ABOUT THE PANELISTS

Ronan Foley, MD, FRCPC
Dr. Foley is a clinical hematologist with an active practice in malignant hematology at the Juravinski Cancer Centre. He is Director of the Stem Cell Laboratory. Dr. Foley is a Professor of Pathology and Molecular Medicine at McMaster University, Past-President of CBMTG, a Director of the Clinical Trials Network and a member of the NIH Consensus Panel for the Diagnosis and Classification of Chronic Graft vs. Host Disease along with several other affiliations. Other activities include board membership on OCREB and panel chair for the CIHR CBT panel. Dr. Foley's current research focus is the development of therapeutic cell-based autologous vaccines. He has held grants with CANVAC, OICR, CIHR, OCRN, and CBCRA.

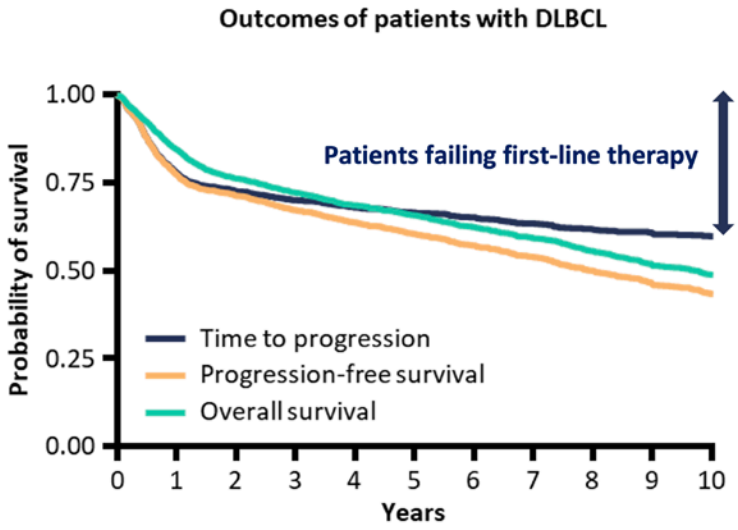
Carolyn Owen, MD
Dr. Carolyn Owen is an Associate Professor in the Division of Hematology & Hematological Malignancies at the University of Calgary. She completed internal medicine training in Ottawa, Hematology training in Vancouver followed by a research fellowship in molecular genetics at Barts and the London School of Medicine in London, UK. Her prior research is focussed on familial myelodysplasia and acute myeloid leukemia. Her current clinical interests are low grade lymphoma and chronic lymphocytic leukemia and she is the local principal investigator at the Tom Baker Cancer Centre for several clinical trials in these areas.

Samer Tabchi, MD
Dr. Samer Tabchi is a hematologist/oncologist currently practicing in Rouyn-Noranda, covering the Abitbi-Temiscaming region of Quebec. He completed his initial medical training in hematology/oncology at Hotel-Dieu de France Hospital in Beirut, Lebanon. He did a Fellowship in thoracic oncology at the Centre Hospitalier de l'Université de Montréal (CHUM) in Quebec, and a second fellowship in lymphoma and myeloma at MD Anderson Cancer Center, Texas. He has also completed an additional Masters in advanced oncology from Ulm University in Germany.

Ghazaleh Shoja E Razavi, MD, PhD
Dr. Ghazaleh graduated from medical school in 1997 and gained her board certification in general internal medicine in 2002. She achieved further board certification in hematology and medical oncology in 2006. Dr Razavi conducted Immuno-oncology research at Georgia Cancer, University of Augusta in 2016 and completed her clinical fellowship in malignant hematology and stem cell transplantation with the Saskatoon Cancer Agency in 2017. She is a practicing hematologist and clinical assistant professor at the University of Calgary since 2019.

PANEL DISCUSSION:
TREATMENT OPTIONS FOR RELAPSED/REFRACTORY DIFFUSE LARGE B CELL LYMPHOMA (R/R DLBCL) PATIENTS

Approximately 40% of Diffuse large B cell lymphoma (DLBCL) patients relapse or do not respond to first line therapy. Deciding whether to pursue intensive therapies in these patients is complex, given the limited therapeutic access landscape for R/R DLCBL patients, as well as the risk of serious adverse events. Emerging therapies open up new possibilities.



