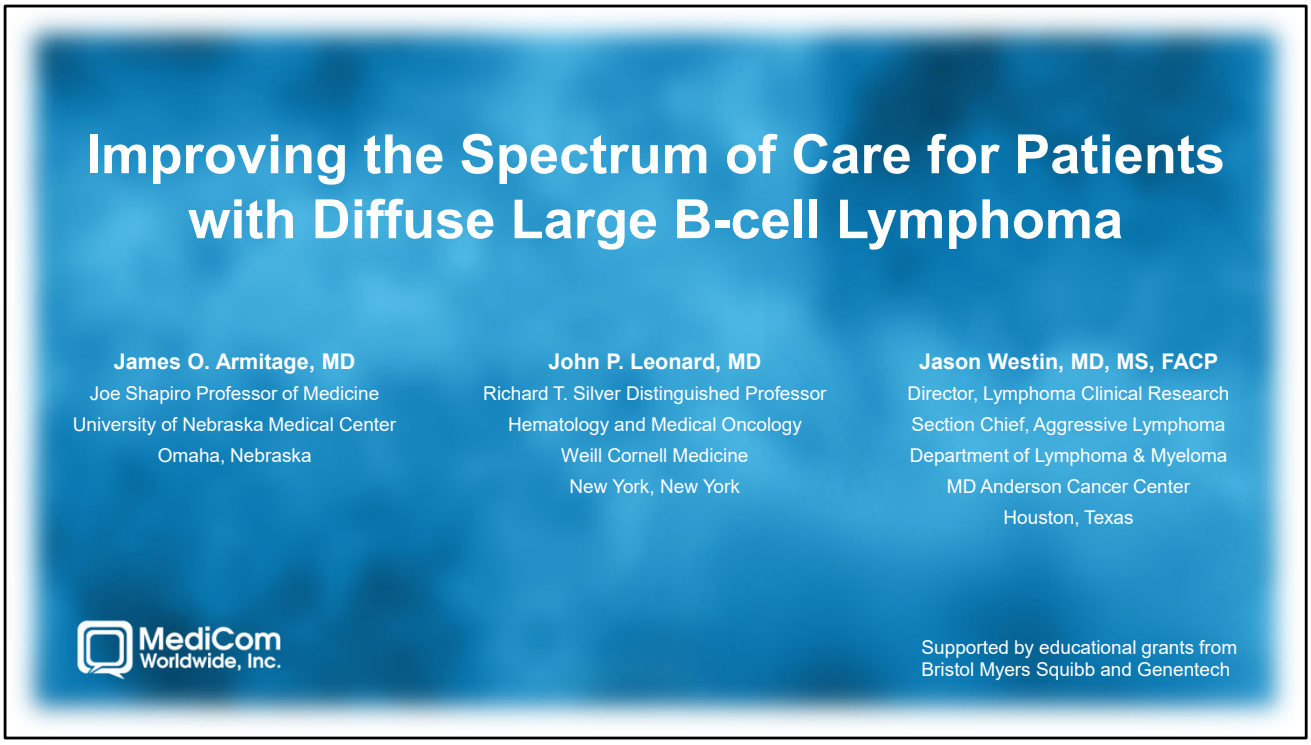
Improving the Spectrum of Care for Patients with Diffuse Large B-cell Lymphoma



Dr. Jim Armitage: Welcome to today's program. My name is Jim Armitage. I'm a Professor of Medicine at the University of Nebraska Medical Center.

Faculty Disclosures

- **Dr. James Armitage** has relevant financial relationships related to advisory activities from Cardiff Oncology, Inc.
- **Dr. John Leonard** has relevant financial relationships related to consulting from AbbVie Inc., Astellas Pharma US, Inc., BeiGene, Calithera BioSciences, Inc., Celgene Corporation – A Bristol-Myers Squibb Company, Constellation Pharmaceuticals, Eisai Co., Ltd., Eli Lilly and Company, Epizyme, Inc., Genentech - A Member of the Roche Group, Genmab A/S, Grail, Inc., Incyte Corporation, Janssen Pharmaceuticals, Inc., Karyopharm Therapeutics, Merck & Co., Inc., Mustang Bio, Pfizer Inc., Second Genome, and Sutro Biopharma.
- **Dr. Jason Westin** has relevant financial relationships related to advisory activities and has received research grant(s) from ADC Therapeutics SA, AstraZeneca, Bristol-Myers Squibb Company, Genentech, Inc., Iksuda Therapeutics, Kite Pharma/Gilead, MorphoSys, Novartis AG, and Merck & Co., Inc., in addition to advisory activities from Monte Rosa Therapeutics, and Umoja Biopharma.

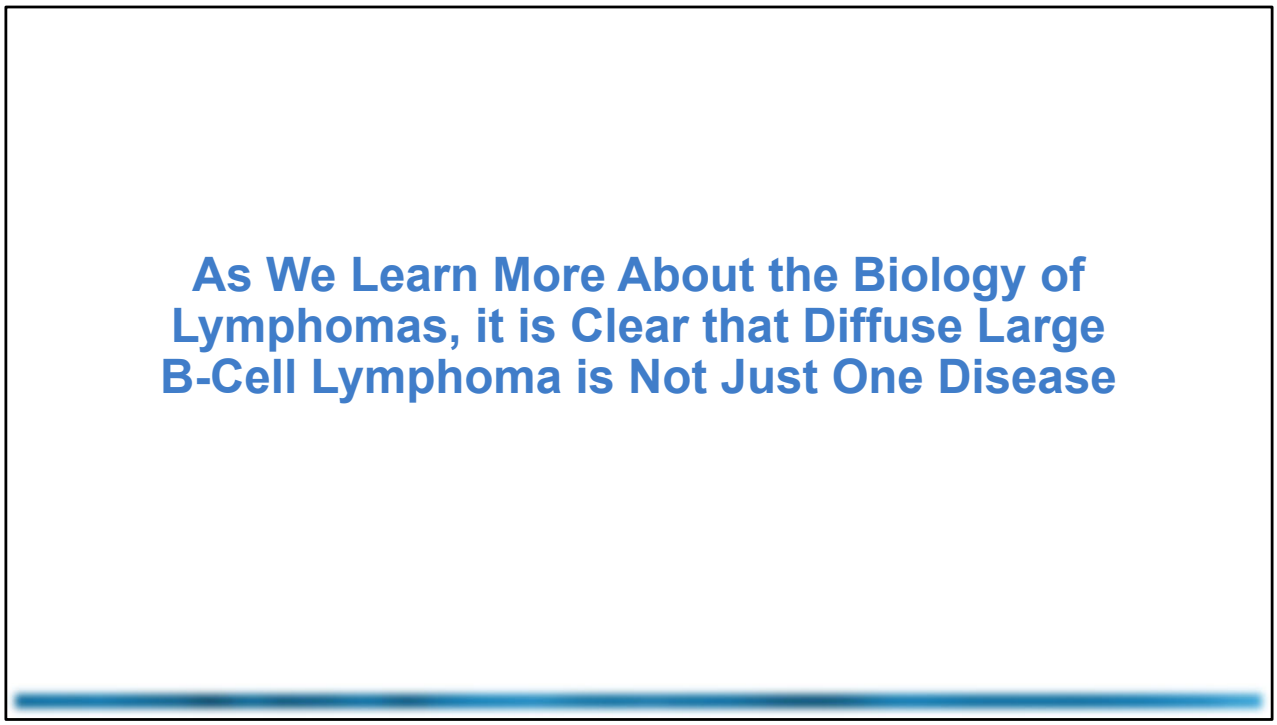
Today I'm joined by Dr. John Leonard, who is a Professor of Hematology and Medical Oncology at Weill Cornell Medicine in New York, and Dr. Jason Westin, who is the Director of the Lymphoma Clinical Research Program at MD Anderson Cancer Center.

Today's presentation will address ways of improving the spectrum of care for patients with diffuse large B-cell lymphoma.

Learning Objectives

- Recall evidence-based guideline recommendations for frontline and relapsed/refractory DLBCL treatment
- Discuss emerging and newly approved therapies for frontline and relapsed/refractory DLBCL treatment
- Identify barriers to optimal treatment of DLBCL that can influence both treatment quality and DLBCL outcomes, including disparities in care, geographic factors, and patient factors
- Summarize key data on DLBCL presented at ASH 2021 and other national conferences and relevant points for practice

In this presentation, I'm going to discuss a few things about classification and treatment advances. I'll make two points that I hope will set the stage as we go forward. Dr. Leonard will then discuss the most up-to-date data reflecting what's currently working, what's currently used, and generally not considered investigational in the first-line therapy of diffuse large B-cell lymphoma, and then Dr. Westin is going to discuss new targets and novel therapies that we hope will be tomorrow's first-line therapy for this disease.



First of all, I'm going to make two quick points. Number one, it has become increasingly clear over the last couple of decades as we've learned more and more about the biology of the diseases that diffuse large lymphoma is not just one disease, in fact, it's not just 10 diseases, it's a mixture of illnesses that we have always treated the same.

Subtypes of Diffuse Large B-Cell Lymphoma in the Updated WHO Classification

Morphology	IHC	Other
DLBCL-NOS	ALK positive	EBV positive
T-Cell/histocyte rich		EBV positive mucocutaneous ulcer
Plasmablastic		With chronic inflammation
High-grade NOS*	**Primary Site**	Lymphomatoid granulomatosis
Genetics	Mediastinal	HHV8 positive
GCB	CNS	Burkitt like 11q abnormality
ABC	Effusion	Fibrin associated
High grade with MYC and BCL2/BCL6*	Intravascular	Fluid overload associated
With IRF4 rearrangement	Skin	Primary in immuno-privileged sites

*No longer DLBCL

This is a current WHO classification, and you can see that the divisions are based on morphology, genetic abnormalities, immunohistochemistry, where the tumor originates, and a variety of other characteristics. These are a lot of different things that we've treated like they were one thing.

A New Molecular Classification for DLBCL

Name	Cell of origin	Some associated genes	Prognosis	Relation to other lymphomas
EZB	GCB	BCL-2, EZH2	Good (except DH)	Follicular
ST2	GCB	TET2, SGK1	Good	MZL
BN2	GCB/ABC	BCL-6, Notch 2	Intermediate	NLPHL, TCRLBCL
A53	ABC	TP53, aneuploidy	Intermediate/poor	?
N1	ABC	Notch 1, IRF2B2	?	CLL
MCD	ABC	MYD88, CD79B	Intermediate/poor	Primary CNS, testes, LPL

Now it gets even more complicated because there's been an effort recently to try to make a molecular classification, which takes patients that would be in the regular diffuse large B-cell lymphoma category, and looking at gene expression patterns, try to lump them together.

As you can see, this leaves us with groups that look like they're related to follicular lymphoma or marginal zone lymphoma, or nodular lymphocyte-predominant Hodgkin lymphoma, or T-cell rich B-cell lymphoma, those with P53 abnormalities, which in most cancers are bad, those that have genetic abnormalities more like CLL, and those that have genetic abnormalities like a variety of things, but including lymphoplasmacytic lymphoma. This has not yet reached clinical care, although there are some studies that are ongoing about it and there's some hints that it might be useful.

Now what I am going to do now is hand the mic over to Dr. Leonard, and John is going to talk about frontline therapy for diffuse large B-cell lymphoma.

Dr. John Leonard: Well, thank you, Jim. I want to also thank the organizers for the chance to be part of this very interesting program. As you heard, I'm going to talk a bit about the initial therapy of large cell lymphoma, which really has not changed for a long time, and then now really is evolving. I think this program is quite timely and important in what we are going to discuss in the next few minutes.

R-CHOP x 6 Has Been the Standard Initial Therapy for Most Patients with DLBCL (Except Maybe...)

- Double hit subtype (MYC, BCL2, BCL6 translocations)
- Primary mediastinal
- HIV associated
- Testicular
- Limited stage (? 4 cycles)
- CNS
- Elderly (mini-R-CHOP)

As this audience likely knows, R-CHOP for six cycles has been the standard initial therapy for most patients with large-cell lymphoma.

There have been a variety of different potential, at least potential, and I say it that way because none of these takes are definitive. Some would argue that in double-hit lymphomas, we should treat patients more aggressively. In primary mediastinal lymphomas, we should potentially use an infusion regimen like dose-adjusted R-EPOCH; that's also been considered for HIV-associated lymphomas. There are data with testicular lymphoma with concerns for CNS prophylaxis in other settings as well that can be considered as well as limiting the amount of treatment, the number of cycles of treatment in limited stage patients, or in older or frailer patients where we often use the mini R-CHOP.

