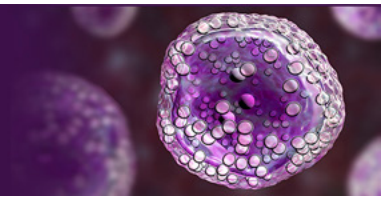
MANAGEMENT OF LARGE B-CELL LYMPHOMAS:
A CRITICAL UPDATE ON RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA AND CAR T-CELL THERAPY



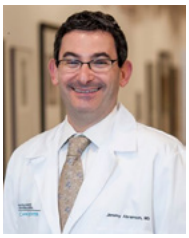
OVERVIEW

B-cell lymphomas consist of a heterogenous group of lymphoproliferative neoplasms originating from B-lymphocytes. Large B-cell lymphomas (LBCLs) are one of the most common subtypes of non-Hodgkin lymphomas and while first-line standard of care has remained unchanged, the treatment paradigm has undergone a shift in recent years due to the development of novel therapeutic agents. These novel therapies include monoclonal antibody (mAb) therapies, mAb-conjugates, and chimeric antigen receptor (CAR)-T cell therapies. Management of relapsed/refractory LBCLs remains a substantial and persistent clinical challenge, including optimal treatment sequencing, therapy evaluation and patient selection, and toxicity management. In this activity, Jeremy Abramson, MD, highlights the significant disease burden of B-cell lymphomas, as well as the latest advances in therapeutics, and practical strategies for integrating novel therapies into practice through patient selection and supportive care management.

CONTENT AREAS

- Clinical features and disease burden
- Novel therapies
- Treatment of relapsed/refractory LBCL
- CAR-T patient selection
- Adverse events

FACULTY



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CE INFORMATION

TARGET AUDIENCE

This activity is intended for regional and national audiences of hematologist-oncologists, pathologists, histologists, advanced practitioners, oncology nurses, pharmacists, and other healthcare professionals involved in the care of patients diagnosed with LBCL.

LEARNING OBJECTIVES

- Review the disease state, clinical and molecular heterogeneity, and unmet needs, including the clinical and healthcare resource burden of LBCL
- Describe the mechanism of action and appraise available clinical safety and efficacy data and indications for new agents for the treatment of LBCL, especially R/R LBCL, to select optimal treatments
- Integrate approaches for identifying patients eligible for chimeric antigen receptor T-cell (CAR T-cell) therapy and applying suitable bridging therapies
- Incorporate approaches for identifying, monitoring, and managing therapy-associated toxicities and AEs, including CAR T-cell–associated toxicities, for patients with LBCL

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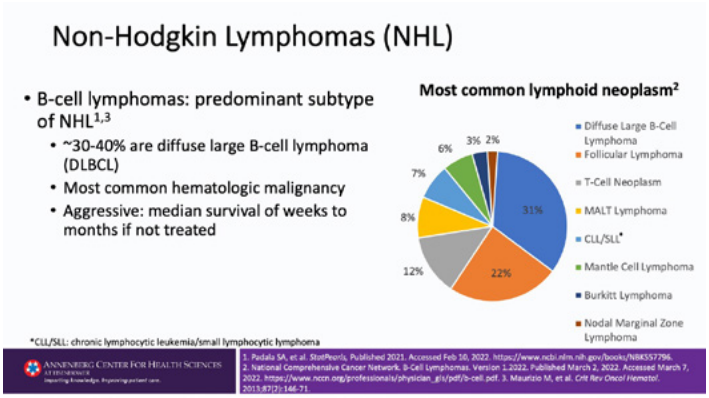
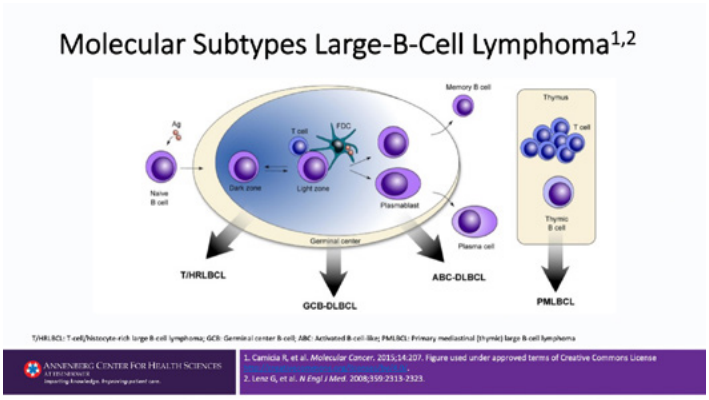
Editor's Note: This is a transcript of a presentation on April 9, 2022. It has been edited and condensed for clarity.

Module 1: Disease Burden and Overview of Large B-Cell Lymphomas

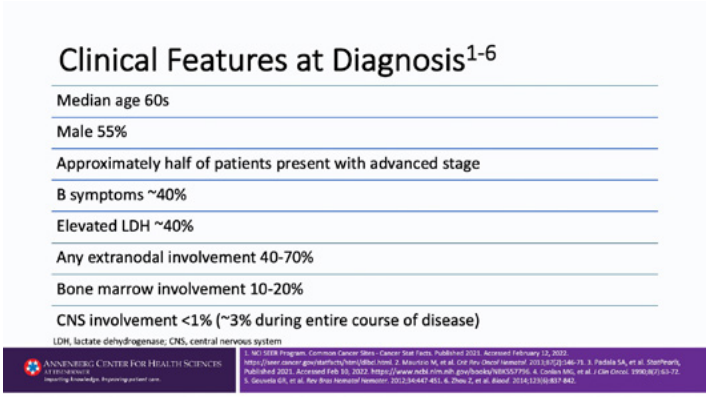
Non-Hodgkin lymphoma (NHL) represents one of the most common cancers, with about 70,000 new cases diagnosed every year. The most common subtype of non-Hodgkin lymphoma is diffuse large B-cell lymphoma (DLBCL) which is an aggressive malignancy and is uniformly fatal if left untreated. However the majority of patients today will be cured of diffuse large B-cell lymphoma with increasingly effective options available in the second-, third-line and later lines for relapsed/refractory disease, if needed.



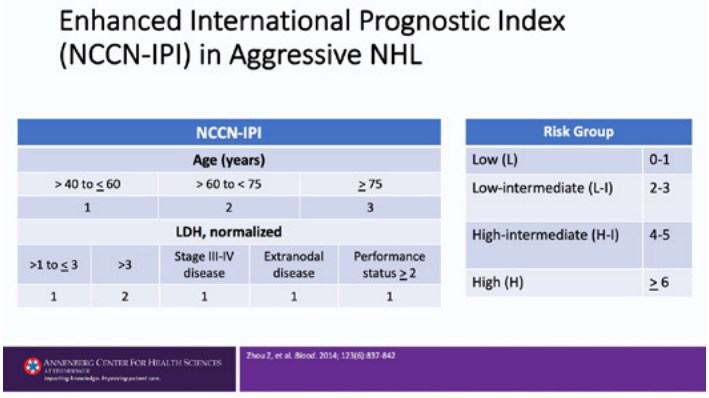
Diffuse large B-cell lymphoma is a clinically and biologically heterogenous disease. We can see multiple different clusters within diffuse large B-cell lymphoma. We commonly describe DLBCL as being either activated B-cell (ABC) type or germinal-center B-cell (GCB) type, reflecting their relationship to normal cells of origin, with the germinal-center subtype of DLBCL having an improved prognosis relative to the ABC-like DLBCLs. Other unique subtypes of diffuse large B-cell lymphoma include primary mediastinal B-cell lymphoma, derived from thymic B-cells, as well as T-cell/histocyte-rich B-cell lymphoma.



In general, DLBCL is a disease of older adults, with a median age in the mid to late 60s. There is a roughly equal male to female predominance of this disease. About half of patients will present at stage III or IV disease and half will present at limited stage or stage I and II. About 40% of patients will have B-symptoms of fevers, drenching night sweats or unintentional

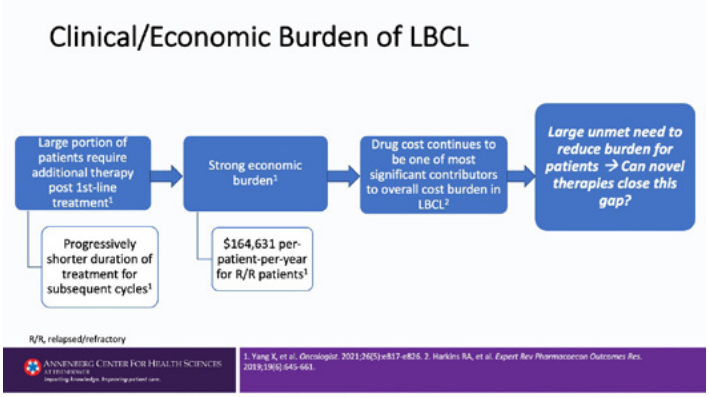


weight loss at the time of diagnosis. About 40% will have an elevated lactate dehydrogenate (LDH), but absence of these symptoms and normal LDH by no means rules out an aggressive, underlying lymphoma, and only a biopsy ultimately gives us the diagnosis. Extranodal disease is common in DLBCL, presenting in just more than half of patients. Bone marrow involvement is uncommon, seen in ~10% to 20% of patients. And involvement of the central nervous system is uncommon, only ~1% at the time of diagnosis, but ~3% of patients with DLBCL can experience central nervous system (CNS) involvement during their disease, which is a particularly challenging clinical scenario to deal with.



We risk-stratify patients using the International Prognostic Index (IPI) which incorporates advanced age, advanced stage, elevated LDH, involvement of multiple sites of extranodal disease or poor performance status. This newer update of the IPI, called the NCCN (National Comprehensive Cancer Network) IPI, can identify 4 risk groups. The lowest risk group has a cure rate of just over 90%. The intermediate, low-intermediate and high-intermediate, risk groups show that the majority of these patients will be cured of their diffuse large B-cell lymphoma with the high-risk groups still identified where only about a third of patients can expect to be cured with standard initial therapy. These data highlight the optimism with DLBCL being a highly-treatable and highly-curable disease, but remind us there is still work left to do, particularly in high-risk patients.

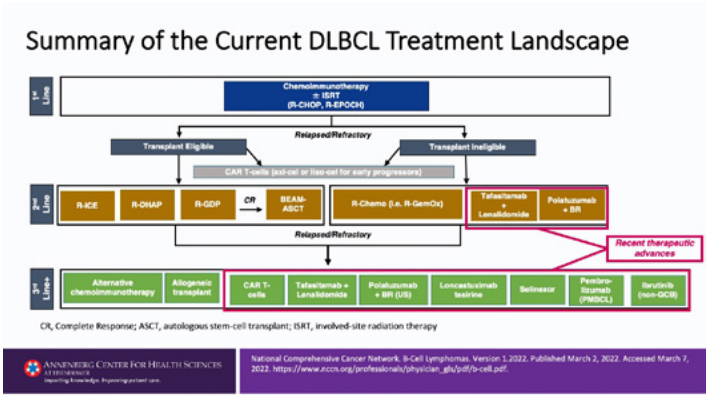
About 30% to 40% of patients will relapse after initial therapy. This creates a significant clinical burden in management of these patients and also an economic burden, as the management of relapsed disease, including multiple relapses, can be a significant cost to the system, particularly with newer drugs which cost a significant amount of money relative to our



older generic options. But it is important to note that newer drugs, even with their cost, ultimately can save money by curing more patients and preventing the need for additional lines of therapy in the future.

