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Event Summary & Evaluation Report

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15 years

In this report...

Acronyms

7+3	7 DAYS OF CYTARABINE AND 3 DAYS OF DAUNORUBICIN
AE	ADVERSE EVENT
AlloSCT	ALLOGENEIC STEM CELL TRANSPLANT
ASCO	AMERICAN SOCIETY OF CLINICAL ONCOLOGY
ASCT	AUTOLOGOUS STEM CELL TRANSPLANT
ASH	AMERICAN SOCIETY OF HEMATOLOGY
Ava-Ven	AZACITIDINE PLUS VENETOCLAX
Axi-cel	AXICABTAGENE CILOLEUCE
BCL2i	BLC2 INHIBITOR
BelaPd	BELANTAMAB MAFODOTIN, POMALIDOMIDE, AND DEXAMETHASONE
BelaVd	BELANTAMAB MAFODOTIN, BORTEZOMIB, AND DEXAMETHASONE
BTK	BRUTON TYROSINE KINASE
BTKi	BRUTON TYROSINE KINASE INHIBITOR
CAR	CHIMERIC ANTIGEN RECEPTOR
cBTKI	COVALENT BTK INHIBITOR
CDA	CANADA'S DRUG AGENCY
cHL	CLASSICAL HODGKIN LYMPHOMA
CHOP	CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE, AND PREDNISOLONE
Cilta-cel	CILTACABTAGENE AUTOLEUCEL
ClbO	CHLORAMBUCIL PLUS OBINUTUZUMAB
CLL	CHRONIC LYMPHOCYTIC LEUKEMIA
CNS	CENTRAL NERVOUS SYSTEM
CODOX-M	CYCLOPHOSPHAMIDE, CYTARABINE, VINCRISTINE, DOXORUBICIN, AND METHOTREXATE

Acronyms con't

CR	COMPLETE RESPONSE
CRS	CYTOKINE RELEASE SYNDROME
DIPSS	DYNAMIC INTERNATIONAL PROGNOSTIC SCORING SYSTEM
DLBCL	DIFFUSE LARGE B-CELL LYMPHOMA
DOR	DURATION OF RESPONSE
DVd	DARATUMUMAB, BORTEZOMIB, AND DEXAMETHASONE
ECG	ELECTROCARDIOGRAM
ECOG	EASTERN COOPERATIVE ONCOLOGY GROUP (PERFORMANCE SCORE)
EHA	EUROPEAN HEMATOLOGY ASSOCIATION
ESMO	EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY
FCR	FLUDARABINE, CYCLOPHOSPHAMIDE, AND RITUXIMAB
FDA	FOOD AND DRUG ADMINISTRATION
FL	FOLLICULAR LYMPHOMA
I+V	IBRUTINIB AND VENETOCLAX
ICANS	IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME
ICML	INTERNATIONAL CONFERENCE ON MALIGNANT LYMPHOMA
Ide-cel	IDECABTAGENE VICLEUCEL
IMiD	IMMUNOMODULATORY DRUG
iNHL	INDOLENT NON-HODGKIN LYMPHOMA
IsaKd	ISATUXIMAB, CARFILZOMIB AND DEXAMETHASONE
Ivo-Aza	IVOSIDENIB AND AZACITIDINE
IxaRd	IXAZOMIB PLUS LENALIDOMIDE AND DEXAMETHASONE
JAKi	JANUS KINASE INHIBITOR
JCO	JOURNAL OF CLINICAL ONCOLOGY

Kd	CARFILZOMIB AND DEXAMETHASONE
Liso-cel	LISOCABTAGENE MARALEUCEL
MATRix	METHOTREXATE-CYTARABINE PLUS RITUXIMAB AND THIOTEPA
MM	MULTIPLE MYELOMA
mOS	MEDIAN OVERALL SURVIVAL
mPFS	MEDIAN PROGRESSION-FREE SURVIVAL
MPN	MYELOPROLIFERATIVE NEOPLASMS
MRD	MINIMAL RESIDUAL DISEASE
MZL	MARGINAL ZONE LYMPHOMA
ncBTKi	NON-COVALENT BTK INHIBITOR
NEJM	NEW ENGLAND JOURNAL OF MEDICINE
NHL	NON-HODGKIN LYMPHOMA
NOS	NOT OTHERWISE SPECIFIED
ORR	OVERALL RESPONSE RATE
OS	OVERALL SURVIVAL
pCPA	PAN-CANADIAN PHARMACEUTICAL ALLIANCE
PFS	PROGRESSION-FREE SURVIVAL
PI	PROTEASOME INHIBITOR
POD24	PROGRESSION OF DISEASE WITHIN 24 MONTHS
Pola-BR	POLATUZUMAB VEDOTIN, BENDAMUSTINE, AND RITUXIMAB
PV	POLYCYTHEMIA VERA
PVd	POMALIDOMIDE, BORTEZOMIB, AND DEXAMETHASONE
R-CHOP	RITUXIMAB, CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE, AND PREDNISOLONE
R-CVP	RITUXIMAB, CYCLOPHOSPHAMIDE, AND VINCRISTINE SULFATE
R-GDP	RITUXIMAB, GEMCITABINE, DEXAMETHASONE AND CISPLATIN
R-MPV-A	RITUXIMAB, METHOTREXATE, PROCARBAZINE, VINCRISTINE, AND CYTARABINE

Acronyms con't

R/R	|	RELAPSE/REFRACTORY
R2	|	LENALIDOMIDE AND RITUXIMAB
SCT	|	STEM-CELL TRANSPLANT
SVd	|	SELINEXOR, BORTEZOMIB, AND DEXAMETHASONE
Tafa-len	|	TAFASITAMAB-LENALIDOMIDE
TEAE	|	TREATMENT-EMERGENT ADVERSE EVENTS
Tisa-cel	|	TISAGENLECLEUCEL
TLS	|	TUMOUR LYSIS SYNDROME
Vd	|	BORTEZOMIB AND DEXAMETHASONE
VenO	|	VENETOCLAX AND OBINUTUZUMAB
VGPR	|	VERY GOOD PARTIAL RESPONSE
XVd	|	SELINEXOR, BORTEZOMIB, AND DEXAMETHASONE

Personalized Medicine: Understanding the Genetic and Molecular Characteristics of CLL and Tailoring Treatment (Sponsored Breakfast Symposium, AstraZeneca Canada)

DR. PHILLIP KURUVILLA

Dr. Kuruvilla outlined the current frontline treatment options for CLL, highlighting there is no benefit to initiating treatment before a patient develops symptomatic CLL. Physicians should thoroughly assess symptomatic patients' fitness and the presence of high-risk genetic markers (*del17p* and *TP53* mutations, as well as unmutated *IGHV*) before initiating treatment. Most patients are treated with a targeted therapy, either a BTKi or VenO. Dr. Kuruvilla highlighted that chemoimmunotherapy is very rarely used for frontline CLL at his academic center, a shift accelerated by the COVID-19 pandemic.

All five trials comparing ibrutinib to chemotherapy regimens in frontline CLL treatment, across a range of young, old, fit, and unfit patients, showed improved PFS with ibrutinib. One study, RESONATE-2, additionally demonstrated an OS benefit. The ELEVATE-TN trial of acalabrutinib and the SEQUOIA trial of zanubrutinib, which enrolled older and unfit treatment-naïve CLL patients, likewise showed improvement in PFS. Second-generation BTKis, acalabrutinib and zanubrutinib, were better tolerated, with lower rates of cardiac toxicities and drug discontinuation.

The efficacy of fixed duration treatment is illustrated by the GAIA/CLL13 trial and the CLL14 trial, which assessed VenO in young patients and in older, unfit patients, respectively. VenO regimens led to improved PFS, compared to chemoimmunotherapy, as well as improved OS in the CLL14 trial.

