

Expert Answers to Common Questions for Improving the Road to Remission with CAR T-Cell Therapies in Large B-Cell Lymphoma:

Considerations for Community Practice

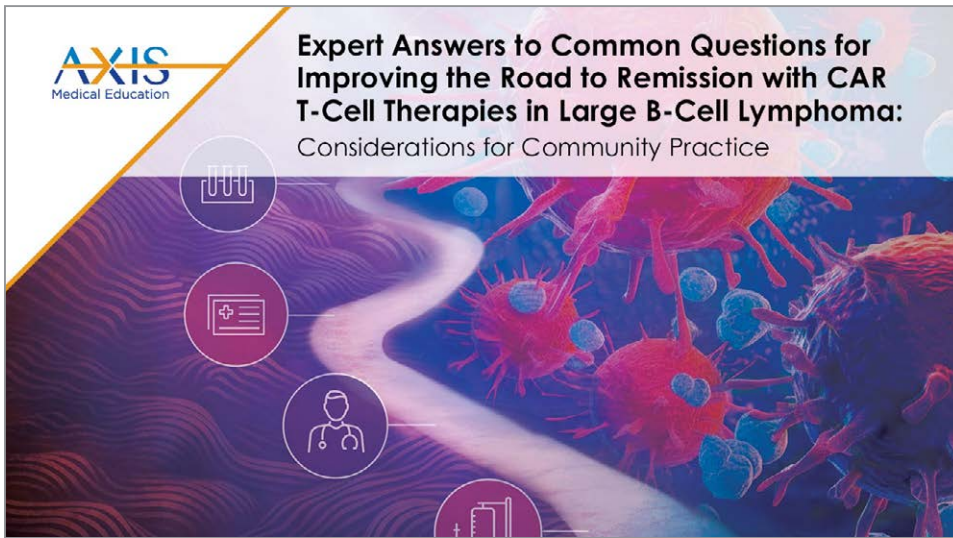
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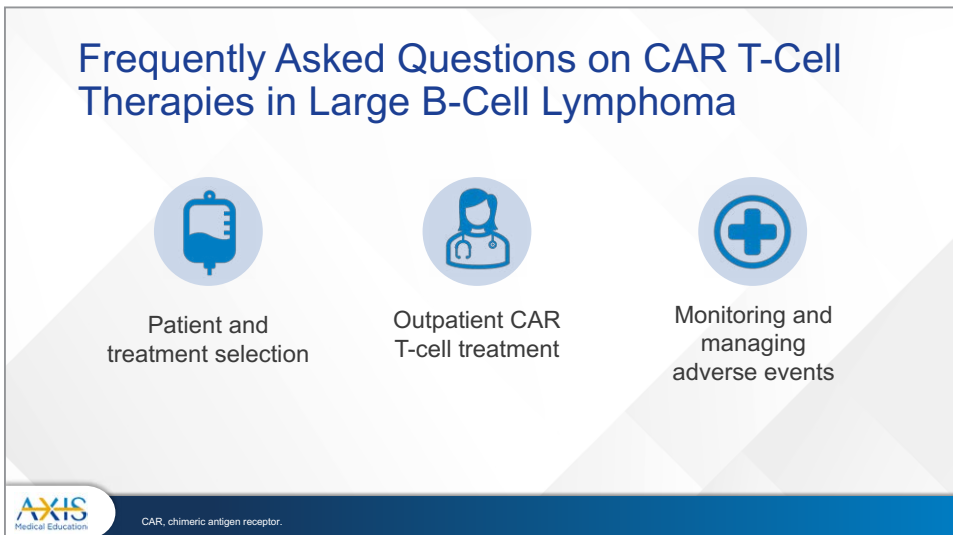
Expert Answers to Common Questions for Improving the Road to Remission with CAR T-Cell Therapies in Large B-Cell Lymphoma: Considerations for Community Practice

Caron Jacobson, MD



► **Caron Jacobson, MD:**

Hello and welcome. I'm Dr. Caron Jacobson, Associate Professor of Medicine at Harvard Medical School and the Dana-Farber Cancer Institute. Today, I will be answering questions that were asked by clinicians during a recent educational series on CAR-T cell therapies in large B cell lymphoma.



► Our questions today will focus on three main topics: the first being patient and treatment selection, the second being outpatient CAR-T cell treatment, and the final topic will be monitoring and managing adverse events. So, let's begin.

