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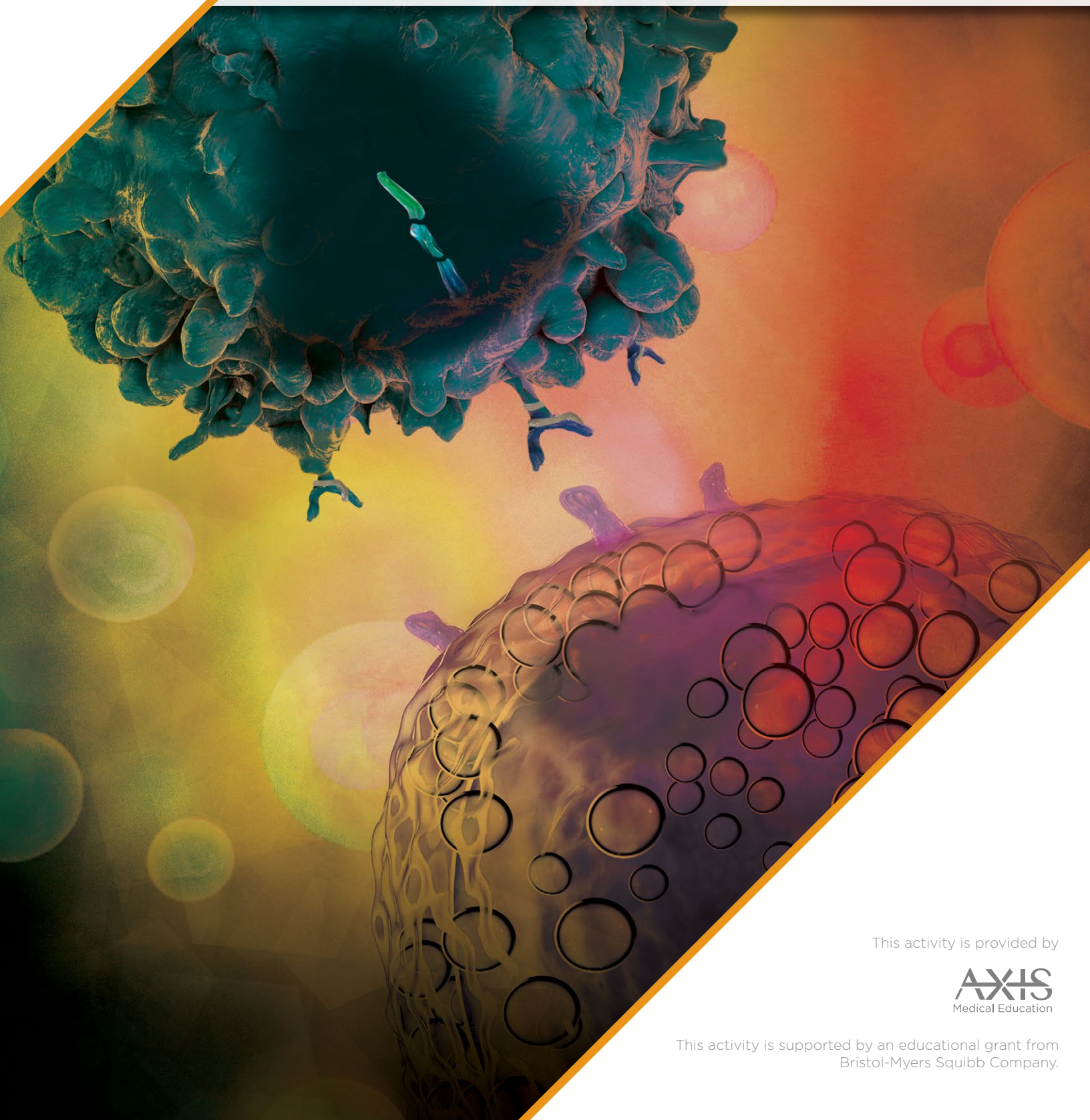
Paradigm Shifts in CAR T-Cell Therapy for Relapsed/Refractory Large B-Cell Lymphoma: A Video Panel Discussion

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



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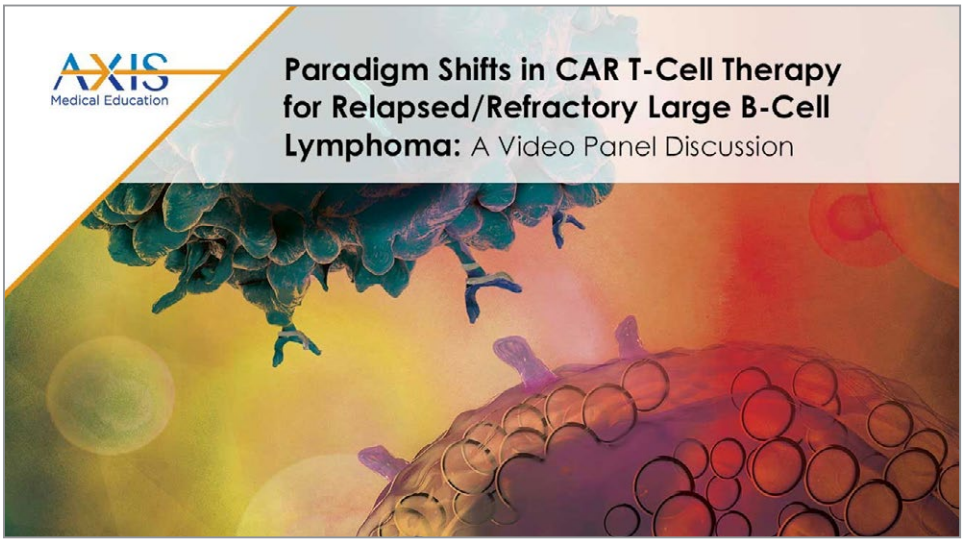
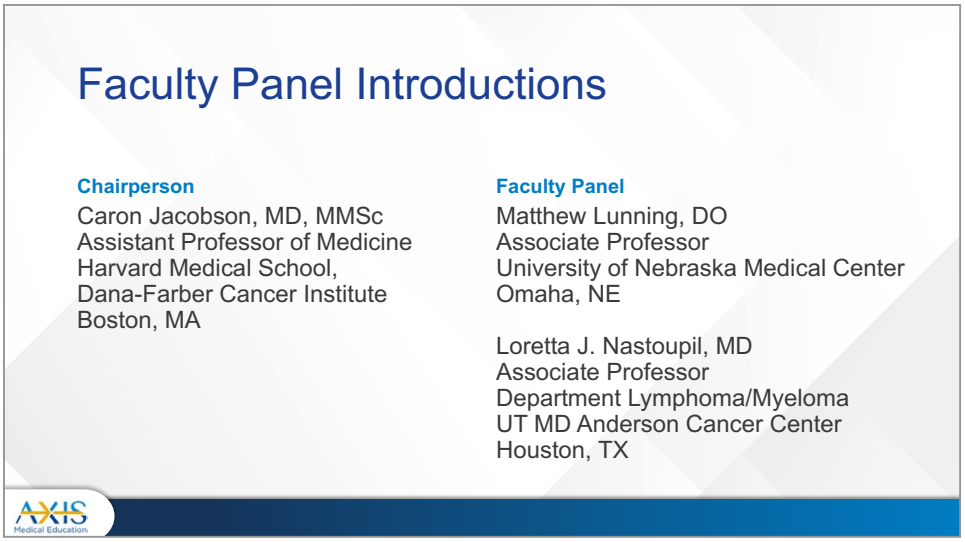
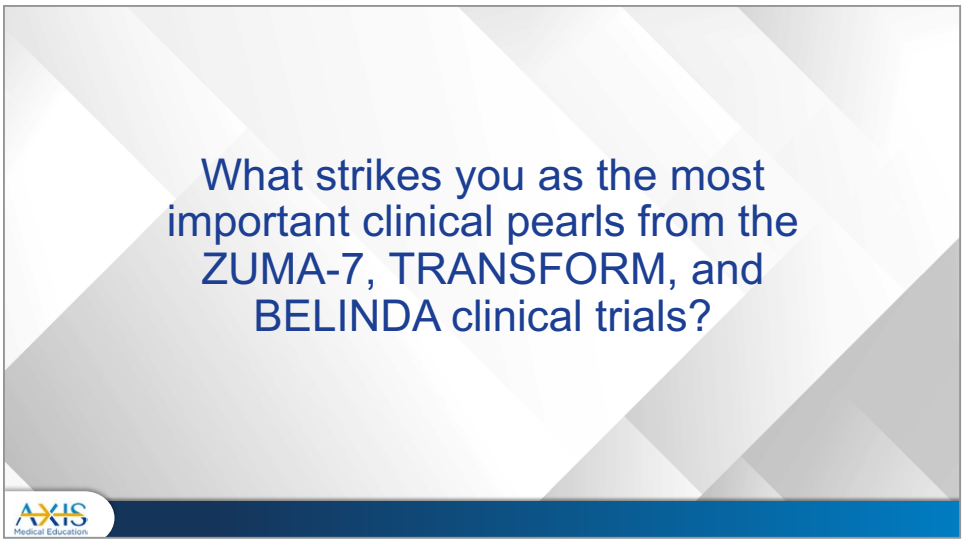
Paradigm Shifts in CAR T-Cell Therapy for Relapsed/Refractory Large B-Cell Lymphoma: A Video Panel Discussion

