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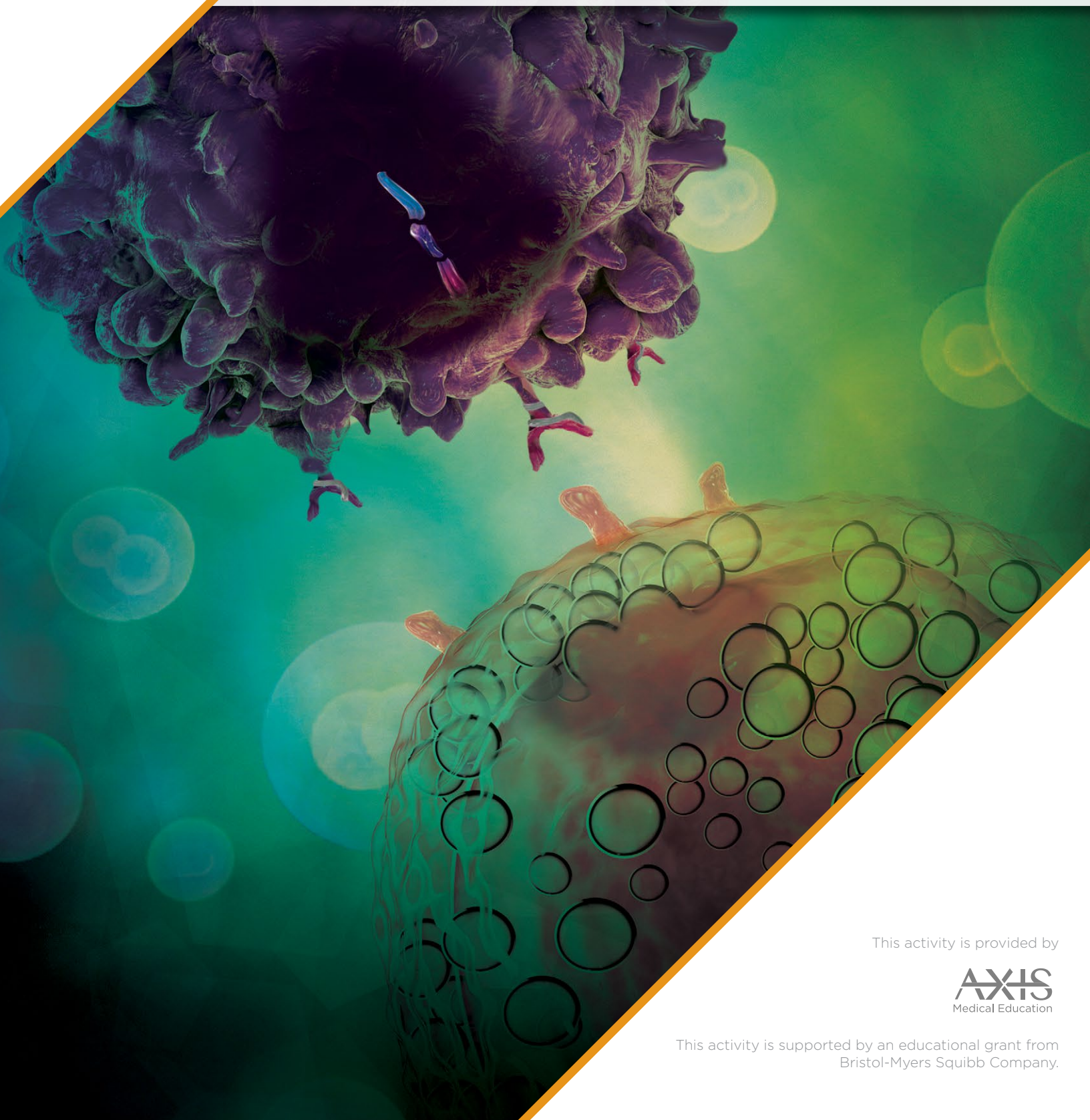
Paradigm Shifts in CAR T-Cell Therapy for Relapsed/Refractory Large B-Cell Lymphoma: A Video Viewpoint

This transcript has been edited for style and clarity and includes all slides from the presentation.



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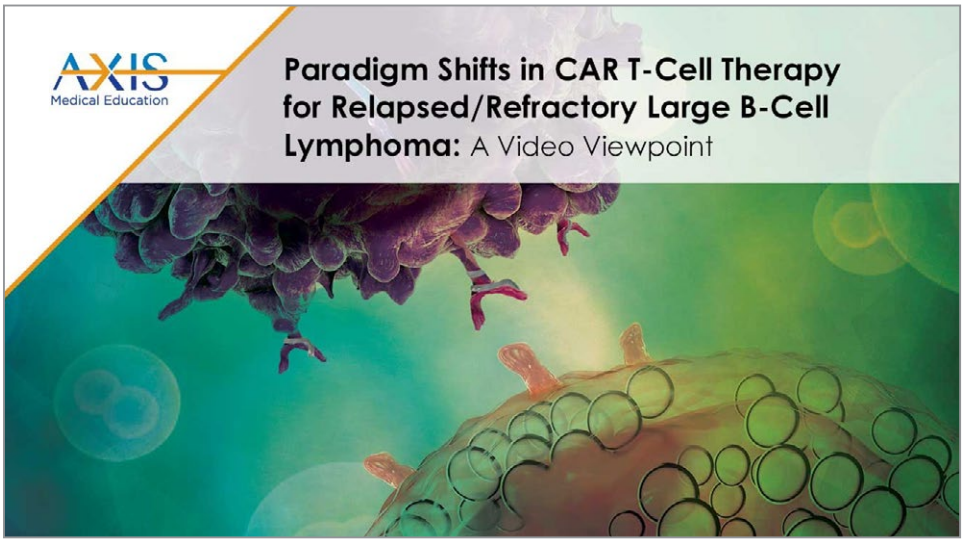
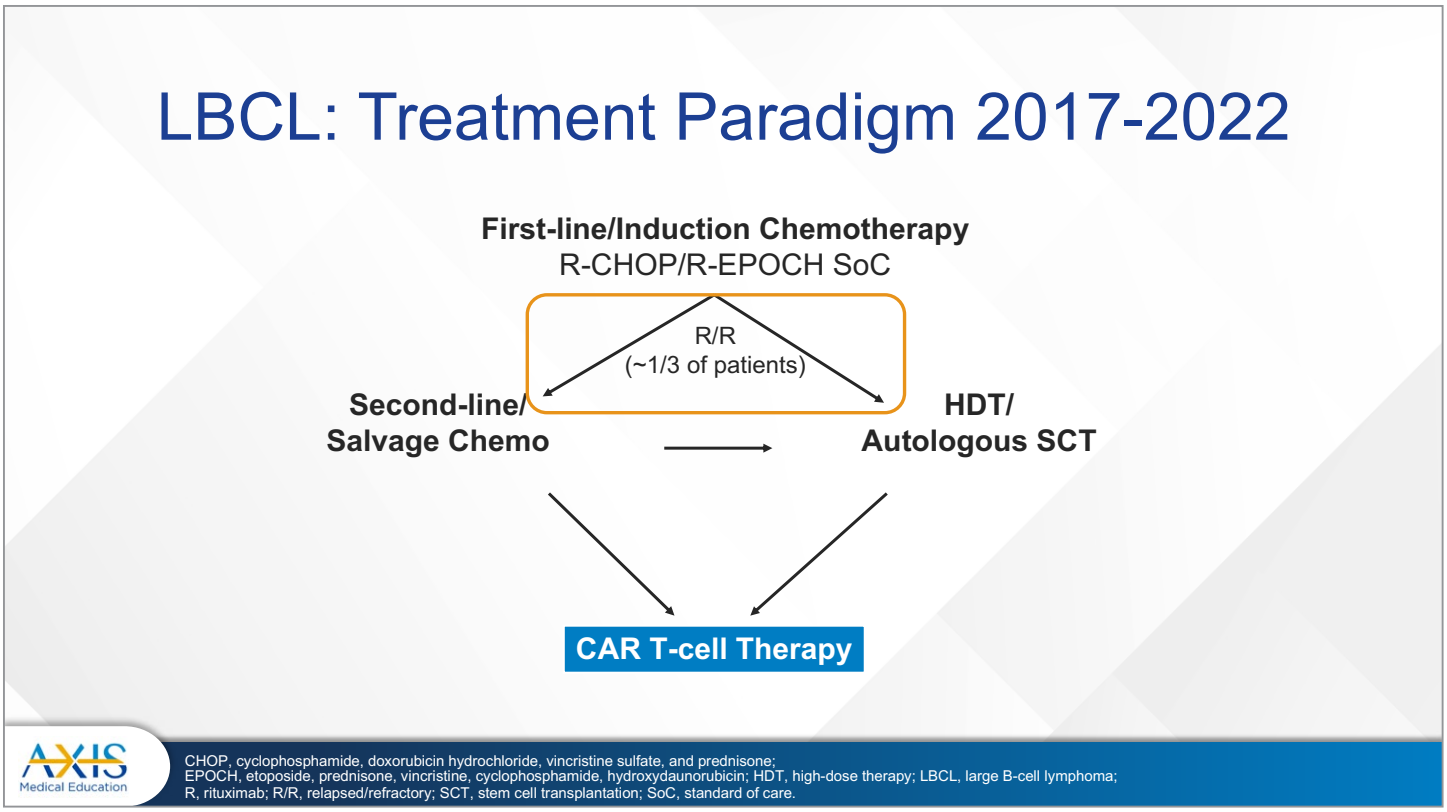
Paradigm Shifts in CAR T-Cell Therapy for Relapsed/Refractory Large B-Cell Lymphoma: A Video ViewPoint

Caron Jacobson, MD, MMSc



Caron Jacobson, MD, MMSc: Hello, and welcome to this educational activity, titled, "*Paradigm Shifts in CAR T-Cell Therapy for Relapsed and Refractory Large B-Cell Lymphoma.*"

I'm Dr. Caron Jacobson, an assistant professor of medicine at the Harvard Medical School and medical director of the Immune Effector Cell Therapy Program at Dana-Farber. Today, I will review the current treatment landscape for CAR T-cell therapies and highlight current and emerging evidence for large B-cell lymphoma in the second-line setting.

