Canadian Hematology Today

2023 Symposium on B-Cell Malignancies

Proceedings of the 2023 Symposium

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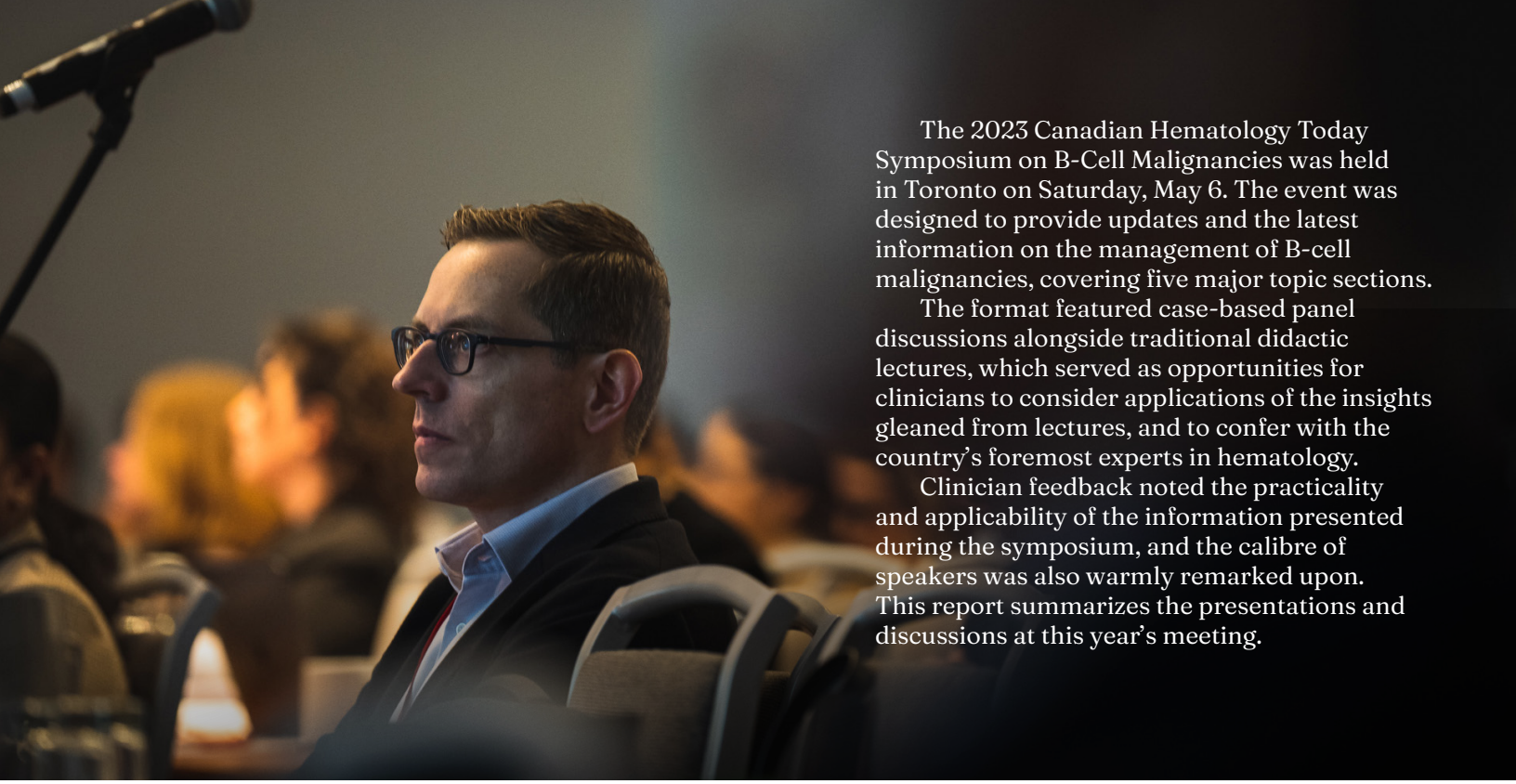


The 2023 Canadian Hematology Today Symposium on B-Cell Malignancies was held in Toronto on Saturday, May 6. The event was designed to provide updates and the latest information on the management of B-cell malignancies, covering five major topic sections.

The format featured case-based panel discussions alongside traditional didactic lectures, which served as opportunities for clinicians to consider applications of the insights gleaned from lectures, and to confer with the country's foremost experts in hematology.

Clinician feedback noted the practicality and applicability of the information presented during the symposium, and the calibre of speakers was also warmly remarked upon. This report summarizes the presentations and discussions at this year's meeting.

In this report...

Optimization of CLL Management: Applying the Data to a Practical Case-Based Discussion

Dr. Nicole Lamanna

Recent advances in therapy choices for in chronic lymphocytic leukemia (CLL) require clinicians to weigh many factors, especially patient preference. Comparing continuous and fixed-duration therapy, Dr. Lamanna highlighted that continuous therapy—BTK inhibitors (BTKis)—is logistically easy to initiate, as tumor lysis syndrome is extremely rare. The indefinite aspect of the therapy may be a drawback for some patients, however. In addition, BTKis have higher risks of cardiac issues, like atrial fibrillation, hypertension, and bleeding. Data suggests patients with high-risk disease (TP53-mutated disease) may experience longer progression-free survival (PFS) on BTKis, compared to BCL2 inhibitor treatment. The advantage of the BCL2 inhibitors (BCL2is), meanwhile, is that they are fixed duration. However, this therapeutic option is more monitoring-intensive, due to the risk of tumor lysis syndrome.

For CLL patients with high-risk features like deletion 17p, Dr. Lamanna recommends continuous therapy, preferably newer generation BTKis (zanubrutinib and acalabrutinib) due to the better side effect profiles in head-to-head comparisons.

Given that younger patients will undergo many therapies in their lifetime, time-limited venetoclax-obinutuzumab (VenG) allows for disease eradication and time off therapy. BTKi and BCL2i combination therapy allows for more convenient outpatient monitoring. Studies show that the combination of ibrutinib and venetoclax achieved durable responses, clinically meaningful PFS, and treatment-free remissions in patients with and without the deletion of 17p, but longer follow up is needed. Combination medications also increase toxicity, therefore, while the BTKi-BCL2i combination is an option for fit younger patients or those with high-risk disease, more data is needed to clarify the sub-types for which this oral combination is most appropriate.

For patients who experience intolerance or progression on BTKis, Dr. Lamanna recommended switching patients to another drug in the same class if the drug has been effective. However, more serious intolerance issues, like CNS hemorrhage, require another therapeutic option. Non-covalent agents like pirtobrutinib and nemtabrutinib may be useful in BTKi-intolerant settings.

For patients who experience progression, current evidence supports treatment with venetoclax as well as non-covalent BTKis (ncBTKis). PI3K inhibitors can also be helpful, especially as a bridging therapy.

Going forward, new trials in bispecific antibodies and BTK degrader medications may bring more options in the multiple relapse setting. Additionally, ncBTKis will be helpful for bridging. With these new options, CAR-T will be delayed further, though the data on CAR T-cell therapy remains good in younger, fitter, and very high-risk individuals.

Keynote Lecture: Complex Immunotherapies

Dr. Michael Jain

While patient factors, tumor factors and CAR T-cell factors all affect CAR T-cell therapy outcomes and toxicity, Dr. Jain explained that clinicians can have the most impact on patient factors, including the microbiome, the patient's level of fitness, T-cell quality, and systemic immunosuppression.