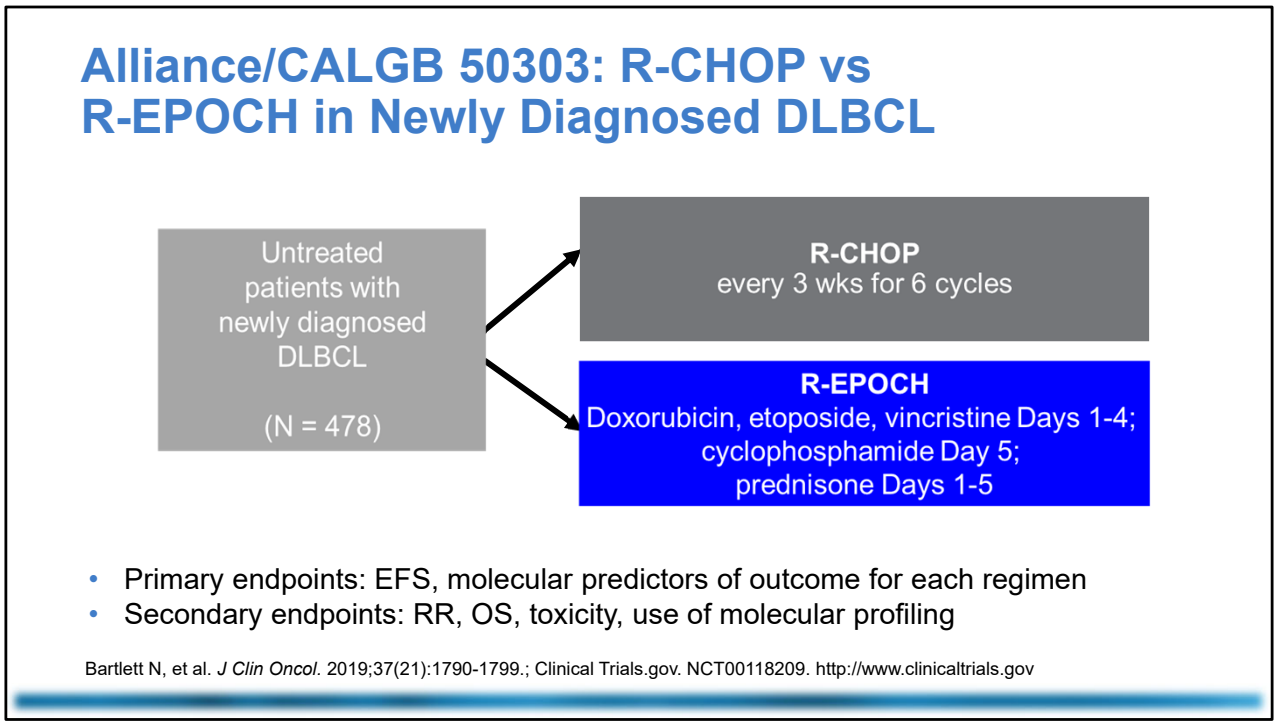
While R-CHOP has been the backbone for most patients, clinically, many of us have used, for certain scenarios, as summarized on the slide variations on this regimen.

What About New Approaches in DLBCL?

- Strategies independent of cell of origin
- Strategies targeting specific cell of origin subtype
- Return to strategies independent of cell of origin

There have been a number of different strategies beyond those tailoring approaches. There have been a number of strategies to try to improve upon therapy, improve upon R-CHOP for six cycles in large cell lymphoma. I would say that these were initially independent of cell of origin. Cell of origin being the sub-setting of large cell lymphoma that about 10 years or so ago, became quite of interest and potentially important therapeutically, although that hasn't quite panned out as well.

We were independent of cell of origin, moved toward being specific for the cell of origin, and now we're back to being agnostic to cell of origin. I'll walk you through this in the next couple of minutes.



One agnostic approach has been to say, "Well, let's give more chemotherapy. Let's use the dose-adjusted R-EPOCH regimen, which adds etoposide, adjust doses over the course of therapy based on tolerability, and is given infusionally, which is obviously more complicated when you have to have central access and treat the patient over 96 hours continually.

Many of you are familiar with this regimen in the Alliance/CALGB, we did a randomized trial comparing dose-adjusted R-EPOCH to the standard R-CHOP approach.

Alliance 50303: Design

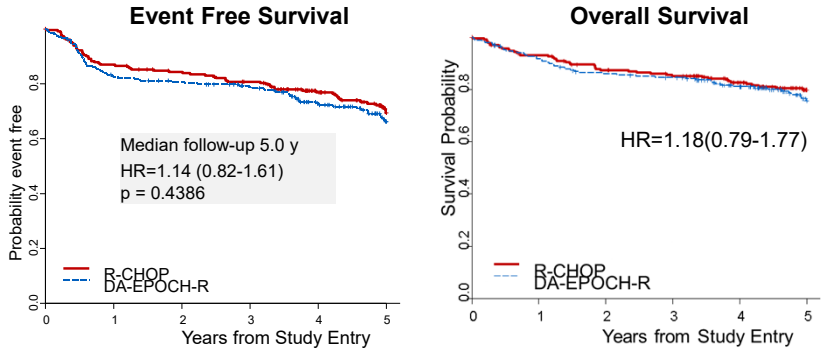
- N = 524; enrolled 2005 – 2013; Data cutoff November 2016
  - Analysis planned after 242 events, but due to low event rate DSMB released data July 2016 with 167 events

Characteristic	R-CHOP (%)	DA-EPOCH R (%)	*P*-value
Median Age (range)	58 (18-86)	57 (19-84)	0.677
ECOG 0-1 vs 2	88 vs 12	87 vs 13	0.518
Stage 3/4	73	77	0.641
IPI 0-2	65	61	0.405
GRADE ≥3 TOXICITY			
Treatment related deaths	2	2	0.975
Platelets	11	65	<0.001
Febrile neutropenia	17	35	<0.001
Infection	**11**	**14**	**0.169**
Neuropathy – sensory/motor	2/1	14/8	<0.001

In fact, what we found was that not surprisingly, dose-adjusted R-EPOCH was more toxic by design. It's a dose escalation approach, so there were more infections, more cytopenias evident.

Alliance 50303: Outcomes

	R-CHOP	DA-EPOCH-R	*P*-value
ORR	89%	89%	0.983
CR/CRu	62%	61%	
PR	27%	27%	



Unfortunately, there was no benefit therapeutically, no difference in event-free survival, no difference in overall survival.

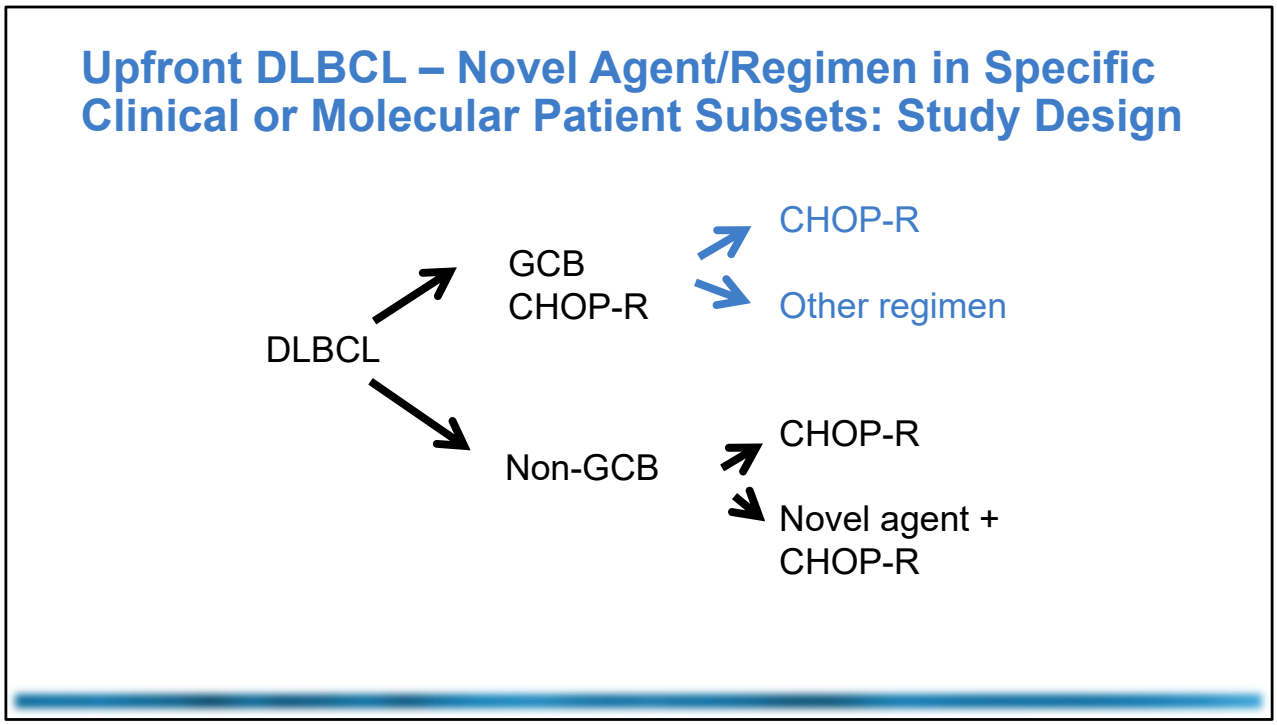
Now, remembering that the vast majority of patients here had run-of-the-mill or standard diffuse large B-cell lymphoma, so we can't quite draw conclusions about some of the subtypes like double-hit or primary mediastinal based on this study. Basically, R-CHOP remained the standard after this approach, and the dose escalation of chemotherapy did not prove to be beneficial and certainly not worth the extra toxicity based on this trial.

Oncogenic Mechanisms and Potential Therapeutic Targets in GCB and ABC DLBCLs

DLBCL subtype	Cell of origin	Oncogenic mechanisms	Potential targets
GCB	Germinal centre B-cell	*BCL2* translocation* *EZH2* mutations‡ *PTEN* deletions§ Loss of PTEN expression	BCL6 EZH2 PI3K/Akt
ABC	Post-germinal centre B-cell	NF-κB activation‖ *CARD11* mutations *MYD88* mutations *CD79B* mutations *A20* deletions	BCR CBM complex IRAK-4 JAK-STAT

*GCB DLBCL frequently has BCL2 translocations and most result in activation of BCL-6, the master transcriptional regulator of the germinal centre. ‡Mutations in EZH2 (21% of GCB DLBCL cases) are specific for this subtype. §Loss of PTEN expression (55% of GCB DLBCL cases) results in activation of the PI3K/Akt pathway for which multiple inhibitors are currently in development. ‖ABC DLBCL is defined by constitutive NF-κB pathway activation and BCR signalling pathways are oncogenically activated in this subtype: mutations in MYD88, CARD11 and CD79B are found in ABC DLBCL along with deletions and mutations of TNFAIP3.
Roschewski M, et al. *Nat. Rev. Clin.* 2013;11:12-23.

That brings us to the cell of origin-based approaches. Really going back now over 10 years, we had several groups largely led by Louis Staudt but others as well subdividing diffuse large B-cell lymphoma into two major, now these are not the only subtypes, but two major subtypes based on cell of origin. The germinal center and the activated B-cell subtypes. As you can see on this slide, there are a number of different oncogenic mechanisms associated with these two different subtypes. These are also connected with a number of different potential targets. You could potentially say, "Well, let's give a drug that's going to target one of these pathways and make the treatment work better."



That has led to a number of studies designed to take the non-germinal center, which is a rough surrogate for the activated B-cell subtype.

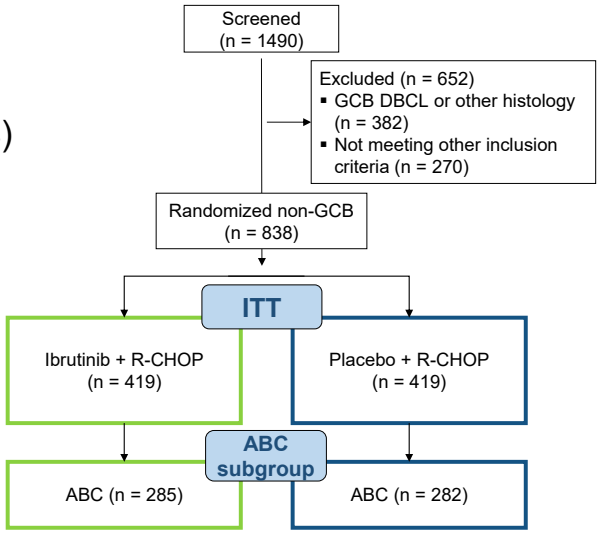
That's the subtype that does less well and said, "Well, why don't we add in a new drug?" There are a number of potential candidates, as on the last slide, that could be added to R-CHOP and try to make R-CHOP work better in that subset where the targeted therapy might make sense biologically. Many of us were very excited about this approach, myself included. There were a number of different efforts to try to subset large cell lymphoma patients into these at least two groups and to target the addition of a new drug to R-CHOP, specifically in the subgroup where it is most likely to work.

In the case of the ABC or non-germinal center subtype, the type that needs the most help, where the prognosis is the poorest.

PHOENIX: R-CHOP +/- Ibrutinib

Key eligibility criteria

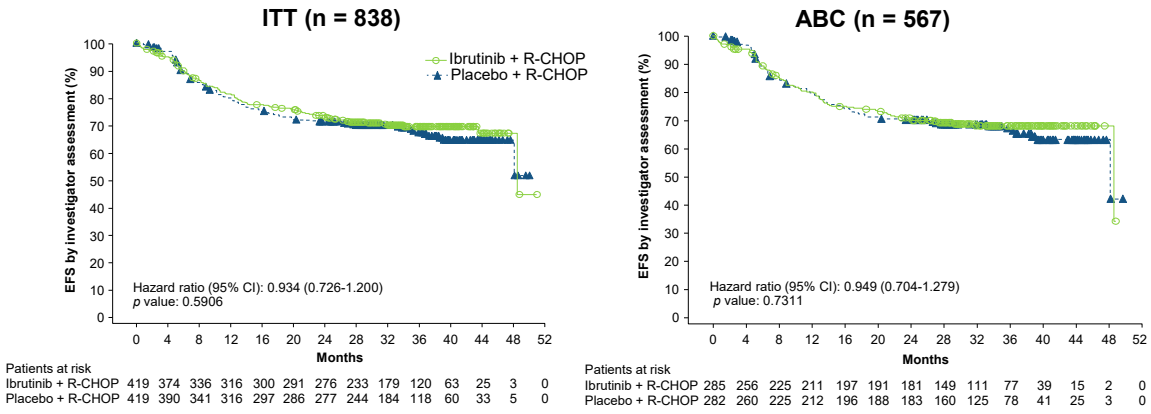
- Untreated non-GCB DLBCL (Hans)
- Stage II to IV disease
- R-IPI ≥1
- ECOG performance status ≤2



Younes A, et al. *J Clin Oncol.* 2019;37(15):1285-1295.

This is one, there are several drugs and several studies that looked at this. This was the PHOENIX study that used ibrutinib. Ibrutinib has a rationale in the non-germinal center or ABC subtype of large cell lymphoma for a variety of different reasons. This was a randomized trial that essentially took patients with non-germinal center and also looked specifically at the ABC-defined group as well, and randomized them to either placebo-R-CHOP on the right or ibrutinib-R-CHOP on the left.