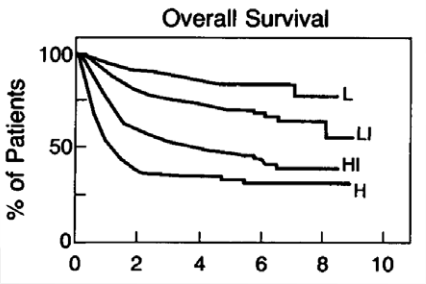


I first wanted to take a look at the large B-cell lymphoma treatment paradigm, really emerging from the time of CAR T-cell therapy approval in third-line large B-cell lymphoma in 2017 through the most recent in 2022. This paradigm really looked like patients all got frontline R-CHOP or R-EPOCH, depending on their risk features for their large B-cell lymphoma. About one-third of these patients, we know, will either be primary refractory or relapsed, at which point they would receive second-line or salvage chemotherapy. Those who respond will go on to have high-dose chemotherapy or an autologous stem cell transplant. For those who don't respond or who relapse after high-dose chemotherapy or autologous stem cell transplant, this is where CAR T-cell therapy was approved, starting in 2017 for relapsed, refractory large B-cell lymphoma.

I want to take a look at the one-third of patients who would be primary refractory or relapsed and see if there's any way that we can identify them ahead of time and think about coming up with new strategies to improve their outcomes, ultimately, with these therapies.

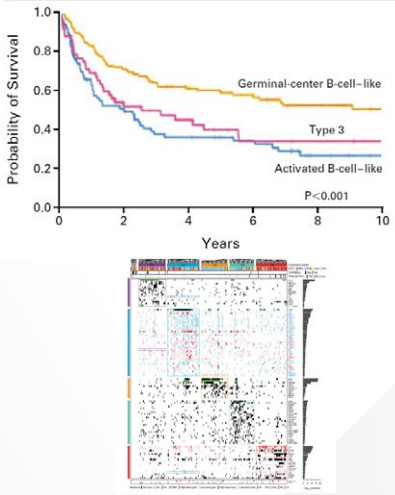
LBCL: How can we determine who will be refractory or will relapse?

International Prognostic Index (IPI)

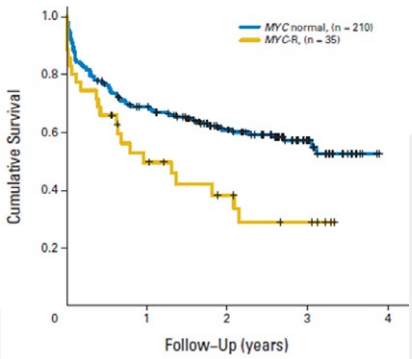


- Age >60
- Stage III/IV
- Elevated LDH
- Performance status >1
- Extranodal sites >1

Gene Expression Profile (GEP) /Genomic Classification



Double/Triple Hit Cytogenetics

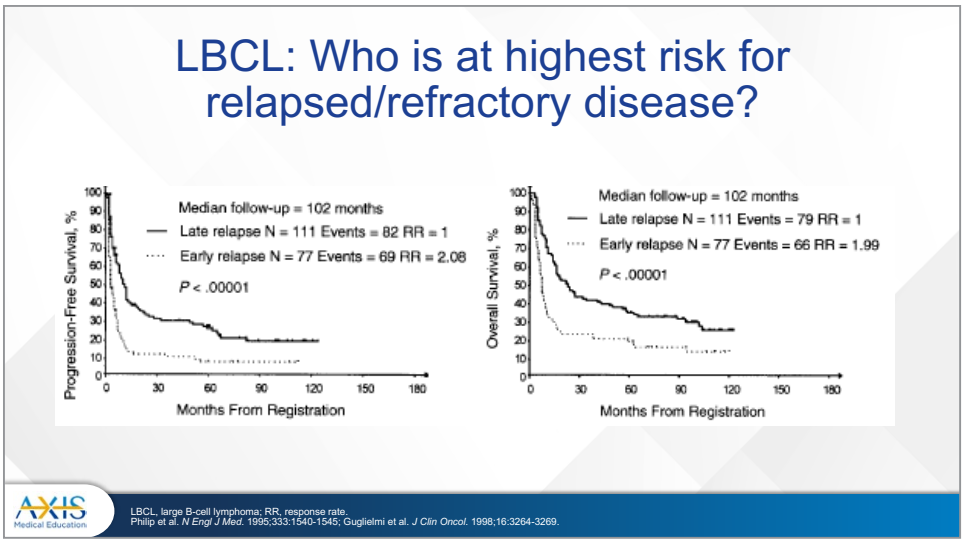


HI, high-intermediate risk; H, high-risk; L, low-risk; LI, low-intermediate risk; LBCL, large B-cell lymphoma; LDH, lactate dehydrogenase.
International Non-Hodgkin's Lymphoma Prognostic Factors Project, *N Engl J Med*. 1993;329:987; Ziepert et al. *J Clin Oncol*. 2010;28:2373; Rosenwald et al. *N Engl J Med*. 2002;346:1937; Chapuy et al *Nat Med*. 2018;24:679-690. Barrans et al. *J Clin Oncol*. 2021;28:3360-3365.

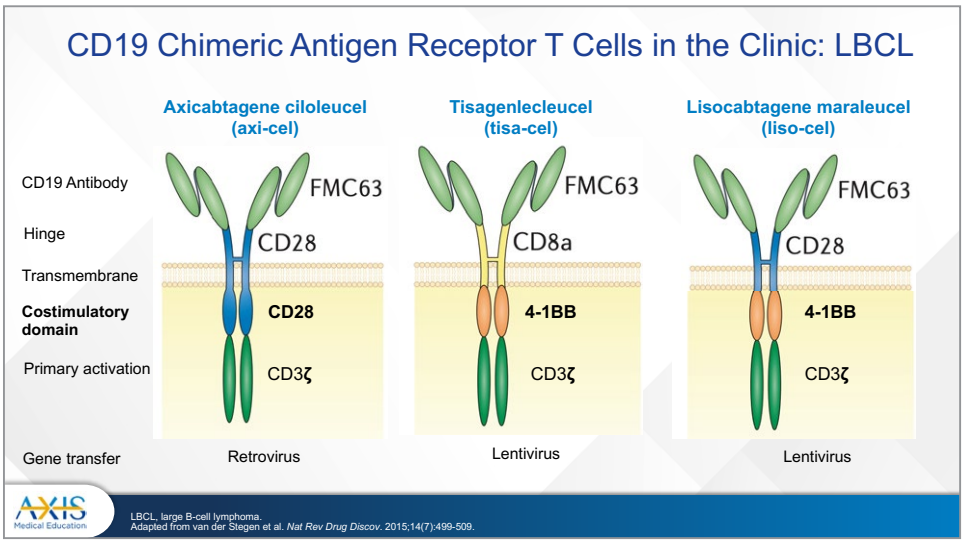
How do we determine who will be refractory or who will relapse with large B-cell lymphoma to R-CHOP or R-EPOCH? So, first, of course, we have the International Prognostic Index, which takes into account 5 different clinical and disease risk factors, including elderly age, advanced stage, a high LDH, a poor performance status, and multiple extranodal sites of disease, ascribing 1 point to each of these risk factors. And the summation will put patients into 4 different risk categories: low, low-intermediate, high-intermediate, and high. The overall survival curves for these risk categories range from upward of about 80% to 90% long-term survival down to closer to 30% to 40% long-term survival. And this risk score, or the IPI, has really survived the test of time and continues to be prognostic, even with current strategies.

We then know that we can categorize these lymphomas based on their gene expression profile, whether they are germinal-center–like or activated B-cell–like, and that these gene expression profiles do correlate with overall prognosis, with patients with germinal-center–like large-cell lymphomas having a better prognosis than those with an activated B-cell–like lymphoma. More recently, we've seen advancement of this genomic classification by 2 different laboratories: the Shipp lab at Dana-Farber and the Staudt Lab at the NCI, which really has made the risk stratification based on genomic classification a little bit more defined. And now there are really 5 different genomic classifications of large-cell lymphoma, all of which have different overall prognoses and sort of different rationales for new and targeted therapies. This hasn't yet really made its way into clinical practice but is fodder for future studies and future risk consideration.

Lastly, we know that patients who have double- and triple-hit cytogenetics, those that have rearrangements in both *MYC* and *BCL2*, or *MYC* and *BCL6* as represented by the yellow curves here on the right, do a lot less well than patients who do not have *MYC* and *BCL2* or *BCL6* translocations. We also know that patients who overexpress *MYC* and *BCL2* or who have high-grade B-cell lymphomas without *MYC* or *BCL2* overexpression are also groups of patients who will do less well compared to the general population.

