New Directions in the Treatment of Relapsed/Refractory DLBCL: Implications for Practice

Dr. James Armitage: Welcome to today's program. My name is Jim Armitage. I'm a Professor of Medicine at the University of Nebraska Medical Center, and today I'm joined by a colleague of mine, Dr. Matthew Lunning, who is an Associate Professor of Medicine, also at UNMC.

Faculty Disclosures

James O. Armitage, MD
Honorarium: Cardiff Oncology, Inc.

Matthew Lunning, DO, FACP
Consultant: AbbVie Inc., Acrotech Biopharma, Inc., ADC Therapeutics, Astellas Pharma US, Inc., AstraZeneca, BeiGene, Bristol Myers Squibb Company, Daiichi Sankyo, Inc., EUSA Pharma, Fate Therapeutics, Genentech - A Member of the Roche Group, Instil Bio, Janssen Pharmaceuticals, Inc., Karyopharm Therapeutics, Kite Pharma, Kyowa Kirin Pharmaceutical Development, Inc., Legend Biotech, MorphoSys, Myeloid Therapeutics, Novartis AG, Nurix Therapeutics, Inc., Sana Biotechnology, Spectrum Pharmaceuticals, Inc., TG Therapeutics, Inc., Verastem, Inc.

These are the disclosures that are pertinent for today's discussions.

Learning Objectives

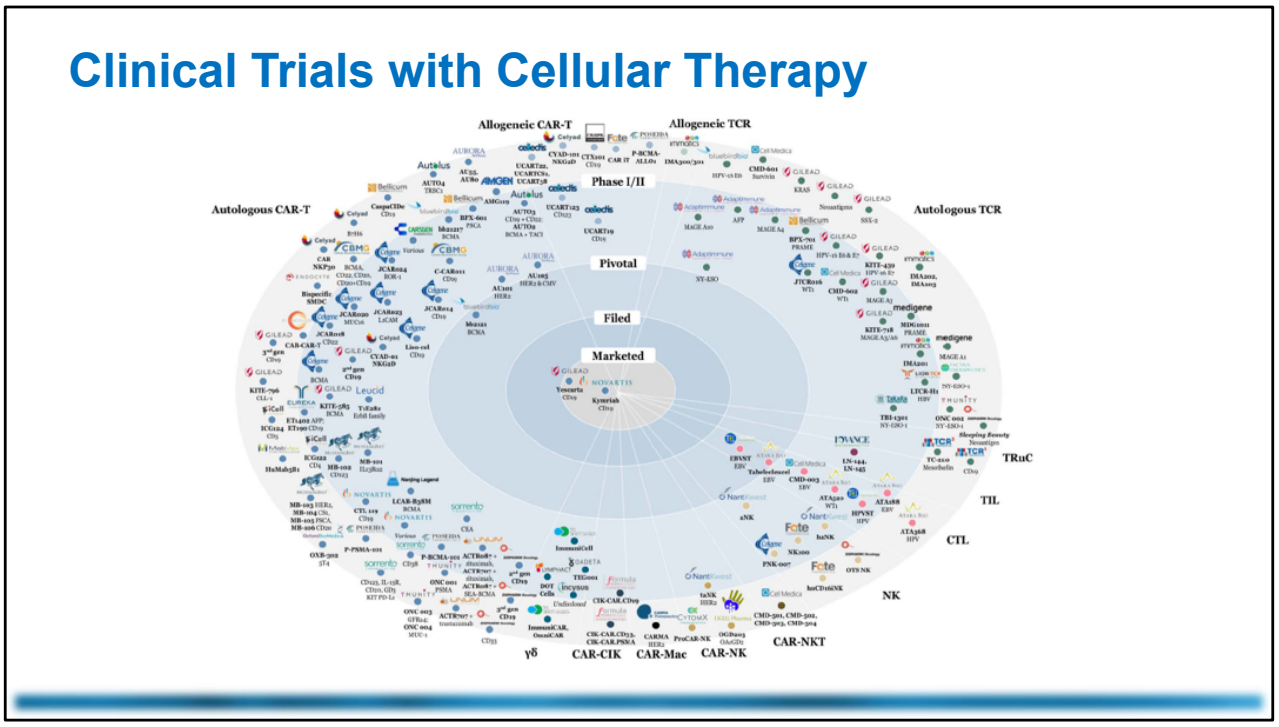
- Discuss key data from recent publications and conferences on current and emerging approaches for the treatment of relapsed/refractory DLBCL
- Describe current and potential practice implications

Now today's presentation is going to discuss new directions in the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL). This is a disease that is a success story in modern oncology, and we cure most people but not anywhere nearly everybody. How to deal with these patients who don't get cured by standard therapy has been a real issue.

Dr. Lunning is going to discuss key data from recent publications and conferences on current and emerging approaches for the treatment of these patients with diffuse large B-cell lymphoma who failed standard therapy. He's going to present to us current and potential practice implications and then we will have a discussion to see how he thinks through these clinical problems.

At this point, I am pleased to turn the presentation over to Matt.

Dr. Matthew Lunning: Thank you, Jim.

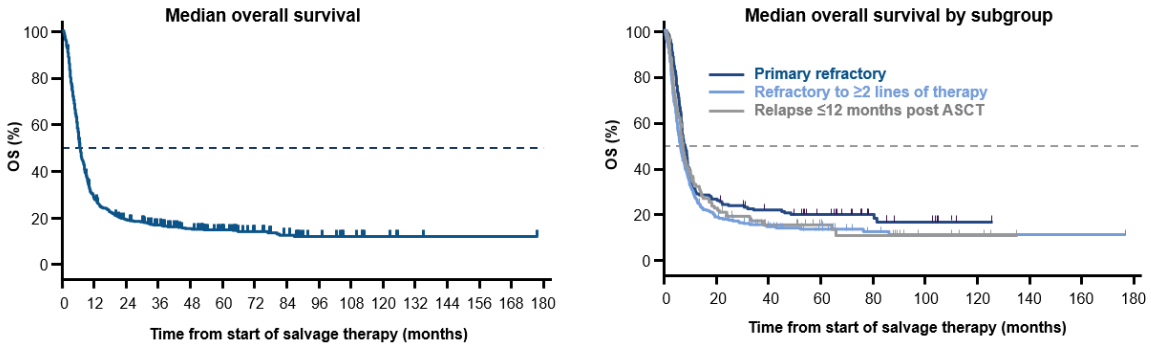


Dr. Matthew Lunning: I want to first start off with, how can you not have a talk about relapsed/refractory diffuse large B-cell lymphoma without talking about leading in, talking about cellular therapy? As you can see here, this is not a picture of the number of satellites revolving around the earth, but the number of clinical trials that have a cellular therapy component in development.

You can see many of them live in the phase 1/2 realm, but some are making their way into pivotal clinical trials. We now have several cellular therapies which are marketed in the commercial environment. Many of those led their approval through the pathway of relapsed/refractory diffuse large B-cell lymphoma. Why is that?