Dr. Jain recommended avoiding treatment delays and multiple lines of therapy, and avoiding antibiotics that can dysregulate the microbiome. Therapies that affect the same CD19 or BCMA targets as CAR T-cell therapy increase the risk of tumor-intrinsic resistance to CAR T-cell therapy. Likewise, he recommended against therapies that worsen T-cell quality (like purine analog medications) for patients who may receive CAR T-cell therapy. Preventing unnecessary system delays and late referrals can prevent high tumor burdens and increase the success of CAR T-cell therapy.

Addressing cytokine release syndrome (CRS), Dr. Jain emphasized that 4-1BB CARs are less toxic than CD28, but safety concerns must be balanced against the efficacy concerns. When treating B-ALL in children, giving doses over three days dramatically improved tolerance; such fractionated dosing schemes may be possible in clinical trial settings. Finally, prophylactic steroids are increasingly being incorporated in practice, as is treating toxicities earlier. Concurrent BTKis or JAK inhibitors throughout CAR T-cell therapy can also help improve tolerance.

Finally, Dr. Jain summarized his treatment approach for CRS, noting that it is important to first rule out infections, especially in patients with severe immunosuppression. Low-risk patients (those with follicular lymphoma, myeloma, low tumor burden, or those on 4-1BB therapy), often don't require treatment for CRS. For higher risk patients, Dr. Jain typically administers tocilizumab and dexamethasone. If patients have clinical CRS progression and a fever despite two doses of tocilizumab, he adds anakinra, noting the need to monitor patients closely for fungal infections.

ICC & WHO Updates: Implications for Aggressive Non-Hodgkin Lymphomas

Dr. Robert Kridel

Dr. Kridel discussed changes to the International Consensus Classification (ICC) and World Health Organization Classification in recent years. For diffuse large B-cell lymphoma (DLBCL), Not Otherwise Specified (NOS), there haven't been any major classification changes. Classification features within DLBCL remain the morphology (such as centroblastic or immunoblastic), the immunophenotype, cytogenetic profile, cell of origin, and genetic subtypes.

There are three cell-of-origin subtypes: germinal-center B-cell-like (GCB) DLBCL (associated with longer PFS), activated B-cell (ABC) DLBCL and unclassified DLBCL. In the Polarix trial, an emerging signal suggests that the ABC subtype DLBCL may preferentially benefit from polatuzumab. In the PHOENIX trial, while the numbers in the study were small, those with ABC subtype benefited from the addition of ibrutinib, and this was particularly true for those with N1 and MCD genetic subtypes, within the ABC group. Dr. Kridel also highlighted the new classification of mediastinal gray zone lymphoma, replacing 'B-cell lymphoma, unclassifiable with features intermediate between DLBCL and classic Hodgkin lymphomas.'

Dr. Kridel explained that as classification becomes more complex, expert review is more important than ever. A comprehensive review in France of over 30,000 cases found diagnostic changes after expert hematopathology review were common, and in some cases, resulted in major classification changes. Molecular subtyping will only grow in importance, as benefits from novel therapies are preferential certain subtypes of DLBCL with specific molecular characteristics.

Upcoming Frontline Treatment Options: When is R-CHOP Not Enough?

Dr. Laurie Sehn

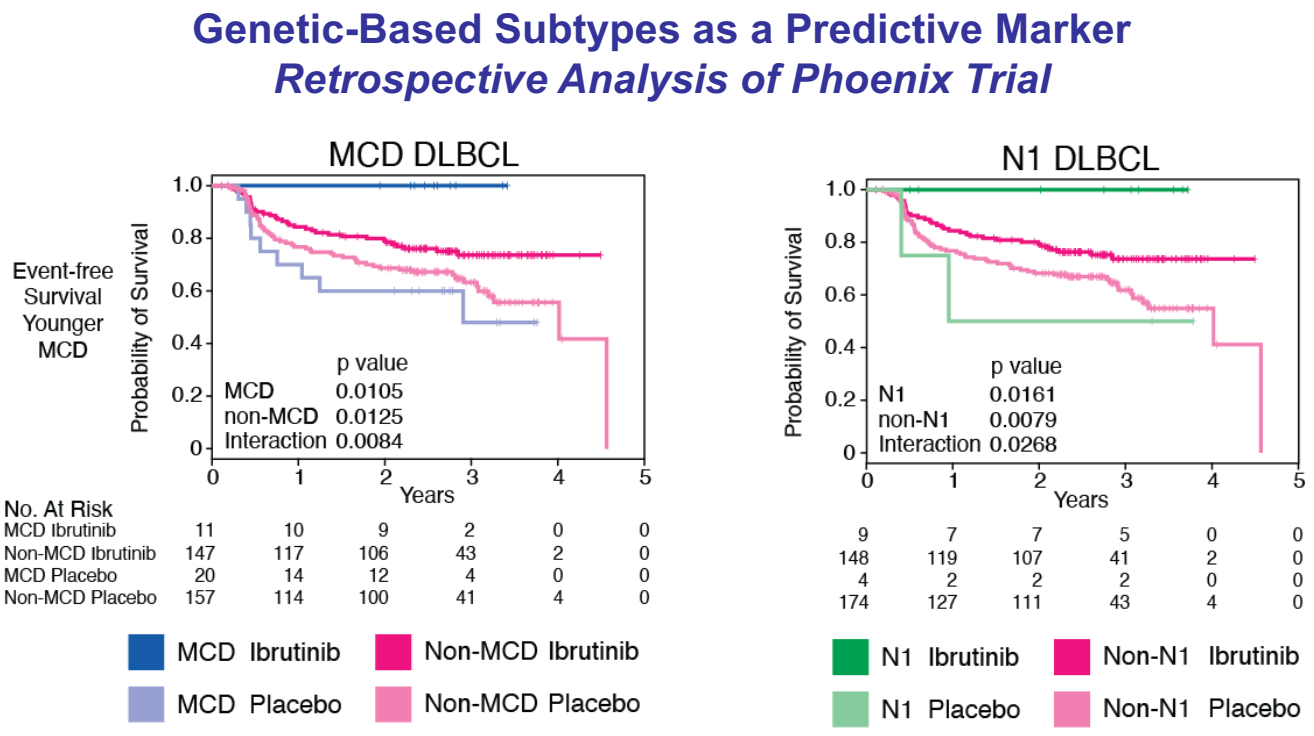
While treatments cure the majority of DLBCL patients, frontline therapy isn't meeting the needs of all DLBCL patients. Dr. Sehn said that in her practice, the treatment algorithm consists of obtaining FISH testing for all DLBCL patients and providing intensive therapy for those with double-hit lymphoma who meet the fitness criteria. However, this is the only subgroup that currently receives differential treatment.

The future for DLBCL therapy centers on novel therapies that target biological differences in DLBCL. While a series of trials targeted to cell-of-origin subtypes did not meet their primary endpoints, emerging evidence suggests greater molecular heterogeneity within the cell-of-origin subtypes than originally recognized. Researchers are getting closer to understanding clinically relevant genomic subgroups within GCB, ABC, and unclassified subtypes.

Previous clinical trials that divided patients based on cell of origin alone may not have been specific enough. A reanalysis of the PHOENIX trial found that several genomic categories benefitted from the addition of ibrutinib (see below).

