Canadian Hematology Today

Canadian Hematology Today 2024 Lymphoma Conference

Event Summary & Evaluation Report

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15 years

In this report...

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Acronyms

ABVD	DOXORUBICIN, BLEOMYCIN, VINBLASTINE, AND DACARBAZINE
ALLOSCT	ALLOGENEIC STEM CELL TRANSPLANT
ASCT	AUTOLOGOUS STEM CELL TRANSPLANT
ASH	AMERICAN SOCIETY OF HEMATOLOGY
AXI-CEL	AXICABTAGENE CILOLEUCEL
BCL2i	BCL2 INHIBITOR
BEAM	CARMUSTINE, ETOPOSIDE, CYTARABINE, AND MELPHALAN
BR	BENDAMUSTINE PLUS RITUXIMAB
BTK	BRUTON TYROSINE KINASE
BTKi	BRUTON TYROSINE KINASE INHIBITOR
BV	BRENTUXIMAB VEDOTIN
BV-AVD	BRENTUXIMAB VEDOTIN AND DOXORUBICIN, VINBLASTINE, AND DACARBAZINE
CAR T-CELL	CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY
CF-DNA	CELL-FREE DNA
cHL	CLASSICAL HODGKIN LYMPHOMA
CHOP	CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE, AND PREDNISOLONE
CILTA-CEL	CILTACABTAGENE AUTOLEUCEL
CIRS-G	CUMULATIVE ILLNESS RATING SCALE-GERIATRIC
CLL	CHRONIC LYMPHOCYTIC LEUKEMIA
CNS	CENTRAL NERVOUS SYSTEM
CODOX-M	CYCLOPHOSPHAMIDE, CYTARABINE, VINCRISTINE, DOXORUBICIN, AND METHOTREXATE
CR	COMPLETE RESPONSE

CRS	CYTOKINE RELEASE SYNDROME
CT-DNA	CIRCULATING TUMOR DNA
DHAP	DEXAMETHASONE, HIGH-DOSE CYTARABINE, AND CISPLATIN
DLBCL	DIFFUSE LARGE B-CELL LYMPHOMA
DOR	DURATION OF RESPONSE
DRD	DARATUMUMAB, LENALIDOMIDE AND DEXAMETHASONE
DVD	DARATUMUMAB, BORTEZOMIB, AND DEXAMETHASONE
ECOG	EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE SCORE
EFS	EVENT-FREE SURVIVAL
FCR	FLUDARABINE, CYCLOPHOSPHAMIDE, AND RITUXIMAB
FL	FOLLICULAR LYMPHOMA
GDP	GEMCITABINE, DEXAMETHASONE, AND CISPLATIN
HGBCL	HIGH-GRADE B-CELL LYMPHOMA
IADL	INSTRUMENTAL ACTIVITIES OF DAILY LIVING
ICANS	IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME
ICML	INTERNATIONAL CONFERENCE ON MALIGNANT LYMPHOMA
IPI	INTERNATIONAL PROGNOSTIC INDEX
ISAKD	ISATUXIMAB, CARFILZOMIB AND DEXAMETHASONE
ISAPD	ISATUXIMAB, POMALIDOMIDE, AND DEXAMETHASONE
IVAC	IFOSFAMIDE, ETOPOSIDE, AND CYTARABINE
IXARD	IXAZOMIB PLUS LENALIDOMIDE AND DEXAMETHASONE
JCO	JOURNAL OF CLINICAL ONCOLOGY
KCD	CARFILZOMIB, CYCLOPHOSPHAMIDE, AND DEXAMETHASONE
KD	CARFILZOMIB AND DEXAMETHASONE

Acronyms con't

KDD	CARFILZOMIB, DEXAMETHASONE, AND DARATUMUMAB
KRD	CARFILZOMIB PLUS LENALIDOMIDE AND DEXAMAETHASONE
LISO-CEL	LISOCABTAGENE MARALEUCEL
MATRIX	METHOTREXATE-CYTARABINE PLUS RITUXIMAB AND THIOTEPA
MM	MULTIPLE MYELOMA
MPFS	MEDIAN PROGRESSION-FREE SURVIVAL
MRD	MINIMAL RESIDUAL DISEASE
MTR-A	METHOTREXATE, TEMOZOLOMIDE, AND RITUXIMAB, FOLLOWED BY ONE CYCLE OF HIGH-DOSE CYTARABINE
MZL	MARGINAL ZONE LYMPHOMA
N-AVD	NIVOLUMAB AND DOXORUBICIN, VINBLASTINE, AND DACARBAZINE
NEJM	NEW ENGLAND JOURNAL OF MEDICINE
NHL	NON-HODGKIN LYMPHOMA
NNT	NUMBER NEEDED TO TREAT
NOS	NOT OTHERWISE SPECIFIED
ORR	OVERALL RESPONSE RATE
OS	OVERALL SURVIVAL
PCD	POMALIDOMIDE, CYCLOPHOSPHAMIDE, AND DEXAMETHASONE
PFS	PROGRESSION-FREE SURVIVAL
PMBCL	PRIMARY MEDIASTINAL B-CELL LYMPHOMA
POD24	PROGRESSION OF DISEASE WITHIN 24 MONTHS
POLA-BR	POLATUZUMAB VEDOTIN, BENDAMUSTINE, AND RITUXIMAB
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
R/R	RELAPSE/REFRACTORY
R2	LENALIDOMIDE AND RITUXIMAB
SVD	SELINEXOR, BORTEZOMIB, AND DEXAMETHASONE
TAFA-LEN	TAFASITAMAB-LENALIDOMIDE
TEAE	TREATMENT-EMERGENT ADVERSE EVENTS
TISA-CEL	TISAGENLECLEUCEL
VD	BORTEZOMIB AND DEXAMETHASONE
VENO	VENETOCLAX AND OBINUTUZUMAB
VENVD	VENETOCLAX, BORTEZOMIB, AND DEXAMETHASONE

Welcome and Opening Remarks

DR. PETER ANGLIN

Dr. Peter Anglin welcomed attendees and thanked all the faculty for their commitment of time and energy. Dr. Anglin also thanked the sponsors for their continued support of this important educational meeting.

Community and academic perspectives on navigating the evolving landscape of R/R DLCBL

DR. SAMER TABCHI

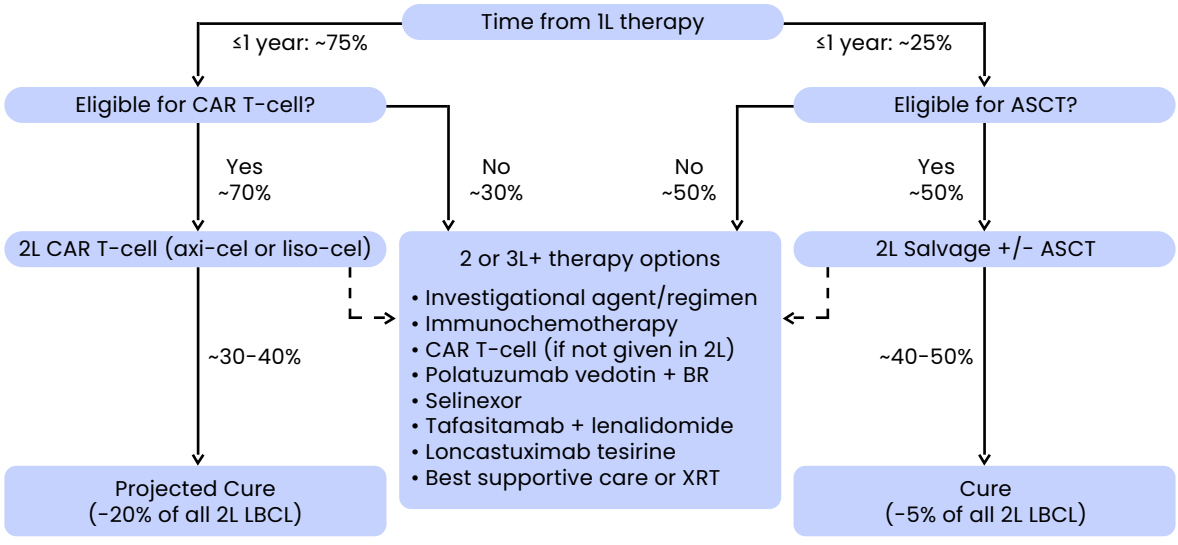
The treatment of R/R DLCBL continues to be challenging. The retrospective SCHOLAR-1 study, the largest analysis of outcomes in patients with refractory DLBCL, reported median OS rates of 6.3 months.

Fortunately, the advent of CAR T-cell therapy is improving the dismal outcomes in R/R DLCBL. Dr. Tabchi stated that CAR T-cell therapy is now the recommended treatment pathway for most patients, while ASCT should be considered for the 25% of R/R DLCBL patients who relapse after 1 year.

All three CAR T-cell products were tested against the standard of care in the second line in patients with high-risk disease. The ZUMA-7 trial of axi-cel and the TRANSFORM trial of liso-cel resulted in similar reductions in disease progression or relapse of 58% and 63% respectively. Due to differences in trial design, it is possible that the ZUMA-7 trial had a larger proportion of patients with more indolent disease vs more aggressive/resistant biology in the BELINDA trial. In addition, that 25% of patients in the BELINDA study experienced progression of disease at 6 weeks prior to the infusion highlights the importance of disease control prior to CAR T-cell infusion.

R/R LBCL TREATMENT LANDSCAPE

Algorithm for Second-line Therapy of LBCL



DR. SAMER TABCHI

For patients ineligible for CAR T-cell therapy, outcomes of ASCT are best highlighted by the PARMA study, which changed practice almost 25 years ago. Another important study for this CAR T-cell therapy-ineligible population is the LY.12 trial, which showed that neither the GDP or DHAP regimens are superior to the other, and the choice is dependent on the patient's prior exposure and institutional practice.

In the third line setting and beyond, there is no standard of care, with treatment selection based on patient characteristics, time of relapse, prior therapies, and available therapeutics. A 2022 *NEJM* study found glofitamab, administered in 12 cycles over approximately 8 months, resulted in CR rates of 39% in the third line setting. The median DOR was 18.4 months, and the adverse events of interest (CRS and ICANS) were mostly grade 1 or 2. Epcoritamab has demonstrated similarly favourable results and low rates of higher-grade CRS and ICANS, with a key difference being that it is administered until progression or unacceptable toxicity. Continuous treatment can be reassuring to patients who have experienced relapse.

A 2024 meta-analysis published in *Blood* demonstrated a pooled CR rate of 51% for CAR T-cell therapy in the third line and beyond, versus 37% for bispecific antibodies in patients who were CAR T-cell therapy naïve. This improved efficacy comes, however, with increased rates of severe CRS, toxicity, and infection. Multivariate analysis demonstrated CAR T-cell therapy should be the preferred modality in patients with double-hit and triple-hit lymphoma.

For patients ineligible for T-cell-engaging therapies, alternative options include Pola-BR and tafa-len. Pola-BR demonstrated CR rates of 42.5% in patients who underwent one or more previous therapies, and a DOR of 11 months. In a phase 2 study, tafa-len demonstrated CR rates of 40% in patients with one to three prior lines of therapy.

Dr. Tabchi highlighted the pressing need for more off-the-shelf therapies for R/R DLCBL for patients who cannot travel to tertiary care hospitals to receive cellular therapies.

Q&A

Question: What systemic treatments do you consider for DLCBL patients aged 70+ in the second-line setting, with comorbidities?

Answer: If relapse occurs before 12 months, CAR T-cell therapy may be available. If they need bridging therapy, Pola-BR is a good option. If the relapse occurs after 12 months, tafa-len is available in Quebec. For patients who achieve a CR on tafa-len, the DOR can be quite favourable, allowing the patient to take time off therapy. I try to avoid Gem-Ox and GDP as much as possible, due to the risk of neuropathy.

Managing older patients with HL

DR. JOANNA RHODES

Patients who are 60+ with cHL generally have far lower survival than younger patients, with 2-year survival rates in the 60+ age group at 65%, compared to 91% in the 40-59 age group and 97% in the 18-39 age group. cHL patients 60 and older are less likely to be treated with intensive chemotherapy.

Anthracycline-based therapies remain the first-line treatment of choice for older patients. The ECHELON-1 study demonstrated 6-year PFS rates of 82.3% for 60+ patients treated with BV-AVD, compared to 74.5% in patients for 60+ patients treated with AV-BVD. In a real-world analysis, the 5-year PFS rate was 67.1% with BV-AVD versus 61.6% with ABVD.

Treatment-related toxicity continues to drive treatment decisions for elderly patients. The ECHELON trial revealed higher rates of in-study death, grade 3 or higher neutropenia, febrile neutropenia, and any-grade pulmonary toxicity in the BV-AVD group, compared to the ABVD group. About 80% of older patients required a dose modification of BV, such as a dose reduction, delay, or discontinuation. Sequential dosing of two cycles of BV, followed by six cycles of ABD, followed by four cycles of BV demonstrated better outcomes in the 60+ population. However, outcomes were much worse for older patients with high CIRS-G scores and IADL loss, underscoring the importance of pre-treatment geriatric assessments.

