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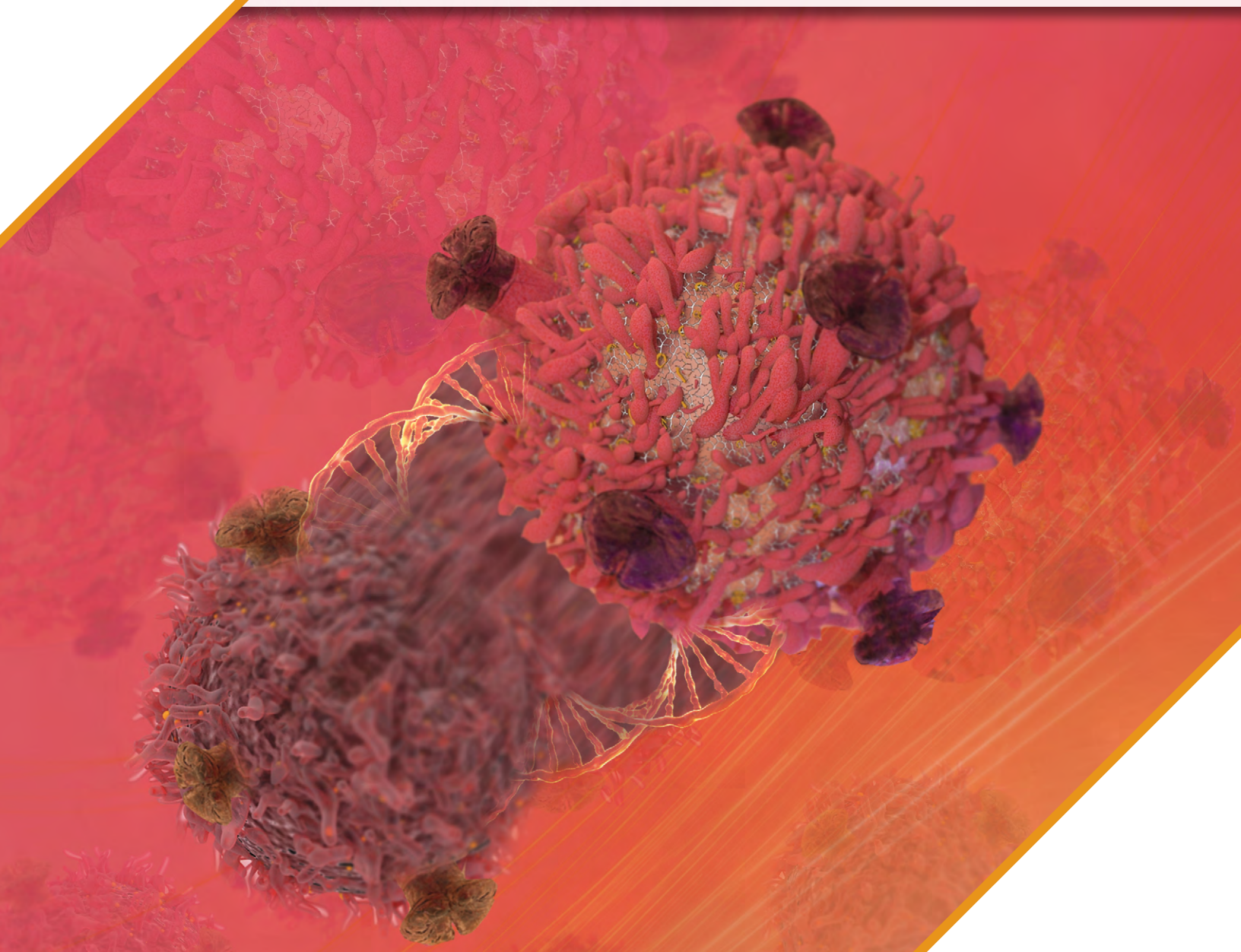
Immunocellular Therapies for Relapsed/ Refractory Heme Malignancies:

A Focus on CAR T-Cell Therapy

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



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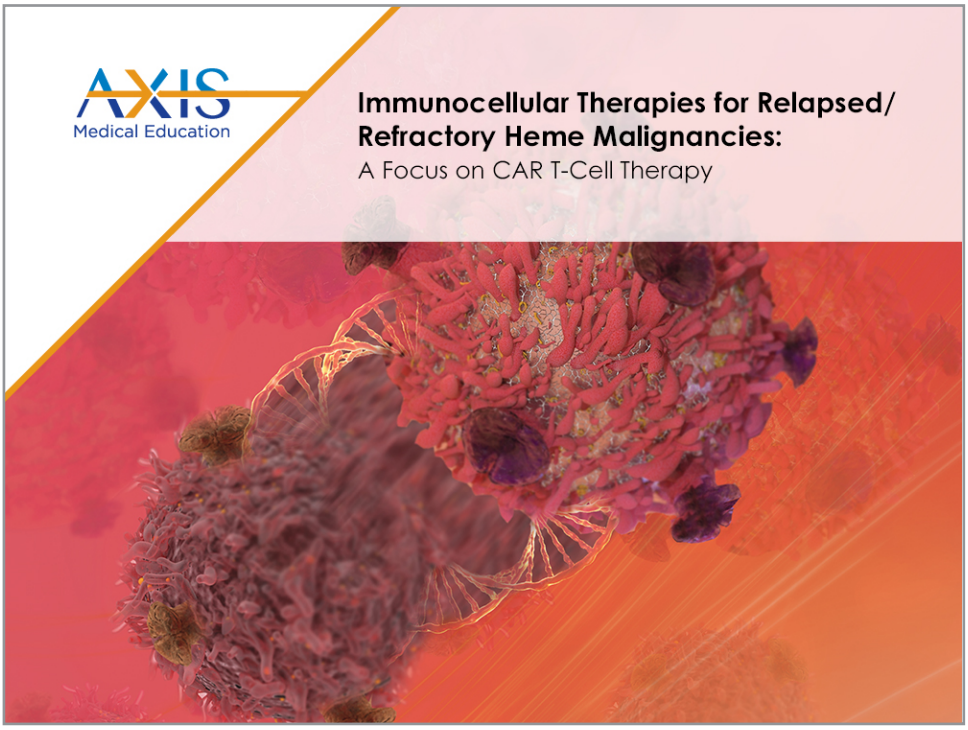
Immunocellular Therapies for Relapsed/Refractory Heme Malignancies: A Focus on CAR T-Cell Therapy

Jae Park, MD & Robert Mocharnuk, MD



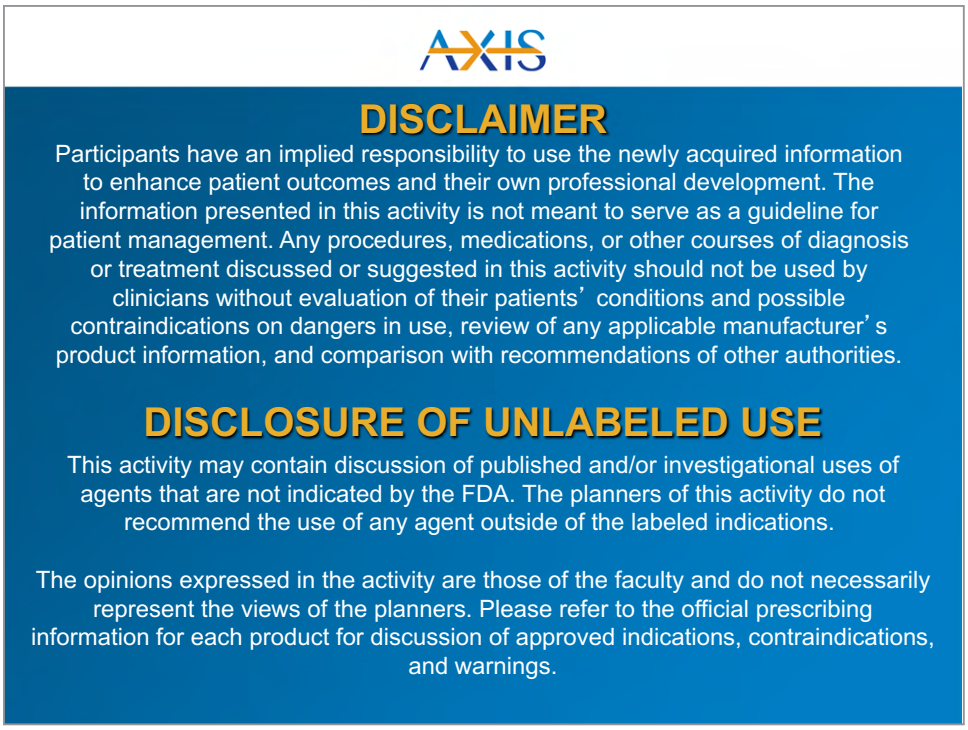
Robert Mocharnuk, MD:

Hello, and welcome to this educational activity, *Immunocellular Therapies for Relapsed/Refractory Heme Malignancies: A Focus on CAR T-Cell Therapy*.

I am Dr. Robert Mocharnuk, Professor of Hematology/Oncology in the Department of Medicine at Southern Illinois University School of Medicine.

I am joined today by Dr. Jae Park, Assistant Attending Physician at Memorial Sloan Kettering Cancer Center in New York.

In this activity, we will discuss and evaluate the latest evidence on chimeric antigen receptor T-cell therapy, known as CAR T-cell therapy, for the treatment of relapsed/refractory hematologic malignancies.



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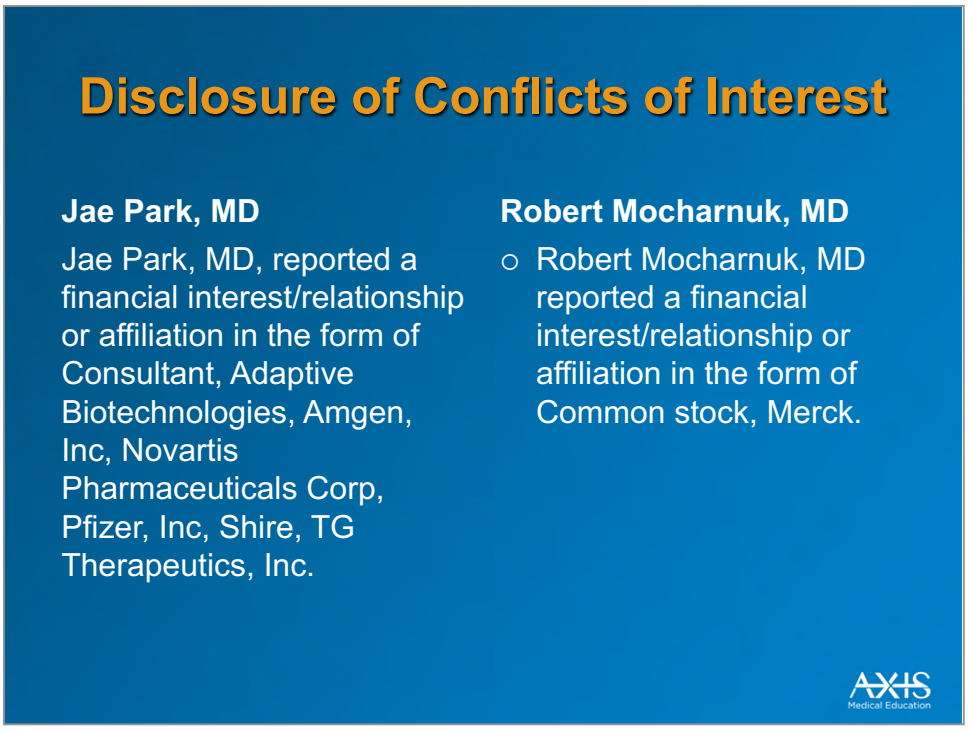
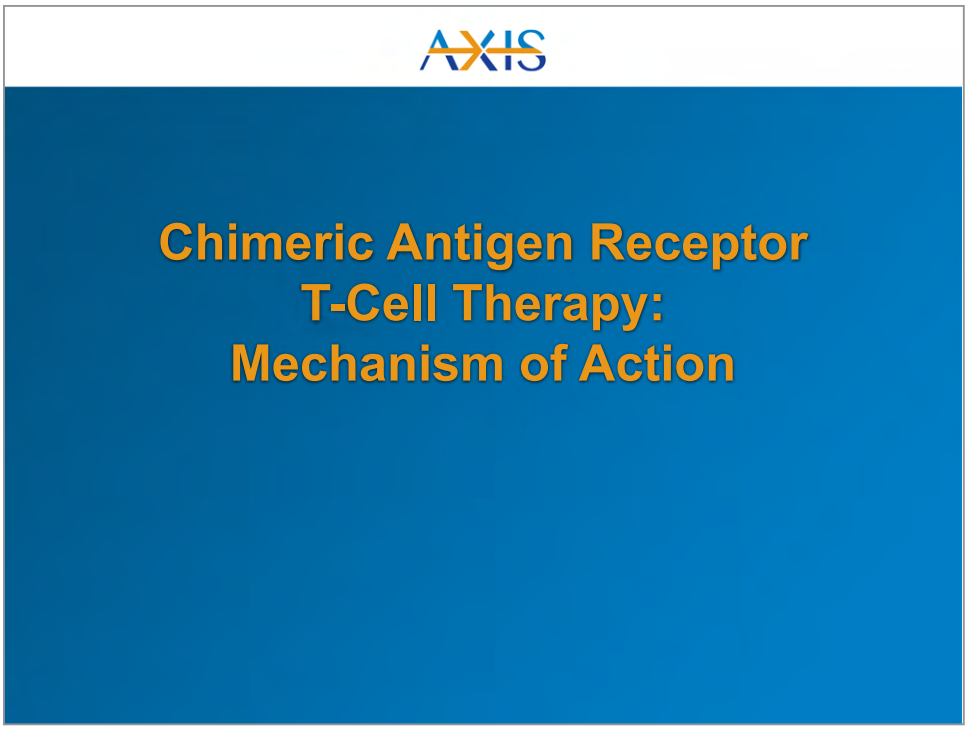


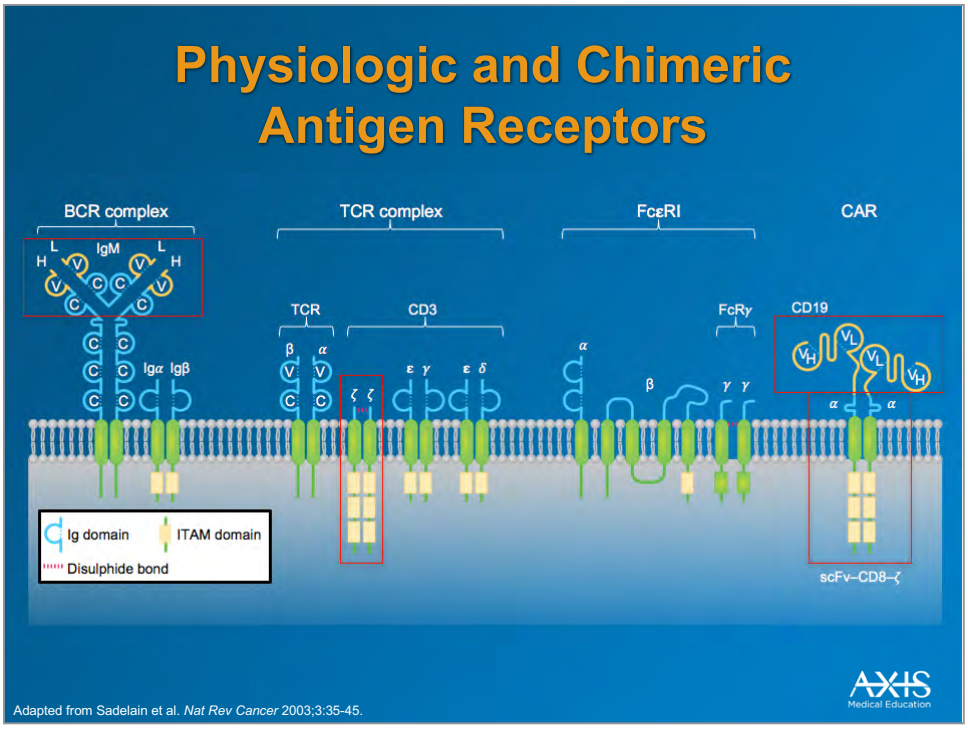
- Here is our financial disclosure information.