Caron Jacobson, MD, MMSc; Matthew Lunning, DO; and Loretta J. Nastoupil, MD

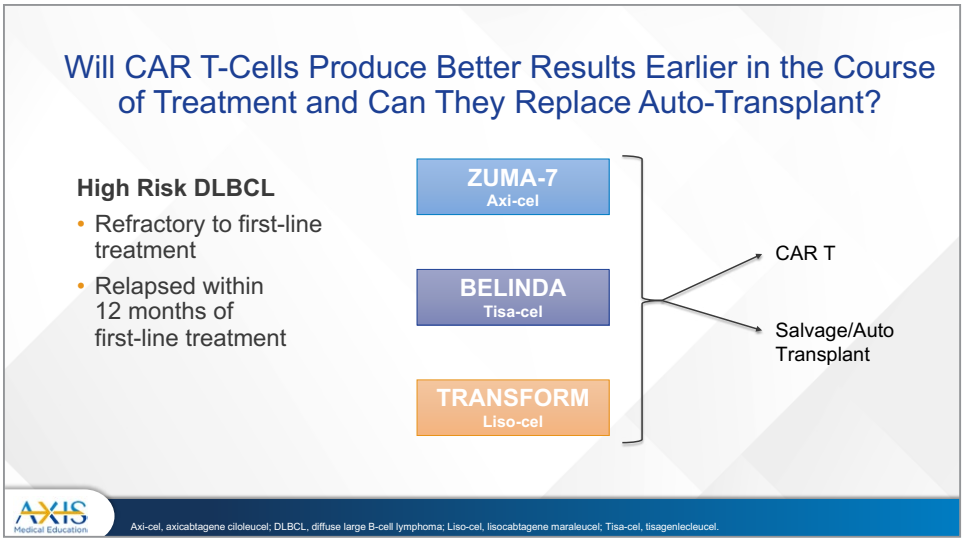




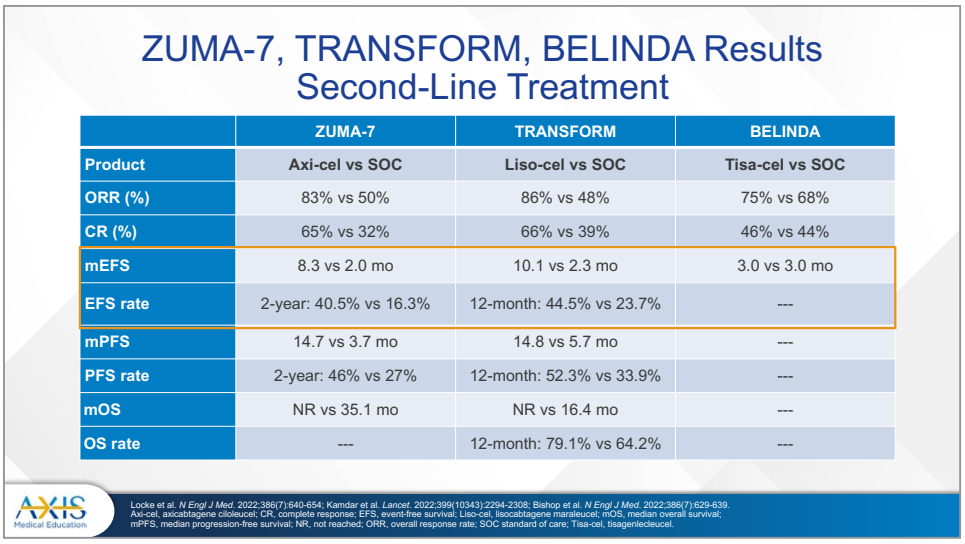
Caron Jacobson, MD, MMSc: Hello and welcome. I'm Dr. Caron Jacobson, Assistant Professor of Medicine at Harvard Medical School, and Medical Director of the Immune Effector Cell Therapy Program at the Dana-Farber Cancer Institute. I'm joined today by Dr. Matthew Lunning, Associate Professor at the University of Nebraska Medical Center, and Dr. Loretta Nastoupil, Associate Professor in the Department of Lymphoma and Myeloma at the MD Anderson Cancer Center. Today we will be discussing our experiences and insights on CAR T-cell therapy for the treatment of large B-cell lymphoma, focusing on the second-line setting and how new evidence can be considered for real-world clinical practice. Let's begin.



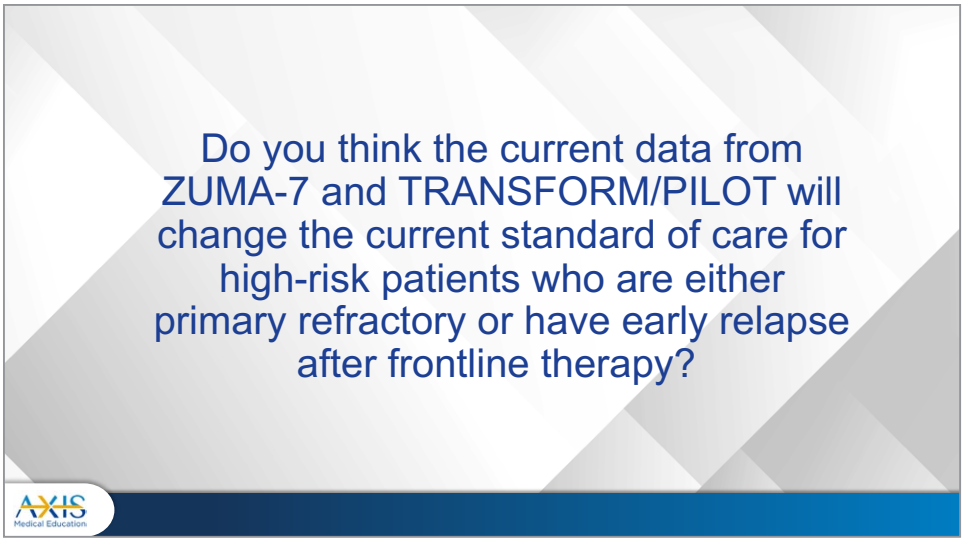
I want to start, Dr. Nastoupil, by asking you your top-line impressions of the randomized ZUMA-7 trial of axi-cel, the TRANSFORM clinical trial of liso-cel, and the BELINDA clinical trial of tisa-cel in terms of their impact on clinical practice and some clinical pearls that you've taken away from those studies.



Loretta J. Nastoupil, MD: Thanks, Caron. We've seen CAR T-cell therapy really transform outcomes for patients with chemorefractory large cell lymphoma in that third-line or later space, so it made sense to take CAR T into second line, potentially. The highest unmet need was for patients who relapsed within 12 months of rituximab and an anthracycline-backed chemotherapy regimen.



- This is the first time we can compare across these CAR constructs, because all 3 studies were done in a similar patient population. My take-home message is that axi-cel and liso-cel are more effective strategies for early relapse patients with large cell lymphoma than traditional salvage chemotherapy.



- **Dr. Jacobson:**
  Great. Dr. Lunning, looking at this data, a lot of us do think that this is practice changing, but how is it changing your practice? How are you implementing the results of these clinical trials into early relapsing and primary refractory patients?

ZUMA-7, TRANSFORM, BELINDA: Key Similarities and Differences 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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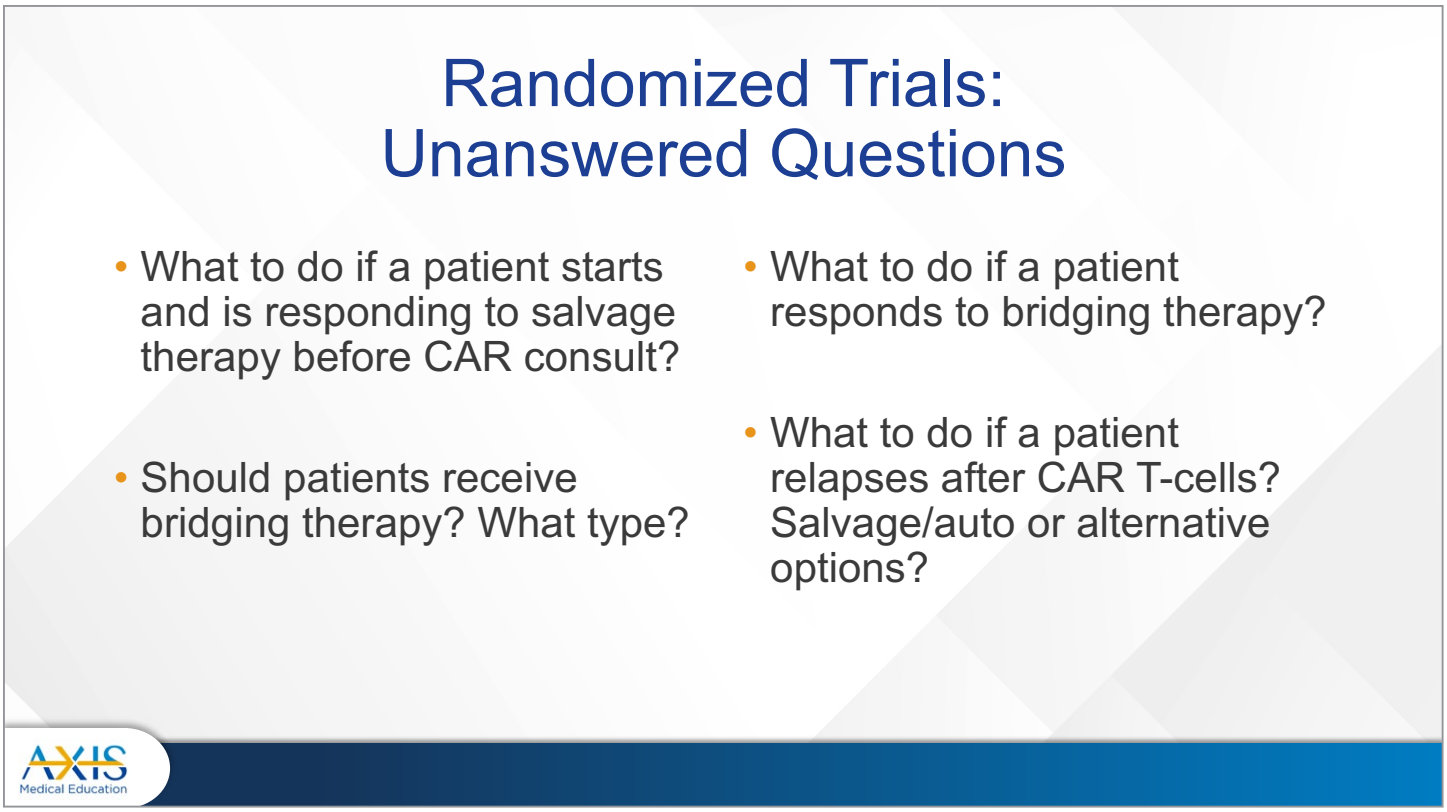
Locke et al. *N Engl J Med*. 2022;386(7):640-654; Kamdar et al. *Lancet*. 2022;399(10343):2294-2308; Bishop et al. *N Engl J Med*. 2022;386(7):629-639.
Axi-cel, axicabtagene ciloleucel; BIRC, blinded independent review committee; CR, complete response; EFS, event-free survival; FC, fludarabine and cyclosphosphamide; 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.

Matthew Lunning, DO: I think we had to get out ahead of this data a little bit, and we've all got our referral networks for the diffuse large B-cell lymphoma space. But getting the referring physicians to understand that now maybe they shouldn't give that second-line chemotherapy for that patient who's relapsing within 1 year of completion of therapy. Sometimes, these patients who are primary refractory, you're getting the phone call and you say, let me see them tomorrow or the next day. Because while the studies were done in this space, when we allow this to move into the commercial environment, there are several other hurdles that we have to deal with, namely, working through the insurance process. You want to be involved in the pre-apheresis bridging period.

We've seen a lot of data coming out now that bendamustine probably isn't your best agent. And it's not like our referring partners in the community or even we ourselves would be using bendamustine in the second line, but perhaps we can get away with less-intensive strategies. In the TRANSFORM trial, bridging was allowed, and typically, that was with one of our standard second-line chemotherapies, whereas in ZUMA-7, bridging beyond steroids wasn't. I think we're going to end up somewhere in the middle. We're probably either going to be using polatuzumab, rituximab as a single agent, or if they're a little bit more aggressive, perhaps going to a middle-road regimen like R-GemOx or just GemOx in general if they're rituximab refractory.

Even though this was in the second-line setting, a fair percentage of these patients are going to require some therapy before apheresis. Now we finally have data; we had a suspicion about that data with regard to bendamustine. Coming out of American Society of Hematology (ASH), we now have a little bit more concrete data that we should stay away from bendamustine as a pre-apheresis because of how it affects not only the T-cell numbers, but likely the T-cell fitness, in giving this high-risk population the best chance of long-term, event-free survival that was demonstrated both in the ZUMA-7 and the TRANSFORM trials.



Dr. Jacobson:
Great. And you bring up a good point: a lot of these patients, for logistical purposes and the fact that they have an aggressive disease, will need some sort of therapy, either before they have their cells collected or after they have their cells collected and as a bridging regimen. What's your strategy if you were to encounter somebody who happens to be responding to pre-apheresis chemotherapy regimens or as a bridge? Do you think these studies really answer the question of what we should be doing for chemotherapy-responsive patients even in this early relapsing and primary refractory group?

Dr. Lunning:
There are people in our community who will say it's much easier to do a CAR T-cell after an auto transplant than it is to do an auto transplant after a CAR T. So, if I've gotten a patient that fits this bill of refractory to first-line therapy or relapse within 12 months, understanding that the relapse within 12 months is arbitrary, I typically think, there's the primary refractory, there's those who relapse within 6 months, and then there are those 6 months and beyond. If they come to me at 9 months after their frontline therapy, where they achieved CR, and then they get ICE or RICE for 2 cycles, and they say, my tumors were this big and now they're this big, maybe I would do a PET scan. And if there isn't a metabolic CR, then I would lean into CAR T but if there is a metabolic CR, I would have that discussion with them. I would utilize their treatment history perhaps to guide me, understanding that that wasn't exactly how the trial was, but I don't think the trial answered the CR question. And in the third-line setting, we weren't allowed to take CRs into CAR T. But I also think that this is a higher-risk population, so it wouldn't be necessarily inappropriate to take CRs into CAR T if they had the right kind of clinical history that led up to that decision.