In the real-world, a single-center retrospective presented at ASH in 2023 found that 2-year PFS and OS were 83% and 88%, respectively, for BV+AVD regimens. When compared to the historical cohort of older patients treated with AVD-based regimens, BV-based regimens demonstrated significantly improved 2-year PFS (65% vs 84%). However, there was no statistically significant difference in the 2-year OS.

For cHL patients who are not eligible for conventional chemotherapy, BV plus dacarbazine or BV plus nivolumab are options. The former led to a mPFS of 47 months in cHL patients over 60 with previously untreated cHL, while PFS was not reached for the BV plus nivolumab group, after 60 months of follow up, according to a study published in *Blood* in 2024. In both groups, median OS has not yet been reached after 60 months. The most frequent adverse event was peripheral neuropathy, at 77% among patients treated with BV plus dacarbazine (27% of events were grade 3), compared to 48% among those treated with BV plus nivolumab.

An exciting treatment option on the horizon is N-AVD. In a study of 60+ patients with newly diagnosed cHL, N-AVD, administered for six cycles demonstrated 2-year PFS over 80% with an OS rate over 90%. A US cooperative study (S1826), comparing BV-AVD to N-AVD, found that 1-year PFS was 64% for BV-AVD and 93% for nivolumab-AVD in patients over 60. There were more deaths in the BV-AVD arm (7 versus 2 patients), due to higher rates of infection and sepsis. Rates of neutropenia were slightly higher in the N-AVD group compared to the BV-AVD group (53% versus 32%), though only 69% of patients in the N-AVD group received growth factor, compared to 92% in the BV-AVD group, suggesting older patients would benefit from growth factor being automatically coupled with these regimens. While anthracycline-based therapy remains the treatment of choice for patients with cHL, N-AVD could become the standard treatment for elderly patients with cHL due to its high efficacy and tolerability in this population.

Q&A

Question: Do you do geriatric assessments in all your patients?

Answer: I'm stricter about these assessments for patients above 70+, however my team is hoping to introduce risk mitigation assessments for all patients above 60+ by partnering with a geriatrician.

Question: Can you comment on the treatment of limited stage Hodgkin's disease in older patients?

Answer: Bulky stage 2b disease can lead to dismal outcomes because patients aren't treated with novel agents in the front line. The on-label option is AVD, with or without radiation. However, earlier stage trials are assessing BV or nivolumab in the frontline setting for limited stage Hodgkin's disease.

Question: Is there a threshold for patients above 70 for whom you would recommend BV-AVD?

Answer: This decision is made on a case-by-case basis; however, I find that most patients over 70 do not tolerate BV-AVD. If I do choose BV-AVD for a patient above 70, I use sequential dosing.

2024 Canadian Hematology Today Lymphoma Conference

Primary CNS Lymphoma in 2024: Who Should Get What Therapy?

PROFESSOR CHRISTOPHER FOX

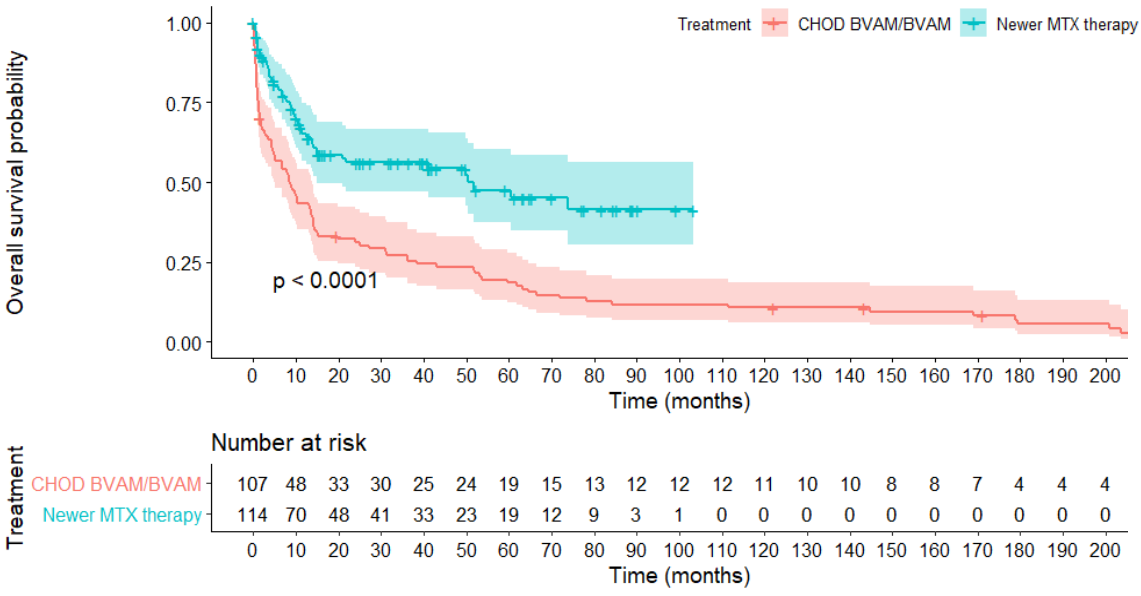
Dr. Fox provided a brief overview of primary CNS lymphoma, which constitutes about 5% of all primary brain tumors, and 2% of B-cell NHL. The rising incidence of primary CNS lymphoma isn't fully explained by improved diagnostics. The median age at diagnosis is 68 to 70, according to French and UK analyses. Patients with primary CNS lymphoma almost always present with neurocognitive dysfunction and have impaired performance status. The blood-brain barrier is a challenge for drug delivery. Another treatment challenge is that brain tissue is highly vulnerable to treatment toxicities. Advanced imaging modalities show that most patients have disease that is multifocal, and Dr. Fox argued primary CNS should be understood as a "whole brain disease."

The improved survival for CNS lymphoma in the last two decades is likely due to a combination of factors, including improved time to treatment, the introduction of the thiotepa/carmustine conditioning regimen for ASCT, and optimized supportive care and delivery of therapy. Age and performance status are the top predictors of survival.

Dr. Fox noted that two randomized trials favour thiotepa-based ASCT over whole-brain radiation, in part due to the neurocognitive dysfunction associated with the latter treatment. Regarding consolidation methods, the phase 2, International Extranodal Lymphoma Study Group-32 trial demonstrated PFS and OS superiority of the quadruplet MATRix regimen over triplet (methotrexate-cytarabine plus rituximab) therapy and methotrexate-cytarabine alone. While MATRix is commonly used, it's not a universal standard of care for the treatment of primary CNS lymphoma in North America. Other induction regimens include R-MPV-A and MTR-A, and there is no international consensus on the best induction regimen. Unfortunately, approximately one third of patients with primary CNS lymphoma don't get to ASCT, and less than two thirds of these patients experience long-term remission post ASCT.

Regarding whether myeloablative chemotherapy improves outcomes over conventional dose chemotherapy, Dr. Fox presented two RCTs that favoured high-dose chemotherapy, one published in 2024 in *Blood Advances* and another presented at ASH in 2022.

OVERALL SURVIVAL FOR PCNSL PATIENTS – CHOD BVAM/BVAM VS. NEWER MTX



PROFESSOR CHRISTOPHER FOX

While there is no prospective data shedding light on the optimal conditioning regimen, retrospective data shows thiopeta-based conditioning to be superior to BEAM conditioning. Based on retrospective data showing a lower dose didn't impact survival, Dr. Fox said he is comfortable dose-reducing thiopeta to 10 mg/kg, for older patients, especially patients in their 70s.

Arguing that physicians should attempt to bring as many patients as possible to thiopeta-based ASCT, including older patients, Dr. Fox presented retrospective data from a UK, French, and German collaboration that showed 2-year PFS rates of 62% after ASCT in patients aged 65-77, despite the fact that 62% had relapsed disease before receiving ASCT.

While significant progress has been made delivering intensified multiagent chemoimmunotherapy, Dr. Fox stressed that future progress in the treatment of primary CNS lymphoma requires a better understanding of disease biology with genomic approaches, advanced MRI testing to assess the disease response, and the optimization of current therapies.

Q&A

Question: How do you manage non-DLCBL CNS lymphoma?

Answer: We occasionally see primary CNS T-cell lymphoma and other rare presentations, but there isn't robust data to definitively guide treatment. I approach primary CNS T-cell lymphoma the same as I do B-cell CNS lymphoma.

Question: What is your approach to patients with CNS lymphoma who are above 75 and ineligible for ASCT?

Answer: We use high-dose methotrexate, rituximab, and procarbazine. My target population for this regimen are patients with good cardiac function and a glomerular filtration rate of 50 mL/min or higher.

Patient Selection and Bridging for CAR T-cell Therapy in Aggressive B-cell Lymphoma

DR. IVAN LANDEGO

When FL patients relapse after second-line treatment, CAR T-cell therapy is recommended. Three studies are important to guide CAR T-cell treatment in the third-line setting, including the ZUMA-5 study (axi-cel), the ELARA trial (tisa-cel) and the TRANSCEND-FL study (liso-cel). The ZUMA-5 trial was a phase two multicenter, open-label study enrolling 124 patients with R/R FL and 24 patients with R/R MZL who had received at least two prior lines of therapy, including an anti-CD20 medication with an alkylating agent. All patients had good performance statuses (ECOG of 0 to 1), 86% had stage III-IV disease, 50% had bulky disease, and 55% were POD24 from initial chemoimmunotherapy. With a median follow up of approximately 3.5 years, the ORR was 94% in the FL cohort and the PFS was 40.2 months in FL, while OS was not reached in both the FL and the MZL groups.

The SCHOLAR-5 study, comparing the ZUMA-5 cohort to an international, real-world cohort of patients from 2014 to 2020 found that the outcomes of axi-cel were superior to the R/R FL standard of care therapies in the third-line setting and beyond.

The eligibility criteria for the ELARA study were similar to ZUMA-5, but ELARA only enrolled patients with FL and these patients were more refractory. More patients in the ELARA trial were heavily pretreated (with a median four lines of therapy), and 71% were refractory to at least two regimens while 63% were POD24. Long-term follow-up data show the estimated 24-month PFS, DOR, and OS in all patients were 57.4%, 66.4%, and 87.7%, respectively. The ORR was 86.2% with CR rates of 68%. Responses among high-risk patients were also impressive, as 59% of patients with POD24 experienced a CR, 40% of patients with a high total metabolic tumor volume had a CR, and 65% of those with bulky disease achieved a CR. These studies suggest that both axi-cel and tisa-cel can maintain durable responses with a highly refractory group of patients.

After almost 19 months of follow-up, early data from the TRANSCEND-FL study suggests high efficacy for liso-cel, with an ORR of 97%, and a CR rate of 94%.

Comparing toxicity outcomes across the three trials, 7% of participants in the ZUMA-5 (axi-cel) trial experienced grade 3 or higher CRS, compared to 0% in the tisa-cel and 1% in the liso-cel trials. The neurological toxicities were also much higher in the ZUMA-5 trial. These differences are likely explained by the relatively poorer understanding of how to manage CRS and ICANS at the time of the ZUMA-5 trial, compared to the later CAR T-cell therapy trials.