Hello, Dr. Park, thank you for joining us today.

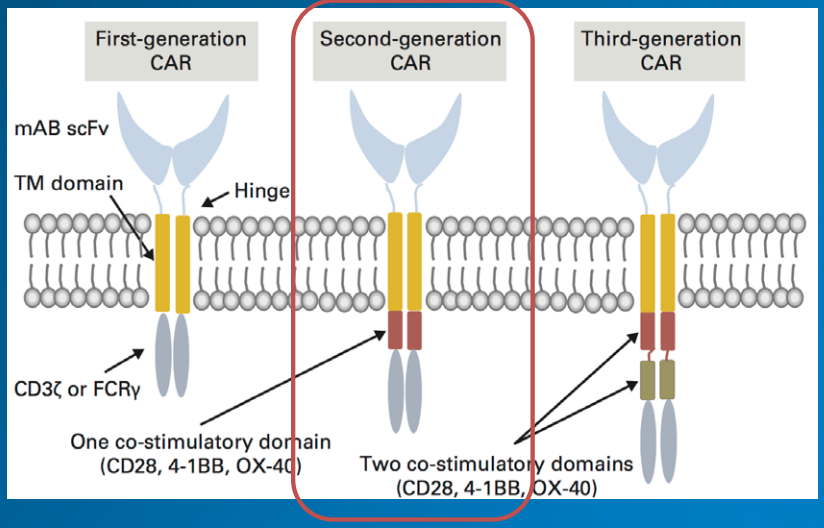
Jae Park, MD:
Hello.

Dr. Mocharnuk:
First, would you describe to us what CAR T-cell therapy is and provide us with an overview of its mechanism of action.



Dr. Park:
So CAR – chimeric antigen receptor – is an artificial T-cell receptor that is composed of the binding domain from an antibody that's fused to a transmembrane in cytoplasmic domain of a T-cell receptor; therefore, it has the binding capacity of an antibody but it acts like T cells, so facilitates cytotoxic capability of T cells.

Evolution of CAR Designs



Park et al. *J Clin Oncol*. 2015;33:651-653.

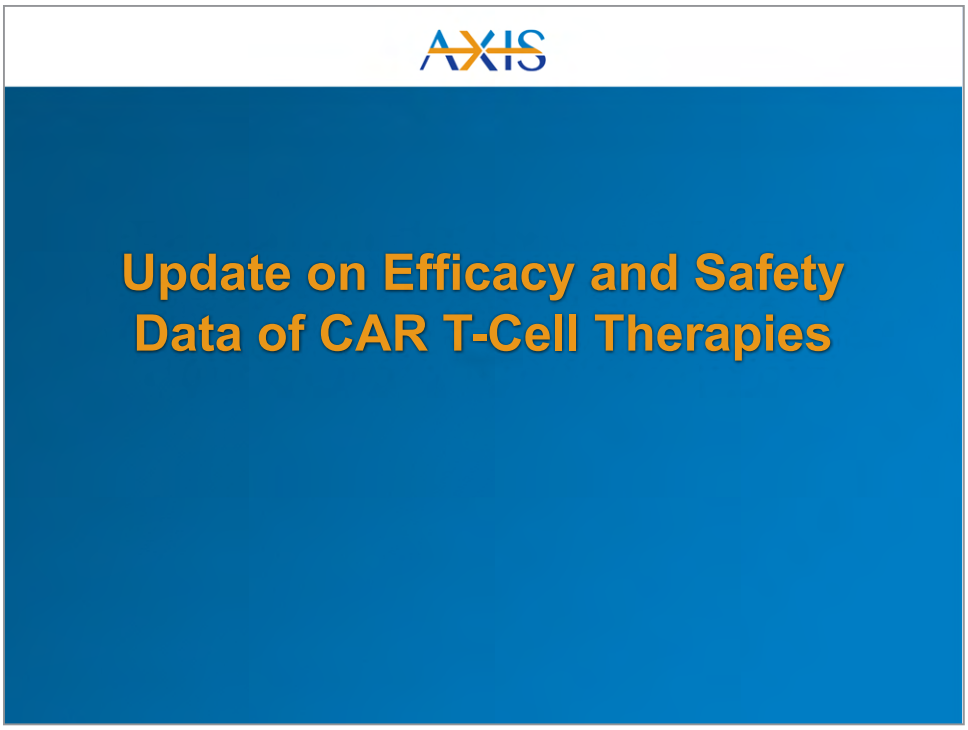
- Chimeric antigen receptors evolved from the first-generation CAR that did not contain a co-stimulatory domain. For the purpose of this discussion, we will be focusing on second-generation CAR T cells. Second-generation CAR is composed of the same construct as the first-generation CAR plus one of the co-stimulatory domains, those most commonly used are CD28 or 4-1BB.

Advantages of CAR Therapy

- HLA-independent antigen recognition, therefore universal application
- Can respond to non-peptides, including glycolipids but extracellular antigen only
- Not limited by HLA down-regulation
- Rapid generation of tumor-specific T cells
- Minimal risk of GVHD
- A living drug: potential for lasting antitumor immunity
- Selective modification of specific T cell subtypes
- Additional modification capability of CAR construct (eg, next generation, armored CARs)

CAR, chimeric antigen receptor; GVHD, graft vs host disease; HLA, human leukocyte antigen.
Modified from https://www.cirm.ca.gov/sites/default/files/files/agenda/Christine%20Brown%20City%20of%20Hope.pdf.

- These are some of the advantages of CAR T-cell therapy. The main thing to highlight here is because we're using a patient's own T cells, there is a minimal risk of graft versus host disease and there is an infinite possibility for genetic modification of this CAR construct, and most importantly, the potential for lasting immunity against tumor cells.



Dr. Mocharnuk:
Thank you, Dr. Park. Next, let's look at the current efficacy and safety data on CAR T-cell therapies, including information on recent FDA approvals.