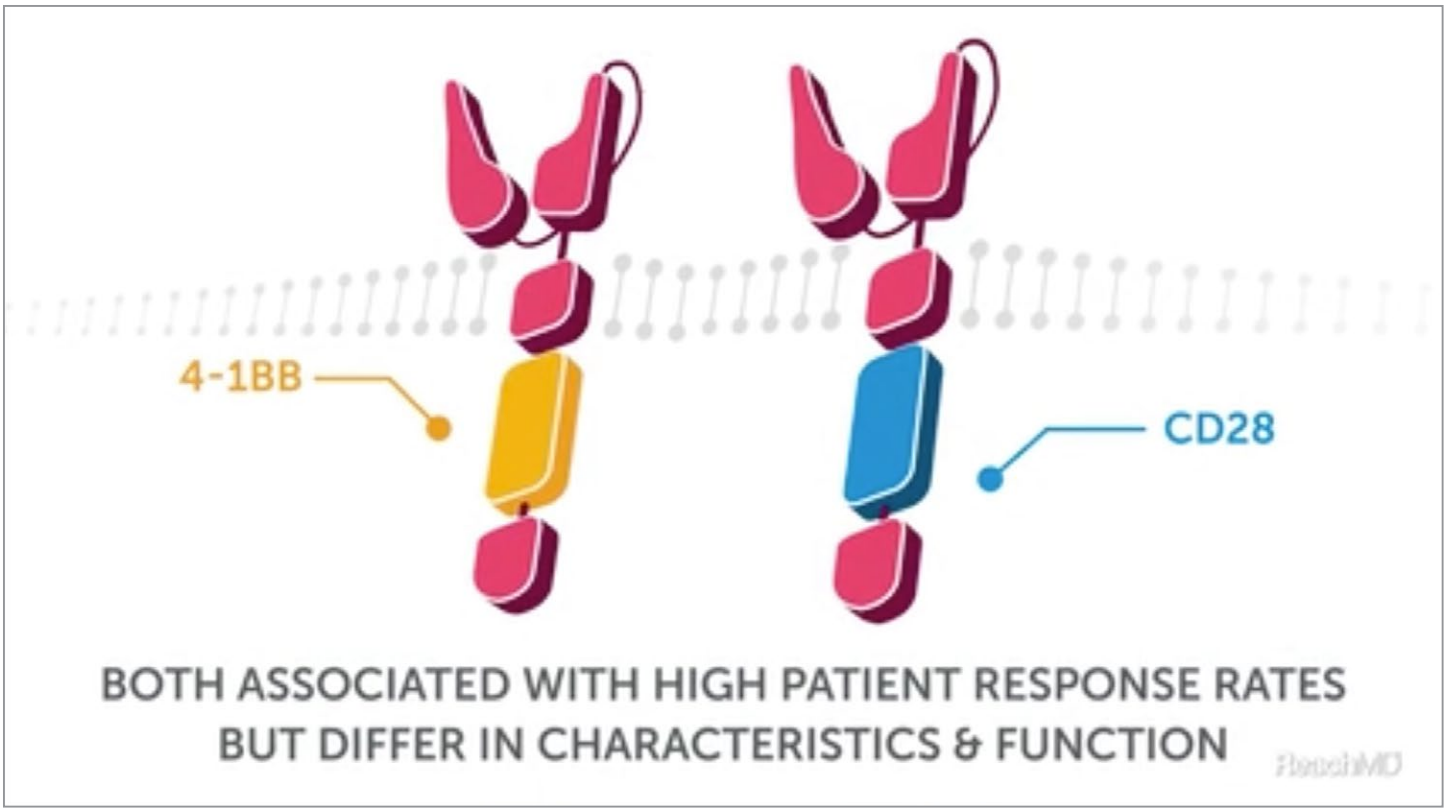


If we followed that treatment paradigm, and we took all the patients that have relapsed/refractory disease after R-CHOP or R-EPOCH, and we took them through salvage chemotherapy and then an autologous stem cell transplant, we know that those who relapsed early, generally within the first year of their frontline chemoimmunotherapy, vs those who relapsed late, a year or later after their frontline chemoimmunotherapy, will do significantly less well both in terms of progression-free and overall survival with what was the current second-line standard of care, namely salvage chemotherapy and autologous stem cell transplant, as depicted by these curves here.



So, let's just introduce the CD19 chimeric antigen receptor, or CAR T cells, that are available in the clinic for large B-cell lymphoma. These include axicabtagene ciloleucel, or axi-cel; tisagenlecleucel, or tisa-cel; and lisocabtagene maraleucel, or liso-cel. All 3 of these CAR T cells share the same extracellular domain, which is the SC variable fragment of an antibody molecule that recognizes CD-19 on normal, healthy, and malignant cells. They all have a CD3ζ activating domain, but they differ from each other in terms of their second costimulatory domain, where axi-cel has a CD28 CAR and tisa-cel and liso-cel have a 4-1BB CAR.

These chimeric antigen receptor T cells are derived from the patient's own T cells through a process called leukapheresis. These T cells are then transfected with the transgene that encodes these chimeric antigen receptors. The gene gets integrated into the nucleus and expressed, and then the receptor gets put on the surface of the T cell. These cells are then expanded to target dose and then returned to the cancer center, where they're ready for infusion into the patient. Once they're infused into the patient, they will bind to CD19 target cells as well as on normal, healthy B cells, which will activate the immune synapse and activate both CD3ζ as well as the other costimulatory domains to activate the T cell. The hope is that the end result is the killing of the tumor cell.



So, now let's pause to review a video clip on similarities and differences within the structure and costimulatory domains of the different CAR T-cell therapies that we just discussed.

CD19-directed CAR T-cell therapy binds to CD19 expressed on the surfaces of tumor and normal B cells. This binding induces activation of CAR T cells, release of pro-inflammatory cytokines, and killing of target cells. Let's take a closer look at the structure of CAR T-cell therapies for large B-cell lymphoma. CAR T-cell therapy consists of four main components: (1) an extracellular target antigen-binding domain, (2) a hinge region, (3) a transmembrane domain, and (4) intracellular signaling domains. Extracellularly, different CARs share the same antigen-binding domain, or receptor, but bear a different hinge. The binding region is composed of a CD19-directed, antibody-derived, single-chain variable fragment. The extracellular receptor and hinge are linked by the transmembrane domain to intracellular signaling domains, which activate the T cells. Intracellularly, CARs can have different costimulatory domains—either CD28-derived or 4-1BB-derived. Both are associated with high patient response rates but differ in their characteristics and function. A CD28 costimulatory domain enhances early and rapid CAR T-cell expansion that can lead to early and higher-grade side effects and more rapid decreases in CAR T-cell levels over time. A 4-1BB costimulatory domain leads to more gradual CAR T-cell expansion and, as such, can lead to later and lower-grade side effects and more delayed decreases in CAR T-cell levels over time.

CD19 CAR T-Cells for DLBCL: Pivotal Trial Results After Two or More Lines of Systemic Therapy

	ZUMA-1	JULIET	TRANSCEND CORE
Product	**Axi-cel**	**Tisa-cel**	**Liso-cel**
Costimulatory domain	CD28	4-1BB	4-1BB
# pheresed	111	165	344
# treated	101	111	269*
ORR, %	82	52	73
CR, %	54	40	53
6-month ORR, %	41	37	NR
mOS, months	27.1	12	21.1
CRS, %	93	48	42
Grade 3+ CRS, %	13	22*	2
ICANS, %	64	21	30
Grade 3+ ICANS, %	28	12	10

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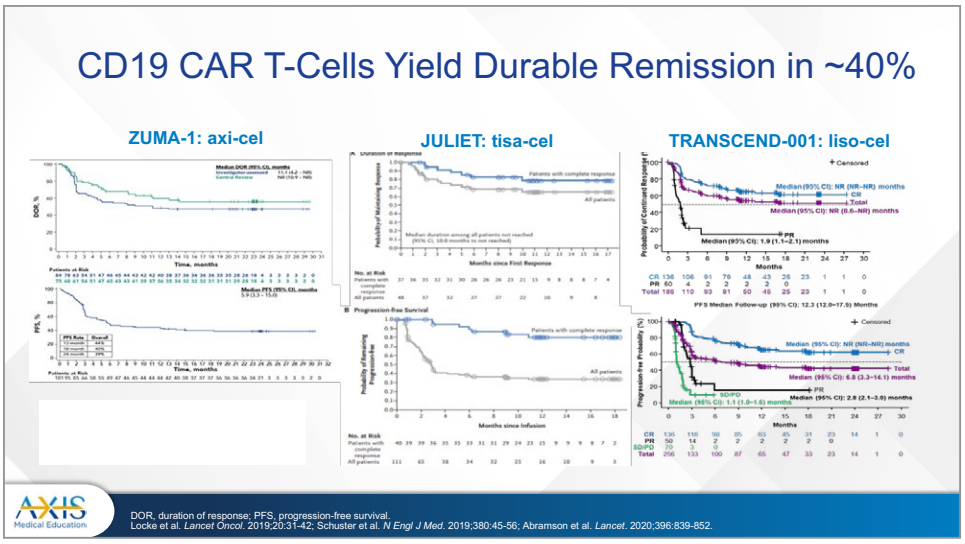
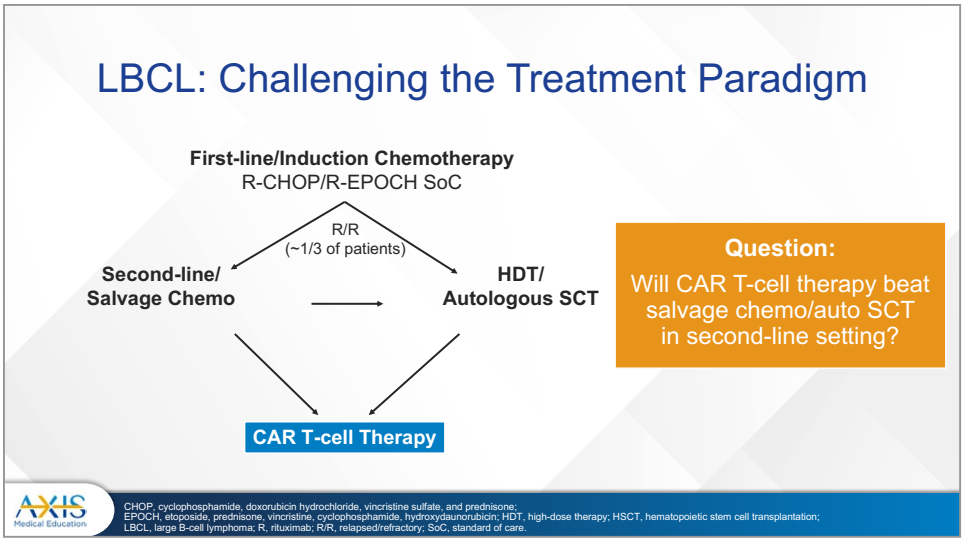
*n = 256 efficacy-evaluable patients.
Neelapu et al. *N Engl J Med.* 2017;377:2531-2544; Locke et al. *Lancet Oncol.* 2019;20:31-42; Schuster et al. *N Engl J Med.* 2019;380:45-56; Abramson et al. *Lancet.* 2020;396:839-852.
Axi-cel, axicabtagene ciloleucel; CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; ICANS, immune effector cell-associated neurotoxicity syndrome; Liso-cel, lisocabtagene maraleucel; mOS, median overall survival; ORR, overall response rate; Tisa-cel, tisagenlecleucel.