Similarly, a five-year follow up of the REMoDL-B trial found a strong signal of benefit with bortezomib and rituximab-cyclophosphamide-doxorubicin hydrochloride, and vincristine sulfate (R-CHOP) among discrete molecular subgroups within the GCB subtype. Dr. Sehn highlighted the importance of learning from the past, and designing trials to pick up on preferential benefits in discrete molecular subgroups. She suggested validating biomarkers earlier to allow decentralized testing, liberalizing exclusion criteria, and allowing an initial cycle of therapy prior to screening to improve trial efficiencies and statistical power.

Dr. Sehn concluded by highlighting the promise of polatuzumab vedotin and R-CHP, and encouraging more research to evaluate its efficacy in molecular subgroups.



Genetic-Based Subtypes as a Predictive Marker: Retrospective Analysis of the PHOENIX Trial.
W. Wilson et al. *Cancer Cell*, 2021.
Slide courtesy of Dr. Laurie Sehn.

Panel: CAR-T vs. Other Immune Therapies for Aggressive Non-Hodgkin Lymphomas

Dr. Anca Prica, Dr. Ronan Foley
Moderator: Dr. Kelly Davison

Dr. Davison asked the panellists how their understanding of autologous stem cell transplant (ASCT) eligibility has evolved in the era of CAR T-cell therapy. Dr. Foley underscored the importance of assessing patients for comorbidities, as many patients with pulmonary and cardiac comorbidities will not be eligible for transplant. Chemosensitivity beyond partial response is necessary for ASCT, in his view. Patients with double-hit and double-expressor DLBCL do poorly with ASCT. Dr. Prica added that, while the age cut-off for transplant was previously 65, with the availability of CAR T-cell therapy, there has been a shift from age cut-offs toward an evaluation of comorbidities and fitness for transplant. In general, patients who are not eligible for gemcitabine, dexamethasone, and cisplatin (GDP) are not likely to be eligible for ASCT.

Dr. Davison also asked about factors that determine CAR T-cell therapy eligibility. Dr. Foley said he considers the patient's lactate dehydrogenase (LDH) levels, the Eastern Cooperative Oncology Group (ECOG) performance score, whether the patient has bulky disease, the pace of disease and the patient's T-cell fitness. Dr. Davison asked about alternative therapies for patients who are not eligible for CAR T-cell therapy. Dr. Prica suggested Pola-R, noting that the potential of CAR T-cell therapy in the future can influence whether or not to incorporate bendamustine. Health Canada's approval of glofitamab may change the treatment landscape. With data showing that patients with a complete response after 12 doses were very unlikely to relapse, BiTE treatments could also offer a curative potential.

Current Treatments in CLL

Dr. Alina Gerrie

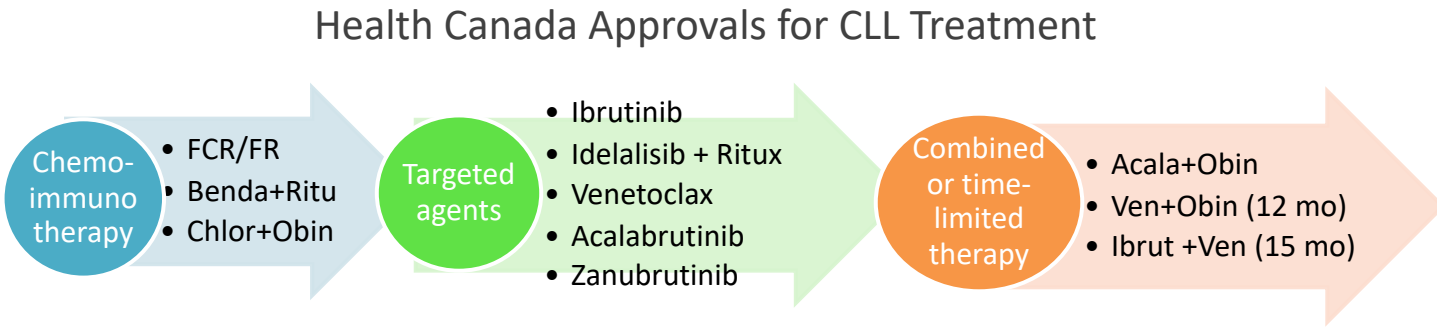
Dr. Gerrie outlined the treatments currently approved in Canada for CLL, noting that availability and access are province-dependent. The paradigm has already moved from chemoimmunotherapy to targeted agents, and research is advancing toward combination and time-limited therapies (see below).

Regarding BTKis, Dr. Gerrie highlighted that PFS was significantly longer with ibrutinib-rituximab versus fludarabine, cyclophosphamide, rituxumab (FCR) among both IGHV-unmutated and IGHV-mutated patients, so BTKis should be considered as an option for IGHV mutated patients. Comparing ibrutinib with acalabrutinib, while the PFS for acalabrutinib is on par with ibrutinib in the high-risk relapse setting, acalabrutinib has fewer AE-related treatment discontinuations. The ALPINE study showed a statistically significant improvement in PFS with zanubrutinib, compared to ibrutinib, and less serious cardiac events (2% in the zanubrutinib arm, compared to 8% in the ibrutinib arm).

In the BCL2 inhibitor class, the four-year PFS rate among those treated with VenG was 75%, compared to 35% in the chlorambucil-obinutuzumab arm. The three-year PFS rate in IGHV-unmutated patients was not significantly different than patients with mutated-IGHV disease. However, del(17p)/TP53 patients saw worse outcomes, with a three-year PFS rate of approximately 60%. Ibrutinib performed better in patients with the del(17p)/TP53 mutation, with a six-year PFS of 60%.

The combination of ibrutinib and venetoclax is a promising new therapeutic option. In the GLOW trial, this combination reduced the risk of progression or death by 79%, versus chlorambucil-obinutuzumab. In the CAPTIVATE trial, fixed duration ibrutinib and venetoclax led to a 36-month PFS rate of 88%; PFS rates were similar in patients with del(17p)/TP53 mutated disease and unmutated disease. Among 22 patients who developed progressive disease, there were no BTK, PLC-2, or BCL-2 mutations associated with resistance to ibrutinib or venetoclax. This suggests time-limited therapy does not introduce resistance. However, ibrutinib-venetoclax is associated with high rates of neutropenia (42%) and infections (67%), as well as atrial fibrillation, bleeding, and hypertension.

The German CLL Study Group will compare ibrutinib-venetoclax, VenG and indefinite BTKi therapy in CLL, which will be crucial to informing treatment decisions in the future.



Health Canada Approvals for CLL Treatment (as of May 5, 2023).
Slide courtesy of Dr. Alina Gerrie.

Upcoming and Future Treatments in CLL

Dr. Inhye Ahn

Dr. Ahn explained that while selective BTKis (acalabrutinib and zanubrutinib) are preferred over ibrutinib, the continuous BTKi approach can lead to drug resistance, has cumulative toxicities, and is costly. Venetoclax-based regimens are associated with tumor lysis syndrome, and require frequent monitoring and infusion visits.

To address these treatment gaps, CLL research is moving toward targeted combination regimens, utilizing minimum residual disease (MRD)-guided treatment cessation. The ibrutinib-venetoclax doublet regimens can achieve undetectable MRD in over half of patients. Triplet regimens include ibrutinib-ventoclax-obinutuzumab (IVO) and acalabrutinib, venetoclax and obinutuzumab (AVO). These regimens can induce high rates of undetectable MRD in the bone marrow aspirate (66% with IVO; 83% with AVO), even in patients with the TP53 aberration.