The newest available combination for frontline CLL patients is I+V. The FLAIR study showed the majority of patients reached MRD negativity in the I+V arm, compared to none of the patients in the ibrutinib alone arm. Funding for this combination may be available in the future.

Dr. Kuruvilla said he frequently treats older patients with BTKis but tends to choose fixed duration therapy for younger patients, who often prefer this approach. However, there is no robust data comparing efficacy and safety outcomes between BTKi and fixed duration therapies in frontline CLL, and the treatment decision depends on comorbidities, accessibility factors, and patient preference. Venetoclax requires ramp-up dosing, and frequent monitoring visits for TLS in the initial months of treatment. However, BTKis require long-term compliance, which can be challenging for some patients, especially those who experience AEs.

Dr. Kuruvilla outlined key treatment considerations with both targeted therapies. Strong CYP3A inhibitors and inducers should be avoided with acalabrutinib and ibrutinib, while strong and moderate CYP3A inducers should be avoided for patients on zanubrutinib and VenO. All patients should be educated about the symptoms of Richter's syndrome, which occurs in approximately 2%–3% of patients, and requires aggressive treatment.

Both targeted therapies are associated with rashes, fatigue, headache, and diarrhea. Dermatologic events (typically red and pruritic rashes) generally respond well to corticosteroids. In rare cases, treatment modification or a treatment switch may be necessary. Fatigue is best managed with diet, exercise, sleep hygiene, and psychosocial interventions, although these are often challenging for patients to implement. For headache, patients should be directed to take acetaminophen and/or caffeine for management. (Anti-inflammatory medication compounds the bleeding risk associated with BTKi treatment and should be avoided for patients on BTKi therapy.) Diarrhea can be managed

with changes in diet (more frequent meals with low-fibre foods, avoidance of caffeine and alcohol) and anti-diarrheal agents.

Regarding more serious AEs, Dr. Kuruvilla highlighted that BTKis are associated with an increased risk of cardiovascular events in patients with CLL, including bleeding, atrial fibrillation, and hypertension. Cardiovascular AEs generally occur less frequently with second-generation compared to first-generation BTKis. Physicians should inform patients on BTKis about the symptoms of major bleeding, hypertension, and arrythmia, and encourage patients to notify the clinic about upcoming surgical and dental procedures (minor bleeding resulting in bruising is common and doesn't require treatment). All patients on BTKis should be screened for atrial fibrillation with an ECG or another heart rhythm monitor. Dr. Kuruvilla added that atrial fibrillation tends to occur early in treatment. Similarly, it is important to monitor patients' blood pressure regularly throughout BTKi therapy, as hypertension tends to gradually increase over the duration of BTKi use.

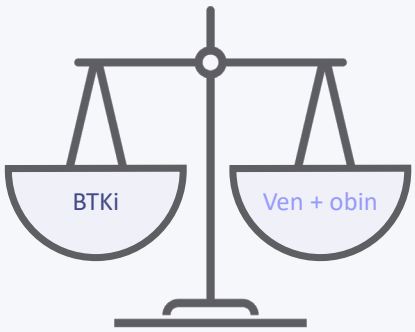
If a patient experiences a major bleeding event, BTKi treatment should be discontinued, and patients should undergo transfusion with platelets until the bleeding is resolved. For atrial fibrillation, management may include withholding or dose-adjusting BTKi, as well as treatment with beta blockers and/or anticoagulants. Treatment discontinuation is required for grade 4 cardiac arrhythmias and may be necessary for grade 3 arrythmias. Hypertension does not require a modification of the BTKi dose but is instead treated with antihypertensive therapy, with caution regarding drug-drug interactions.

The most important VenO-specific consideration is TLS, which can result in renal failure and cardiac arrhythmias. Treaters should assess the risk of TLS in patients before initiating venetoclax, by monitoring white blood cell count and ordering a CT scan to assess lymph node size. Allopurinol, rasburicase, and oral or IV hydration are options to minimize the risk of TLS. Dr. Kuruvilla recommended an institution-wide protocol to assess TLS risk and monitor outpatients for TLS symptoms, including hyperphosphatemia, hypocalcemia, and hyperuricemia.

Finally, Dr. Kuruvilla stressed the importance of educating all patients on the consequences of poor adherence to oral therapies, including decreased efficacy and poor survival. Multidisciplinary management and pharmacist consultation is critical to avoid drug interactions, identify and manage adverse effects, and ultimately improve compliance.

FACTORS TO CONSIDER: FRONTLINE BTKi vs. VO

- Convenience (no infusions, TLS monitoring)
- Phase III data compared with FCR and BR
- Longer-term efficacy data with BTKi
- Continuous treatment



- Potential for 1 year time-limited therapy
- Phase III data compared with FCR and BR
- No known cardiac or bleeding risks
- Less concern for long-term adherence
- Potential for cost saving if 1 year of therapy is durable

Abbriviations: BR: bendamustine/rituximab; **BTKi:** bruton's tyrosine kinase inhibitors; **FCR:** fludarabine + cyclophosphamide + rituximab; **obi:** obinutuzumab; **TLS:** tumour lysis syndrome; **Ven:** venetoclax.

Q&A

Question: Monitoring in the initial phase of VenO treatment can be challenging. Is it appropriate to initiate young patients on BTKi therapy, due to geographical barriers?

Answer: For VenO therapy, a patient needs to be able and willing to attend all the monitoring requirements needed to mitigate TLS. BTKi therapy is appropriate when this is not possible for patients, regardless of age. Partnering with community providers and laboratories to assist with monitoring can increase accessibility to BTKi therapy. However, patients may be less compliant to monitoring requirements without frequent education from the tertiary care center.

Question: What is the role of I+V, especially given this combination includes a first-generation BTKi?

Answer: I predict that in the near future, we will move to combination treatment with a BCL2-targeting agent and a BTKi, and this treatment will be MRD-guided. The advantage of I+V is that the cardiovascular toxicity risk is substantially lower due to the fixed duration.

Approaches to Multiple Myeloma: Novel Agents in a Relapse Setting

DR. DARRELL WHITE

Presenting the 2024 provisional funding algorithm from the CDA, Dr. White highlighted that common second-line treatment options include Kd, IsaKd, and XVd. Although DVd is funded, combinations that include an anti-CD38 therapy are generally more effective.

Despite advances in MM treatment, the condition remains incurable, and increasingly refractory and difficult to treat in later lines of therapy. Real-world outcomes in Canada for patients refractory to anti-CD38 therapy demonstrate that mOS and mPFS is 14 months and 4.6 months, respectively. Comparing the outcomes for patients who are non-triple-class-refractory and those who are triple-class-refractory, the mOS was 17.5 months and 10.5 months respectively. Dr. White added that once quadruplet therapy is available in the first line, patients may be triple-class refractory in the second-line setting.

Options for patients refractory to anti-CD38 therapy include monoclonal antibodies, the antibody-drug conjugate belantamab mafodotin (Bela), and bispecific antibodies. Cilta-cel and ide-cel are also approved in adult patients with MM who have received at least 3 prior therapies, including an IMiD, PI, and anti-CD38 antibody, and who are refractory to their last treatment. The CARTITUDE-4 study showed cilta-cel reduced the risk of progression or death versus the standard of care by 65% in MM patients with one prior line of therapy and 73% in patients with one prior line of therapy and functionally high-risk disease. The mPFS was not reached at 17 months. Patients with high-risk cytogenetics also respond well to cilta-cel therapy. However, CAR T-cell therapy poses logistical challenges and up to 80% of patients experience CRS. Grade 3–4 hematologic AEs are also common, and this therapy carries a higher risk of ICANS and movement and neurocognitive TEAEs. As CAR T-cell therapy is not curative in MM, it may not receive funding. Dr. White noted that patients who receive a bispecific antibody may not be eligible to receive an anti-BMCA CAR T-cell therapy, but the data may support bispecific antibody therapy after anti-BMCA CAR T-cell therapy.