Adapted from Sehn, Laurie H., and Gilles Salles. New England Journal of Medicine, 2021

Ronan Foley (Moderator): When a DLBCL patient is relapsing or refractory to R-CHOP, what are the main clinical and non-clinical reasons a patient would not pursue autologous stem cell transplant (ASCT) or CAR-T?

Carolyn Owen: A patient who is not eligible for a 100% dose of R-CHOP is also likely not eligible for a stem cell transplant. This includes patients over age 75 with aggressive lymphoma. I would also include those above 70 who were unable to complete their planned 6 treatment courses with R-CHOP due to tolerance. We usually don't use CAR-T therapy for patients who are not eligible for another intensive therapy (particularly as current funding requires patients to fail 2 lines of curative intent treatment). Tafasitamab plus lenalidomide (TAFA + LEN) can be appropriate in these patients, if they aren't too unwell. We also give continuous oral chemotherapy as palliative care, such as procarbazine, cyclophosphamide, prednisone, whichever they tolerate best.

Samer Tabchi: The patient's comorbidity index and organ compromise are often factors that make me decide not to pursue ASCT. Age also plays a role, as we usually don't pursue autografts in patients above 70 to 75 years of age. However, there is a wide spectrum of reserve status and fitness levels among older patients.

Ghazaleh Razavi: The other group that we usually consider ineligible for ASCT transplant are patients who are primary refractory to chemotherapy, meaning that the disease progresses after three or four cycles of chemo, or early relapse patients, within the first six months of R-CHOP chemotherapy. If the cells are not responsive to chemotherapy, then a high-dose chemotherapy will not work either.

R.F.: Are there patients who are considered ineligible for an autograft, but could be considered for CAR-T cell infusion?

C.O.: Yes, but that's a pretty small group of patients. Most of us are still not comfortable giving an auto transplant to a patient who is above 75 years of age, even without any comorbidities. Some of these patients may be eligible for CAR-T therapy. Based on our current funding definition, they need to be fit enough to get a second intensive therapy, such as rituximab, gemcitabine, cisplatin, and dexamethasone (RGDP) or gemcitabine/oxaliplatin (Gem-Ox).

S.T.: For patients who may not be eligible for CAR-T therapy, you also have to consider logistics. Patients who don't have access to tertiary care centres may prefer less intensive therapy. I recently had this experience with an older patient who would have potentially been eligible for CAR-T therapy, but, after discussion, opted for TAFA+LEN.

G.R.: CAR-T therapy is very limited in 3L+ DLBCL patients especially if the disease is rapidly progressing. In this clinical setting, you don't have a good bridging therapy to reduce lymphoma burden prior to CAR-T. The other limitation with CAR-T is keeping the patient's performance status to a level so that the patient will still be eligible for another curative line of treatment.

R.F.: Has the recent emergence and approval of newer therapeutic options to treat non-transplant-eligible R/R DLBCL changed your practice or treatment goals? Do your patients have access to all these newer options?

S.T.: TAFA+LEN would be at the top of the list because it's currently accessible through the manufacturer's compassionate use program. Unfortunately, in Quebec polatuzumab vedotin, bendamustine and rituximab (POLA-BR) was not funded. TAFA+LEN offers a compelling rationale, with promising duration of response and complete response data. This makes it a very good option for those patients who might not have access to other therapies.

G.R.: TAFA+LEN is the most practical, as it's an oral agent combined with a monoclonal antibody, and it doesn't increase the risk of infection. However, sometimes you may not achieve a complete response with TAFA+LEN in some patients. POLA-BR has a much higher toxicity, and the availability of this therapy is a concern, especially in small centres.

R.F.: What about the bispecific T-cell engager (BiTE)s – mosunetuzumab, glofitamab, or epcoritamab – as an alternative to CAR-T therapy?

S.T.: Definitely, if these agents are accessible in the community setting, they could be potentially managed without the need for a complicated support system to manage toxicities.

C.O.: It would be great to be able to have mosunetuzumab, glofitamab, or epcoritamab as an option for the patients that aren't eligible for CAR-T therapy. However, there are not that many patients who can fail R-CHOP, fail another intensive line of therapy, and are well enough to pursue the bispecific antibodies, as they still have some toxicity and currently all require clinical trials for access.