Module 2: Treatment of Large B-Cell Lymphoma: MOA and Clinical Efficacy Data of Novel Therapies

The modern era of management of diffuse large B-cell lymphoma was ushered in with the introduction of rituximab to the cyclophosphamide + doxorubicin + vincristine + prednisone (CHOP) regimen. The landmark Groupe d'Etude des Lymphomes de l'Adulte (GELA) trial, which was initially published in 2002 in the New England Journal of Medicine, in older adults with diffuse large B-cell lymphoma, clearly showed a substantial improvement in overall survival with the addition of rituximab to CHOP compared to CHOP alone. More contemporary data, from the GOYA trial, which compared rituximab-CHOP to obinutuzumab-CHOP, and found no added benefit to obinutuzumab, does show the ongoing persistence of benefit for the rituximab-CHOP (R-CHOP) regimen with cure seen in about 70% of patients treated with R-CHOP in the GOYA trial.



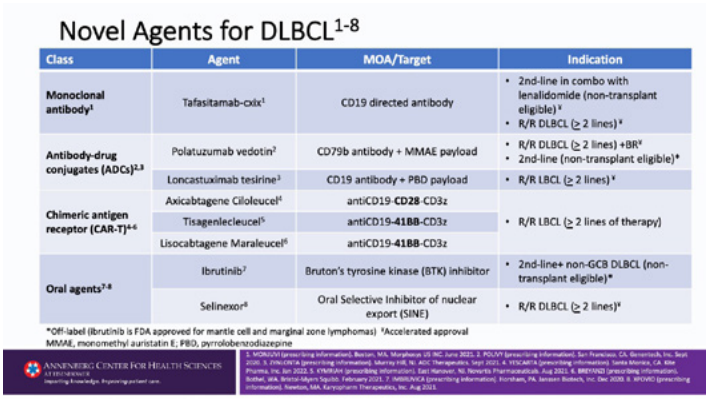
There is an increasingly complicated landscape at the time of relapsed/refractory disease. Typically, when patients relapse after initial therapy of diffuse large B-cell lymphoma, we consider whether they are eligible for transplant or not, meaning high-dose chemotherapy with autologous stem cell support. Historically, patients who are considered sufficiently young and fit to undergo high-dose chemotherapy would receive a platinum-based, second-line regimen, such as R-ICE (rituximab + ifosfamide + carboplatin + etoposide), R-DHAP (rituximab + dexamethasone + cytarabine + cisplatin) or R-GDP (rituximab + gemcitabine + cisplatin) and go to BEAM (carmustine + etoposide + cytarabine + melphalan)-conditioned auto stem cell transplant for chemotherapy-sensitive disease, whereas transplant-ineligible patients would be treated with a palliative-intent regimen without the goal of cure.

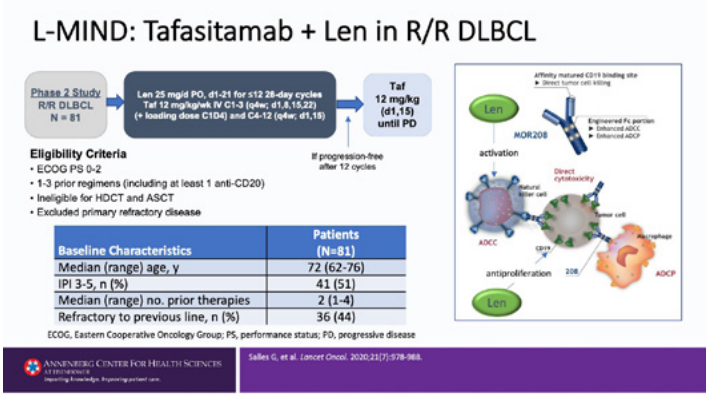
This has actually been turned on its head recently with the presentation of 2 important trials which compared anti-CD (cluster of differentiation) 19-CAR (chimeric antigen receptor) T-cells to a salvage chemotherapy and transplant-based approach in patients with early relapsed or primary refractory DLBCL. And 2 of those clinical trials, using either axicabtagene ciloleucel (axi-cel) or lisocabtagene maraleucel (liso-cel), showed significant superiority of CAR T-cells in the second-line setting for those high-risk patients.

So today, at first relapse, for a patient who's relapsing early or is primary refractory, we would ask not are they transplant-eligible, but are they CAR T-cell-eligible? And for a patient who is a candidate for CAR T-cells and has access to CAR T-cells, either axi-cel or liso-cel would be the best possible second-line treatment. For patients who are transplant-eligible and relapsing later, meaning beyond 1 year from their initial chemo-immunotherapy, then standard salvage chemotherapy and transplant can still be considered for those patients. Whereas transplant-ineligible or CAR T-cell-ineligible patients would still be considered for palliative-based approaches which, today, would include newer options, including tafasitamab-lenalidomide and polatuzumab combined with bendamustine and rituximab (BR). And the next line of setting, you have even more options available. We still have CAR T-cells available in the third-line or later setting for patients who did not receive them in second-line. Tafasitamab/lenalidomide and polatuzumab BR are available for patients who didn't receive them in second-line, and additional newer agents, including the anti-CD19-directed antibody drug conjugate, loncastuximab tesirine, XPO1 (exportin 1 gene) inhibitor selinexor, or in certain subsets of patients, other novel agents, such as the immune checkpoint inhibitor, pembrolizumab, in primary mediastinal B-cell lymphoma or the BTK (Bruton's tyrosine kinase) inhibitor, ibrutinib, in non-germinal-center activated B-cell type diffuse large B-cell lymphoma.

Here is a quick summary of some of those drugs, highlighting their mechanism of action, be they the anti-CD19 antibody, tafasitamab combined with lenalidomide, the anti-CD79b antibody drug conjugate, polatuzumab combined with BR, loncastuximab tesirine, as I already mentioned, any of 3 available CAR-T cells in the third line or later setting, as well as BTK inhibitors and the XPO1 inhibitor, selinexor.

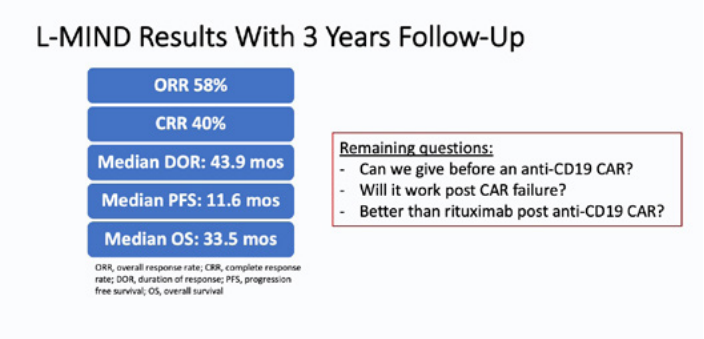
The L-MIND trial evaluated tafasitamab, the anti-CD19 monoclonal antibody, combined with lenalidomide with the goal of enhancing antibody-dependent cell-mediated cytotoxicity. The lenalidomide was administered





at 25 mg a day on days 1 through 21 of each 28-day cycle for up to 1 year. Often, patients required dose-reductions as that can be a high dose and result in significant cytopenias. The tafasitamab was administered intravenously once a week for the first 3 months and then once every other week until progression, which is a lot of infusions for patients who are maintaining response. These eligibility criteria veered towards a lower-risk patient population overall. These patients had to be considered transplant-ineligible, but could have received no more than 3 prior lines of therapy, and this study excluded patients with primary refractory disease as well as patients with double hit lymphoma. This was a lower-risk patient population.

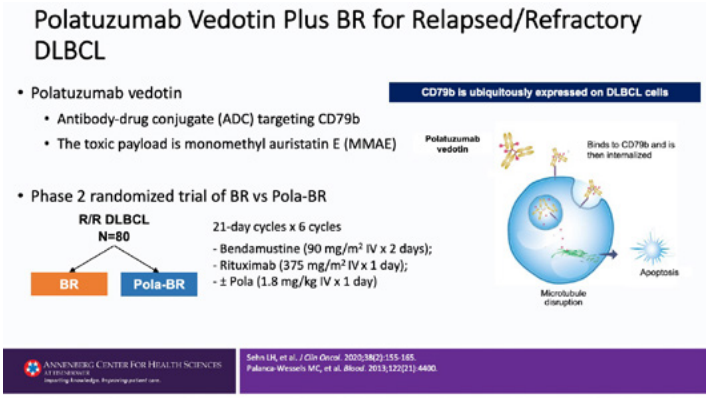
Eighty-one patients were enrolled. The median age was an older population, at 72 years old. Half of these patients had IPI scores of 3 to 5. The median number of prior regimens was 2, but a number of patients were receiving this as second-line therapy after just 1 prior treatment and 44% of patients were refractory of their prior line of therapy. Again, none of the patients were primary refractory to their up-front regimen.



The response rates and durability actually appear quite excellent. The overall response rate is 58%, with a complete response rate of 40%. With extended follow-up now beyond 3 years, the median duration of response among responding patients was a very encouraging 43.9 months. The median progression-free survival for the entire population was 11.6 months and the median overall survival was just under 3 years. Responding patients can have encouraging durability of their responses, particularly in the second-line setting where tafasitamab-lenalidomide has become my preferred option for a nontransplant, non-CAR T cell-eligible patient in the second-line treatment setting for diffuse large B-cell lymphomas.

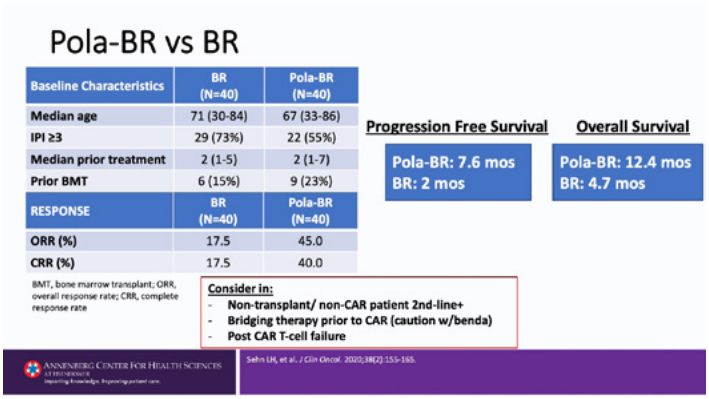
There are some remaining questions related to this drug. It does target CD19, which is the same target as CAR T-cells, which we use with a goal of cure. Can we give tafasitamab prior to CAR T-cells in a patient we might ultimately take to CAR T-cell therapy in the third-line setting? We don't know yet whether giving a prior CD19-directed regimen might impair the curative intent of a subsequent CAR T-cell, so in general I currently avoid the use of a different CD19-directed regimen in the second-line setting for a patient I intend to take to a CD19-directed CAR T-cell if needed in the third-line setting. For a patient without intent to ultimately take to a CAR T-cell, I think this would be reasonable as a second-line option.