Dr. White highlighted that bispecific antibodies work well for MM patients with relatively functional T cells. Teclistamab and elranatamab are approved in patients with R/R MM who are triple-class exposed, and have demonstrated disease progression on their last therapy. A trial published in the *NEJM* in 2022 showed that, at 14 months of follow-up, 63% of patients responded to teclistamab; mPFS was 11.3 months and mOS was 18.3 months. Longer follow-up data, presented at ASCO in 2024, showed that 61% of patients who achieve a CR on teclistamab were progression-free at 30 months, and mPFS was not reached in this group. The mPFS was 26.7 months in patients with a VGPR. The most common AEs remained cytopenia, infections, and CRS; there were 118 grade 1 or 2 CRS events and only 1 grade 3 CRS event. All CRS and ICANS events resolved.

In the MagnetisMM-3 trial, elranatamab, was evaluated in a patient population that was 97% triple-class refractory, with a 25% rate of high-risk cytogenetics and a 32% rate of extramedullary disease. The ORR was similar to teclistamab, at 61%; the mPFS was 17 months and the mOS was 24.6 months. Patients with stage 3 MM didn't respond well in the MagnetisMM-3 trial, which may suggest the treatment toxicity outweighs the benefits in these patients. Regarding AEs, CRS occurred at a rate of 56.3% and ICANS at a rate of 3.4%. There were no grade 3 or 4 CRS or ICANS events. As with teclistamab, infections were common. Infection-related deaths occurred at a rate of 6.5%, highlighting the need for routine gamma globulin (less than half of the patients in the MagnetismMM-3 trial received gamma globulin; current bispecific antibody trials require this treatment). Dose reductions also help to mitigate the infection risk.

Dr. White presented the DREAM-7 and DREAM-8 trials, of BelaVd versus DVd and BelaPd versus PVd, respectively. BelaVd led to a mPFS of 36 months versus 13.4 months for DVd. The mPFS for B-Pd in the DREAM-8 trial was not reached with more than 30 months of follow-up, while the mPFS in the PVd arm was approximately 12 months. These impressive results suggest these combinations could be available as a second-line or third-line option.

Selinexor, the first-in-class oral, selective, nuclear export inhibitor is another exciting treatment option in R/R MM. The BOSTON trial of XVd compared to Vd showed improved PFS, with a 30% reduced risk of progression or death.

Dr. White summarized that sequencing myeloma treatments has become more complex as promising agents continue to be developed. Currently, CD38 and BCMA are the most important targets for

monoclonal therapies, but small molecules are also being developed and may play an important role in MM management, including a potentially synergistic role with anti-BCMA agents.

Q&A

Question: The CADTH algorithm says patients treated with a BCMA T-cell engager won't be able to access cilta-cel. In a patient who is slowly progressing, how do you choose between bispecific antibodies or cilta-cel? How might your approach change when Bela-Vd vs DVd and Bela-Pd are available in the future?

Answer: Some patients have raised concern about CAR T-cell therapy ineligibility after bispecific antibody treatment, as support groups have raised awareness about this possibility. I think the treatment decision comes down to the capacity of CAR T-cell therapy centers as well as patient preference (with bispecific antibodies, the infection challenge monitoring requirements can impede travel, for example). A challenge with Bela is ocular toxicity, which was managed by ophthalmologists in clinical trials but will be more difficult to manage in the real world, as routine prophylaxis therapy wouldn't likely be funded.

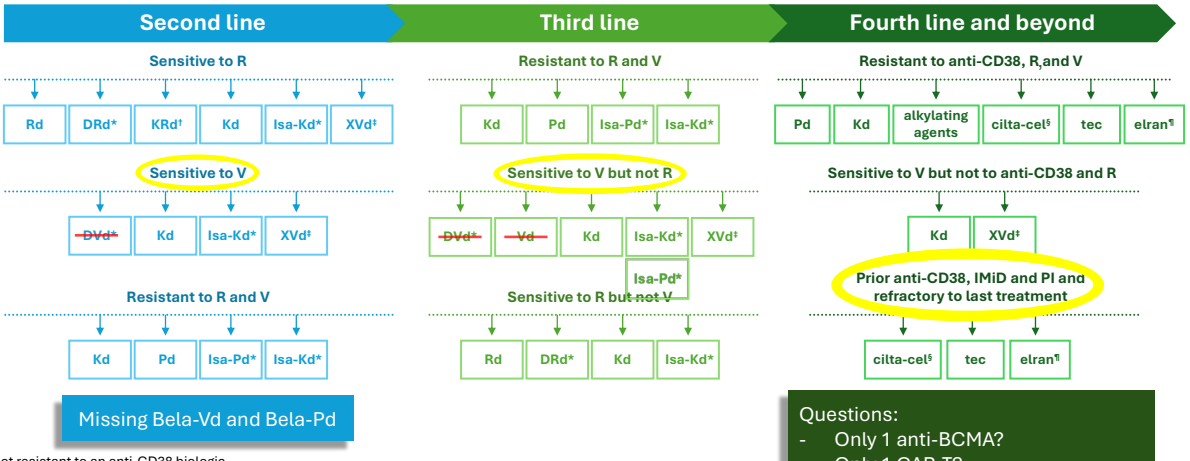
Question: How do you decide when a bispecific antibody is not appropriate for an older patient with multiple comorbidities?

Answer: While I don't think there should be an age-based cut-off, I think patients should be relatively fit. Some of the side effects can be very challenging for older patients.

Question: What do you recommend for institutions seeking to implement a protocol for managing CRS in the community?

Answer: Based on what we're hearing from colleagues in the U.S., it will be important for patients to stay close to the center, rather than returning home, if they live more than 30 minutes from the hospital. A protocol should provide an alternative to the emergency department when patients experience low-grade CRS symptoms. The Jewish General Hospital in Montreal has started a pilot project in which patients who receive a bispecific antibody receive a wearable device. A nurse will be available 24/7 to remotely monitor patients' temperature and blood pressure. These innovative solutions could make outpatient CRS prevention and treatment more successful.

2024 CANADA'S DRUG AGENCY (CDA-AMC) PROVISIONAL FUNDING ALGORITHM



* If not resistant to an anti-CD38 biologic.
† Only if also sensitive to R and V.
‡ Must have a PI treatment-free interval of at least 6 months before first day of XVd.
§ If no prior treatment with any therapy that targets BCMA or any CAR-T therapy.
¶ If no prior treatment with any therapy that targets BCMA.

Reference: CDA-AMC. Available at: https://www.cda-amc.ca/sites/default/files/DRR/2024/PH0047_Multiple_Myeloma.pdf. Accessed Aug 16, 2024.

Adapted from CDA-AMC, 2024.

Management of Acute Myeloid Leukemia in 2024: Frontline Therapy

DR. JULIE BERGERON

Dr. Bergeron summarized key evolutions in the management of frontline AML. The SAL Dauno-Double Trial randomized patients to receive a 60 mg vs 90 mg daunorubicin with the 7+3 induction regimen and found that there was no difference in PFS and OS between the groups, leading to a move to a 60 mg daunorubicin dose. The trial also randomized patients who had a good early response to receive another induction (double induction) or not receive a second induction. There were no significant differences in 3-year OS after single versus double induction.

A study from the French Backbone Intergroup, presented at ASH in 2023, compared consolidation approaches of high-dose cytarabine of 3g/m^2 versus intermediate-dose cytarabine of 1.5g/m^2 in over 1,000 patients. The study found that the OS was non-inferior in the intermediate-dose cytarabine group. Based on this study, Dr. Bergeron said she is confident in lowering the cytarabine dose in younger patients. However, she continues to offer high-dose cytarabine to young patients with core-binding factor AML, due to a small retrospective analysis suggesting a high risk of relapse when these patients are given intermediate-dose cytarabine.