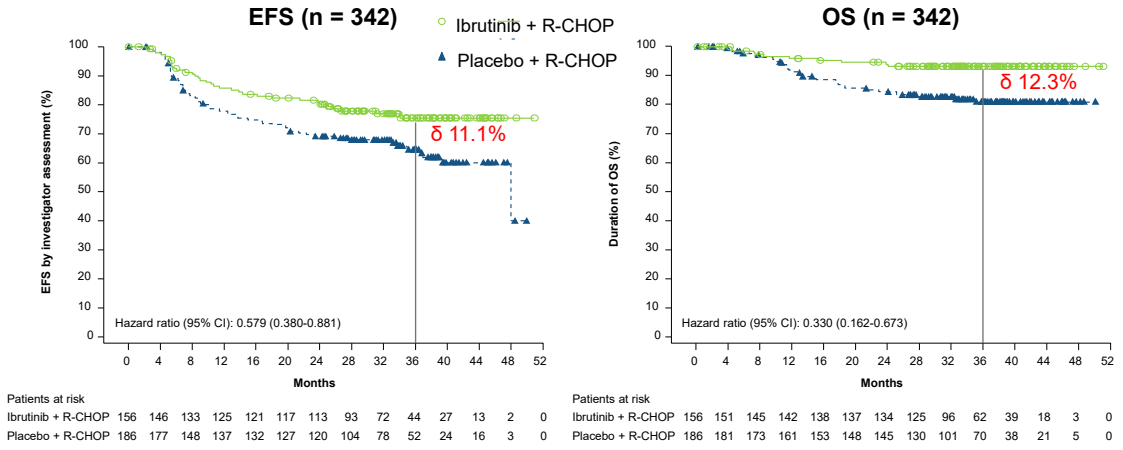
PHOENIX: Primary Endpoint - EFS in ITT and ABC Population



Younes A, et al. *J Clin Oncol.* 2019;37(15):1285-1295.

The net of this study was quite disappointing. At the end of the day, there was no difference in response rates, no real difference in CR rates, and no difference in event-free survival, which was the primary endpoint. Whether you looked at the entire non-germinal center subtype or the specifically ABC subtype, as you can see, the outcomes were the same. This was and is disappointing.

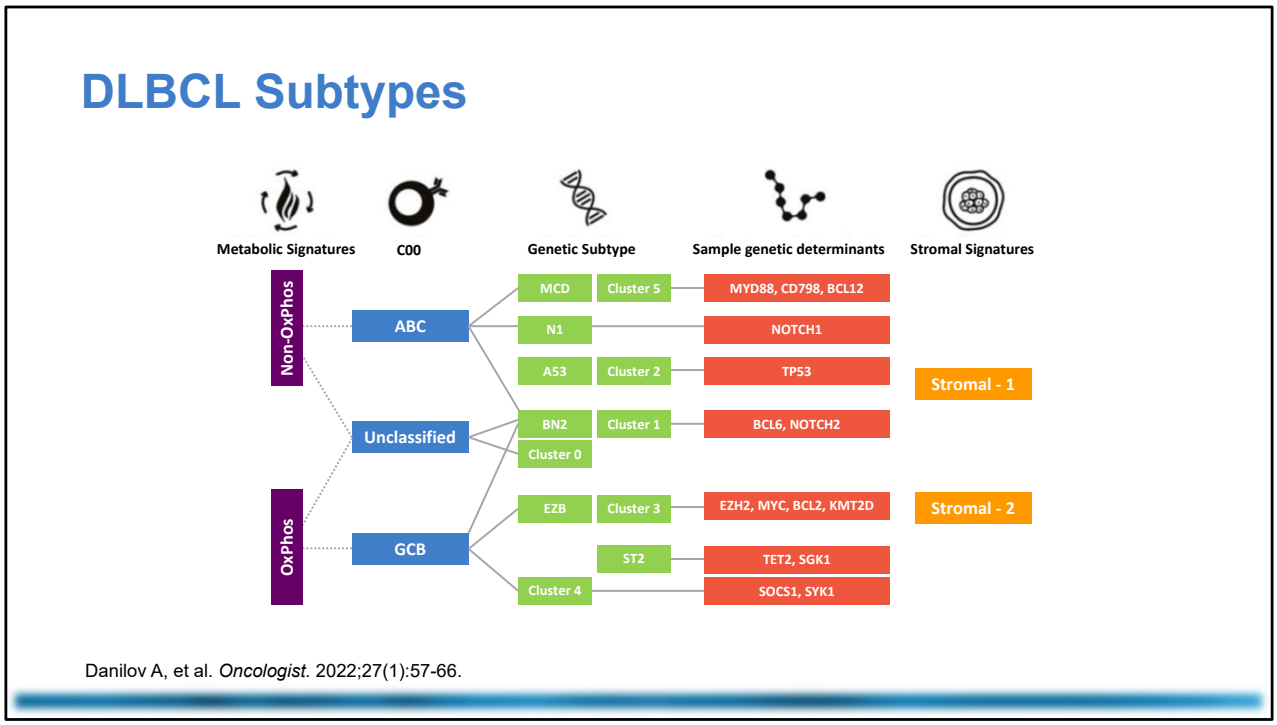
PHOENIX: EFS and OS in Patients <60 Years



Younes A, et al. *J Clin Oncol.* 2019;37(15):1285-1295.

However, an interesting observation was that in the younger patients, there was a difference, about a 10-12% difference between the two groups in younger patients.

This was attributed to the fact that there was more toxicity to the addition of ibrutinib, that that toxicity was more pronounced and more relevant in the older patient population where the net effect of the toxicity overwhelmed any effect on efficacy. In fact, in the younger patients who were better able to tolerate the therapy outcomes were improved by the addition of ibrutinib. This is a subset, it's not a definitive answer to this question, but it does at least lead one to wonder if this approach does have value just in the right patient population who can tolerate it. In fact, this approach is being studied in different contexts with other BTK inhibitors at the present time.



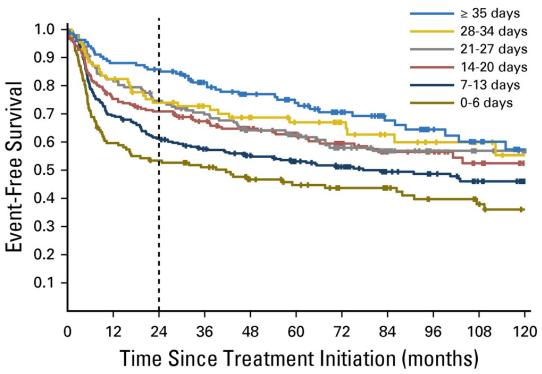
Danilov A, et al. *Oncologist*. 2022;27(1):57-66.

Now, another reason why this approach perhaps hasn't worked is that diffuse large B-cell lymphoma is not as cleanly subdivided into ABC and GCB subtypes. In fact, there are several groups, again led in part by Louis Staudt and colleagues, that identified a variety of different approaches, or I should say further sub-setting the diffuse large B-cell lymphoma, and you see them summarized in the slide, I don't have time to get into the details of this. The net is that the sub-setting of large cell lymphoma into even smaller and smaller pieces of the pie leads one to wonder, are we able to target these even smaller subsets effectively?

The reason why our manipulations are adding of a drug like ibrutinib looking at a broad class is that really that is not as targeted as we need to be. We really need to zero in on the subset specifically that can benefit from ibrutinib, and in fact, as an example, that these subsets are much narrower than we thought. That's another reason why this approach potentially has failed at least thus far.

Diagnosis to Treatment Interval (DTI) is Important Clinical Factor in DLBCL; Implications for Trials

- Shorter DTI was strongly associated with adverse clinical factors
  - LDH, IPI, PS
- These patients had worse outcomes, and are almost certainly underrepresented in clinical trials



Maurer M, et al. *J Clin Oncol.* 2018;36(16):1603-1610.

Finally, another reason why these strategies of targeting subsets of large cell lymphoma based on cell of origin or something else have failed is that the time to subset the patient, to profile the patient by one or another mechanism to identify what subset they fit in, and therefore what trial or what novel agent is appropriate for their subset takes time. What we've learned is that when you implement steps that take time as part of a clinical trial, that results in a more favorable patient population.

It's intuitive. The person that shows up in your emergency room tonight can't wait around for a week to go on a clinical trial. Whereas the person who has a relatively good diffuse large B-cell lymphoma who's not sick, can wait around or can go through the steps to go on a trial. In fact, the diagnosis to treatment interval correlates with outcomes. These are data from Matt Maurer and the Mayo Group suggesting that basically trials are enriched for patients with a longer diagnosis-to-treatment interval because the process of going on a trial skews you toward more patients who can go through those steps.

That raises the idea that perhaps many of these approaches that require a selection criteria to go on the trial such as an immunohistochemistry or other molecular sub-setting is going to weed out the patients that can benefit the most from a novel approach because those patients may be too sick to go through the process of getting on the trial. These are all reasons why at least thus far, these targeted subsets of large cell lymphoma patients really have not seemed to benefit from these interventions. Again, it may be that the drug doesn't work, it may be that the patient population or the toxicity may not be appropriate. It may be that the disease is just more complicated than we thought and that our clinical trial strategies have to be able to adapt to the idea that we have to be able to get patients on studies quickly in order to benefit those who are the sickest.

What About New Approaches in DLBCL?

- Strategies targeting specific cell of origin subtype
- Bortezomib, ibrutinib, lenalidomide not successful to date
- Strategies independent of cell of origin (now “coming back”)
- Active in relapsed setting
  - CAR-T, tafasitamab/lenalidomide, selinexor, loncastuximab, bispecifics
- Polatuzumab now relevant in upfront setting

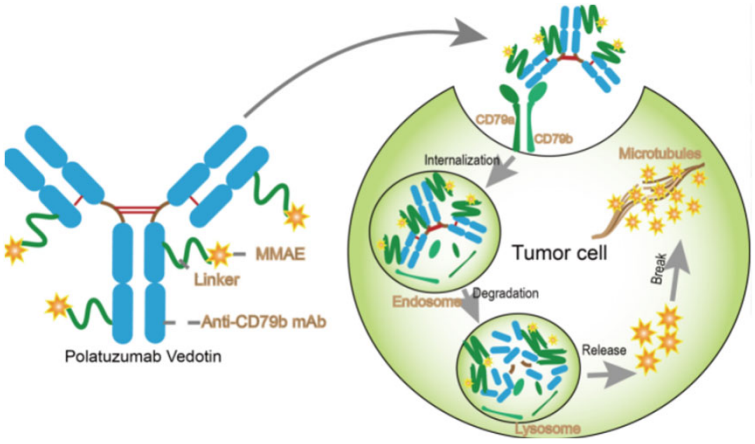
While that all has happened, other approaches, and again, just to summarize, I should say, all of these cell-of-origin approaches, whether it is bortezomib, ibrutinib, lenalidomide so far have not been successful. In the meantime, we have a number of new drugs that have been approved in relapsed large cell lymphoma.

For the most part, these appear to be agnostic to cell of origin. We really don't have good biomarkers to say, "Who is going to respond to CAR T-cells? Who is going to respond to tafasitamab, selinexor, loncastuximab, bispecifics?" These are all drugs that have activity and approvals in recurrent large-cell lymphoma. Bispecifics not yet approved, but some think they may be approved in the near future so that these do not seem, at least for right now, to rely on a molecular sub-setting to decide who needs them.

Again, maybe that will sort itself out over time, but right now, in the relapse setting, we are acting in an agnostic fashion as to when we apply these drugs specifically in regard to whether or not a patient has one cell of origin type of lymphoma or another.

Polatuzumab has come onto the scene.

Polatuzumab Vedotin (Anti-CD79b Antibody Drug Conjugate)



https://www.creativebiolabs.net/polatuzumab-vedotin-overview.htm

Polatuzumab is an anti-CD79B antibody-drug conjugate. You're familiar with ADCs now, they get internalized into the cell, drop off their payload, in this case anti-tubulin agent. That essentially has an anti-tumor effect, essentially delivering chemotherapy more specifically to the tumor cells.

Polatuzumab Vedotin Single-agent Activity

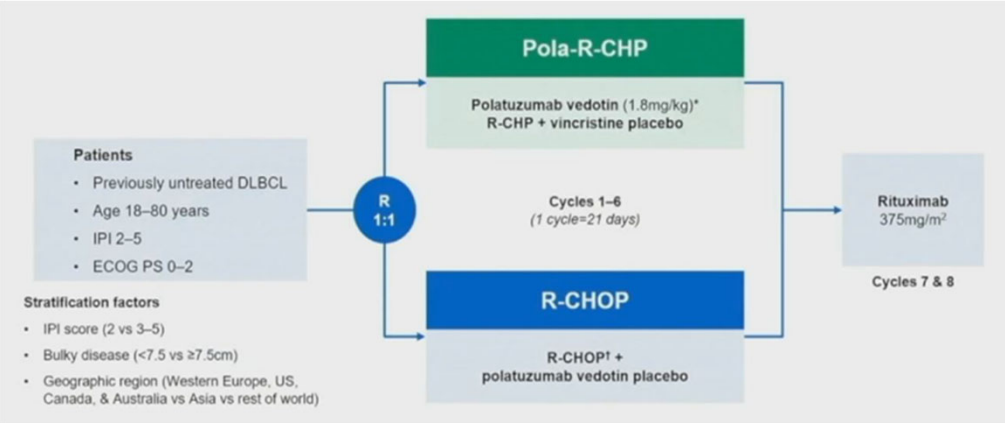
- Up to 2.4 mg/kg in phase I trial (alone and with rituximab)
- Grade 3/4 AE included neutropenia, anemia, peripheral neuropathy
- 14/25 patients with recurrent DLBCL had objective responses

Palanca-Wessels M, et al. *Lancet Oncol.* 2015;16(6):704-715.

This drug was evaluated in single-agent studies. The main toxicities include neuropathy and cytopenias, and in recurrent large-cell lymphoma, a reasonable percentage, in fact, the majority of patients had objective responses to polatuzumab as a single agent.

