BTKi.

Efforts are underway to improve OS by combining BTKis with other therapies. However, phase I and II studies investigating ibrutinib with rituximab; ibrutinib, rituximab and lenalidomide; ibrutinib, obinutuzumab and venetoclax, and other combinations suggest outcomes are similar to single-agent BTKi therapy alone, with more associated toxicity.

Cellular therapy products have also been approved for use in MCL, based on the ZUMA-2 study of brexucel in patients with R/R MCL, who previously received BTKis. Response rates were high, with 93% of patients responding to therapy and approximately two thirds achieving a complete response. Dr. Maddocks highlighted that 93% of patients had CRS, of which 15% were grade 3 or higher. Two thirds of patients experienced neurotoxicity. Almost all patients had grade 3 or higher cytopenia, a third of patients had infections, and there were four cases of Grade 5 toxicities in the trial. Three-year follow up shows that mPFS is 25.8 months and median OS is 46 months.

Non-covalent BTKis are an effective option following covalent BTKi. Pirtobrutinib was approved in the U.S. in January of this year, based on the BRUIN study. Of 90 patients with previous covalent BTKi exposure, 58% responded, with a mPFS of approximately 8 months and a median duration of response of 22 months. The toxicity profile is similar to with the non-covalent BTKis, but the incidence of cardiac and bleeding toxicities is lower, and only 3% of patients discontinued treatment due to toxicity. For the majority of patients who discontinued a covalent BTKi due to a severe adverse event, that toxicity did not reoccur with pirtobrutinib, suggesting that non-covalent BTKis are an option for those who do not tolerate covalent BTKis.

Panel Discussion

Dr. John Kuruvilla, Dr Kami Maddocks
Moderator: Dr. Peter Anglin

- Dr. Vijenthira asked the panelists how they would approach TP53-mutated disease in patients not eligible for clinical trials.
- Dr. Maddocks said her approach is to start with a lower toxicity agent, knowing they will very likely require second-line therapy. While not approved in the first-line, she would ideally choose a BTKi, with the goal of an earlier CAR-T therapy if they don't respond, or if they progress after BTKi response.
- Dr. Siddiqui asked about blastoid variant MCL, and whether glofitimab would be a good option.
- Dr. Maddocks said her approach would be similar to those with TP53-mutated disease, with either a less toxic chemotherapy regimen of a BTKI inhibitor in the frontline. Dr. Maddocks said in the future, combinations of BTKi and glofitimab in the frontline setting may show benefit.
- Dr. Patel asked whether there could be a role in the future for CAR-T therapy in these especially high-risk patients.
- Dr. Maddocks said a BTKi immediately before CAR T-cell collection could potentially be beneficial. However, these high-risk patients are likely to relapse after CAR-T therapy. The next step may be a bispecific medication or, in young patients, potentially alloSCT.
- Dr. LaCasce enquired about frontline therapy in elderly patients?
- Dr. Kuruvilla said dose-adjusted BR is generally used in Canada for these patients. Single agent rituximab is an option for frail patients, based on patient goals.
- Dr. Maddocks said she would use BR or BTKi, depending on the older patient's age and comorbidities.
- Dr. Foley asked about transitioning to BTKi therapy in the third-line, prior to CAR-T therapy.
- Dr. Maddocks said that her approach is to continue BTKi until immediately after CAR-T infusion. In patients who are progressing, she may add venetoclax, or radiation prior to CAR-T therapy.
- Dr. Crump asked if the panelists recommended TP53 mutation status testing for all or selected patients.
- Dr. Maddocks said the testing is done in all patients at diagnosis in her center. If access to testing is limited, it should be used in patients who have rapid progression, and high Ki67 expression.

CLL Frontline Therapy: Fixed Duration vs Treat to Progression

Dr. Abi Vijenthira

Princess Margaret Cancer Centre

Dr. Vijenthira provided an overview of the data supporting the primarily used continuous therapy (BTKis) versus fixed duration regimens, including chemoimmunotherapy, venetoclax-obinutuzumab, and ibrutinib-venetoclax. The toxicities of BTKis discussed in previous panel presentations suggest finite therapies will provide better overall benefit, but finite therapies also have access challenges. For example, only up to 20% will be eligible for FCR therapy.