The other natural question is will it work after CAR T-cell failure, meaning in a patient who's received CAR T-cells and subsequently relapsed? We have no data in that setting, but that warrants ongoing investigation and it's certainly an FDA (US Food and Drug Administration)-approved, available option for a patient who's relapsing after CAR T-cells. Is tafasitamab better than rituximab in the setting of CAR T-cell failure? We don't know. Neither has been studied in that context, but if we're using lenalidomide, then the tafasitamab-lenalidomide regimen, based on the L-MIND data, is my preferred approach when using a lenalidomide-based therapy now in diffuse large B-cell lymphomas.



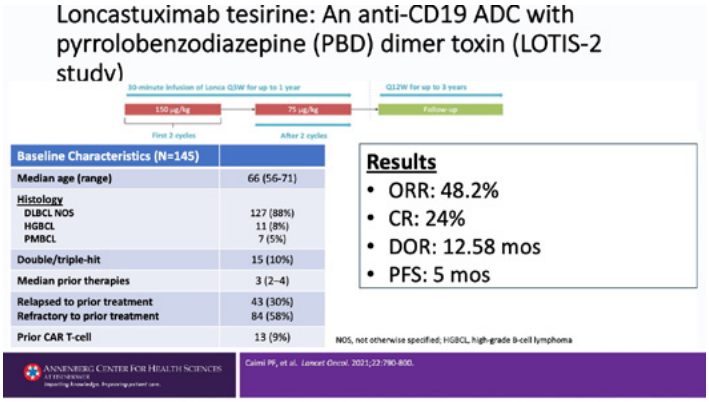
Polatuzumab vedotin is another appealing option that can be used as early as second-line therapy and, may even be appropriate in the front-line setting. But in the relapsed/refractory setting, polatuzumab vedotin was combined with bendamustine/rituximab (Pola-BR) and compared to BR alone in patients with relapsed or refractory DLBCL. Polatuzumab is an anti-CD79b monoclonal antibody covalently linked to monomethyl auristatin E (MMAE), which is a microtubule toxin, in this antibody drug conjugate. Patients received fixed-duration therapy with Pola-BR administered on days 1 and 2 of a 21-day cycle for a total of 6 cycles.

Forty patients were treated in both arms. The median age was 70 years. Most of these patients did have high IPI risk disease and the median prior regimens was 2. The overall response rate was 45%, with 40% of patients achieving a complete response. A similar complete response rate as was seen in the L-MIND trial of tafasitamab-lenalidomide.



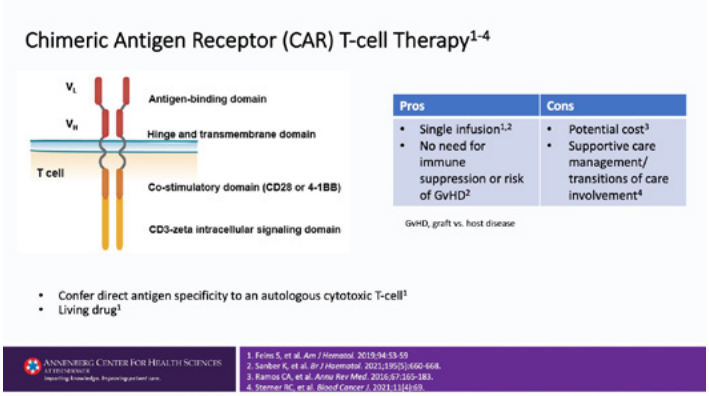
The progression-free survival was substantially better for Pola BR compared to BR alone. BR performed fairly badly in this trial, with a median PFS (progression-free survival) of only 2 months and a median PFS of the Pola BR arm of 7½ months. This doesn't look quite as favorable as the tafasitamab-lenalidomide data where the progression-free survival is closer to 1 year, but this population had some higher-risk patients than the L-MIND trial, and also the L-MIND regimen administers ongoing tafasitamab every 2 weeks until progression, whereas this has a fixed-duration regimen. These are all considerations that can be taken into account when selecting second-line or later therapy for patients with DLBCL.

I consider Pola-BR a good option in nontransplant, non-CAR T-cell patients in the second-line or later setting. For a patient who might go to CAR T-cells in the third-line setting, I will often use Pola-R (polatuzumab vedotin + rituximab) in the second-line if I need that regimen or as bridging therapy, but I'll avoid the use of bendamustine in that context because I don't want to poison the patient's T-cells with bendamustine if I might ultimately want those T-cells to be manufactured into CAR T-cells. I do use polatuzumab/rituximab in patients who are relapsing after CAR T-cell therapy as well, and I also have caution using bendamustine in the post-CAR T-cell setting as those patients are often very chemotherapy-refractory and have also received fludarabine as part of their lympho-depleting chemotherapy and so they might have very little hematologic reserve for the bendamustine. But polatuzumab/rituximab, even without the bendamustine, can be a very effective treatment for relapsed and refractory DLBCL.



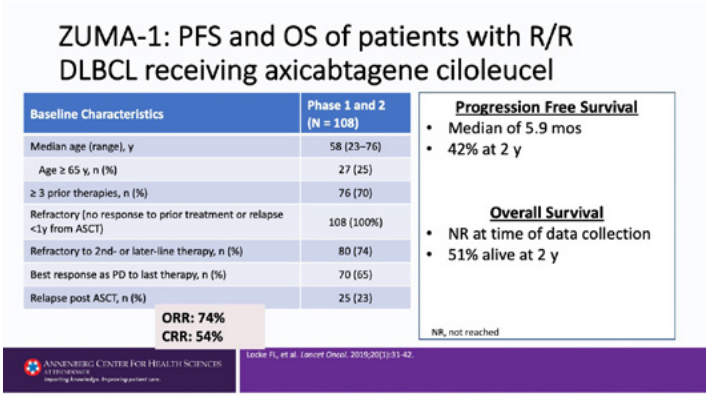
Loncastuximab tesirine is another antibody drug conjugate (ADC). This drug also targets CD19 and this uses a pyrrolobenzodiazepine (PBD) dimer toxin and was studied in the LOTIS-2 trial. This was a monotherapy trial of loncastuximab tesirine in 145 patients with relapsed/refractory DLBCL. This was also time-limited therapy which was given every 3 weeks for up to 1 year of treatment. This was a high-risk population. Patients had a median age of 66. This did include patients not only with DLBCL, but also patients with high-grade B-cell lymphoma, including 10% of patients with double-hit lymphoma. These were more heavily pretreated patients than in either the L-MIND study or the study of polatuzumab-BR. These patients had a median of 3 prior lines of therapy and 58% of them were refractory to their prior line of therapy. Nine percent of patients had relapsed after a prior CAR T-cell. Despite the high-risk nature of this population, the overall response rate was 48%, with half of those patients achieving a complete response.

The median duration of response among the 70 responding patients was quite good, at about 13 months, with a median progression-free survival for the entire population of 5 months. There is a unique toxicity profile associated with loncastuximab tesirine. You can see cytopenias. You can also see some nausea and vomiting as with many chemotherapy agents, including antibody drug conjugates. You can see some LFT (liver function test) elevations with loncastuximab and a unique toxicity is a peripheral edema syndrome, mitigation of which requires a dexamethasone pretreatment with dexamethasone administered the day before, the day of, and the day after each loncastuximab tesirine treatment.



Turning attention to chimeric antigen receptor modified T-cells. These important drugs offer the opportunity for cure in patients with previously incurable relapsed or refractory DLBCL, and a chimeric antigen receptor incorporates a direct antigen-binding domain, usually CD19, that is linked intracellularly to a costimulatory domain, usually 4-1BB or CD28, to fully activate the T-cell in concert with the CD3-zeta intracellular signaling domain.

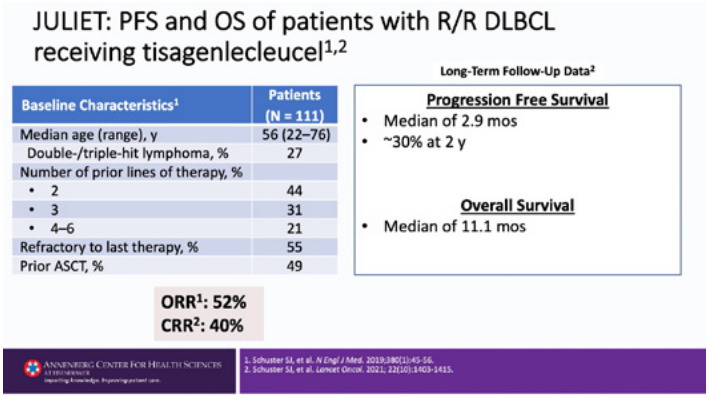
This chimeric antigen receptor is transduced into the T-cell using a lentiviral or retroviral vector. Those cells are then propagated ex vivo and then reinfused into the patient after administration of lymphodepleting chemotherapy to prevent rejection of the modified T-cell. This is a single infusion of a living drug, and it can ideally eradicate disease in a way that, unlike allogeneic transplant, requires no immunosuppression and no risk of graft vs host disease. There are, of course, costs associated with this regimen. There are logistics associated with the apheresis and manufacturing, and unique approaches to supportive care and management of immune-related toxicities.



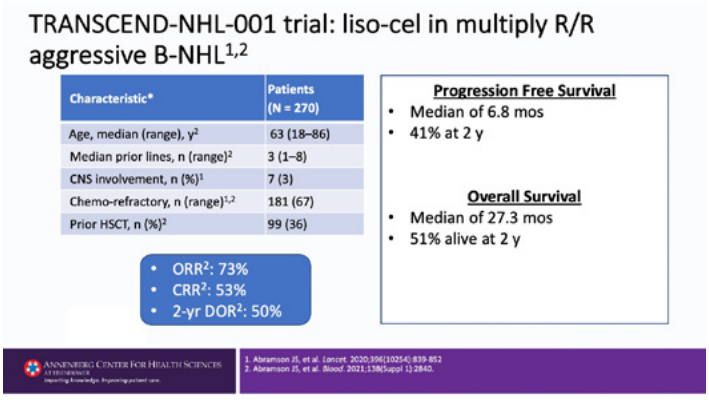
The first approved CAR T-cell for diffuse large B-cell lymphoma was axicel, which was studied in the ZUMA-1 trial in patients with chemotherapy-refractory DLBCL. The median age in the ZUMA-1 trial was 58 years. A quarter of patients were 65 years or older, who might not be considered candidates for stem cell transplant, for example. These were heavily pretreated by definition, 100% of these patients were chemotherapy-

refractory, defined as having no response to their prior treatment, or relapsing within 1 year of an autologous stem cell transplant.