Who is Eligible for CAR T-Cell Therapy?



Patient and treatment selection

- Eligibility is expanding with time, given improved toxicity mitigation and increased experience
 - Early referral remains the most important risk factor to maximize efficacy and minimize toxicity
- There are no risk scores or stratification that should rule-out CAR T-cell therapy for any patient
 - No current alternative therapy is better than CAR T-cell for highest-risk patients
- Patients with baseline comorbidities are eligible for CAR T-cell therapy
 - Heart failure
 - Pulmonary disease
 - Renal failure
- Ultimately, the CAR T-cell treatment center decides
- Refer all eligible patients as early as possible
 - Ideally one line of therapy BEFORE it is indicated
 - Regardless of age or comorbidities: let the treating center decide
 - Know your CAR T-cell MDs for easier and direct referral
 - Education, screening, insurance authorization are all managed by the CAR T-cell treatment center



CAR, chimeric antigen receptor.

► So, the first topic we're going to talk about today is patient and treatment selection. A question we get asked frequently is: Are there patients who are ineligible for CAR-T cell therapy? And more and more the answer to that question is no. Patients who would historically have been ineligible for autologous stem cell transplant are eligible for CAR-T cell therapy because patients can have less reserve in terms of baseline organ function

and age, and still manage to get through CAR-T cell therapy successfully.

There's no centralized algorithm to determine whether patients are eligible for CAR-T cell therapy. Instead, every center will have their own eligibility criteria. But these are dynamic, and centers have been broadening those eligibility criteria since 2017 when CAR-T cells were first approved as we've gotten

more and more comfortable with toxicity management and treating patients with baseline comorbidities. So, we do treat patients with baseline heart failure, pulmonary disease, renal failure, and there are some patients that we may meet and decide that the risk is ultimately too great. But that really has to be a decision at the CAR-T cell treatment center.

Screening and Referral Recommendations: How Has the 2nd-Line Approval Changed Clinical Practice?

Screening patients in first remission

Pre-approval:

No routine surveillance screening, waited for clinical relapse

Post-approval:

Perform on surveillance PET or CT scan just prior to 12 months from the completion of frontline chemoimmunotherapy

Optimal referral practices change with 2L approval

- CAR T-cell therapy is always easiest and quickest if the patient is known to the CAR T-cell treatment center
- Advocate for referring patients one line of therapy **BEFORE** CAR T cells are needed

3rd-line CAR:

Refer at the time of first relapse

2nd-line CAR:

- Refer high-risk patients (HGBL, DHL/THL, IPI 4-5 LBCL) at or around diagnosis
 - Especially pertinent now that randomized trials in frontline are open
- Refer any patient without complete response mid treatment
- For all others, need to refer at time of relapse
 - Provide availability to consult regarding "bridging" strategies before and after apheresis in real-time



Courtesy of Caron Jacobson, MD.
CAR, chimeric antigen receptor; CT, computed tomography; DHL, double-hit lymphoma; HGBL, high grade B-cell lymphoma; IPI, International Prognostic Index; LBCL, large B-cell lymphoma; PET, positron emission tomography; THL, triple-hit lymphoma.

► And so, I would encourage people to refer patients in. And they should be referred in as early as they possibly can. Generally speaking, I like to have patients referred in a line of therapy earlier than CAR-T cell therapy would be indicated.

So, if we're talking about patients in the third-line, that would be when they need second-line treatment. And now that we have CAR-T cell approvals in the second-line, I would advocate for referring high-risk patients in at diagnosis or during their frontline chemoimmunotherapy in case they end up being primary refractory or early relapsing, or anyone who has sort of a slow response either on mid-treatment PET scans or sort of clinical assessment during their frontline chemoimmunotherapy.

CAR T Cell Patient Journey



Patient Identification (meets FDA label)

- LBCL 2+ or 3+L
- MCL 2+L
- FL 3+L
- No age cut-off
- No requirement for CD19+
- CAR centers will have variable eligibility criteria so best to refer and let them decide
- Patients can be CAR candidates who are not auto-transplant candidates
- The earlier the referral the better!