Dr. Jacobson:
Yeah. Dr. Nastoupil, do you agree with that? Is that what you're doing at MD Anderson for patients that are having some hint of chemo-responsive disease prior to your plan for CAR T-cell therapy?

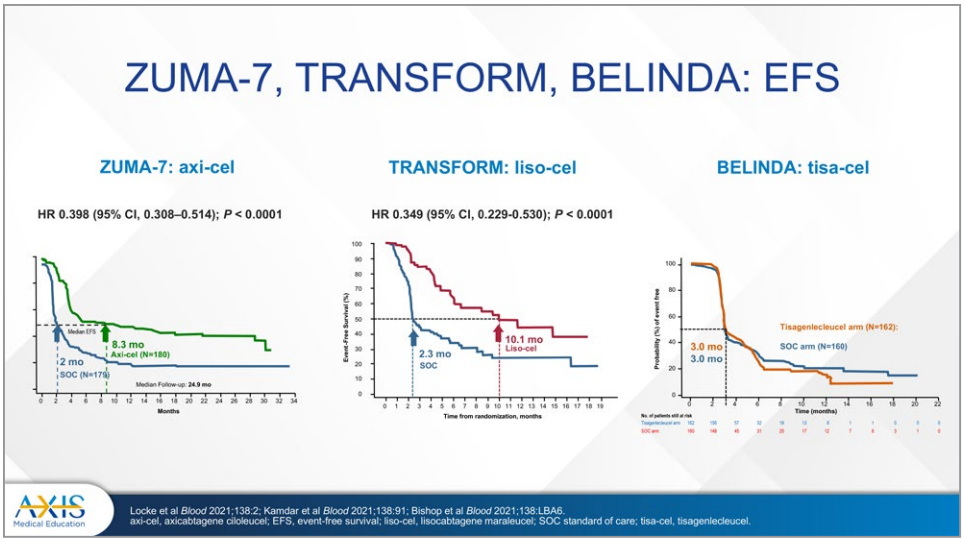
Dr. Nastoupil:
I think Matt hit on some key points. Most of these patients have aggressive disease, and it requires communication early so that we can get these patients into these certified centers as quickly as possible. If a patient is going to have disease that outpaces our ability to secure financial approval, manufacture, and

deliver the therapy, then we need to do everything within our tool kit to try and stabilize that disease. And so open communication is going to be key, as that will have implications in terms of when we might even select those cells.

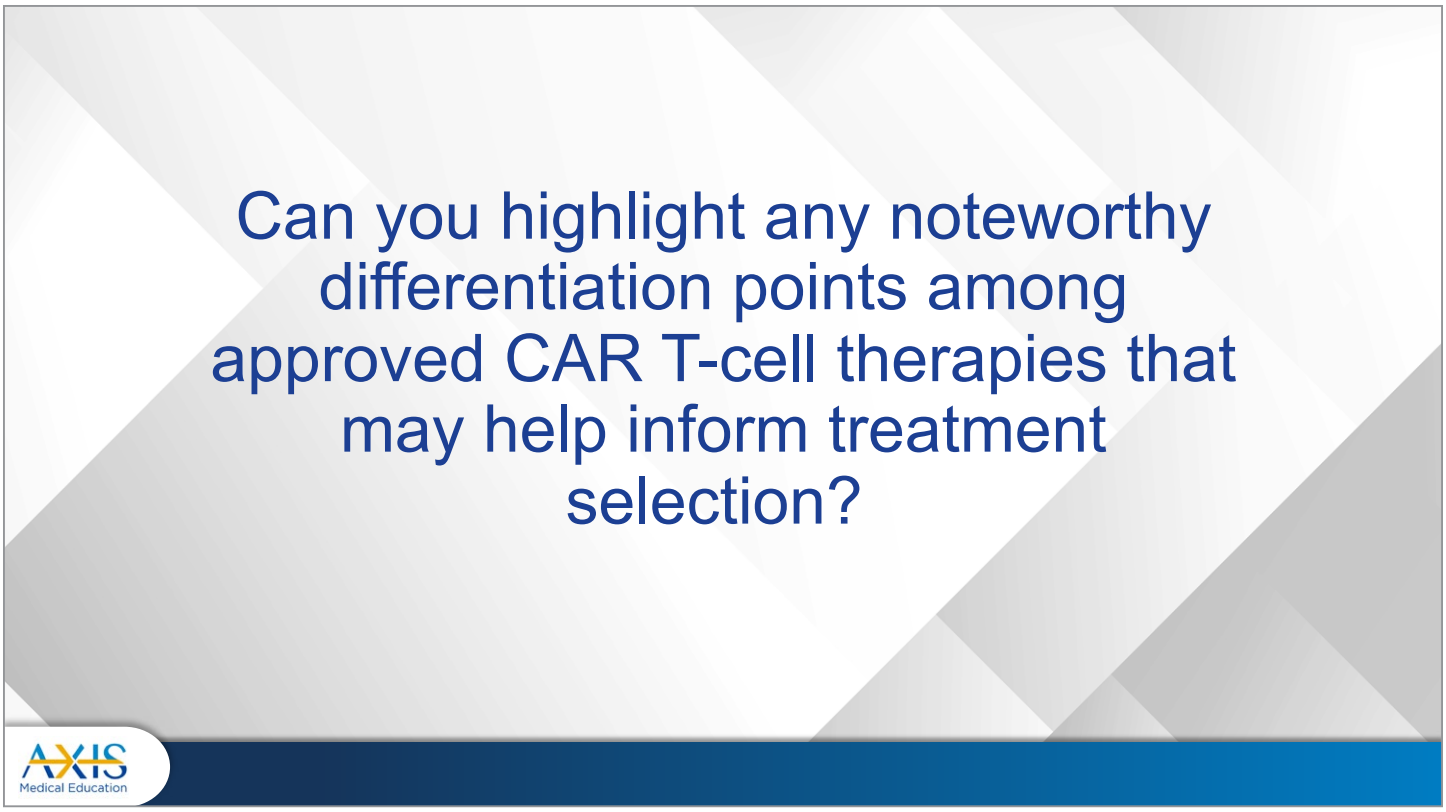
Obviously, we'd like to collect a patient who's proceeding to auto CAR as soon as possible to try and minimize the impact of that prior therapy on the fitness of those T cells. But again, we also recognize that most patients who are considered for CAR but never make it to cell infusion, it's due to disease progression. Everything that can be done to try and stabilize that disease is considered.

Where we will struggle is: what happens for those patients who are destined for CAR, but they do get 1 cycle of salvage chemotherapy and they have clinical signs that they are improving? Either reduction in peripheral nodes … we undergo scans oftentimes in preparation for CAR, and what if they're in a CR before we've collected those cells? I do think it makes sense to proceed with a plan for high-dose therapy, auto stem cell transplant for those patients. The flip side of that coin, if we've already collected those cells, and we've done a PET scan as part of restaging prior to proceeding with LD chemo and infusion of those cells, for those patients who are in a CR, I suspect we will continue with the CAR because that was the planned therapy. And we know that going into CAR with the lowest amount of disease burden is likely going to result in better outcomes, both from an efficacy and toxicity standpoint.

I think it depends where we are in terms of the process more so than how these prospective studies were conducted.



Dr. Jacobson:
Yeah, those are really good points. I'm going to ask you a potentially harder question. We know that the ZUMA-7 study and the TRANSFORM study were positive studies where axi-cel and liso-cel, respectively, were superior to standard of care, whereas the BELINDA study was a negative study where tisagenlecleucel did not beat standard of care in terms of event-free survival. We also know that liso-cel is approved not only in early relapsing or primary refractory patients in the second line, but in any second-line relapsing patient who is considered transplant ineligible because of age and medical comorbidities.



So in the summation of this data, Dr. Nastoupil, how do you choose a product for the patient who's sitting in front of you?

Dr. Nastoupil:
One of the things that we want to caution, but—it's hard not to conclude—is that maybe tisa-cel is the least effective of the CARs. I think there were challenges in terms of the BELINDA study design that make it impossible to draw that conclusion. But one key takeaway is time from enrollment to cell infusion was much longer on the CAR T arm of the BELINDA trial. And that highlights that time really does matter. And so I think that is one of the major factors in terms of how I'm navigating these treatment options. For my early relapse patients, CAR T is my preferred approach, and I want to get it as quickly as possible.

I know that with axi-cel, they have the highest rates of manufacturing success, meaning I'm going to get a commercial product and in the shortest timeline. So that matters to me. Where liso-cel may have a potential advantage is the safety profile. So if I have an older or frailer patient where I'm worried about them tolerating the toxicity of axi-cel, and the disease pace is one that will lend itself to a longer manufacturing time, that slightly higher risk of having an out-of-spec product, which is going to require us to treat these patients on an expanded access protocol, then I might still pursue liso-cel just based off its toxicity profile.

If everything were equal, and that's never true, but if manufacturing was equally effective in a similar timeline, I think it's hard not to choose a better-tolerated CAR such as liso-cel. But to date, we've not seen that. So, we're more often prescribing axi-cel just based off its availability.

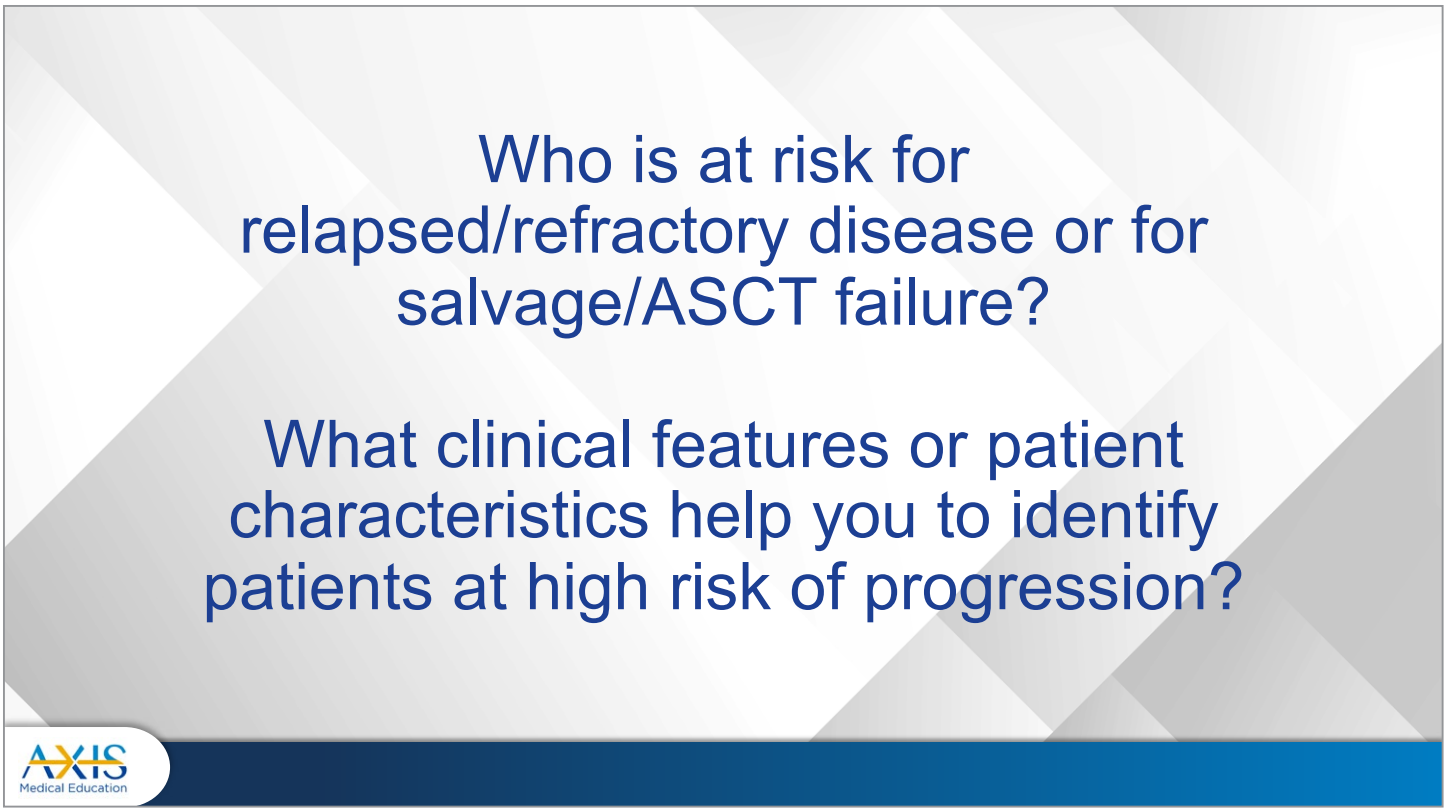
Dr. Jacobson:
Great. Dr. Lunning, do you agree or do you have anything to add?