Nineteen-year follow up data for FCR shows mPFS in patients with IGHV mutation of 15 years. In patients who achieved undetectable MRD, 80% are functionally cured. The rate of acute myeloid lymphoma and myelodysplastic syndrome was reported at 6.3%.

In Ontario, venetoclax and obinutuzumab is most-often used as a fixed-duration therapy in patients with CLL. In fit patients without 17p deletion, venetoclax-obinutuzumab and ibrutinib-venetoclax-obinutuzumab are superior to chemotherapy, but this is not the case in patients with mutated disease.

A six-year follow up of CLL14, which looked at patients with comorbidities and renal dysfunction, randomizing them to venetoclax-obinutuzumab versus chlorambucil-obinutuzumab, reveals that half of patients are still in remission and 65% have not required any new treatment. A small, subgroup analysis of 25 patients those with TP53 mutation and/or 17p deletion showed patients had a mPFS of slightly above four years. The CLL15 trial, which is only enrolling patients with TP53 aberrations will provide more clarity. Cardiac toxicities were similar in the CLL14 trial across both arms, and treatment-related mortality associated with venetoclax-obinutuzumab was 1%. Adverse effects largely dissipated after treatment, though neutropenia persisted in 3.8% of patients in the treatment arm.

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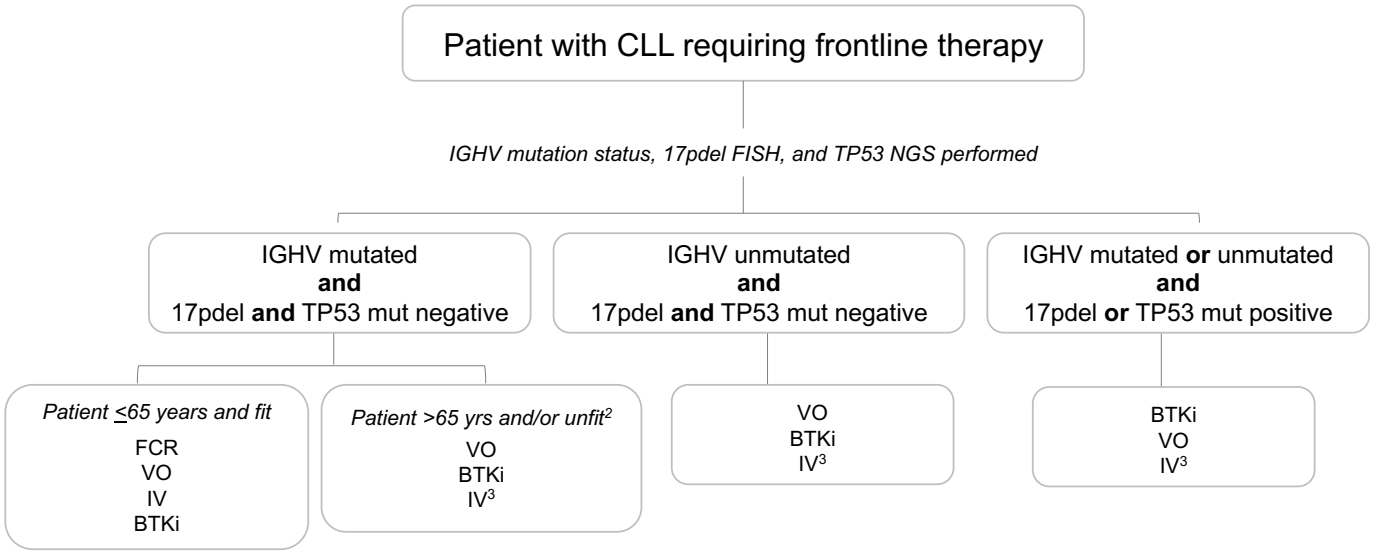
Ibrutinib-venetoclax is another fixed-duration therapy available in Canada, but not yet approved for reimbursement. Approval was based on the phase III GLOW trial, which demonstrated a 3.5-year PFS rate of 75% and the phase II CAPTIVATE study, with a 4-year PFS rate of 79%. Treatment-related mortality of 7% in the GLOW trial is a concern (especially in comparison to the treatment-related mortality of the CLL14 trial), suggesting this combination may not be appropriate for many older patients.