Improving the Spectrum of Care for Patients with Diffuse Large B-cell Lymphoma

R-CHOP vs Polatuzumab-R-CHP in DLBCL (IPI 2-5)



*IV on Day 1; †R-CHOP; IV rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and vincristine 1.4 mg/m² (max 2 mg) on Day 1, plus oral prednisone 100 mg once daily on Days 1-5.
IPI=International Prognostic Index; ECOG PS= Eastern Cooperative Oncology Group performance status; R=randomized
Tilly H, et al. *N Engl J Med.* 2022;386(4):351-363.

This led to its approval in combination with bendamustine-rituximab in the relapse setting. Then more relevant to this discussion led to these recent data that have randomized patients to R-CHOP versus polatuzumab R-CHP as initial therapy for diffuse large B-cell lymphoma in patients that have international prognostic index scores of two through five.

The idea here is that polatuzumab is swapped in to the R-CHOP regimen, swapped in for vincristine because again, both drugs cause neuropathy. The question is really what is the benefit of swapping in polatuzumab for vincristine in this particular setting?

R-CHOP vs Polatuzumab-R-CHP in DLBCL

Characteristic-	Pola-R-CHP (N=440)	R-CHOP (N=439)
Median age (range) — yr	65 (19–80)	66 (19–80)
Age category — no. (%)		
≤60 yr	140 (31.8)	131 (29.8)
>60 yr	300 (68.2)	308 (70.2)
Female sex — no. (%)	201 (45.7)	205 (46.7)
Geographic region — no. (%)		
Western Europe, United States, Canada, and Australia	302 (68.6)	301 (68.6)
Asia	81 (18.4)	79 (18.0)
Rest of world	57 (13.0)	59 (13.4)
Ann Arbor stage — no. (%)		
I or II	47 (10.7)	52 (11.8)
III or IV	393 (89.3)	387 (88.2)
No. of extranodal sites — no. (%)		
0 or 1	227 (51.6)	226 (51.5)
≥2	213 (48.4)	213 (48.5)
Bulky disease — no. (%)	193 (43.9)	192 (43.7)

Tilly H, et al. *N Engl J Med.* 2022;386(4):351-363.

Many of you have seen this data, this study was published in the *New England Journal of Medicine*. This was a group of patients with large cell lymphoma, median age in their mid-'60s, almost all advanced stage disease.

R-CHOP vs Polatuzumab-R-CHP in DLBCL

Characteristic	Pola-R-CHP (N=440)	R-CHOP (N=439)
ECOG performance status score — no. (%)		
0 or 1	374 (85.0)	363 (82.7)
2	66 (15.0)	75 (17.1)
Lactate dehydrogenase level — no. (%)		
Normal	146 (33.2)	154 (35.1)
Elevated	291 (66.1)	284 (64.7)
IPI score — no. (%)		
2	167 (38.0)	167 (38.0)
3 to 5	273 (62.0)	272 (62.0)
Median time from initial diagnosis to treatment initiation (IQR) — days	26 (16.0–37.5)	27 (19.0–41.0)
Cell of origin — no./total no. (%)		
Germinal-center B-cell–like subtype	184/330 (55.8)	168/338 (49.7)
Activated B-cell–like subtype	102/330 (30.9)	119/338 (35.2)
Unclassified	44/330 (13.3)	51/338 (15.1)
Double-expressor lymphoma — no./total no. (%)	139/362 (38.4)	151/366 (41.3)
Double-hit or triple-hit lymphoma — no./total no. (%)	26/331 (7.9)	19/334 (5.7)

Tilly H, et al. *N Engl J Med.* 2022;386(4):351-363.

Generally had good performance status. About two-thirds of them had an elevated LDH. About two-thirds of them also had IPI scores of three through five, from skewed to a higher-risk group of large-cell lymphoma patients. You can see the germinal center and ABC subtype patients both were included. Very few patients with double-hit and triple-hit lymphoma, so we can't draw big conclusions about that from this study.

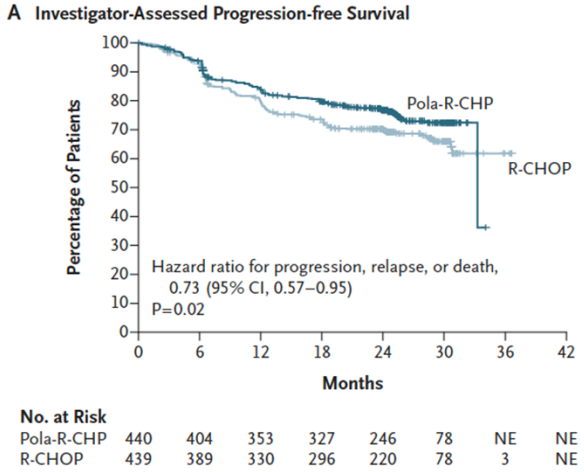
R-CHOP vs Polatuzumab-R-CHP in DLBCL - Toxicity

Adverse Event	Pola-R-CHP (N=435)		R-CHOP (N=438)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Peripheral neuropathy	230 (52.9)	7 (1.6)	236 (53.9)	5 (1.1)
Nausea	181 (41.6)	5 (1.1)	161 (36.8)	2 (0.5)
Neutropenia	134 (30.8)	123 (28.3)	143 (32.6)	135 (30.8)
Diarrhea	134 (30.8)	17 (3.9)	88 (20.1)	8 (1.8)
Anemia	125 (28.7)	52 (12.0)	114 (26.0)	37 (8.4)
Constipation	125 (28.7)	5 (1.1)	127 (29.0)	1 (0.2)
Fatigue	112 (25.7)	4 (0.9)	116 (26.5)	11 (2.5)
Alopecia	106 (24.4)	0	105 (24.0)	1 (0.2)
Decreased appetite	71 (16.3)	5 (1.1)	62 (14.2)	3 (0.7)
Pyrexia	68 (15.6)	6 (1.4)	55 (12.6)	0
Vomiting	65 (14.9)	5 (1.1)	63 (14.4)	3 (0.7)
Febrile neutropenia	62 (14.3)	60 (13.8)	35 (8.0)	35 (8.0)
Headache	56 (12.9)	1 (0.2)	57 (13.0)	4 (0.9)
Cough	56 (12.9)	0	53 (12.1)	0
Decreased weight	55 (12.6)	4 (0.9)	52 (11.9)	1 (0.2)
Asthenia	53 (12.2)	7 (1.6)	53 (12.1)	2 (0.5)
Dysgeusia	49 (11.3)	0	57 (13.0)	0

Tilly H, et al. *N Engl J Med.* 2022;386(4):351-363.

Importantly, the toxicity and the font here is small, but that's okay. The toxicity is quite similar, really just a little bit more in the way of infectious toxicity, but importantly, no difference in neuropathy as a result of this. I think it's important to note that R-CHOP does have meaningful neuropathy as part of it. That was not worsened by the substitution of polatuzumab for vincristine.

R-CHOP vs Polatuzumab-R-CHP in DLBCL - PFS

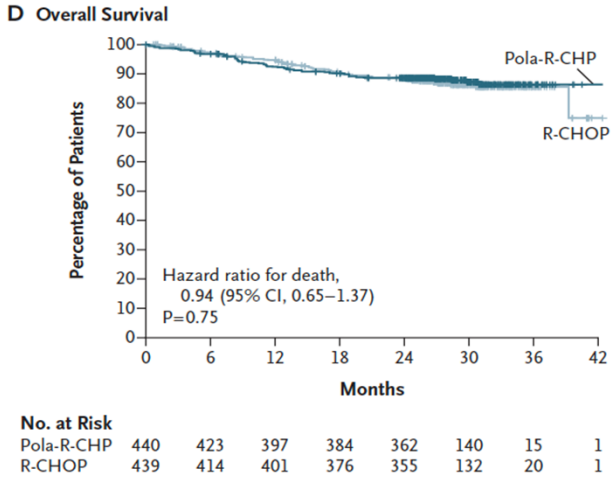


24 mo PFS:
76.7% Pola-R-CHP
70.2% R-CHOP

Tilly H, et al. *N Engl J Med.* 2022;386(4):351-363.

The key primary endpoint of the study, about 6.5% absolute difference in 24-month progression-free survival. PFS was improved by swapping in polatuzumab for vincristine and R-CHOP again by about 6.5%.

R-CHOP vs Polatuzumab-R-CHP in DLBCL - OS

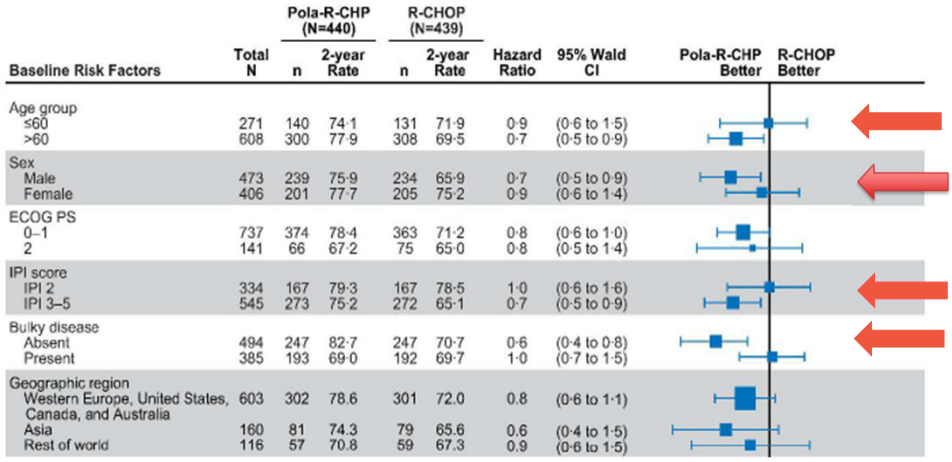


Tilly H, et al. *N Engl J Med.* 2022;386(4):351-363.

However, overall survival is no difference. Now, whether or not this will change over time, whether or not this will never change because we have more effective second line and beyond regimens all remains to be seen.

That is an important caveat of this study and something that a variety of people have said, "Well, these are less compelling because we don't see an overall survival benefit at this point in time."

R-CHOP vs Polatuzumab-R-CHP in DLBCL - Subgroups



Baseline Risk Factors	Total N	Pola-R-CHP (N=440) n	Pola-R-CHP (N=440) 2-year Rate	R-CHOP (N=439) n	R-CHOP (N=439) 2-year Rate	Hazard Ratio	95% Wald CI
Age group							
≤60	271	140	74·1	131	71·9	0·9	(0·6 to 1·5)
>60	608	300	77·9	308	69·5	0·7	(0·5 to 0·9)
Sex							
Male	473	239	75·9	234	65·9	0·7	(0·5 to 0·9)
Female	406	201	77·7	205	75·2	0·9	(0·6 to 1·4)
ECOG PS							
0–1	737	374	78·4	363	71·2	0·8	(0·6 to 1·0)
2	141	66	67·2	75	65·0	0·8	(0·5 to 1·4)
IPI score							
IPI 2	334	167	79·3	167	78·5	1·0	(0·6 to 1·6)
IPI 3–5	545	273	75·2	272	65·1	0·7	(0·5 to 0·9)
Bulky disease							
Absent	494	247	82·7	247	70·7	0·6	(0·4 to 0·8)
Present	385	193	69·0	192	69·7	1·0	(0·7 to 1·5)
Geographic region							
Western Europe, United States, Canada, and Australia	603	302	78.6	301	72.0	0.8	(0·6 to 1·1)
Asia	160	81	74.3	79	65.6	0.6	(0·4 to 1·5)
Rest of world	116	57	70.8	59	67.3	0.9	(0·6 to 1·5)

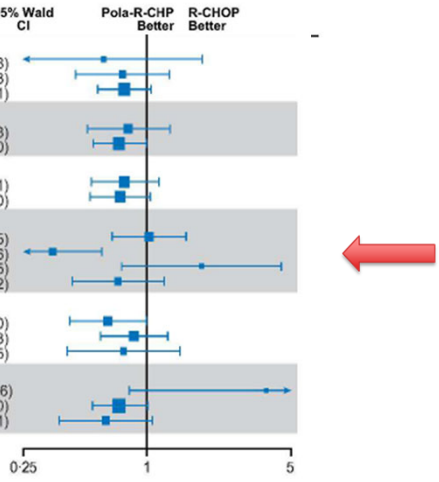
Tilly H, et al. *N Engl J Med.* 2022;386(4):351-363.

Then, like always we try to look at subgroups of patients who benefit. I've used some arrows here to show you where there were some differences. Older patients seem to benefit from the polatuzumab. Men seem to benefit from polatuzumab. Higher-risk IPI patients seemed to benefit more, as did patients who did not have bulky disease.

Again, these are sub-set analyses that are of interest. Whether or not we change our practice and restrict our use of this drug to subsets of patients, I think is a debatable issue we'll come back to in a second.

R-CHOP vs Polatuzumab-R-CHP in DLBCL - Subgroups

Baseline Risk Factors	Total N	Pola-R-CHP (N=440) n	Pola-R-CHP (N=440) 2-year Rate	R-CHOP (N=439) n	R-CHOP (N=439) 2-year Rate	Hazard Ratio	95% Wald CI
Ann Arbor stage							
I–II	99	47	89·1	52	85·5	0·6	(0·2 to 1·8)
III	232	124	80·7	108	73·6	0·8	(0·5 to 1·3)
IV	548	269	72·6	279	66·1	0·8	(0·6 to 1·1)
Baseline LDH							
≤ULN	300	146	78·9	154	75·6	0·8	(0·5 to 1·3)
>ULN	575	291	75·4	284	67·2	0·7	(0·5 to 1·0)
No. of extranodal sites							
0–1	453	227	80·2	226	74·5	0·8	(0·5 to 1·1)
≥2	426	213	73·0	213	65·8	0·7	(0·5 to 1·0)
Cell-of-origin							
GCB	352	184	75·1	168	76·9	1·0	(0·7 to 1·5)
ABC	221	102	83·9	119	58·8	0·4	(0·2 to 0·6)
Unclassified	95	44	73·0	51	86·2	1·9	(0·8 to 4·5)
Unknown	211	110	73·8	101	64·3	0·7	(0·4 to 1·2)
Double expressor by IHC							
DEL	290	139	75·5	151	63·1	0·6	(0·4 to 1·0)
Non DEL	438	223	77·7	215	75·7	0·9	(0·6 to 1·3)
Unknown	151	78	76·0	73	69·8	0·8	(0·4 to 1·5)
Double- or triple-hit lymphoma							
Yes	45	26	69·0	19	88·9	3·8	(0·8 to 17·6)
No	620	305	76·8	315	70·3	0·7	(0·5 to 1·0)
Unknown	214	109	78·5	105	66·4	0·6	(0·4 to 1·1)



Tilly H, et al. *N Engl J Med.* 2022;386(4):351-363.