In Canada, axi-cel is reimbursed in adult patients with R/R grade 1, 2, 3a FL or MZL who have received two or more lines of chemoimmunotherapy. Tisa-cel and liso-cel are pending funding approval in

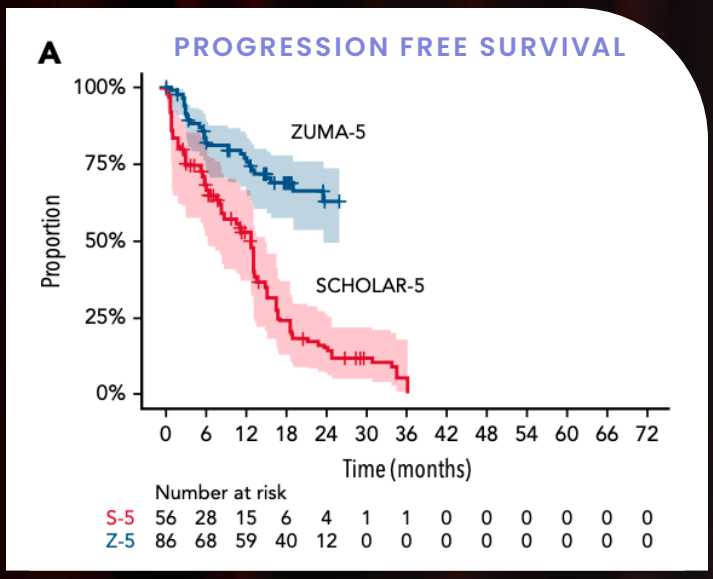
PATIENT SELECTION FOR CAR-T

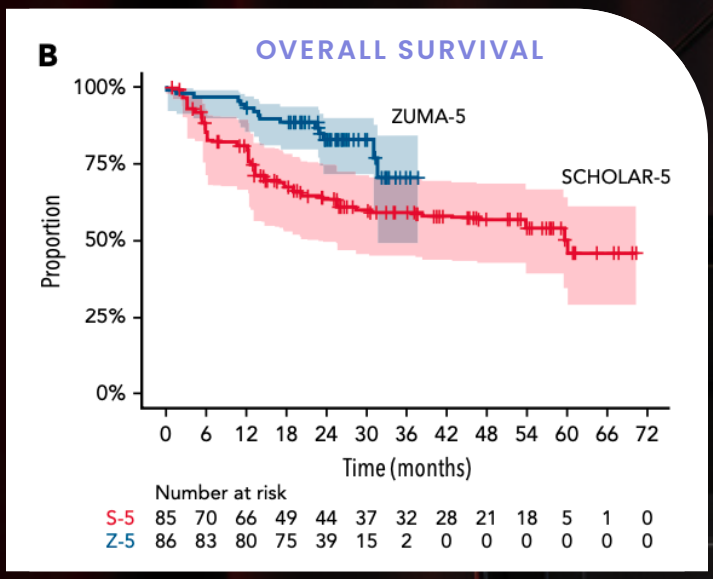
Patient Characteristics
- Age
- ECOG/ KPS
- Comorbidities/ Organ function
- Prior Therapies (2L/ 3L)
- Frailty/ Reserve
- Hematopoietic reserve

CAR-T product
- Access
- Apheresis slot availability/ manufacturing turnaround time
- CD28 versus 41-BB

Tumor
- Tumor microenvironment/ inflammatory milieu
- Disease biology and burden
- Antigen expression

Administration Considerations
- Inpatient versus outpatient
- Caregiver support





Canada for FL. Dr. Landego emphasized the importance of considering multiple patient, tumor, product, and administration factors when selecting patients for CAR T-cell therapy.

For R/R FL patients in the community who may be eligible for CAR T-cell therapy, Dr. Landego recommended seeking early referral as patients may need holding therapy prior to apheresis. Bridging therapy is generally beneficial for patients with rapidly progressive disease, bulky disease, symptomatic disease, or disease-causing organ dysfunction, and in cases where there is a prolonged manufacturing period.

Q&A

Question: What is your opinion on administering bispecific therapies prior to CAR T-cell therapy?

Answer: A recent study of large B-cell lymphoma showed that bispecific antibodies prior to CAR T-cell therapy was safe and didn't compromise the efficacy of CAR T-cell therapy, but studies haven't been conducted in FL and more research is needed.

Post CAR T-cell Therapy Management in the Community

DR. MICHAEL JAIN

Only about 15% to 20% of patients benefit from the second-line standard of care in DLCBL: a platinum-based chemotherapy (typically R-GDP) followed by ASCT. Three RCTs – ZUMA-7 (axi-cel), TRANSFORM (liso-cel) and BELINDA (tisa-cel) – revealed that more patients benefited from CAR T-cell therapy, compared to the standard of care, in the second-line setting.

Dr. Jain highlighted that the ZUMA-7 trial revealed high attrition rates with non-curative therapy. One third of patients who did not get ASCT within the standard of care arm did not go on to receive CAR T-cell therapy. These attrition rates are likely higher in real-world settings.

Regarding prognostic indicators in the second-line setting, the ZUMA-7 trial once again demonstrated that high tumor burdens are associated with worse outcomes for both CAR T-cell therapy and standard of care therapies. However, the patients who had high tumor burden had better outcomes with CAR T-cell therapy, compared to the outcomes of patients with low tumor burden on standard of care therapy.

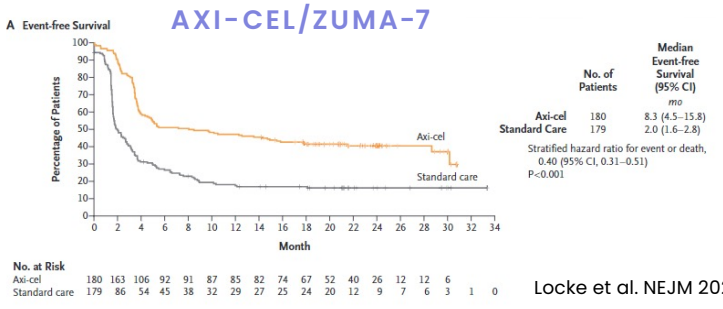
The ALYCANTE study of ASCT-ineligible patients revealed the outcomes and toxicities of CAR T-cell therapy were similar to that of younger patients. This was also found in the PILOT study of liso-cel, as 46% of patients in the study were over 75. Rates of severe CRS was 0% while the severe ICANS was 5% in the PILOT study.

In the second-line setting, there are many ambiguities around whether or not patients indeed meet CAR T-cell therapy criteria, however. There is ambiguity about whether DLCBL relapse should be defined based on PET-residual disease, PET-stable disease, or PET progression, for example. In addition, intermediary therapies are often more successful in the second-line and put the patient in remission, leading to greater uncertainty about how to proceed.

In the US, almost a third of patients received "holding" therapy before proceeding to CAR T-cell therapy in the second line. This was associated with a longer time to apheresis and worse efficacy of CAR T-cell therapy.

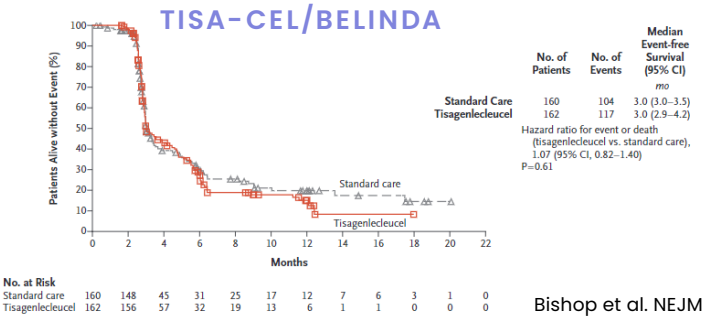
SECOND LINE DLBCL - THREE RCTs OF CAR T CELLS

AXI-CEL/ZUMA-7



Locke et al. NEJM 2021

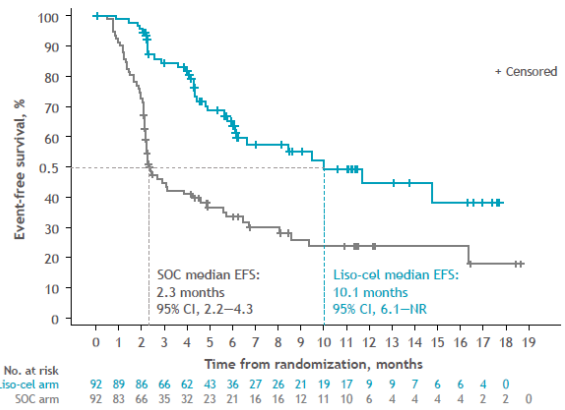
TISA-CEL/BELINDA



Bishop et al. NEJM 2021

medium follow-up in both arms: 6.2 months

LISO-CEL/TRANSFORM



Kamdar et al. ASH 2021

Dr. Jain concluded by reiterating that in the second-line there is a greater opportunity to intervene on patients before attrition occurs, thereby expanding access to curative intent therapy for transplant-ineligible patients.

Q&A

Question: Are you frequently using platinum-based chemotherapy as second-line therapy for R/R DLBCL patients?

Answer: We are moving away from using chemotherapy in the second line, as we're trying to bridge patients much more with bispecific antibodies.

Question: Which R/R DLCBL patients would you consider CAR T-cell therapy ineligible?

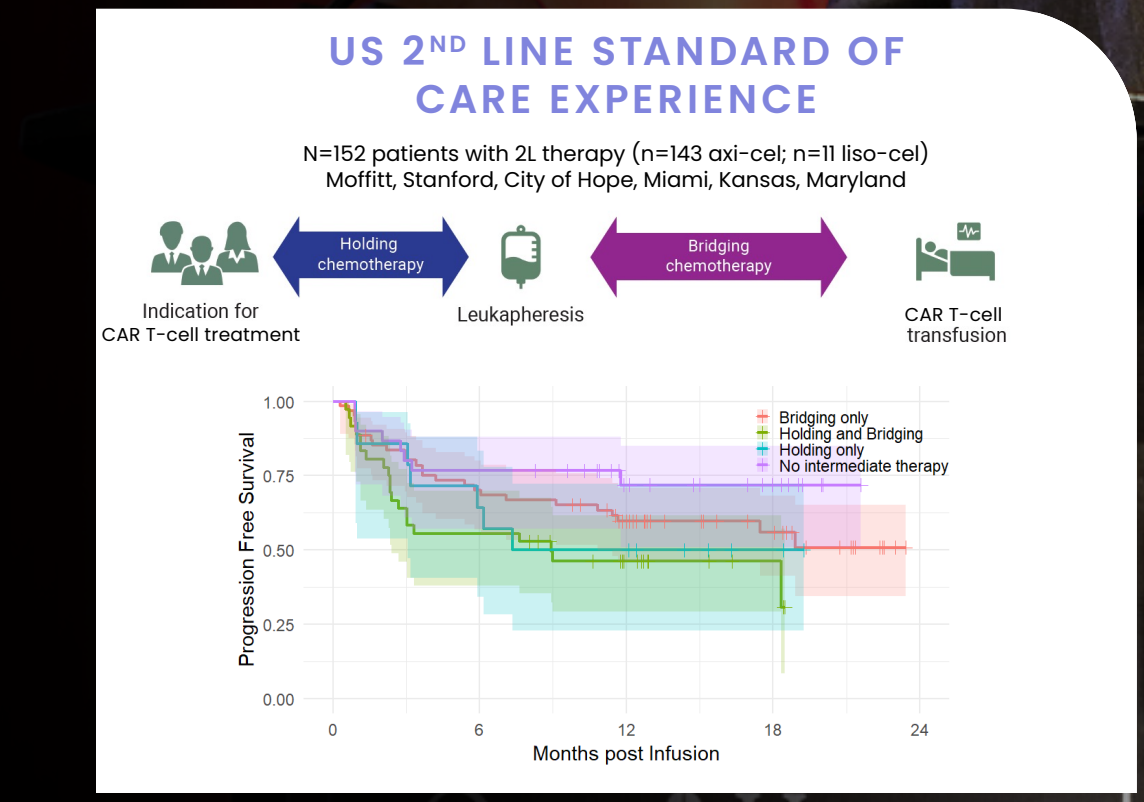
Answer: For our practice, this often comes down to patient preference. Patients who don't have a caregiver who can live nearby the center with them are often not inclined to proceed to CAR T-cell therapy. Patients' tolerance of CRS is generally not related to comorbidities, especially with the current usage of techniques to prevent CRS in older patients.

Question: How do you select between the available CAR T-cell therapies?

Answer: The main two products we have available are axi-cel and liso-cel. The manufacturing for axi-cel is reliable, so we often choose axi-cel if CAR T-cell therapy is urgently needed. Liso-cel is predominantly used in older patients.

Question: If patients have a relapse 2 years later, do you still recommend CAR T-cell therapy or is ASCT appropriate for these patients?

Answer: About 25% of patients are low-risk patients, who relapse after one year. For these patients, ASCT has cure rates of 60% and is often an ideal choice. If they relapse after ASCT, CAR T-cell therapy remains an option. While the treatment pathway is ambiguous in patients who relapse between nine and 15 months, I'm comfortable proceeding to ASCT for patients who relapse after 15 months.



Bispecific antibodies in aggressive B-cell lymphomas: A review of the current state

DR. JOHN KURUVILLA

The current treatment landscape is evolving in R/R DLCBL, with bispecific antibodies increasingly being incorporated in the third-line therapeutic setting and beyond.