Median Overall Survival For Patients with R/R DLBCL

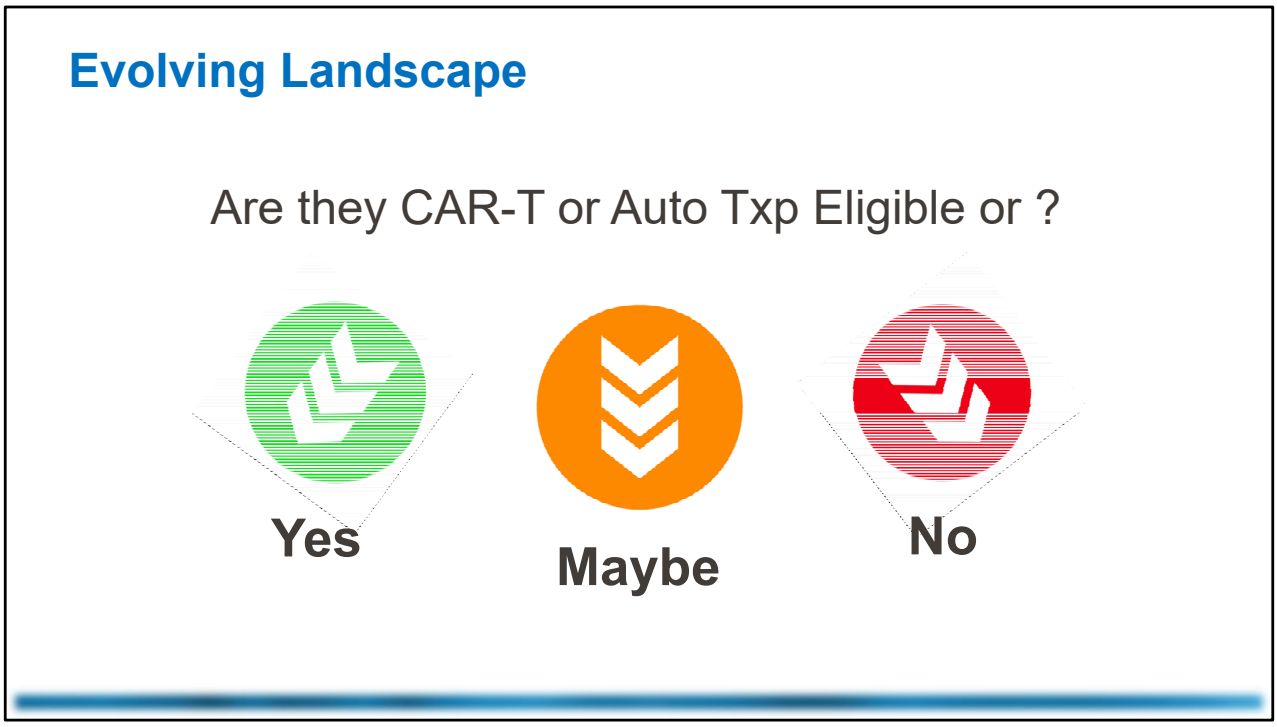
SCHOLAR-1: Retrospective analysis of outcomes in patients with R/R DLBCL (N = 636)



Crump M, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood*. 2017;130(16):1800-1808.

As Dr. Armitage alluded to, many of the patients with diffuse large B-cell lymphoma, approximately 60% to 70% are cured with first-line chemoimmunotherapy namely, rituximab R-CHOP, potentially being unseated based upon data from the POLARIX which is beyond this presentation today. However, for those patients who have primary refractory disease or have refractory disease to two lines or more, or who have relapsed within 12 months of autologous stem cell transplant, the prognosis is quite poor. You can see here based upon the SCHOLAR-1 data, that the median overall survival of these three groups is approximately six months.

Again, I'll repeat that. The median overall survival in these three populations is around six months. That is what has made CAR T-cell or cellular therapy such an important part of the management of relapsed/refractory diffuse large B-cell lymphoma.

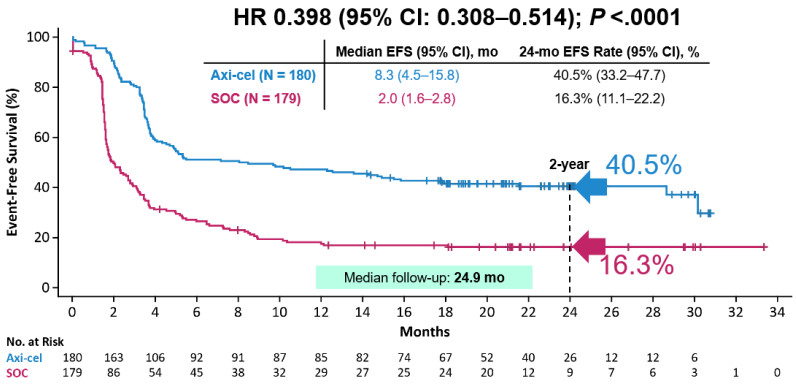


Recently though, the landscape has been changing to the point where we knew CAR T-cells were very well cemented in the second-line or third-line and beyond treatment. However, now based upon randomized trials, and an enriched high-risk population of patients with diffuse large B-cell lymphoma, based upon the randomized data, now CAR T-cell is moving into the second line. Really when I think about a relapsed/ refractory patient, I used to ask myself, are these patients auto transplant eligible?
Now I'm asking myself, are these patients CAR T-cell eligible? Should they still get an auto transplant or is there another therapy that they should be getting in lieu of CAR T or an auto transplant?

Really, we are walking down the path of yes, maybe, or no. Let's go through the emerging data that led to the second-line approval of CAR T-cell therapy.

ZUMA-7: Axicabtagene-Ciloleucel* vs SoC in R/R Large B-Cell Lymphoma

Global, multicenter, randomized phase III trial



*Axicabtagene-Ciloleucel is approved by the FDA for the treatment of adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy.
Axicabtagene ciloleucel is not indicated for the treatment of patients with primary central nervous system lymphoma.

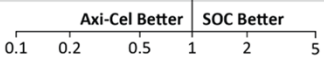
Locke FL, et al. *New Engl J Med*. 2022;386(7):640-654.

The first trial was the ZUMA-7 trial, and this pitted axi-cel, a CD19 CAR-modified T-cell product, against standard of care. As you can see, this was a randomized trial and those patients going to axi-cel could receive no bridging therapy, whereas the patients in the standard of care received standard second-line chemotherapy and if they had a response amenable to transplant, proceeded on to transplant versus those randomized to axi-cel went on to receive axi-cel once the patients were apheresis they received lymphedema chemotherapy followed by infusion of the CAR-modified T-cells. The primary endpoint here was median EFS. You can see here there was a statistically significant outcome in favor of axi-cel with a hazard ratio of 0.39. You can see the two-year event-free survival in the axi-cel arm was 40.5, and in the standard of care arm, only 16.3.

ZUMA-7: Axi-cel* vs. SoC as Second-Line Therapy in Primary Refractory or Early Relapsed B-Cell Lymphomas

Who Benefits?