For high-risk patients, the PFS has shown to be superior with BTKi therapy compared to fixed-duration regimens, in small studies. Given the benefit of retreatment with fixed duration therapy, the total therapy benefit of fixed duration approaches is currently being explored with Phase II retreatment trials. A Canadian cost-effectiveness analysis led by Dr. Carolyn Owen found fixed duration therapies are more cost effective than long-term therapies.

In summary, Dr. Vijenthira recommended continuous duration therapies in patients with high-risk disease and those who prefer the convenience of BTKi therapy. Fixed duration therapies should be considered for most patients, with ibrutinib-venetoclax requiring caution in older or less fit patients.

Treatment approach in a Canadian landscape

treatments are in order of preference, with editorial comments below

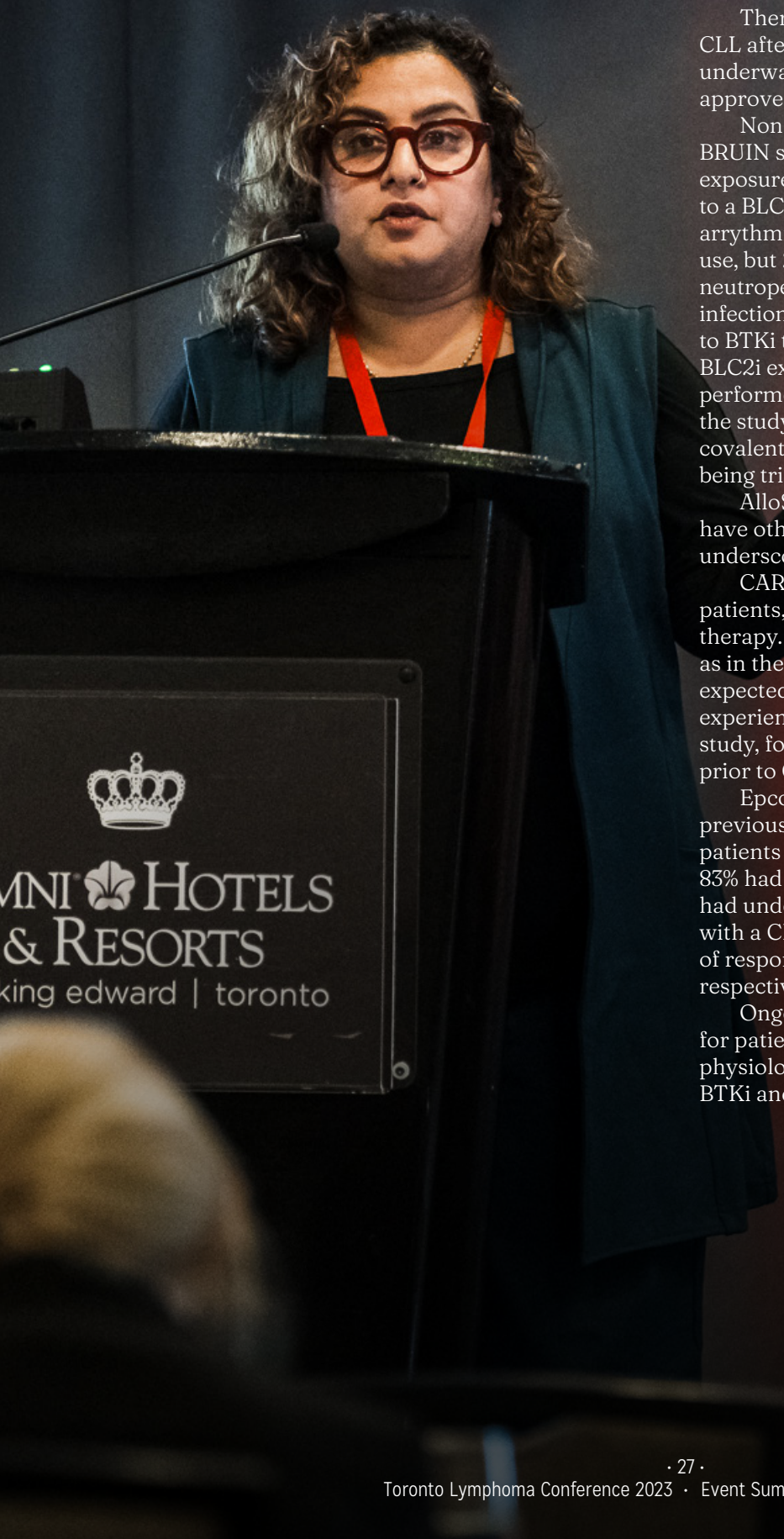


1. Additional considerations using currently available testing: absence of mIGHV subset 2, 11qdel
2. In frail older patients with mIGHV in whom simpler time-limited therapy is preferred, CO (5-year PFS 50%) is reasonable
3. Caution in older/less fit patients

Owen. Leuk Res. 2023. Published online ahead of print.