- Patients remain within 2 hours of CAR center for 4 weeks after CAR T-cell infusion
- Monitor for late CRS/NT and/or ongoing cytopenias
- First response assessment often at 4-week mark

Referral to CAR T-Cell Specialist

- Eligibility evaluation
- Insurance authorization
- Consent and education

T-Cell Collection

LD Chemotherapy and T-Cell Infusion

- LD chemo mostly outpatient (i.e. Flu/Cy x 3 days)
- CAR infusion can be inpatient or outpatient
- Post-CAR monitoring involves daily labs, close vital sign monitoring, and exams for at least 7 days to assess for CRS/NT

Acute post-CAR Monitoring



Close Monitoring +/- Bridging Therapy

- Is the patient experiencing significant symptoms or at risk for organ function impairment?
- Bridging could include steroids, palliative RT, chemotherapy, and/or newer targeted agents



Long-term post-CAR Monitoring



Auto, autologous; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; FDA, U.S. Food and Drug Administration; FL, follicular lymphoma; Flu/Cy, fludarabine/cyclophosphamide; LBCL, large B-cell lymphoma; LD, low-dose; MCL, mantle cell lymphoma; NT, neurotoxicity; RT, radiation therapy.

► There's no age cutoff for CAR-T cell therapy. And as I mentioned before, we are treating patients with kidney dysfunction, even patients on dialysis. It's actually the patients that have that creatinine clearance of 20 to 40 that I worry a little bit more about because it makes it hard to manage successfully with supportive care during cytokine release syndrome.

Bridging Therapy: How Has the 2nd-Line Approval Changed Clinical Practice?

Bridging and managing patients

- Patients are largely primary refractory and have rapidly progressive and large volume disease
- Patients are largely unknown to CAR T-cell treatment centers, so therapy is delayed beyond just insurance approval and manufacturing time, but also now includes time to initial consult
- Bridging now needs to be started **BEFORE** apheresis as well as **DURING** manufacturing

What if patient responds to bridging therapy?

- If primary refractory or relapsing <6 months: would take to CAR-T no matter what
- If relapsing 6-12 months: could consider switching to consolidating auto-transplant...
 - But in reality, it is logistically and financially challenging to switch to auto-transplant given prior insurance authorization
 - Sticking with CAR-T may be clinically the right thing to do anyway given the survival benefits



Courtesy of Caron Jacobson, MD.
Defer bendamustine use in bridging until after apheresis.
auto, autologous; CAR, chimeric antigen receptor.

▶ Another question we get asked is if patients do get bridging therapy and have a really tremendous, even complete response to bridging therapy, what do you do then in terms of their CAR-T cell therapy? And historically, we had been waiting for them to relapse in order to treat them. But there's more and more data to suggest that these patients may do very well getting CAR-T cell therapy with sort of a minimal disease state. And so, there are many centers that are treating patients at that point.

The last question that we get asked a lot is about equity both

in terms of socioeconomic status, in terms of geographic distribution across the world, and specifically our country, and then also across areas of different racial diversity. And this is an issue for CAR-T cell therapy because in very densely populated areas, there are many CAR-T cell centers and patients don't have to travel very far to reach a CAR-T cell treatment center. But in large portions of our country, patients have to travel 200, 300, 400 miles in order to get to a CAR-T cell treatment center. And sometimes they come from

places or occupations that don't allow them and their family to take a month off work in order to get through the CAR-T cell treatment episode. And so, this is an area that needs further improvement in terms of increasing access. And there's a focus on trying to do that and trying to get more centers, especially in not densely populated areas, up and running and to increase support and patient support for their CAR-T cell treatment episode.

Determining Who Can Get CAR T Cells Outpatient



Outpatient CAR T-cell Treatment

- Expanding CAR T-cell therapies in lymphoma and myeloma are taxing the system
- Outpatient CAR T-cell therapy may address issues with inpatient capacity
- Outpatient CAR T-cell programs can follow two different models and patient selection depends on them:

Select low-risk patients and products:

- Reliable and willing caregiver
- Means to pay for travel/housing/food
- Patients/caregivers taught how to monitor vitals and mental status and log results
- Wearable devices could help
- Seen once/day with labs
- Phone check-in once/evening

Offer all patients and products outpatient:

- Requires increased infrastructure (centralized housing with potential remote nursing services)
- Requires means to reimburse or prorate patients for travel, lodging, food
- Requires means to monitor the patient 24h/d, 7d/wk
- Wearable devices become more important



CAR, chimeric antigen receptor.

