A Special Supplement

2023 Clinical and Policy Summit: Dialogues in B-Cell Malignancy

January 26th, 2023

Welcome and Introductions

Rohit Khanna, President Catalytic Health

On January 26, 2023, Catalytic Health hosted a virtual conference on the clinical and policy-related challenges faced by doctors and patients advocating for better treatments for B-cell malignancies. The event was sponsored by BeiGene Canada.

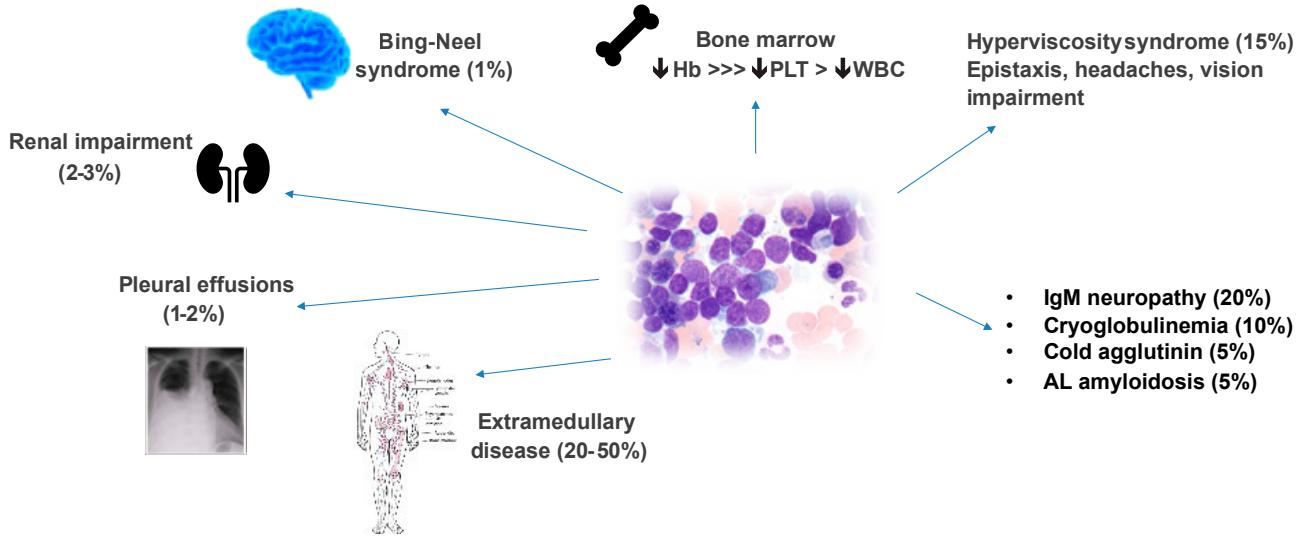
Rohit thanked BeiGene for their unrestricted educational grant support for the meeting. He introduced the speakers and noted that this conversation is one of many that will move the objective forward of bringing novel agents to Canadian patients who suffer from B-cell malignancies.

Current and Future Treatment Options in Waldenström Macroglobulinemia (WM)

Dr. Amaris Balitsky, *Malignant Hematologist, Juravinski Cancer Center, Hamilton Health Sciences*

Dr. Balitsky reviewed the presentation, manifestations, and diagnosis of WM; the current treatment options; new treatment options; and updates from the American Society of Hematology (ASH) 2022 conference.

She described the many possible complications of WM as follows:



Dr. Balitsky outlined the diagnostic work-up and criteria for WM. She noted that WM patients may have mutations in *MYD88* gene alone, *MYD88* and *CXCR4* genes, or no mutation. Patients who have mutations in both genes are more likely to present with a large burden of bone marrow involvement, a higher serum IgM level, more hyperviscosity. These patients are also more likely to acquire von Willebrand disease.

She pointed out that not everyone needs to be treated early for WM, as treatment promotes resistance, can cause toxicity, and there is no evidence that treating early prolongs survival. In one study of approximately 400 patients, approximately 30% of WM patients had indications that required treatment after two years.[1]

Risk factors for progression include a higher IgM (≥ 4,500 mg/dL), a higher bone marrow burden of disease, high ß2-microglobulin (≥4 mg/dL), and low albumin (<3.5 g/dL). Patients who have all four of the risk factors have a 60% chance of progression. Patients with none of those risk factors have less than a 10% chance of developing an indication requiring treatment at two years.