Lisaftoclax is a novel medication targeting BCL2, and trial has used a daily ramp up strategy of venetoclax to reduce time to treatment response. In addition, ncBTKis, such as pirtobrutinib and nemtabrutinib, are active against BTKi- or BCL2i-resistant CLL. Ongoing research is evaluating these agents as earlier line therapy.

Novel BTKi mutations that can emerge after therapy has been a challenge in this field but NX-2127 (BTK degrader) can overcome these novel mutations. Early data suggests that the bispecific antibody epcoritamab may be a preferable option in challenging-to-treat patients with Richter's transformation.

Panel: FDT vs. Continuous Therapies for CLL

Dr. Carolyn Owen, Dr. Nicole Lamanna
Moderator: Dr. Versha Banerji

Dr. Banerji presented a case of a 56-year-old male with asymptomatic lymphocytosis, determined to be Rai stage II disease. Four years later, he presented with painful splenomegaly. If the CLL is IGVH-mutated with no P53 abnormality, Dr. Owen said that FCR or VenG would be appropriate treatment options. There is no efficacy data to support one over the other, and it is possible that FCR may have a higher myelodysplastic syndrome risk that previously thought. Dr. Owen said she would engage in shared decision making with the patient, presenting both options.

Dr. Lamanna said that for younger, fitter patients, time-limited therapy is preferable. Randomized trials currently underway in CLL will be greatly informative in helping clinicians choose between chronic BTKis, oral BTKi-BCL2 combinations, chemotherapy, and VenG.

Dr. Banerji asked the panellists how they would treat a high-risk patient who has a del(17p)/TP53 mutation. Dr. Owen said the studies of ibrutinib plus venetoclax aren't powered to provide clear treatment direction for patients with del(17p); instead they're included as subgroups. Given the tolerability of the new second generation covalent inhibitors, and given this high-risk population is very small, she would prefer to prescribe indefinite BTKi treatment.

Dr. Lamanna agreed that she prefers second-generation BTKis in higher-risk patients, and ideally with time, combination oral therapy will present MRD data that will help guide MRD-based treatment decisions for higher-risk patients.

Dr. Banerji asked whether emerging research on the potential for resistance to other therapies poses concern about using the newer generation BTKis earlier. Dr. Owen said this is a concern, and longer-term follow-up data comparing ibrutinib versus pirtobrutinib will soon be available to provide additional evidence on any risk associated with switching the order of therapy.

The Standard of Care in Canada for Waldenström Macroglobulinemia

Dr. Christine Chen

Dr. Chen described the current diagnostic standard of care, emphasizing the importance of testing for both MYD88 and CXCR4 mutations. If patients are negative for MYD88 and WM is likely, Dr. Chen recommended testing for other important variants (V217F, S219C, M232T, S243T, S243N). Approximately one third of patients have the CXCR4 mutation, which predicts a shorter time to treatment. The absence of MYD88 and CXCR4 predicts a short time to treatment and poor survival.

Dr. Chen provided an overview of standard-of-care treatments, highlighting that bendamustine-rituximab (BR) remains the most common standard-of-care therapy in the frontline setting. Ibrutinib-rituximab is a newer treatment option, for frontline and relapsed disease. Follow-up data from the iNNOVATE trial, published in 2020, showed the overall response rate (ORR) was 75%, and responses were sustained over time. Advantages of the therapy is that it is convenient, there is no IgM flare, no neuropathy, and it's well-tolerated. Disadvantages include that it is a continuous therapy and involves toxicities, including the rare but concerning cardiovascular toxicities, such as ventricular arrythmias.

Zanubrutinib, a covalent BTKi that acts in the same sites as ibrutinib, is more specifically targeted than ibrutinib, and therefore has fewer toxicities. The ASPEN trial demonstrated slightly superior efficacy of zanubrutinib, compared to ibrutinib, in longer term follow-up, as well as decreased cardiac toxicities. Drug discontinuation due to side effects were much lower than with zanubrutinib (4%) compared to ibrutinib (9%).

In the relapsed/refractory setting, venetoclax can benefit patients, but is not yet funded for the treatment of WM. Stem cell transplants (SCT) are not recommended, except for patients with concurrent amyloid and failure after Dara-CyBorD, as evidence shows that 50% of patients with WM relapse within five years after autologous or allogeneic SCT. Dr. Chen underscored the need for treatment for WM patients who have failed BTKi and chemoimmunotherapy.

What's New in Waldenström Macroglobulinemia

Dr. Steven P. Treon

Although Waldenström macroglobulinemia (WM) primarily presents with bone marrow disease, extramedullary disease can also occur, and in rare cases, WM can penetrate the central nervous system (see below).

In the pivotal trial leading to the approval for ibrutinib in the treatment of WM, over 90% of patients responded, and 80% saw a major response. However, mutation status plays an important role. Those with wild type WM (no MYD88 mutation) did not respond to the medication and for those with CXCR4-mutated disease, the time to major response was seven months, compared to two months for those without CXCR4-mutated disease.

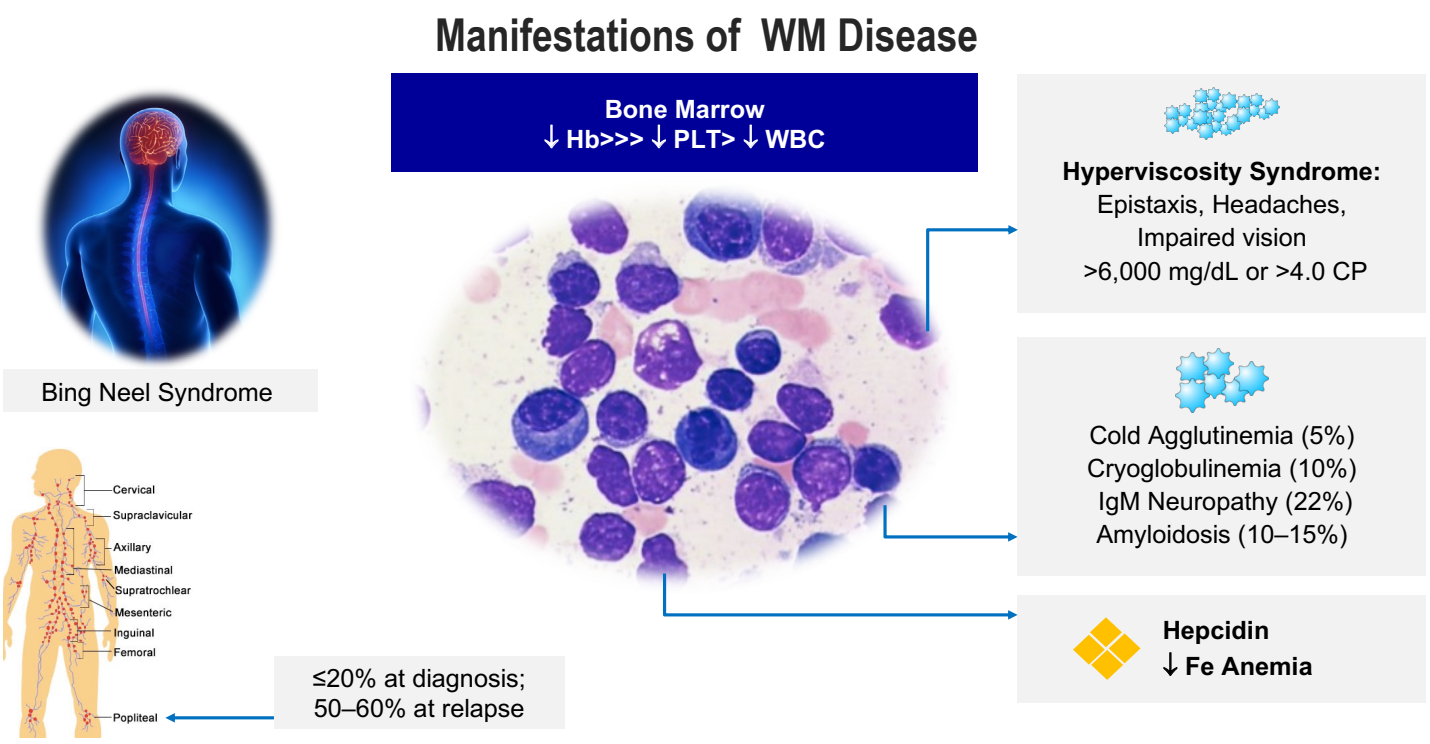
The ASPEN trial found unexpected activity with zanubrutinib in MYD88 wild-type patients, which could be due to important off-target effects with the drug, compared to ibrutinib. The pharmacokinetics may play a role as well, as zanubrutinib is administered twice a day, rather than once a day. While there is much less atrial fibrillation with zanubrutinib, there was more neutropenia. This did not translate into an infection signal, however. Research presented at the International Workshop on WM in 2022 showed patients with CXCR4 mutations having a better response on zanubrutinib, compared to ibrutinib.