Two studies demonstrated the superiority of high-dose cytarabine consolidation in day 1, 2, and 3 compared to the day 1 to 5 approach. A German study comparing two retrospective cohorts found that both regimens had the same efficacy, but patients who underwent the 3-day regimen had faster neutrophil recovery and lower rates of hospitalization, infections, and platelet transfusions. These results were further supported by a 2020 French study.

Finally, a phase 3 study published in the *JCO* in 2018 found the molar ratio 5:1 cytarabine/daunorubicin (Vyxeos) led to better outcomes, compared to 7+3 induction, in 60- to 75-year-olds with high-risk or secondary AML. CR rates were 48% with Vyxeos versus 33% with the 7+3 regimen, and mOS was 10 versus 6 months favouring Vyxeos over the 7+3 regimen. More patients in the Vyxeos arm underwent SCT. Based on the evidence, Vyxeos is now the preferred bridge to transplant for patients with unfavourable risk disease, regardless of age.

Midostaurin has become standard for AML patients with a FLT3, ITD and TKD-mutated patients. While patients in the trial for midostaurin were 60 or younger, there is no age limit if patients are considered fit for 7+3 induction.

A 2020 *JCO* paper showed that sorafenib maintenance after AlloSCT improved PFS outcomes in 83 patients with a *FLT3* mutation, compared to placebo. However, sorafenib is not approved for AML in Canada. Oral azacitidine maintenance, examined in patients 55 years and older in CR after intensive chemotherapy, demonstrated a mOS of 25 months versus 15 months in the best standard of care arm. NPM1-mutated patients benefitted the most from this maintenance therapy, with a mOS of 47 months, compared to 16 months on placebo. Based on this evidence, Dr. Bergeron suggested that patients with an *NPM1* mutation who are not eligible for SCT after the first CR are the ideal patients for this therapy.

For unfit patients, the VIALE-A trial of Aza-Ven demonstrated a mOS improvement of almost 15 months, compared to just under 10 months for patients who received azacitidine plus placebo. CR rates were 66% for the venetoclax combination, versus 28% for azacitidine plus placebo. Patients with *IDH2* and *NPM1* mutations had especially good outcomes on the Aza-Ven combination, while patients with *IDH1* mutations had similar outcomes to patients without *IDH1* mutations. The combination showed no survival advantage in patients with the *TP53* mutation, despite a higher response rate in this population. This finding is likely due to the high rates of thrombocytopenia and neutropenia associated with the combination.

A phase 3 study of Ivo-Aza in *IDH1*-mutated AML versus azacitidine and placebo found OS rates of 24 months versus 8 months, positioning this combination as a clear choice for unfit patients with *IDH1*-mutated disease. The Ivo-Aza combination seemed to result in lower rates of thrombocytopenia and neutropenia, compared to the Aza-Ven combination.

Q&A

Question: What is your advice for holding and adjusting doses with Aza-Ven in response to cytopenia?

Answer: After confirming that the cytopenia is due to the drug, rather than the disease, I reduce the venetoclax duration from 21 days to 14 days, and even 7 days, if necessary. I then reduce Aza, if necessary. I heavily treat patients with Grastofil.

Question: Will it be possible to treat patients through the outpatient unit during the ramp-up period for Ivo-Aza?

Answer: The combination seems much less intensive, in terms of cytopenia, and I don't think patients would need to be admitted for the ramp-up period. However, Ivo-Aza requires monitoring for leukocytosis. I suspect Ivo-Aza will require weekly and biweekly monitoring and patient education about symptoms of bleeding and weight gain.

Question: How do the results of the myeloid panel affect your treatment choice?

Answer: I find it hard to make a treatment decision without the myeloid panel results. If a patient has *IDH2* or *FLT3* medications, I may be more likely to choose Aza-Ven, and if patients have a *TP53* mutation and a borderline fitness status, I won't treat these patients with high-dose chemotherapy.

Updates on the Management of Myeloproliferative Neoplasms: Current Agents and Approaches to Treatment in First and Second-line Therapies

DR. VIKAS GUPTA

Dr. Gupta set the stage by discussing the burden of the symptoms for patients and the high health care utilization among patients with MPN with essential thrombocythemia, PV, or myelofibrosis.

The treatment algorithm for PV is aspirin for all patients, and cytoreductive therapy for patients with a high risk of thrombosis. Phlebotomy is recommended for all PV patients, to reduce hematocrit below 45%.

Rusfertide, a hepcidin mimetic is a novel treatment agent for PV that restricts the availability of iron for erythrocytosis. A phase 2 trial published in the *NEJM* earlier this year showed that rusfertide improves hematocrit control, compared to placebo. A phase 3 trial of this product is ongoing, with results expected early next year.

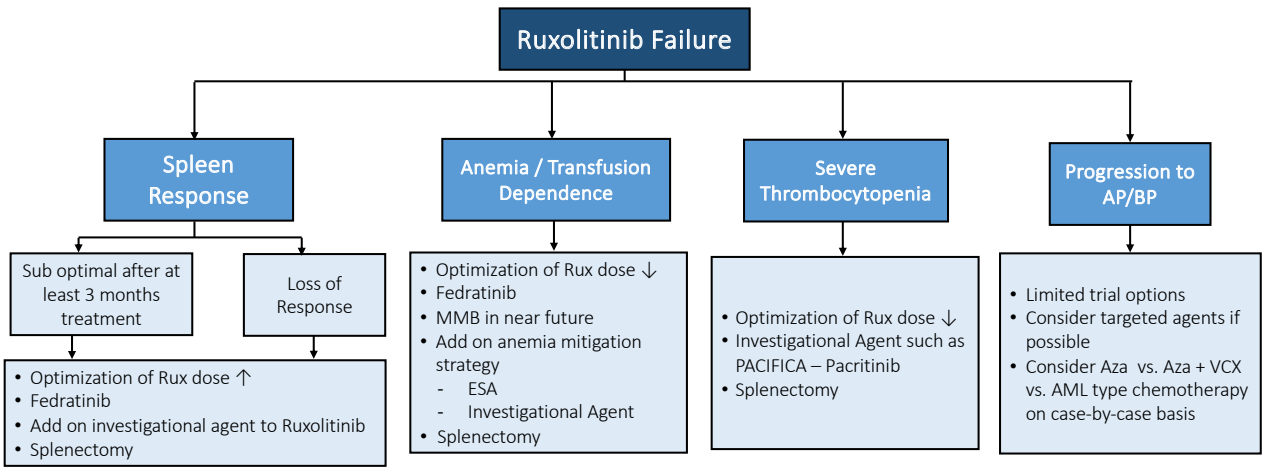
Interferon is not currently funded in Ontario for the treatment of PV, however this may change in the future with the new interferon formulation, ropeginterferon. While the hematological responses across treatment and control arms were similar in the PROUD-PV trial of ropeginterferon, a long-term analysis, CONTI-PV, demonstrated a significant reduction in the JAK2 allele burden in patients treated with ropeginterferon.