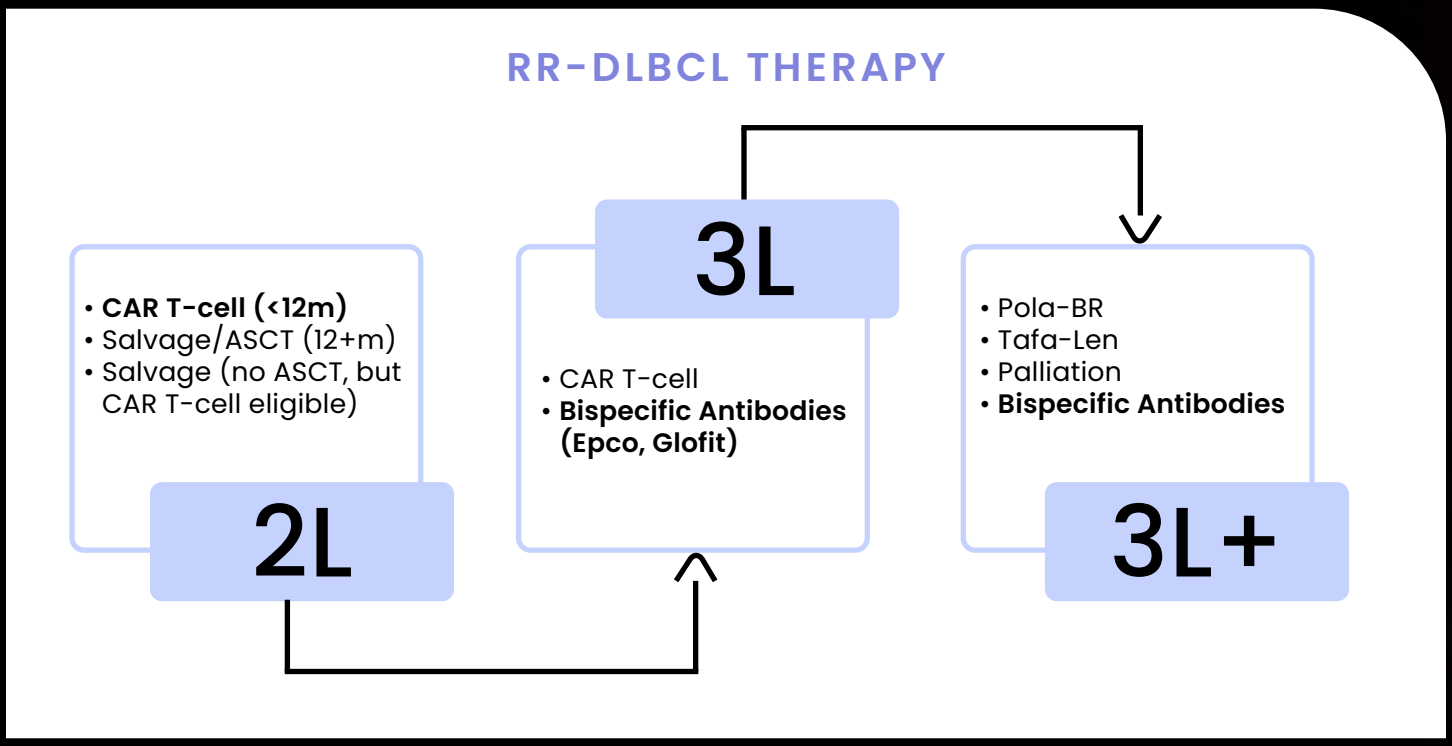
Dr. Kuruvilla discussed longer follow-up data of glofitamab monotherapy in R/R DLCBL, presented at ASH in 2023. The inclusion criteria for the single-arm, phase 2 study was a diagnosis of DLCBL NOS, HGBCL, transformed FL, or PMBCL, with an ECOG of 0-1, and at least two prior therapies. The fixed duration treatment was administered for up to 12 cycles, and CRS mitigation strategies included obinutuzumab IV pre-treatment and C1 step-up dosing. Approximately 33% of the patients had received prior CAR T-cell therapy.

With 32 months median follow-up, glofitamab showed high response rates, including a 40% CR rate, and durable remissions across subgroups. Of patients with a CR at the third cycle, a high proportion (63.5%) remained progression-free at 24 months.

CRS occurred in 64% of patients; 48% was Grade 1, 12% was grade 2, and 3% was grade 3. Grade 4 events occurred at a rate below 1%. Higher baseline total metabolic tumor outcome increased the risk of experiencing a Grade ≥2 CRS event.

In the EPCORE NHL-1 trial, epcoritamab was administered in a similar patient population, although ECOG 2 patients were eligible. The therapy was administered subcutaneously on a weekly, biweekly, and then quarterly basis, up to disease progression. About 70% of the patients had three or more lines of therapy prior to CAR T-cell therapy, and 38% had received CAR T-cell therapy, with 74% of these patients refractory to CAR T-cell therapy.

Long term follow-up data presented at ICML in 2023 showed that the most common TEAEs of any grade were CRS (51%), neutropenia (24%), fatigue (23%), nausea (22%), and diarrhea (21%). Only 3% of patients experienced grade 3 CRS, the majority were grade 1 or 2, and occurred after the first dose. While most safety events occur before 48 weeks, infections



can occur later, due to the impact of longer-term B-cell depletion. This requires ongoing vigilance from clinicians. In DLCBL, the ORR was 62% and the CR rate was 40%. The median time to response was 1.4 months, and the median DOR was 15.5 months. The median OS was 19 months in patients with DLBCL.

Dr. Kuruvilla highlighted that the median time to CRS onset after the first dose was 14 hours for glofitamab and 20 hours for epcoritamab. This data can be used to guide timing of the first dose to avoid a CRS event in the middle of the night.

While efficacy and safety of bispecific antibodies are well established, Dr. Kuruvilla emphasized that only 35-40% of patients achieve long term remission on bispecific antibodies in clinical trials. Given bispecific antibodies can be delivered in the community, a decrement in outcomes compared to clinical trials is expected. Due to toxicity, there remain a group of lymphoma patients that should receive palliative care instead of bispecific antibodies. Dr. Kuruvilla highlighted the importance of establishing patient care pathways to appropriately manage both short- and longer-term toxicities associated with bispecific antibodies.

Q&A

Question: How do you manage CRS that is worsening?

Answer: Dr. Kuruvilla said that CRS tends to evolve to a higher grade quickly. When fever develops, patients are typically treated immediately with steroids. When fever and hypotension continue on steroids, tocilizumab is the go-to treatment for patients with CRS.

Question: Do you think standardized guidelines will be helpful for physicians managing CRS?

Answer: The Crombie paper presented at ASH is helpful. However, it could be tweaked to be more specific to the local context. Given that emergency department physicians are frequently the physicians who encounter CRS, a simple, one-size-fits-all approach would be ideal. I think it would be reasonable to request that Ontario Health distributes such guidance.

CLL for the Front Line: Many choices, What to Do?

DR. GRAEME FRASER

Dr. Fraser highlighted that first line CLL treatment options include time-limited therapy, such as chemoimmunotherapy (FCR), VenO, and BTKi-BCL2i therapy, as well as continuous BTKi therapy.

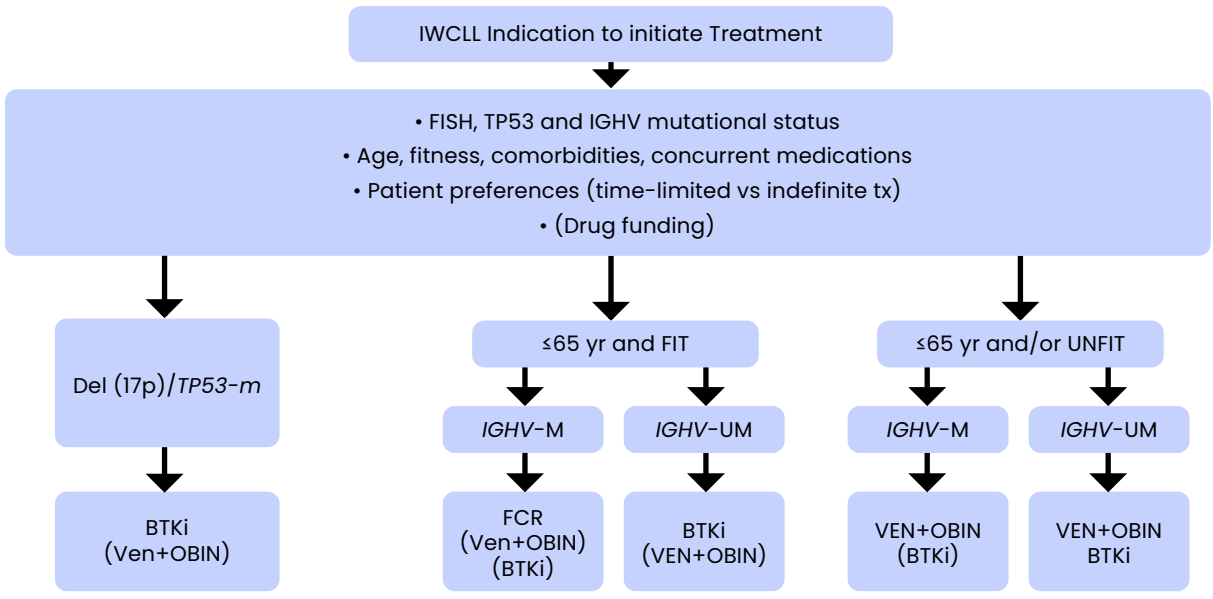
For high-risk CLL, the optimal therapy is continuous BTKi therapy. A pooled analysis from four trials of ibrutinib shows that continuous BTKi treatment in previously untreated *TP53*-aberrant CLL results in a 4-year PFS rate of 79%. This is remarkable, considering that the mPFS for chemotherapy regimens is less than a year. Updated data suggests the mPFS will be in the 6- to 7-year range. The ALPINE trial comparing zanubrutinib and ibrutinib suggests that zanubrutinib offers superior treatment outcomes.

VenO is also much more efficacious than chemotherapy in *TP53*-aberrant CLL, with 5-year PFS rates of 40%, according to a 2023 *Nature Communications* publication. VenO is a reasonable approach for patients for whom continuous BTKi isn't appropriate.

For low-risk disease (IGHV mutated disease), long-term follow-up from multiple trials shows that FCR provides long-term disease control. The downside of chemoimmunotherapy is the potential of infections in the short term and myeloid malignancies in the long term. While the rate of myeloid malignancies is difficult to estimate, a 6% risk is commonly shared with patients.

While ibrutinib in low-risk CLL patients could lead to intolerance and resistance over a long period, a time-limited treatment approach could improve on the toxicities associated with FCR. GAIA, a four-arm phase 3 trial, enrolled untreated patients who were considered fit by both CIRS score (≤6) and creatine clearance, and did not have a known del 17p or *TP53* mutation. The four arms included a standard chemoimmunotherapy arm of FCR or BR, venetoclax and rituximab, VenO, and ibrutinib plus VenO. The ibrutinib was stopped after 12 to 15 months in patients with undetectable MRD and continued up to 36 months if they were MRD-positive. The two VenO therapies proved superior from a clinical and an MRD perspective. The toxicity profiles were in line with expectations, with patients in the chemoimmunotherapy more likely to experience febrile neutropenia and infections. Second primary malignancies and cardiovascular events were both

SELECTION OF FIRST LINE CLL THERAPY

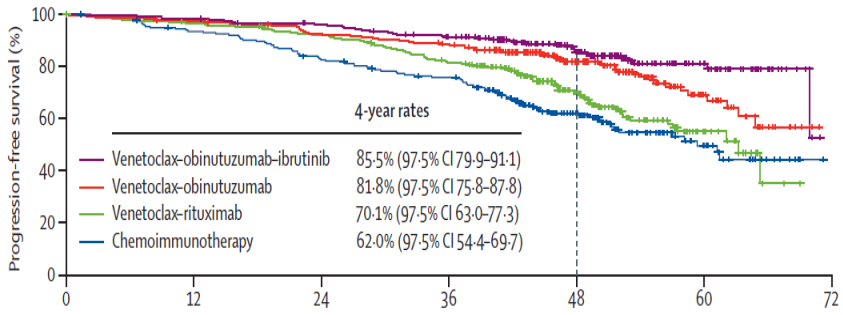


slightly increased in the ibrutinib-containing arm, at 2.4% and 15% respectively. For patients with unmutated IGHV disease, the modest improvement in PFS for ibrutinib+VenO versus VenO was offset by increased toxicity and more frequent treatment discontinuation. There was, therefore, no difference in OS between the two arms.

For patients in whom FCR would be inappropriate, the GLOW trial is instructional. The trial evaluated ibrutinib-venetoclax versus obinutuzumab-chlorambucil in patients who were over 65 or had multiple comorbidities, and no del(17p) mutation. Results demonstrated superiority of the ibrutinib-venetoclax therapy, with 2-year PFS rates of 44% in the obinutuzumab-chlorambucil arm and 85% in the ibrutinib-venetoclax arm. Regarding toxicities, chemoimmunotherapy resulted in higher rates of neutropenia and thrombocytopenia, while the rates of infection and cardiovascular toxicity were higher in the ibrutinib-containing arm.

In light of the evidence, Dr. Fraser explained he frequently recommends VenO, due to the favorable long-term outcomes in both low- and high-risk disease, good tolerability profile, and because many patients prefer a time limited approach. Current advocacy across Canada from CLL treaters is focused on expanding VenO for low-risk patients.

CLL 13/GAIA TRIAL: 1⁰ ENDPOINT PFS



Q&A

Question: For patients with high tumor volume, do you provide any pre-treatment before obinutuzumab?