The overall response rate in this trial was a remarkable 74%, with 54% of patients achieving a complete response, and the progression-free survival curve shows durable responses with 42% of patients progression-free and alive at 2 years, meaning cured at that time point. Just over half of patients remain alive at 2 years, which is significantly better than what one would expect with conventional therapies.



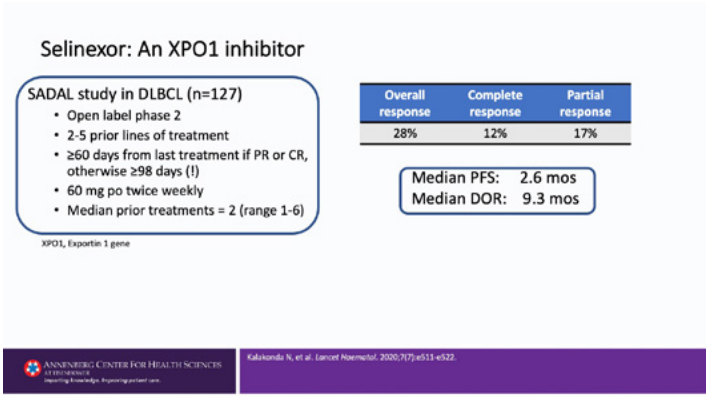
The JULIET trial studied tisagenlecleucel (tisa-cel) in a similar population, though slightly lower-risk because these patients were not required to be chemotherapy refractory. A quarter of these patients had double-hit lymphoma and just over half of patients were refractory to their immediate prior line of therapy. About half of these patients had relapsed after prior auto transplant. The overall response rate was 52%, with 40% of patients achieving a complete response. Two years later, about 30% of patients remain in ongoing progression-free survival.



The TRANSCEND trial evaluated the third CAR T-cell product evaluated in multiply relapsed large B-cell lymphoma. This is a study of lisocabtagene maraleucel or liso-cel. Liso-cel was studied in the TRANSCEND trial, which was the largest CAR T-cell trial reported to date, with 270 evaluable patients. This study included patients that previously were not included in any pivotal trial for CAR T-cells. That included patients with secondary CNS involvement by their lymphoma. It also included patients with grade 3B follicular lymphoma (FL) and patients with transformed lymphoma from diseases other than follicular lymphoma, meaning transformed marginal zone, small lymphocytic lymphoma and Waldenstrom's who were excluded from other studies.

This study also did not require any minimal hematologic parameters, no minimal absolute lymphocyte count and allowed patients with moderate renal or cardiac dysfunction. Potentially enrolled more of a real-world population of patients with relapsed/refractory DLBCL.

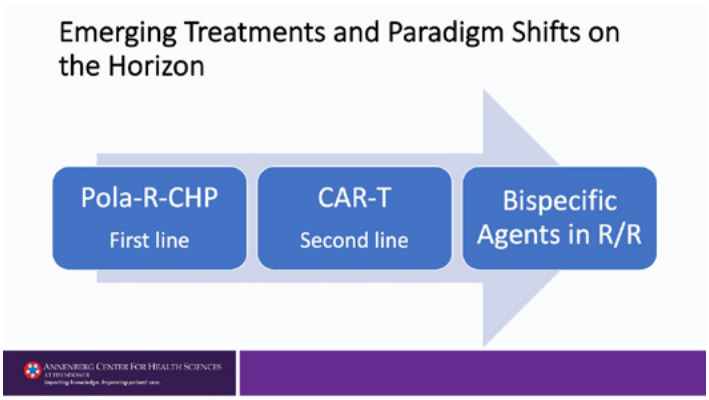
The overall response rate was quite good at 73%, with 53% of patients achieving a complete response, and half of patients in ongoing response at 2 years. Follow-up of this study at 2 years, the 2-year progression-free survival is 41%, pretty much identical to axi-cel in the ZUMA-1 study, with an overall survival also similar to axi-cel of 51% at 2 years.



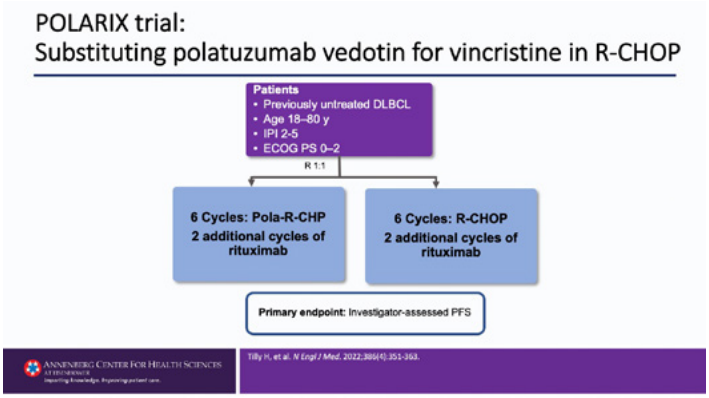
An additional regimen that's available now for patients with relapsed-refractory large cell lymphoma is selinexor, which is an oral XPO1 inhibitor or a selective inhibitor of nuclear export. This is an oral agent administered twice weekly and gained FDA approval in the 127-patient SADAL trial. This trial had fairly selective eligibility criteria. I think the most important eligibility criteria can be noted for patients who had responded to their prior line of therapy for DLBCL, they had to be 2 months away from their prior treatment. But for patients who had no response to their prior treatment, meaning they had stable disease or progressive disease after their prior chemotherapy, they had to wait 98 days or longer before enrolling on this trial.

Now, of course, there aren't many patients who fail to respond to their prior line of therapy and can then wait 98 days to go on another treatment. Effectively, this trial excluded patients who were not responding to their prior line of therapy for a more low-risk patient population.

The overall response rate and complete response rate are fair, but I would say not akin to the other options we have available, with a complete response rate of only 12%, a median progression-free survival of less than 3 months. This drug is also associated with significant toxicities, including gastrointestinal toxicities, anorexia, feelings of malaise and asthenia, and can be a very difficult drug to tolerate. As a result of its fairly minimal efficacy and significant toxicity, it is not a drug that has gained widespread use in the treatment for relapsed/refractory DLBCL, but nonetheless remains a treatment option.

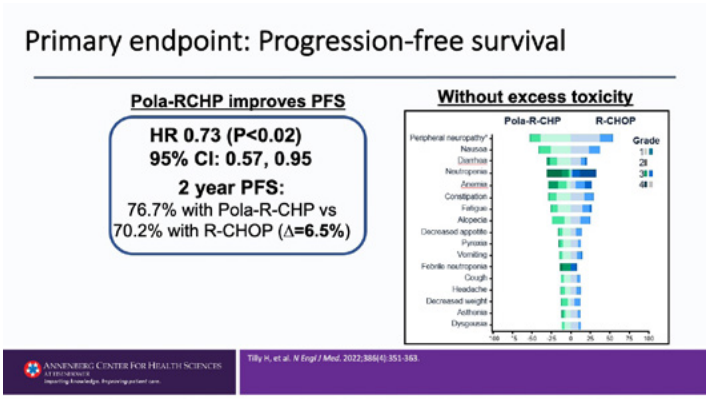


There are paradigm shifts that are moving the ground beneath us in how we manage diffuse large B-cell lymphoma. Polatuzumab was recently studied as a component of up-front therapy from the POLARIX trial. CAR T-cells have been studied in the second-line setting compared to standard salvage chemotherapy and transplant. And a very exciting new class of drugs, bispecific antibodies that bind both B-cell lymphomas and T-cells to enhance cell-mediated cytotoxicity, are increasingly showing encouraging benefit in relapsed/refractory disease.



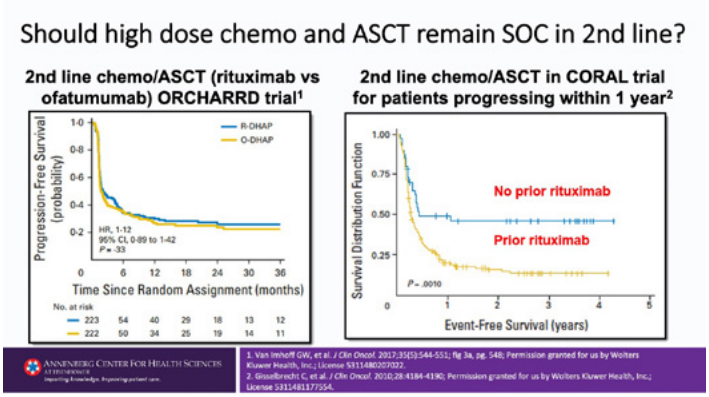
The POLARIX trial, which substituted polatuzumab vedotin for vincristine in the R-CHOP regimen, in patients with previously untreated DLBCL with an IPI score of 2 to 5, selecting for higher-risk patients, were randomized 1:1 to 6 cycles of Pola-R-CHP (polatuzumab vedotin + rituximab + cyclophosphamide + doxorubicin + prednisone) or standard R-CHOP. Patients in both arms received 2 additional doses of rituximab. The primary endpoint was progression-free survival.

The analysis for the primary endpoint which shows significant improvement in progression-free survival favoring Pola-R-CHP relative to R-CHOP. The hazard ratio is 0.73 which amounts to a 27% reduction in the risk of progression or death, favoring Pola-R-CHP, which translates to an absolute benefit in terms of 6.5% with a 2-year PFS of ~77% for Pola-R-CHP and ~70% for R-CHOP.



These regimens were similarly well tolerated, with peripheral neuropathy being similar in both arms, that being the predominant side effect of polatuzumab vedotin, but can also be seen with vincristine. We see nausea, cytopenias, GI (gastrointestinal) toxicity, slightly increased rate of neutropenic fever with the Pola-R-CHP arm, but not in the range of clinical significance. Pola-R-CHP modestly improves progression-free survival without adding significant toxicity and is expected to earn FDA approval as an up-front therapy in patients with diffuse large B-cell lymphoma.

The next question that is emerging is optimal management of second-line treatment. Now, the standard second-line therapy, going back for quite some time, has been salvage platinum-based chemotherapy for transplant-eligible patients, followed by high-dose chemotherapy with autologous stem cell transplant (ASCT) for patients with chemotherapy-sensitive disease. Historically, in the pre-rituximab era, this cured about half of patients, as reflected in the CORAL (Collaborative Trial in Relapsed Aggressive Lymphoma) trial of giving salvage chemotherapy in patients who relapsed after R-CHOP alone. But in the modern era, reflected in the ORCHARRD (Ofatumumab Versus Rituximab Salvage Chemoimmunotherapy in Relapsed or Refractory Diffuse Large B-Cell Lymphoma) trial, patrons relapsing after R-CHOP, and then treated with rituximab- or ofatumumab-based salvage chemotherapy, actually had very low rates of complete response. Only a minority of these patients can actually proceed to transplant because they usually do not have chemotherapy-sensitive disease, with only about a quarter of patients remaining progression-free at a year-and-a-half.