She described the currently available treatments for WM, including chemotherapy and proteasome inhibitors. Their overall response rates (ORR) and PFS rates are as follows:

Chemoimmunotherapy

	ORR	PFS (months)
Bendamustine/rituximab	80-90%	69 m
Cyclophosphamide-based R-CHOP, CVPR, CDR	70-80%	30-36 m
Nucleoside analogue FCR, FR	70-90%	36-62 m

Buske et al., Leukemia 2009; Dimopoulos et al., Blood 2014; Treon et al., Blood 2015; Rummel et al., Lancet 2013

1 Bustoros et al, JCO 2019

Proteasome Inhibitors

	ORR	PFS (months)
BDR	88%	66 m
CaRD	87%	46 m
IDR	70-90%	40 m

Treon et al.,JCO 2009; Dimopoulos et al., Blood 2013; Treon et al., Blood 2015; Castillo et al., Blood Adv 2020

Regarding new treatments for WM, Dr. Balitsky noted that the *MYD88* mutation results in an upregulation of the bruton tyrosine kinase (BTK) pathway. The three approved BTK inhibitors (BTKi)– ibrutinib, acalabrutinib, and zanubrutinib – have adverse effects associated with infection and bleeding. Ibrutinib also has an increased risk of hypertension and atrial fibrillation. However, their efficacy is high. In relapse/ refractory patients, the five-year progression-free survival (PFS) was 54%, but in those with a *MYD88* mutation only, the PFS was 70%.[2]

In another study, the combination of ibrutinib and rituximab in patients with previously or untreated WM showed an improved PFS of 82%, versus 28% for the placebo and rituximab arm.[3] Another study looked at ibrutinib monotherapy in patients who were treatment naïve, with symptomatic WM, and had a mutation in the *MYD88* gene. For patients who did not have a *CXCR4* mutation, the ORR was 100% and time to major response was 1.8 months.[4] If patients additionally had the *CXCR4* mutation, the ORR was 83% and the time to major response was 7.3 months. Novel therapies targeting the *CXCR4* mutation include ulocuplumab and mavorixafor. In addition, BLC-2 inhibition is being explored with venetoclax.

From ASH 2022, Dr. Balitsky highlighted a real-world study looking at the long-term follow up of patients treated with BR.[5] The ORR was 97%, the median PFS was 82 months and secondary malignancies occurred in 15.9% (11/69) of patients. This data is helpful for patient counselling.

Dr. Balitsky also highlighted a study with BR and acalabrutinib[6] in patients with untreated, symptomatic WM. The interim analysis, with a median follow-up of five months for eight patients, shows that all patients achieved a very good partial response by cycle 7. This is an important study to continue to follow.

Rohit asked about recently published guidelines in the treatment of WM. Dr. Balitsky noted that in Ontario guidelines recommend BR and this treatment combination is a good option for many patients. In the relapse setting however she would like to see guidelines incorporate novel drugs including BTKi.
Rohit asked if the Canadian government should pay for BTKis in refractory and relapse WM. Dr. Balitsky said yes the data supports access to this medication for patients with refractory/relapse WM.
A participant asked if there is any role for CAR-T therapy or bispecific T cell engagers (BiTE) in WM patients. Dr. Balitsky said the Zuma 25 trial is examining CAR-T therapy in WM patients but has not yet reported results. She is not aware of any BiTE trials in WM patients.

2 Treon et al., NEJM 2015; Treon et al., JCO 2020.
3 Dimopoulos NEJM 2018
4 Treon et al, JCO, 2018
5 Laribi et al. Blood 2022
6 Bernstein et al., Blood 2022

Drug Access Navigation: Pearls and Pitfalls

Alan Birch, *Associate Director of Provider Solutions, Oncology at Sentrex Health Solutions; Former Drug Access Navigator at North York General Hospital*

Alan described the role of a drug access navigator, and reviewed the past, present, and future of chronic lymphocytic leukemia from the perspective of a former drug access navigator" after the (CLL).

Alan worked as a drug access navigator for eight years. A drug access navigator (also called a medication reimbursement specialist and drug access coordinator) is someone who is tasked with removing barriers to drug access, typically in a cancer center. This involves connecting patients with different manufacturer and government programs, which can be challenging for patients to navigate. Helping patients access drugs for as little cost as possible is important for CLL patients, where therapies may anywhere from hundreds of dollars to more than $10,000 per month.