Answer: Typically, I don't use a debulking strategy before starting obinutuzumab. It's not unreasonable, but patients often react to the first dose of 100 mg, regardless of pretreatment, and it's important to be ready with prophylactic treatment. In my experience, very few patients react to the second dose of 900 mg.

Question: We often have to dose reduce BTKis due to tolerability concerns. How low of a dose is too low to be effective?

Answer: My experience has been that with the selective BTKis, tolerability has been better. If I do need to dose reduce, it's often due to arthralgia/myalgia or bleeding. I typically will drop down to a 70% dose. When reducing the dose further is necessary, I would recommend re-escalating treatment, when possible, as tolerability issues tend to occur in the early stages of treatment.

Targeting BTK for Treatment of CLL: From Inhibitors to Degraders (Sponsored Lunch Symposium, BeiGene Canada)

DR. MAZYAR SHADMAN

Currently, there are three treatment strategies in CLL, presented in the figure below as A, B, and C:

In the absence of head-to-head trials, doctors choose between the three strategies based on a combination of patient and disease factors.

A pooled post-hoc analysis shows that OS for patients with CLL who received first-line ibrutinib treatment have the same OS rates at 12 years as an age-matched general population cohort. For patients with unmutated IGHV or *TP53* alterations, the mPFS was approximately 67 and 81 months, respectively.

The SEQUOIA trial of zanubrutinib found the PFS rate, at a median follow-up of 44 months, was 82.4%. Zanubrutinib showed superior PFS results to chemotherapy in both the unmutated and mutated IGHV population. Zanubrutinib has shown to be more effective than ibrutinib, including in patients with *TP53* aberrations.

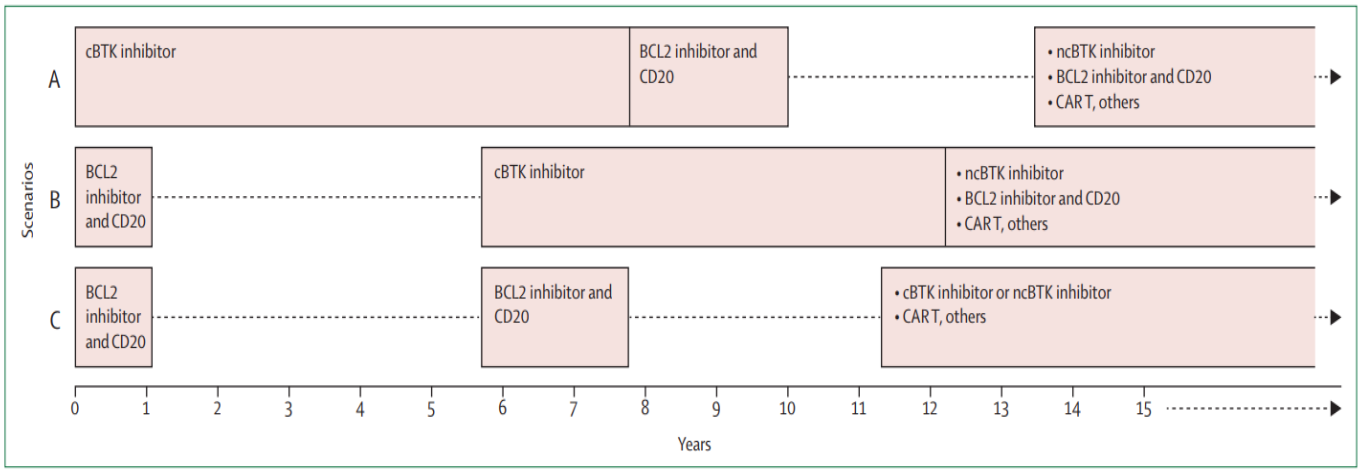
Likewise, a pooled analysis shows that *TP53* alterations do not seem to predict the PFS for patients treated with acalabrutinib in the frontline setting, in contrast to venetoclax-based therapy.

With the hypothesis that BTKis can promote the pro-apoptotic activity of BCL2 inhibitors, a number of clinical trials assessing these therapies in combination have been completed or are ongoing, including the ongoing AMPLIFY and MAJIC trials.

Data presented at the 2023 ASH meeting by Dr. Tam, based on almost 10 months of follow-up, found the safety signals with the zanubrutinib and sonrotoclax combination in patients with treatment-naïve CLL were on par with venetoclax combination therapy.

Reassuringly, treatment with acalabrutinib is feasible after an ibrutinib intolerance, and treatment with zanubrutinib is feasible after an acalabrutinib or ibrutinib intolerance. A 2019 *Blood Advances* study showed that of 61 ibrutinib-related adverse events associated with intolerance, 72% did not recur and 13% recurred at a lower grade with acalabrutinib. A 2023 ASH presentation by Dr. Shadman showed that 70% of intolerance events associated with acalabrutinib did not recur at any grade during

TREATMENT STRATEGIES IN CLL/SLL



zanubrutinib treatment and of the intolerance events that did recur, all recurred at the same grade or a lower grade.

Non-covalent BTKis are a treatment option after covalent BTKi and venetoclax treatment. Pirtobrutinib showed effectiveness in a high-risk population in a phase 1/2 study. In BCL2i naïve patients, the PFS rates were 72% at 12 months and 48.3% at 24 months, while in BCL2i-exposed patients, PFS rates were 61% at 12 months and 24.3% at 24 months. Due to its high response rates, and shorter response durations, pirtobrutinib is a good bridging candidate to ASCT or CAR T-cell therapy.

Approximately 20% of CLL patients achieve undetectable MRD and CR with CAR T-cell therapy, and these patients tend to achieve long-term remission. For patients who don't achieve a CR and undetectable MRD with CAR T-cell therapy, Dr. Shadman recommended retreating with pirtobrutinib as a bridge to ASCT or clinical trials. There is an unmet need in the double refractory population.

Very early data for BTK degraders show promising activity in high-risk and heavily pretreated patients, the potential opportunity for BTK degraders to treat patients who progress on a covalent BTKi or non-covalent BTKi, and potential superiority in BTKi-naïve patients. BTK degraders are well tolerated, based on short-term follow-up.

Q&A

Question: Combining novel agents will cause patients to become double-refractory much earlier. Are you concerned by this?

Answer: With fixed duration therapy, the risk of resistance mutations is lower, based on data from the CAPTIVATE trial and CLL 14 data. However, randomized trials like CLL17 and MAJIC will be extremely important to shed light on this question.

Later Lines/Cellular Therapy in CLL

DR. MICHAEL JAIN

While CLL was one of the first diseases to be treated in clinical trials with CAR T-cell therapy, the results have been much less impressive, compared to other forms of lymphoma. The first CAR T-cell therapy approval for CLL didn't come until 2024 with liso-cel. The trial that led to liso-cel's approval, published in *Lancet* in 2023, assessed liso-cel in patients with R/R CLL. Of the 70 patients in this trial who were refractory to both BTKi or venetoclax (with a median age of 66), the CR rate was approximately 18% and the ORR was 43%. Regrading toxicities, grade 3 or higher CRS was 9% and grade 3 or higher ICANS was 18%. Remarkably, of patients who achieve a CR, remissions are very long, while partial responders experienced a mPFS of 26.2 months. As with other types of lymphoma, high tumor burden is associated with worse outcomes, with an ORR of 31% in patients with bulky disease compared to 63% in patients with non-bulky disease. Double-refractory patients performed similarly to the overall study population.

Explaining why CAR T-cell therapy doesn't work as well in CLL, Dr. Jain presented data showing that a T-cell deficit is common in CLL. BTKi therapy is a way to address this T-cell deficit, but T-cell recovery takes many months of BTKi treatment. A study published in *Blood Advances* in 2022 assessed CAR T-cell therapy after CLL patients received ibrutinib for 6 months. Patients who did not achieve a CR on ibrutinib proceeded to CAR T-cell therapy, through which 72% achieved MRD-negative status at 1 year.

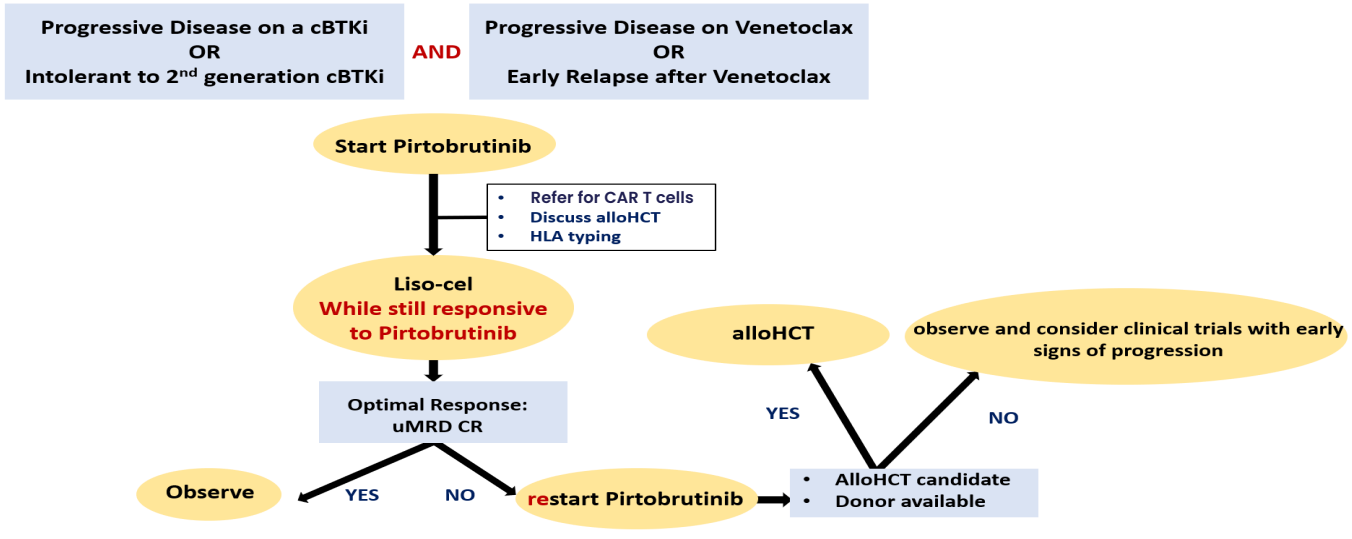
Dr. Jain described his current treatment approach for patients with R/R CLL. He noted that CAR T-cell therapy works better with a low tumor burden, so it is ideal to bridge with pirtobrutinib before CAR T-cell therapy. Patients who do not attain CR after 6 months with CAR T-cell therapy should be treated with pirtobrutinib with the goal of alloSCT. For patients with Richter transformation, the optimal approach is unknown, though treatment approaches include BTKi therapy plus 4-1BB CAR T-cell therapy like liso-cel or tisa-cel, or alloSCT.

Q&A

Question: How do BTK inhibitors affect T-cell quality?

Answer: Ibrutinib is unique among BTKis, in that it targets a T-cell kinase called ITK. The hypothesis is blocking ITK improves the T-cell fitness. Various tumor characteristics can influence T-cell quality, so shrinking the tumor overall is likely also beneficial.

SUGGESTED APPROACH FOR TREATING PATIENTS WITH "DOUBLE REFRACTORY" CLL



2024 Canadian Hematology Today Lymphoma Conference

High Grade and Aggressive B-Cell Lymphoma: What is it and How to Treat?