Dr. Lunning:
Yeah, 100%, I agree with Dr. Nastoupil's comments there. You know, every day matters in this disease, in this situation. While I often want to try to get the liso-cel, sometimes the disease demands axi-cel. I can't do a CAR T cell on an individual that's not alive, or their disease is just exploding to where I can't even get them to the apheresis time point. I do take very good care in asking the patient about, you know, tell me the pace of your disease, when did you feel it? And sometimes you can feel out those TRANSFORM patients in that scenario. But

certainly, you can get those patients who are having a robust doubling time in the size of their tumor, who you just know are going to probably need a more intensive chemo strategy in the bridging, but also are probably going to need axi-cel just because of the infusion time or the access to apheresis slots, as well as the vein-to-vein time.

As Dr. Nastoupil stated, all things being equal, I think that I do agree that liso-cel does appear to have a safer toxicity profile. But it isn't to say that axi-cel hasn't tried to improve upon that, with several of the changes that have been done in the risk-mitigation strategy along the way, of earlier treatment for lower-grade toxicities, as well as consideration of prophylactic dexamethasone.

Dr. Jacobson:
Great. I want to take a step back and think about how high risk was defined in these randomized studies, specifically in terms of being primary refractory and early relapse, and think a little bit about what the other risk factors are even before you see that early relapse or that primary refractory disease that would kind of clue you in to somebody being likely to relapse early, and likely to not do well with salvage on an auto. Because up until this approval, here at Dana-Farber we didn't routinely scan our patients with large cell lymphoma in remission after frontline chemoimmunotherapy. But given this cutoff of, less than 1 year or greater than 1 year, it certainly has caused us to sort of take a step back and think, should we be scanning our patients within that first year to catch one of these early relapses to allow them to proceed to CAR? Maybe that's an all-comer strategy, or maybe that's thinking about specific high-risk groups.



- So I wanted to ask you, Dr. Lunning, what is your strategy for following these patients after frontline chemoimmunotherapy? And are there patients that you're screening a little bit more actively in the first year of follow-up to see if they're going to ultimately need CAR T-cell therapy?

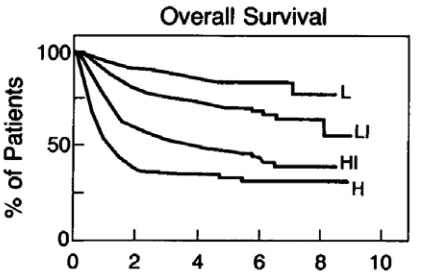
Dr. Lunning:
Yeah, I think we approached broadly diffuse large B-cell lymphoma before second-line CAR very similarly, where if you were in a CR based upon PET/CT, we didn't necessarily go on and do surveillance imaging every 6 months for 2 years—what the NCCN Guidelines would allow. We really use physical exam, laboratory results, and the patient to tell us how they were feeling.

But in that situation, when you're not doing surveillance imaging, you must have a very low threshold to image those individuals. I always tell my fellows that I'm walking in the room, and the patient, their labs, and my physical exam have to convince me not to do a scan. If you take that approach, then I think that's reasonable.

And now this data has moved, and CAR T-cell continues to move up and be efficacious, and I think that lower-burden disease probably does matter, not only when you're trying to start from an intent-to-CAR standpoint, which is much longer than these trials ever were, maybe a month to 2 months to actually get them to apheresis. So, having some lead time can be incredibly important.

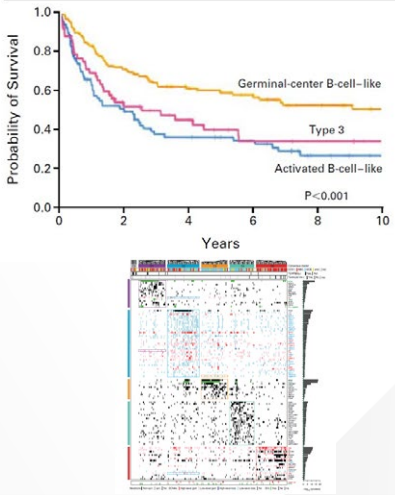
LBCL: How Can We Determine Who Will Be Refractory or Will Relapse?

International Prognostic Index

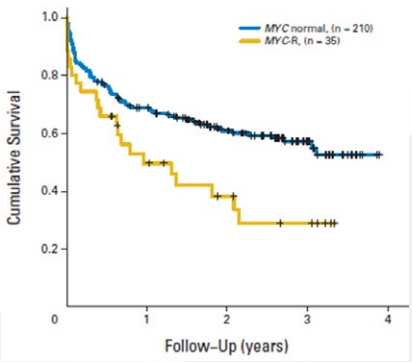


- Age >60
- Stage III/IV
- Elevated LDH
- Performance status >1
- Extranodal sites >1

GEP/Genomic Classification



Double/Triple Hit Cytogenetics



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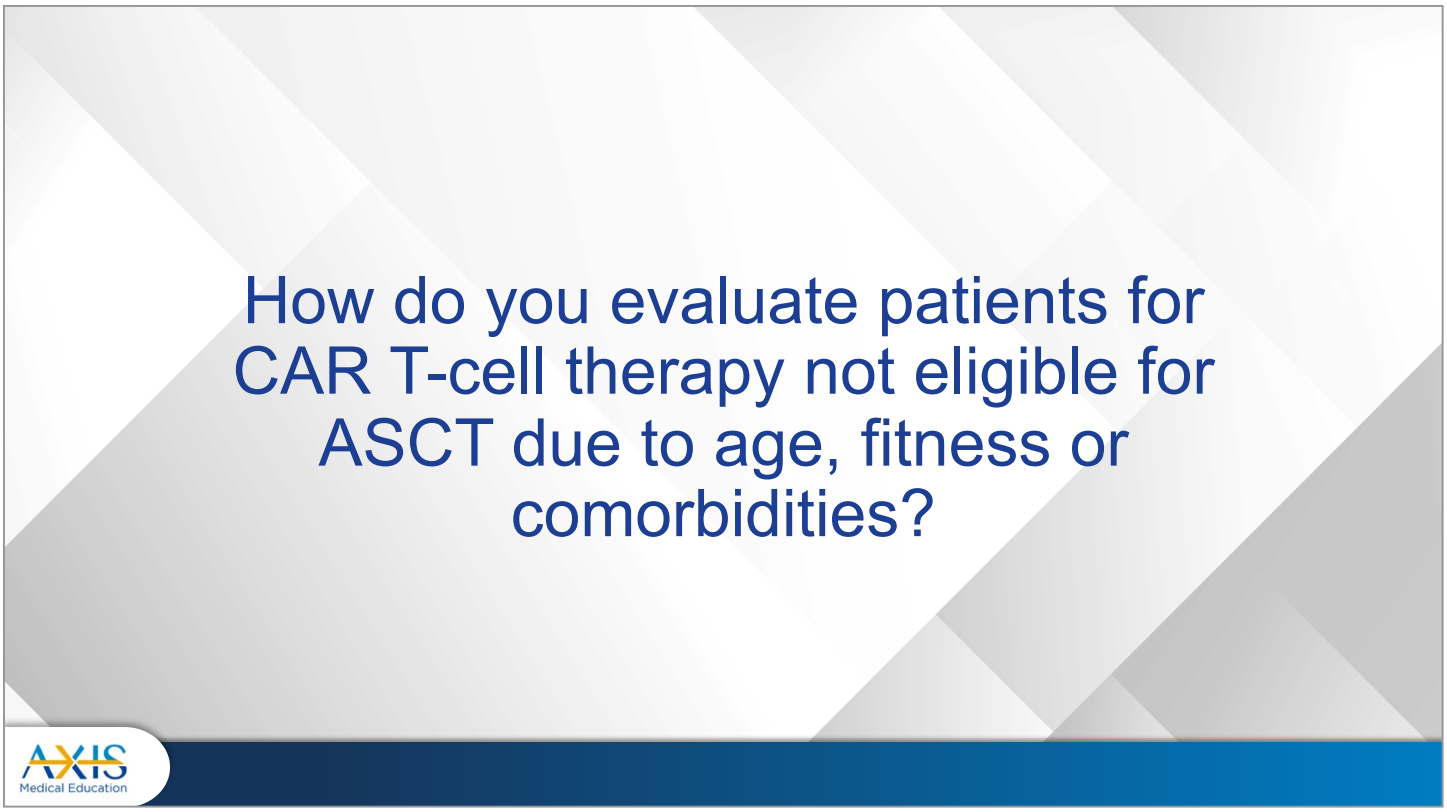
GEP, genome expression profiling; LBCL, large B-cell lymphoma; LDH, lactate dehydrogenase.
International Non-Hodgkin's Lymphoma Prognostic Factors Project, *N Engl J Med*. 1993;329:987; Ziepert et al. *J Clin Oncol*. 2010;28:2373; Rosenwald et al. *N Engl J Med*. 2002;346:1937; Chapuy et al *Nat Med*.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

How do I consider enrichment for a higher-risk population? Well, I think you can use the prospective, first-line trials to allude to that. Maybe your IPI 4/5, or if the patient was treated in the hospital or in the ICU at the outset of their diffuse large B-cell lymphoma, double hits or your high-grade B-cell lymphomas with MYC and/or BCL2 or BCL6 rearrangement, your classic double-hit, triple-hit lymphomas, those are the 2 or 3 scenarios.

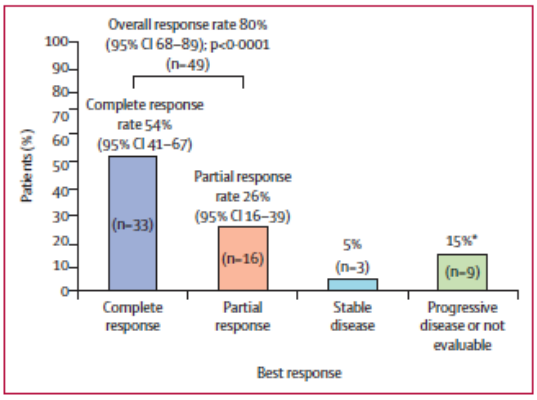
For the ICU admission, one has some retrospective data along with it too, but those are the ones that make me scratch my head. They are also the key populations that I will consider doing interim imaging to make sure that there aren't primary progressors and that my chemotherapy that I'm giving, let's say cycle 5 or 6, it's just driving toxicity with no benefit to the disease.