Current treatment options for patients with CLL include:

- Chemotherapy (fludarabine, cyclophosphamide, bendamustine)
- Anti-CD20 monoclonal antibodies (rituximab, obinutuzumab)
- BTKi (ibrutinib, acalabrutinib, zanubrutinib)
- PI3K (idelalisib)
- BCL2 inhibitors (venetoclax)

Alan noted that treatment is moving away from nonspecific chemotherapy toward targeted therapies, which is leading to better patient outcomes. A major access challenge is that many patients require combination therapy and drug manufacturers can only provide access to their drug, and not the other drug in the combination regimen, resulting in onerous paperwork and administration. There are also questions about who funds the infusion of the combination therapy regimen.

Alan said that another trend is that genetic testing is increasingly required to access a therapy, to ensure that medications are used appropriately. However, the testing is not publicly reimbursed, and patients may not be able to afford the test. Alan noted that patient support programs (PSPs) are often a lifeline to patients. He noted that patients on the Trillium Drug Program may have to pay deductibles that can amount to thousands of dollars per year. PSPs can fill this gap. However, PSPs don't have access to patient charts. Communication from health care providers about the patient's medical information is therefore vital to ensuring that patients are eligible for support.

Regarding the future, Alan stated that he is excited about new medications, some of which may be available in the next decade. It will be important to ensure that as new medications become available, the right drug is provided to the right patient. In addition, for novel treatments like CAR-T, eligibility requirements and geographical barriers for patients will be important to consider.

He stressed the importance of patients having access to minimal residual disease testing, which can show when patients no longer have detectable disease and may be able to discontinue treatment. The ability to discontinue drugs can improve the patient's quality of life and will greatly reduce health system costs.

He also said that it will be important to generate real-world evidence from PSPs to better inform physicians, and to utilize this data for regulators.

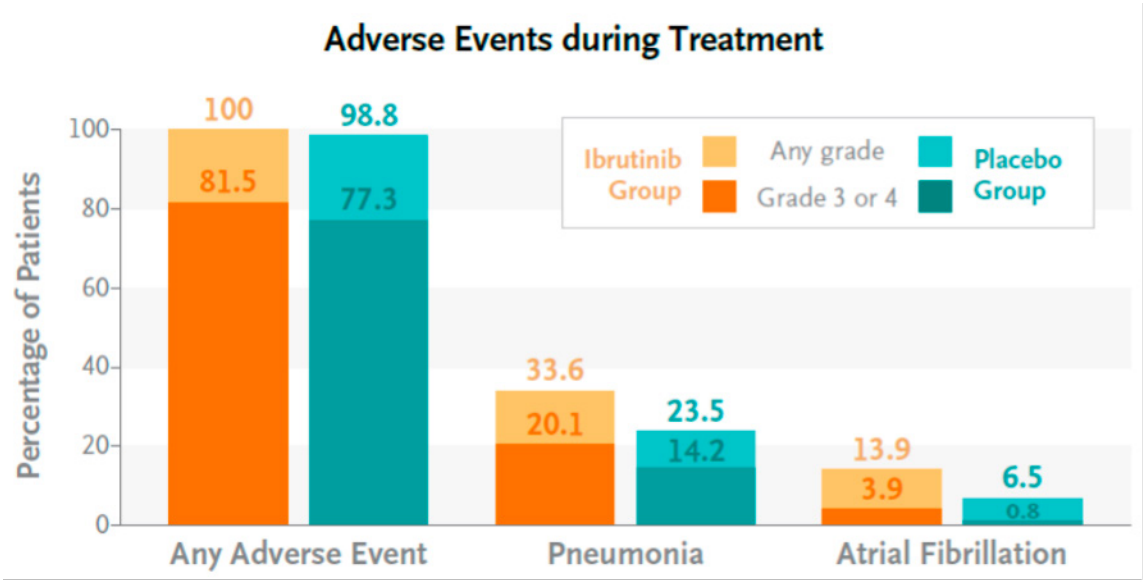
Rohit asked Alan if North York General Hospital was able to generate data that could be useful for drug reimbursement decisions. Alan said that due to poor funding and inadequate human resources they were not able to gather and analyze data that could benefit a health technology assessment.