	Axi-Cel EFS Event/N	SOC EFS Event/N	HR (95% CI)
Overall	108/180	144/179	0.398 (0.308-0.514)
Age, years			
<65	81/129	96/121	0.490 (0.361-0.666)
≥65	27/51	48/58	0.276 (0.164-0.465)
Response to 1L therapy at randomization			
Primary refractory	85/133	106/131	0.426 (0.319-0.570)
Relapse ≤12 months of 1L therapy	23/47	38/48	0.342 (0.202-0.579)
sAAIPI			
0-1	54/98	73/100	0.407 (0.285-0.582)
2-3	54/82	71/79	0.388 (0.269-0.561)
Prognostic marker per central laboratory			
HGBL-double/triple hit	15/31	21/25	0.285 (0.137-0.593)
Double expressor lymphoma	35/57	50/62	0.424 (0.268-0.671)



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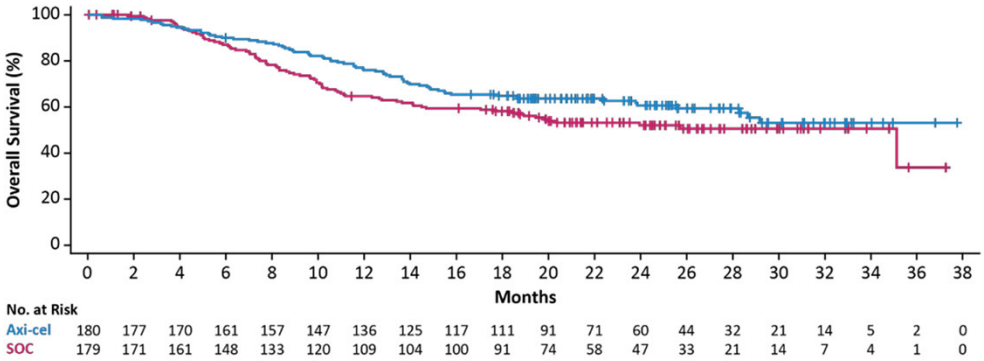
Locke FL, et al. *New Engl J Med*. 2022;386(7):640-654.

Who benefited in this trial? A statistician would tell you here that all patients appear to benefit regardless of subtype, or different age, or characteristics of their disease, patients benefited if they received the axi-cel product. You can see here that the dots are fairly well aligned on the side with confidence intervals not crossing one.

ZUMA-7: Axi-cel* vs. SoC as Second-Line Therapy in Primary Refractory or Early Relapsed B-Cell Lymphomas

Overall Survival



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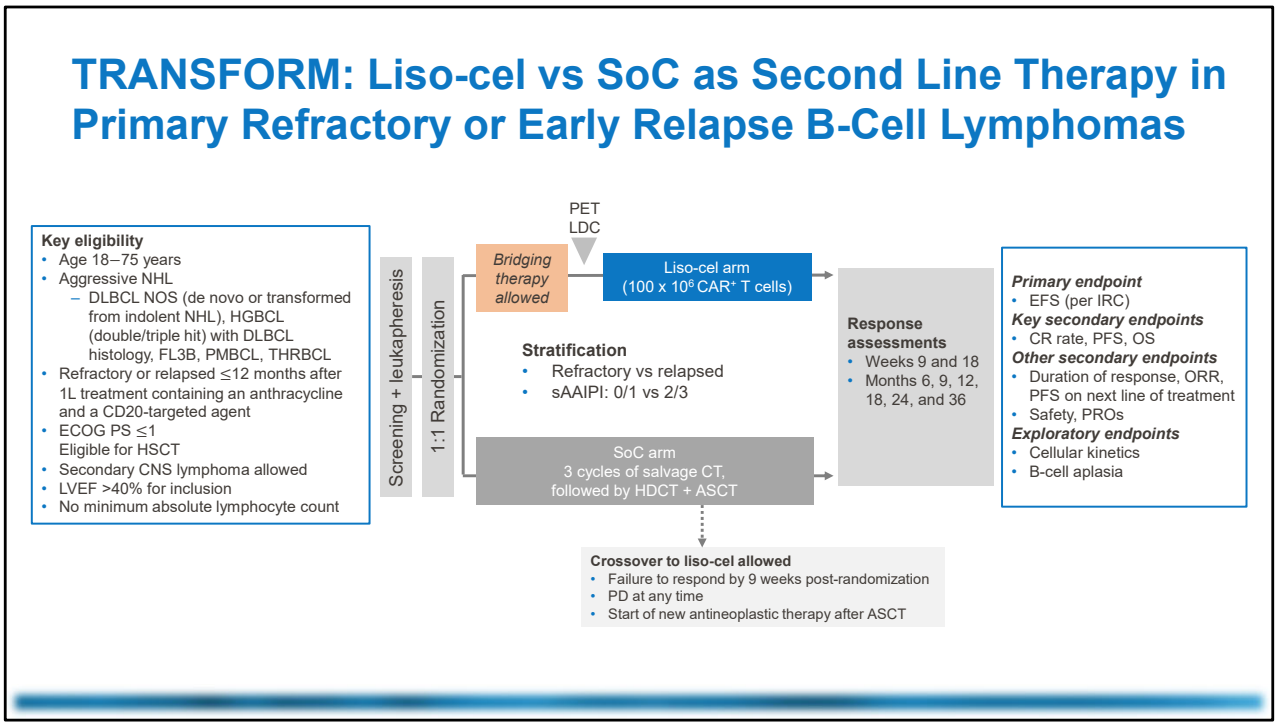
Locke FL, et al. *New Engl J Med*. 2022;386(7):640-654.

Overall survival, while this is the most mature of our randomized trials, was in favor of a ZUMA-7 and we'll have to see with longer follow-up, whether or not this trends towards a difference in overall survival for the CAR T-cell group.

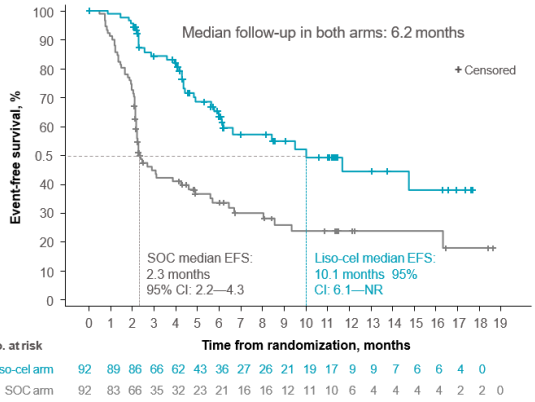


A second trial that was done concurrently but was reported later, was the TRANSFORM trial. This was done in a similar patient population of those patients who had either primary refractory or diffuse large B-cell lymphoma which relapsed within one year of the end of chemotherapy. Slightly different in this trial, which was still randomized to standard of care versus CAR T-cell was in this trial, patients could receive bridging chemotherapy in the experimental arm and then go on to receive the liso-cel CD19 CAR-modified T-cells. Again, in the standard of care arm, if those patients had a response amenable to stem cell transplant, they would continue to proceed on.

In this situation, or in this trial, these patients did have their CAR T-cells manufactured or apheresis before, and then if an event were to occur in the standard of care arm, they could go on and have a crossover to receive liso-cel on trial. Whereas in the ZUMA-7 trial, patients would have to receive their CAR T-cell therapy after a progression event in the standard of care arm, either in the commercial environment or potentially in a different clinical trial.