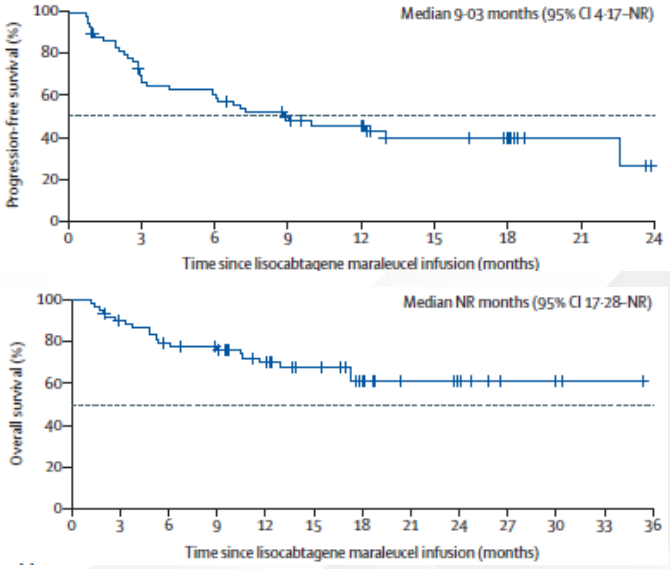


Dr. Jacobson:
Great. I agree with a lot of what you just said, Dr. Lunning. And Dr. Nastoupil, when we think about the patients that meet the PILOT liso-cel FDA label for second-line CAR T cells who are transplant ineligible, what does that patient look like to you? How do you define somebody who's eligible for CAR but not eligible for auto transplant?

Dr. Nastoupil:
Traditionally, when we're thinking about the toxicity profile, the auto transplant, it's tied to the high-dose therapy that precedes the stem cell rescue. I think oncologists are generally quite skilled at determining who's unlikely to tolerate intensive chemotherapy approaches and that usually boils down to organ function, such as cardiopulmonary reserve, renal function, performance status, fitness level. The challenge, though, with CAR T, as we've seen now over and over, that that's not the best way to predict for toxicity or outcomes with the cellular therapy approach. And more so, again, the tempo of the disease, can we safely get them through the first 30 days, which does not align with the same characteristics that we've utilized now for years to predict outcomes following chemotherapy.

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

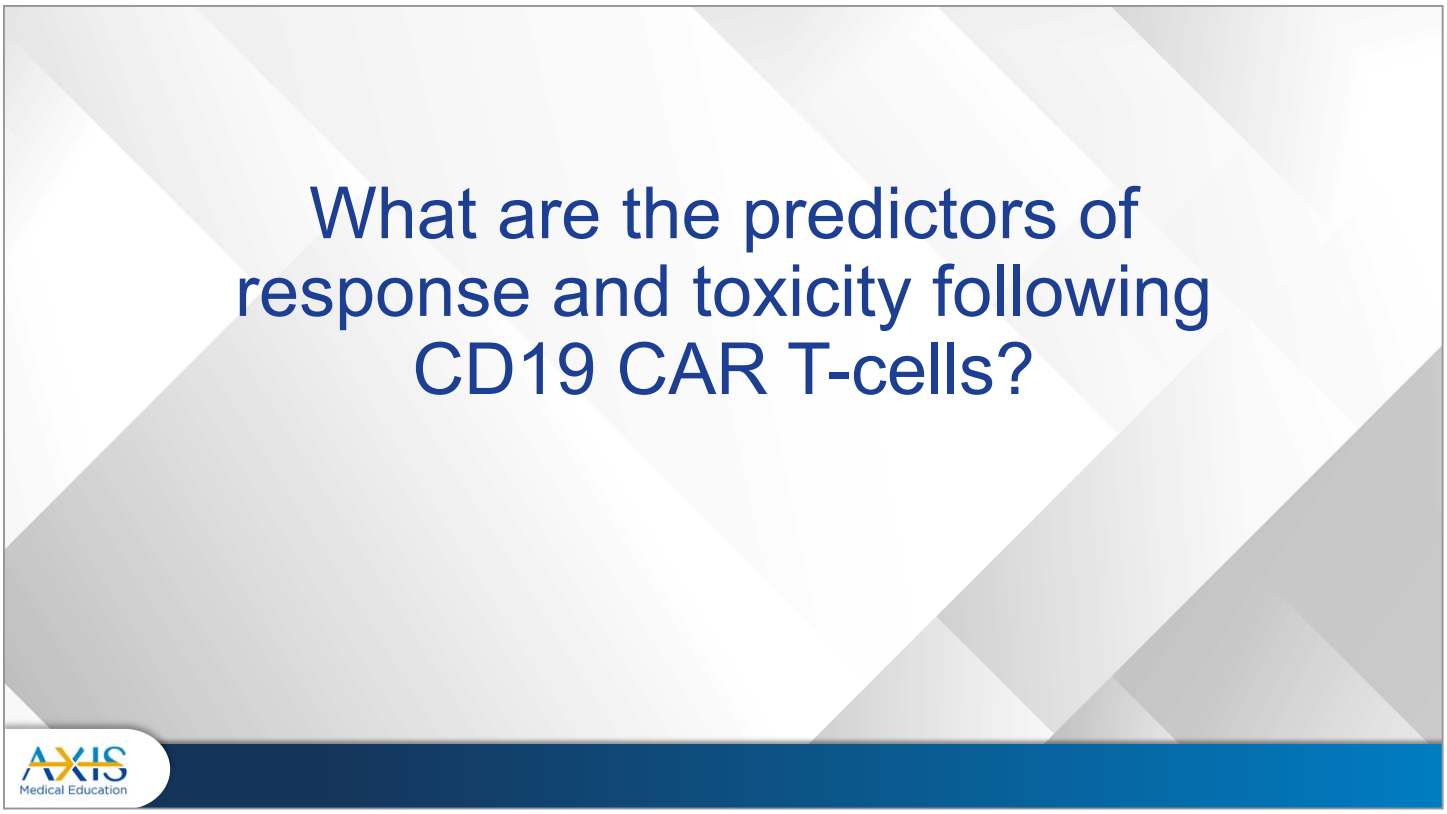




- CRS any/high grade: 38%/2%
- ICANS any/high grade: 31%/5%

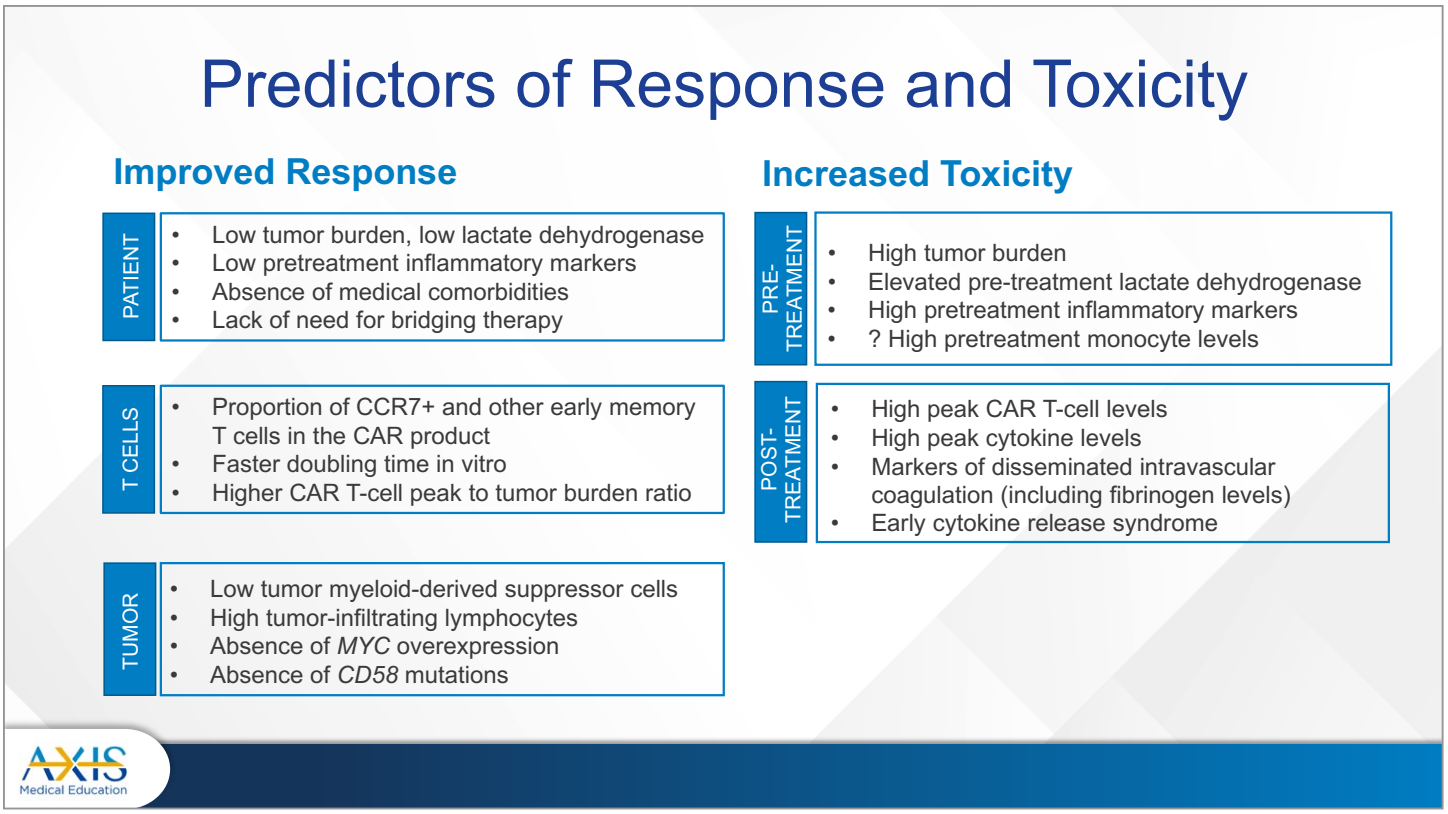
Sehgal et al. *Lancet Oncol*. 2022;23:1066-1077.
CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; Liso-cel, lisocabtagene maraleucel; NR, not reached.

I do think that every patient should be at least considered for CAR in the relapsed/refractory setting. And obviously, we need to fall within the FDA-approved labels. The PILOT study does allow us to think outside of just the TRANSFORM or ZUMA-7 population, which, to qualify for those trials, you had to be appropriate for the control arm, which was salvage chemotherapy followed by high-dose auto transplant for those chemo-sensitive patients. PILOT took those patients that were not considered appropriate for intensive therapy. So in Europe, it's pretty easy to define that; it's anyone over the age of 70. In the United States, because we don't have an age limit for high-dose therapy, but more functional capacity, again this boils down to fitness level. Do they have any significant comorbidities that would suggest they're not going to do well in the first 30 days if they develop cytokine release syndrome or neurotoxicity? I do think as we get larger series of patients, we'll have more refined criteria. But right now, at centers like ours, it just boils down to do they meet the label? Do we feel that they're going to live long enough to get to CAR and through the first 30 days post-infusion? Do they have any active infections? That might be one thing. Again, that's a unique criterion that would preclude us from moving forward.



Dr. Jacobson:
I think both of you just really set me up for my next question for both of you, which, I think, Dr. Lunning, you talked a little bit about the risk factors that we would use to predict failure of a chemotherapy approach like an autologous stem cell transplant. You talked about the IPI; you talked about double- and triple-hit lymphomas. We talked about primary refractory disease and early relapsing disease. Dr. Nastoupil, you did just talk about the predictors of toxicity for auto transplant vs CAR T. I'll start with Dr. Lunning—maybe you can focus on what do we know about the predictors of outcomes for CAR T?

I'll have you talk about efficacy and then maybe I'll ask Dr. Nastoupil about toxicity. What are some of the things that we know predict for better outcomes following CAR T-cell therapy in our patients?