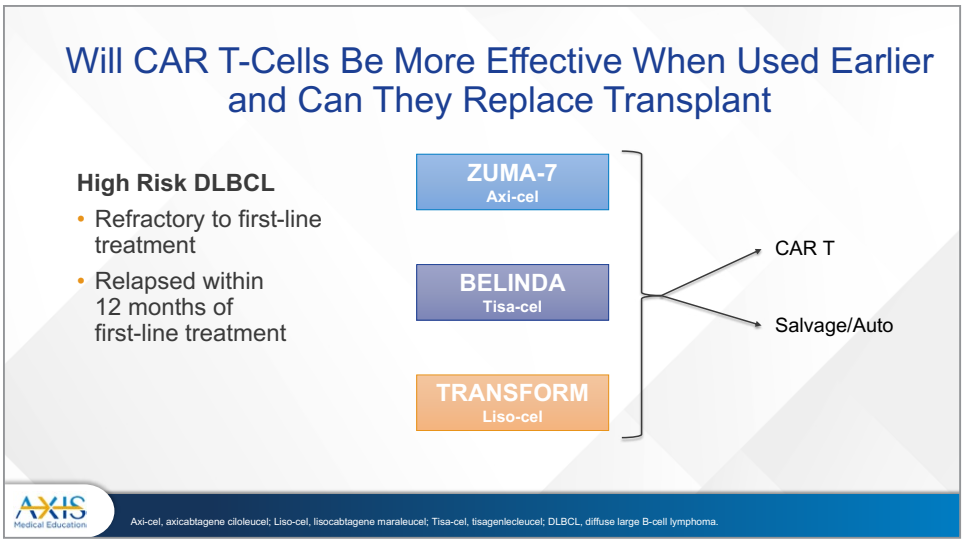
So, now that we understand what the different CAR T-cell therapies are that are available for large B-cell lymphoma, let's take a look at the results of these CAR T-cell therapies in chemotherapy-refractory patients. These are the pivotal trials treating large B-cell lymphoma patients after 2 or more systemic lines of therapy: the ZUMA-1 study of axi-cel, the JULIET study of tisa-cel, and the TRANSCEND study of liso-cel. These are all open-label, phase 2 studies, and they took patients that really had very low likelihood of responding to available agents. We know that at the time of these clinical trials, available agents would lead to responses in about 20% of patients and complete responses in fewer than 10% of patients. With these CAR T cells, we're seeing responses in anywhere between 50% and 80% of patients, and we're seeing complete responses in anywhere between 40% and 55% of patients. More importantly than seeing these high response rates, we're seeing durability of response. At 6 months, very few patients will relapse; we're seeing that about 40% of patients are maintaining their response past that critical time point. Now these CAR T cells have some unique toxicities. They cause cytokine release syndrome based on the cytokine cascade that follows CAR activation, and they also can cause immune effector cell neurologic toxicity, or neurotoxicity syndrome (ICANS), which is, in part, related to breakdown of the blood-brain barrier and immune effector cells and cytokines making their way into the brain and the CNS, where they lead to brain inflammation. Across these trials, rates of CRS and ICANS range from about 50% to 90% for CRS and about 20% to 60% for ICANS, with the CD28 CAR axi-cel having higher rates of CRS and ICANS than the 4-1BB CARs like tisa-cel and liso-cel. The CD28 CARs also have higher rates of high-grade CRS and neurologic toxicity.



- In addition to having a very high 6-month overall response rate, we now have multiyear data follow-up for these clinical trials, both in terms of durability of response as well as progression-free survival. And what we can see is that, across the 3 different trials, somewhere between 35% and 45% of patients will have a durable remission, and for many of these patients, this lasts beyond 2 to 3 years, in some cases even 4 or 5 years, and really makes us very encouraged that these patients are likely cured of their large B-cell lymphoma.



- So, I want to go back to the treatment paradigm for large B-cell lymphoma that I introduced earlier on and ask the question, “If CAR T cells work so well in the multiply relapsed setting, will they beat salvage chemotherapy and an auto transplant in the second-line setting?”



To answer this question, there were 3 randomized trials: the ZUMA-7 trial of axi-cel, the BELINDA trial of tisa-cel, and the TRANSFORM trial of liso-cel, which all enrolled high-risk relapsing large B-cell lymphoma patients. These are patients who, after frontline therapy, were either primary refractory or relapsed within the first 12 months. I showed you those curves showing that these patients will do poorly with salvage chemo and an auto transplant earlier. These patients were randomized in a 1:1 fashion to either receive their respective CAR T-cell therapy or to receive salvage chemotherapy with a platinum-based salvage chemotherapy regimen. And, if they have a response, they would go on to receive an autologous stem cell transplant.

ZUMA-7, TRANSFORM, BELINDA: Key Similarities and Differences in Second-Line Treatment

	ZUMA-7	TRANSFORM	BELINDA
Product	**Axi-cel**	**Liso-cel**	**Tisa-cel**
Patient Population	primary refractory, early relapsed	primary refractory, early relapsed, PMBCL; upper age limit 75 years	primary refractory, early relapsed
Trial Numbers	359	184	322
Timing of apheresis	after enrollment	Prior to enrollment	prior to enrollment
Comparator	SOC (curative)	SOC (curative)	SOC (curative)
Bridging therapy	Corticosteroids	Chemotherapy	Chemotherapy
LD chemotherapy	FC	FC	FC or bendamustine
Crossover	Off protocol	On protocol	On protocol
Primary endpoint	EFS (definition different)	EFS (definition different)	EFS (definition different)
EFS definition	Time from randomization to: • earliest date of disease progression as per Lugano Classification (2014) • commencement of new lymphoma therapy • or death from any cause as determined by blinded central review *At day 150*	Time from randomization to: • death from any cause • PD, failure to achieve a CR or PR • or start of new antineoplastic therapy due to efficacy concerns *9-12 weeks*	Time from date of randomization to: • date of first documented PD/SD at or after the Week 12+/-1 assessment, as assessed by BIRC per Lugano criteria • or death due to any cause, at any time *At 12 weeks*
Secondary endpoints	OS	OS	OS

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Locke et al. *N Engl J Med.* 2022;386(7):640-654; Kamdar et al. *Lancet.* 2022;399(10343):2294-2308; Bishop et al. *N Engl J Med.* 2022;386(7):629-639.
Axi-cel, axicabtagene ciloleucel; BIRC, blind independent review committee; CR, complete response; EFS, event-free survival; FC, fludarabine and cyclosphosphamide; Liso-cel, lisocabtagene maraleucel; LD, low-dose; OS, overall survival; PMBCL, primary mediastinal large B-cell lymphoma; PD, progressive disease; PR, partial response; SD, stable disease; SOC, standard of care; Tisa-cel, tisagenlecleucel.

There were some key differences and similarities between the studies. Ultimately, the study designs were quite similar across the board. The comparator and standard-of-care arms were very similar. There were different allowances for bridging therapy across the studies for the experimental CAR T-cell arms. So, between pheresis and CAR T-cell infusion, during CAR T-cell manufacturing, only corticosteroids were allowed on the ZUMA-7 clinical trial, whereas patients were allowed to get 1 cycle of chemotherapy on the TRANSFORM study and up to 2 cycles of chemotherapy on the BELINDA study. Patients were not allowed to cross over on the ZUMA-7 study; however, crossover was allowed on protocol for patients treated on the TRANSFORM and the BELINDA studies. Patients were allowed to receive 2 or 3 cycles of salvage chemotherapy on the ZUMA-7 study; all patients received 3 cycles of salvage chemotherapy on the TRANSFORM study and on the BELINDA study. If patients had stable disease and not progressive disease but not a response after the first line of salvage chemotherapy in the standard-of-care arm, they actually were allowed to have a second line of salvage chemotherapy to try to get them to an autologous stem cell transplant. The end result is that patients got their CAR T cells a lot faster on the ZUMA-7 study than they did on the TRANSFORM or the BELINDA studies. The primary endpoint of these studies was event-free survival.