DR. MICHAEL CRUMP

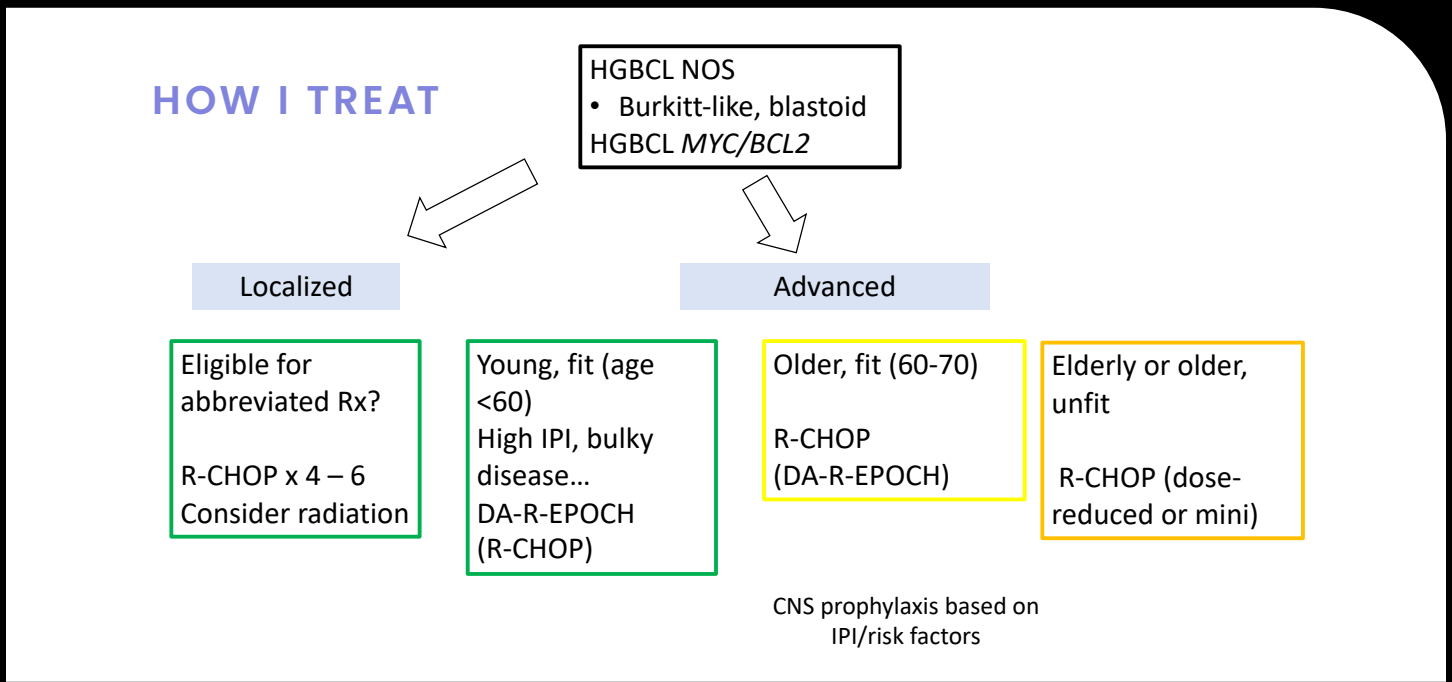
Molecular HGBCL encompasses approximately 9% of DLCBL, based on data from the UK REMoDL-B and POLARIX trials. Detailing the evidence for first-line treatment of HGBCL, Dr. Crump began with the REMoDL-B trial, a randomized phase 3 trial comparing R-CHOP and bortezomib-R-CHOP. While the primary analysis found no differences of PFS or OS, a secondary analysis found that patients with molecular HGBCL had improved event-free survival on bortezomib-R-CHOP compared to R-CHOP. This analysis was not large enough to be statistically significant.

A retrospective study of patients with double- or triple-hit lymphoma, from 14 academic cancer centres in France, suggests that patients who receive intensive chemotherapy, including R-EPOCH, R-ACVBP, or R-COPADEM have a better PFS outcome at 4 years than patients who receive R-CHOP (52% versus 28%). However, there is no difference in OS, and there are concerns about selection bias.

A retrospective analysis published in 2023 in the *Blood Cancer Journal* demonstrated that patients with a MYC/BCL6 translocation did as well on therapy as patients with a MYC translocation only, and treatment outcomes were improved with intensive therapy, compared to R-CHOP, when the analysis was stratified by cytogenetics. However, it's important to note that patients who received R-CHOP were older (by approximately 10 years) and had worse performance status compared to patients who received intensive therapy.

A *Haematologica* 2023 publication assessed the Flatiron database, including patients with newly diagnosed DLCBL from 280 cancer centres. About 8% of the patients were positive for MYC/BCL2, THL, or MYC/BCL6 translocations. Of the HGBCL patients, OS was improved in patients who received an intensive regimen, compared to R-CHOP. There are limitations with the dataset, however, including that the number of cycles and dose reductions are not specified.

For limited-stage HGBCL, a number of retrospective studies found no differences between R-CHOP and intensified regimens. Dr. Crump recommended treating limited stage HGBCL with four to six cycles of R-CHOP chemotherapy



(depending on IPI risk factors); incorporating radiation depending on PET4 assessments.

Response rates to salvage therapy in HGBCL patients is unfortunately very low, with OS rates of 5 months. In the future, CAR T-cell therapy could prove to improve these dismal outcomes.

Q&A

Question: Does the possibility of CAR T-cell therapy for HGBCL patients change frontline therapy?

Answer: I think we should still be giving the best treatment upfront. It remains to be seen whether CAR T-cell therapy will increase the survival of patients with HGBCL.

High Grade and Aggressive B-Cell Lymphoma: What is it and How to Treat?

PROFESSOR CHRISTOPHER FOX

In the last 40 years, there has been little improvement in preventing CNS relapse. CNS relapse is a devastating event with poor outcomes for most people. Accurately identifying patients at risk of a CNS event is difficult, and prophylactic interventions confer risks of additional toxicity.

The population of patients experiencing a CNS relapse is heterogeneous. Only one in three patients who experience a CNS relapse display a high-risk CNS-IPI and experience an isolated CNS relapse (as opposed to a systemic and CNS relapse). Therefore, only about a third of CNS relapse can be prevented with a prophylactic approach.

A paper published in JCO in 2016 determined that the positive predictive value of CNS-IPI is approximately 10% to 15%. If an intervention reduced the CNS risk by half, a positive predictive value of 10% would result in an NNT of 20 patients. That is, to prevent one isolated CNS relapse, approximately 20 'at risk' patients need to receive CNS prophylaxis, and face serious toxicity risks.

Dr. Fox described efforts to better understand which patients are at a high risk of an isolated CNS relapse and reduce this NNT. An analysis from the GLOW study found that patients with ABC cell of origin (COO) or unclassified COO gene expressions were at higher risk of CNS events. Within the ABC group, patients with the MCD gene expression have an especially high prevalence of CNS relapse.

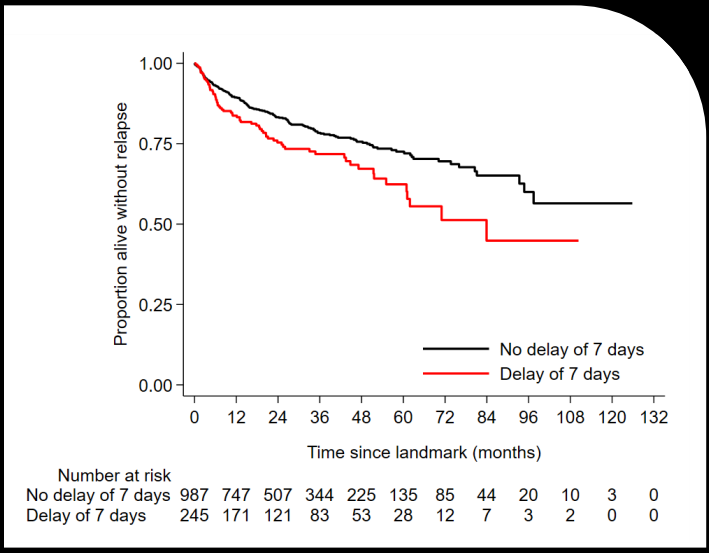
A *Blood Advances* study found that 8 out of 22 patients at a high risk for CNS had detectable cerebrospinal fluid ctDNA, and positive ctDNA was associated with a 29% risk of CNS recurrence. Still, even as ctDNA is more sensitive, the question remains whether patients with a positive ctDNA should undergo CNS directed-treatment.

Dr. Fox underscored that uncertainty remains because sample sizes are too small, given that CNS events are rare; selection bias is a major problem; most studies do not distinguish isolated CNS relapse and concurrent systemic relapse; and the timing and nature of prophylactic interventions are variable.

Discussing prophylactic options, a large international retrospective analysis published in the *JCO* in 2023 found that the 5-year risk of CNS relapse was 8.5% in patients with no high-dose methotrexate versus 6.9% in patients who received high-dose methotrexate. In patients who had a CR after treatment, the benefit was 6.5% versus 5%, respectively. While the study was not definitive, it suggests that if methotrexate has a benefit, the benefit is small.

The British Society for Haematology recommends considering baseline CNS screening (including an MRI of the brain and spine with contrast and/or cerebrospinal fluid analysis) for patients with disease in close proximity to the CNS and those at high risk of CNS relapse (those with a CNS-IPI of 5/6; 3 or more extranodal sites; and renal/adrenal, testicular or breast involvement).

If CNS lymphoma is confirmed on baseline investigation, the guideline recommends offering intensified chemoimmunotherapy with CNS-penetrating agents where possible. Regarding CNS prophylaxis, the guideline recommended offering either intrathecal chemotherapy and/or high-dose methotrexate to patients with testicular DLBCL. High dose methotrexate prophylaxis could be considered for other patients at the highest risk of relapse (a CNS-IPI of 5/6, 3 or more extranodal sites and with renal/adrenal, testicular or breast involvement),



PROFESSOR CHRISTOPHER FOX

weighing the risk versus benefit on an individual patient basis. When high-dose methotrexate is used, the guideline stressed it should be delivered at the end of treatment, after confirmation of a complete metabolic response, and at a maximum of 2 cycles.

Q&A

Question: Do you provide methotrexate in a patient with breast involvement?

Answer: The evidence base is quite conflicted. If patients have localized disease, they don't have a high risk of CNS relapse. However, CNS relapse is more common in patients with advance disease with breast involvement.

Question: How do you treat patients with HGBCL at risk of CNS relapse?

Answer: We occasionally use more intensive regimens, like CODOX-M and IVAC for young patients with high IPI scores and the HGBCL phenotype. For these patients, we provide intrathecal prophylaxis, based on the CODOX-M protocol.

Question: For testicular DLCBL, do you treat with radiation before high-dose methotrexate?

Answer: No, we do radiation after methotrexate treatment, because of the early CNS events in the population.

Question: What is your treatment approach for patients who have baseline CNS involvement in the context of systemic disease?

Answer: I recommend a secondary CNS lymphoma protocol for these patients. At my institution, we use the MARIETTA pprotocol.

Follicular lymphoma at 1st and 2nd Relapse: Is there a Standard?

DR. JONATHAN FRIEDBERG

Detailing treatment options for R/R FL, Dr. Friedberg described the AUGMENT trial, including 358 patients with R/R MZL and FL. In patients randomized to rituximab alone or R2, the PFS in patients who received R2 was substantially better than rituximab alone. Outcomes were very similar whether or not patients were classified as POD24. The regimen was also superior in chemotherapy-resistant patients.

The GALEN trial, assessing obinutuzumab and lenalidomide in R/R FL, also showed improved outcomes, which were potentially superior to R2.

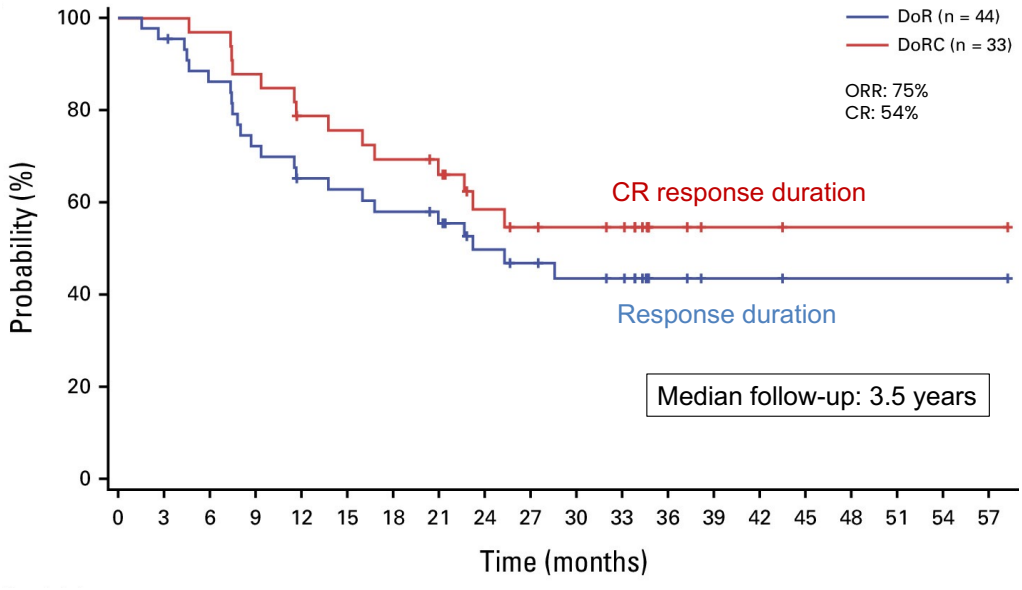
Moving on to bispecific antibodies, Dr. Friedberg presented data on mosunetuzumab, the first therapy of this class approved for FL. Despite an impressive ORR of 75% and CR of 54%, most patients progressed after the first year. The plateauing PFS curve may push the use of bispecific antibodies earlier in R/R FL therapy.

Epcoritamab, most recently approved in R/R FL, demonstrates similar PFS outcomes to mosunetuzumab, with more than 2 years of follow-up. As with mosunetuzumab, resistance to initial chemoimmunotherapy does not predict worse outcomes on this therapy. Dr. Friedberg noted that the subcutaneous dosing of epcoritamab may be preferrable to many patients. He added the durable responses for bispecific antibodies suggest the possibility of delaying or avoiding CAR T-cell therapy in patients who achieve a CR with bispecific antibodies.