► The second topic we're going to talk about today is outpatient CAR-T cell treatment. So, this is definitely something that is increasing in frequency and more and more centers are starting outpatient CAR-T cell programs. You might ask, what are the advantages to doing outpatient CAR-T cell treatment?

So, for some centers, there is an economic advantage. There's better reimbursement patterns if patients can get their CAR-T cells out of the hospital, and actually stay out of the hospital for the first several days after that infusion. And for other centers the reimbursement

doesn't necessarily matter if the patients are treated in the hospital or out of the hospital. But there are still some advantages to doing outpatient treatment. So, one is obviously bed availability. Our hospitals are crowded and so having patients who are not actually in the midst of their toxicities from CAR-T cells, but just waiting for them to start does tax the system. And so, keeping those beds open for patients who have medical issues that require hospital care is important.

I think the other is for patient satisfaction. I think many, many patients would prefer

to stay in either a hotel room near the treating center or even in their home if they live nearby and be able to come and go as they please, especially during the time period where they're not having toxicities. And so, for all of these reasons, there's an increased emphasis on trying to develop these outpatient CAR-T cell programs. Now these programs can either offer all of the CAR-T cell therapy as outpatient, or offer select products that are associated with either delayed or lower intensity side effects to select patients who are felt to be at decreased risk of developing these side effects.

Developing an Outpatient CAR T-Cell Therapy Program

How do you manage outpatient toxicities that arise?

Admit all Grade 1 CRS:

- Necessary if patients need to pass through ED and cannot be directly admitted
- Necessary if ability to give outpatient TOCI/DEX limited/impossible
- Necessary for certain medically and socially at-risk patients

Manage Grade 1 CRS outpatient, admit for Grade 2+:

- Possible if TOCI/DEX are readily available to outpatients and outpatient hours are conducive
- Reliant on a reserved "crash bed" for direct inpatient admission and a clinical team able to meet the patient upon presentation to the hospital



CAR, chimeric antigen receptor; CRS, cytokine release syndrome; DEX, dexamethasone; ED, emergency department; TOCI, tocilizumab.

► And then how we bring these patients into the hospital also differs. There are some centers that are comfortable treating grade 1 CRS as an outpatient with close outpatient monitoring. And there are other centers that bring all the patients in at grade 1 CRS. That means probably sending patients through the emergency room, which requires quite a bit of education and handholding with the emergency room and ways to alert the emergency room that these patients are coming, because these patients obviously need to get managed and assessed quickly the same as someone who's coming in with chest pain or stroke-like symptoms.

Short-Term Monitoring: Days to Weeks From Infusion

Outpatient

- Patient housed near treating center for **4 weeks**
- Patient instructed on how to take vital signs and monitor for neurologic toxicity and given tools (eg, thermometers) for assessing and recording these data
- Patient scheduled to return to the treating center daily for at least **7 days** for labs and review of vital signs/labs
- Patient admitted at the onset of fever and/or confusion until resolution of CRS and/or NT

Inpatient

- Patient is admitted for up to **7 days** or until the resolution of CRS and/or NT
- After discharge, patients remain within 2 hours of the treating center for up to **4 weeks**
 - **Abstain from driving for up to 8 weeks** following CAR T cell infusion due to a low risk of recurrent CRS and/or NT
- Patients are monitored for ongoing cytopenias, hydration status; first response assessment at **4 weeks**

Caregiver present 24h a day for whatever portion of the 4 weeks post-CAR-T is spent out of the hospital



CAR, chimeric antigen receptor; CRS, cytokine release syndrome; NT, neurotoxicity.

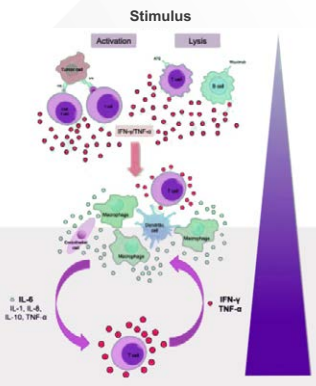
► I think another thing that really aids these programs is having centralized housing, even potentially with outpatient nursing services, which is something that I think the field has to develop. Certain centers have already done this, and others are moving towards that.