ZUMA-7, TRANSFORM, BELINDA Results: Second-Line Treatment

	ZUMA-7	TRANSFORM	BELINDA
Product	**Axi-cel vs SOC**	**Liso-cel vs SOC**	**Tisa-cel vs SOC**
Costimulatory domain	CD28	4-1BB	4-1BB
ORR (%)	83% vs 50%	86% vs 48%	75% vs 68%
CR (%)	65% vs 32%	66% vs 39%	46% vs 44%
mEFS (months)	8.3 vs 2.0	10.1 vs 2.3	3.0 vs 3.0
EFS rate (%)	2-year: 40.5% vs 16.3%	12-month: 44.5% vs 23.7%	---
mPFS (months)	14.7 vs 3.7	14.8 vs 5.7	---
PFS rate (%)	2-year: 46% vs 27%	12-month: 52.3% vs 33.9%	---
mOS (months)	NR vs 35.1	NR vs 16.4	---
OS rate (%)	---	12-month: 79.1% vs 64.2%	---

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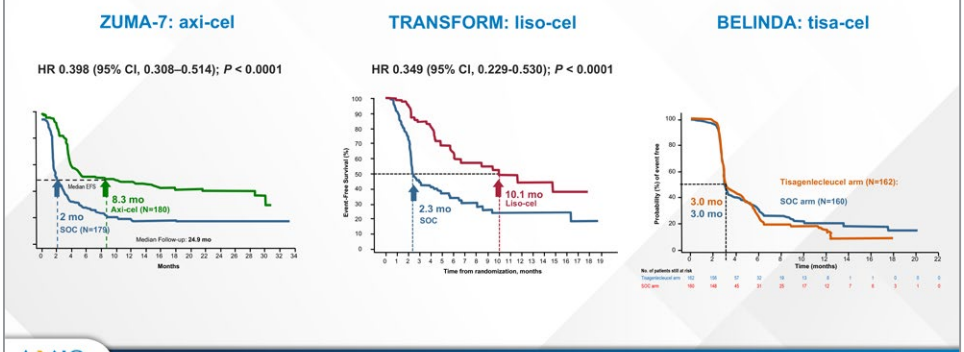
Locke et al. *N Engl J Med.* 2022;386(7):640-654; Kamdar et al. *Lancet.* 2022;399(10343):2294-2308; Bishop et al. *N Engl J Med.* 2022;386(7):629-639.
Axi-cel, axicabtagene ciloleucel; CR, complete response; Liso-cel, lisocabtagene maraleucel; mOS, median overall survival; mEFS, median event-free survival; mPFS, median progression-free survival; NR, not reached; ORR, overall response rate; SOC standard of care; Tisa-cel, tisagenlecleucel.

- The ZUMA-7 and the TRANSFORM studies were positive studies, and the median and 2-year event-free survivals for the experimental CAR T-cell arms were superior to the standard-of-care arms in both studies. The BELINDA study, however, was a negative study, where the median event-free survival was identical in both groups.

ZUMA-7, TRANSFORM, BELINDA: EFS



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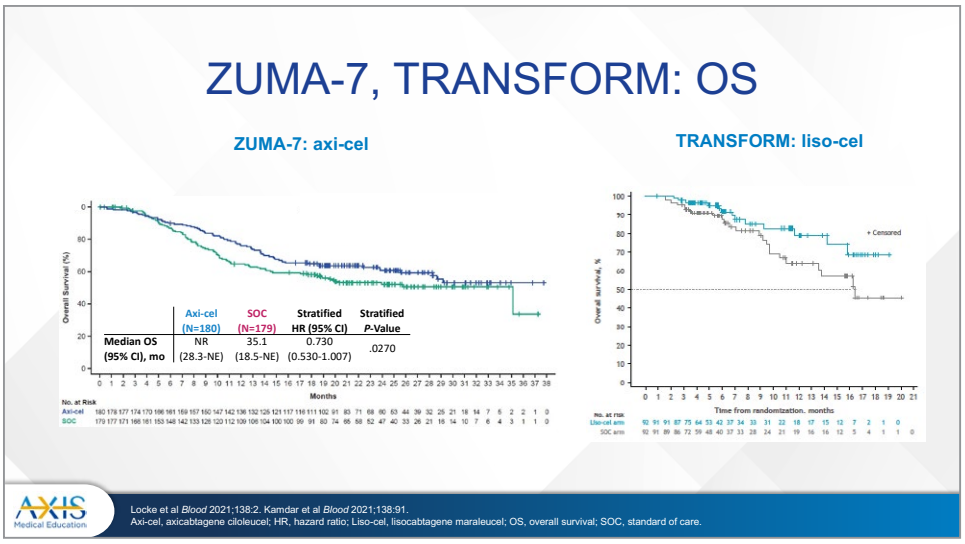
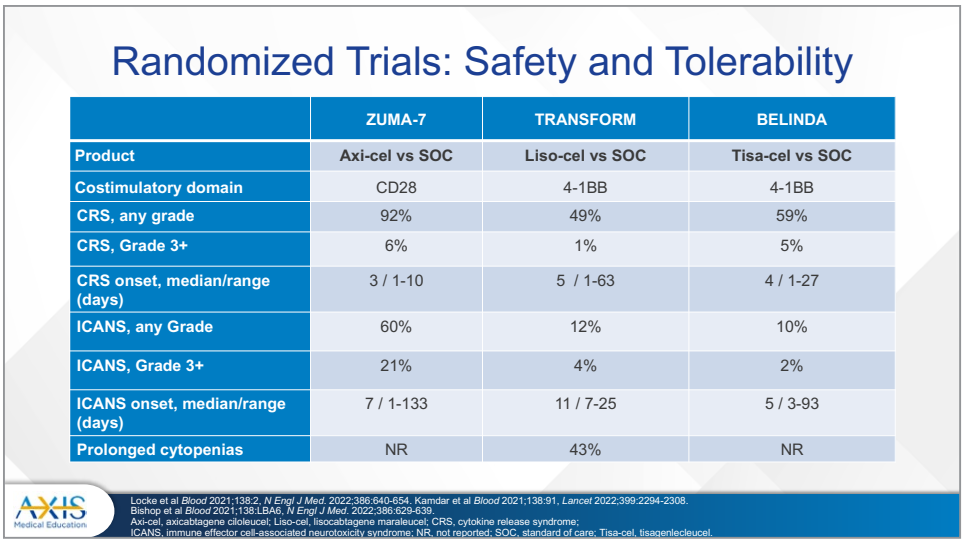
Locke et al *Blood* 2021;138:2; Kamdar et al *Blood* 2021;138:91; Bishop et al *Blood* 2021;138:LBA6.
Axi-cel, axicabtagene ciloleucel; EFS, event-free survival; Liso-cel, lisocabtagene maraleucel; SOC standard of care; Tisa-cel, tisagenlecleucel.

- Here's a look at the event-free survival curves. Patients treated on ZUMA-7 and TRANSFORM had superior event-free survival compared with patients who received standard of care, but the curves are really overlapping on the BELINDA study.

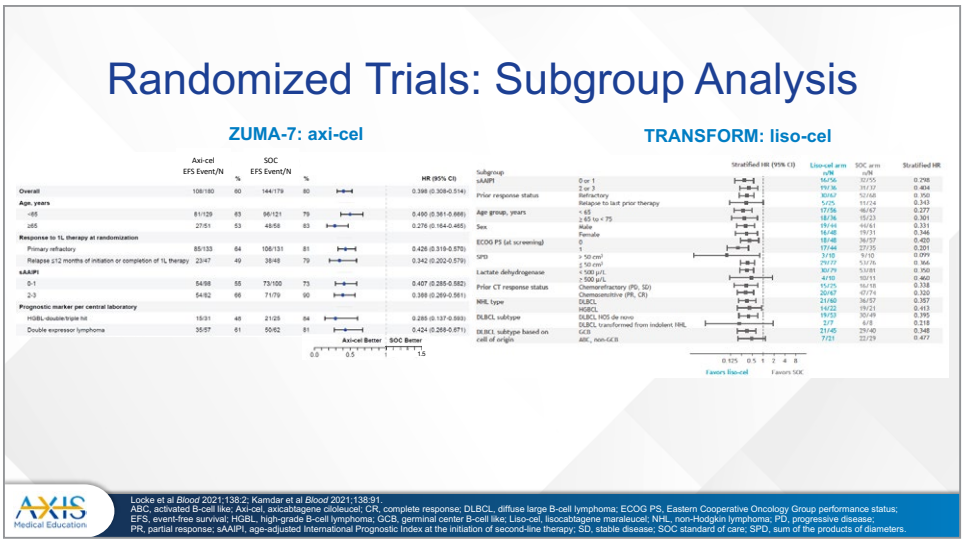


- And just a look at overall survival, which these studies were not powered to detect and which was not expected to be a significant endpoint, given the number of patients that were allowed to ultimately cross over and get CAR T cells in the third line. There is a separation of the curves, however, where patients treated with the experimental arm did have better overall survival, although not statistically significant, on the ZUMA-7 and TRANSFORM studies, which did raise the question of, "Is waiting for CAR T cells in the third line as advantageous as getting CAR T cells in the second line?"