Dr. Lunning:
I think that the easy ones are things that are readily available, things like LDH, right? As long as the specimen is not hemolyzed and you get a false result there, I think that's a simple and cheap assessment. The next one being, what is the size or the volume of that patient's tumor going into their CAR T cell?

And it's hard to put an engine on what gear the lymphoma is, but I, classically, I can't really have data, because we can't put it on the CRF form, this person's disease doubling time. You just feel it going into CAR T cell. I guess in some ways, I see that the disease that's kind of running at the pace of a dog is probably a little bit easier to CAR T cell than the disease that's running at the pace of a cheetah. I don't have data for that as much as I do clinical gut. But I think the other 2 are more well validated.

Dr. Jacobson:
I think that those are excellent points. We do know that patients with increased tumor bulk and with a high LDH do less well.

You referenced some patient and tumor characteristics that can help us understand. You were the one who brought up avoiding bendamustine before leukapheresis. What do you think about the quality of the T cells? And what have we learned about T-cell fitness that can help us understand how to maximize that for success after CAR T-cell therapy?

Dr. Lunning:
I think the ongoing debate is whether we can find out for that population at the time of diagnosis whether they are at high risk for relapse, and pull their T cells out before we ever give them a drop of chemotherapy. I think now we're seeing trials that are moving CAR T-cell therapy earlier and earlier for a population that is showing us at least radiographic signs. I'm commenting on the ZUMA-12 data here. Maybe because we are going to pull out those T cells only after a few cycles of chemotherapy, the T cells will be fitter, and we'll be able to eradicate a disease, which was just by the natural history of it going to be chemo-refractory.

The other pearl here is that maybe there are therapeutics out there that make the T cells better. We've heard this, and with some data now about ibrutinib changing the T-cell phenotype to a more potentially cytotoxic-like phenotype that may be advantageous going into CAR T. And I think we've seen some clinical trials now that are reporting out. I believe there was an ibrutinib plus tisagenlecleucel trial looking at that. And I know that there

were other studies in, for instance, CLL with liso-cel, that had an ibrutinib lead-in arm. It was neat to tell the story about how that was encountered when you wouldn't have often thought about it intuitively.

Dr. Jacobson:
Yeah, absolutely. Dr. Nastoupil, you said something very interesting earlier, that if you were taking someone to second-line CAR T-cell therapy, and you collected their T cells, but they had a great response to bridging therapy, you felt committed to taking them to CAR T cells. We have some data that would suggest CAR T cells will perform better in that setting than if the patient was progressing through whatever their last line of therapy was. I think we have it from the negative BELINDA study, where the patients who were in a CR after bridging did better with tisa-cel in terms of event-free survival. And even some data from the ZUMA-1 study really shows that the tumor volume and tumor microenvironment have a direct effect on both the T cells that we collect from those patients, as well as what happens to the T cells once we give them back. What do you think is the optimal way to prepare someone to go forward with CAR T-cell therapy to optimize T-cell function and optimize outcomes?

Dr. Nastoupil:
Well, my answer is simple. We want to move forward in as little disease state as possible with as good a product as we can get our hands on. And so how might we mitigate that? Moving forward with patients that are as less heavily pretreated as possible, that's your best shot of having a situation where you have as low amount of disease as possible.

Most of the data that you alluded to were in patients that had already declared themselves as having bad disease. And what I mean by that is this was studied in patients who had had at least 2 prior lines of therapy or were in a scenario where we know standard of care in early relapse patients rarely results in good outcomes. You can get very favorable outcomes in the setting of CR; we would all assume that those patients still had some underlying disease that was just below the detection of what the PET could identify.

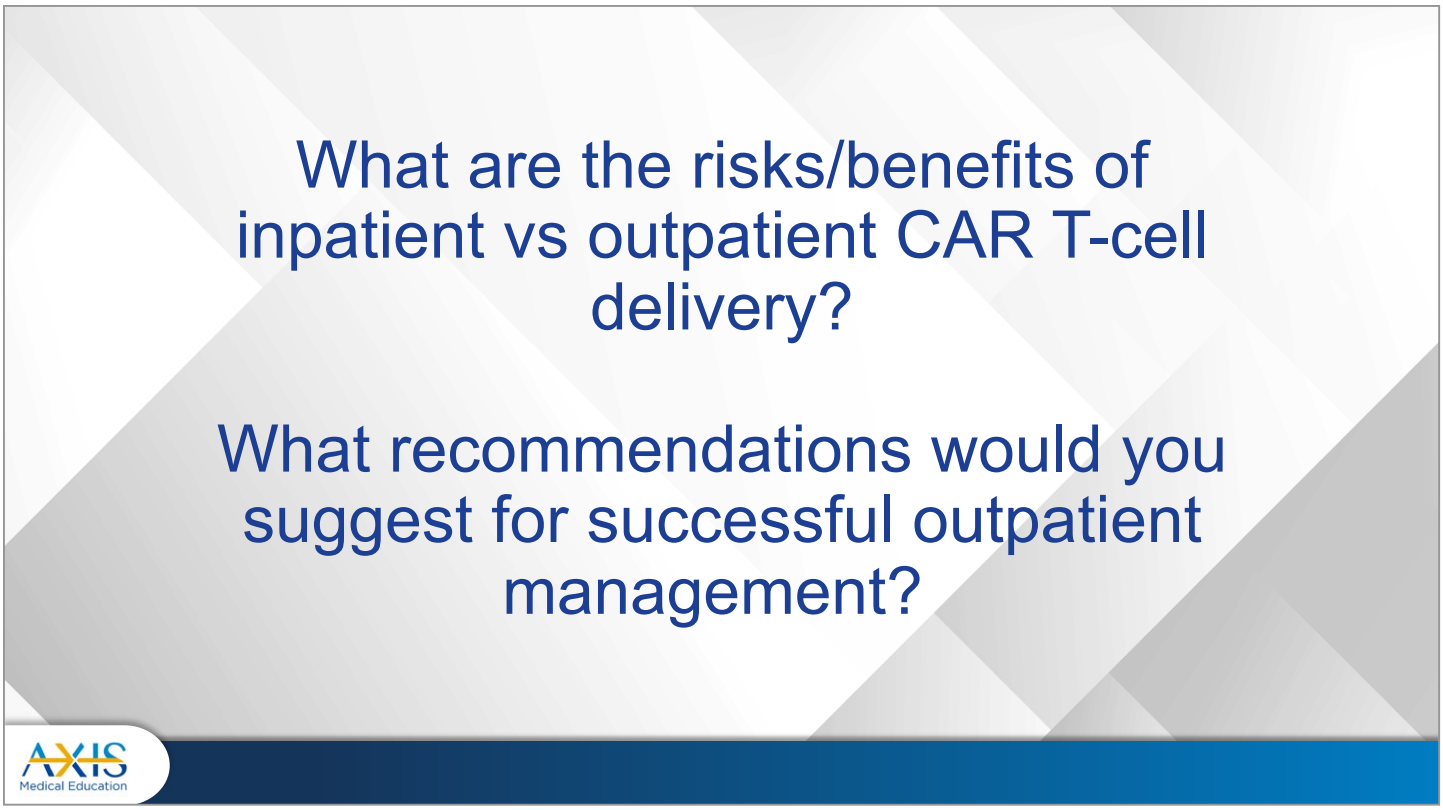
I don't view CAR as being a consolidated effort, just given the logistical challenges, the cost. But if we can optimize patients to get the best outcome, both from a safety and efficacy standpoint, I do like to go into CAR with as little disease as possible.

Dr. Jacobson:
I totally agree. And then I'm going to ask you the second part of the question that I had promised to direct to you earlier, which is what are the patient and disease characteristics that seem to predict for these toxicities that you already discussed, mainly CRS and ICANS following CAR T cells?

Dr. Nastoupil:
It's the same things that Dr. Lunning's already alluded to—patient-specific characteristics. So how much disease do they have? How high are their pretreatment lab values such as LDH or inflammatory markers such as CRP or ferritin? The disease itself, we do see varying rates of toxicity between indolent lymphomas and aggressive lymphomas, for instance, without safety profiles being much more favorable with the same construct in follicular, for instance, vs marginal zone lymphoma or mantle cell, with the outlier there being marginal zone lymphoma, where it doesn't seem to follow that pattern.

Then there are the construct-specific characteristics. For instance, axi-cel being a CD28 costimulatory domain has much more rapid T-cell expansion in the first 7 days. As a result, we do tend to see higher rates of neurotoxicity that are grade 3 or higher.

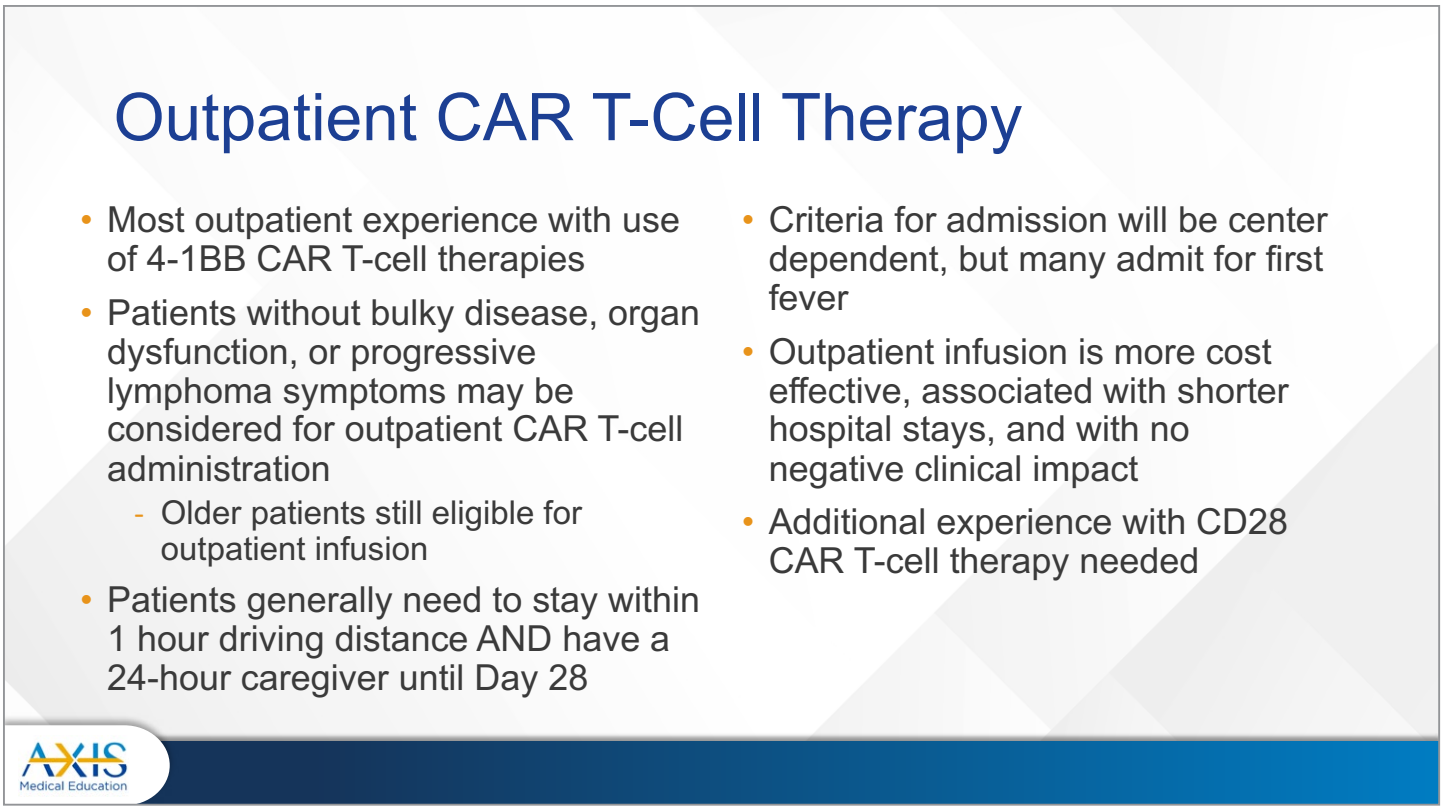
Now, fortunately for all patients, nearly all of this toxicity is reversible. So again, predicting when you're going to have those peak values—in terms of peak expansion that's going to translate into risk for CRS and neurotoxicity—can be very helpful in terms of do you do this inpatient or outpatient? Some of the mitigating strategies: how soon do you intervene with drugs such as IL-6 blocking agents or corticosteroids? And so having a handle on the toxicity can be helpful in terms of knowing when to intervene and when to watch. But I do think there are patient- and construct-specific features that can help you.