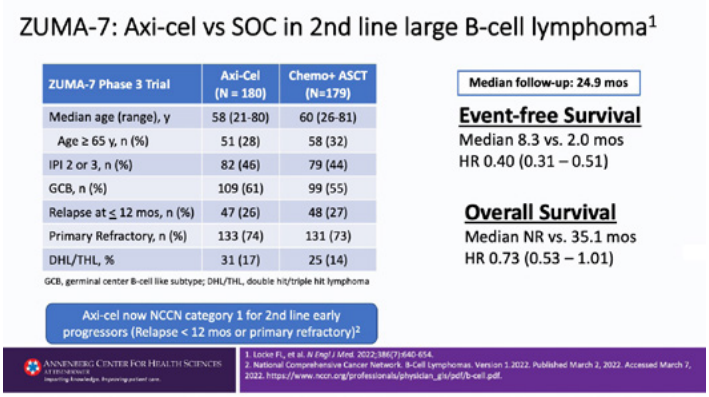


This tells us that high-dose chemotherapy and salvage platinum-based chemotherapy tend to fail the majority of patients with relapsed/refractory DLBCL in the modern era. That's particularly true for patients relapsing early after R-CHOP, reflected in the curve on the right in the gold color. These are patients who relapsed within 1 year after R-CHOP therapy, and then received rituximab-based platinum chemotherapy and transplant. You can see fewer than 20% of these patients achieved a durable remission, showing we need to do better.

How can we do better? Well, a natural question is take 1 of those anti-CD19 CAR T-cells that's working so well in inducing durable remissions and cures in the third-line or later setting, and compare them to a standard of care approach of salvage chemotherapy and transplant in the second-line setting. We now have no fewer than 3 randomized trials that have done just that.

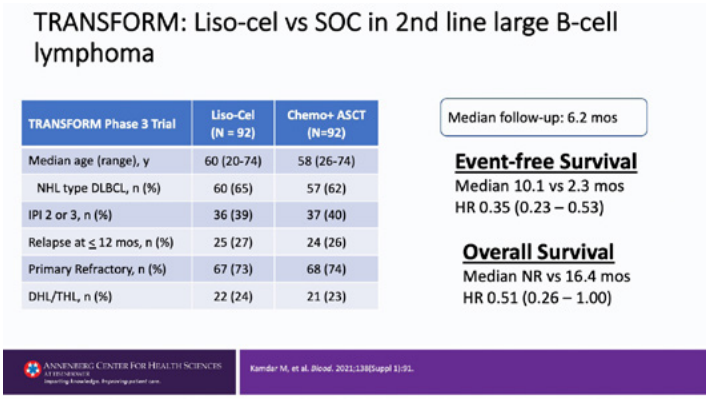
The ZUMA-7 evaluated axi-cel compared to the standard of care of platinum-based chemotherapy and high-dose chemotherapy for chemosensitive disease in patients with second-line diffuse large B-cell lymphoma. These patients were all transplant-eligible so they had a median age of 59 years old. These patients were either relapsed or primary refractory and importantly, the majority of these patients were primary refractory with three-quarters of patients having not had a complete response to their initial chemoimmunotherapy. The remaining quarter of patients relapsed within 1 year of R-CHOP-like treatment. About 15% of these patients had double-hit lymphoma.

The primary endpoint of event-free survival was fairly dramatically superior, favoring axi-cel over the standard of care with a hazard ratio



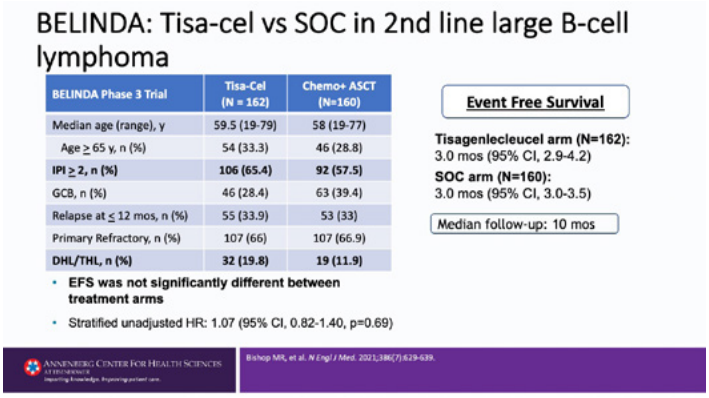
0.40, which is a 60% reduction in risk of progression, death, primary treatment failure or need for new cancer therapy. This reflected a median event-free survival of 8 months for CAR T-cell-treated patients and only 2 months in patients treated with a standard of care. The overall survival is trending in favor of axi-cel as well, however does not quite reach statistical significance at this time.

Based on these encouraging data, axi-cel has now been FDA-approved as a second-line therapy for patients with diffuse large B-cell lymphoma that is primary refractory or relapsing within 1 year of up-front chemoimmunotherapy. It is also included as a category 1 recommendation in the NCCN guideline. From my perspective, any second-line patient who is primary refractory or relapsing within 1 year should be considered for a CAR T-cell, such as axi-cel, as their second-line treatment today, which is clearly superior to the prior standard of care of platinum-based chemotherapy and transplant.



The second trial in this study to show an improvement for CAR T-cells was the TRANSFORM trial with liso-cel vs standard of care. This study enrolled 184 patients to either liso-cel or the standard of care, again platinum-based chemotherapy followed by autologous transplant for patients with chemotherapy-sensitive disease. These patients were primarily primary refractory patients with three-quarters of patients being primary refractory, and a quarter of patients in this study had double-hit lymphoma.

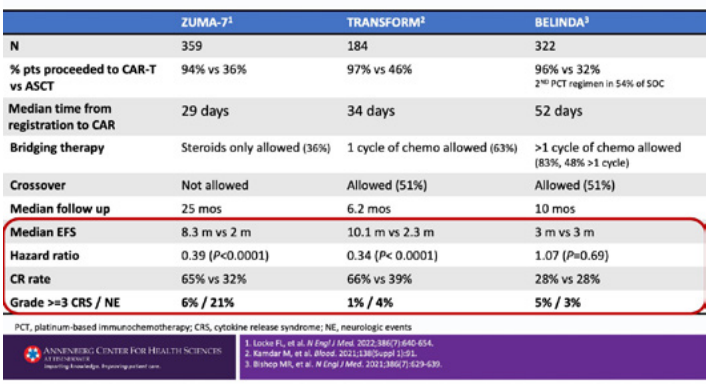
The event-free survival was significantly superior favoring CAR T-cells over standard of care with a 65% reduction in risk of treatment failure, death or need for new cancer therapy, with a median EFS (event-free survival) of 10 months for liso-cel and only 2 months in standard of care. This study has a shorter median follow-up of only 6.2 months, but the overall survival curve shows a clear trend in favor of liso-cel, with a hazard ratio suggesting a 49% reduction in risk of death in these patients, but a confidence interval that just reaches 1. It will be interesting to see how this overall survival curve looks with ongoing follow-up. These curves in overall survival are separating despite the fact that patients in the TRANSFORM trial, unlike patients in the ZUMA-7 trial, had built-in crossover. So, patients who are failing the standard of care arm could cross over and receive liso-cel at the time of treatment failure for the standard of care arm and, in fact, more than half of patients on the standard of care arm did indeed cross over and receive liso-cel as a third-line therapy.



A third trial has also been reported and now published. This is looking at tisa-cel vs standard of care, a similar trial as ZUMA-7 and TRANSFORM, though with some slight differences in the design. There was a longer time to receiving CAR T-cells in this trial compared to the other 2 trials, and patients often had to fail more than 1 type of salvage platinum-based chemotherapy before proceeding to CAR T-cells. This was also a large study, and unlike the prior 2 studies, as shown on the event-free survival curve, tisa-cel showed no difference compared to standard of care in the second-line setting.

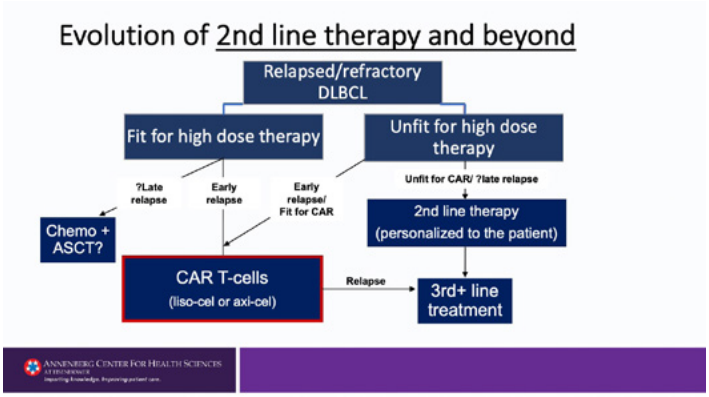
Unfortunately, the median event-free survival for tisa-cel was 3 months and it was also 3 months in the standard of care arm, with a median follow-up of 10 months on this study. This means that tisa-cel is not an appropriate second-line therapy, whereas liso-cel and axi-cel both significantly improve outcomes in second-line DLBCL compared to the standard of care of platinum-based chemotherapy. That means axi-cel or liso-cel, once it's FDA-approved, should be considered the standard second-line therapy for a primary refractory or early relapsed patient with DLBCL who is an appropriate candidate for CAR T-cell therapy. Noting that the majority of patients, in my opinion, who are not eligible for a transplant may still be eligible for CAR T-cells in the second-line setting.

Now, of course, we cannot consider CAR T-cells without also considering their unique toxicity profiles. Obviously, these 3 randomized trials in



the second-line setting emerged showing that either axi-cel or liso-cel is superior to standard of care as a second-line treatment, though there were differences in some of these designs. But I also want to highlight the toxicities. Despite ZUMA-7 and TRANSFORM showing superior efficacy, they also showed unique toxicity profiles. Severe cytokine release syndrome (CRS) occurred in 6% of patients who received axi-cel, and severe neurologic toxicities occurred in 21% of patients treated with axi-cel on the ZUMA-7 trial. Now, both CRS and neurotoxicity can be identified and reversed in the vast majority of patients. These are time-limited toxicities that can be successfully managed, usually with tocilizumab with or without corticosteroids.