How to treat CLL after BTKi and BCL2i

Dr. Versha Banerji
CancerCare Manitoba



There is little evidence to guide the treatment of CLL after BTKi and BCL2i failures, but many studies are underway. BTKi and venetoclax-rituximab are currently approved, depending on frontline treatment received.

Non-covalent BTKis offer a new alternative. The BRUIN study examined pirtobrutinib in patients who had exposure to a covalent BTKi, with 40% having exposure to a BLC2i. Rates of atrial fibrillation, hypertension, and arrythmia were lower, compared to BTKis currently in use, but 20% of patients experienced treatment-related neutropenia and 12% experienced treatment-related infections. The ORR was 73% in patients who had exposure to BTKi therapy, and 70% for those with both BTKi and BLC2i exposures. In a subgroup analysis, pirtobrutinib performed more poorly in the 18 patients enrolled in the study who had a PLGC2 mutation. Other new non-covalent BTKi, including nemtabrutinib are currently being trialled against the current standard of care.

AlloSCT is funded for Canadian patients who don't have other treatment options, however, Dr. Banerji underscored alloSCT is extremely rare.

CAR-T therapy (liso-cel) has been studied in 96 patients, 53 who had exposure to both BTKi and BCL2 therapy. The CR was 18% in the total population, as well as in the dual-exposed population. Toxicities were as expected, with 85% experiencing CRS. However, only 9% experienced grade 3 CRS. There were five deaths in the study, four of which occurred due to disease progression prior to CAR T-cell infusion.

Epcoritamab is another treatment for patients previously treated with BTK and BCL2 inhibitors. All patients enrolled in the study were treated with BTKis, 83% had been treated with a BCL-2 inhibitor and 4% had undergone CAR T-cell therapy. The ORR was 82% with a CR of 33%. At 9 months, the estimated duration of response, PFS, and OS was 83%, 67%, and 81%, respectively.

Ongoing trials provide important opportunities for patients facing an incurable disease, and patient physiology and immunology will be key drivers post-BTKi and -BCL2 therapies.

Richter's Syndrome: State-of-the-Art Management

Dr. Tanya Siddiqi

City of Hope National Medical Center, Duarte, CA

Richter's syndrome continues to have a high and urgent unmet medical need for curative treatment options. It is important to ascertain the clonal relationship of DLBCL to CLL, if possible, as well as prior CLL therapy and TP53 mutation status, as these factors significantly impact outcomes for patients with Richter's syndrome.

Getting to alloSCT remains the goal of Richter's syndrome therapy. Chemotherapy regimens and single agent BTKis have had low efficacy in Richter's. Non-covalent BTKis have been slightly more effective, with a CR of 10% in patients receiving pirtobrutinib and a response duration of 6 months in a study of 82 patients with Richter's syndrome.

Trials combining novel agents, including BTKis and venetoclax, with chemoimmunotherapy show additional benefit. For example, studies of R-CHOP and venetoclax demonstrate CR rates of 50% with mPFS of 7 to 10 months. For patients who are not a candidate for intensive chemotherapy, studies examining combinations of ibrutinib and nivolumab; zanubrutinib and tislelizumab; duvelisib and venetoclax; and copanlisib and nivolumab suggest these combinations could also be beneficial as a bridge to alloSCT.

Bispecific antibodies may be promising, in combinations. Epcoritimab led to a 50% complete metabolic response in five patients with Richter's, but the follow-up period is short. Glofitimab is also being tried in a small cohort of Richter's syndrome patients. Similar to epcoritamab, 45% of patients experienced serious CRS events, and the early response rates are promising, with a CR rate of 46% and ORR rate of 63.6%.