R.F.: Do you see a role for emerging medications, such as Bcl-2 inhibitors, selinexor, or ibrutinib?

C.O.: Ibrutinib data in systemic DLCBL is rather poor. Selinexor has concerning adverse effects. I am most hopeful about the bispecific antibody class, but they're competing in a very saturated space. I don't see them coming to our clinics as fast as we would like.

R.F.: In your practice, what is the proportion of potential CAR-T patients that end up actually receiving CAR-T?

S.T.: Approximately 60% of the patients I refer will eventually get CAR-T Cells. Those who don't end up receiving it are often excluded because of frailty. Uncontrolled CNS involvement may preclude CAR-T and a high tumor burden is also associated with inferior outcomes and more toxicity. This raises the question of the optimal bridging therapy.

C.O.: I would say my success rate has been less than 60%. Our overall use of CAR-T therapy has been significantly less than what the province predicted. It's not based on the biology of the disease, but the progressive nature of the disease. The patients who have progressive disease, despite intensive therapies, usually either don't make it to CAR-T therapy or will not do well with it. Even though it may take only three to four weeks in a tertiary care centre to collect, prepare, and manufacture CAR-T cells, very active disease can often progress in those few weeks to the point where patients are no longer eligible.

R.F.: Let's discuss a case. John is a 77-year-old male that achieved DLBCL remission with R-CHOP as a first line therapy. John recently relapsed after 7 months and is non-transplant eligible due to not being a candidate for salvage chemotherapy. John's had bad experience with hospitalization, adverse events and reduced mobility. John's ECOG is 1-2 and he needs to rely on friends and/or family. John fears complex treatments that require hospitalization and trusts the close relationship with his local care team. What would you propose as a second line treatment for John?

S.T.: Given that we don't have access to Pola-BR in Quebec, I would look to TAFA+LEN. He doesn't want complex therapeutics or hospitalization, so CAR-T cells are probably off the table.

R.F.: My two cents is, given he has relapsed within 12 months, if you look at the CORAL or LY.12 or the recent control arms of the Belinda, Zuma 7 and Transform trials, the event-free survival for this specific group of patients with an autograft is limited. Event-free survival would be 15% to 20%.

G.R.: TAFA+LEN is a good choice, especially if the patient's overall condition is not great due to the lymphoma itself. However, Pola-BR may also be another option. In the latter, you would have to consider the risk of cytopenias and subsequent infections.

C.O.: I would consider Pola-BR or TAFA+LEN. It's a difficult decision, because the studies are small and the patients in the clinical trials were not as sick as our patients in our practices. In my practice, it's easier for us to get Pola-BR than to use the compassionate program to get TAFA+LEN. I would want the patient to participate in the decision.

R.F.: For non-transplant-eligible R/R DLBCL patients like John, what rate and duration of response would you expect with your selected treatment option?

S.T.: We know there is a 60% response rate, with 40% having complete responses with TAFA+LEN. Approximately 80% of these patients maintain these responses three years out.

G.R.: If you want a longer duration of response, TAFA+LEN would be a better option because the duration of response with Pola-BR isn't as long. If you want to reduce a high burden of lymphoma in a short period of time, Pola-BR is a good option. I would choose either therapy according to the tumor burden, and how rapidly it is progressing, and drug availability. TAFA+LEN is usually easier to handle in a community-based practice.

R.F.: Regarding Pola-BR's Phase II data, what do you think is the most clinically relevant data? In what patient type would you be using this regimen over R-Chemo?

G.R.: I have only used Pola-BR so far in a couple of patients, but it has been better tolerated compared to RGDP, which has been considered the salvage chemotherapy option. R-GemOx is a better tolerated salvage chemotherapy option, but it also comes with risks of febrile neutropenia and thrombocytopenia.

C.O.: It's hard to take too much from the data, because it's a randomized phase II study, against a non-standard comparator. Our guidelines have been recommending against giving everybody Pola-BR as a salvage therapy, because it's very expensive, and still a palliative therapy. With better progression-free survival in the Phase II study, there is a subgroup of patients who probably should be targeted for Pola-BR. But I wouldn't say we should give it to everybody.