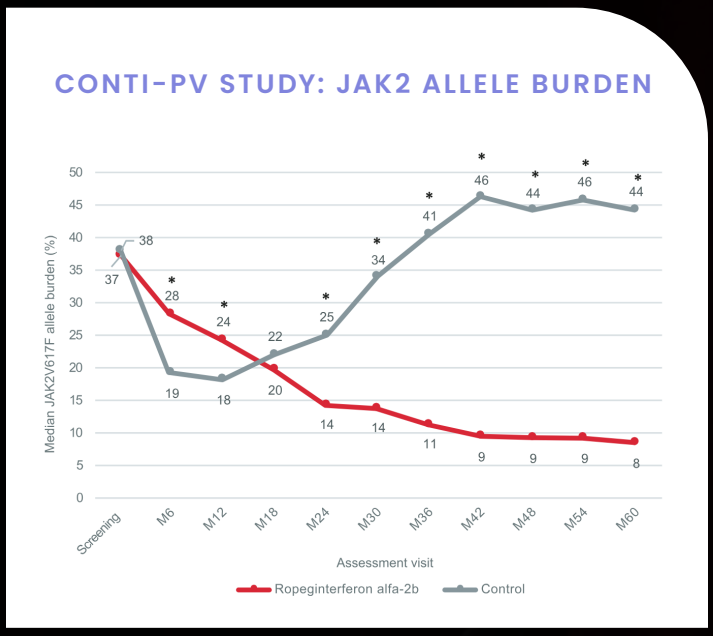
Moving to myelofibrosis, Dr. Gupta summarized the European LeukemiaNet Management Recommendations, which advise that JAKi therapy should be considered based on symptom burden and disease risk. Patients who have symptomatic splenomegaly should be considered for hydroxyurea or JAKi if they have Int-1 risk, and should be treated with a JAKi, and considered for splenectomy, if they are symptomatic with Int-2 risk. SCT should be considered for eligible Int-2 risk patients.

Outlining the data for transplants in myelofibrosis, Dr. Gutpa explained the utilization of haploidentical transplants have increased, from less than 5% of all transplants in 2013 to close to 20% in 2019. A 2024 study published in *Blood Advances* showed that, although matched sibling donor transplants still have the best survival outcomes, the survival differences between matched sibling donor, matched unrelated, mismatched unrelated, and haploidentical transplants are much smaller than they were 10 years ago.

Given that only 10% of myelofibrosis patients are eligible for transplant, JAKi therapies remain a cornerstone of treatment. In Canada, approved JAKis include ruxolitinib and fedratinib; the expectation is that momelotinib will be approved in the coming months, and pacritinib could be available in the future. Trials show that all JAKis similarly reduce spleen volume and symptom burden. However, toxicities differ. The SIMPLIFY1 trial found that rates of grade 3/4 anemia were lower with momelotinib therapy, compared to ruxolitinib therapy.

MY APPROACH TO RUXOLITINIB FAILURE IN PATIENTS WITH MF





The challenge remains that JAKi therapies have limited anti-clonal activity. A JAK2 allele burden reduction by 20% or more occurs in only a small proportion of patients. In addition, the average DOR to a JAKi is approximately 2 years. A study published in *Blood Advances* in 2017 found that JAKis perform less well in patients with a high DIPSS score, *ASXL1* or *EZH2* mutations, or pre-JAKi transfusion dependence. Patients with these risk factors should be considered for earlier transplant and upfront novel therapy trials. Dr. Gupta then discussed his approach to patients with myelofibrosis who experience ruxolitinib failure (see chart on previous page).

Second-line JAKis may improve outcomes for patients with myelofibrosis. Fedratinib is funded in the second-line setting in Canada. The FREEDOM2 trial showed a significant improvement in spleen volume and a beneficial impact on symptom burden in patients who failed ruxolitinib.

The SIIMPLIFY-2 trial of momelotinib demonstrated that patients on the second-line JAKi had fewer red-blood cell transfusions and higher rates of transfusion independence, compared to ruxolitinib (43% versus 21% by week 24). The MOMENTUM trial revealed that more patients on momelotinib developed transfusion independence by week 24, compared to the danazol arm.

Data from the PERSIST-2 trial show improved outcomes on pacritinib, compared to other JAKis, for patients with thrombocytopenia. The PACIFICA trial is assessing pacritinib in patients with platelet counts below $50x10^9/L$.

Discussing the potential for combinations in myelofibrosis treatment, Dr. Gupta highlighted a phase 2 study of the novel agent luspatercept that demonstrated benefit for transfusion-dependent myelofibrosis patients, both as a single agent and in combination with ruxolitinib study. Results from a phase 3 study are expected in early 2024.

Mutant *CALR*-directed therapies hold the most promise for disease-modifying treatment. A murine model showed significant reduction in megakaryocytes and fibrosis with the monoclonal antibody INCA033989. The clinical trial for the B-specific T-cell directing antibody, JNJ-88549968, has begun to enrol patients.

Q&A

Question: What is the role of the myeloid panel in MPN treatment?

Answer: In Ontario, a myeloid panel is funded for any patients with AML, MPN, or myelodysplastic syndrome, irrespective of whether they are candidates for transplant. In myelofibrosis patients, the myeloid panel is an important risk stratification tool to determine transplant candidacy and also to predict which patients will experience more durable benefit on JAKi therapy. Patients who have less durable benefits could be considered for early clinical trials.

Question: When should clinicians refer MPN patients to a quaternary center?

Answer: If you have a patient with essential thrombocytopenia who is not doing well on first-line therapy and has a *CALR* mutation, refer them early. I also recommend referring patients with polycythemia vera who fail first-line treatment. Specialists at a quaternary center can help if the results of a myeloid panel are unexpected or unclear. Our center can help with interpreting results and guiding treatment.

Updates on the Management of Chronic Lymphocytic Leukemia: Current Agents and Approaches to Treatment in a Relapse Setting

DR. MONA SHAFEY

Dr. Shafey briefly described frontline CLL treatment to set the stage for the treatment of relapsed CLL. The funded options in Canada in low-risk CLL in the first line are FCR, chemoimmunotherapy, and VenO. For patients with high-risk cytogenetic markers, the first-line treatment option is a BTKi therapy. I+V is under review for funding in the first line for both high and low-risk CLL patients. Fixed duration combinations will likely be utilized routinely as frontline CLL treatment in the near future. In other words, most patients will be exposed to a novel agent in the first line.

Dr. Shafey provided an overview of the treatment options for relapsed CLL, based on the ESMO Guidelines of 2024. Treatment options depend on whether patients have had venetoclax-based treatment, whether they progressed on a BTKi, mutation status, and when relapse occurs. For patients who experienced a long remission, the guidelines recommend repeating the venetoclax regimen with I+V, venetoclax and rituximab, or moving to BTKi therapy. If patients relapse early on a venetoclax-based regimen, BTKi therapy is recommended. Likewise, patients who progress on a BTKi should switch treatment classes to venetoclax.

For patients who are refractory to both venetoclax-based regimens and cBTKis, ncBTKis, including pirtobrutinib and nemtabrutinib, are an option. Studies show the ncBTKis work in patients who have acquired BTK mutations. Data from the BRUIN study, recently presented at ASH, demonstrated efficacy of pirtobrutinib in a heavily pretreated population, with a median of four prior lines of system therapy. More than 50% of the patients enrolled in the study had a *TP53* mutation. Most patients achieved a partial response, with results showing an ORR of 83% in BCL2i-naïve patients and 80% in BLC2i-exposed patients. The mPFS was 23 months in BCL2i-naïve patients and 16 months in BLC2i-exposed patients. This suggests pirtobrutinib should be used earlier if possible, rather than after patients have exhausted all other treatments. AEs included infection (31% grade 3 or above), bruising, and rash. Neutropenia was more common, compared to clinical trials of cBTKi, affecting 34% of patients.

Certain mutations acquired on cBTKi lead to resistance to ncBTKis. It is likely that BTK mutation testing will be incorporated into treatment decisions in the relapse setting in the future. BTK degraders are an alternative to ncBTKis. The therapy is being tested in patients who have previously been exposed to a BTKi or have been double-exposed to venetoclax and BTKi therapy. The CaDAnCe-101 phase 1 trial is enrolling patients with selected R/R B-cell malignancies including CLL, to assess toxicity and the maximum tolerated dose. In 49 high-risk and heavily pretreated CLL/SLL patients enrolled, the ORR was 72% overall, and 88% in the higher-dose (200 mg) group. Most TEAEs were treatable or low-grade and the 3 on-treatment deaths were not deemed to be related to the drug itself.