A large, multi-centre study comparing BR to ibrutinib found deeper responses with BR, but no differences in PFS and OS. However, an important biomarker analysis also presented in the Madrid International Workshop in 2022 demonstrated high rates of TP53 mutations among patients previously treated patients (25% among patients with MYD88 mutations). Almost all of the patients with TP53 mutations had been treated with an alkylating agent, and almost a quarter of them had seen a nucleoside analog. Therefore, it may be more prudent to start with BTKi in the frontline setting.

Efforts to study BTKi and chemoimmunotherapy in combination are now underway, including the combination of ibrutinib and BR, as well as zanubrutinib with BR. These trials may lead to limited duration therapy, which is important for many patients.

In BTKi resistant disease, previously treated patients who received single agent venetoclax had a median PFS of 30 months. Pirtobrutinib led to high response rates in BTKi-resistance disease, but a low durability of response, with a PFS of 11 months. The combination of pirtobrutinib and venetoclax may be more promising.

Dr. Treon recommended prioritizing BTKis in MYD88-mutated patients, but considering BR or a proteasome inhibitor-based therapy in double-mutated patients who need a more rapid response to treatment. If a rapid response is not needed, zanubrutinib is preferable to ibrutinib in patients with CXCR4-mutated disease.



Manifestations of WM Disease. S. Treon. *Hematological Oncology*, 2013; 31:76-80.
Slide courtesy of Dr. Steven P. Treon.

Panel: Cases in Waldenstrom Macroglobulinemia

Dr. Anthea Peters, Dr. Rajshekhar Chakraborty, Dr. Irwindeep Sandhu
Moderator: Dr. Julie Stakiw

Dr. Stakiw asked about a case of a 72-year-old male with the following investigation results:

- White blood cell (WBC) count: 6.58
- Hemoglobin: 117 g/dL
- Platelets 318 × 10^9/L
- IgM total 58.50g/L
- Viscosity 2.8
- Bone Marrow: lymphoplasmacytic lymphoma (LPL)
- CT scan: bulky lymphadenopathy (largest was 8cm)
- Lymph node biopsy consistent with LPL and follicular lymphoma in situ (t14;18)

Regarding additional investigations, the panellists recommended assessing iron levels, to see if the patient has hepcidin dysfunction, as well as MYD88 and CXCR4 testing, and possibly a WM risk score. The latter includes beta-2 microglobulin, which can factor into prognosis predictions. Dr. Peters suggested haemolytic markers, including direct antiglobulin testing (DAT) and cryoglobulin baseline testing. Dr. Chakraborty said he would send patients for an ophthalmology exam if their IgM is above 30 g/L.

Dr. Stakiw asked whether the panellists would initiate treatment for this patient. Dr. Peters said she would treat the patient, given the bulky lymphadenopathy, starting with BR, due to the challenges of reimbursement for BTKis in Canada.

Dr. Stakiw explained that as the patient presented in 2017, when BTKis weren't available, he received six cycles of BR and achieved a PR. Four years later, the patient's IgM values had increased to 18.8g/L; and the CT scan showed larger lymph nodes in the abdomen (1-2 cm). The patient's hemoglobin was 114 g/dL. The patient was taking a PD1 inhibitor for carcinoma. Dr. Stakiw asked the panellists if they would recommend additional therapy for WM in this case.

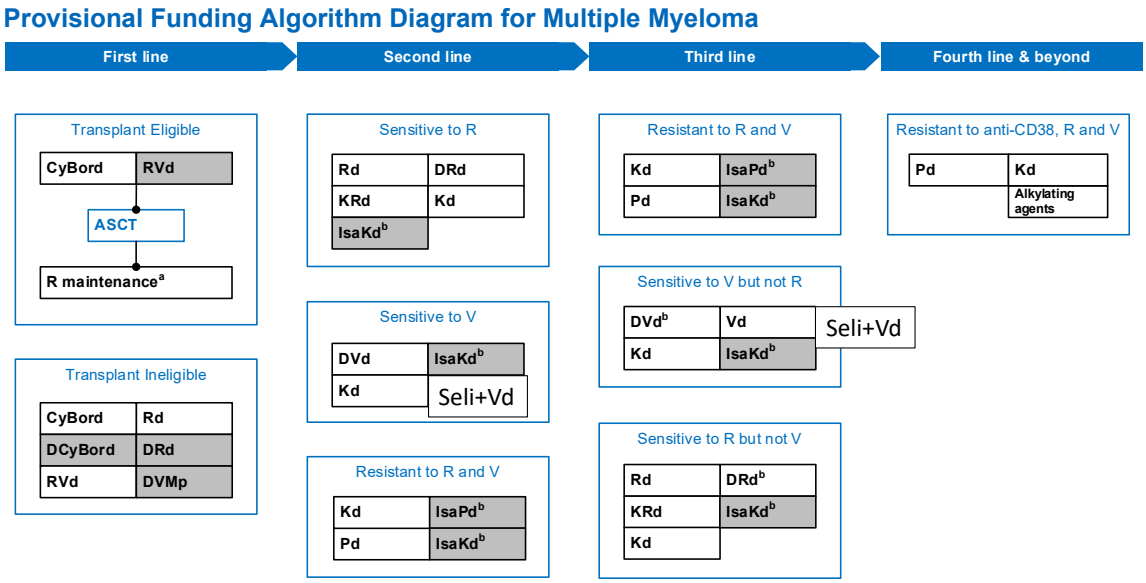
Dr. Peters and Dr. Chakraborty said they would monitor the patient. If he progressed to the point of having symptoms, Dr. Chakraborty said he would start zanubrutinib, as the ASPEN data suggests zanubrutinib is preferable to ibrutinib.

The CADTH Algorithm: Implications for Multiple Myeloma

Dr. Chris Venner

Dr. Venner presented the CADTH Provisional Funding Algorithm, noting that it was created before the approval of selinexor-bortezomib-dexamethasone.