Finally, another subset that interestingly seemed to potentially benefit more is the ABC subtype seemed to benefit more from the addition of polatuzumab. I preface this by saying this was a cell-of-origin agnostic treatment, but interestingly, there's a subgroup that seems to benefit more, the ABC subtype. Whether or not we may restrict this use to the ABC subtype, I think is a topic of pretty open debate right now. Again, you can only draw so many conclusions from subgroup analyses in the context of a positive overall study.

Implications of POLARIX Study

- Positive trial (6.5% benefit in PFS), no OS benefit in IPI 2-5 DLBCL patients
- Generally comparable toxicity
- Older, male patients, higher risk and ABC subtype benefited most
- Saves 6.5% (1 of 15 patients) from relapse and more therapy
- 6 doses x $15,669/dose/80kg pt x 15 patients

  = $1.4 million/relapse saved

What are my takeaways for the implications of this study? Well, this is a positive trial. There was no overall survival benefit, but there was a PFS benefit. If you can prevent 6 or so out of 100 patients from relapsing and needing more therapy, that's probably a good thing, particularly since there was generally comparable toxicity between the regimens. There are these subsets, as listed here, that seem to benefit more. Now, again, in the context of an overall positive study, it's debatable whether or not we restrict to these subsets or just use the primary endpoint of the study and the study population as a whole.

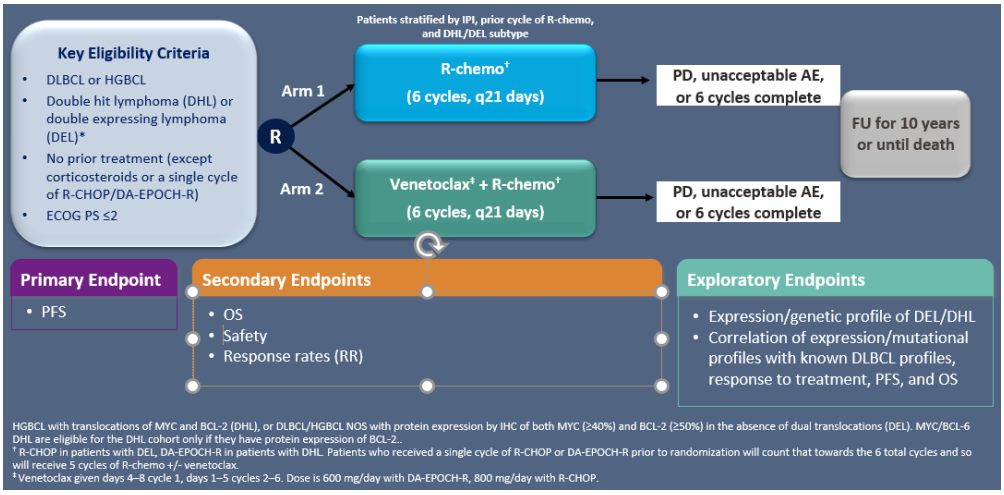
If you do the math here, you end up saving 1 out of 15 patients from relapse and needing more therapy. If you look at the cost from a societal perspective, this turns out to be fairly substantial in that you're spending about $1.4 million to prevent one person from relapsing with the same overall survival. I think this is an interesting and debatable issue in some ways perhaps answered differently if you're thinking about the societal issue as opposed to the patient in front of you who probably wants to do all they can not to relapse, particularly if they have access to a drug and it doesn't add extra toxicity.

My POLARIX Conclusions

- Polatuzumab + R-CHP a new option for patients with newly diagnosed DLBCL (IPI 2-5)
- In setting of overall positive trial would focus on full study population rather than subgroups
- When/if available would offer/recommend to patients in this category

To conclude on this study, I think this is a new option for patients, and it's nice to see a new option for patients in a setting of an overall positive trial. I do focus on this full study population rather than the subgroups, but that's open to debate. I think if and when that's available in the future, I think I would generally offer and recommend this option to patients if they have the drug available to them.

Alliance 051701 (Ph 2/3) Venetoclax + Chemoimmunotherapy for MYC/BCL-2 Double Hit and Double Expressing Lymphomas

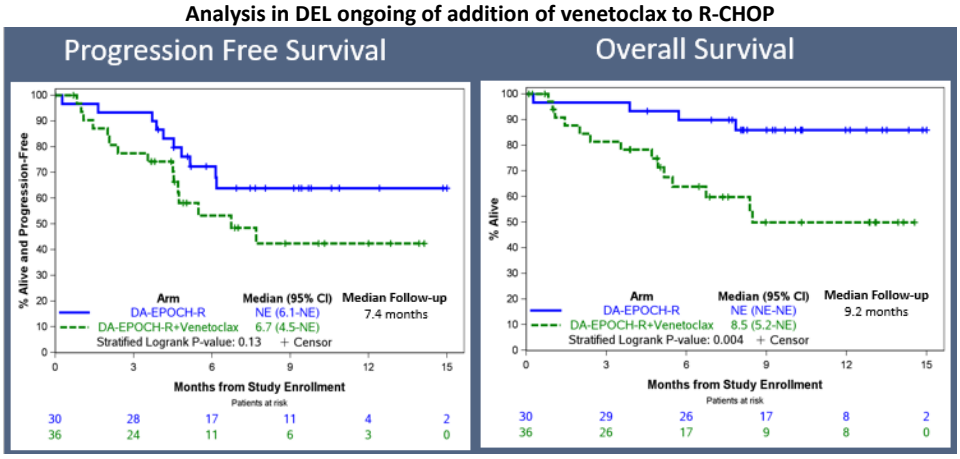


Abramson JS, et al. ASH 2021. Abstract 523.

I just wanted to make one other point about a targeted therapy. This is a little less positive. This is our data. A study that we presented at the ASH meeting in 2021, led by Jeremy Abramson in the unfavorable double-hit lymphoma group of patients. It also looked at the double expressor group. I'm just going to focus on the double-hit group, where we looked at venetoclax, the BCL-2 inhibitor in combination with either R-CHOP or our R-EPOCH in either double-expressor or double-hit lymphomas.

Alliance 051701 (Ph 2/3) Venetoclax + Chemoimmunotherapy for MYC/BCL-2 Double Hit and Double Expressing Lymphomas

In DHL, adding venetoclax to DA-R-EPOCH worsened outcomes due to toxicity
Analysis in DEL ongoing of addition of venetoclax to R-CHOP



Abramson JS, et al. ASH 2021. Abstract 523.

To focus on the double-expressor group, what we unfortunately found was that adding venetoclax to dose-adjusted R-EPOCH actually worsened outcomes. It worsened progression-free survival and worsened overall survival because of toxicity.

This was obviously quite disappointing that adding a new targeted drug, not surprisingly, added some toxicity, but the fact that this toxicity was significant enough to worsen overall survival really says that we have to be very careful about these toxicity approaches or these toxic agents, despite the fact that they might have a strong rationale. We're still pursuing this with R-CHOP and venetoclax or other data that suggests that that can be safely done, but that's going to really require randomized trials to see what the trade-offs are of adding venetoclax in a subset where that could be beneficial.

Key Aspects for Novel Strategies for Upfront Therapy in Diffuse Large B Lymphoma

- Biomarkers apparently of meaningful predictive value
- Lots of active drugs some targeted to specific subsets, some more broadly targeted
- Subsets becoming more and more subclassified
- "Patient selection" may be an issue in operationalizing a targeted approach to maximal effect
- Thus far most "recently impactful" drugs are largely agnostic of subset

To wrap up, I think the key aspects that I would take forward are that we have a variety of different biomarkers. They seem to be of some predictive value, and they seem to be at least guiding us in some ways to potentially consider the use of certain drugs that may be targeting certain subsets. These subsets are more and more becoming subclassified even further that make testing these agents in combination with standard therapy even more and more challenging, patient selection might be an issue in really clarifying all this, the diagnosis-to-treatment interval.

Really, thus far, for a variety of reasons, we seem to be seeing that the most recent and impactful drug polatuzumab swapped into R-CHOP up front, and then some of the other agents, including CAR-T cells in the relapse setting, right now, they are largely agnostic of the subset, but I think there's still a lot of work going on to try to sort out further who can benefit the most from these exciting and active new agents.

With that, I'll stop, and I look forward to additional discussion.

Improving the Spectrum of Care for Patients with Diffuse Large B-cell Lymphoma

Dr. Jim Armitage: What we're going to do now since you're a real expert in this, I'll be like the other people that are watching, asking questions that come up in practice routinely, the, "What do you do?" I'm going to ask you several as long as we have time.

As you pointed out, this disease is a moving target and that we're learning more about biology and the names are changing. Are any of those new classification systems, including the more sophisticated ones that you mentioned, the multiple different subtypes, would you direct therapy based on any of those?

Dr. John Leonard: Well, I think going back to my earlier slides a little bit, the scenarios where I would do something different or I think about doing something different come into the double-hit lymphomas and primary mediastinal lymphomas, I'll put aside the CNS prophylaxis issue, I'll put aside the issue of limited-stage disease. I think of the scenarios that I think about, the most common ones where I might do something different is primary mediastinal and double-hit. Double-hit lymphoma, we have lots of data, almost all retrospective that dose adjusted R-EPOCH or something more aggressive or something similar, more aggressive than R-CHOP does better.

I was impressed by the Alliance data that we had, for dose adjustment R-EPOCH, actually that group of patients did pretty well, actually did better than some of the historical data with double-hit lymphoma. Now, that may be because, again, the same selection biases of who goes on a prospective versus retrospective study, but that's a scenario where I think there are data all over the place as to whether or not R-CHOP is as good as something more or something more is better. I think the consequences of being wrong about that are that you may be missing out. Particularly in younger patients that can tolerate a more aggressive regimen, I tend to use dose-adjusted
R-EPOCH for those patients.

If I have an older patient that can only get R-CHOP, I'm okay with giving them R-CHOP for double-hit lymphoma. Finally, the primary mediastinal group of patients, again, no randomized data but as you know, one of the things that we are trying to avoid in primary mediastinal lymphoma, which preferentially affects younger women is mediastinal radiation and breast radiation and long-term toxicity. There are some hints that an infusion regimen can probably reduce the chance of having a positive PET scan at the end and needing radiation, which is the clinically relevant part of things, although that's obviously also a very debatable thing around the world.

Dr. Jim Armitage: You and I do things about the same way. I'm agreeing with another thing you said that is as you learn more about these new entities and you look more for them, you find out they aren't all necessarily terrible, like localized double-hits or it may be that certainly they are not all the same. Anyway, all right, next thing, EPOCH-R, you and I would both give it in certain situations.

Are there any things other than the standard ones that you just outlined? For example, diffuse large B-cell lymphoma that looks like a diffuse large B-cell lymphoma but has a greater than 90% proliferative fraction, so it's almost like a Burkitt would you use it there? Is there any other situation where you would be tempted to give EPOCH-R rather than CHOP-R?

Dr. John Leonard: Well, I would say that we don't have data, or at least I don't know of data that really establishes that. We looked at, for instance, in the 5030 3 CALGB study double-expressor lymphoma. It didn't seem to make a difference in that group of patients. I don't know that we had, and that study for the reasons we talked about was relatively enriched for more favorable patients. Again, for the same reasons we've talked about, it's hard to get on a clinical trial, and who ends up there tends to be not the sickest patients so to speak.

I would say even if we looked at that particular issue, and we may have to a limited extent, I don't think we have enough patients of that category to draw a big conclusion. I think the more practical scenario, what you describe is that you have someone who's sick, who needs therapy, who has a high Ki-67 and you don't have the FISH results back, but we want to get started on therapy.

In those scenarios that may be one where I start them on dose-adjusted R-EPOCH, I'm suspicious of a double-hit, but I don't have the FISH or I'm waiting for more tissue or whatever as far to get the FISH done. I might start them on dose-adjusted R-EPOCH, and depending on how it goes then switch them over to R-CHOP based on the laboratory findings and so on. Again, obviously, that's in a patient who I think can tolerate that regimen.

Dr. Jim Armitage: All right, John, there's a bunch of things in our business where interim PET scans are important. Obvious one is a number of situations in Hodgkin lymphoma where it's important. Mostly, we don't have any really good data that you should be doing interim PET scans in diffuse large B-cell lymphoma. Most of our data is once you are after six cycles of something. Do you ever do them?

Dr. John Leonard: Well, I think it's a good question. I think we end up getting them because we end up restaging the patient, and we are generally able to get a PET scan to restage the patient and you get some more information. I'm going to generally feel better about a patient that is PET negative after say three cycles if I'm getting it. I'm getting the scan because I want to restage the patient and see progress. If I have the choice between a CT and a PET, I'll get the PET just because I like that extra information.

That being said, if I couldn't get the CT, doesn't change my management, let's put it that way. It's pretty rare for a patient to have a positive PET in a new area without something new on a CT scan in the interim stage, that early progressive-- First of all, that's rare to begin with, and second, it's normally evident with a new mass somewhere or something else going on.

I would say that I end up getting those interim PETs, I rarely if ever change treatment on that basis, certainly would be doing a biopsy, generally speaking before I change anything. I get the information just because it's a little bit more helpful and makes me feel a little bit better. It's certainly not mandatory for practice for the vast majority of people.