CAR T-cell therapy can be effective for some patients but has been less successful in CLL than other NHL types. The TRANSCEND CLL 004 study, a phase 1/2 open label study, assessed liso-cel in heavily pretreated patients and demonstrated a CR rate of 19%. However, for those who achieved a CR, the PFS was not reached after 24 months of follow up. Age and the presence of high-risk genomic features didn't seem to impact the outcomes for patients on liso-cel. For those who have a partial response, the outcomes are similar to pirtobrutinib. Given the outcomes and the availability of effective treatments in the second and third line, CAR T-cell therapy, which carries a high risk of CRS and ICANs, may not be funded for the CLL population. However, Dr. Shafey noted that CAR T-cell therapy could fit an unmet need for a younger, fit patient who is double-refractory and would be otherwise considered for alloSCT.

Q&A

Question: Can you talk about bispecific therapy in CLL?

Answer: That's an important future direction for future CLL treatment. There was an abstract at EHA this past year on epcoritamab in CLL. Immunotherapy works in CLL, and the bispecific antibody versus CAR T-cell debate is going to play out in CLL, just as it is in other lymphomas.

Question: Is there a difference in the development of resistant mutations with BTKis. For example, does acalabrutinib lead to lower rates of resistance, compared to ibrutinib?

Answer: I don't think we have data on the incidence of mutation development with any of the treatments.

Question: When do you consider the CLIC-01 trial for double-class-refractory patients?

Answer: The CLIC-01 trial is assessing a new CD19-directed CAR T-cell therapy. I believe the two actively recruiting sites are Vancouver and Ottawa. I think clinical trials in general are the way to go for these this patient population. Even if the clinical trial site is an hour away, you should at least mention it to your patients. That said, clinical trials are a big commitment and not appropriate for everyone.

Updates on the Management of Follicular Lymphoma and Aggressive B-cell Lymphoma: Current Agents and Approaches to Treatment in a Relapse Setting

DR. JOHN KURUVILLA

It is an exciting, but also challenging time, to treat aggressive B-cell lymphomas and R/R FL, because the treatment landscape is changing so rapidly. Dr. Kuruvilla highlighted that fewer clinicians are opting for ASCT in treating R/R FL, thanks to the availability of novel agents.

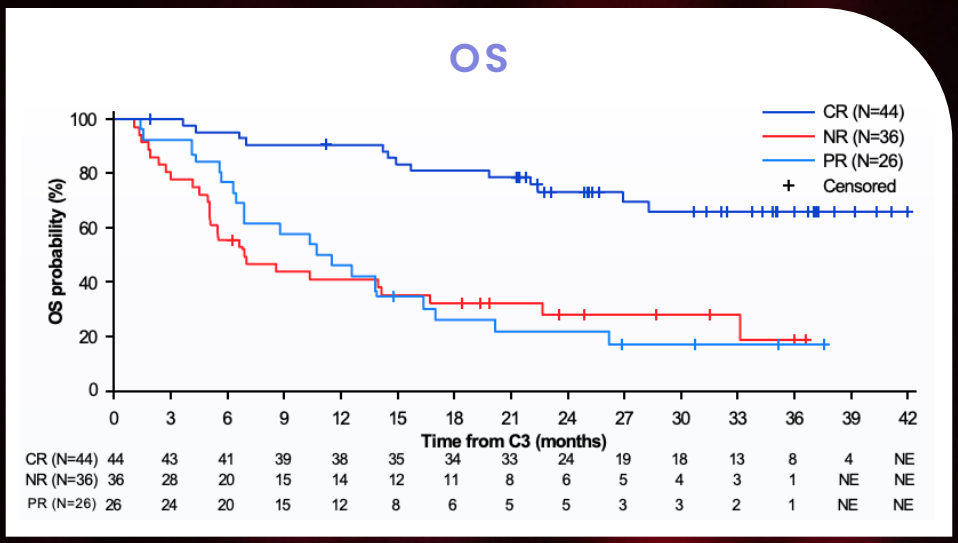
Noting that axi-cel is now publicly reimbursed in Canada in the third-line setting, Dr. Kuruvilla summarized ZUMA-5, a single-arm phase 2 study in iNHL, including FL and MZL. Patients must have had at least two prior lines of therapy, including an anti-CD20 agent and an alkylating agent. Eligibility criteria included an ECOG of 0 or 1; a third of the patients were over 65, and 44% had a high-risk FL score. In this population, the ORR was 92%, with CR rates of 79% in FL and 65% in MZL, with the difference likely attributed to the small number of MZL patients enrolled in the study. CRS and ICANS rates are slightly lower in iNHL, compared to aggressive lymphomas, which may be due to differences in inflammatory states at baseline as well as improved CRS and ICANS management when the trial was conducted. There was one grade 5 CRS event related to axi-cel. More than half of the patients experienced infection, and 18% experienced grade 3 or higher infectious events. The mOS was not reached after 24 months of follow-up patients, including in POD24 patients.

The question remains as to whether CAR T-cell therapy could be a curative treatment in FL. Tisa-cel and liso-cel are also showing impressive CR, PFS, and OS results in phase 2 trials in R/R FL. Another key question these results raise is whether POD24 patients should continue to receive ASCT, given the availability of CAR T-cell therapy.

Shifting gears to DLBCL, Dr. Kuruvilla highlighted that CD19-targetd CAR T-cell therapy is now the standard of care and can be curative in third-line DLBCL. Comparing the ZUMA-1 (axi-cel) cohort to SCHOLAR-1, the mOS was 31 months, compared to just over 5 months with standard salvage regimens. The ZUMA-7 study compared axi-cel versus the standard of care in the second line in R/R/ DLCBL. Results, published in NEJM in 2023 showed significant improvement in OS. Real-world studies of CAR T-cell therapy have shown results consistent with clinical trials, as CAR T-cell therapy selects out those with poor performance status. About 30% of patients don't make it to CAR T-cell therapy as a result, so it is important to keep in mind that results would not be as remarkable if they included the entire intent-to-treat population.

SINGLE-AGENT PHASE 1 STUDIES OF BISPECIFIC CD3/CD20 ANTIBODIES IN B-NHL

Bispecific antibody	Aggressive B-NHL			Indolent B-NHL			CRS / > gr 2
	N	ORR	CR	N	ORR	CR	
Mosunetuzumab	124	35%	19%	68	66%	49%	27% / 1%
Glofitamab	69	61%	49%	29	69%	59%	50% / 3.5%
Odronextamab	45	40%	36%	32	91%	72%	91% / 7%
Epcoritamab	22	68%	45%	10	90%	50%	59% / 0%



For post-CAR T-cell and CAR T-cell therapy-ineligible patients, PolaBR is an option. The therapy demonstrated an OS advantage over BR, but it is not yet funded in Canada. Tafa-len, reimbursed in Quebec, demonstrated an mPFS of approximately 12 months, and a mOS of 33.5 months. Tafa-len performs less well in real-world settings, especially among refractory or dose-adjusted patients.

Bispecific antibodies are broadly active in aggressive and indolent B-cell lymphoma. While CRS is common, grade 3 or higher CRS rates are very low.

The pivotal phase 2 study of glofitamab monotherapy in R/R DLCBL enrolled patients with good ECOG performance status in the third-line setting, and utilized obinutuzumab IV pre-treatment and step-up dosing to mitigate CRS. A third of patients had prior CAR T-cell therapy and 85% were refractory to the last prior therapy. The ORR was 80% and 40% achieved a CR. The median DOR was more than 2 years for patients who achieved a CR, however the treatment performed poorly in patients who had a partial response or didn't respond.