CAR T-Cell Toxicities



Monitoring and managing adverse events

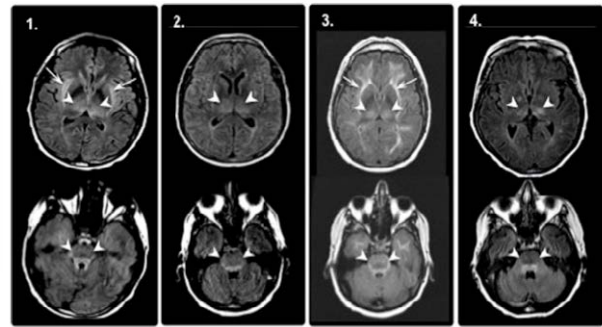
Cytokine Release Syndrome (CRS)



CRS Grading

- Grade 1**
 - Fever
 - Constitutional symptoms
- Grade 2**
 - Hypotension responding to fluids/low dose vasopressors
 - Grade 2 organ toxicities
- Grade 3**
 - Shock requiring high dose/multiple vasopressors
 - Hypoxia requiring $\geq 40\%$ FIO₂
 - Grade 3 organ toxicities, grade 4 transaminases
- Grade 4**
 - Mechanical ventilation
 - Grade 4 organ toxicities (excl. transaminases)

Neurotoxicity/ICANS



Adapted from Shimabukuro-Vornhagen A, et al. *J Immunother Cancer*. 2018;6:56.
CAR, chimeric antigen receptor; FIO₂, fraction of inspired oxygen; ICANS, immune effector cell-associated neurotoxicity syndrome; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

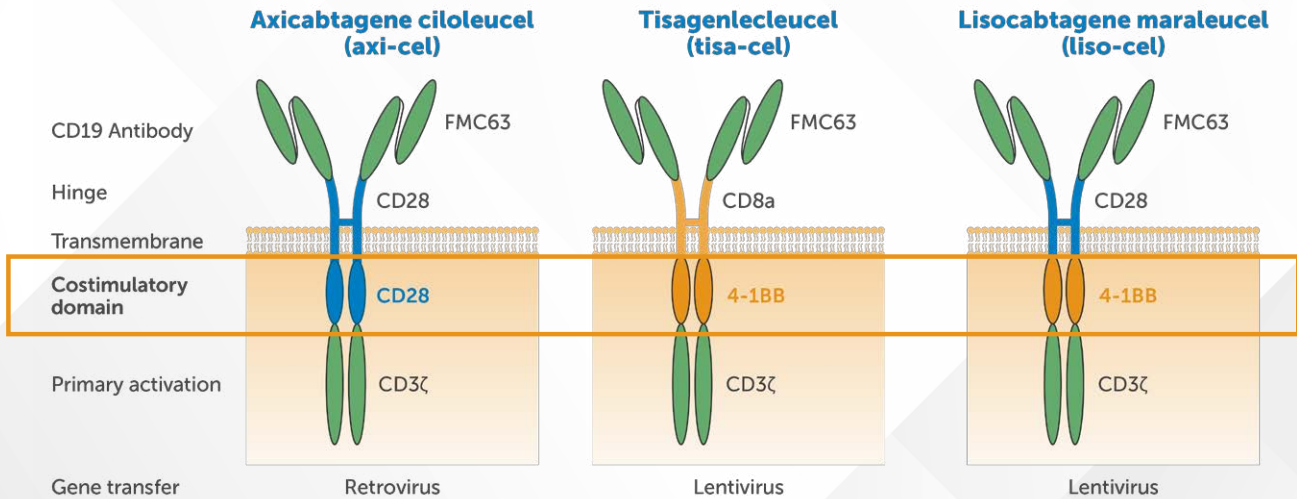
► And then the last topic we're going to talk about today is monitoring and adverse events, which is a good jumping-off topic based on our last discussion about outpatient CAR-T cell therapies, specifically about how we manage these adverse events when they arise.

And so obviously, the most immediate adverse events we see following CAR-T cell therapy relates to cytokine release syndrome and neurologic toxicity. One of the questions we get is, what is the mechanism

of action of cytokine release syndrome? And it is T-cell activation upon reinfusion and seeing the tumor antigen. In the case of large B cell lymphoma, of course, that's CD19. This leads to the release of inflammatory cytokines, which then leads to activation of other immune effector cells like macrophages and monocytes and other lymphocytes, which then leads to further cytokine elaboration. And the end result of that is that patients can experience, at a minimum, flu-

like symptoms with fevers and body aches and malaise and fatigue, but that can progress to leaky capillaries, which can lead to low blood pressure and fluid leaking into the lungs and hypoxemia. And then if that progresses to the point where patients require vasopressor support or intensive respiratory support, they often may require an ICU. Thankfully, that's rare. It happens less than 10% of the time with all of the CAR-T cell products.