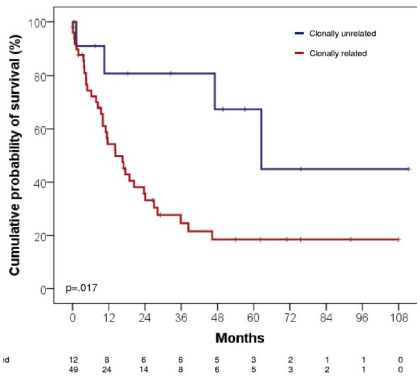
AlloSCT may be the only curative option, but it is often not possible, and comes with high rates of relapse and non-relapse mortality in retrospective studies.

For patients who can't achieve a CR or otherwise access alloSCT, CAR-T is an option. An abstract this year by Dr. Adam Kittai found a CR of about 45% in patients with Richter's transformation receiving CAR-T therapy and an OS of approximately 8.5 months.

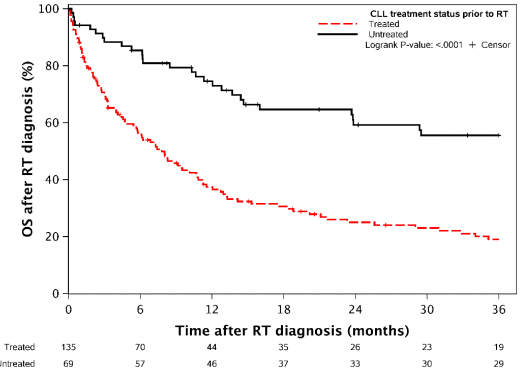
Work is ongoing in designing alloCARS, with the goal of mitigating toxicities and enhancing efficacy. There is no Richter's syndrome-specific trial for any of these agents.

Outcomes of patients with Richter's syndrome

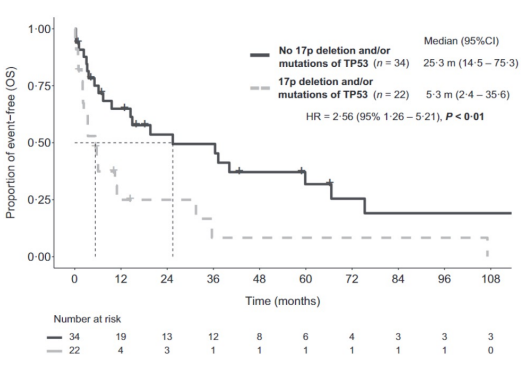
Clonal relationship of CLL to DLBCL[1]



Prior CLL Therapy[2]



***TP53* Disruption status[3]**



Panel Discussion

Dr. Abi Vijenthira, Dr. Versha Banerji, Dr. Tanya Siddiqi
Moderator: Dr. John Kuruvilla

- Dr. Anglin asked about testing methods to establish a clonal relationship?
- Dr. Siddiqui said this testing is difficult. In most cases, physicians will not have access to the original baseline CLL sample.
- Dr. Crump asked what happens to normal BTK cells when exposed to a BTK degrader?
- Dr. Banerji said there is likely degradation at both the normal lymphocyte level and the diseased lymphocyte level.
- Dr. Siddiqui said she would assume BTK degradation may preferentially target the malignant cells because of overactivity.
- Dr. Anglin asked about the status of MRD in clinical practice?
- Dr. Vijenthira said MRD is available in Ontario, but at this point, it doesn't take treatment.
- Dr. Patel asked if rates of transformation are reducing with the use of potentially less toxic therapies at a genomic level?
- Dr. Siddiqui said it appears that obinutuzumab combinations and ibrutinib-venetoclax treatment is leading to less Richter's transformation, at least early on in treatment. However, given that patients are living longer of CLL, she expects more Richter's cases over time.
- Dr. Anglin outlined the case of a 70-year-old, relatively fit patient on ibrutinib, previously on rituximab-venetoclax, who is progressing. Pirtobrutinib is a challenge to access. How should this patient be managed?
- Dr. Vijenthira said in the Canadian landscape, the only option is transplant, if the patient is not eligible for a clinical trial.
- Dr. Vijenthira said if the goal is transplant, it would be reasonable to retreat with VR if they sustained a 12-month interval without the treatment. It may be possible to add a BTKi on a compassionate basis. If the patient hasn't been treated with chemotherapy and they don't have a TP53 mutation, chemotherapy would be another potential option.
- Dr. Anglin asked if there are any patients for whom venetoclax is not appropriate.
- Dr. Vijenthira said frail patients who cannot manage the frequent hospital trips could benefit from BTKi treatment, instead of venetoclax.

Event Summary & Evaluation Report

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