Axicabtagene Ciloleucel in R/R DLBCL [ZUMA-1]: Baseline Patient Characteristics

Baseline Characteristics	Patients (N = 111)
Median age, yr (range) • ≥ 65 yr, %	58 (23-76) 24
Histology, % • DLBCL • Transformed FL	 73 27
No. prior lines of antineoplastic tx • ≥3	 69
Prior autologous HSCT	21

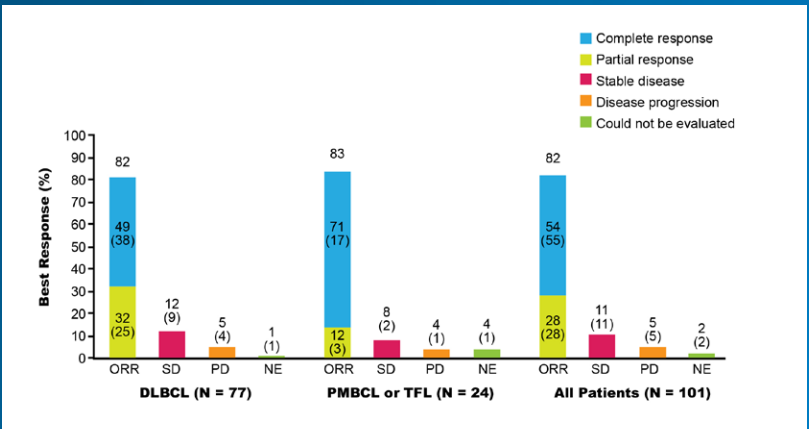
- Primary endpoint: overall response
- Conditioning regimen: Flu 30 mg/m^2 and Cy 500 mg/m^2 × 3 days
- CAR T cell dose: 2 × 10^6 CAR T cells/kg

CAR, chimeric antigen receptor; Cy, cyclophosphamide; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; Flu, fludarabine; HSCT, hematopoietic stem cell transplantation; R/R, refractory/relapsed; tx, treatment.
Neelapu et al. *N Engl J Med* 2017;377:2531-2544.

Dr. Park:
These are the latest data about axicabtagene, CD19-targeted CAR T cells with CD28 co-stimulatory domain, so essentially second-generation CAR, in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) from a multicenter, phase 2 clinical trial. These were heavily pretreated patients, with 69% having greater than 3 prior lines of therapy, 77% refractory to second or subsequent lines of therapy, and 21% had undergone autologous transplantation.

The primary endpoint of the study was overall response. In this study, there was a uniform conditioning chemotherapy regimen with fludarabine and cyclophosphamide, and the CAR T-cell dose was 2 million CAR T cells per kilogram.

Axicabtagene Ciloleucel in R/R DLBCL [ZUMA-1]: Overall Response

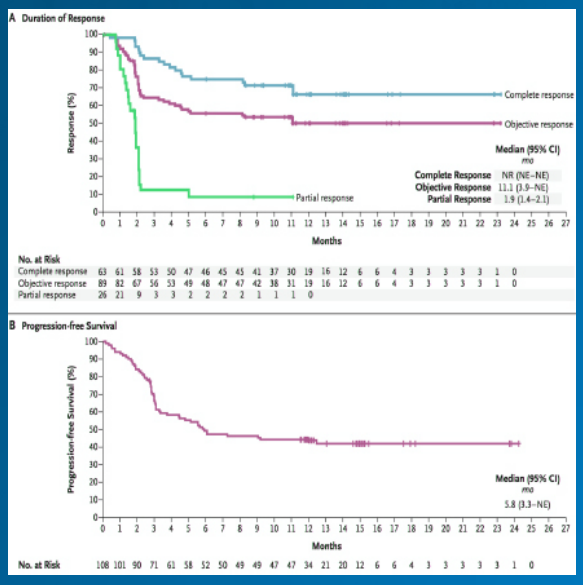


- Overall response rate: 82% (54% CR + 28% PR)

CR, complete response; DLBCL, diffuse large B cell lymphoma; NE, not evaluated; ORR, overall response rate; PD, progressive disease; PMBCL, primary mediastinal B-cell lymphoma; SD, stable disease; TFL, transformed follicular lymphoma; R/R, refractory/relapsed; tx, treatment.
Adapted from Neelapu et al. *N Engl J Med* 2017;377:2531-2544.

- The study reported the best overall response rate (ORR) of 82%, with a 54% complete response (CR) and 28% partial response (PR) rates.

Axicabtagene in R/R DLBCL: Survival



Median F/u: 15.4 months
OS at 18 months: 52%

F/u, follow-up; DLBCL, diffuse large B cell lymphoma; OS, overall survival; R/R, refractory/relapsed.
Adapted from Neelapu et al. *N Engl J Med* 2017;377:2531-2544.

- With a median follow-up of 15.4 months, overall survival at 18 months was 52%. While most patients with a PR experienced disease relapse, the study reported durable remissions in a subset of the patients who achieved a CR.

Axicabtagene Ciloleucel in R/R DLBCL [ZUMA-1]: Adverse Events

Adverse Event	Any Grade	Grade 1-2	≥ Grade 3
Cytokine release syndrome	**93%**	**80%**	**13%**
Hematologic toxicities			
Neutropenia	84%	6%	78%
Anemia	66%	24%	43%
Thrombocytopenia	58%	21%	38%
Neurologic event	**64%**	**37%**	**28%**
Encephalopathy	34%	13%	21%
Aphasia	18%	11%	7%
Memory impairment	7%	6%	1%

- 2 patients experienced Grade 5 CRS

CRS, cytokine release syndrome; DLBCL, diffuse large B cell lymphoma; OS, overall survival; R/R, refractory/relapsed.
Neelapu et al. *N Engl J Med* 2017;377:2531-2544.

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- The most common toxicities associated with the CD19-targeted CAR T cells in this study were cytokine release syndrome (CRS) and neurological toxicities. Cytokine release syndrome of any grade was reported in 93% of the patients, with 13% of the patients experiencing grade 3 or higher CRS. Any grade neurologic events were reported for 64%, including 28% of the patients having grade 3 or higher neurotoxicities, most commonly encephalopathy.

  I should also point out there were 2 patients who experienced grade 5 CRS in this particular study.

Axicabtagene Ciloleucel for Large B-Cell Lymphoma

- FDA approved October 18th, 2017 for treatment of adult patients with relapsed or refractory DLBCL after ≥2 lines of systemic therapy, including DLBCL not otherwise specified, PMBCL, high-grade B-cell lymphoma, and DLBCL arising from FL
- FDA approved in tandem with a Risk Evaluation and Mitigation Strategy

DLBCL, diffuse large B cell lymphoma; FDA, US Food & Drug Administration; FL, follicular lymphoma;
PMBCL, primary mediastinal B-cell lymphoma.
US Food & Drug Administration. 2017. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm581296.htm.

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- So based on these encouraging clinical data, axicabtagene was approved by the FDA on October 18, 2017 for treatment of adult patients with relapsed or refractory DLBCL after 2 or greater lines of systemic therapy, and the approval was in tandem with a Risk Evaluation and Mitigation Strategy.

Tisagenlecleucel in R/R DLBCL [JULIET]: Baseline Patient Characteristics

Baseline Characteristics	Patients (N = 99)
Median age, yrs (range) • ≥ 65 yrs, %	56 (22-76) 23
Histology, % • DLBCL • TFL	 80 19
No. prior lines of antineoplastic tx (%) • ≥3	 50
Response to last tx (%) • Refractory • Relapsed	 52 48
Prior autologous HSCT (%)	47

- CAR T cell dose, median (range): 3.1×10^8 CAR T cells (0.1-6.0)
- Conditioning chemotherapy: variable

DLBCL, diffuse large B-cell lymphoma; HSCT, hematopoietic stem cell transplantation; R/R, relapsed/refractory; TFL, transformed follicular lymphoma; tx, treatment.
Schuster et al. ASH 2017. https://ash.confex.com/ash/2017/webprogram/Paper105399.html.

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- Another CD19-targeted CAR T cell therapy with a 4-1BB co-stimulatory domain containing CAR was studied in a global phase 2, multicenter trial with a variable conditioning chemotherapy regimen, also with a variable CAR T-cell dose. In this patient population, median age was 56, 80% had DLBCL, 50% had 3 or greater prior lines of chemotherapy, 52% had DLBCL that was refractory to last treatment prior to enrollment to the study, and 47% had undergone autologous transplantation.