TRANSFORM: Liso-cel* vs. SoC as Second-Line Therapy in Primary Refractory or Early Relapsed B-Cell Lymphomas

Event-free Survival



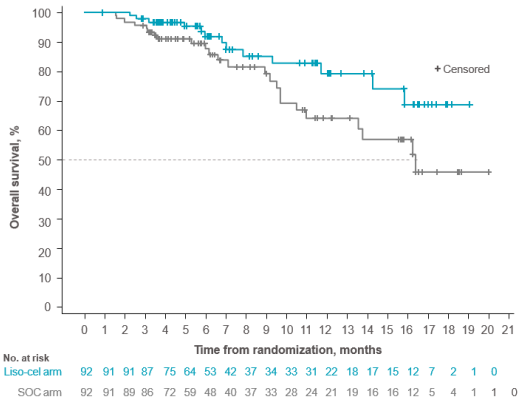
*On 2/5/21 the FDA approved lisocabtagene-maraleucel for the treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B.

Kamdar M, et al. *Lancet*. 2022;399(10343):2294-2308.

As you can see here, the median follow-up is much shorter in the TRANSFORM trial compared to the ZUMA-7 trial, at 6.2 months. However, there was an event-free survival advantage in the liso-cel arm at 10.1 months, versus a standard-of-care arm with a median of 2.3 months. Very similar outcomes in both standard-of-care arms in this trial.

TRANSFORM: Liso-cel* vs. SoC as Second-Line Therapy in Primary Refractory or Early Relapsed B-Cell Lymphomas

Overall Survival



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Kamdar M, et al. *Lancet*. 2022;399(10343):2294-2308.

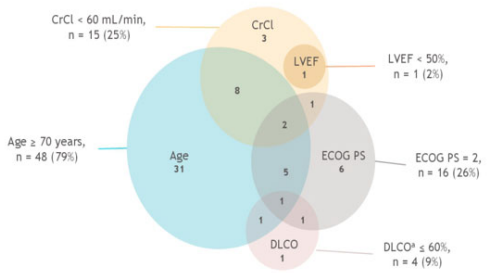
Again, a trend towards overall survival potential differences, but we'll continue to need longer follow-up to see how this plays out.

PILOT: Lisocabtagene maraleucel (liso-cel) as second-line therapy for R/R large B-cell lymphoma (LBCL) in patients not intended for hematopoietic stem cell transplantation (HSCT)

Patient Eligibility

Patient eligibility

- Age ≥ 18 years
- LBCL: DLBCL NOS (de novo; transformed from FL), HGBCL with rearrangements in *MYC* and *BCL2* and/or *BCL6* (double/triple hit), or FL3B
- One prior line of therapy containing an anthracycline and a CD20-targeted agent
- Not intended for HSCT by investigator and met ≥ 1 of the following TNI criteria: age ≥ 70 years, ECOG PS of 2, DLCO ≤ 60% (adjusted for sex-specific hemoglobin concentration), LVEF < 50%, CrCl < 60 mL/min (calculated using Cockcroft-Gault), and/or AST/ALT > 2 × ULN
- Adequate organ function[a]
- Patients with secondary CNS lymphoma were allowed



On 6/24/22 the FDA approved lisocabtagene-maraleucel for R/R large B-cell lymphoma after one prior line of therapy.

Sehgal A, et al. *J Clin Oncol.* 2022;40(16 suppl):7062.

Another trial that was done concurrently with the TRANSFORM trial was the PILOT trial. I like to highlight this because I think some individuals think that, if you're not a transplant candidate, then you're no longer a CAR T-cell candidate. The PILOT trial really challenged that, and I'll show you here on this slide that this was meant for patients who were not transplant eligible, and that could be defined by many a different criteria but you had to have at least one of these, which was either age greater than 70, EGOC performance status of two, DLCO of less than 60%, a LVEF less than 50% but greater than 40%, a creatinine clearance less than 60 mils per minute, but greater than 30 mills per minute.

You can see here that this is on the right-hand side, is a Venn diagram showing off overlapping risk factors. Mainly driven by age, but certainly there were some other aspects that I think are clearly relevant, namely creatinine clearance, especially in advanced-age individuals. In my mind, there is no upper limit of age for CAR T-cell therapy to be delivered.

Based upon the PILOT data, there was very similar overall response rates and CR rates that had been seen in the TRANSCEND data set. We're really talking about overall response rates in the 70% to 80% with CR rates into 50% to 60%. I believe in this PILOT population, this is still a reasonable option. This was seen in the expansion of the label to transplant not eligible patients in the second-line setting.

Transitioning to Commercial Environment

- Patient access
- Intent to CAR → Brain to Vein
- Figuring out best Vein to Vein therapy (bridging)
- Adding to CAR-T in “high risk populations”
- Early CAR T failure vs Late CAR-T failure
- Identifying mechanisms of CAR-T failure
- Allies vs adversaries regarding available agents

As we think about transitioning CAR T-cell to the commercial environment, one of the things that has been noted as we've been trying to use this in the third- line and beyond is really patient access. Right now I think the data supports that maybe one in five patients who could get a CAR T-cell are actually getting their CAR T-cell. Why is that?

I think the question is you're really looking at what I call the intent to CAR or the brain-to-vein time. When you and I as an oncologist and the patient and their families sit down and say, "We want to move to CAR T-cell," there are certain hurdles that exist in this brain-to-vein time before we even apheresis the individual. That can be prior authorization, negotiation of single case agreements, allocation of apheresis slot time. Really, I think in intent to CAR analysis, we have to take in consideration the brain-to-vein time.

In clinical trials, we've really only looked at the vein-to-vein time, or the time taken between apheresis of the T-cells to reinfusion and then incorporating it into the outcomes in the post-infusion environment. Otherwise, called the vein-to-gain time, at least in my opinion.

I think that we've figured out the vein-to-vein time. We've started to figure out bridging during the vein-to-vein time, but we really needed to think about the pre-apheresis or the bridging during the brain-to-vein time that really could impact the fidelity of the CAR T-cells.

Transitioning to Commercial Environment (cont'd)

- Patient access
- Intent to CAR → Brain to Vein
- Figuring out best Vein to Vein therapy (bridging)
- Adding to CAR-T in "high risk populations"
- Early CAR T failure vs Late CAR-T failure
- Identifying mechanisms of CAR-T failure
- Allies vs adversaries regarding available agents

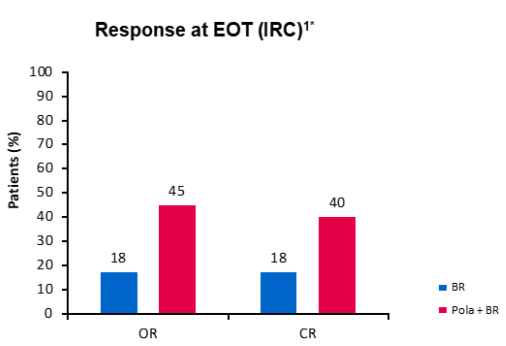
I think that CAR T-cells, we need to continue to add onto them. I think the outcomes could be better, especially in the high-risk populations. We need to find adjunctive therapies to try to make the CAR T-cells better.