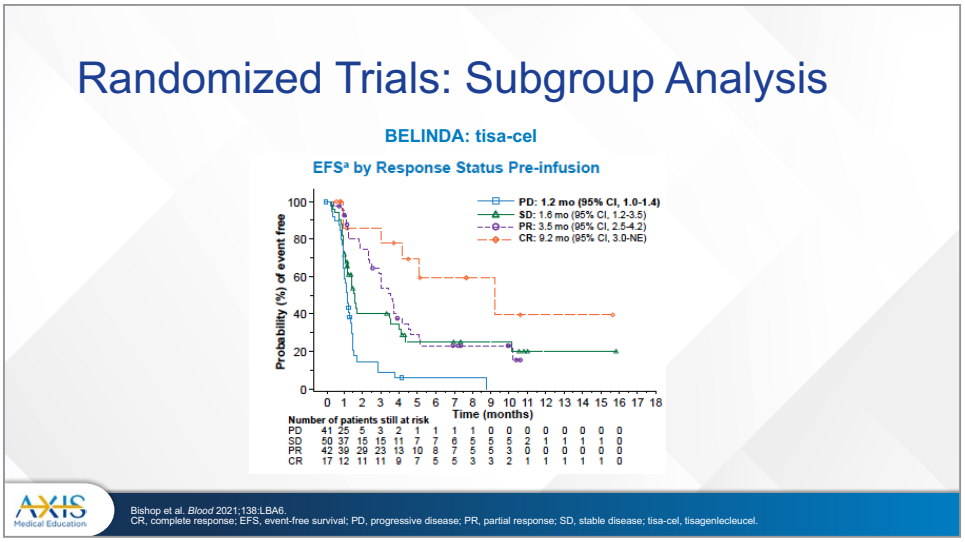
	ZUMA-7	TRANSFORM	BELINDA
Product	**Axi-cel vs SOC**	**Liso-cel vs SOC**	**Tisa-cel vs SOC**
Costimulatory domain	CD28	4-1BB	4-1BB
CRS, any grade	92%	49%	59%
CRS, Grade 3+	6%	1%	5%
CRS onset, median/range (days)	3 / 1-10	5 / 1-63	4 / 1-27
ICANS, any Grade	60%	12%	10%
ICANS, Grade 3+	21%	4%	2%
ICANS onset, median/range (days)	7 / 1-133	11 / 7-25	5 / 3-93
Prolonged cytopenias	NR	43%	NR

- The safety and tolerability of these CAR T cells on these different trials looks very, very similar to what we saw in the phase 2 pivotal trials in the third line and beyond, where rates of any high-grade CRS and any high-grade ICANS actually closely mirror what we saw on the phase 2 studies, and in multiply relapsed patients, where the rates of these toxicities are, again, higher on the ZUMA-7 study with axi-cel compared to the TRANSFORM study and BELINDA study of liso-cel and tisa-cel, respectively.



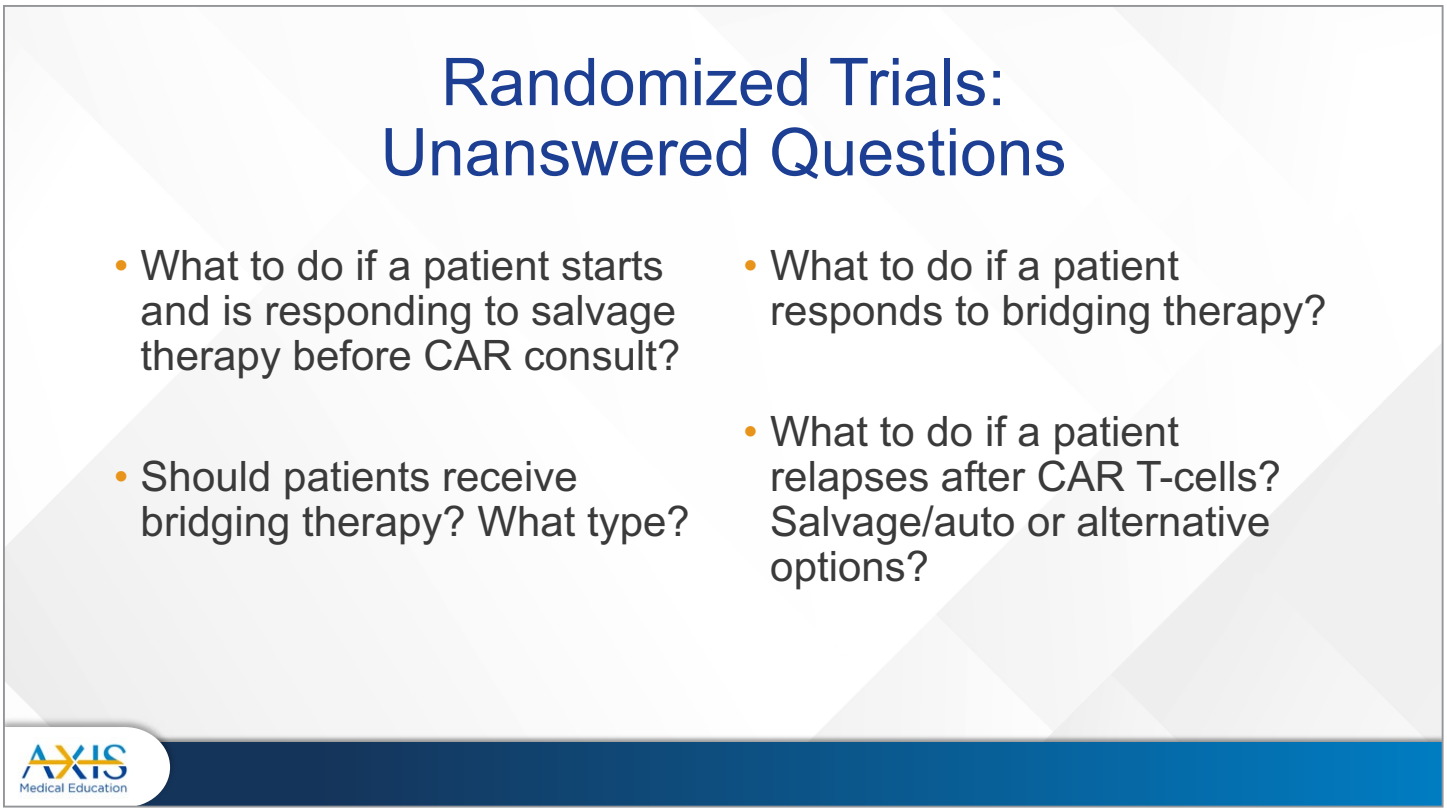
Locke et al *Blood* 2021;138:2; Kamdar et al *Blood* 2021;138:91.
ABC, activated B-cell like; Axi-cel, axicabtagene ciloleucel; CR, complete response; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; HGBL, high-grade B-cell lymphoma; GCB, germinal center B-cell like; Liso-cel, lisocabtagene maraleucel; NHL, non-Hodgkin lymphoma; PD, progressive disease; PR, partial response; sAAIPI, age-adjusted International Prognostic Index at the initiation of second-line therapy; SD, stable disease; SOC standard of care; SPD, sum of the products of diameters.

- A look at the subgroup analysis both for ZUMA-7 and for TRANSFORM: the experimental arm, the CAR T-cell arm, benefited all patients across the board, regardless of their risk group, whether they were young or old, whether they were primary refractory or relapsing within 12 months, whether they had a low or high age-adjusted IPI, whether they were double- or triple-hit lymphomas, whether they were transformed lymphomas or other high-grade B-cell lymphomas. All patient groups benefited from CAR T cells over standard-of-care therapy.



Bishop et al. *Blood* 2021;138:LBA6.
CR, complete response; EFS, event-free survival; PD, progressive disease; PR, partial response; SD, stable disease; tisa-cel, tisagenlecleucel.

- Although the BELINDA study was a negative study, they did look at the event-free survival by response status before the patients were infused with their CAR T cells. Remember, these patients could get 1 or 2 cycles of salvage chemotherapy and they were all restaged. And those who were actually in a complete response following 1 or 2 cycles of salvage chemotherapy did do better, in terms of their event-free survival, compared with patients who were in partial response, stable disease, and of course, progressive disease.



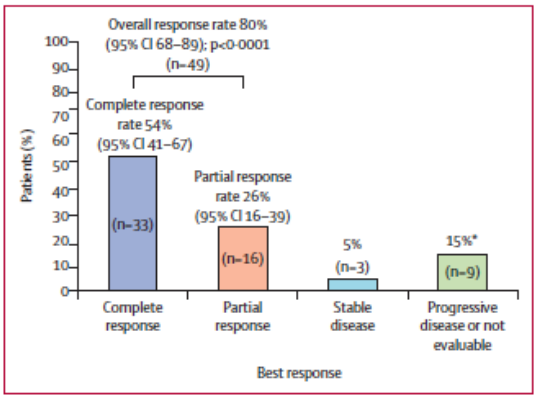
There are some unanswered questions from these randomized trials. Specifically, what do you do if a patient starts and is responding to salvage chemotherapy before their CAR T-cell consult? This is something we really do encounter in the real world. What these studies don't answer is whether CAR T cells are better for patients who are responding to salvage chemotherapy than autologous stem cell transplant. Really, these studies answer whether, for patients where the intention is to transplant, is CAR T-cell therapy better than the entire process of salvage and an auto transplant? My practice continues to be that, if someone is responding to salvage chemotherapy before I meet them, I may continue them on that salvage chemotherapy and assess their response. If they're in a CR, we take them to an autologous stem cell transplant. But that is definitely debatable. For someone who has a double-hit lymphoma or a high-grade B-cell lymphoma, and they were primary refractory, those patients I may continue with CAR T-cell therapy even if they are transiently responding to salvage chemotherapy. But, for all others, I might keep them on the standard-of-care route.