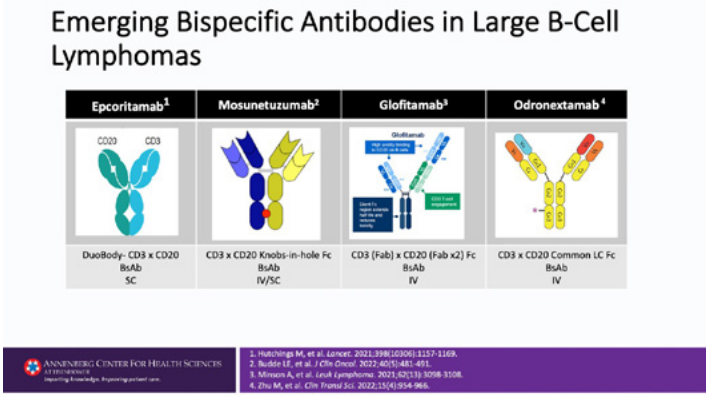
Lisocabtagene maraleucel, or liso-cel, which is studied in the TRANSFORM trial, is associated with lower rates of cytokine release syndrome and neurologic toxicities. Patients who received liso-cel on the TRANSFORM study had only a 1% rate of severe cytokine release syndrome and only a 4% rate of severe neurologic toxicities. So, between these 2 products, they both show similar benefit in the second-line setting, but with a more favorable toxicity profile favoring liso-cel.



This is how I now approach second-line therapy and later in relapsed/refractory diffuse large B-cell lymphoma. We can still consider whether a patient is fit for high-dose chemotherapy or not fit for high-dose chemotherapy, but ultimately high-dose chemotherapy is probably not the best option for most patients with relapsed/refractory DLBCL. For patients who are relapsing early or primary refractory, I'll ask whether those patients are fit for CAR T-cell therapy and whether they are transplant-eligible or not. Patients who are CAR T-cell eligible with early relapsed or primary refractory DLBCL will go to CAR T-cell therapy with either axi-cel or liso-cel once that drug also earns FDA approval.

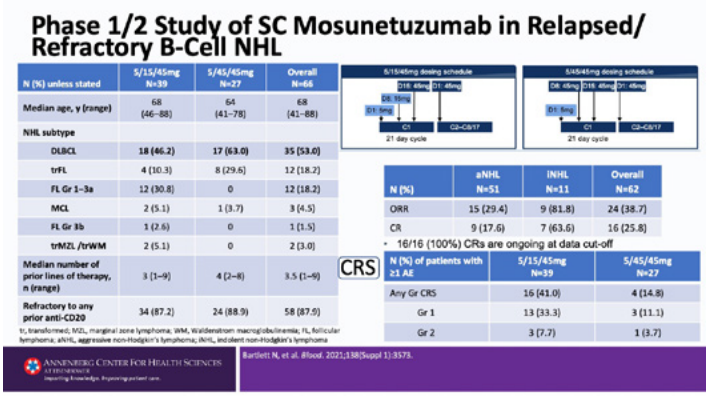
Patients who are fit for high-dose chemotherapy and relapse later than 1 year should still be considered for standard platinum-based chemotherapy and autologous transplant. For patients unfit for high-dose chemotherapy, who are also unfit for CAR T-cells, they would go to a second-line regimen which is personalized to the patient. For that patient population, I usually select tafasitamab/lenalidomide based on the L-MIND data, but polatuzumab-BR or even R-GemOx (rituximab + gemcitabine + oxaliplatin) would be other options in that setting. Once patients relapse after second-line setting, the third-line treatment is personalized based on what they received in a prior line of therapy and includes the options I just mentioned, as well as loncastuximab tesirine and others.

As the field moves forward, we are seeing this very exciting emerging class of drugs called bispecific antibodies which bind to both CD20 on the surface of the B-cell lymphoma and CD3 on the surface of the T-cell. Think of this as this antibody binding to the tumor cell and then throwing



a lasso around the patient's own T effector cell, bringing it in and having it exert cytotoxicity and directly kill the patient's lymphoma cell. There are 4 bispecific antibodies targeting CD20 and CD3 in advanced development for diffuse large B-cell lymphoma. These include epcoritamab, mosunetuzumab, glofitamab and odronextamab.

This is the phase 1/2 study of mosunetuzumab administered as a subcutaneous antibody. By directly engaging T-cells, we can see cytokine release syndrome similar to what we see with CAR T-cell therapy. A dosing strategy that leads to a ramp up in dosing over the first 21-day cycle has been shown to mitigate the risk of cytokine release syndrome. This phase 1/2 study includes 51 patients with aggressive NHL and 11 patients with indolent NHL. You can see the overall response rate among aggressive NHL was 29%. Among indolent disease, it was 82%. And for the complete response rates, it was 18% for aggressive NHL and an impressive 64% for indolent NHL.



The cytokine release syndrome was more favorable in a step-up dosing strategy that started with 5 mg, then went to 45 mg and 45 mg again. In those 27 patients, the risk of cytokine release syndrome was 15%, and that was entirely low grade. Importantly, all complete responders in the study were ongoing at the time of last follow-up, but follow-up remains limited at the time of this report.

Glofitamab is another bispecific antibody. Glofitamab is administered intravenously. It also gives a clearing dose of obinutuzumab which binds to a different CD20 moiety than the glofitamab does. That allows clearance of CD20-positive cells to try and minimize the risk of cytokine release syndrome. This study gave obinutuzumab pretreatment, and then a slow dose escalation of the glofitamab, followed by fixed dosing every 3 weeks for up to 12 total cycles. This was a large study, 258 patients, treated with a median of 3 prior therapies, with most of these patients having diffuse large B-cell lymphoma, 29% having follicular lymphoma.

Glofitamab in Relapsed/Refractory NHL

- Treatment: Obinutuzumab 1000 mg followed 7 days later by glofitamab by step-up dosing followed by fixed dosing at increasing dose levels every 3 weeks for 12 cycles

Baseline characteristics	Patients (N = 258)
Age, median (range), y	64 (22–86)
Median prior lines, n (range)	3 (1–12)
Aggressive B-NHL, n (%) DLBCL, n=98 Mantle cell, n=26 Transformed follicular, n=31 Transformed CLL, n=11	183 (71%)
Indolent B-NHL, n (%) All grade 1-2 follicular	75 (29%)

RP2D, recommended phase 2 study dose

	aNHL, all doses N=175	aNHL RP2D N=14	iNHL, all doses N=75
ORR, n (%)	94 (54%)	11 (79%)	61 (81%)
CRR, n (%)	69 (39%)	10 (71%)	52 (69%)

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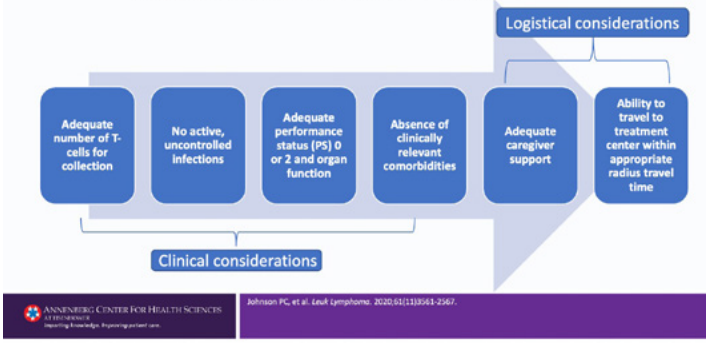
Dickinson MJ, et al. *Blood*. 2021;138(Suppl 1):2478.

The overall response rate for aggressive NHL was 54%, but that increased to 79% of patients treated at the recommended phase 2 dose, with 71% of patients at the recommended phase 2 dose achieving a complete response in aggressive NHL. This is an encouraging antibody in that population. We also see excellent results in indolent NHL as was seen in the prior study of mosunetuzumab with an 81% overall response rate and a complete response rate of 69%.

Module 3: Principles of Chimeric Antigen Receptor T-cell (CAR-T) Therapy in Large B-Cell Lymphoma: Patient Selection Strategies

There are a number of considerations that go into determining whether a patient is appropriate for CAR T-cell treatment. Of course, they have to be sufficiently fit to undergo CAR T-cells. Again, these are generally easier therapy than high-dose chemotherapy. It does not require platinum-based chemotherapy and it doesn't require high-dose chemotherapy with BEAM. It does, however, require a single cycle of fludarabine and cyclophosphamide (flu/cy). So, patients do have to be appropriate to receive a single cycle of flu/cy. That usually means that patients have an ECOG (Eastern Cooperative Oncology Group) performance status ideally of 0 to 1, but we typically do consider patients up to an ECOG performance status of 2 if all other eligibility criteria are met.

Patient Evaluation for CAR-T



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Johnson PC, et al. *Leuk Lymphoma*. 2020;61(11):3561-2567.

Patients must have sufficient hematologic function to tolerate lympho-depleting chemotherapy and have adequate organ function. Different thresholds have been used with different CAR T-cell products. On the TRANSCEND trial with liso-cel, patients were allowed with creatinine clearance as low as 30 and left ventricular ejection fractions as low as 40%. Importantly, for patients with moderate renal insufficiency, it's critically important to dose-reduce the fludarabine as that can lead to significant toxicities if not dose-reduced.

Patients also cannot have any active, uncontrolled infections or significant comorbidities that prevent successful treatment with CAR T-cell therapy. Patients also must have adequate T-cells for collection. Both the studies of tisa-cel and axi-cel have required minimal absolute lymphocyte counts in order to enroll on those trials, however the studies of lisocabtagene maraleucel have provided no mandatory minimum absolute lymphocyte count and was still able to produce product. I do not typically look at the number of T-cells when I am selecting a patient for CAR T-cell therapy.

Then there are issues related to the ability to care for these patients during and after their CAR T-cell treatment. Because of the risks of neurologic toxicities and cytokine release syndrome, we like patients to live within an hour of being able to reach the center, closer is better, should they develop a fever, for example, or confusion once they're in the outpatient setting and they need to have attention from an adequate caregiver who is paying close attention to these patients in the immediate CAR T-cell setting, making sure medications are being taken appropriately, making sure mental status is intact, as a patient undergoing neurologic toxicities might not realize they are having neurologic toxicities if they are confused or might develop aphasia. And caregivers who can alert providers if patients develop a fever or neurologic toxicities.