Dr. Jim Armitage: You brought up before, CNS prophylaxis. I would guess that the people watching would like to know what Dr. Leonard does for CNS prophylaxis. To whom do you recommend it?

Dr. John Leonard: Well, how I look at it is how concerned am I about CNS relapse risk and how well the patient is likely to tolerate prophylaxis knowing that the evidence for prophylaxis for most settings is quite minimal. Also, what is the downside of not prophylaxing someone who could have benefited from it?

When you roll all that up together, it comes down to the risk of the patient based on the CNS-IPI, which is largely the IPI score plus adrenal and renal areas. That, to me, for most scenarios, in addition, when would add things like testicular involvement et cetera, then it's what is the downside of missing something, which is pretty high for most patients.

In other words, if the true value of CNS prophylaxis is meaningful and you didn't do it, then the downside of not doing it is significant. The other piece of the puzzle is how well is the person going to be able to tolerate the treatment. That being said, there's a lot of variability, I would say, in what I do. I think that in most patients that have risk factors, I will do one LP, look for evidence of CNS involvement with flow and give them one dose of intrathecal methotrexate. I would tend to use systemic methotrexate in patients where they are higher on the risk score, and particularly that they're younger and can tolerate it.

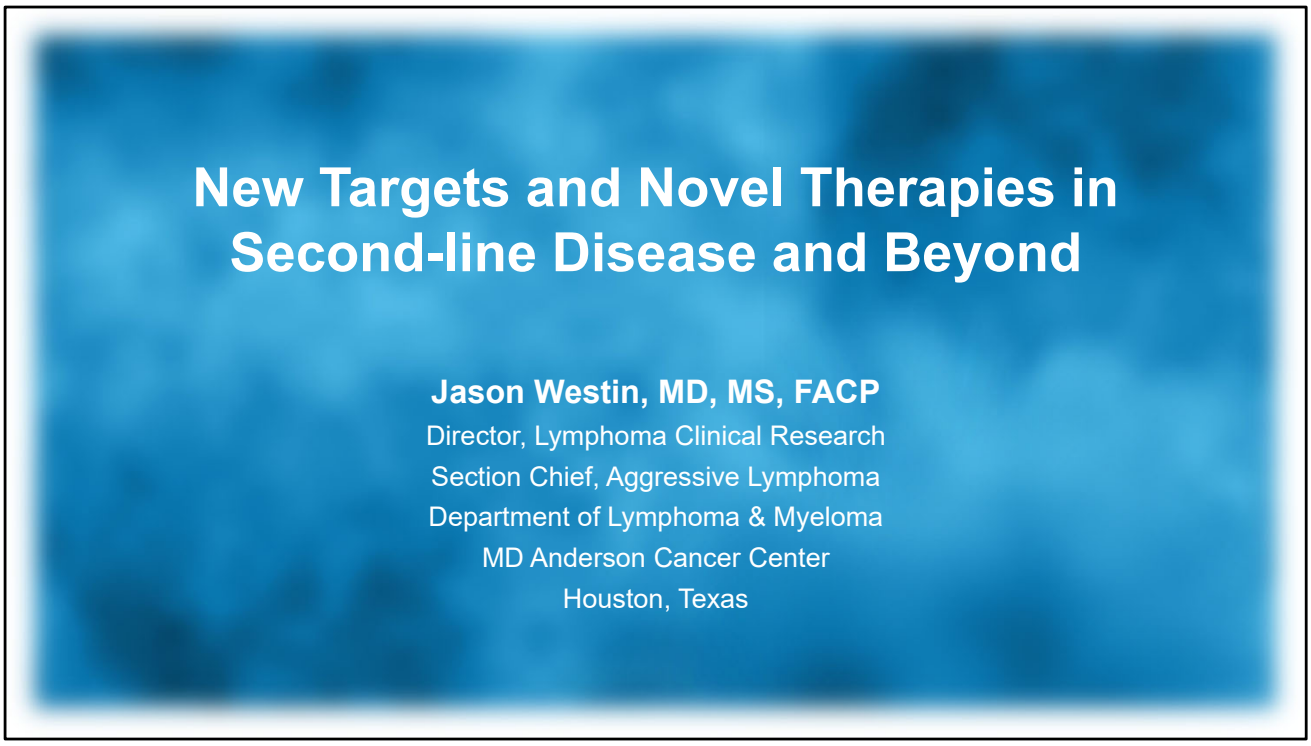
How I'm going to approach a frailer, older patient is going to be different than a 20-year-old, where I think getting methotrexate when you are 20 years old, systemic methotrexate is an easier thing to put up with in obviously certain groups of patients versus others. That's something I talk with people about, I think we also have data that you can give methotrexate at the end rather than trying to slice it in between the treatments, like on day 15. That makes it longer if you give the methotrexate at the end after the R-CHOP is done. Really, I would say that it really comes down to the stew of all of those factors that I just talked about and where we go from there. It's not a very easy and straightforward algorithm for me, and I'm guessing for most people in practice because this comes up very, very often, as you know.

Dr. Jim Armitage: Right. We're pushing the time, but there's one more thing you could answer just real quickly, that we talked about earlier and people would probably like to know. You have a person who presented to you with a 10 or 11 or 12 or 15 or 20-centimeter mass, do you still use radiotherapy after completing the chemotherapy?

Dr. John Leonard: I tend to not use radiotherapy as consolidation after say R-CHOP for bulky diffuse large B-cell lymphoma. I will typically look at those patients and watch them if their PET is still positive. The common scenario very briefly is that they have a high SUV at the beginning and they have a much lower but not normal SUV afterwards. Those are patients that I might do a follow-up PET scan and just watch for a while more often than giving radiation. I know that there are different opinions on that as well.

Dr. Jim Armitage: John thank you very much, that was a wonderful presentation. I hope everybody else enjoyed as much as I do listening to you analyze different complicated things that come up in the care of these patients. Thank you again.

Dr. John Leonard: Thanks very much, it’s been a great discussion.



Dr. Jim Armitage: Now, Dr. Jason Westin is going to discuss emerging agents that we hope are the future standard frontline therapy, or at least some of them will be, for diffuse large B-cell lymphoma because if that's not true, we're not going to get better and we want to cure more patients. Jason.

Dr. Jason Westin: Wonderful. Thank you, Dr. Armitage, and thank you Dr. Leonard for that great presentation. I'm now going to take over and talk about new targets and novel therapies in the second-line for diffuse large B-cell lymphoma and beyond, hoping that some of these therapies can move eventually into frontline and improve our standard of care.

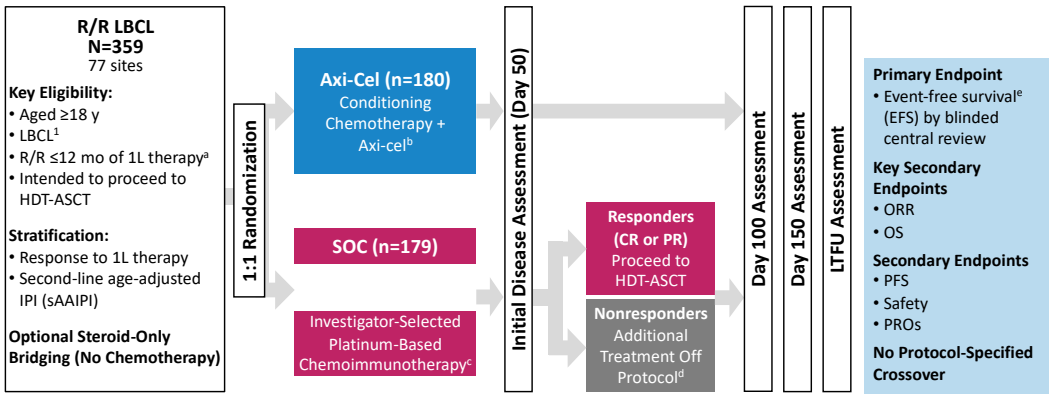
Dr. Jason Westin: I'll focus first on CAR T-cell therapies, then I'll talk about SINES, bispecific engagers, and lastly, antibody drug conjugates. We have a great problem to have right now in large B-cell lymphoma of an avalanche of new very promising therapies.

The first of which is something called CAR T-cell therapy. Here the CAR doesn't sound like something you drive, it stands for chimeric antigen receptor.

These are a patient's own immune cells, their own T-cells, which are genetically modified to now express a surface molecule that can see an antigen on a tumor target. Here we target CD19. Effectively these immune cells are weaponized so they can now see the wolf in sheep's clothing, the cancer that's been hiding in plain sight. These have now been approved in third-line therapy.

There are three CAR T- cells approved for diffuse large B-cell lymphoma, but evaluating if they could do better and move into second-line therapy, taking on the longtime standard of care of autologous stem cell transplant in patients with chemosensitive disease. We've recently seen three large randomized phase III trials. We'll briefly go through the data that was presented with these three trials.

ZUMA-7 Study Schema and Endpoints: Axi-Cel vs SOC as Second-line Therapy in Patients with R/R LBCL

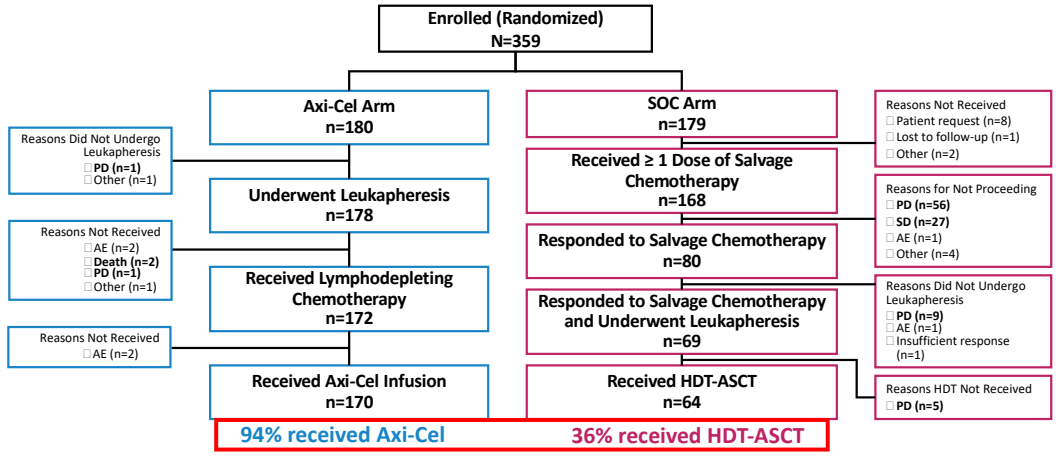


[a] Refractory disease was defined as no CR to 1L therapy; relapsed disease was defined as CR followed by biopsy-proven disease relapse ≤12 months from completion of 1L therapy. [b] Axi-cel patients underwent leukapheresis followed by conditioning chemotherapy with cyclophosphamide (500 mg/m²/day) and fludarabine (30 mg/m²/day) 5, 4, and 3 days before receiving a single axi-cel infusion (target intravenous dose, 2×10⁶ CAR T cells/kg). [c] Protocol-defined SOC regimens included R-GDP, R-DHAP, R-ICE, or R-ESHAP. [d] 56% of patients received subsequent cellular immunotherapy. [e] EFS was defined as time from randomization to the earliest date of disease progression per Lugano Classification,[2] commencement of new lymphoma therapy, or death from any cause.

Locke F, et al. ASH 2021. Abstract 2.; [1]Swerdlow SH, et al. *Blood*. 2016;127:2375-2390. [2]Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068.

The first of which is the ZUMA-7 clinical trial, which was evaluating axicabtagene ciloleucel, or axi-cel, in comparison to patients with standard of care. Now these were patients who had prior first-line therapy and had relapsed within 12 months or were refractory and never responded. These patients were randomized 1:1 to receive axi-cel or standard of care, and those who responded to standard care would go on to get a transplant. The primary endpoint was event free survival.

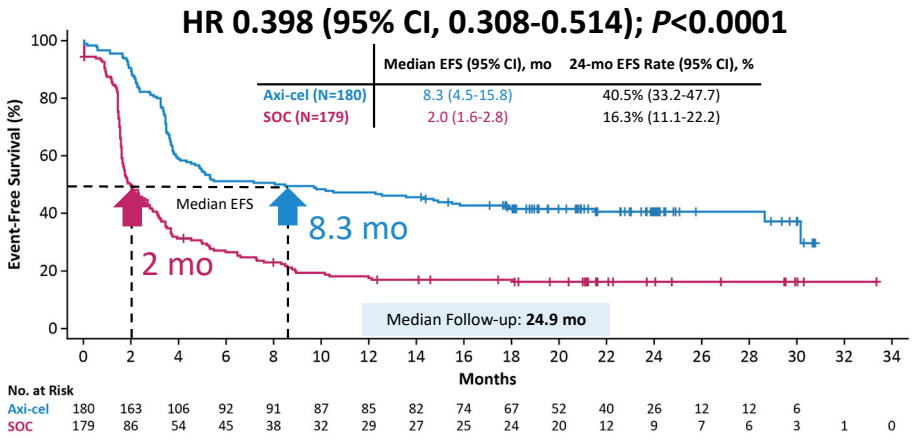
Patient Disposition: Nearly 3x as Many Axi-Cel Patients Received Definitive Therapy vs SOC Patients



Locke F, et al. ASH 2021. Abstract 2.

You can see here in the disposition slide that 94% of patients who were randomized to receive the CAR T-cell therapy axi-cel did so, versus only 36% who were randomized to receive transplant did so largely due to lack of response to chemotherapy in this highly chemotherapy refractory population. Nearly three quarters of patients were refractory to their initial treatment, and that showed here with a lack of chemo sensitivity.