He explained that the standard of care going forward has dramatically changed from recent years. Transplant-eligible patients should receive revlimid, velcade, and dexamethasone (RVD), followed by ASCT and lenalidomide maintenance. For transplant-ineligible patients, daratumumab-lenalidomide-dexa-methasone (DRD) is the standard of care, based on the Phase 3 MAIA Study.



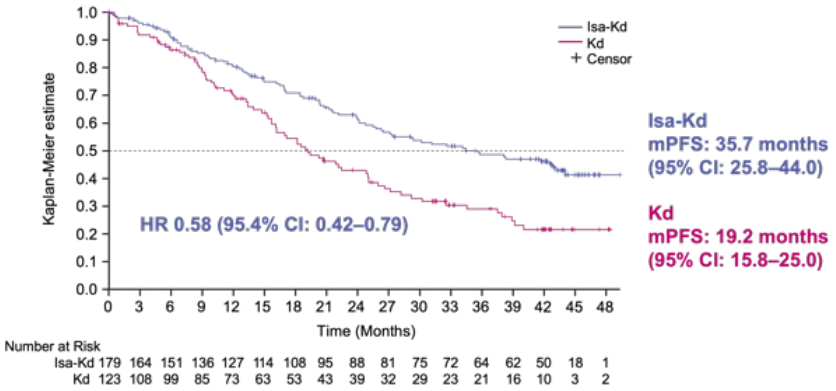
Provisional Funding Algorithm. *Canadian Agency for Drugs and Technologies in Health (CADTH)*, May 2022. **Slide courtesy of Dr. Chris Venner.**

In second-line setting, patients not exposed to lenalidomide now receive DRD. Carfilzomib-lenalidomide-dexamethasone (KRd) is also approved, but DRD led to more favourable PFS of 44 months, which is remarkable for the second-line setting. As most patients have been exposed to or have progressed on lenalidomide, however, daratumumab, bortezomib, and dexamethasone (DVD) is the only currently funded option. KCd could be tried, if the patient wasn't resistant to the bortezomib, but that would preclude early access to an anti CD38.

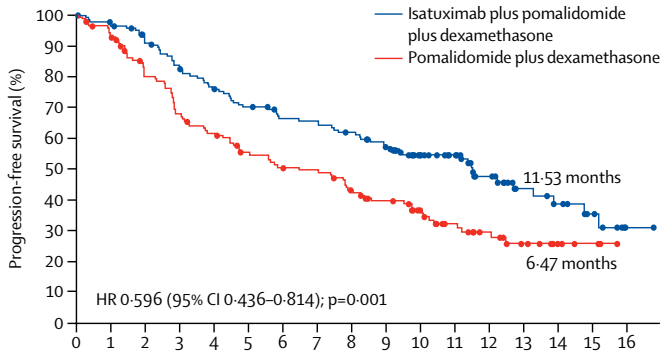
The median PFS with DVD is around 8 months, in the context of prior lenalidomide exposure. In the near future, isatuximab-based regimens will be available, which will likely be more efficacious than DVD in the post-lenalidomide setting.

In the third line, the options are very limited, as the vast majority of patients will have exposure to a proteasome inhibitor, lenalidomide, and an anti-CD38 regimen. Cilta-cel was recently given provisional approval through CADTH. It will be available after three prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody, and patients must be refractory to their last line of therapy. The CARTITUDE-1 trial found a stringent complete response of over 80% of patients, which is remarkable in this group of heavily treated patients and suggests that cilta-cel will be a new standard in the third-line setting.

Novel Isatuximab-based therapies



ICARIA study: Isatuximab-Kd vs Kd.
M. Attal et al, *Lancet*, 2019.



IKEMA study: Isatuximab-Pd vs Pd.
M. Attal et al, *Lancet*, 2019; A. Perrot et al. EHA 2021.

Slide courtesy of Dr. Chris Venner.

Complex Immunotherapies in Multiple Myeloma

Dr. Ajai Chari

Dr. Chari began by discussing T- and NK-cell engaging antibody clinical trials in multiple myeloma. Most of the BCMA compounds currently being studied are administered intravenously on a weekly basis. The response rates are 50% to 75% across the trials, which is remarkable, considering many patients in the trial had five to six lines of previous therapy. The median PFS is 11 months for teclistamab and 11 to 13 months in the ABBV-383 trials. The duration of response is 18 months.

Regarding toxicities, CRS is common, with grade I and II CRS ranging from 20% to 70%. The rates of infections and neutropenia are concerning, and deaths due to toxicities have occurred. Given that the infection risk is cumulative, fixed duration treatment may help, with retreatment at the time of relapse. A change of the dose or the dosing schedule could also reduce toxicities.

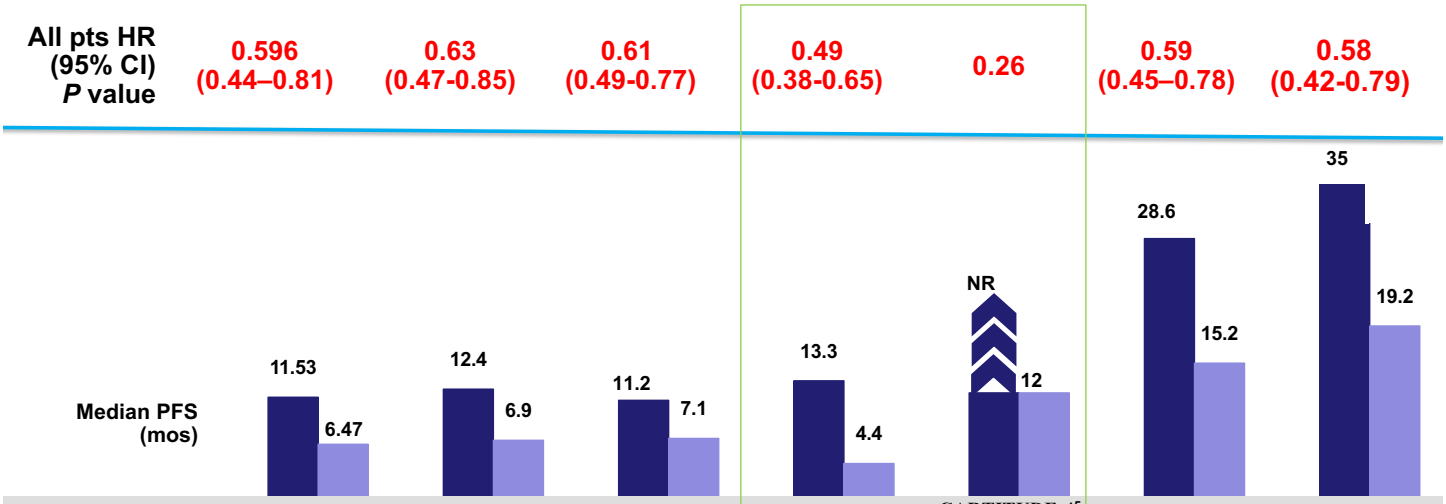
In comparison, non-BCMA-targeted bispecific antibodies are mostly subcutaneous, and administered weekly to every three weeks. In heavily treated patients, response rates are 50% to 60% and the PFS is 8–12 months. These bispecific antibodies have lower rates of AEs, with infections at or above grade 3 at 10% to 20% and neutropenia at 12% to 30%. Combinations, such as talquetamab, daratumumab and lenaldomide, have demonstrated high response rates, but very high infection and neutropenia rates.