CD19 Chimeric Antigen Receptor T Cells: Costimulatory Domains



Adapted from van der Stegen SJC, et al. *Nat Rev Drug Discov.* 2015;14(7):499-509. LBCL, large B-cell lymphoma.

► But we do know that high-grade cytokine release syndrome happens more frequently with axicabtagene ciloleucel, or axi-cel, compared to liso-cel, or lisocabtagene maraleucel, or tisa-cel, or tisagenlecleucel and that has to do with what the costimulatory domain is with those three different CARs.

It's CD28 with axi-cel, and it's 4-1BB with liso-cel and tisa-cel, which changes the pharmacokinetics of how the CAR-T cells expand and are activated upon reinfusion. And the second toxicity we see is neurologic toxicity or immune effector cell-

associated neurologic syndrome. And that toxicity happens towards the tail-end of cytokine release syndrome and is also more frequent and more often higher grade with axi-cel, compared to liso-cel or tisa-cel.

Second-Line Treatment: Efficacy and Safety

	ZUMA-7	TRANSFORM	PILOT	BELINDA
CAR-T Product	Axi-cel vs SoC	Liso-cel vs SoC	Liso-cel (transplant ineligible)	Tisa-cel vs SoC
Costimulatory domain	CD28	4-1BB	4-1BB	4-1BB
ORR, %	83% vs 50%	87% vs 49%	80%	75% vs 68%
CR, %	65% vs 32%	74% vs 43%	54%	46% vs 44%
mEFS, months	10.8 vs 2.3	NR vs 2.4		3.0 vs 3.0
mPFS, months	14.7 vs 3.7	NR vs 6.2	9.03	---
mOS, months	NR vs 31.1	NR vs 29	NR	---
CRS, %	92	49	38	61
Grade 3+ CRS, %	6	1	2	5
Median onset, days	3	5	-	4
ICANS, %	60	11	31	10
Grade 3+ ICANS, %	21	4	5	2
Median onset, days	7	11	-	5

Cross-trial comparisons are for discussion purposes only.



Locke FL, et al. *N Engl J Med.* 2022;386(7):640-654. Westin J, et al. *N Engl J Med.* 2023;389:149-157. Kamdar et al. *Lancet.* 2022;399(10343):2294-2308. Abramson et al. *Blood.* 2023;141(14):1675-1684. Bishop et al. *N Engl J Med.* 2022;386(7):629-639. Neelapu SS, et al. *N Engl J Med.* 2017;377:2531-2544. Schuster SJ, et al. *N Engl J Med.* 2019;380:45-56. Sehgal A, et al. *Lancet Oncol.* 2022;23:1066-1077.
Axi-cel, axicabtagene ciloleucel; CR, complete response; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; 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.

► Now, that being said you might say, then why don't we treat almost uniformly all patients with the less toxic CAR-T cell therapy? And some of that has to do with the fact that although axi-cel has the highest-grade toxicities, it has the most reliable and quickest turnaround time for these CAR-T cells. And so, many of our patients have too much disease at the time that we collect their T cells, and we're worried about how quickly we can get them to CAR-T cells. And even though there is more toxicity with axi-cel we are very good at managing that toxicity and getting patients through it. And so, it becomes more important that we're able to get a product back and get the product into the patient

and give them a chance to respond, than it is about whether they might have more toxicity. And what that amounts to is that, generally for patients with really bad lymphomas, we're picking axi-cel, and then for patients with better-behaving lymphomas, but who maybe have more comorbidities or are of older age, they tend to get liso-cel, and less frequently tisa-cel.