Tisagenlecleucel in R/R DLBCL [JULIET]: Overall Response

Response	≥3 Mo Best Response (n = 81)	3-Mo Response (n = 81)	6-Mo Response (n = 46)
ORR (CR + PR)	53%	38%	37%
• CR	39%	32%	30%
• PR	14%	6%	7%

- Responses observed across entire dose range
- Most patients in CR at 3 months remained in CR
- **FDA Breakthrough Therapy designation** in April 2017 for the treatment of adult patients with R/R DLBCL after failure of ≥2 prior therapies

CR, complete response; DLBCL, diffuse large B-cell lymphoma; ORR, overall response rate; PR, partial response; R/R, relapsed/refractory; TFL, transformed follicular lymphoma; tx, treatment.
Schuster et al. ASH 2017. https://ash.confex.com/ash/2017/webprogram/Paper105399.html.

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- In this study, the best ORR was 53%, with a CR rate of 39% and PR rate of 14%. Between the 3-month and 6-month response rates, there are very few drop-offs; 32% of the CR was observed at 3 months and 30% of the response was observed at 6 months.

  Based on these data, this particular product received FDA Breakthrough Therapy designation in April 2017 for the treatment of adult patients with relapsed/refractory DLBCL after failure of 2 or greater prior lines of therapy.

Tisagenlecleucel in R/R DLBCL [JULIET]: Adverse Events

AEs of Special Interest Within 8 wk After Infusion	Patients (N = 99)		
	All Grades	Grade 3	Grade 4
Cytokine release syndrome	**58**	**15**	**8**
Neurologic events	**21**	**8**	**4**
Prolonged cytopenia (at Day 28)	36	15	12
Infections	34	18	2
Febrile neutropenia	13	11	2

- CAR T-cell dose was associated with severity of CRS but not neurologic side effects

AEs, adverse events; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; R/R, relapsed/refractory.
Schuster et al. ASH 2017. https://ash.confex.com/ash/2017/webprogram/Paper105399.html.

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- These are the toxicity data from the same study. In this study, CRS was observed in 58% of the patients, with 23% of patients experiencing grade 3 or higher CRS, and 12% of patients experiencing grade 3 or higher neurologic side effects. In this study, the CAR T-cell dose was associated with severity of CRS but not with the neurologic side effects.

Tisagenlecleucel for Relapsed or Refractory Large B-Cell Lymphoma

- FDA approved May 1st, 2018 for treatment of adult patients with relapsed or refractory large B-cell lymphoma after ≥2 lines of systemic therapy. Indications include DLBCL, high-grade B-cell lymphoma, and DLBCL arising from FL
- ORR of 50%, with 32% of patients achieving a CR and 18% achieving a PR in 68 patients evaluated for efficacy
- Available through a Risk Evaluation and Mitigation Strategy program

CR, complete response; DLBCL, diffuse large B cell lymphoma; FDA, US Food & Drug Administration; FL, follicular lymphoma; ORR, overall response rate; PR, partial response.
US Food & Drug Administration. 2018. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm606540.htm.

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JCAR017 in R/R DLBCL [TRANSCEND]: Baseline Patient Characteristics

Baseline Characteristics	Patients (N = 55)
Median age, yr (range) • ≥65 yr, %	61 (29-82) 22 (40)
Histology, % • DLBCL • TFL	 73 26
No. prior lines of antineoplastic tx, median (range)	3 (1-11)
Prior autologous HSCT (%)	44

DLBCL, diffuse large B-cell lymphoma; HSCT, hematopoietic stem cell transplantation; R/R, relapsed/refractory; TFL, transformed follicular lymphoma; tx, treatment.
Abramson et al. *Hematol Oncol*. 2017;35(S2):138.

- The third study was conducted with a CD19-targeted T cell product called JCAR017 that contains 4-1BB co-stimulatory domain, and this particular product had a CD4/CD8-defined ratio. This was studied in a multicenter, phase 2 clinical trial. The median prior lines of therapy in this study was 3, and 44% of the patients had undergone autologous transplantation.

JCAR017 in R/R DLBCL [TRANSCEND]: Overall Response

Outcome	All Dose Levels	Dose Level 1	Dose Level 2
Best ORR (n/N)	75% (51/68)		
3-mo ORR (n/N)	49% (27/55)	40% (12/30; 95% CI 23-59)	63% (12/19; 95% CI 38-84)
6-mo ORR (n/N)	40% (14/35)		
Best CR (n/N)	56% (38/68)		
3-mo CR (n/N)	40% (22/55)	27% (8/30; 95% CI: 12-46)	58% (11/19; 95% CI 34-80)
6-mo CR (n/N)	37% (13/35)		

- Dose Level 1: 5 x 10^7 CAR T cells
- Dose Level 2: 1 x 10^8 CAR T cells
- Conditioning chemotherapy: Flu 30 mg/m^2 and Cy 300 mg/m^2 x 3 days

CAR, chimeric antigen receptor; CR, complete response; Cy, cyclophosphamide; DLBCL, diffuse large B-cell lymphoma; Flu, fludarabine; ORR, overall response rate; R/R, relapsed/refractory.
Abramson et al. https://ash.confex.com/ash/2017/webprogram/Paper102372.html.

- The best ORR in this study was 75%; that included 49% ORR at 3 months and 40% ORR at 6 months. The best CR rate was 56%; at 3 months, 40%; and at 6 months, 37%.

  This was a phase 1 dose-escalation study, so dose level 1 included 5 x 10^7 CAR T cells, and dose level 2 had 1 x 10^8 CAR T cells. This study also included uniform conditioning chemotherapy with fludarabine and cyclophosphamide.

JCAR017 in R/R DLBCL [TRANSCEND]: Adverse Events

Adverse Events of Special Interest	Patients (N = 69)	
	All Grades	Grade 3-4
Cytokine release syndrome	30%	1%
Neurotoxicity events	20%	14%

- No differences in incidences of cytokine release syndrome and neurotoxicity between dose levels
- 1% received tocilizumab, 9% received dexamethasone, and 9% received both as intervention for these adverse events

DLBCL, diffuse large B-cell lymphoma; R/R, relapsed/refractory.
Abramson et al. https://ash.confex.com/ash/2017/webprogram/Paper102372.html.

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- These were the key adverse events from this study. All-grade CRS was observed in 30% of all patients; only 1% experienced grade 3 or higher CRS, and 14% experienced grade 3 or higher neurologic toxicities.

  There was no difference in incidences of CRS and neurotoxicity between dose levels, and only 1% of the patients received tocilizumab.

Tisagenlecleucel in Children and Young Adults With R/R B-ALL

- Phase 2, global, 25-center study
  - Primary endpoint: Overall remission rate in 3 months
- 75 patients treated
  - Median age: 11 y (range, 3-23)
  - Median prior number of treatments: 3 (range, 1-8)
  - Prior allogeneic HSCT: 61%
- Conditioning regimen: Cy and Flu
- T cell dose (median): 3.1 × 10^6 CAR T cells/kg

B-ALL, B-cell acute lymphoblastic leukemia; CAR, chimeric antigen receptor; Cy, cyclophosphamide; Flu, fludarabine; HSCT, hematopoietic stem cell transplantation; R/R, relapsed/refractory.
Maude et al. *N Engl J Med* 2018;378:439-48

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- Another CD19-targeted CAR T cell therapy with a 4-1BB co-stimulatory-containing CAR T cells was studied in children and young adults with relapsed/refractory B-cell acute lymphoblastic leukemia (B-ALL). This was a phase 2, global study that included 25 centers. The primary endpoint of this study was overall remission rate at 3 months.

  This study included 75 patients, with a median age of 11 years. This study included a conditioning chemotherapy regimen of cyclophosphamide and fludarabine, and the median T cell dose was 3.1 x 10^6 CAR T cells per kilogram.