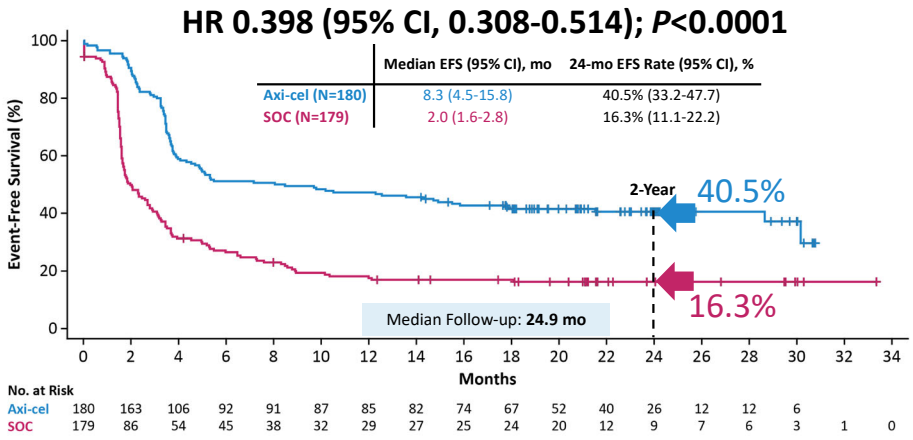
Primary EFS Endpoint: Axi-Cel Is Superior to SOC



Locke F, et al. ASH 2021. Abstract 2.; Locke FL. EMBT-EHA 4th European CAR T-cell meeting, 2022. Poster 55.

The primary endpoint of this trial showed that axi-cel was superior to standard of care with a median of eight months versus two months.

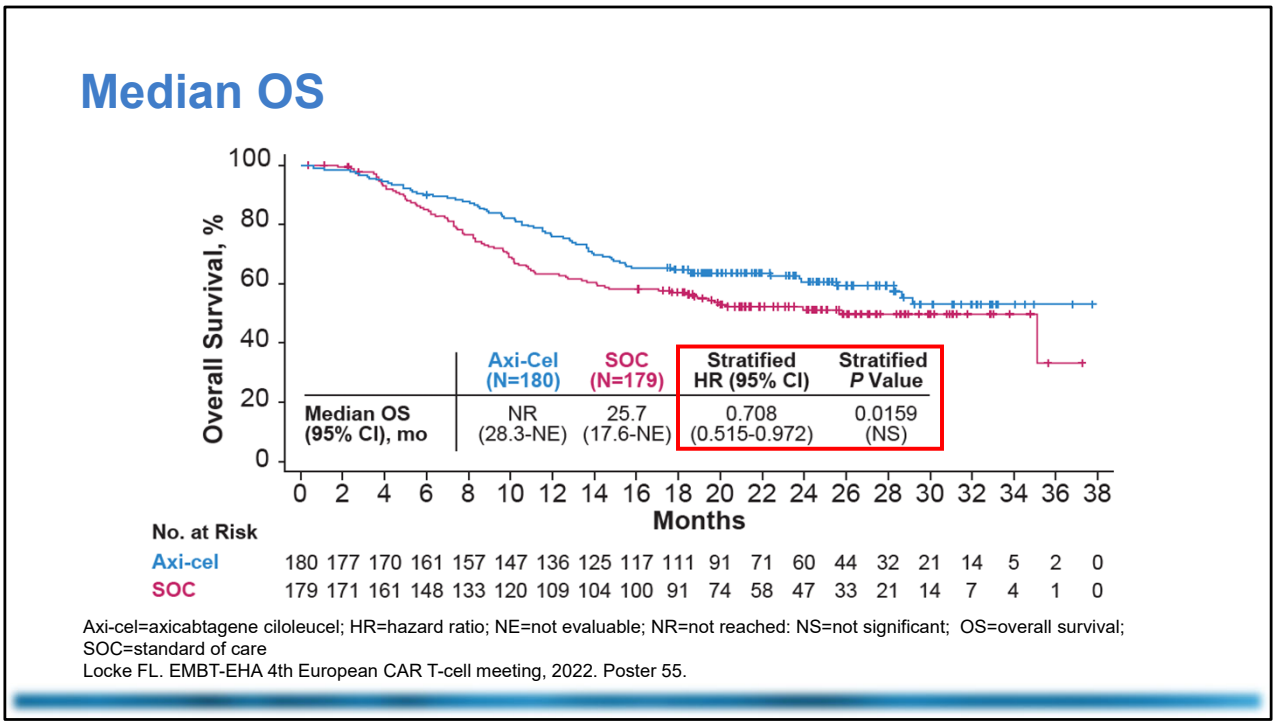
Primary EFS Endpoint: Axi-Cel Is Superior to SOC



Locke F, et al. ASH 2021. Abstract 2.; Locke FL. EMBT-EHA 4th European CAR T-cell meeting, 2022. Poster 55.

and at two years of 40% versus 16%. A dramatic difference.

Improving the Spectrum of Care for Patients with Diffuse Large B-cell Lymphoma

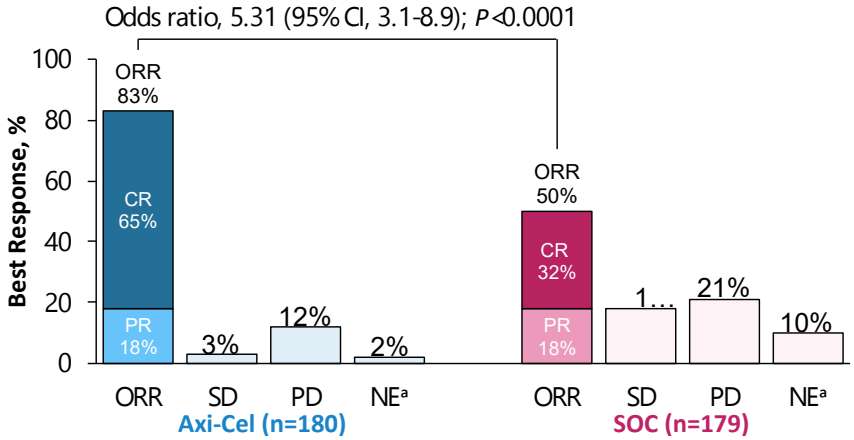


Axi-cel=axicabtagene ciloleucel; HR=hazard ratio; NE=not evaluable; NR=not reached: NS=not significant; OS=overall survival; SOC=standard of care

Locke FL. EMBT-EHA 4th European CAR T-cell meeting, 2022. Poster 55.

The median overall survival is an interim analysis, not yet mature, but does show a trend towards the CAR T-cell product here with an updated presentation earlier this year showing a P value of 0.015, which is not yet mature enough for final analysis but stay tuned for that perhaps next year.

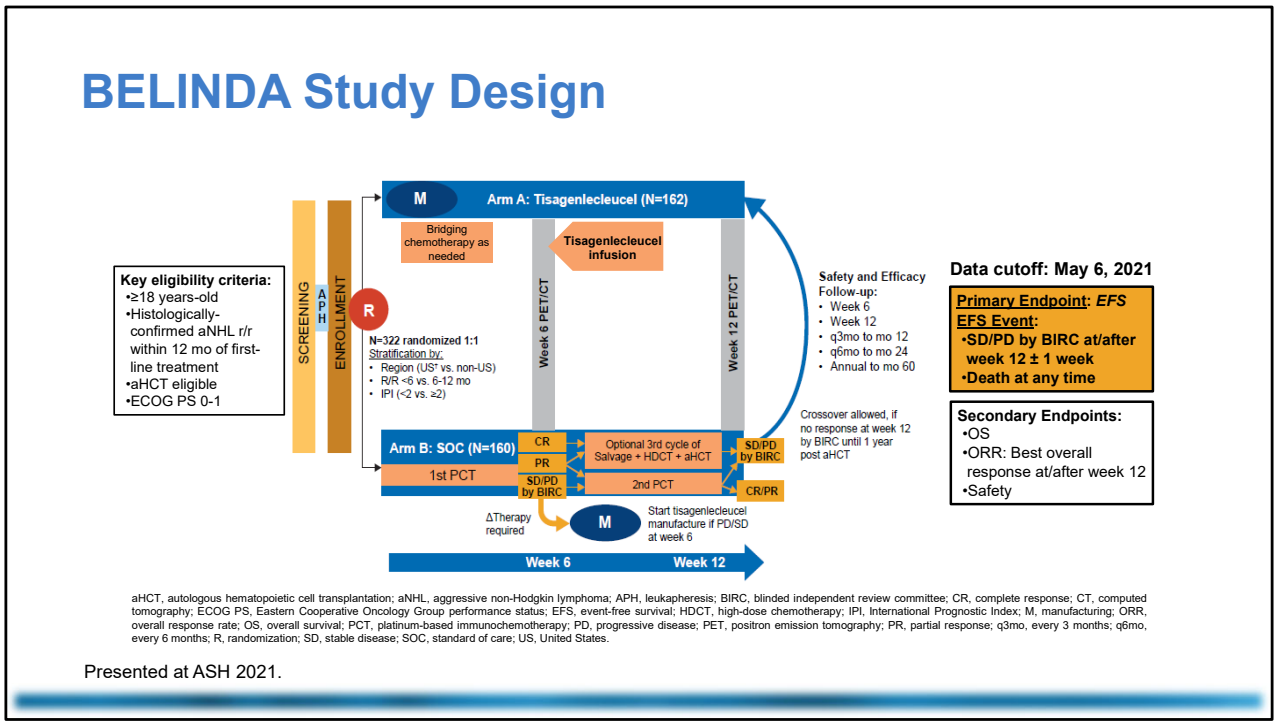
ORR was Significantly Higher in Axi-Cel vs SOC Patients



[a] Not evaluable (NE: In the axi-cel arm, response assessments were not done for 4 patients in the SOC arm, there were 4 patients with unidentified disease and 14 who did not have response assessments done.
Locke F, et al. ASH 2021. Abstract 2.

The overall response rates were significantly better for CAR T-cell, 80% versus 50%, and the complete response rate was more than double, 65% versus 32%. That's the ZUMA-7 clinical trial.

Improving the Spectrum of Care for Patients with Diffuse Large B-cell Lymphoma



aHCT, autologous hematopoietic cell transplantation; aNHL, aggressive non-Hodgkin lymphoma; APH, leukapheresis; BIRC, blinded independent review committee; CR, complete response; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; HDCT, high-dose chemotherapy; IPI, International Prognostic Index; M, manufacturing; ORR, overall response rate; OS, overall survival; PCT, platinum-based immunochemotherapy; PD, progressive disease; PET, positron emission tomography; PR, partial response; q3mo, every 3 months; q6mo, every 6 months; R, randomization; SD, stable disease; SOC, standard of care; US, United States.

Presented at ASH 2021.

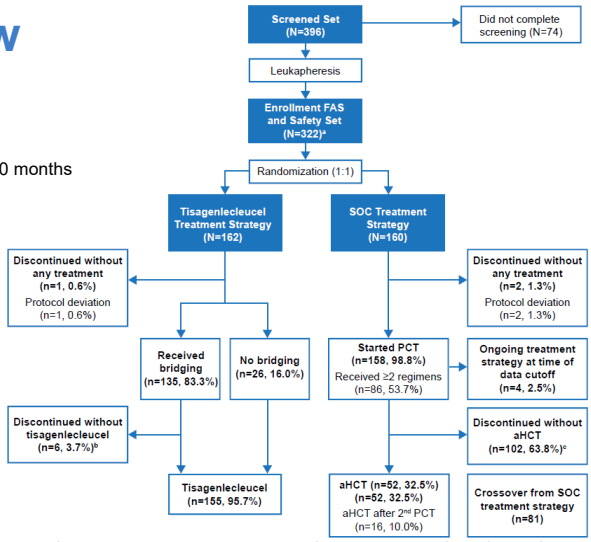
Now let's move on to talk about the BELINDA Clinical trial. This is evaluating a different CAR T-cell product, one called tisagenlecleucel. This clinical trial is a slightly more complicated design where patients are randomized 1:1 to receive the CAR T-cell product or standard of care. There was a longer manufacturing time here in this trial of about six weeks, which is quite a long time for a large B-cell lymphoma patient to wait, and the standard of care arm, if there was lack of response, they would go on to receive a second salvage regimen, effectively a second bite at the apple to try to get to transplant.

The long time to receive the CAR T-cell and a second version of salvage chemotherapy administered gave a few differences in the design for this trial versus the ZUMA-7 trial.

Improving the Spectrum of Care for Patients with Diffuse Large B-cell Lymphoma

Patient Flow

- Median follow-up: 10 months (range, 2.9-23.2)



[a]FAS and safety sets used to compare efficacy and safety between the 2 treatment strategies during the safety comparison period, defined as from day of randomization to the earlier of 56 days after last dose of study treatment or start date of new anticancer therapy. [b]Reasons for discontinuation without tisagenlecleucel infusion include physician decision (n=2, 1.2%), PD (n=2, 1.2%), Manufacturing issue (n=1, 0.6%), and patient decision (n=1, 0.6%). [c]Reasons for discontinuation without aHCT include PD (n=76, 47.5%), physician decision (n=14, 8.8%), death (n=7, 4.4%), patient decision (n=2, 1.3%), technical problems (n=2, 1.3%), and protocol deviation (n=1, 0.6%). aHCT, autologous hematopoietic cell transplantation; FAS, full analysis set; PCT, platinum-based immunochemotherapy; SOC, standard of care.

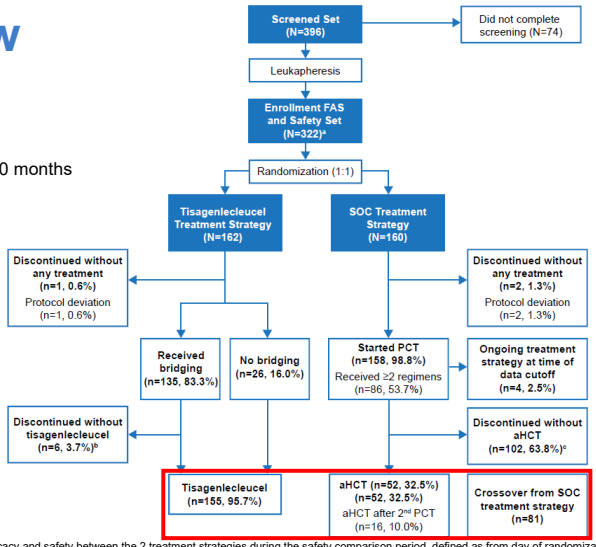
Presented at ASH 2021.