There was a cohort on one of the axi-cel studies that did give prophylactic dexamethasone: a dose on day 0 of the CAR-T cell infusion, a dose the day after, and a dose the day after that as a preventative measure to try to decrease the rates of grade 3 CRS and grade 3 neurologic

toxicity. And they did do that; they cut those rates by about 50%. And it didn't seem to impact efficacy, although it was a relatively small cohort. And so, I wouldn't say there's been uniform adoption of prophylactic dexamethasone, but if you are taking somebody into CAR-T cell therapy who maybe has borderline organ function or borderline performance status or very high pretreatment inflammatory markers, those may be patients that we're worried about, in terms of both having higher-grade toxicity, as well as maybe not being able to tolerate it as well. And so, those may be patients that we do choose to use prophylactic dexamethasone.

CAR T Cells Long-Term Toxicities

B-cell aplasia/ hypogammaglobulinemia

- ~40-50% B-NHL patients s/p CD19 CAR-Ts will NOT have IgG recovery by 24 months
- Immunoglobulin levels should be monitored following therapy

Cytopenias

- Grade ≥ 3 cytopenias unresolved by Day 30 post treatment occur in 25-30% of patients
- Median time to recovery 6 months
- Blood counts should be monitored

Infections

- Occurred in 35-50% of patients treated with approved agents in pivotal trials
- Median time to infection is 1 month for bacterial infections, and 2-3 months for viral and fungal infections



B-NHL, B-cell non-Hodgkin lymphoma; CAR, chimeric antigen receptor; IgG, immunoglobulin G.

► So, there are some side effects that can happen later after that initial sort of first 2 to 4 weeks where patients are at risk of CRS and neurologic toxicity. And these include things related to the immune suppression of CAR-T cells. So, we know that CD19 CARs have an on-target off-tumor effect on normal

healthy B cells, causing B cell aplasia. Lymphodepletion also leads to T-cell lymphopenia for quite a while after CAR-T cell infusion; it can even be up to 12 to 18 months. And then about a quarter of patients will have prolonged cytopenias, which means that they have cytopenias

that last beyond day 30 is often with neutropenia and thrombocytopenia. And we don't know exactly why that is, but we do believe it's an immunologic phenomenon that usually can get better within 3 to 6 months after CAR-T cell infusion.

Long-Term Monitoring: Weeks to Months from Infusion

- Patients should be monitored for:
 - Prolonged cytopenias
 - > Transfuse as indicated
 - > G-CSF as needed
 - B-cell aplasia (IgG levels)
 - > Replete with IVIG for levels < 400
 - Infection
 - Relapse
 - Secondary malignancies
- Anti-infective (herpes and PJP) prophylaxis
 - Variable practices – we continue for at least 6 months at which time we measure the CD4 count and only discontinue when >200



G-CSF, granulocyte colony stimulating factor; IgG, immunoglobulin G; IVIG, intravenous immunoglobulin; PJP, Pneumocystis jirovecii pneumonia.

► And so, we need to think about how to manage these patients both preventatively as well as how to survey them for opportunistic infections. And so, we do keep patients on prophylactic herpes virus prophylaxis, usually with acyclovir, and PJP prophylaxis usually with Bactrim for at least 6 months, and only stop those when their CD4 count is over 200. We also monitor IgG levels and tend to replete them especially in patients with frequent infections if they fall below 400.

There were questions about fungal prophylaxis and CMV monitoring. And our infectious disease doctors actually looked at all of our patients, even the ones with prolonged cytopenias to track the incidence of fungal infections in our patients, and they were quite low. They ultimately concluded that fungal prophylaxis was not necessary, even for patients with prolonged neutropenia. But we do know that CMV reactivation can be a problem for some of our patients, especially

patients who got protracted steroids to treat toxicities while they were in their acute post-monitoring period. And so, our rule of thumb is if someone has had more than 5 doses of dexamethasone at 10 mg or higher, we usually do weekly CMV monitoring as well as fungal monitoring for at least the first month following CAR-T cell infusion.

Key Takeaways

- There's almost no patient who's automatically ineligible for CAR T-cell therapy
- Refer patients if they meet the label for CAR T-cells, and let the CAR T-cell treatment center decide on eligibility
- Early referral is the best way to both maximize efficacy and minimize toxicity
- Early relapsing or transplant ineligible patients should get CAR T-cells
- Third-line patients should get CAR T-cells

FDA Approvals in Second-Line

- **Axicabtagene ciloleucel**
 - Adult patients with LBCL that is refractory to first-line chemoimmunotherapy or relapses within 12 months of first-line chemoimmunotherapy
- **Lisocabtagene maraleucel**
 - Adult patients with LBCL who have refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy
 - Adult patients with LBCL who have refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for HSCT due to comorbidities or age



FDA. April 1, 2022. FDA. June 24, 2022.