Tisagenlecleucel in R/R B-ALL: Response and Toxicity

- **Overall Response Rate: 81% (60% CR + 21% CRi)**

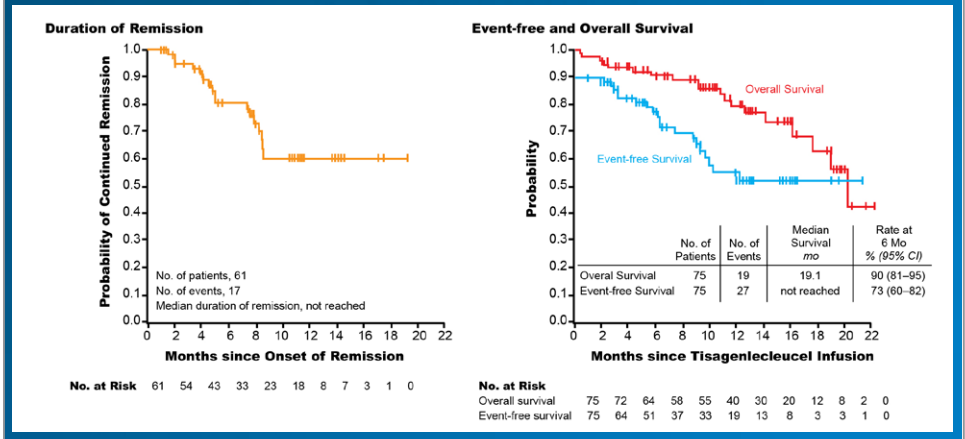
Adverse Event	Any Grade	Grade 3	Grade 4
Cytokine release syndrome	89%	21%	25%
Neurologic Event	40%	13%	0%
Encephalopathy	34%	13%	21%
Aphasia	18%	11%	7%
Memory impairment	7%	6%	1%
Infection	43%	21%	3%
Cytopenia >28 days	37%	16%	16%

B-ALL, B-cell acute lymphoblastic leukemia; CR, complete response; CRi, complete response with incomplete hematologic recovery; R/R, relapsed/refractory.
Maude et al. *N Engl J Med* 2018;378:439-48

- The ORR in this study was 81%, with 60% of the patients achieving CR and 20% of the patients attaining CR with incomplete hematologic recovery.

  Any-grade CRS was noted in 89% of all patients; 21% experienced grade 3 and 25% experienced grade 4 CRS. Any-grade neurologic side effects were observed in 40% of the patients; 13% experienced grade 3 neurologic toxicity, and no patient experienced grade 4 neurologic toxicity in this study.

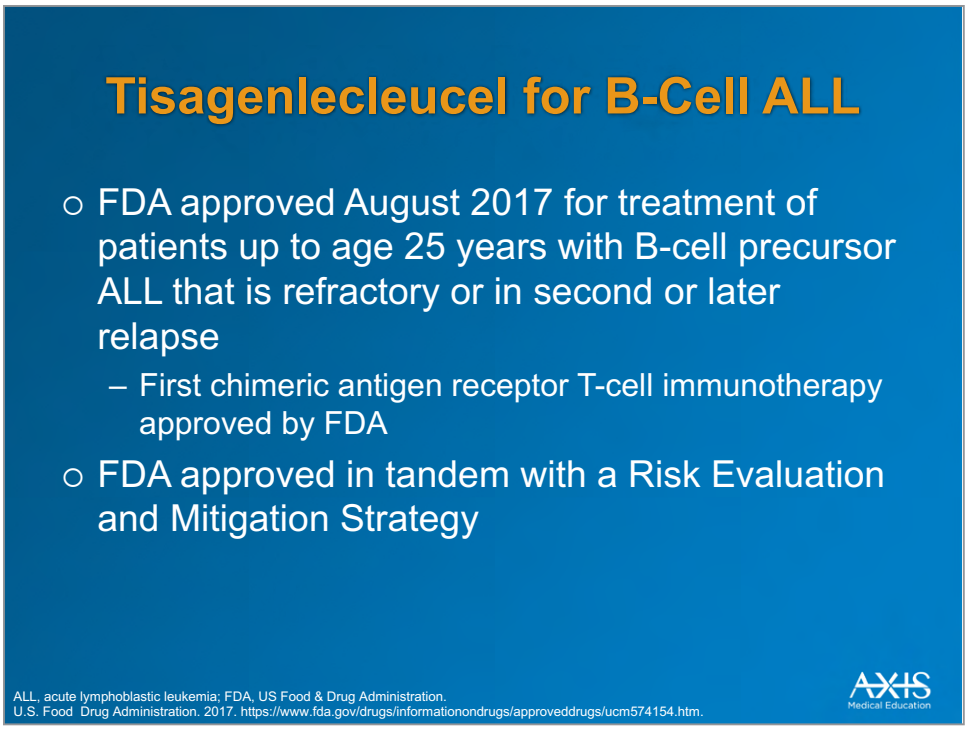
Tisagenlecleucel in R/R B-ALL: Long-Term Outcome



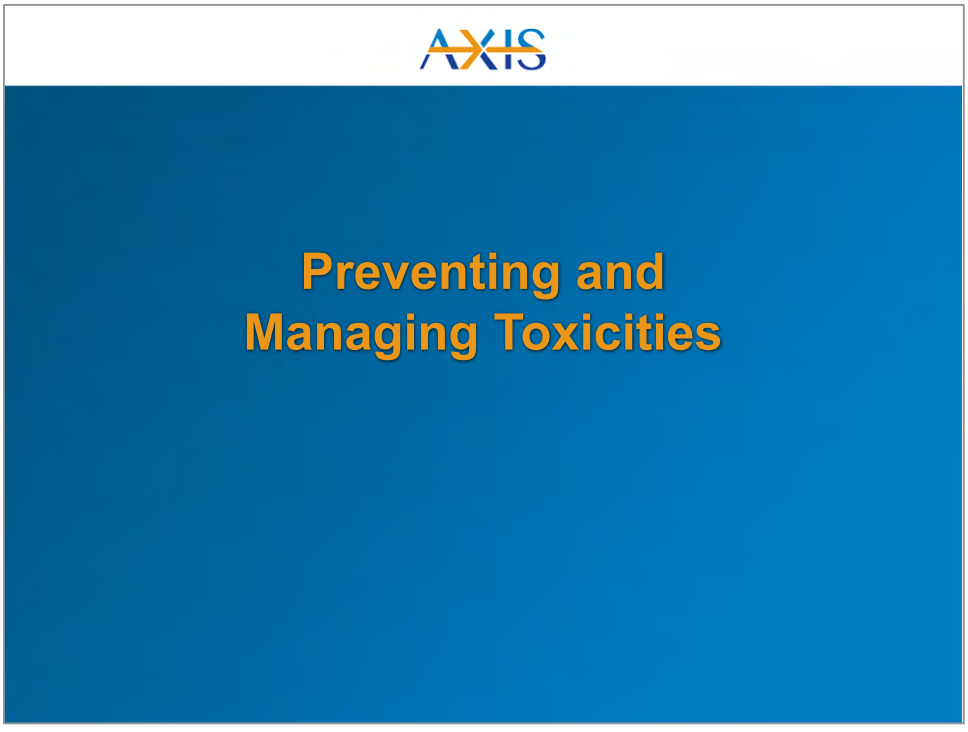
EFS at 12 months: 50%
OS at 12 months: 76%

B-ALL, B-cell acute lymphoblastic leukemia; EFS, event-free survival; OS, overall survival; R/R, relapsed/refractory.
Adapted from Maude et al. *N Engl J Med* 2018;378:439-48