Patients ineligible for ASCT/those who do not qualify for CAR-T clinical trial may still be CAR-T candidates[1,2]

Characteristics	Real World Post-Approval Experience[3-5]			ZUMA-1[6]	JULIET (Tisa-cel)[7]
Cellular therapy	Axi-cel[3]	Axi-cel[4]	Tisa-cel[5]	Axi-cel	Tisa-cel
n	91	274	63	108	111
Median age (range)	64 (21-80)	60 (21-83)	65 (18-81)	59 (23-76)	56 (22-76)
ECOG PS 0-1	90%	81%	82%	100%	100%
High risk IPI (≥ 3)	46%	55%	NR	44%	NR
Bridging therapy	40%	NR	NR	0%	92%
Prior ASCT	27%	33%	21%	23%	49%
Ineligible for pivotal trial	60%	43%	NR	NA	NA
Outcomes				Outcomes	
ORR	71%	81%	66%	83%	52%
CR	44%	57%	42%	58%	40%
≥Grade 3 CRS	16%	7%	<5%	13%	23%
≥ Grade 3 neurotoxicity	39%	33%	4%	28%	12%

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1. Johnson PC, et al. *Leuk Lymphoma*. 2020;61(11):3561-2567. 2. Cahill KE, et al. *Leuk Lymphoma*. 2020;61(4):799-807. 3. Jacobson CA, et al. *Blood*. 2018;132(Suppl):92. 4. Nastoupil LJ, et al. *Blood*. 2018;132(Suppl):91. 5. Pasquini MC, et al. *Blood*. 2019;134(Supp 1):764. 6. Neelapu SS, et al. *N Engl J Med*. 2017;377(26):2531-44. 7. Schuster SJ, et al. *N Engl J Med*. 2019;380(1):45-56.

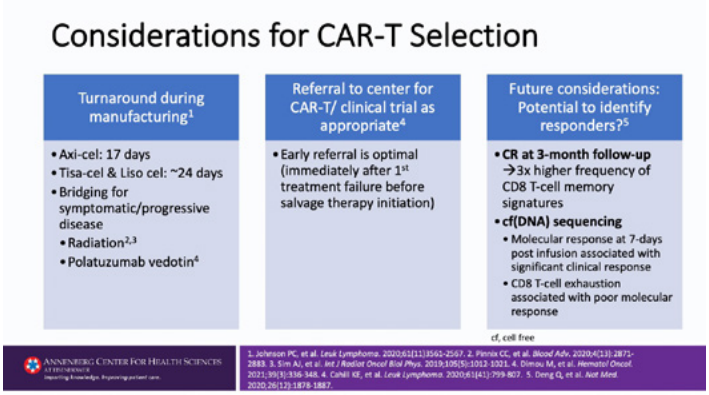
A number of patients who were not eligible for pivotal trials of CAR T-cells are appropriate to receive CAR T-cells in the real-world setting. Studies that have looked at real-world experiences with either axi-cel or even tisa-cel have shown a significant proportion of patients who received those products in the real-world setting would not have even qualified to enroll in the pivotal CAR T-cell trials. That includes up to 60% of patients who have been treated with commercial product with axicabtagene ciloleucel. This includes, based on their performance status, based on whether they received bridging therapy which has not been included in axi-cel clinical trials, or based on whether these patients had secondary CNS involvement by their lymphoma, for example.

What we can see is the efficacy looks quite similar in these patients who would not have otherwise been eligible for CAR T-cells in the real-world setting with similar rates of cytokine release syndrome and neurologic toxicities.

We're comparing those, therefore, to the pivotal trials of ZUMA-1 and JULIET with axi-cel and tisa-cel. The overall response rates, complete response rates, and incidence of toxicities actually appear extremely similar across these, showing us that the pivotal trial results truly do translate into the real-world setting and importantly, that real-world setting

includes patients who might not have even qualified for the stringent eligibility criteria of the pivotal CAR T-cell trials.

When we think about other considerations, one consideration is how quickly the patient needs their treatment. There are differences in the turnaround time. Axi-cel is turned around the most quickly, 17 days from apheresis to return of product to the treating center, whereas tisa-cel and liso-cel both take about 24 days. That week difference does not really make a difference for most patients, who can wait 1 more week for a CAR T-cell product, but for those patients who need their treatment, and every day counts, axi-cel certainly gives a more rapid, reliable turnaround of product.



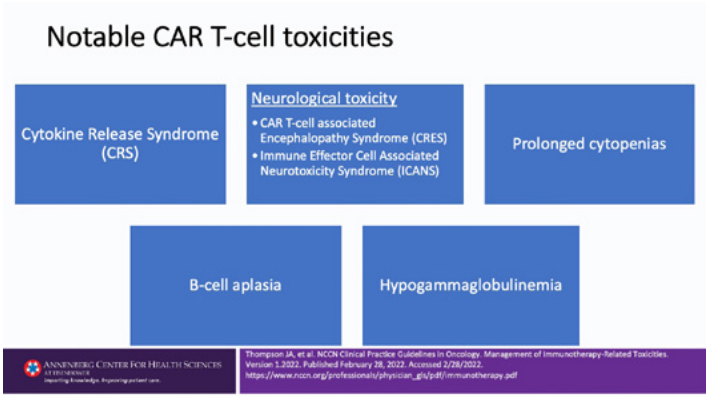
We also know that bridging therapy has been successfully used with tisa-cel and liso-cel on clinical trials, bridging therapy being the treatment patients can receive from the time that their cells were apheresed until the CAR T-cell product is returned to them. There are multiple options for bridging therapy. I commonly use polatuzumab vedotin. It is well tolerated and can help offer disease control while awaiting return of the CAR T-cell product, and doesn't offer the same degree of toxicity as platinum-based chemotherapy. Radiation therapy is a very good potential option for patients with a discrete site of symptomatic disease, and even corticosteroids alone might be beneficial in helping sequel the disease progression until CAR T-cells become available. I would avoid CD19-directed therapies in the bridging setting.

Another important option is whether patients have access to CAR T-cells. CAR T-cells are currently available predominantly at large academic centers, and some patients may have to travel to receive these therapies. It is critically important for patients to be referred early to a CAR T-cell center in order to be evaluated for their efficacy and candidacy for a CAR T-cell treatment. Ideally, at the time of first relapse, those patients should be referred for consideration of second-line CAR T-cells, or if they are not eligible for second-line CAR T-cells, to make sure that patient is known to the CAR T-cell center so they can receive CAR T-cells as a third-line treatment option if second-line treatment fails those particular patients.

Additional future considerations include how do we best identify those patients likeliest to garner a durable complete response? There are a number of potential ways that this is being looked at, including different T-cell phenotypes for patients receiving the CAR T-cells, including baseline cytokine measures, including persistence of a stem memory cell phenotype of the CAR T-cell, for example, as well as looking at circulating cell-free (cf) DNA as a way to early assess an MRD (minimal residual disease)-negative response of patients who are likeliest to achieve the most durable remission. These, and other areas, are undergoing ongoing evaluation to optimally target patients likeliest to benefit from CAR T-cell treatment.

Module 4: Management of Adverse Effects Associated With Novel Therapies

Diving deeper into evaluation of CAR T-cell toxicities, cytokine release syndrome, neurologic toxicity which we now call immune effector cell associated neurologic syndrome (ICANS). We also see some prolonged cytopenias, with about a third of patients having ongoing grade 3 or 4 cytopenias 1 month after CAR T-cell treatment. Then we see on-target B-cell aplasia and hypogammaglobulinemia, a result of depleting CD19-positive B-cells.



Axi-cel has been associated with the highest rate of cytokine release syndrome. Patients with axi-cel had a 93% rate of cytokine release syndrome which was severe in 13%. Compare that to lisocabtagene maraleucel which used the same CRS grading scale and, in that study, the CRS rate was only 42%, with a severe CRS rate of only 2%. So, clearly lower any grade and severe CRS favoring liso-cel and tisa-cel over axi-cel. The likely explanation for that is primarily the costimulation domain, whereas the CD28 costimulation domain in axi-cel leads to a much more rapid and earlier peak expansion and then earlier drop-off in persistence, whereas liso-cel and tisa-cel use 4-1BB which leads to a slower, but ultimately prolonged persistence of CAR T-cell therapy and a more blunted onset of CRS and neurologic toxicities. Neurologic toxicities were also seen in the majority of patients treated with axi-cel, with two-thirds of patients having any grade of neurologic toxicities and severe in 28%. This is much lower with tisa-cel and liso-cel which occurred at any grade neurologic toxicities at 21% and 30% respectively, with severe neurotoxicity in only 12% and 10% of patients treated with tisa-cel and liso-cel respectively.

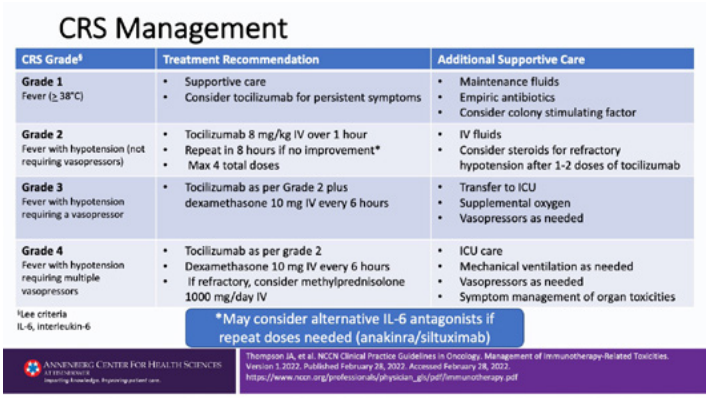
Toxicity of 3 Major CAR T-cell Products for Relapsed/Refractory DLBCL[1-3]

	Axicabtagene Ciloleucel[1]	Tisagenlecleucel[2]	Lisocabtagene Maraleucel[3]
Construct	antiCD19-**CD28**-CD3z	antiCD19-**41BB**-CD3z	antiCD19-**41BB**-CD3z
n	101	111	269
Any CRS Median time to onset	93% 2 days	58% 3 days	42% 5 days
≥ Gr 3 CRS†	13%	23%	2%
Any neurotoxicity	64%	21%	30%
≥ Gr 3 neurotoxicity	28%	12%	10%
Tocilizumab use	43%	14%	20%
Steroid use	27%	10%	21%

* Caveats in cross trial comparisons: Different eligibility criteria, phase of study, dose levels
†CRS toxicity grading scales differ across studies. Axi-Cel and Liso-cel used Lee criteria. Tisa-cel used Penn criteria

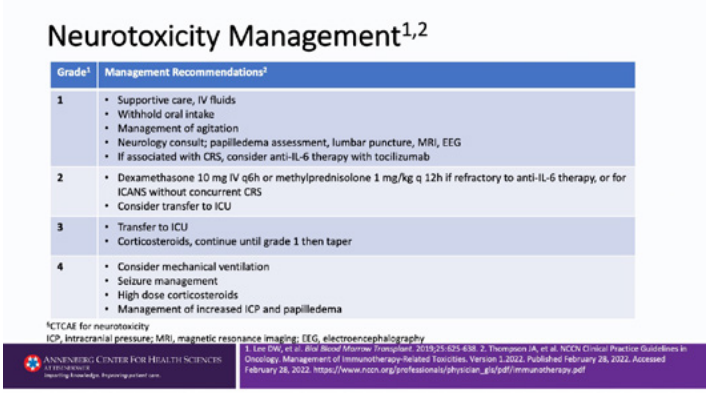
This is reflected in the lower use of rescue medications, tocilizumab and corticosteroids, which are required in a significant proportion of patients treated with axi-cel, but lower rates of use with tisa-cel and liso-cel. Importantly, cytokine release syndrome and neurologic toxicities are identifiable and reversible in the vast majority of patients receiving any 3 of these CAR T-cell products.