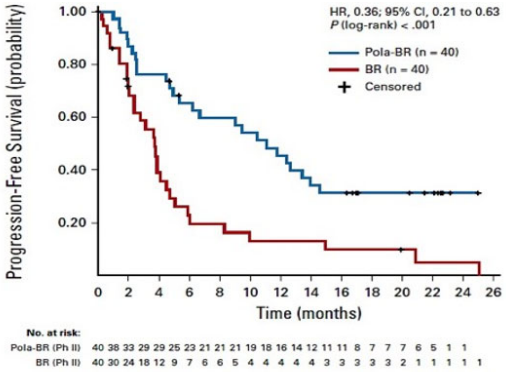
I think we've sorted out how well CAR T-cells will do in the second line in early CAR T-cell failures, but what is the role for CAR T-cell in late failures? In my opinion, those patients should still go on to receive second-line chemotherapy, an autologous stem cell transplant as I still believe that is a curative intent option, but CAR T-cell could still be used if those patients relapse.

We continue to learn about the mechanisms of CAR T-cell failure and trying to enhance our CAR T-cells through clinical trials.

As we pivot now to talking about non-CAR T-cell therapies and relapsed/refractory large cell lymphoma, we really need to think about these therapies as potential allies to cellular therapy rather than adversaries and an adversarial relationship that would work towards not promoting patients to getting CAR T-cell therapy.

Polatuzumab Bendamustine Rituximab vs. Bendamustine Rituximab





Pola-BR = polatuzumab bendamustine rituximab
BR = bendamustine rituximab

Sehn L, et al. *Blood Adv.* 2022;6(2):533–543.

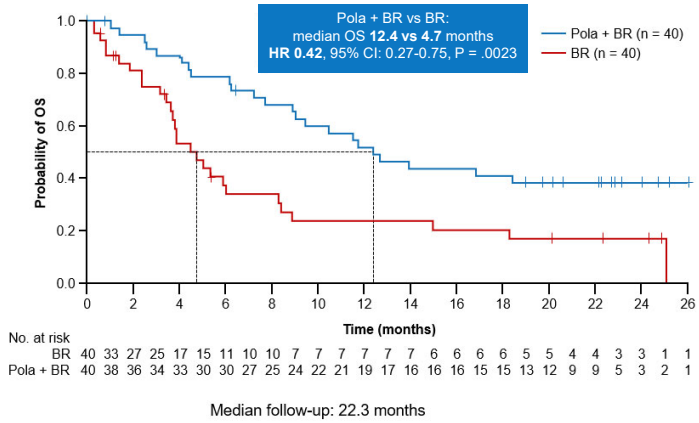
The first non-CAR T-cell trial that I will talk about in the relapsed/refractory DLBCL spectrum is polatuzumab bendamustine rituximab (pola-BR) versus bendamustine rituximab (BR).

This was a trial that was very small but was a randomized phase two. You can see here that the overall response rate and the CR rate was much higher in the pola-BR arm. What's obviously missing in this trial is a polatuzumab-only arm, but you have to think that the heavy lifting is being done by the polatuzumab here. The surprise was that in this trial, there was an overall survival advantage in those patients who received polatuzumab-BR. That led the FDA to come knocking and polatuzumab-BR was approved for the treatment of relapsed/refractory diffuse large B-cell lymphoma.

Many of you may know in the NCCN guidelines now, it now states polatuzumab plus minus bendamustine plus minus rituximab. It has given us the option on how to use this regimen in clinical practice. This still remains my number one bridging strategy in the pre-apheresis environment is to give single agent polatuzumab or single agent polatuzumab rituximab if still rituximab sensitive.

Polatuzumab vedotin plus bendamustine and rituximab in relapsed/refractory DLBCL

Median Overall Survival



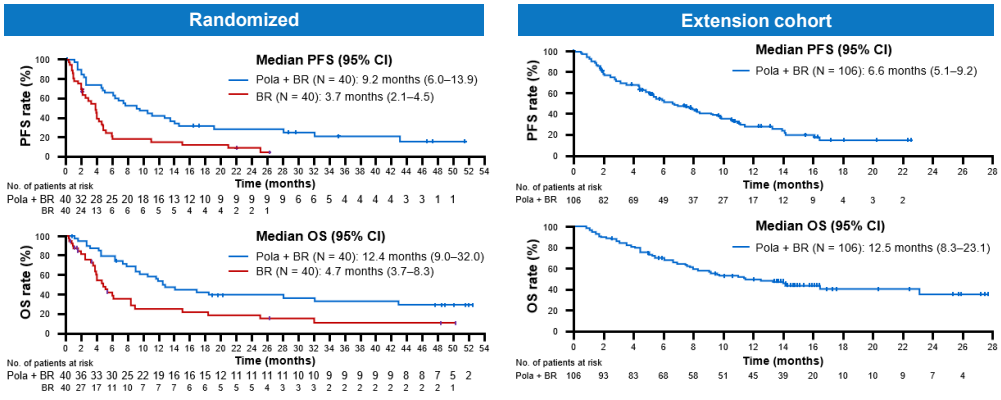
Median follow-up: 22.3 months

Sehn L, et al. *Blood Adv.* 2022;6(2):533–543.

Here's the median overall survival curve showing the survival advantage of polatuzumab rituximab at 12.4 months versus 4.7 months.

Polatuzumab vedotin plus bendamustine and rituximab in relapsed/refractory DLBCL

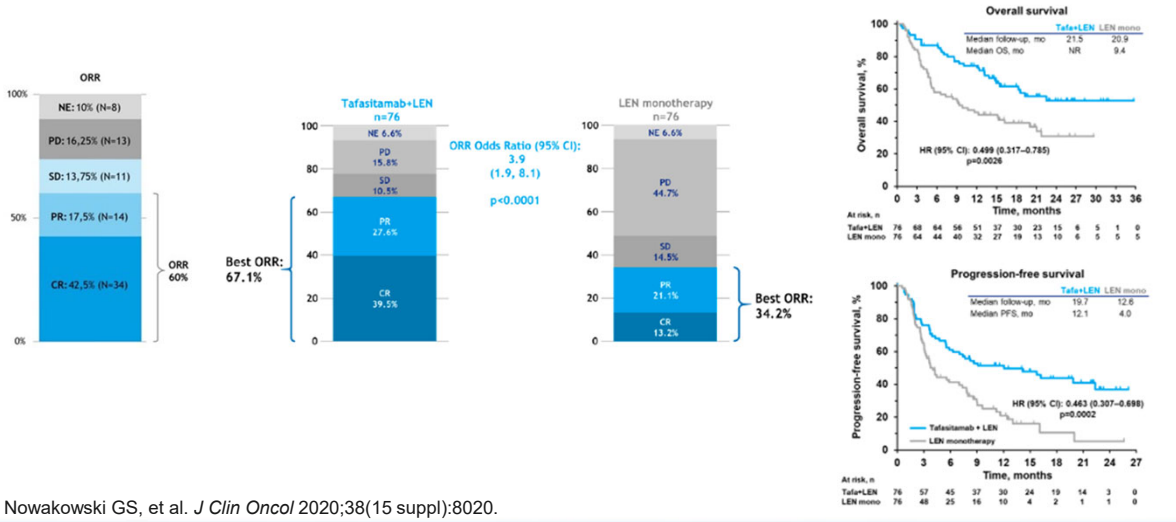
Expansion COHORT STUDY



Sehn L, et al. *Blood Adv.* 2022;6(2):533–543.