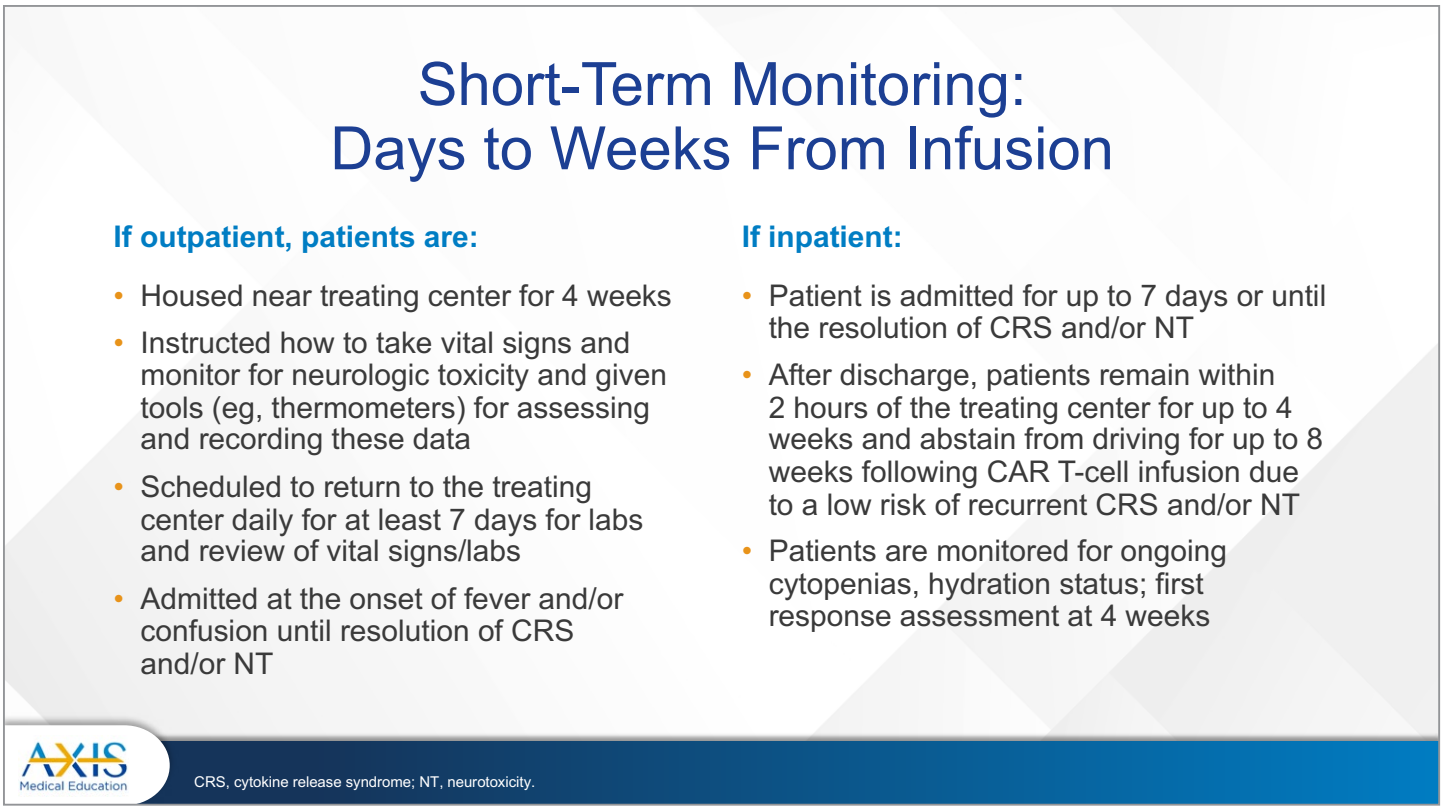
Dr. Jacobson:
Great. So the next thing I want to discuss is ways to optimize the CAR T-cell patient journey. We know that this is a complicated procedure. We know that it involves intense communication between multiple different parties and multiple different disciplines. I want to get a sense of what you've learned over the years that has really helped, both the community oncologists as well as all of the different parties that are involved in the care at the CAR T-cell treatment center.

But first, I want to ask you both a very quick question. I'll start with you, Dr. Lunning. Does your center do outpatient CAR? And if it does or doesn't, how would you imagine choosing patients for outpatient CAR? And what would be some of the advantages to outpatient vs inpatient treatment?

Dr. Lunning:
You know, we have classically done outpatient transplants, and we were all set up to do outpatient CAR T cell on and off both in clinical trial and commercially. Then this little thing called COVID hit, and we really didn't feel we had the right setup. How do we judge CRS as an outpatient coming in, and then when we had to discern whether it was COVID positive or COVID negative, and just the level of services that individual would need just because of the complexity. So, we are just transitioning back to an environment where we would consider doing CAR T cells as an outpatient more because we have logistical hurdles. I think we never stopped doing CAR T cells in the darkest days of COVID, because the disease needed that therapy for that individual to be alive.



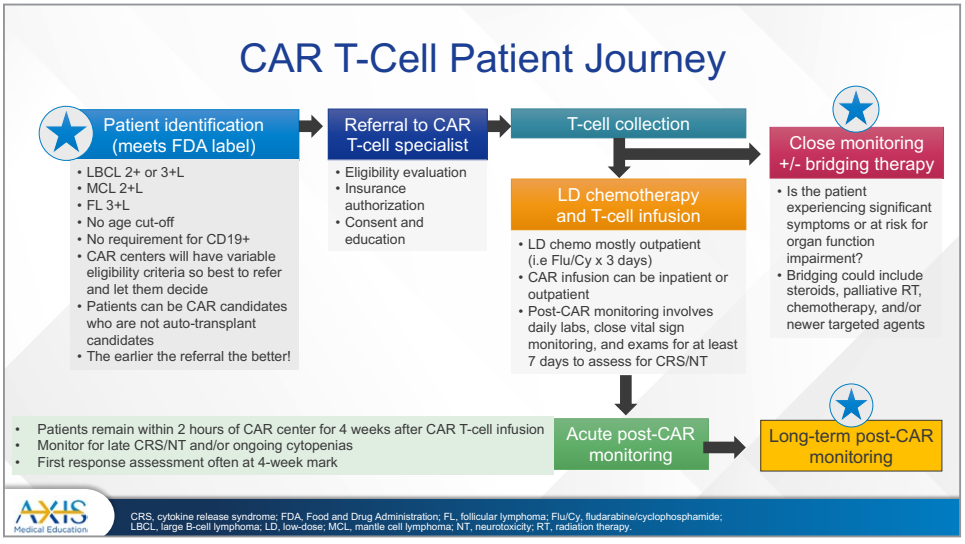
But who is an outpatient CAR T-cell candidate? I don't personally think it's defined by age. I think the biggest barrier often is that they have a caregiver 24/7 and that they can find a place that is reasonable to get them to a facility of need when it is needed, and at any time of the day. Right? You know, CRS doesn't just come between 9 and 5 on Monday through Friday. In fact, CRS probably more often comes when the sun is down. So, we have to have the environment that's right, the care that's right. And the ability to really triage these patients that may need immediate admission, or at least attention when we're all running with hospitals that are almost near capacity, dealing with staffing shortages.



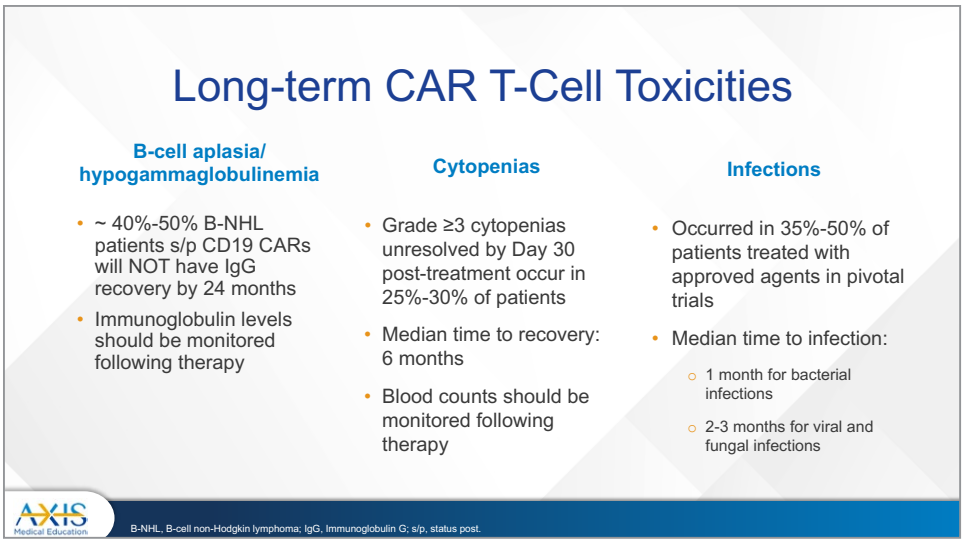
Dr. Jacobson:
Absolutely. Dr. Nastoupil, do you do outpatient CAR? And how do you select patients for it?

Dr. Nastoupil:
Yeah, I mean, I think Dr. Lunning nailed all the key points. We have the option to do outpatient CAR, though we rarely do it. Now, I think we'll get better at this over time. And the key bottleneck right now is transitioning those folks who are currently starting outpatient to inpatient in a timely manner. And because we have a lot of healthy concerns about who's going to field that first call. We live in a large city where there are many hospitals within a small radius. What if they go to a center that's not certified to address that acute toxicity? A lot of it is speculation and healthy fear surrounding what would happen to that patient who's currently being managed outpatient outside of the hours where we're fully staffed. And how do we transition them from outpatient to inpatient? So as a result, the vast majority of our patients start inpatient. And I think we have done a slightly better job of the transition from inpatient to outpatient when they're no longer at risk. As a result of that, we've had very good outcomes as it relates to toxicity in the first 30 days at a center like ours.

Dr. Jacobson:
Great. So regardless of where patients get their CAR T cells, there are a couple of key moments in the patient journey where there needs to be a coordinated hand-off and discussion between the local or outpatient oncologists and the CAR T-cell treatment center. Dr. Lunning, where do you identify those key touchpoints? And how do you ensure good communication there?