Regarding CAR T-cell therapy, response rates are 60% to 100% in heavily treated patients, with 80% of patients on cilta-cel achieving CR. However, for those who have had eight lines of previous therapy, the PFS is less than a year. These datasets should give pause in regards to BCMA-directed therapies prior to BCMA CAR-T therapies.

Dr. Chari presented the data comparing CAR-T options to other standard of care treatments.

He highlighted the need for additional subgroup data. Bispecific medications are preferred if the PFS on CAR-T therapy is predicted to be less than one year, but CAR-T therapy is superior for patients for whom the PFS is predicted to be above one year.

Pomalidomide/CART/Carfilzomib Randomized Phase 3 Studies



	ICARIA-MM[1] Isa-Pd vs Pd	APOLLO[2] D-Pd vs Pd	OPTIMISMM[3] PVd vs Vd	KarMMa-3[4] Ide-cel vs SOC	CARTITUDE-4[5] Ciltacel vs DPd or DVd	CANDOR[6] DKd vs Kd	IKEMA[7] IsaKd vs Kd
Total N	154 vs 153	151 vs 153	281 vs 278	254 vs:132**	208 (175 +20) infus vs 183 or 28	312 vs 154	179 vs 123
No. prior lines	3	2	2	3	1-3 (~33% 1 LOT)	2	2
Len refractory (%)	~90	~80	71 vs 69	~75		~33	~33
PI refractory (%)	~75	~48	9 vs 12%	~73	~50%		
mFU (months)	11.6	16.9	15.9	18.6	16	27.8 vs 27.0	20.7
≥CR (%)	5 vs 1	24.5 vs 3.9	15.7 vs 3.9	39 vs 5	73 vs 22	33 vs 13	39.7 vs 27.6
OS HR	NR	0.91 (0.61-1.35)	NR	NR	0.78 (0.5-1.2)		

**DPD, DVd, IRd, Kd, EPd

1) Attal M et al. *Lancet*. 2019. **2)** M.A. Dimopoulos et al. ASH 2020. **3)** M. Sebag et al. ASH 2020. **4)** P. Rodriguez Otero et al. *N Engl J Med*. 2023 Feb 10. **5)** Legend Biotech leaked abstract. **6)** Usmani et al. *Lancet Oncol*, 2022. **7)** P. Moreau et al. ESMO plenary 2022.

Slide courtesy of Dr. Ajai Chari.

Panel: Optimal Sequencing for Multiple Myeloma Therapies

Dr. Guido Lancman, Dr. Arleigh McCurdy, Dr. Richard LeBlanc
Moderator: Dr. Hira Mian

Dr. Mian presented the case of a 72-year-old female with a new diagnosis of multiple myeloma. She had mildly reduced estimated glomerular filtration rate (eGFR), was determined to be fit, and her disease stage was R-ISS Stage III; t (4;14). She asked about the panellists' treatment considerations.

Dr. McCurdy and Dr. Lancman said they would offer the patient a stem cell transplant. Dr. Lancman said transplanted patients in this age group have good outcomes, if they don't have concerning comorbidities and they're fit. The PFS will be similar for either treatment with a DRD regimen or transplant, but the treatment options will be more limited post-DRD.

Dr. LeBlanc said that transplant wouldn't be appropriate for this patient, given her age, and based on the median PFS data from the MAIA trial. If the patient were 68, he would consider transplant, however, mortality with transplant increases with age, as does the risk of myelodysplastic syndrome.

Dr. Mian said the patient was treated with DRD. After an initially strong response, the patient had a biochemical and clinical relapse. Dr. Lancman said that any patient who has relapsed should be evaluated for clinical trials, and he would recommend the strongest therapy they can tolerate. If the patient is fit enough, he would suggest KCd. Dr. LeBlanc recognized that using KCd in patients refractory to anti-CD38 monoclonal antibodies and lenalidomide would mean bortezomib is no longer a future treatment option. He would consider selinexor, bortezomib and dexamethasone for this patient. Dr. McCurdy said the data shows that, regardless of the sequence of pomalidomide- or carfilzomib-based treatments, the PFS and OS is very similar. In this case, the treatment decision would be based on access to reimbursement.

What's New in First-Line Therapies for Mantle Cell Lymphoma?

Dr. Diego Villa

In the BC database of mantle cell lymphoma (MCL) cases from 1998 to 2014, 83% of patients required early treatment, and 17% did not require treatment in the first three months. A small proportion of patients never require treatment. Patients who have only GI presentation (usually polyps) require therapy later than the patients with nodal involvement. Observing patients and treatment deferral/delay does not impact their OS.

The median PFS of R-CHOP, alternating with rituximab-cisplatin, cytosine arabinoside and dexamethasone (R-DHAP), followed by transplant, is 10 years. R-DHAP requires in-patient administration and is associated with more toxicities. In BC, a retrospective comparison of CHOP-R and R-DHAP, using an adjusted analysis of the European MCL Younger trial, found no difference in OS. Dr. Villa explained the comparison is limited by differences in the treatment cohorts.

Comparing BTKi treatment and transplant, the Triangle study found the ibrutinib-treated, non-transplant arm had statistically significant superior survival to the non-ibrutinib arm with transplant. Long-term follow-up will determine whether there is separation between the ibrutinib-only and ibrutinib plus transplant arms; however, many clinicians see these initial results as sufficient data to consider omitting transplant in many patients with mantle cell lymphoma.

For patients who are not transplant-eligible, standards of care include BR, R-CHOP, VR-CAP (bortezomib and rituximab-cyclophosphamide, epirubicin and prednisone), and R-lenalidomide, with BR being the most common. Data supports BR over R-CHOP. However, patients with high-risk mantle cell lymphoma have high rates of treatment failure with BR. The effectiveness of maintenance after BR remains an open question, with the randomized MAINTAIN study not finding statistically significant differences between maintenance and observed arms, while real-world data from the BC Flatiron Health EHR did show benefit.

In the BTKi realm, the SHINE trial found more toxicity with the BR and ibrutinib combination, compared to BR alone, but there was a two-year improvement in PFS with the addition of ibrutinib.

Finally, BTKis are showing promise in the first-line setting, in combination with rituximab or obinutuzumab +/- chemoimmunotherapy. In a small study, IVO led to MRD negativity in all patients by cycle 3. Other studies of first-line BTKi show positive effects, despite small numbers of enrollment. MRD is being increasingly used as an endpoint in studies of novel combinations.

Studies of 1L BTKi in MCL

Study	n	Intervention	MRD test (threshold)	MRD(-) in blood
OASIS LeGouill, Blood 2021	15	Ibrutinib + venetoclax + obinutuzumab	ASO-qPCR (10^{-5})	100% @cycle 6
IMCL-2015 Gine, JCO 2022	50	Ibrutinib + rituximab	RT-PCR (10^{-5})	87% @cycle 12
ACE-LY-106 Wang, ASH 2022	21	Acalabrutinib + venetoclax + rituximab	ClonoSeq (10^{-4} through $^{-6}$)	67% @cycle 12
US phase II Ruan, ASH 2022	24	Acalabrutinib + lenalidomide + rituximab	ClonoSeq (10^{-6})	50% @cycle 6 71% @cycle 12 82% @cycle 24

Studies of first-line BTKi in MCL.
Slide courtesy of Dr. Diego Villa.