Mantle Cell Lymphoma: A Canadian Framework for Treatment and Management

Dr. Diego Villa, *Medical Oncologist, BC Cancer Agency and Vancouver General Hospital*
Associate Professor, University of British Columbia

Dr. Villa presented a summary from the report entitled, Updates in the Treatment of Mantle Cell Lymphoma (MCL): A Canadian Expert Framework. Dr. Villa noted that median overall survival in MCL has increased to nearly seven years, with bendamustine and other new agents, which compares to three years when cytotoxic chemotherapy was the only treatment option (the case until 2002). He opined that there is clearly still a great need to improve outcomes for patients. He stated that the median time to treatment for MCL patients is approximately three years, and that approximately 20% of patients never need treatment. Dr. Villa pointed out that treatment deferral does not negatively impact overall survival, but that careful selection and close monitoring of patients for observation is important, as most patients will require therapy. Dr. Villa said that for young patients, the standard of care is intensified immunochemotherapy, followed by autologous stem cell transplantation (ASCT), followed by rituximab maintenance. He reinforced that front-line treatment choices are largely based on patients' age, fitness, and disease biology.

Dr. Villa said that the standard of care for MCL has shifted from rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) to bendamustine-rituximab (BR) in recent years, which is associated with improved overall survival. However, the use of maintenance rituximab after BR has remained an open question. A retrospective, non-randomized study of electronic health records of over 4,000 patients suggests that maintenance rituximab after BR is associated with better outcomes.[7] The SHINE trial showed that a frontline BTKi can improve PFS by two years, in patients who are ASCT ineligible. Other BTKi trials are ongoing, which are important to further elucidate how these agents differ with respect to outcomes and toxicities in MCL patients.



Wang, NEJM 2022

In Canada, BTKi are not available for first-line therapy but should be considered for second-line therapy. In a relapse setting, most clinicians agree that BTKi are the standard of care. The earlier a BTKi is introduced as part of the patient's treatment course, the more favourable the long-term outcomes. Toxicities are less frequent with second-generation BTKi, but not absent. One of the biggest areas of unmet need is treatment for patients when they develop resistance to a BTKi. Other treatment options for relapse/refractory MCL include chemoimmunotherapy, proteasome inhibitors, lenalidomide, BCL-2 inhibitors, and allogeneic stem cell transplantation. Future options include non-covalent BTKi, zilovertamab vedotin, bispecific antibodies, and a greater availability of CAR-T cell therapy. There is reason to be very hopeful about future treatment options.

In the relapse/refractory setting, the currently available BTKi options are ibrutinib, acalabrutinib, and zanubrutinib. Dr. Villa presented a pooled analysis of efficacy data and cross-trial safety data for the available BTKis, noting comparisons are challenging due to differences in patient populations, sample size, duration on therapy, and length of follow-up.

7 Martin, JCO 2022

Approved BTKi in R/R MCL: Efficacy

BTKi	Patients with R/R MCL			ORR	CR	Median PFS
	Number of Patients	Median Lines of Prior Therapy	Patients with High-Risk Features (%)*			
Ibrutinib Wang et al., 2015 Dreyling et al., 2016	111 139 **	3 2	49 22	67% 72%	23% 19%	13.6 months 14.6 months
Acalabrutinib Wang et al., 2019	124	2	17	81%	43%	20 months
Zanubrutinib Song et al., 2020 Tam et al., 2019	68 37 ***	2 1	38.4 37.5	84% 84%	59% 22%	22.1 months 18.5 months

** Based on the calculated MIPI score; ** 280 patients were included; 139 were treated with ibrutinib and 141 with temsirolimus; 48 MCL patients were included in the study, 37 of whom had R/R MCL*

Approved BTKi in relapse/refractory MCL: Toxicity

	Infection Grade 3+ (%)	Bleeding Grade 3+ (%)	HTN (%)	AF (%)	Diarrhea Grade 3+ (%)	MSK Grade 3+ (%)	Other Grade 3 (%)
Ibrutinib	14-29	6	19	11	5	6	Rash 3 Headache 2
Acalabrutinib	11-18	3	5	0	1	1	Rash <1 Headache 1
Zanubrutinib	13	3	3	1	1	3	Rash 0 Headache 1

Dr. Villa then presented the Zuma-2 trial, to evaluate the efficacy of brexucabtagene autoleucel in patients with R/R MCL. The trial included patients who had previously received a BTKi; 62% were refractory to the BTKi. The most updated published follow-up, at three years, show excellent outcomes: an ORR of 91% and a CRR of 68%.[9]

Additional therapies for R/R MCL with different mechanisms of action are currently being evaluated in prospective studies.