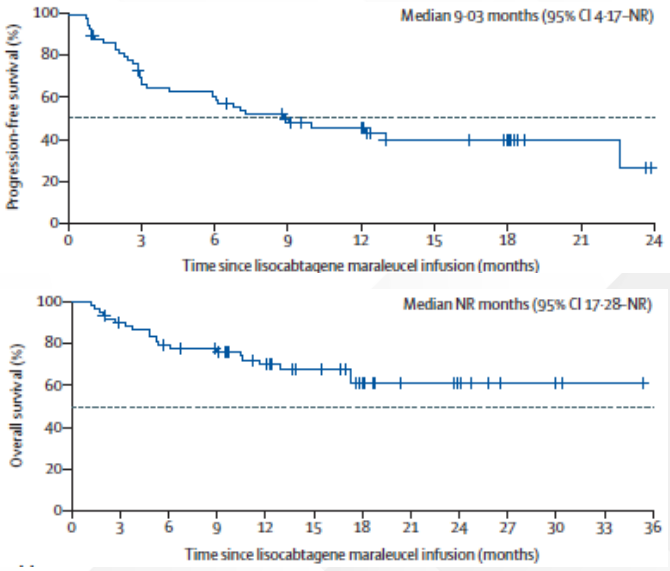
The other question is, should patients receive bridging therapy? And what type? We saw that each of the trials used different bridging therapies, and they used different types of bridging therapies. In addition to some of these platinum-containing regimens, we now have other agents that have been approved for large B-cell lymphoma, including things like polatuzumab that have a lot of activity in chemotherapy-refractory disease. Will that be better than standard platinum-based bridging therapy for these, basically, chemotherapy-refractory patients? That is really an unanswered question.

What do you do if a patient responds to that bridging therapy? I think this is a theoretical question, but practically speaking, once we commit a patient to a CAR T-cell treatment pathway, there are a lot of steps that go into that, including insurance authorization. It's hard to walk back from that. I think, from a practical standpoint, if a patient's responding to bridging therapy, they continue with CAR T cells because it's very hard to switch over from an insurance and other pathway perspective.

And then, what do you do if a patient relapses after CAR T cells? Is salvage and an auto transplant still an option for these patients? Or do we always proceed to alternative options, just as we would if someone was relapsing after CAR T cells in the third line and beyond? I don't have any good answers to these questions, but they will surely be addressed with research in the coming years.

PILOT Study: Liso-cel in Second-line Transplant Ineligible

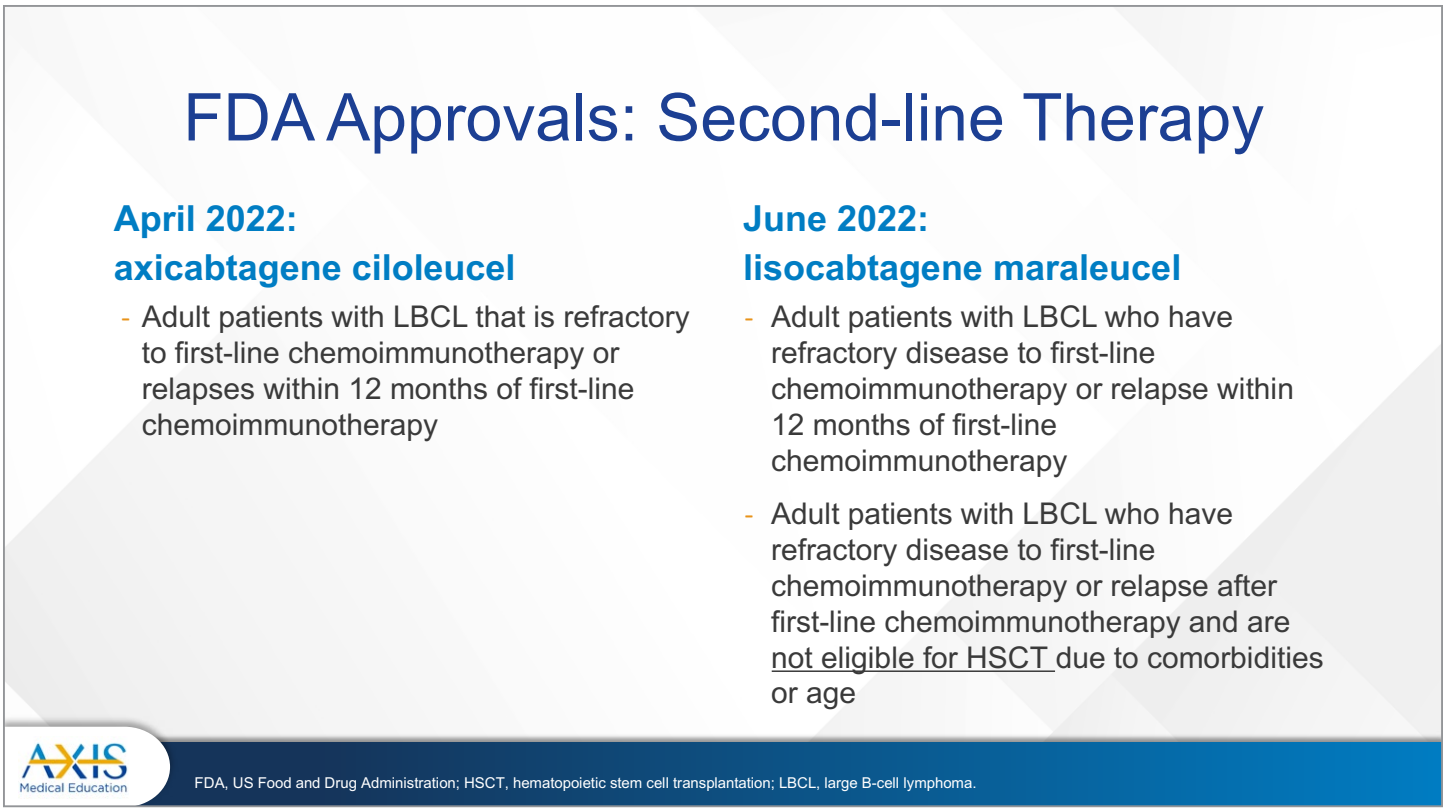




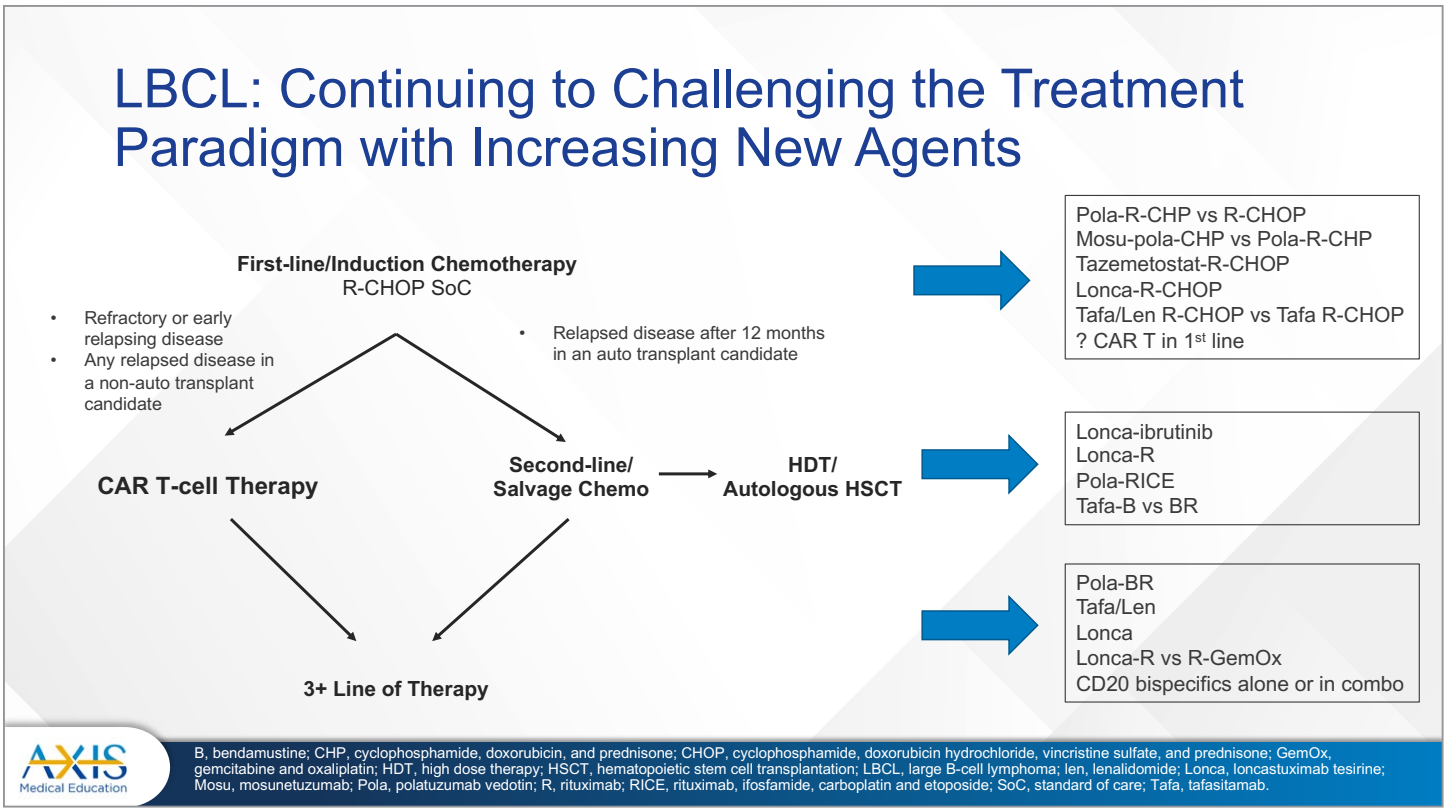
- CRS any/high grade: 38%/2%
- ICANS any/high grade: 31%/5%

Sehgal et al. *Lancet Oncol*. 2022;23:1066-1077.
CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; Liso-cel, lisocabtagene maraleucel; NR, not reported.