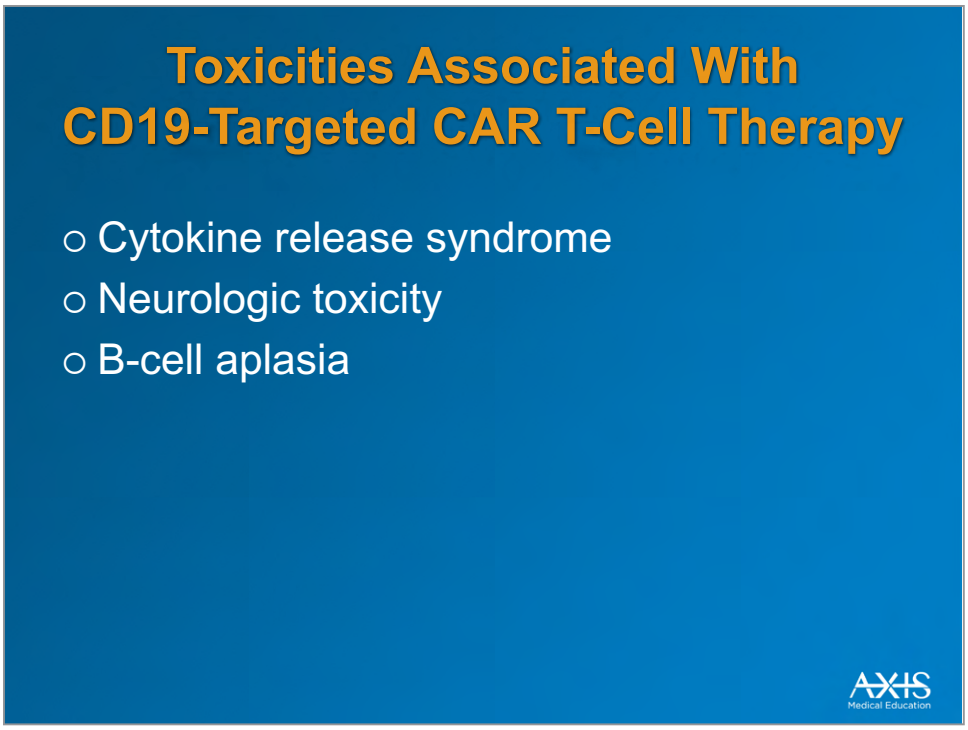
- These are the long-term outcome data from the same study in children and young adults with relapsed/refractory B-ALL. Event-free survival at 12 months was 50%, and overall survival at 12 months was 76%. Even though the follow-up is relatively short in this particular study, it is encouraging that the subset of the patients experienced durable remissions.



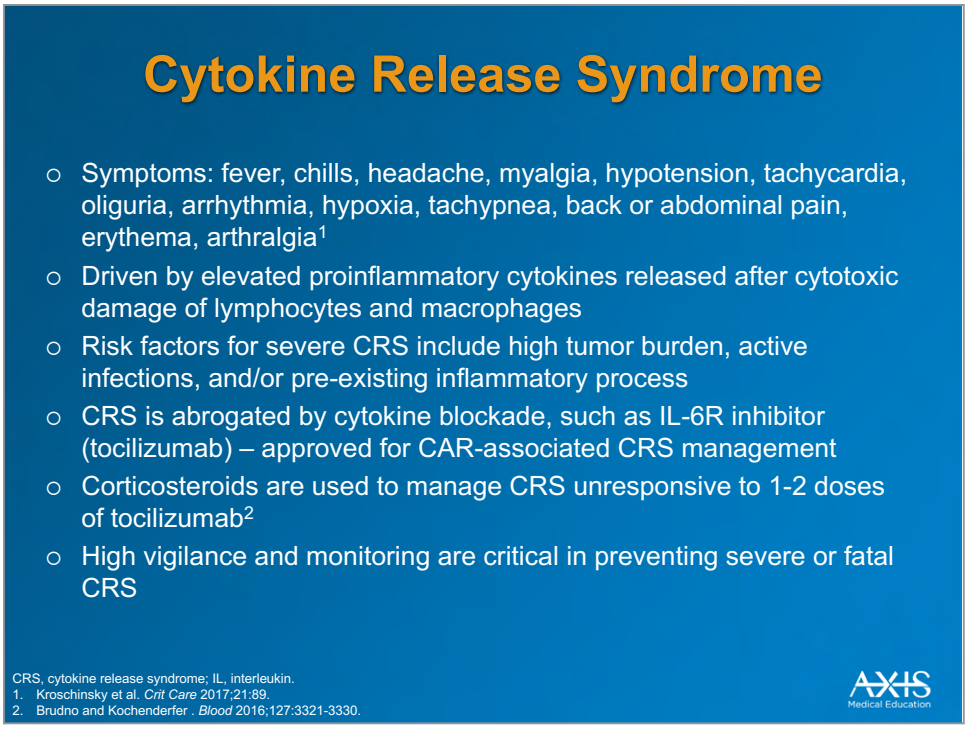
- Based on these encouraging data, this product was FDA approved in August 2017 for the treatment of patients up to age 25 years with B-ALL that is refractory or in second or later relapse. This was also FDA approved in tandem with a Risk Evaluation and Mitigation Strategy.



- **Dr. Mocharnuk:** Thank you for that review. Now, I understand that there are a few toxicities associated with CAR T-cell therapy that we should probably discuss in more detail.



Dr. Park:
So some of the key toxicities associated with CD19-targeted CAR T-cell therapy include CRS, neurologic toxicities, and B-cell aplasia.



CRS symptoms include fever, chills, headaches, myalgia, hypotension, tachycardia, arrhythmia, hypoxia, and tachypnea; essentially it's very similar to what we observe with a serous or a sepsis-like syndrome. It is driven by elevated proinflammatory cytokines that are released after cytotoxic damage of the lymphocytes and macrophages.

There are some studies that reported risk factors for severe CRS that include high tumor burden, active infections, and/or pre-existing inflammatory processes, and it does appear that patients with a ALL are more likely to experience a severe degree of CRS compared to patients with a large cell lymphoma.

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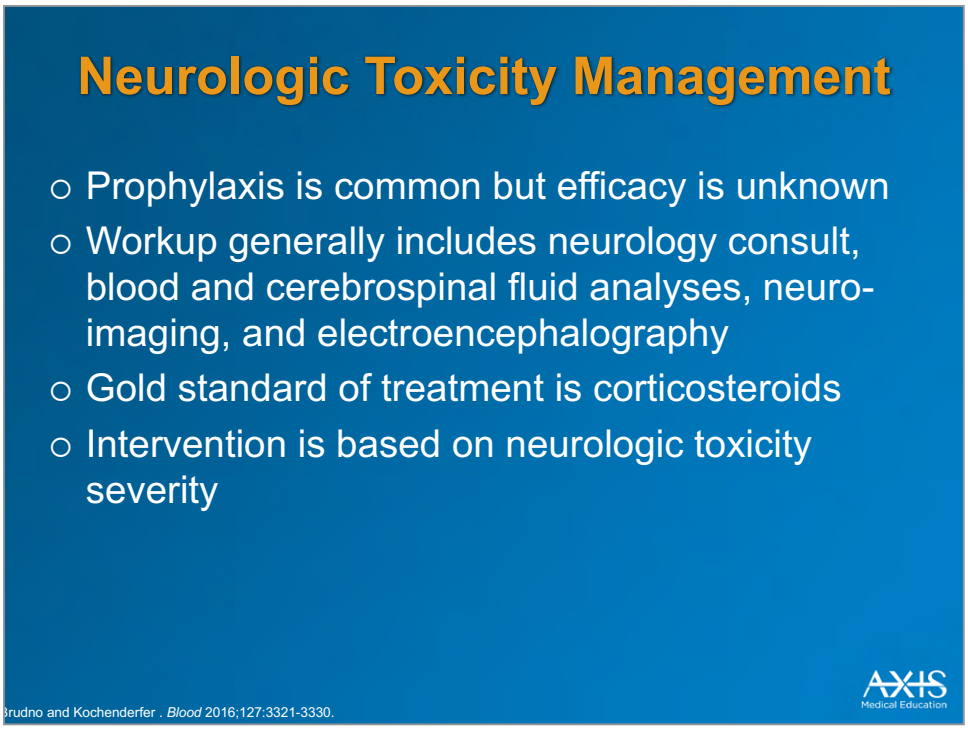
CRS is abrogated by cytokine blockade; the IL-6 receptor inhibitor tocilizumab has been approved specifically for this indication for CAR-associated CRS management. However, in the case where CRS is not responsive to tocilizumab after 1 or 2 doses, corticosteroids are highly encouraged and are quite effective in managing CRS.