Dr. Balitsky noted that the SHINE trial did not find an overall survival benefit and asked if or how the data should direct clinical decisions.
Dr. Villa noted that he personally recommends sequentially treating with BR, followed by a BTKi, as there are often not treatment options after BTKis in MCL patients.

8 Burkart, J Personalized Med 2022
9 Wang, JCO 2022

What can stakeholders do to get ready for new therapeutic agents?

Martine Elias, *Executive Director, Myeloma Canada*
Alan Birch, *Associate Director of Provider Solutions, Oncology at Sentrex Health Solutions, Former Drug Access Navigator at North York General Hospital*
Michelle Forman, *Nurse, Burnaby Cancer Center*

Rohit opened the discussion by asking the panelists how they keep up to date with the new therapeutic agents and clinical evidence.

Alan said that the drug access navigators rely heavily on drug representatives who provide clinical information about newly available drugs.
Michelle said industry representatives help to keep nurses abreast of the new treatment options. In addition it is beneficial to attend conferences, journal clubs and to network with colleagues who have experiences using the drugs.
Martine highlighted the challenge of learning about the evidence not only behind the drugs but also the combinations and the best sequencing. Representatives of Myeloma Canada attend conferences to learn as much as they can about the therapeutic options. In addition patients are doing their own research and sharing their findings. She also expressed gratitude for the meeting today which has offered many important takeaways on the latest treatment evidence. She added that patients and Myeloma Canada representatives also benefit from the Myeloma Canada Scientific Roundtable.
Rohit asked Michelle if she prefers to have information about a drug in the pre-launch period or if she prefers to wait for the Health Technology Assessment (HTAs) process to play out and then invest the time in learning. Michelle says it's important to know what's coming down the pipeline as patients are asking questions before drugs are available and it's important to be prepared.
Alan agreed it's very important in the hospital setting to know what new products are coming to be able to begin to create protocols for safety and to understand how to manage side effects. This process takes a month at least, so early information is critical.
Michelle highlighted that there are many complex problems facing the Canadian health system including poor access to primary care physicians. With complex treatments like CAR-T therapy there is a major administrative component but also serious side effects such as cytokine release syndrome. Pharmacare, while a start, will not resolve these problems. Many other reforms to the health care system are necessary.

The changing paradigm in accelerating the availability of new therapies for patients

Zal Press, *Executive Director, Patient Commando; Vice Chair, CADTH Patient and Community Advisory Committee*

Zal noted that in 2020, various organizations, including the International Network of Agencies for Health Technology Assessment, introduced a new definition of HTAs. The definition notes that HTAs consider ethical, social, cultural, and legal issues, as well as implications for the patient, relatives, and caregivers.

Research from the Netherlands found that patients were typically involved too late in the process to have an impact on drug approval and reimbursement decision making. The study also found that patients' voices were not included in HTA decision making, unless they were part of an organized group. Marginalized voices, including youth, BIPOC, and LGBTQ+ voices are rarely heard. The level of unpaid caregiver labour is also not considered.

Given this background, it is vital to rethink how patients are involved. In France, an organization called France Assos Santé, a conglomerate of 85 patient organizations, advocated for the inclusion of a law (in 2016), which mandated the conglomerate's inclusion in the public health act. The conglomerate's mandate is to ensure patient and public involvement in hospital committees , other care environments, and the HTA, and to advocate for patient rights and patient safety. Its representation includes people with disabilities, the elderly, and vulnerable populations.