Relapsed/Refractory Follicular Lymphoma and Marginal Zone Lymphoma

Dr. Isabelle Fleury

Dr. Fleury explained that follicular lymphoma (FL) and marginal zone lymphoma (MZL) are heterogenous diseases. Within a single patient with FL, there is clonal diversity and evolution. MZL is associated with different infections and autoimmune diseases and the genetic changes are distinct, according to the primary site involved. Patients typically have repeated cycles of remission and progression. About 20% patients with relapsed/refractory FL and MZL have POD24, defined as progression within 24 months of frontline chemoimmunotherapy. Up to 76% of FL patients with the POD24 designation after BR are transformed, so a PET-guided biopsy is warranted in these patients. Once patients have transformed disease, patients are treated with large B-cell lymphoma regimens (anthracyclines in naive patients and ASCT in selected cases).

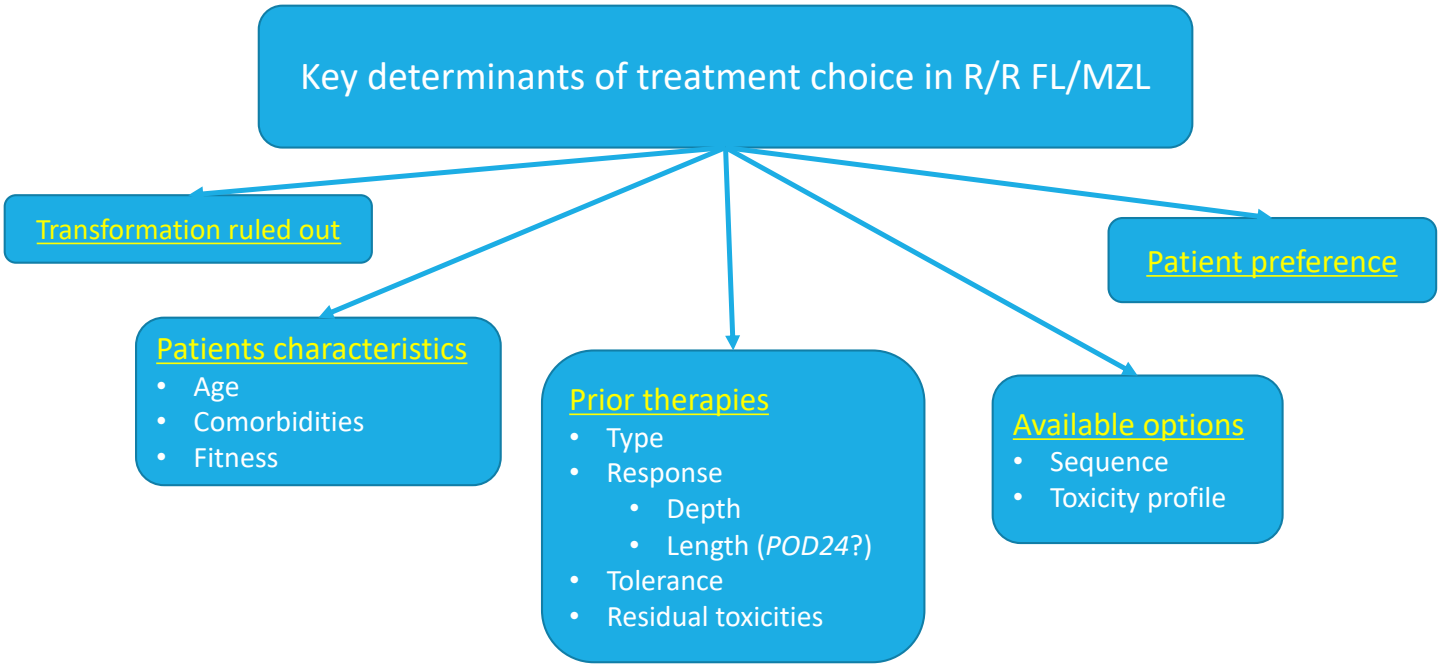
Dr. Fleury described the factors impacting treatment decisions in relapsed/refractory patients (see below).

BTKis are available for patients who are relapsed/refractory after one or more anti-CD20-based therapies. Dr. Fleury highlighted the improved toxicity profile of the second-generation BTKis, and the impressive two-year PFS of 71% among patients on zanubrutinib. The R2 regimen has also shown promise. The AUGMENT trial found the median PFS was 28 months with the R2 regimen, compared to 14 months for rituximab alone. A trial of lenalidomide-obinutuzumab has found no prognostic impact of POD24 on PFS and OS at two years.

In the third- or higher-line setting, CAR T-cell therapy (axicabtagene ciloleucel therapy in the ZUMA-5 trial) found an ORR rate of 92%, with a complete remission rate of 74%. The PFS at three years was 54%. Tisagenlecleucel, another CAR T-cell therapy, achieved a two-year PFS rate of 57%. Mosunetuzumab, a BiTE therapy, demonstrated a two-year PFS rate of 51% and a median PFS of 24 months versus 12 months with the prior line therapy. Tazemetostat offers a new target, as an EZH2 inhibitor. A Phase II study found a PFS of 14 months; POD24 did not impact the EZH2 mutation outcome.

Allogeneic stem cell transplant is a potential curative option in relapsed/refractory FL, but comes at a high risk. A study of 1,567 patients receiving ASCT found the PFS rate at five years reached 50%, but with a 29% treatment-related mortality rate.

Dr. Fleury emphasized that there are few randomized trials comparing treatment strategies, and clinical trials are paramount to improving patients' prognosis and quality of life, as well as guiding the sequence of therapies.



Key determinants of treatment choice in R/R/FL/MZL.
Slide courtesy of Dr. Isabelle Fleury.

Panel: Cases in Indolent Non-Hodgkin Lymphomas

Dr. Roopesh Kansara, Dr. Douglas Stewart, Dr. Gwynivere Davies
Moderator: Dr. Diego Villa

Dr. Villa presented a case of a 72-year-old man with suspected marginal zone lymphoma. His CT scan showed splenomegaly of 22 cm. Peripheral blood flow cytometry results showed monoclonal B-cell CD19 and CD20 positivity. The bone marrow biopsy found 15% infiltration of the cellular marrow by a low-grade B-cell lymphoma, identical IHC, cyclin D1 (-), and Ki67 10%.

Dr. Davies said she would want to do a MYD88, and that she would look for monoclonal protein. Dr. Kansara said he would look at hemolytic markers, to rule out hemodialysis.

Dr. Stewart said he would offer the patient rituximab, and consider rituximab maintenance. In this situation, there is no evidence that chemoimmunotherapy results in better long term overall survival rates.

Dr. Kansara recommended against a splenectomy, noting the patient would be immunosuppressed and may need monoclonal immunotherapy. However, Dr. Villa said that splenectomies are common in BC; if the disease is spleen-dominant, it can regress without requiring further treatment. Dr. Villa said that the patient did have a splenectomy, but six years later developed pancytopenia. Dr. Davies said, at that point, she would treat with a BR combination. Dr. Stewart said that given the patient's advanced age and higher frailty, he would consider reducing the BR dose or starting with rituximab, and adding BR later. Dr. Kansara said he would drop BR dosing by about 25%.

The second case was a 41-year-old man. His neck node biopsy found pleomorphic mantle cell lymphoma. The bone marrow biopsy revealed ~40% infiltration. Dr. Kansara said he would prescribe R-CHOP/R-DHAP, followed by stem cell transplant and maintenance for two years. Dr. Stewart said he would test the patient for the TP53 mutation, which, if positive, would lead to a more aggressive strategy. If the patient did not have a TP53 mutation, the frontline therapy would be BR, followed by rituximab/cytarabine, followed by a transplant and maintenance, if necessary.