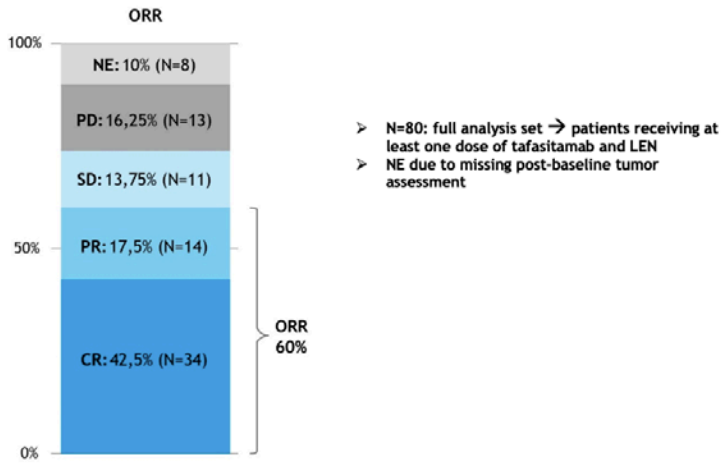
I think the clinically relevant data is overall survival in a real-world population. It's an economic analysis, and whether the clinical outcomes justify the cost. The reality is nothing works great in the relapse setting so it's rather futile to be giving expensive novel therapies for DLBCL in 3rd line and beyond. However, if a new agent is really effective, it will find a place earlier in therapy, and that's where the patients will benefit the most.

S.T.: I managed to get a patient to stem cell transplant with Pola-BR and he still has a complete response two years later. The problem with the usual palliative salvage regimens is that they can be difficult to manage with modest response rates and overall survival according to the benchmark established by the SCHOLAR study. I would probably consider Pola-BR as well if it were accessible.

In the third line setting, it's always difficult to do the Phase III studies we want to have, so unfortunately, we do have to rely on Phase II data.

R.F.: One of the newer therapeutic options is tafasitamab + lenalidomide. What is the most clinically relevant data for this drug? In what patient type would you be using this regimen over R-Chemo and why?

G.R.: The L-MIND study data is relevant, as it aimed to include the patient population that would receive this treatment in the real world. We've been using lenalidomide for more than 20 years. The side effects are more manageable, compared to a combination of chemo plus a monoclonal antibody. I have a patient who has been on TAFA+LEN for 18 months. She hasn't had a single hospital admission. She has had no neutropenia, and her hemoglobin is almost unchanged. She hasn't had a complete response, but her disease is stable. The patient's quality of life and tolerance to this treatment is significantly better compared with those patients I've had on RGDP, who have frequently been admitted to the hospital with febrile neutropenia. In light of the safety profile and the response rate, TAFA+LEN is the preferred treatment choice over chemo-immunotherapy, such as R-GDP or R-GemOx in this clinical setting.



CR, complete response; LEN, Lenalidomide; NE, not evaluable; ORR, overall response rate; PET, positron emission tomography; PR, partial response; PD, progressive disease; SD, stable disease

L-MIND study Primary endpoint: Overall Response Rate (ORR) by IRC; Adapted from Salles G et al, Lancet Oncol. 2020

S.T.: The duration of responses, the overall responses, and the survival rates in the L-MIND study are compelling, given such low survival in this setting. I usually start with TAFA+LEN in patients with R/R DLBCL, rather than starting with R-chemo. In the L-Mind study, patients who received TAFA+LEN after one only one line of therapy seemed to have better outcomes than patients who had two or more lines of therapy. However, the small number of patients in the study should be taken into consideration.

C.O.: The PFS curve that you see with the L-MIND study, and the way it continues flat, is really compelling. I'm not sure we'll see the same results in the real world. But, if even one out of ten patients could be potentially cured, that's worth it.

R.F.: Thank you very much, everyone. There is a huge unmet need with R/R DLCBL patients, and I appreciate you speaking so openly and insightfully on this challenging area. While access remains an ongoing challenge, the use of emerging therapies in this patient population holds much promise and as clinicians we are encouraged by the both the published and real-world data that we see with some of these agents.