Outlining CAR T-cell therapy, Dr. Friedberg presented the results of the ZUMA-5 (axi-cel) trial, showing a mPFS of approximately 40 months, and an ORR of 95%, with 79% of patients achieving a CR. There were no outcome differences between patients who received axi-cel in the second or third line. Of the patients enrolled in the study, 55% were POD24. The ELARA (tisa-cel) and TRANSCEND (liso-cel) trials demonstrated similar outcomes, and Dr. Freidberg emphasized that CAR T-cell therapy choice is often driven by availability. He noted, however, that tisa-cel is better tolerated in FL.

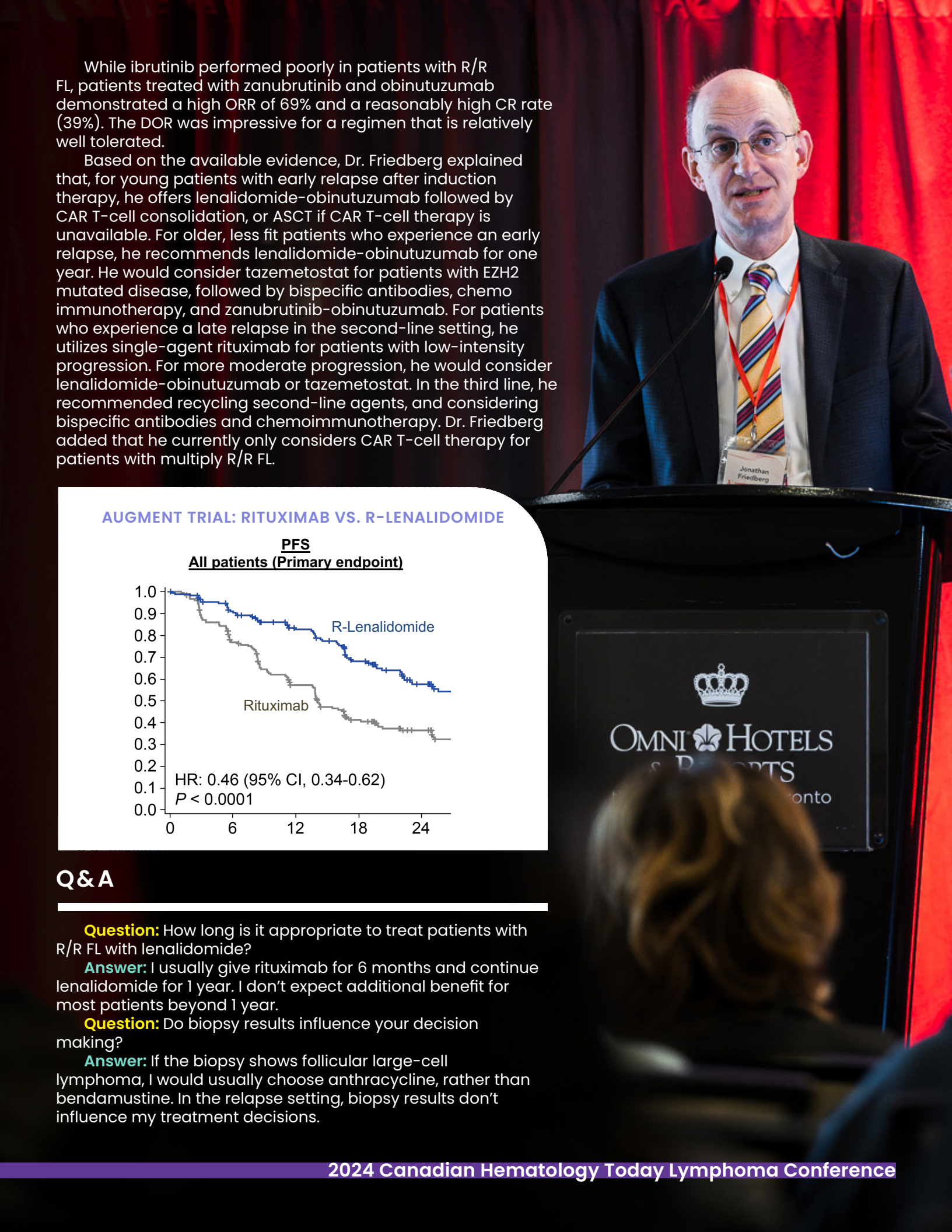
Targeted therapy is beneficial for some patients. In a study comparing wild-type and mutated EZH2 FL, the response rate to tazemetostat was much higher in patients who had mutated EZH2, compared to wild type (mPFS of 14 versus 11 months). While the PFS curves were not as impressive as bispecific antibodies, tazemetostat is extremely well tolerated.

MOSUNETUZUMAB: CD3/CD20 BISPECIFIC: DURABLE RESPONSES



While ibrutinib performed poorly in patients with R/R FL, patients treated with zanubrutinib and obinutuzumab demonstrated a high ORR of 69% and a reasonably high CR rate (39%). The DOR was impressive for a regimen that is relatively well tolerated.

Based on the available evidence, Dr. Friedberg explained that, for young patients with early relapse after induction therapy, he offers lenalidomide-obinutuzumab followed by CAR T-cell consolidation, or ASCT if CAR T-cell therapy is unavailable. For older, less fit patients who experience an early relapse, he recommends lenalidomide-obinutuzumab for one year. He would consider tazemetostat for patients with EZH2 mutated disease, followed by bispecific antibodies, chemo immunotherapy, and zanubrutinib-obinutuzumab. For patients who experience a late relapse in the second-line setting, he utilizes single-agent rituximab for patients with low-intensity progression. For more moderate progression, he would consider lenalidomide-obinutuzumab or tazemetostat. In the third line, he recommended recycling second-line agents, and considering bispecific antibodies and chemoimmunotherapy. Dr. Friedberg added that he currently only considers CAR T-cell therapy for patients with multiply R/R FL.



AUGMENT TRIAL: RITUXIMAB VS. R-LENALIDOMIDE

Q&A

Question: How long is it appropriate to treat patients with R/R FL with lenalidomide?

Answer: I usually give rituximab for 6 months and continue lenalidomide for 1 year. I don't expect additional benefit for most patients beyond 1 year.

Question: Do biopsy results influence your decision making?

Answer: If the biopsy shows follicular large-cell lymphoma, I would usually choose anthracycline, rather than bendamustine. In the relapse setting, biopsy results don't influence my treatment decisions.

Current Use of Bispecific Antibodies in MM

DR. CHRISTINE CHEN

The most common target antigen for MM is BCMA, due to its role in promoting MM cell survival and proliferation. In Canada, there are two currently approved BCMA-targeted bispecific antibodies: teclistamab and elranatamab, while the approval of talquetamab is expected next year.

Teclistamab was studied in patients who were triple class-exposed (76% triple class refractory), including 25% who had high-risk cytogenetics and 16% of whom were 75 or older. In this difficult-to-treat population, the ORR was 63% and almost half of patients achieved a CR. Although the overall mPFS was 11 months, for those who had a CR, the 30-month PFS rate was 60%. Subgroup analyses of the MAJESTEC-1 trial showed inferior outcomes for those with high-risk cytogenetics, high tumor burden, extramedullary disease, or heavy pre-treatment.

The MAGNETISMM-3 trial of elranatamab showed similar results, with a high ORR and durable responses. Dr. Chen added it is difficult to compare elranatamab and teclistamab, due to patient population heterogeneity.

In Canada, elranatamab and teclistamab are currently approved in the fourth line, after triple-class exposure. Provincial funding is expected for cilta-cel for the same patient population. Regarding whether to use a bispecific antibody or CAR T-cell therapy, small subgroup analyses suggest it is better to sequence CAR T-cell therapy first. A subset of the CARTITUDE-2 trial suggest outcomes of cilta-cel after bispecific antibodies are poor, with a PFS of 5 months in patients previously treated with bispecific antibodies. On the other hand, small data sets demonstrate similar response rates to bispecific antibodies, regardless of prior CAR T-cell therapy.

However, Dr. Chen noted that bispecific antibodies may be a better upfront choice in older, less-fit patients. Serious CRS and ICANS is much less common with bispecific antibodies, compared to CAR T-cell therapy, and step-up dosing works well to mitigate CRS. Tocilizumab remains the first-line choice for treating CRS due to bispecific antibodies. Only a third of patients who experience CRS due to this therapy need tocilizumab and most only need one dose. Unlike CAR T-cell therapy, second-line agents are very rarely necessary to treat CRS with

Type	Medication	Start and Duration
Viral	**Valacyclovir** 500 mg PO BID OR **Acyclovir** 400 mg PO BID	Start on day of first step-up dose and continue until 3 months after cessation. May be continued beyond at physician discretion.
Bacterial	**Ciprofloxacin** 500 mg PO BID OR **Levofloxacin** 500 mg PO daily	Start on day of first step-up dose and continue at minimum to the end of cycle 1. May be continued beyond at physician discretion.
Pneumocystis jirovecii pneumonia (PJP)	**Septra** DS 1 tablet (800 mg/160 mg) PO M,W,F Alternatives if Septra intolerant or cytopenic: - **Atovaquone** suspension 1500 mg = 10 mL PO daily (if Septra allergy) - **Pentamidine** 300 mg inhaled once monthly	Start on day of first step-up dose and continue until 1 month after cessation. May be continued beyond at physician discretion, especially if continued steroid therapy or prolonged neutropenia.
Fungal	**Fluconazole** 400 mg PO daily	For selected patients only who have prior history of systemic or extensive localized fungal infection. Start on day of first step-up dose and continue until 1 month after cessation.
Immunoglobulin replacement	Monthly **IV immunoglobulin** OR Weekly/Monthly **subcutaneous immunoglobulin**	Recommended routinely to start within 1-2 weeks of first step-up dose and continue for minimum 6 months after cessation of bispecific antibody. May be continued beyond at physician direction.
Immunizations	Prevnar 20 and SHINGRIX vaccines COVID-19 and Influenza boosters	Strongly recommended to receive **prior** to starting bispecific antibody therapy.

bispecific antibodies.

The most concerning toxicity with bispecific antibodies is long-term infections. In the MAJESTEC trial, 80% of patients developed infections on teclistamab, and half were severe; 12% of patients died due to an infection, mostly due to COVID-19 (the study largely occurred before COVID-19 vaccination was available). Dr. Chen emphasized the need for continuous vigilance, and shared the infection prevention protocol developed at UHN (see chart previous page).

Talquetamab, which will be available in the near future, targets GPRC5D instead of the BCMA receptor. The response rates are similar to the other bispecific antibodies. Key toxicities include dysgeusia and skin-related changes; however, the rate of infections are far less than the BCMA-targeting bispecific antibodies. (Severe infections occurred at a rate of 15%.)

Although bispecific antibodies are currently indicated for heavily pretreated patients, ongoing studies suggest these therapies will soon be available in earlier lines. Bispecific antibody combination treatment may also be on the horizon, as the RedirecTT-1 TRIAL shows encouraging results with the combination of teclistamab and talquetamab, potentially allowing for durable responses and time off treatment.

Q&A

Question: Funding for CAR T-cell therapy for myeloma may be available in early 2025. How will that affect bispecific antibodies funding?

Answer: Both funding for bispecific antibodies and CAR T-cell therapy are anticipated to become available around the same time. This underscores the importance of determining which treatment option is ideal for which patients.

1st relapse of MM: Many Choices

DR. SITA BHELLA

Dr. Bhella discussed the current and potential future options for managing first relapse for myeloma. Salvage transplant is appropriate for patients who progress at or beyond 26 months when not on maintenance therapy, or at or beyond 46 months on maintenance therapy.

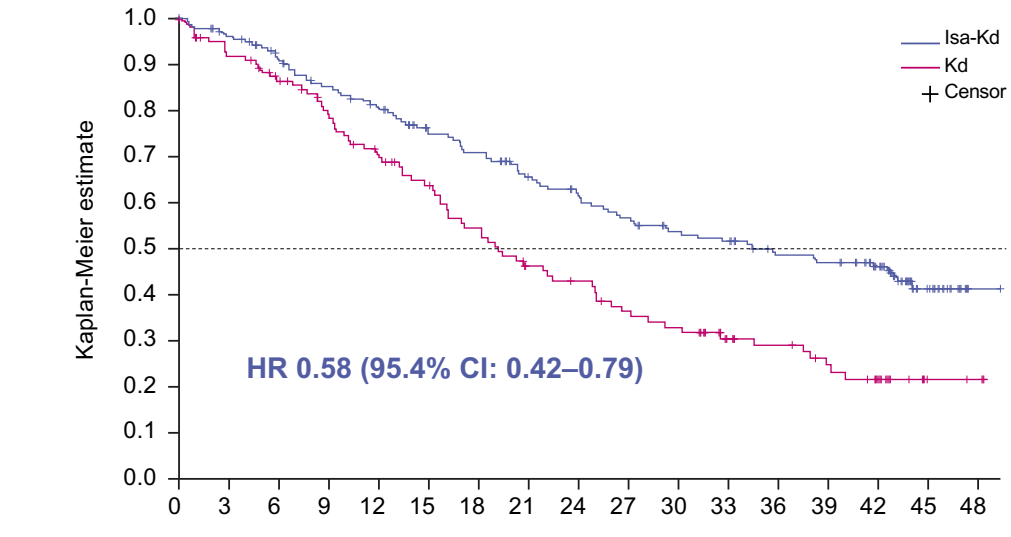
For patients who are lenalidomide-naïve or non-lenalidomide-refractory, the most effective regimens are triplet regimens including dexamethasone. Options include DRd, KRd and IxaRd. The choice among these regimens is influenced by patient factors, disease related factors, the toxicity profile, and drug reimbursement availability.