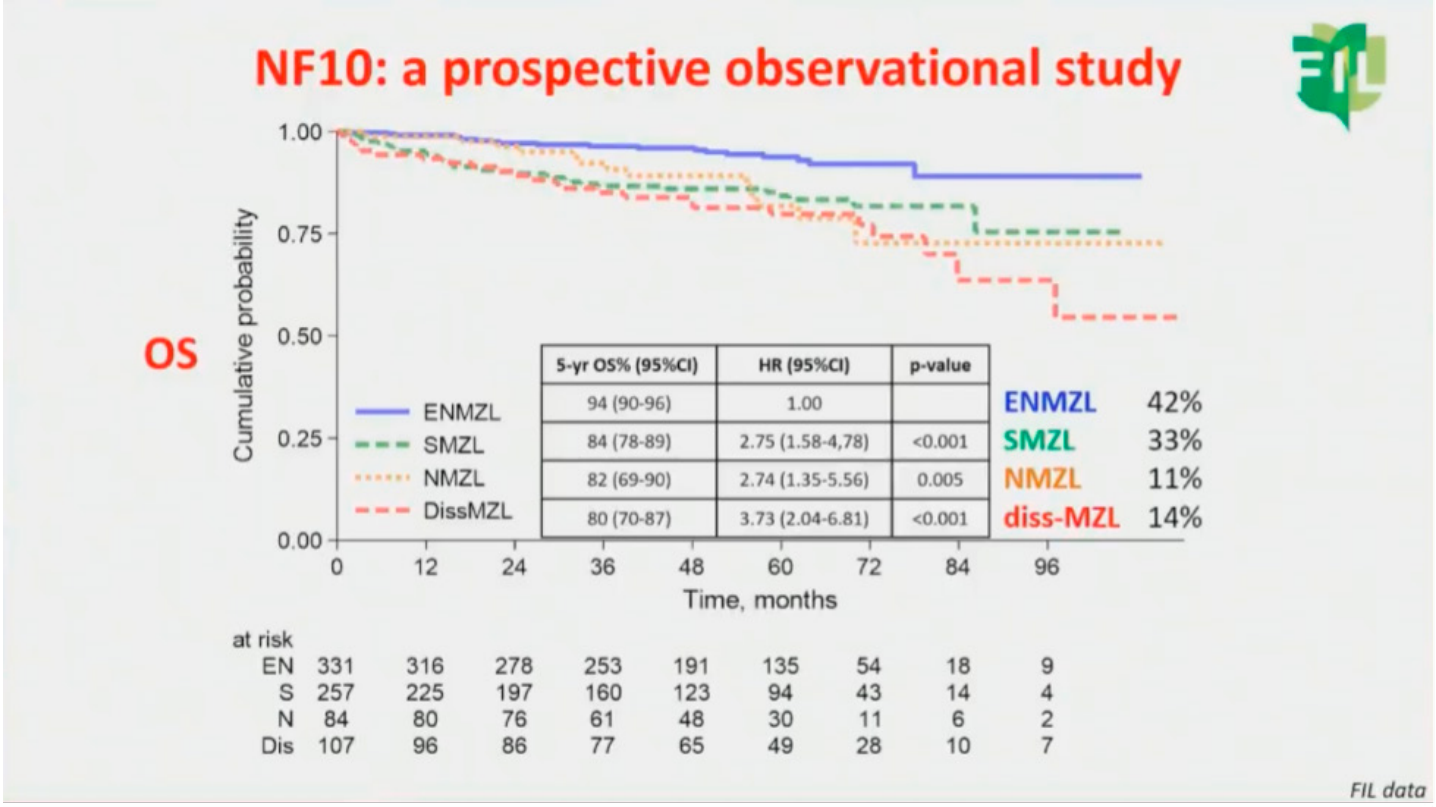
Given the changes to the HTA definition, as well as the principles that the Canadian Agency for Drugs and Technologies in Health (CADTH) and other HTAs ascribe to, including partnering with patient communities and modelling transparency, it follows that patients should be involved from setting the research agenda, designing research trials, and throughout the regulatory and approval process as well as the post-market drug evaluation. Zal stressed the importance of involving patients early in the process, before it is too late for their voices to impact policy.

Rohit asked whether the French patient conglomerate has impacted patient care?
Zal noted that in the French case, it is too early to measure their impact. He said patients may be able to have the most impact on influencing drug prices, in the short term.

MZL Treatment and Management: Where Are We Today?

Dr. Peter Anglin, *Physician Lead, Stronach Regional Cancer Centre at Southlake Regional Health Center*

Dr. Anglin noted that marginal zone lymphoma (MZL) represents approximately 10% of all lymphomas. There are three different types of MZL. Extranodal MZL, or MALT lymphoma, is slow-growing and can appear in the stomach, eye, lung, skin thyroid, and salivary glands. The second type, nodal lymphoma, is commonly found in the lymph nodes. The third type, splenic MZL, results in an enlarged spleen and elevated lymphocyte count. Local MZL can be cured with antibiotics, or with radiation, and are therefore treated. Disseminated low-grade lymphomas are usually initially observed rather than treated.