There are well-defined algorithms for the management of cytokine release syndrome. CRS is graded as shown here, beginning with isolated fever, which is usually treated with just supportive care alone, whereas persistent or prolonged grade 1 CRS can be treated with tocilizumab as well as supportive care. Grade 2 CRS includes some hypotension, but not hypotension requiring anything more than IV (intravenous) fluid boluses. This is where we typically incorporate tocilizumab with or without corticosteroids.



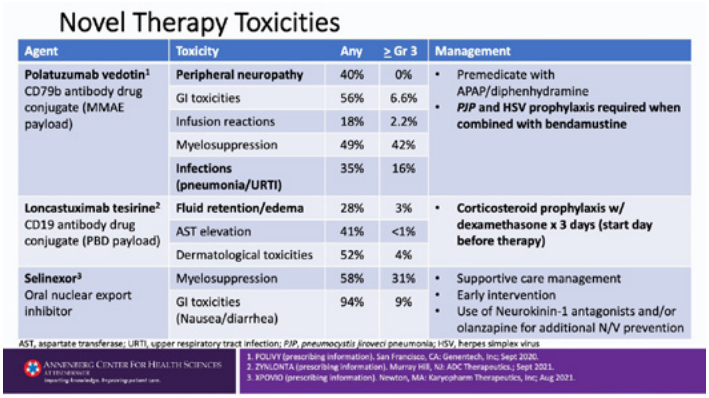
Grade 3 CRS means vasopressor-requiring cytokine release syndrome and hypotension. These patients are usually moved to an intensive care unit (ICU). These patients always receive a combination of tocilizumab and corticosteroids as well as supportive care. Grade 4, which is hypotension requiring multiple vasopressors, these patients are in the ICU and receive tocilizumab as well as high-dose dexamethasone. There is some limited data for patients who have refractory CRS, despite tocilizumab and dexamethasone, of giving an alternate IL-6 (interleukin-6) antagonist, siltuximab or the drug anakinra.

Neurologic toxicities begin with grade 1 neurotoxicity being mild confusion, agitation, word-finding difficulties. We typically involve neurology, and think about other causes for altered mental status, but treat with supportive care. Grade 2 neurologic toxicity, this is where patients are starting to have difficulty with their activities of daily living. We would incorporate dexamethasone. Corticosteroids are the key treatment for mitigating neurologic toxicities. We would include tocilizumab for these patients only if they have concurrent cytokine release syndrome, but tocilizumab is otherwise not a treatment for isolated neurologic toxicities.



Once patients have severe neurologic toxicities, these patients are typically transferred to an intensive care unit and are given high doses of corticosteroids. Grade 4, which might include rare patients with increased intracranial pressure and cerebral edema, these patients are treated with high-dose methylprednisolone and may have status epilepticus requiring treatment with antiepileptic drugs.

Any patient, even with grade 1 neurologic toxicities, we typically start these patients on an antiepileptic drug as prophylaxis, with a goal that these patients never develop seizure activity, and the majority of patients will not develop epileptiform activity.



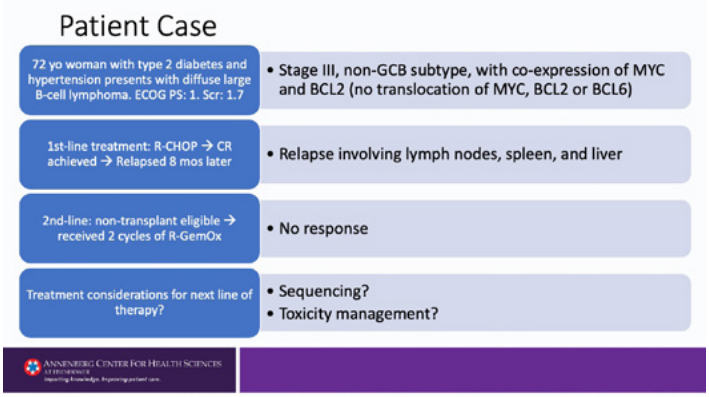
Polatuzumab vedotin, the anti-CD79b drug conjugate, has expected toxicities associated with the MMAE, the same toxic payload associated with the antibody drug conjugate, brentuximab vedotin, in Hodgkin lymphoma and ALCL (anaplastic large cell lymphoma). The primary toxicity of this drug is peripheral neuropathy and it is important to dose-reduce this drug for any patient who develops anything more than mildly-limiting peripheral neuropathy. Anybody with functionally-limiting peripheral neuropathy requires a dose reduction of polatuzumab.

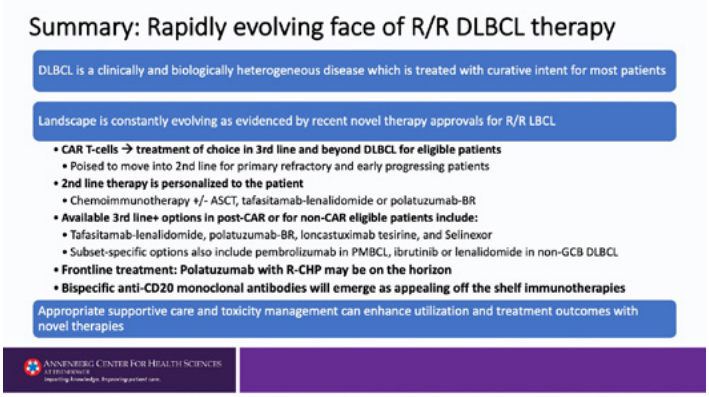
This drug, particularly when combined with bendamustine, can also induce myelosuppression and infections, as well as GI toxicities. Any patient receiving bendamustine-based therapy should also receive pneumocystis prophylaxis and HSV (Herpes simplex virus) prophylaxis, though that is not required for a patient receiving polatuzumab without bendamustine.

Loncastuximab, the anti-CD19 PBD antibody drug conjugate, that unique toxicity associated with fluid retention and edema that requires the dexamethasone pretreatment starting the day before, day of, and then day after, each loncastuximab treatment, as well as the increase in LFTs and occasional rashes.

Selinexor, the XPO1 inhibitor, has very significant GI toxicities, including significant nausea and diarrhea. This requires a lot of supportive care, including olanzapine for these patients. These patients can still have asthenia, loss of appetite, weight loss and myelosuppression, and require significant dose reductions sometimes in order for patients to tolerate this oral agent.

This case is a 72-year-old woman with type 2 diabetes and hypertension who is diagnosed with diffuse large B-cell lymphoma. Her ECOG performance status is 1. Her creatinine is 1.7 and her staging is stage III, non-germinal center subtype of diffuse large B-cell lymphoma with expression of MYC and BCL2 (B-cell leukemia/lymphoma 2 protein), but without translocations of MYC (MYCL proto-oncogene), BCL2 or BCL6 (B-cell leukemia/lymphoma 6 protein). This is not a double-hit lymphoma.





This patient is appropriately treated with R-CHOP and achieves a complete response, but unfortunately relapses 8 months later. This patient now has disease involving the lymph nodes, spleen and liver, and this patient has an early relapse of DLBCL.

This patient is considered nontransplant-eligible and receives R-GemOx as a second-line therapy, without response, and is now under consideration for treatment in the third-line setting.

Now, this is an interesting case with rapidly-evolving care. At the time of early relapse in less than 1 year after R-CHOP, I would consider this patient a candidate for CAR T-cells in the second-line setting, ideally with lisocabtagene maraleucel, given the patient's age and comorbidities, that product would likely be better-tolerated than axi-cel. But, as of today, axi-cel is the FDA-approved product with liso-cel approval expected in the future, and so I would still consider this patient a candidate for axi-cel with very close attention to supportive care in the second-line setting.

Now, this patient received R-GemOx in the second-line setting and is now progressing. I would now consider this patient for third-line CAR T-cells and among the available products, choose liso-cel or tisa-cel for this patient, again given the lower risk of cytokine release syndrome and neurologic toxicities. If this patient did not have access to either liso-cel or tisa-cel, or relapsed after liso-cel or tisa-cel, I would consider alternate options, including tafasitamab/lenalidomide, which could be a very good option for this patient, or polatuzumab with rituximab with or without inclusion of bendamustine.

We'll summarize by saying that diffuse large B-cell lymphoma is a clinically and biologically heterogeneous disease, but is treated with curative intent in the vast majority of patients. We have a rapidly evolving landscape in the up-front and relapsed/refractory setting. CAR T-cells have emerged now as the treatment of choice in third-line or later DLBCL with axi-cel, liso-cel and tisa-cel all available in that setting and is now moving into the second-line setting for primary refractory and early relapsing patients, with both axi-cel and liso-cel showing superiority over standard of care in transplant-eligible early relapse or primary refractory DLBCL.

Second-line therapy is further personalized to the patient, and in a patient who is relapsing late or is nontransplant-eligible, those patients can still be considered for chemotherapy, with or without autologous transplant for a late relapsed, transplant-eligible patient, whereas nontransplant-eligible patients in the second-line setting, who are not CAR T-cell candidates, can be considered for tafasitamab/lenalidomide or polatuzumab BR.

In the third-line setting, in patients who have received CAR T-cells, have relapsed after CAR T-cells or non-CAR T-cell candidates, again tafasitamab/lenalidomide and polatuzumab-BR remain options, as does the very appealing activity of loncastuximab tesirine which was studied in the LOTIS-2 trial. Selinexor is also an option, but usually I would not use it earlier than other available options due to the modest efficacy and associated toxicities.

There are some subset-specific treatments to always consider, including the immune checkpoint inhibitor, pembrolizumab, in a relapsed/refractory primary mediastinal B-cell lymphoma, as well as selective activity of ibrutinib or lenalidomide in patients with non-GCB DLBCL. Front-line therapy is also poised for a big shift. We await FDA approval of polatuzumab vedotin in combination with R-CHP based on the superior progression-free survival in the POLARIX trial of pola R-CHP vs R-CHOP in patients with DLBCL and an IPI score of 2 or greater.

Bispecific anti-CD20 monoclonal antibodies not yet FDA approved, but looking very exciting both in relapsed/refractory indolent lymphomas as well as relapsed/refractory diffuse large B-cell lymphomas where they are likely to join our treatment armamentarium as an off-the-shelf immunotherapy option for our patients. And certainly, with any new class of drugs and new drugs in different lines of therapy, we always have to consider the toxicity profiles associated with these novel agents, be they antibody drug conjugates, naked monoclonal antibodies, bispecific antibodies or CAR T-cells. But, by understanding the toxicity profile, we can be prepared to manage these toxicities with supportive care with toxicity-specific regimens to reverse those associated toxicities, and dose modifications as needed, and thus provide the optimal efficacy and safety of care to all of our patients with diffuse large B-cell lymphoma.