The EPCORE NHL-1 trial assessed epcoritamab in a similar, highly refractory population but allowed study entry for those patients with an ECOG performance status of 2. Unlike the fixed duration glofitamab, epcoritamab is administered until disease progression. Safety results show that toxicities reduced over time, aside from anemia and infections. Grade 3, non-COVID infections peaked between weeks 48 to 60, highlighting the importance of long-term vigilance. CRS occurred in 51% of patients, but only 3% were grade 3. CRS occurred primarily following the first full dose, generally resolved within a couple of days, and only led to treatment discontinuation in 1 patient. Of patients with DLCBL, 40% achieved a CR, and the median time to response was 1.4 months, while the median time to CR was below 3 months. In patients who achieved a complete response, the response rates were durable. It is important to note that, similar to CAR T-cell therapy, the majority of patients do not benefit from bispecific antibodies in clinical trials. With bispecific antibodies, real-world outcomes are expected to be worse than clinical trials. Dr. Kuruvilla added that some lymphoma patients remain palliative and should not receive these intensive therapies. In the future, the degree of CD20 antigen expression may drive the treatment decision between bispecific antibodies or CAR T-cell therapy, but this data is not yet available to guide clinical decision-making.

Q&A

Question: For indolent lymphoma, both bispecific antibodies and CAR T-cell therapy appear to be similar in efficacy. I expect I will opt for bispecific antibodies, due to the flexibility with administration and given that the response is evident quickly. Do you agree with this approach?

Answer: I agree. Most indolent lymphoma patients are over 70, and I expect that CAR T-cell therapy will be reserved mostly for younger iNHL patients. Many patients will also prefer a close-to-home therapy. For ABC subtype patients, acalabrutinib plus R-CHOP therapy may be the optimal option, due to the convenience of an oral agent.

Question: How much do geographic disparities play a role in who can access CAR T-cell therapy?

Answer: There are many barriers, including geography, language, and financing. There are people in our group very interested in capturing the socioeconomic data so they can target solutions to address disparities, but this will take time.

Important Tips & Pearls: Reimbursement, Compassionate Use, Access, Path to Approval, Patient Support Program, Resources for Patients

DR. DARRELL WHITE

Dr. White described the approval and reimbursement pathway in Canada. The first step is that Health Canada issues a Notice of Compliance, determining a product meets efficacy and safety standards. This process takes about a year. A health technology assessment is the next step. This is an econometric evaluation conducted by Canada's Drug Agency (formerly the Canadian Agency for Drugs and Technologies and Health). From there, the pCPA occurs, which is a negotiation between the manufacturing or licensing company and the provinces. As the chief negotiating province seeks alignment from the other provinces, this process can also take many months. Once the national price of the drug is determined, hospitals, public and cancer agencies can choose to reimburse the product right away or wait for the next budget cycle. The Patented Medicine Prices Review Board advises provinces and payers about a therapy's price. Compared to the U.S., Canada's cost-effectiveness analyses can add more than a year to the length of time it takes to get drug reimbursement.

Health Canada decisions also often take more time than FDA decisions. A 2015 paper found that it took about 4 months longer for the same oncology medications to be approved in Canada, compared to the U.S. The paper also assessed the time form Health Canada Approval to provincial formulary listing and found the median time to reimbursement ranged from almost 11 months in British Columbia to almost 22 months in Newfoundland.

Project Orbis is an international partnership designed to give cancer patients faster access to promising cancer treatments, including in Canada and the U.S. Unfortunately, a retrospective analysis published in *Lancet Oncology* in 2024 suggests that Project Orbis isn't having the desired impact. Of 244 FDA-approved cancer drugs from 2019 to 2023, of which 33% were reviewed through Project Orbis, the median time difference from FDA approval to Health Canada approval was 148 days, while median time difference from FDA approval to CADTH approval was 377 days. The median time difference from FDA approval to Health Canada approval increased from 49 days in 2020 to 235 days in 2023.

Outside of public funding, products can be prescribed and paid for by private insurance, a hospital budget, or out-of-pocket once a drug is Health Canada approved and assigned a drug identification number. Various insurance companies may be more or less conservative with funding decisions, and one company may have more than one insurance policy type for employees.

Once a drug has a drug identification number, the manufacturing/licensing company may also choose to sponsor a compassionate program, often covering the entire price of the medication for a finite time for select patients in need. While pCPA negotiations are ongoing, companies may open a "patient support program" providing the medication for free to everyone for a finite time.

Dr. White concluded by noting that clinicians have opportunities to provide input at the level of CDA, and physician influence can be an important factor in the CDA decision process.

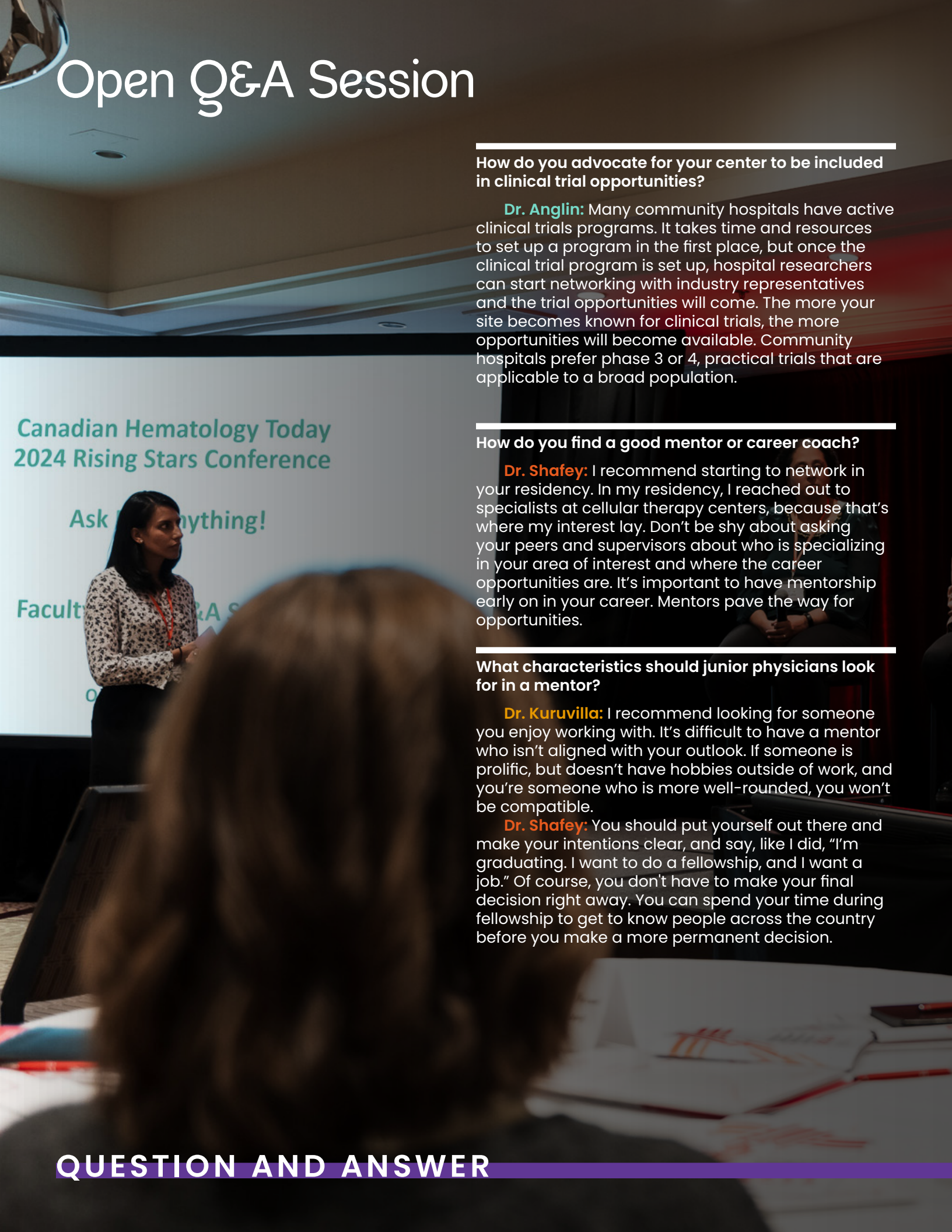
Q&A

Question: How do you know if a compassionate access program is available?