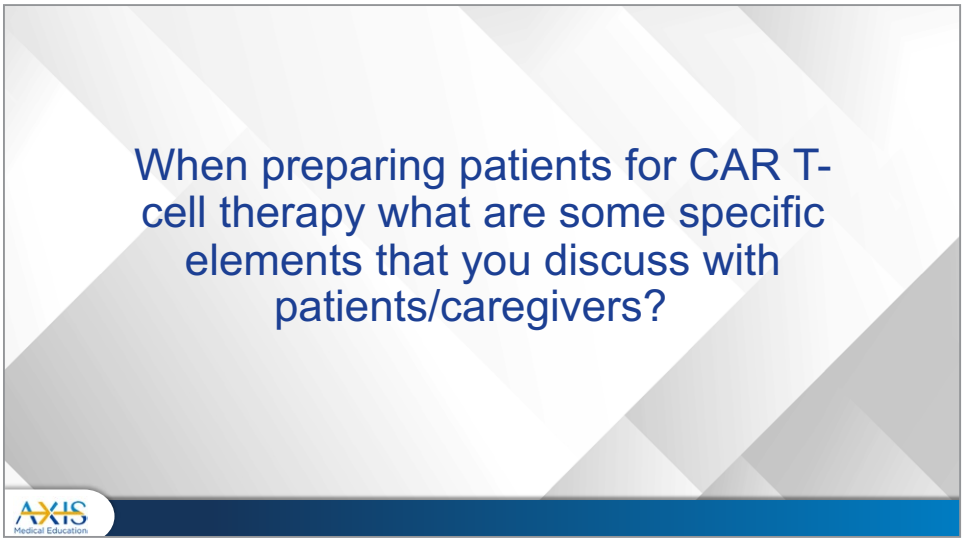


Dr. Lunning:
The first contact is incredibly important to get the referring physician onboard, so that they are part of this journey for this individual, if we're going to do this safely and successfully. It's not only when we're talking about the communication about pre-apheresis bridging, that sometimes is necessary. Perhaps we may do something differently in the vein-to-vein time, after apheresis, prior to infusion. Typically within the first 28 days, they're close to me and my team in regards to the management of any acute issues when that second drop of neutropenia happens. But at that day-28, -29 mark, when they're going to return out to their community, not only do you have to advise them that there's no driving the car, the combine, or their four-wheeler for 8 weeks, but you're also reaching back out to their physician that sent them or the care team that sent them to you, and reminding them that cytopenias can occur.

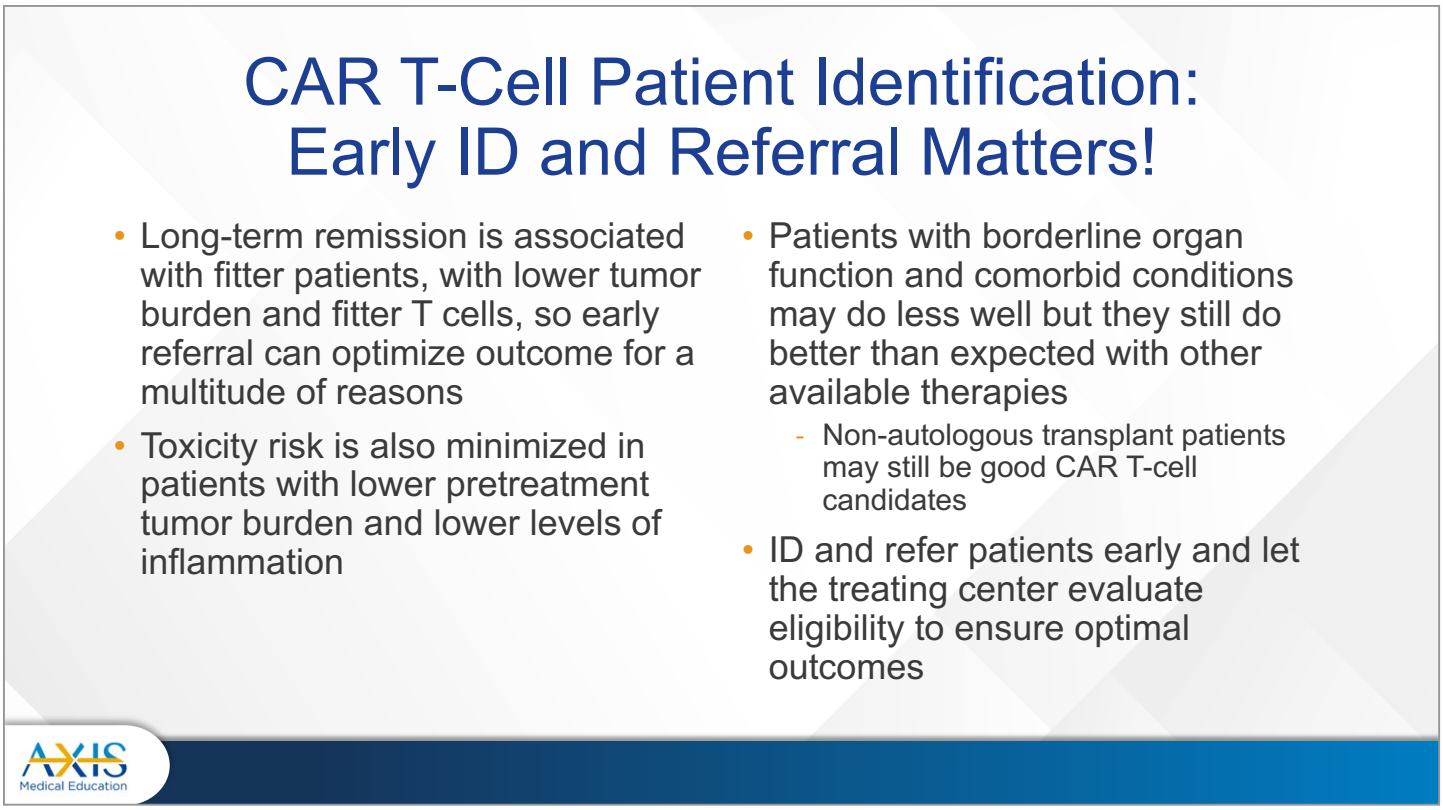


- Many times these patients are anemic, they are thrombocytopenic, and they may need periodic growth factor support to prevent the long-term risks of infections. The crux is making sure that they know that they may require transfusions, but they will improve over time.

  I think sometimes the toxicity profiles, the hematologic toxicity is misleading, in that, I think we should be reporting out to the community, how often are these patients needing platelet transfusions? How often are they needing red blood cell transfusions? Because really, the CTCAE criteria don't really get at that too much. And so, in some ways, I fear that they're not getting sent because of the ambiguity that exists in that day 29 and beyond about what the patient is going to look like in that period of time. And I can tell you that the community can manage those patients successfully, and they can participate as part of this journey. And I think that they should, and we want them to.



- **Dr. Jacobson:**
  Great. Those are really good points. Dr. Nastoupil, this is a complicated therapy to explain to a patient. Some of the side effects are somewhat unpredictable. People can have a totally uncomplicated course, or they could end up in the hospital for a couple of weeks. How do you talk to patients and their caregivers about CAR T-cell therapy, to prepare them for it, and then to help make the decision of whether this is the right path for them to take?



Dr. Nastoupil:
I think it's an important discussion. I think one of the most critical things to making sure we're successful is managing expectations, because of all the things you outlined that are unpredictable. There's the expectation of the patient, they want therapy that's going to get rid of their lymphoma, because again, we're using this in the highest-risk patients. They're facing the chance of death with their disease. And so obviously, they're all in if there's any chance that they're going to have a potential at cure. And I do think that we cure at least 40% of patients with this therapy.

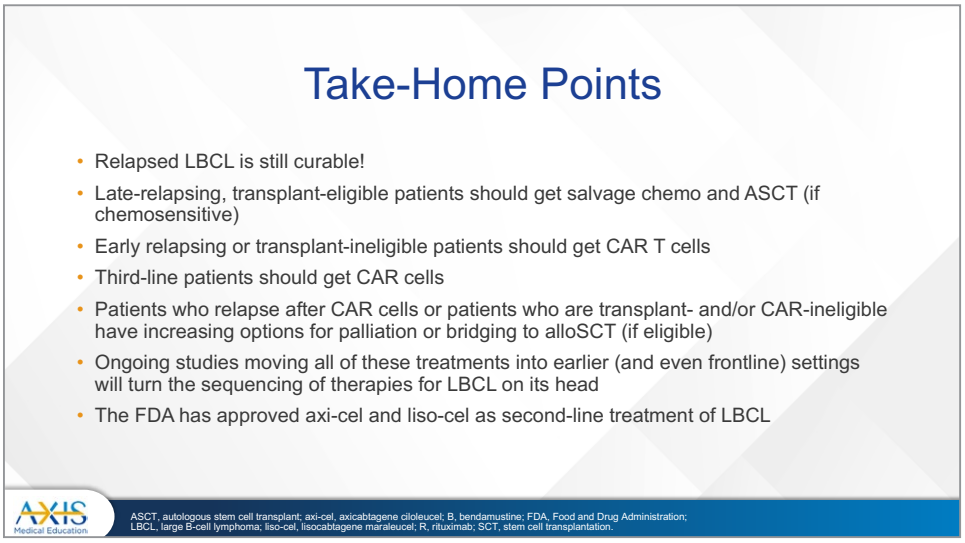
But how do we manage the expectations of the 60% that are not likely to have a good outcome? I'm honest with patients about that. I do think we can sometimes look at 10 patients and pick out the ones that are more likely to have a favorable outcome. And it gets to all the factors we highlighted earlier, how much disease, how heavily pretreated, the tempo of the disease, etc. I think choosing the optimal candidate up front is one of the first steps and, walking someone through, if I don't think this is the right time for CAR, but I'm excited for them to have the opportunity at a later time, I may say let's do something else right now so that I can get better control of your disease so you're more likely to have success with this.

Managing the expectation of the caregiver: it's a lot on them burden-wise, they have to be available during that 4 weeks of monitoring. Generally speaking, that's a 24-hour caregiver. It doesn't have to be the same person, but that's a strain on them. There are a lot of visits, once the patient is discharged, between their first hospital stay till that day 28 or 30 assessment, and they can't drive, as you just heard. Again, there's a lot of understanding what will be expected for patients and their caregivers, educating them about the toxicity that they're going to be monitoring for. I think that one major advantage to having someone on the inpatient service is that the caregiver doesn't have the burden of being on the lookout for 24 hours a day for any toxicity. But then once we discharge them, we have to educate them on what warrants a return trip back to the ER vs something that can be managed at home.

I 100% agree that for patients who arise out of the community, they come to us just for this therapy, they go home, they have to be prepared for what we're watching for. And they have to be educated on what warrants

a call back to us vs what can be easily managed by their local oncologist. So what do we do about cytopenias? How do we mitigate risk for infection? What do we do if the lymphoma comes back? That's a really long conversation to have. And I will highlight bits and pieces of that depending on where the patient is in that journey. So upfront, before we undergo leukapheresis, is this the right therapy for you? And what do the next 30 days look like?

Once we've collected and we're about to proceed with LD chemo, this is the toxicity that's likely to occur over the next 30 days. What are we going to do about it? When they hit that day-30 response assessment, this is where we are from your disease standpoint. What does the next 6 months look like? And where are you going to be? That's generally how I try and take on this extensive conversation and break it down into bits and pieces.



Dr. Jacobson:
You can only digest so much at any given time. I think breaking it up is really important.

Well, this has certainly been a fascinating conversation. I'd like to provide a few take-home messages. Relapsed large B-cell lymphoma is still curable. It is curable for chemotherapy-refractory patients and curable for late relapsers as well. Those who relapsed late and are transplant eligible should still get salvage chemo and an auto transplant if they're chemosensitive. But if they're not chemosensitive or they relapse after auto transplant, that is still an indication for CAR T-cell therapy with curative intent.

For patients with early relapsing or transplant-ineligible patients in the second line, those patients should get CAR T-cell therapy based on the current approvals and the results of randomized studies.

Patients who relapse after CAR T cells or patients who are transplant or CAR ineligible have increasing options for palliative treatments or to be used as bridging to an allotransplant.

And finally, ongoing studies moving all of these treatments into earlier and even frontline settings will turn the sequencing of therapies for large B-cell lymphoma on its head, and I can't wait to see the results and how things shake up.

Unfortunately, that's all the time we have today. I want to thank our audience for listening. And thank you, Dr. Lunning and Dr. Nastoupil, for joining me and for sharing all of your valuable insights and expertise. It was really great speaking with you today.

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