Many of us thought this may be a fluke. A larger expansion study was done showing very similar results in the expansion cohort with the median PFS of the pola-BR being 6.6 months and the overall survival being 12.5 months. Again, confirming the initial data set.

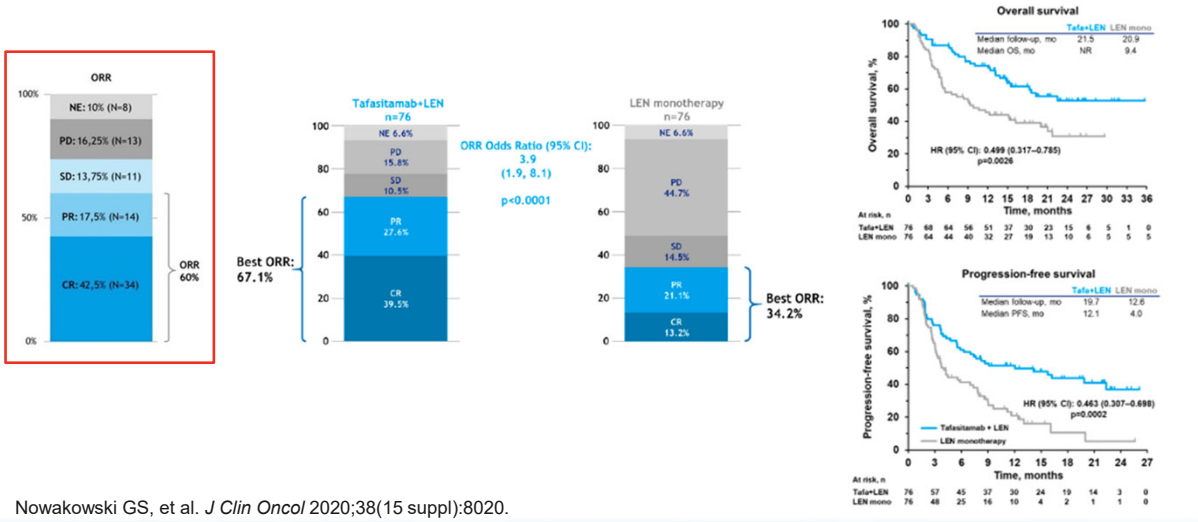
RE-MIND study: A propensity score-based 1:1 matched comparison of tafasitamab + lenalidomide (L-MIND) versus lenalidomide monotherapy (real-world data) in transplant-ineligible patients with R/R diffuse large B-cell lymphoma



Nowakowski GS, et al. *J Clin Oncol* 2020;38(15 suppl):8020.

The next regimen that I'd like to highlight is a successive model of analyzing data. The initial study was the L-MIND study, which was tafasitamab, which is a CD19 antibody paired with lenalidomide or immunomodulatory agent.

RE-MIND study: A propensity score-based 1:1 matched comparison of tafasitamab + lenalidomide (L-MIND) versus lenalidomide monotherapy (real-world data) in transplant-ineligible patients with R/R diffuse large B-cell lymphoma

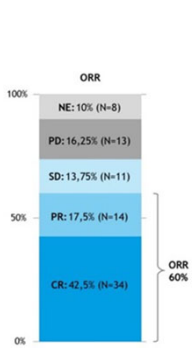


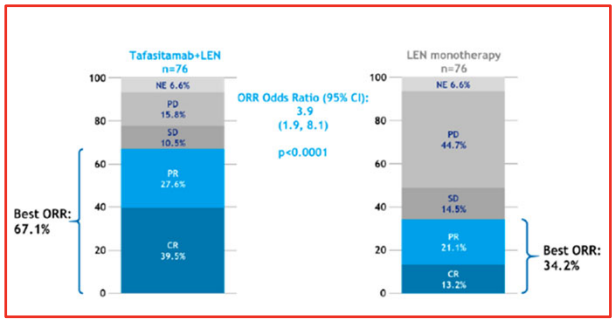
Nowakowski GS, et al. *J Clin Oncol* 2020;38(15 suppl):8020.

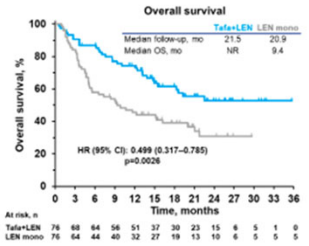
You can see individually, neither of these drugs would get response rates in the 60%, but together, you can see here, the overall response rate was 60% with a whopping 42% CR rate. This was in an early, at second line, up to I believe four lines of therapy could be enrolled in this trial.

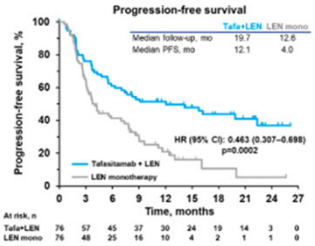
What they then did based upon their initial data set was look at a retrospective cohort. These were in the RE-MIND study.

RE-MIND study: A propensity score-based 1:1 matched comparison of tafasitamab + lenalidomide (L-MIND) versus lenalidomide monotherapy (real-world data) in transplant-ineligible patients with R/R diffuse large B-cell lymphoma





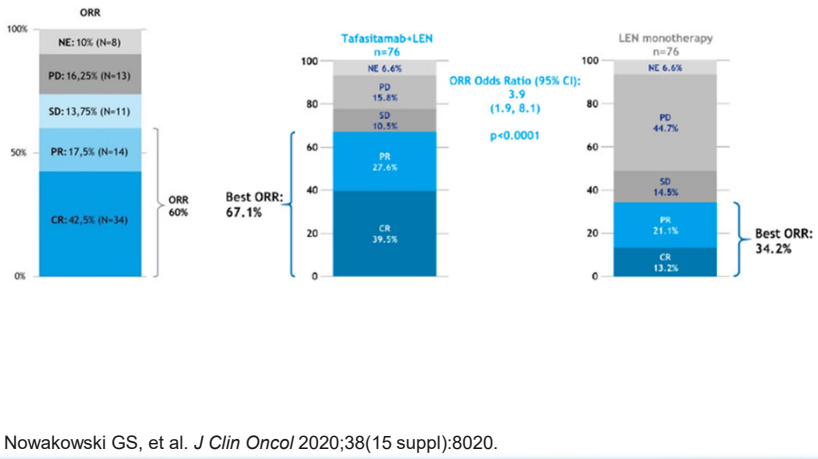


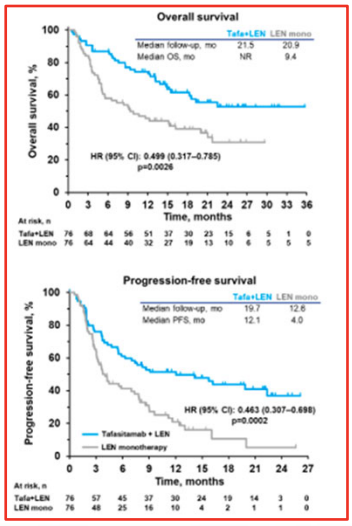


Nowakowski GS, et al. *J Clin Oncol* 2020;38(15 suppl):8020.