I do just want to call your attention to one other study, the PILOT study, which looked at lisocabtagene maraleucel, or liso-cel, in relapsing patients in the second line who were transplant ineligible. This was an open-label, phase 2 study where all of these patients who were ineligible for a transplant, either because of age or other medical comorbidities, were treated with liso-cel in the second line. And what this study showed is that patients did very, very well, with a CR rate of 54%. They did very, very well in terms of progression-free survival, with a median progression-free survival of 9 months but still about 35% to 40% of patients maintaining that response over years of follow-up. Median overall survival had not been reached at the time of this reporting. And rates of any high-grade CRS or any high-grade ICANS are actually quite comparable to how liso-cel performs in other patient populations, making it also a safe option for these patients. Based on this study in 49 patients, the FDA also approved liso-cel for large B-cell lymphoma in the second line for transplant-ineligible patients.

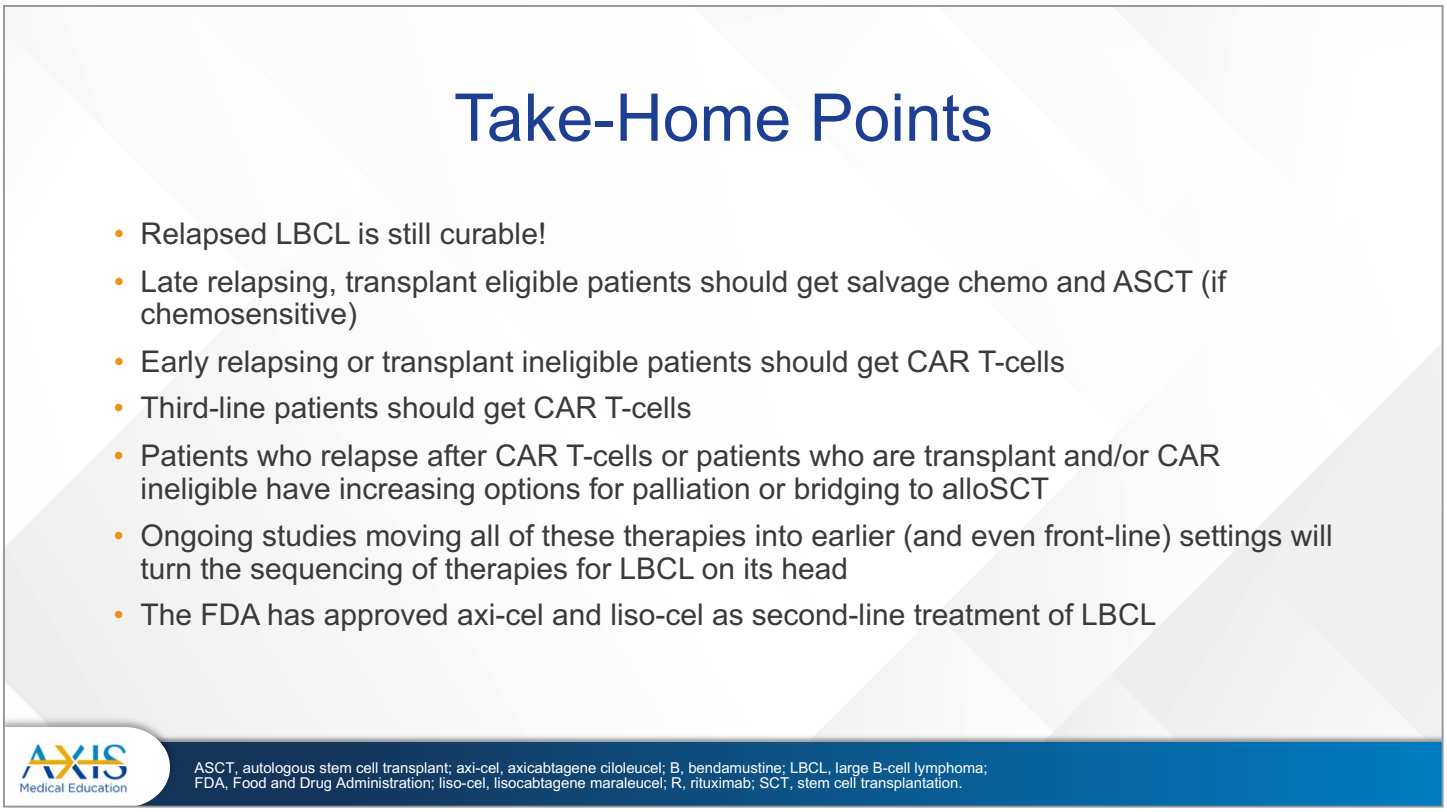


So, I just again to review the FDA approvals in second-line therapy, axicabtagene ciloleucel was approved for adult patients with large B-cell lymphoma that's refractory to frontline chemoimmunotherapy or relapses within 12 months of that chemotherapy. Lisocabtagene maraleucel also had that disease status added to its label. In addition, patients who are relapsing after frontline chemoimmunotherapy but who are not transplant eligible due to comorbidities or age are also approved for liso-cel in the second line.

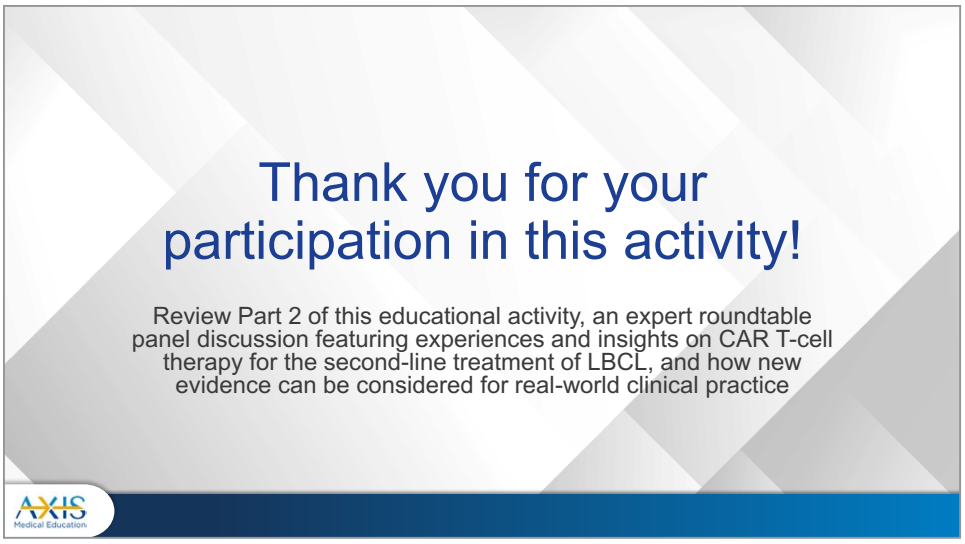


I want to go back to our large B-cell lymphoma treatment paradigm and say that we're continuing to challenge it with new treatments and increasing new agents. We've already seen the addition of CAR T-cell therapy in the second line for early relapsing or primary refractory patients or patients who are relapsing at any time point that are not auto transplant candidates.

For patients that relapse after 12 months and are an auto transplant candidate, they would go down the route of second-line chemo and salvage, and possibly an autologous stem cell transplant if they if they respond. Our patients who get CAR T cells in the second line, if they relapse, they have an option of getting second-line salvage chemo and an auto transplant if they respond. Or both of these groups of patients, if they don't respond, can go on to get third-line therapies. But at each of these time points, in the frontline, in the second line, and then the third line, we're seeing ongoing clinical trials looking at new agents. We await the readout of these studies to see what the new standards of care will be going into the next decade.



So, just some take-home points. It's really important to remember that relapsed large B-cell lymphoma is still curable, even in your 75- or 80-year-old, now that we have CAR T cells available. Late-relapsing, transplant-eligible patients should get salvage chemo and an auto transplant if they are chemo-sensitive, based on the data we have to date. But early relapsing or transplant-ineligible patients should get CAR T cells in 2022. Third-line patients who had relapsed at a later time point and didn't respond to salvage or relapsed after an auto transplant should also be getting CAR T cells in 2022. Patients who relapsed after CAR T cells or patients who are transplant and/or CAR ineligible have increasing options for palliation and bridging, such as allogeneic stem cell transplant, which would represent a definitive option for these patients. And ongoing studies moving all of these therapies into earlier and even frontline settings will turn the sequence of therapies for large B-cell lymphoma on its head. I really do await the results of these studies so we can find out what to do next. Finally, the FDA has approved axi-cel and liso-cel as second-line treatment for large B-cell lymphoma and, just to reiterate, for early relapsing or transplant-ineligible patients, they should be getting these therapies in the second line, based on randomized data.



- Thank you for your participation in this activity. Please also review part 2 of this educational activity, an expert roundtable panel discussion featuring experiences and insights on CAR T-cell therapy for the second-line treatment of large B-cell lymphoma and how new evidence can be considered for real-world clinical practice. Thanks for listening.

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