The key in managing CRS is high vigilance and monitoring, and these are the critical components to preventing severe or fatal CRS.



- Unlike CRS, the mechanism and optimum management of neurologic toxicities is relatively unknown; therefore, workup generally includes neurologic consult, blood and cerebrospinal fluid analysis, neuroimaging including MRI of the brain and CT of the head, and EEG in some cases in which a seizure may be suspected.

  While we don't know the mechanism of action clearly, the gold standard of treatment for neurologic management associated with the CD19-targeted CAR T cells is corticosteroids. It does appear that tocilizumab may not be as effective in managing neurotoxicity as opposed to CRS, so we encourage use of corticosteroids and early intervention to prevent severe or sometimes fatal neurologic toxicities.

B-Cell Aplasia

- Detected by blood and/or bone marrow flow cytometry
- Also detected by measuring serum immunoglobulins (IgG)
- An on-target, off-tumor toxicity because CD19 is expressed on developing and mature B cells
- Toxicities from prolonged B cell aplasia have not been described but as more patients are treated, infectious complications are anticipated
- Managed with antibiotics and/or infusion of intravenous IgG until B cells recover

Davila and Brentjens. *Clin Adv Hematol Oncol*. 2016;14:802-808.

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- Because CD19-targeted CAR T cells attack CD19 that's expressed in both normal and malignant B cells, B-cell aplasia is an expected side effect of CD19 CAR T cells. This can be managed with an infusion of IgG; however, toxicity from prolonged B-cell aplasia has not been described. However, as more patients are treated, infectious complications are anticipated, and we need to stay on top of that to manage those complications.

Conclusion

- CD19 CAR T cells induce high CR rates in DLBCL and ALL regardless of CAR designs (CD28 vs 41BB costim domains)
- With long-term follow-up, durable remission lasting 3-5 years have been observed
- Two CD19 CAR therapies are approved for treatment of hematologic malignancies
  - Tisagenlecleucel (41BB containing CAR) in children and young adults with R/R ALL, and in adults with R/R large B-cell lymphoma
  - Axicabtagene ciloleucel (CD28 containing CAR) in adults with R/R DLBCL
- Several other CD19 CAR therapies are under investigation for NHL, ALL, and CLL
- Future studies will focus on optimizing the safety and efficacy of current second-generation CAR T-cells, and successful clinical translation of the next-generation or "armored CAR" T cells

ALL, acute lymphoblastic leukemia; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; CR, complete response; DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin lymphoma; R/R, relapsed/refractory.

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- In conclusion from the clinical data that we have reviewed, we have seen that CD19-targeted CAR T cells can induce high CR rates in heavily pretreated patients with DLBCL and ALL regardless of the CAR design, whether they contain CD28 or 4-1BB co-stimulatory domains; so these are the second-generation CAR T cells as studied in clinical trials and approved now. With long-term follow-up, durable remissions lasting 3 to 5 years have been observed after single infusion of these CAR T cells.

  Two CD19 CAR T-cell therapies are approved for the treatment of hematologic malignancies; however, encouraging findings surrounding several other CD19 CAR T-cell therapies are under investigation for non-Hodgkin lymphoma and chronic lymphocytic leukemia.

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In the next several years, we will also see next-generation CAR T cells that are further modified to increase the potency of the CAR T cells that can generate more endogenous immune reactions against more difficult-to-treat tumors.

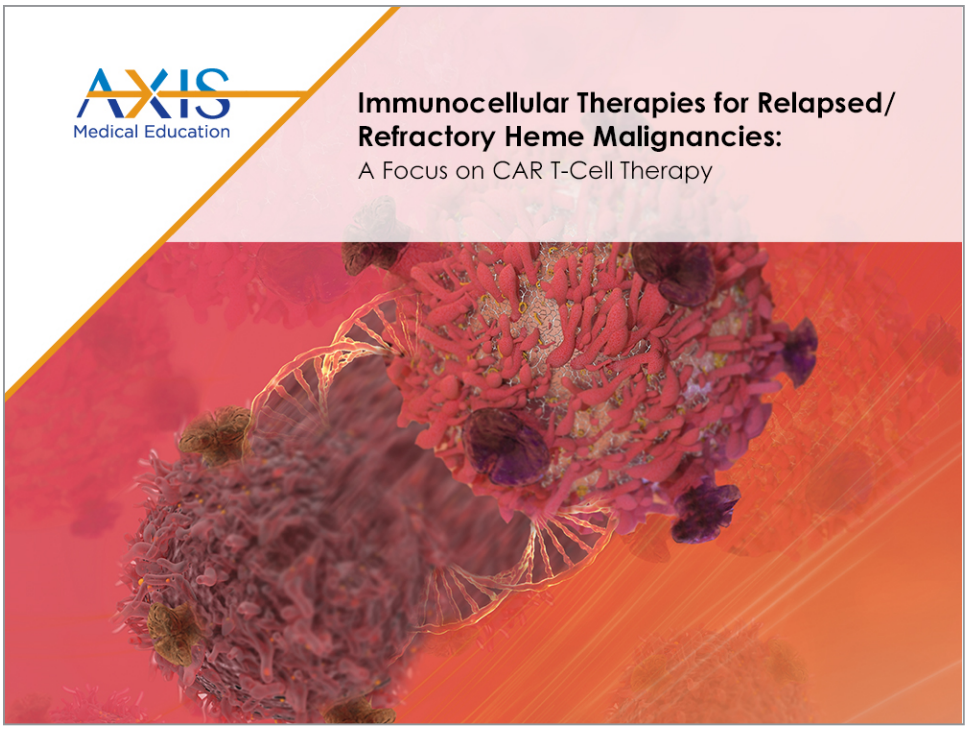
Dr. Mocharnuk:
Let's conclude with the discussion about the differences among agents in this class of drugs, and how you would see these agents transforming future treatments.

Dr. Park:
While all these agents target the same CD19 antigen, there are several differences in these particular studies, including the construction of CARs—whether these include what type of second-generation CAR they are studying—cell manufacturing process, infused T-cell dose, patient populations—even though they all include patients with relapsed disease, they're not exactly the same and the remission duration of these studies as well as toxicities differ.

While we don't exactly know whether one product is better than the other, I think it's important to keep these factors in mind when we interpret the data.

Dr. Mocharnuk:
Dr. Park, how do you see this class of agents transforming treatments in the future?

Dr. Park:
In the next several years, I anticipate clinical trials of these CAR T-cells to challenge current standard practice and move to earlier lines of therapy, which is already happening. We actually do believe that this type of immunocelluar immunotherapy may have even better efficacy when these T cells are extracted from patients in the less treated setting. However, as we do so, we need to be aware of some of the changes in toxicity profiles to make this therapy not only better, but also safer.



Dr. Mocharnuk:
Thank you, Dr. Park, so much for providing your expert insights on CAR T-cell therapy for the treatment of relapsed/refractory hematologic malignancies. And we want to thank you for your participation in this activity.

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