For patients refractory to lenalidomide, various proteasome-inhibitor-based combinations demonstrate similar PFS rates. The ENDEAVOR trial of Kd, the CASTOR trial of DVd and the OPTIMISMM trial of PVd demonstrated that the PFS of these combinations for patients who are lenalidomide-refractory ranged from approximately 8 to 9.5 months.

Options for lenalidomide-refractory patients with private insurance include DKd and IsaKd. The CANDOR trial of KdD and the IKEMA trial of IsaKD enrolled patients with a median of two prior lines of therapy, comparing against a Kd arm. Approximately a third of patients were lenalidomide-refractory. The mPFS was 28.6 months with DKd and 35.7 months for IsaKd. There was a 10% rate of fatal AEs in the DKd arm, compared to 3% in the IsaKd arm. Rates of respiratory infections and thrombocytopenia were higher in both trials, compared to the Kd arms.

Dr. Bhella noted that carfilzomib-based regimens may pose tolerability issues for elderly patients. Future options include SVd, which demonstrated an mPFS of 14 months in the BOSTON trial, and a

UPDATED PFS (PRIMARY ENDPOINT) - IRC ASSESSMENT (ITT)



Isa-Kd
mPFS: 35.7 months
(95% CI: 25.8–44.0)

Kd
mPFS: 19.2 months
(95% CI: 15.8–25.0)

With 2 additional years of follow-up, Isa-Kd showed the longest PFS on a PI-based backbone in the relapsed MM setting, with 42% reduction vs Kd in the risk of progression or death

30% reduced risk of progression, compared to Vd alone. SVd can cause significant GI adverse effects, however, as well as severe cytopenia. The BELLINI trial assessed another future option, VenVD, and showed a remarkable mPFS was 22 months, with an increased benefit in patients with t(11;14) status. There were, however, increased treatment-emergent deaths in this trial, largely attributed to infectious disease complications.

For patients who are double refractory, options include PCd; KCd for patients who are not refractory to a proteasome inhibitor; or IsaPd for those not refractory to anti-CD38 therapy. While therapies for triple-refractory patients are limited, trials for BCMA-targeted modalities are demonstrating unprecedented response rates and are expected to be transformative for MM patients in the future.

ct-DNA in Lymphoma: Moving Diagnostics to the Clinic

DR. ROBERT KRIDEL

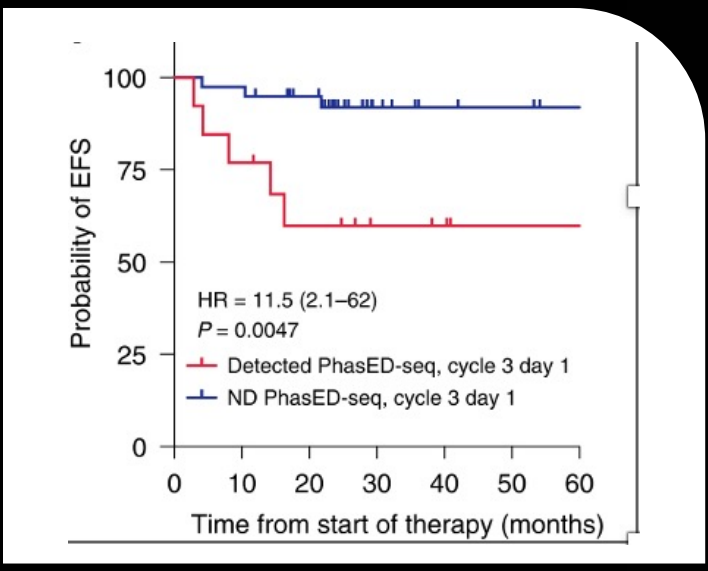
There is tremendous potential for ctDNA testing to advance lymphoma treatment, including:

- Early detection and diagnosis
- Differentiating cancer subtypes
- Non-invasive genomic profiling for precision medicine
- Prognostic biomarker
- Treatment response monitoring
- Identifying treatment resistance
- Minimal residual disease monitoring

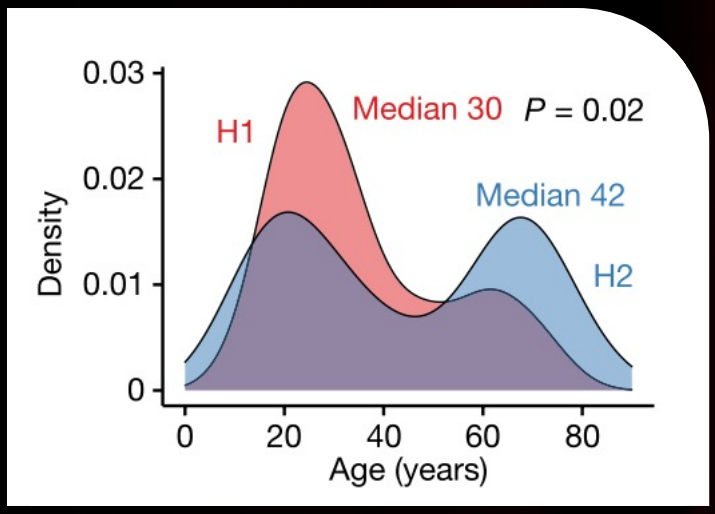
Recent years have seen important breakthroughs correlating ctDNA test results with patient outcomes. For example, a study published in *Blood* in 2017, including normal germline control samples, demonstrated a sensitivity of 82% in detecting tumour mutations in plasma that correlated to mutations in tumour tissue.

A study published in *JCO* in 2018 used the CAPP-Seq assay which targeted over 1000 genomic regions from 268 genes and analyzed samples from over 200 patients. Higher pretreatment ctDNA concentration in the plasma was associated with higher IPI and worse event-free survival. The analysis also revealed that patients with an early molecular response, based on ctDNA, have substantially improved event-free survival, compared to those who don't have an early molecular response.

Building on the CAPP-Seq assay, the PhasED-Seq assesses multiple mutations in DNA fragments to improve the sensitivity of ctDNA detection. Compared to the CAPP-Seq, the PhasED-Seq more strongly predicts outcomes. The probability of EFS remained very high after 60 months in patients with no ctDNA detected by PhasED-Seq.



A study published earlier this year that applied PhasED-Seq to a large cohort of patients with Hodgkin lymphoma revealed two distinct cHL genomic subtypes, H1 and H2. The H1 subtype was more common in younger patients, in their early 20s.



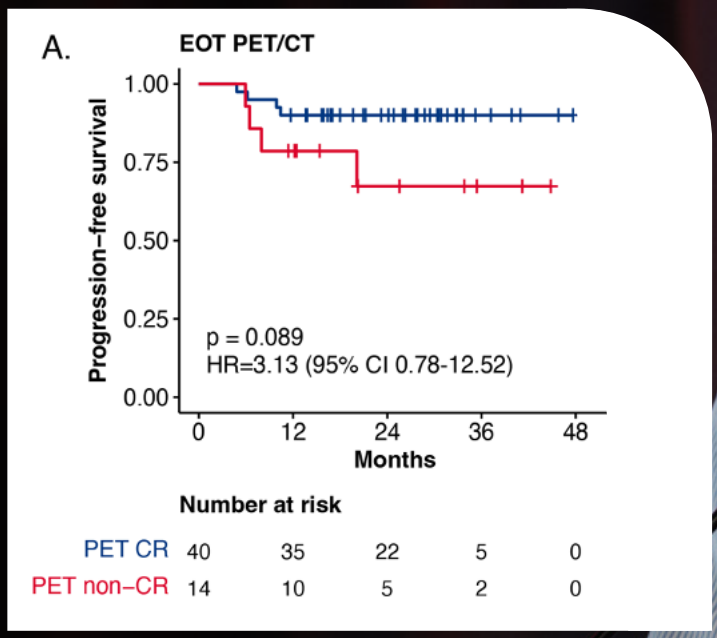
Relevant to potential clinic usage, a study presented at ASH in 2023 revealed ctDNA, evaluated through the PhasED-Seq assay, was more predictive for relapse than end-of-treatment PET scans. Seven of the 14 patients with positive end-of-treatment PET-CT scans had undetectable ctDNA and none of these patients progressed. The 2-year PFS rates for patients with detectable ctDNA was 33%, compared to 98% with undetectable ctDNA.

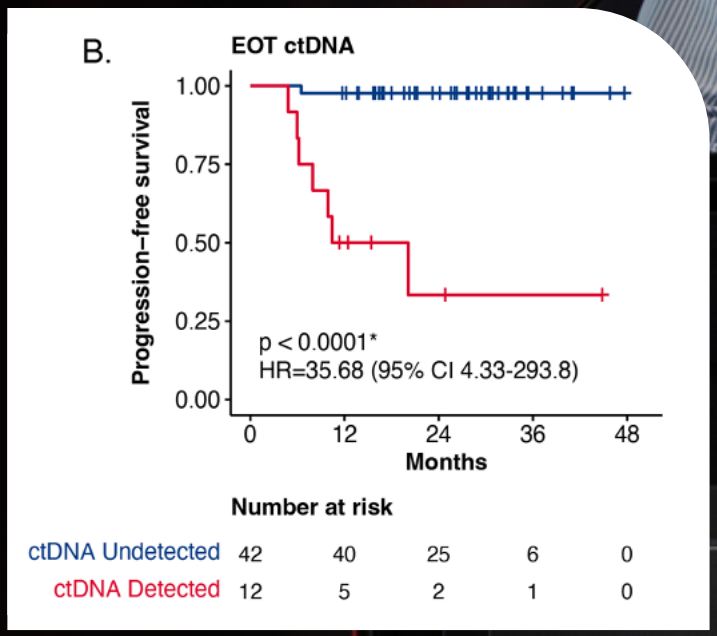
Another important technological innovation is cell-free DNA (cfDNA) methylation profiling, which leverages the methylation patterns of tissue-specific cfDNA. This technology has a broad application for both early cancer detection and monitoring disease progression, positioning it as a promising tool for clinical oncology. The cfMeDIP-seq cfDNA methylation profiling method can distinguish several lymphoma subtypes from healthy controls, most notably Hodgkin lymphoma.

Dr. Kridel and his colleagues at Princess Margaret Cancer Centre are currently enrolling patients with R/R DLBCL to assess the feasibility of

DR. ROBERT KRIDEL

a ctDNA and FDG-PET interim response-adapted approach for primary DLCBL therapy. Patients who have favourable risk results based on ctDNA and PET2 scans will receive abbreviated chemotherapy while those with unfavourable ctDNA or PET2 will receive a novel treatment approach (R-CHOP and glofitamab).





Closing Remarks & Adjournment

DR. JOHN KURUVILLA

Dr. Kuruvilla thanked the sponsors of the event. He thanked the speakers and attendees for their engagement and insights. The meeting was adjourned.

Attendee Feedback

Overall, the topics covered during the conference provided a comprehensive discussion of lymphoproliferative disease.

Clinician feedback survey prompt

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

100% AFFIRMATIVE

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

Clinician feedback survey prompt

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

100% AFFIRMATIVE

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

Clinician feedback survey prompt

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

100% AFFIRMATIVE

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

STRONGLY AGREE	95%
AGREE	5%
DISAGREE	0%
STRONGLY DISAGREE	0%

100% AFFIRMATIVE

Clinician feedback survey prompt

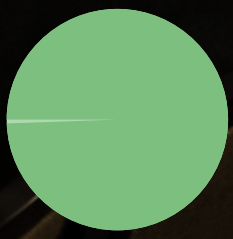
Overall, the conference offered good networking opportunities with colleagues and industry representatives.

STRONGLY AGREE	97%
AGREE	3%
DISAGREE	0%
STRONGLY DISAGREE	0%

100% AFFIRMATIVE

Clinician feedback survey prompt

Overall, the conference was well-organized.



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

100% AFFIRMATIVE

Clinician feedback survey prompt

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