Answer: I ask colleagues. I tend to be well informed through Myeloma Canada about compassionate programs for myeloma patients. For those at a smaller center, I recommend networking with hematologists at a larger center to ensure you stay updated about compassionate access programs, as well as clinical trials. Another option is calling the pharmaceutical representative to ask if a compassionate program is available. Pharmacists can also help explore funding options.

2024 Canadian Hematology Today Rising Stars Conference

Open Q&A Session



How do you advocate for your center to be included in clinical trial opportunities?

Dr. Anglin: Many community hospitals have active clinical trials programs. It takes time and resources to set up a program in the first place, but once the clinical trial program is set up, hospital researchers can start networking with industry representatives and the trial opportunities will come. The more your site becomes known for clinical trials, the more opportunities will become available. Community hospitals prefer phase 3 or 4, practical trials that are applicable to a broad population.

How do you find a good mentor or career coach?

Dr. Shafey: I recommend starting to network in your residency. In my residency, I reached out to specialists at cellular therapy centers, because that's where my interest lay. Don't be shy about asking your peers and supervisors about who is specializing in your area of interest and where the career opportunities are. It's important to have mentorship early on in your career. Mentors pave the way for opportunities.

What characteristics should junior physicians look for in a mentor?

Dr. Kuruvilla: I recommend looking for someone you enjoy working with. It's difficult to have a mentor who isn't aligned with your outlook. If someone is prolific, but doesn't have hobbies outside of work, and you're someone who is more well-rounded, you won't be compatible.

Dr. Shafey: You should put yourself out there and make your intentions clear, and say, like I did, "I'm graduating. I want to do a fellowship, and I want a job." Of course, you don't have to make your final decision right away. You can spend your time during fellowship to get to know people across the country before you make a more permanent decision.

Do you have any advice for early career clinician investigators?

Dr. Shafey: Consider how much time you want to spend clinically and how much time you want to protect for research. Those expectations are negotiable, and you should outline them when you're signing your contract. Don't be afraid to ask your preceptors, "What is your independent contract? How much clinical work do you do?" Senior physicians are usually happy to share this information.

Dr. Bergeron: You can also ask questions like "What's the worst thing about your job?" That can be a very helpful question when deciding where you want to work.

What supports should junior hematologists ask about when considering clinical programs?

Dr. Bergeron: The challenge is that supports are determined by administrators at hospitals, who are often not physicians. Unity is always helpful. It's necessary to advocate as a team of clinicians with a common goal, and to speak with one voice.

What should you look for in a practice?

Dr. White: You want to gauge whether the group gets along. That can be difficult to tell, in a one-day interview. Doing an elective for a month or two can be helpful to assess the culture of a practice.

Dr. Visram: If you're interested in research, you also want to assess the research capabilities of the institution, including what databases and research supports they have, and how you would be involved in their clinical trial programs. It's important to have those conversations upfront.

Are there any tools, external assessments, or other methods you use to try to optimize your practice or workflow?

Dr. Anglin: I think wherever you go to work, one of your commitments will be working on a committee or initiative to improve the quality of the institution, including by improving process flows, patient experience, and provider experience.

Dr. Kuruvilla: I recommend trying to find ways to become more efficient in the first five years of your practice. Ultimately, that will mean you won't have to work as much later. Work that can be done by non-physicians is continually being downloaded to physicians. It's important to identify other people who can do tasks that don't require your involvement as a physician. Institutions often don't independently find ways to reduce physician workload. The person who is most likely to look out for you is you.

How do you see AI being incorporated into the field of hematology?

Dr. Kuruvilla: AI analysis can help select the top candidates from preclinical studies to bring forward to clinical studies, ultimately lowering the costs and time it takes to develop new drugs. I think there is naivety behind the idea that AI can comb through a giant dataset and find the molecular markers of cancer. The datasets that we have are too small and limited.

How did you break into clinical trials and clinical teaching?

Dr. Kuruvilla: I think it's an iterative process. Dr. Michael Crump, an experienced clinical trialist, was my mentor when I first started working on clinical trials. I learned from him through each stage of the process. I also read his grant applications and when I wrote my first application, I sent it to him to edit. I also recommend specialized programming like ASH's Clinical Training Research Institute, which provides training on clinical research methods, statistical analysis, and more.

Dr. Visram: I did the Clinical Training Research Institute program this year, and it was amazing. The American Association for Cancer Research has a cell therapy clinical design workshop as well.

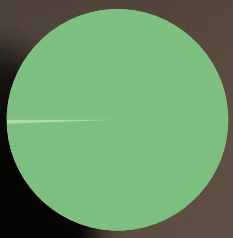
Closing Remarks & Adjournment

DR. ANGLIN

Dr. Anglin thanked the attendees for taking time out of their busy schedules to attend the inaugural Rising Stars in Hematology symposium; he also thanked all the sponsors for their commitment to continuing the support of early-in-practice clinicians. Dr. Anglin stated that he looks forward to seeing many of the attendees back in future years. The meeting was adjourned.

Attendee Feedback

Overall, the topics covered during the conference provided a comprehensive discussion of hematologic malignancies.

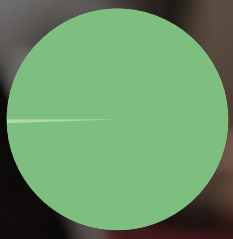


STRONGLY AGREE	98%
AGREE	1%
DISAGREE	0%
STRONGLY DISAGREE	0%

100% AFFIRMATIVE

Clinician feedback survey prompt

Overall, the information presented during the conference was high-quality, useful, and relevant to my hematology practice.



STRONGLY AGREE	99%
AGREE	1%
DISAGREE	0%
STRONGLY DISAGREE	0%

100% AFFIRMATIVE

Clinician feedback survey prompt

Overall, conference presentations were appropriate for my level and provided new information or perspectives.

STRONGLY AGREE	100%
AGREE	0%
DISAGREE	0%
STRONGLY DISAGREE	0%

100% AFFIRMATIVE

Clinician feedback survey prompt

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

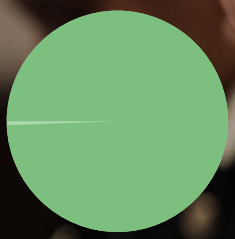
Clinician feedback survey prompt

STRONGLY AGREE	99%
AGREE	1%
DISAGREE	0%
STRONGLY DISAGREE	0%

100% AFFIRMATIVE

Overall, the conference offered good networking opportunities with colleagues and industry representatives.

Clinician feedback survey prompt

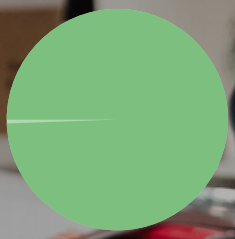


STRONGLY AGREE	98%
AGREE	2%
DISAGREE	0%
STRONGLY DISAGREE	0%

100% AFFIRMATIVE

Overall, the conference was well-organized.

Clinician feedback survey prompt



STRONGLY AGREE	99%
AGREE	1%
DISAGREE	0%
STRONGLY DISAGREE	0%

100% AFFIRMATIVE

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