FDA, US Food and Drug Administration; HSCT, hematopoietic stem cell transplantation; LBCL, large B-cell lymphoma.

► So, this has been a great opportunity to answer clinician's questions about CAR-T cell therapy for the treatment of large B cell lymphoma. I'd like to wrap up by providing a few take-home messages.

I think the most important thing to take away from these questions and the responses to these questions is that there's almost no patient who's automatically ineligible for CAR-T cell therapy these days. We really do encourage patients to be referred if they meet the label for CAR-T cells at this point and let the CAR-T cell treatment center decide on eligibility. So, there may be patients that are a little bit too borderline and may not be able to move forward. And there may be patients who opt not to move forward because of a discussion about the toxicities or the logistics of CAR-T cells. But every patient should get that chance.

And so, I would encourage patients to be referred. And early referrals absolutely is the best way to both maximize efficacy and minimize toxicity. And so again, I recommend referral one line of therapy before the CAR-T cell therapy is needed so the patient is already plugged in and known to the CAR-T cell treatment center. So again, if that is in the third-line we would recommend when salvage chemotherapy is being started, to refer that patient into the CAR-T cell treatment center. And if we're thinking that the patient might end up being a second-line candidate because they are likely to be early refractory, or to be primary refractory or early relapsing, we would encourage referral during the initial frontline treatment phase.

And then finally, the logistics of CAR-T cells because of the

toxicities we see and the need to be close to a CAR-T cell treatment center still creates an issue for access for a good proportion of patients across the United States and the globe and this is something that needs attention and further resources to support.

So, we just had our annual ASH meeting in San Diego and there wasn't a ton of new data related to CAR-T cell therapy for lymphoma. But there was a lot of real-world data to support the use of CAR-T cell therapy in broader patient populations. So once again, as we use these products in more and more patients, many of whom would not have been eligible for the pivotal clinical trials we see that the efficacy is maintained, and the toxicity is actually improving over time.

An interesting study is the ZUMA-12 study which looked at axi-cel in frontline large B

cell lymphoma and is actually the steppingstone for a current randomized frontline study of axi-cel versus standard of care for high-risk frontline large B cell lymphoma. We saw a 3-year update on that data which showed that 75% of patients who received axi-cel after

two cycles of R-CHOP-like chemotherapy with high-risk disease, meaning IPI 3, 4, or 5, or double-hit lymphomas actually were alive and maintaining their response at that 3-year time point, which is very exciting and tells us that we may not have reached

the limit of where we can use CAR-T cell therapy in large B cell lymphoma.

So, with that, we'll end today's session. I want to thank our audience for listening and goodbye.

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About AXIS Medical Education, Inc.

AXIS Medical Education, Inc. is a full-service continuing education company that designs and implements live, web-based, and print-based educational activities for healthcare professionals. AXIS provides convenient opportunities to engage learners based on their individual learning preferences through a full spectrum of educational offerings.

The executive leadership of AXIS combines 75 years of experience in adult learning theory, curriculum design/implementation/assessment, continuing education accreditation standards, and medical meeting planning and logistics. Our team has a deep understanding of the governing guidelines overseeing the medical education industry to ensure compliant delivery of all activities.

AXIS employs an experienced team of medical and scientific experts, medical writers, project managers, meeting planners, and logistics professionals. This team is dedicated to meeting the unmet educational needs of healthcare professionals, with the goal of improving patient outcomes.

AXIS believes that partnerships are crucial in our mission to deliver timely, relevant, and high-quality medical education to healthcare professionals. To that end, AXIS partners with other organizations and accredited providers to offer added expertise and assist in expanding access to our educational interventions. AXIS also partners with numerous patient advocacy organizations to provide recommended patient education and caregiver resources in specific disease areas. AXIS finds value in these partnerships because they complement our core clinical curriculum with validated and relevant supplemental resources for busy clinicians and their patients.

The mission of AXIS is to enhance the knowledge, skills, competence, and performance of the interprofessional healthcare team to ensure patients receive quality care, resulting in improved patient outcomes. We engage healthcare professionals in fair-balanced, scientifically rigorous, expert-led certified educational activities designed to foster lifelong learning that is applicable to clinical practice and patient-centered care.

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