They looked at those patients who had received tafasitamab lenalidomide, and then they matched them with certain disease characteristics and compared them to retrospective outcomes with lenalidomide monotherapy.

RE-MIND study: A propensity score-based 1:1 matched comparison of tafasitamab + lenalidomide (L-MIND) versus lenalidomide monotherapy (real-world data) in transplant-ineligible patients with R/R diffuse large B-cell lymphoma





Nowakowski GS, et al. *J Clin Oncol* 2020;38(15 suppl):8020.

You can see here, just in a prospective/retrospective review of just the significant advantage not only in regards to best overall response rate, but also CR rate.

One of the unique characteristics of the L-MIND data has been the durability that's been seen if a patient can achieve a CR. This is, I believe now out to a three-year follow-up showing that there potentially may be a tail to this curve. However, it should be noted that patients do need to continue on the tafasitamab indefinitely, whereas the lenalidomide is stopped after 12 cycles or one year.

Re-MIND2: Tafasitamab Plus Lenalidomide Versus Pola-BR, R2, and CAR T: Comparing Outcomes from RE-MIND2, an Observational, Retrospective Cohort Study in R/R Diffuse Large B-Cell Lymphoma

ORR and CR Rate

ORR and CR rate for tafasitamab + LEN vs systemic therapies pooled, BR, and R-GemOX

	MAS for systemic therapies pooled		MAS for BR		MAS for R-GemOx	
	Tafasitamab + LEN (n=76)	Systemic therapies pooled (n=76)	Tafasitamab + LEN (n=75)	BR (n=75)	Tafasitamab + LEN (n=74)	R-GemOx (n=74)
ORR, n (%) (95% CI)	51 (67.1) (55.4–77.5)	37 (48.7) (37.0–60.4)	50 (66.7) (54.8–77.1)	41 (54.7) (42.7–66.2)	51 (68.9) (57.1–79.2)	34 (45.9) (34.3–57.9)
Fisher's exact test p-value of ORR	0.032		0.181		0.007	
CR rate as best response, n (%) (95% CI)	29 (38.2) (27.2–50.0)	16 (21.1) (12.5–31.9)	29 (38.7) (27.6–50.6)	21 (28.0) (18.2–39.6)	29 (39.2) (28.0–51.2)	17 (23.0) (14.0–34.2)
Fisher's exact p-value of CR rate	0.032		0.225		0.050	

BR-bendamustine + rituximab; CI – confidence interval; CR – complete response; LEN – lenalidomide; MAS – matched analysis set; ORR – overall response rate; R-GemOX – rituximab + gemcitabine + oxaliplatin

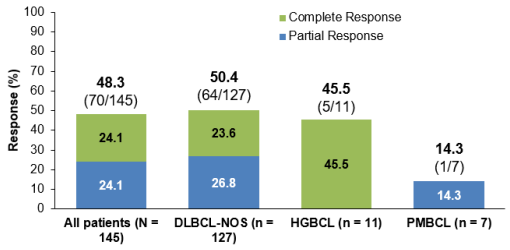
Nowakowski GS, et al. *J Clin Oncol* 2020;38(15 suppl):8020.

They went on in the RE-MIND II trial to look at further regimens compared against the prospective tafa-len regimen. You can see here the advantage in overall response rate as well as in CR rate compared to pooled systemic therapies, also in comparison to bendamustine rituximab. Then lastly, in regards to R-GemOx which is I guess a favorite relapsed/refractory regimen that some may give, especially if a transplant may be patient population, or those who are felt not to be transplant eligible.

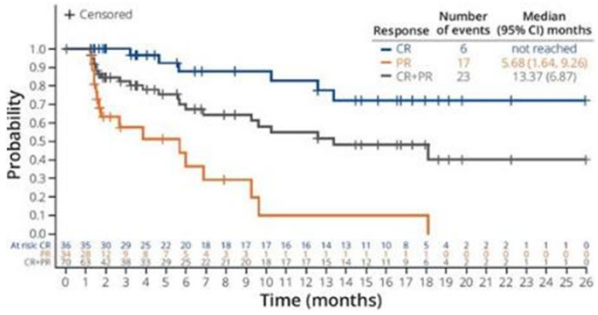
Really, I think tafasitamab lenalidomide has really taken off the table, lenalidomide rituximab in the relapsed/refractory large cell lymphoma space. I think that there is data in a retrospective fashion that is interesting support in regards to utilization of tafasitamab lenalidomide potentially over chemoimmunotherapy in patients who have previously been refractory to chemoimmunotherapy and diffuse large B-cell lymphoma.

LOTIS-2: Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma, a multicentre, open-label, single-arm, phase 2 trial

Response Rate



Median DOR: 10.25 months (95% CI: 5.98–NR)



Caimi PF, et al. *Lancet Oncol*. 2021;22(6):790-800.

The last drug that I'll talk about is loncastuximab tesirine, or Lonca-T which is an antibody-drug conjugate against CD79B. It carries a novel PDB warhead. This is different than drugs like brentuximab vedotin. This is a pyrrolobenzodiazepines, so it's a different mechanism of action. This drug is given uniquely at a higher dose for the first two cycles, and then the dose is halved using certain supportive measures to reduce the risk of pleural effusions or edema that had been seen with different dosing and different schedules.

You can see here in the study, the overall response rate was 48.3% in all patients with a CR rate of 24.1 months. Again, what is interesting here is that for those patients that do respond, there may be the potential for durability and at least at this data cut in those patients who are in CR, the median had not yet been reached.

LOTIS-2: Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma, a multicentre, open-label, single-arm, phase 2 trial

Side Effect Profile

Preferred Term, n (%)	Patients (N = 145)
Patients with any TEAE	**143 (98.6)**
GGT increased	59 (40.7)
Neutropenia	57 (39.3)
Thrombocytopenia	48 (33.1)
Fatigue	40 (27.6)
Anemia	38 (26.2)
Nausea	34 (23.4)
Cough	32 (22.1)
Alkaline phosphatase increased	29 (20.0)
Peripheral edema	29 (20.0)

Caimi PF, et al. *Lancet Oncol*. 2021;22(6):790-800.

Over the side effect profile of lonca-T, one of those things that we don't really know what to do with is increased GGT. Whether or not this is a laboratory abnormality, there was not a significant number of liver issues reported with this drug. There can be some hematologic side effects, but mainly the one that I call out and use the pre- and post-dosing of dexamethasone is peripheral edema or pleural effusion. This is something to know about this drug and to be aware of.

Conclusion

- CAR-T is now an option in primary refractory and early 1st relapse DLBCL
- Autologous transplant remains an option for late relapsed (>1 post completion of induction therapy) in DLBCL
- Multiple agents for relapsed/refractory DLBCL are now available with minimal data on sequencing before or after CAR-T, especially in those that target CD19

With that, I'll go into my concluding statement. I think CAR T-cell is now an option in primary refractory or early relapsed diffuse large B-cell lymphoma.

Autologous stem cell transplant remains an option for late relapses. Those who relapse greater than one year post-induction therapy.

Multiple agents for relapsed/refractory diffuse large B-cell lymphoma are now available, but there's minimal data on the sequencing before or after CAR T-cell, especially those that target CD19. With that, I open it up for some discussion.