Fondazione Italiana Linfomi (FIL) NF10 data on overall survival by MZL type

These low-grade malignancies are only treated when patients experience symptoms, including weight loss, fatigue, low blood counts, enlarged lymph nodes and a large spleen. The preferred first-line treatment options for advanced disseminated MZL include:

- Bendamustine with rituximab (BR)
- Cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab (R-CHOP)
- Cyclophosphamide, vincristine, and prednisone (CVP) with rituximab
- Rituximab for those with splenic MZL or those who are older or unwell

Dr. Anglin noted that in many cases, a 6-week course of rituximab, with or without maintenance therapy can prevent disseminated MZL from progressing for 10+ years. The most common and effective therapy is BR, and this is the standard for patients who can tolerate bendamustine.

Second-line and next-line options include ibrutinib, zanubrutinib, and lenalidomide. Relapse MZL patients also respond well to novel targeted drugs, including parsaclisib, copanlisib, and zandelisib; however PFS rates are lower in the R/R setting. Dr. Anglin noted that relapse is extremely rare. He added that newer, second-generation BTKi options like zanubrutinib have a lower toxicity profile than ibrutinib. Umbralisib, belonging to another class of drug, is another effective option to treat MZL; however in a Phase II study, a quarter of patients discontinued the drug due to adverse events.[10] Dr. Anglin noted that research is also exploring CAR-T therapy for the treatment of relapse MZL.

10 Fowler. J Clin Oncol. 2021

Second-line and next-line therapy options	
Preferred options	Bendamustine with obinutuzumab or rituximab (not recommended if you had bendamustine before) Ibrutinib Zanubrutinib Cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab (RCHOP) Cyclophosphamide, vincristine, and prednisone (CVP) with rituximab Lenalidomide with rituximab Rituximab
Other recommended	Copanlisib for relapsed/refractory disease after two prior therapies Rituximab britumomab tiuxetan Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) with obinutuzumab CVP with obinutuzumab Lenalidomide with obinutuzumab
	For those who are older or unwell: Chlorambucil with or without rituximab Cyclophosphamide with or without rituximab

NCCN Guidelines: 2nd and later lines for advanced disease requiring therapy; Sept 2022

Rohit asked whether clinicians should move to only using second generation BTKi for disseminated MZLs.
Dr. Anglin said he recommends zanubrutinib because of its much better side effect profile.
Dr. Kevin Imrie, Clinical Hematologist at the Odette Cancer Centre at Sunnybrook Health Sciences Centre, said the simplicity of accessing the zanubrutinib compassionate program has allowed many physicians to become comfortable with the drug.

Panel Discussion: In five years, B-Cell Malignancies will be different because…

Dr. Julie Stakiw, *Medical Director, Oncology & Clinical Professor Hematological Oncology, University of Saskatchewan*

Dr. Stakiw noted that Phase III data in B-Cell malignancies is very rare; overall survival is difficult to show, due to the effectiveness of the therapies. She asked the panelists about solutions to this challenge.

Dr. Anglin noted that the compassionate programs of manufacturers are excellent, but the concern is that they will be shut down due to delays in public and private funding. The manufacturers' strategy has been to bring therapies to patients, and count on both patients and caregivers to advocate for their reimbursement approval.
Dr. Imrie noted that current front-line treatments work well; the predominant need is in second-line treatment and beyond. The challenge is that patients need to take the second line and next-line therapies for the rest of their lives. Even the newer generation BTKi can cause intolerance in some patients.
Dr. Malcolm Brigden said that realistically, he doesn't expect there to be approval of many of the therapies that the clinician and patient community would like to have available. He compared the size of patient advocacy organizations for solid tumours like breast cancer and noted the difficulty of competing with expensive therapies like those for funding.
Dr. Stakiw asked if there was another way to define clinical benefit to improve the HTA assessment. Dr. Balitsky noted that in multiple sclerosis, quality of life data is a key driver in drug approval and funding. In addition to quality-of-life data, she would like to see more biomarker data, to identify patients who are likely to respond well to second-generation BTKi.

Closing Remarks

Rohit thanked the speakers and panelists for their presentations and insights, and for the great discussion. He reiterated his thanks to BeiGene Canada for their continued support in elevating discussions with Canadian clinicians and policy makers and he encouraged everyone to come back in 2024 for the next Clinical & Policy Summit.

To download this report or watch videos from Dialogues in B-cell Malignancy, please visits us here.