Dr. James Armitage: Really good job, Matt. I enjoyed that tremendously. I do have a number of questions, some more or less exactly related to what you said, but are things that will have to be taken into account by the people listening to your presentation when they try to use the data.

First one, we know that diffuse large B-cell lymphoma is not a uniform disease and there are some famous subsets, like double hits and then there's a new molecular classification. Do any of those subsets impact your decision-making when you're treating somebody with relapsed/refractory disease?

Dr. Matthew Lunning: I think it depends upon what I'm doing. I think one of the unique things that I try to show in the forest plot in the ZUMA-7 data is that really cellular therapy or CAR T-cell therapy directed at CD19, has been agnostic to certain molecular features. Whether or not you're going in through gene expression profiling, or if you're using IHC to define subtypes, or even your double hits or triple hits. It seems like CAR T-cells can take care of the worst of the worst with regards to primary refractory disease, or double refractory disease, and it can take care of double hits,
just as well.

Dr. James Armitage: There's a famous saying in medicine that I remember from medical school, that you shouldn't ever be the first or last to take up a new treatment. Are there any of the things you discussed that would be, you shouldn't do it yet, because we don't have enough data, you shouldn't be the first? Or the opposite end, if you're not doing them, you're not practicing good medicine. Any of those you'd put into one of the two extreme categories?

Dr. Matthew Lunning: I think I have caution about giving a CD19 monoclonal antibody or CD19 antibody-drug conjugate, especially if I'm going to apherese a person, for CAR T-cells in the next 30 to 60 days. I think there is data to support with tafasitamab, while it is in vivo data that you do see down-regulation of the CD19 antigen on the cell surface. If you're going to try to go in and use a pre-apheresis bridging or bridging strategy with one of those agents, if the patient can wait 100 days, at least the data supports that there is CD19 recovery, potentially after exposure to those agents.

I don't really know that there's a significant amount of data of one of those agents with apheresis and then reinfusion of CAR T-cells to know truly what to do in that situation. That being said, you can't do a CAR T-cell on a person that's not alive. If that therapy is felt to be necessary to keep the individual alive, to get them to have the potential to get a CAR T-cell, I guess I can't fault that from that manner. That is why I currently still use polatuzumab-based either pre-apheresis or post-apheresis bridging if I need to. I do sometimes in significant bulky disease potential use bendamustine hopefully after apheresis if I need to.

Dr. James Armitage: Matt, do you think there is a patient that you could tell us that shouldn't have CAR T-cells therapy? There's a patient that's referred to you a subset of patients who part of their characteristics that just shouldn't get CAR T-cells therapy? Or is there no one?

Dr. Matthew Lunning: Personally, when I see people say, "I've sent your referral for CAR T-cells therapy," I think it's a much broader consultation that I'm seeing then for a relapsed/refractory diffuse large B-cell lymphoma. I think CAR T-cells are one of the options. To say, who shouldn't get a CAR T-cell, I think you probably shouldn't give a CAR T-cell to a person who's refractory to another CD19 CAR T-cell. That's certainly one population that I can easily call out. I do think that there needs to be clinical trials, though, with patients being eligible to receive a different cellular therapy, potentially with a different mechanism, either a different construct or a second antigen that then could take out 19 and 20 or 19 and 22.

If you think about organ function and performance status, performance status may be a situation where you may exclude them from CAR T-cell. Remember, performance status is often very subjective. I think that if the performance status is poor, and it's because of disease characteristics, then I may have a risk-benefit discussion with the patient about proceeding or not. If the performance status is due to some other comorbidity not related to the lymphoma and I'm very concerned that even a grade one CRS, or grade one ICANS would be significantly detrimental to their quality of life or potentially be lethal, then I would advise against CAR T-cell.

I think we have to see the patients in order to make that determination.

Dr. James Armitage: Does radiotherapy still have a place in your treatment plans for patients like these?

Dr. Matthew Lunning: Yes, I think that that's an area where there's a dearth of data. I think there was some initial concerns about what radiation does to the circulating CAR T-cells in the post-CAR T-cell environment. Where CAR T-cells don't always work very well is in the area of bulky or large lesions. I use the analogy of CAR T-cells like peeling an onion. You've got to get all the way to the core of the onion in order to eradicate the disease. I think the intent here is curative for each CAR T-cell that's being done.

In that regard, if I see a lesion that becomes PET negative, but the size started off in "a bulky range" and then reduced by 50% or more, I may have the discussion about post-CAR T-cell radiation with that patient because I am concerned that that's the area where the CAR T-cells are struggling to get to the core.

Dr. James Armitage: As you look to the future, do you think that the bispecific antibodies are a threat to CAR T-cell therapy? That is, could they replace it?

Dr. Matthew Lunning: I'm not sure that they will replace it. When I mentioned the allies versus adversary conversation or bullet point, I think that's the class that I'm most concerned about potentially being adversarial rather than an alliance with CAR T-cell. It isn't such that the drugs like epcoritamab or glofitamab that are likely to find their way into relapsed/refractory diffuse large B-cell lymphoma, inhibit the same antigen like tafasitamab or lonca-T does. What we don't know is what is the fitness or the fidelity of the T-cell in a patient who progresses through bispecifics.

Then you try to manufacture and take out those same T-cells that have just been fighting a war that's been brought to them the bispecifics and how well do those CAR T-cells manufacture and how well do they work? I think there is emerging data with bispecific after CAR T-cell showing that it can work and there are CRs and so I see it right now positioned after CAR T-cell. I think if we're going to move into the bispecific before CAR T-cell world, it best be done in the clinical trial, where you can then look at what the manufacturing output is, rather than doing it by a real-world experience.

I fear that we're only going to learn by real-world experience once we see these drugs enter the relapsed/refractory large cell space.

Dr. James Armitage: One last question, a very practical one for the people listening to this presentation. We've known for some time, we think we have known, that if you couldn't have an autologous transplant, or rarely an ALLO transplant and you truly had progressive or refractory diffuse large B-cell lymphoma, your only hope is direct divine intervention to be cured. That was your chance. Now, you've just showed us that there are these other therapies, CAR T-cell therapy, and perhaps some of the others can literally snatch people from the jaws of death. You can cure people who are in a terrible position.

Has salvage therapy become so effective that you shouldn't be referring people to palliative care, you should always give them a chance to try to be cured by things like CAR T-cell therapy?

Dr. Matthew Lunning: I think it truly is what is driving them towards palliative care. If it is the disease, in my opinion, unless they have end-stage COPD or end-stage heart failure, or end-stage liver disease, at least allowing them to have that discussion about what do they feel from a risk-benefit standpoint. Is it worth that to them? Is it worth that to the commitment to the family? CAR T-cell it is a logistical process. It is being away from your home, your farm, your community for a period of time. It's different than other therapies like ALLO transplant.

ALLO transplant, often that carrot is dangled in front of people but you have to have good disease control in order to have likely good outcomes. Here with CAR T-cell, yes the amount of disease may matter but there are still patients that I know that are alive because of cellular therapy that wouldn't otherwise be just based upon the odds.

Dr. James Armitage: Matt, thank you very much. Thank you very much for that wonderful presentation. I hope all of you listening have enjoyed it and will benefit by this and start applying some of these things to your practice that you might not have thought of before.