Here, the disposition showed that 96% of patients receive tisagenlecleucel versus only 33% that received transplant. A consistent theme here of these second-line trials that despite the intention of going to transplant, a minority of patients actually do receive it.

Improving the Spectrum of Care for Patients with Diffuse Large B-cell Lymphoma

Patient Flow

- Median follow-up: 10 months (range, 2.9-23.2)



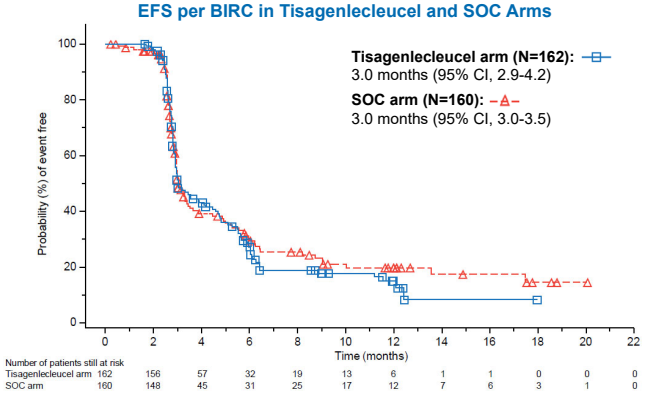
[a]FAS and safety sets used to compare efficacy and safety between the 2 treatment strategies during the safety comparison period, defined as from day of randomization to the earlier of 56 days after last dose of study treatment or start date of new anticancer therapy. [b]Reasons for discontinuation without tisagenlecleucel infusion include physician decision (n=2, 1.2%), PD (n=2, 1.2%), Manufacturing issue (n=1, 0.6%), and patient decision (n=1, 0.6%). [c]Reasons for discontinuation without aHCT include PD (n=76, 47.5%), physician decision (n=14, 8.8%), death (n=7, 4.4%), patient decision (n=2, 1.3%), technical problems (n=2, 1.3%), and protocol deviation (n=1, 0.6%). aHCT, autologous hematopoietic cell transplantation; FAS, full analysis set; PCT, platinum-based immunochemotherapy; SOC, standard of care.

Presented at ASH 2021.

Here, the ability to cross over was embedded in the trial, and more patients on the standard of care arm actually received a CAR T-cell in third-line as a crossover.

No Difference in EFS Between Treatment Arms

EFS per BIRC in Tisagenlecleucel and SOC Arms



- EFS[a] was not significantly different between treatment arms
  - Primary analysis: Stratified unadjusted HR: 1.07 (95% CI, 0.82-1.40, p[b]=0.69)
  - Supportive analysis: Stratified adjusted[c] HR: 0.95 (95% CI, 0.72-1.25)
  - *6 patients responded to tisagenlecleucel infusion, but were captured as an EFS event due to SD/PD before or soon after infusion[d]*

[a]EFS events defined as PD/SD after day 71 or death at any time. [b]p-value derived from 1-sided stratified log-rank test. [c]Adjusted for for potential imbalances in patient characteristics with pre-specified covariates of age, sex, race, ECOG performance status, histological subgroup, disease stage, and disease subtype. [d]Stratified adjusted HR accounting for delayed responses in both arms yield HR of 0.84 (95% CI: 0.63, 1.12).
BIRC, blinded independent review committee; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; OS, overall survival; PD, progressive disease; SD, stable disease; SOC, standard of care.

Presented at ASH 2021.

Unfortunately, this trial showed no difference in the event free survival. Tisagenlecleucel was the same as standard of care showing no improvement in event free survival.

ORR at Week 6 and Best Overall Response

	Week 6 Assessment[a] (Response to PCT)		Best Overall Response (at/after Week 12 Assessment)[b]	
	Tisagenlecleucel Arm (N=162)	SOC Arm (N=160)	Tisagenlecleucel Arm (N=162)	SOC Arm (N=160)
ORR				
CR+PR – no. (%)	62 (38.3)	86 (53.8)	75 (46.3)	68 (42.5)
95% CI	(30.8-46.2)	(45.7-61.7)	(38.4-54.3)	(34.7-50.6)
Best Overall Response – no. (%)				
CR	18 (11.1)	31 (19.4)	46 (28.4)	44 (27.5)
PR	44 (27.2)	55 (34.4)	29 (17.9)	24 (15.0)
SD	48 (29.6)	46 (28.8)	19 (11.7)	22 (13.8)
PD	42 (25.9)	22 (13.8)	50 (30.9)	46 (28.8)
UNK	10 (6.2)	6 (3.8)	18 (11.1)	24 (15.0)

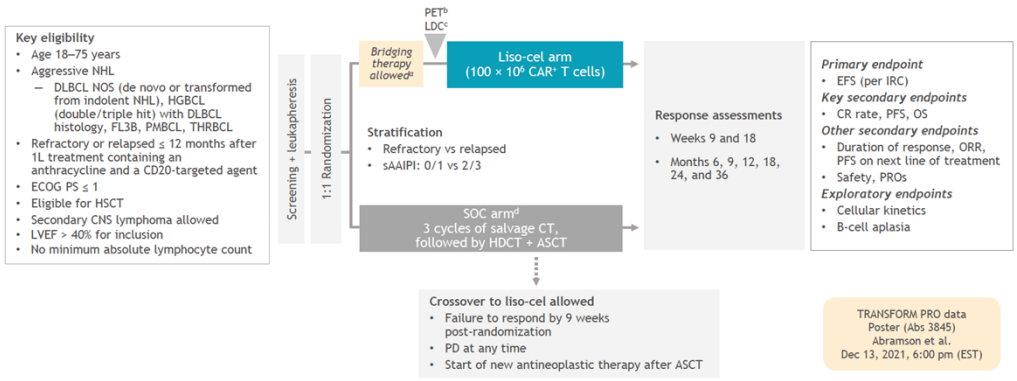
[a]Prior to tisagenlecleucel infusion as per protocol. Week 6 assessment considered as the earliest assessment on or after day 29 and on or before the earliest of day 70 or new anticancer therapy date and per protocol reflected last disease assessment prior to infusion in the tisagenlecleucel arm and disease status after first PCT in the SOC arm. [b]After tisagenlecleucel infusion as per protocol. BOR considers efficacy assessments on or after day 71 and until SD/PD or start of new therapy. Six patients in the tisagenlecleucel arm and 1 patient in the SOC arm responded after initial SD/PD and without starting a new therapy, but were considered nonresponders for ORR as defined per protocol.
BIRC, blinded independent review committee; CI, confidence interval; CR, complete response; mBOR, modified best overall response; mORR, modified overall response rate; ORR, overall response rate; PCT, platinum-based immunochemotherapy; PD, progressive disease; PR, partial response; SD, stable disease; SOC, standard of care; UNK, unknown.

11

Presented at ASH 2021.

This may be due in part to the design features I mentioned, but also due to the relatively poor response of tisagenlecleucel in this trial, the overall response rate was only 46%, and the complete response rate was only 28%. I say “only” because in comparison to what we just heard from ZUMA-7, and what I'll show you in a moment about the other randomized trial, these numbers are not as good as we would've expected for a CAR T-cell product.

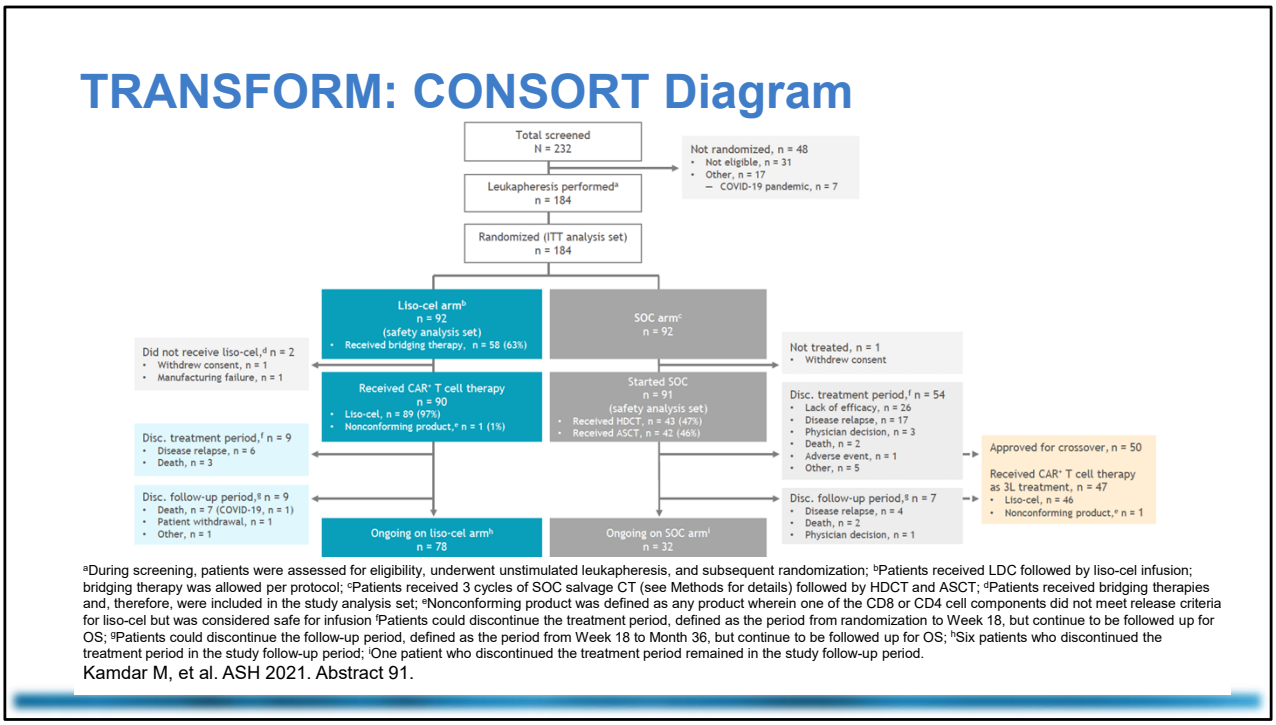
TRANSFORM Study Design



Kamdar M, et al. ASH 2021. Abstract 91.

The third and final randomized phase III trial looking at autologous CAR T-cell is the TRANSFORM study. This is evaluating liso-cel or lisocabtagene maraleucel in comparison to the same standard of care approach of salvage chemotherapy followed by a transplant in patients who do respond or crossover to liso-cel after one salvage regimen with lack of response.

Improving the Spectrum of Care for Patients with Diffuse Large B-cell Lymphoma

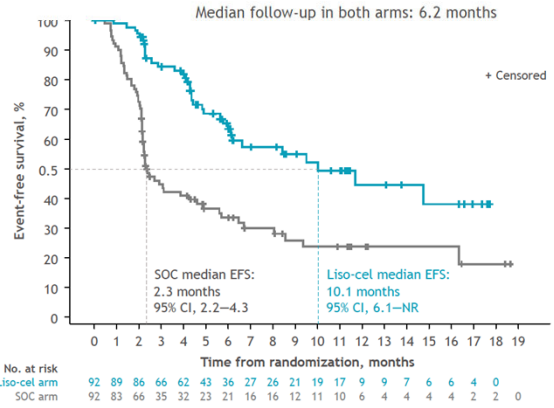


[a]During screening, patients were assessed for eligibility, underwent unstimulated leukapheresis, and subsequent randomization; [b]Patients received LDC followed by liso-cel infusion; bridging therapy was allowed per protocol; [c]Patients received 3 cycles of SOC salvage CT (see Methods for details) followed by HDCT and ASCT; [d]Patients received bridging therapies and, therefore, were included in the study analysis set; [e]Nonconforming product was defined as any product wherein one of the CD8 or CD4 cell components did not meet release criteria for liso-cel but was considered safe for infusion [f]Patients could discontinue the treatment period, defined as the period from randomization to Week 18, but continue to be followed up for OS; [g]Patients could discontinue the follow-up period, defined as the period from Week 18 to Month 36, but continue to be followed up for OS; [h]Six patients who discontinued the treatment period in the study follow-up period; [i]One patient who discontinued the treatment period remained in the study follow-up period.

Kamdar M, et al. ASH 2021. Abstract 91.

Here, the disposition showed a consistent theme that 97% of patients received the CAR T-cell versus 47% received the transplant.

TRANSFORM: Event-free Survival per IRC (ITT Set; Primary Endpoint)



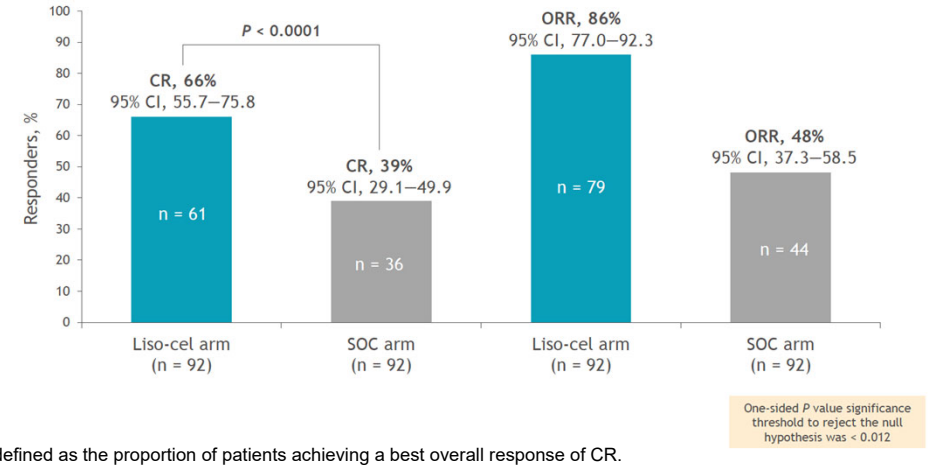
	Liso-cel arm (n = 92)	SOC arm (n = 92)
Patients with events, n	35	63
Stratified HR (95% CI)	0.349 (0.229–0.530)	
	P < 0.0001	
6-month EFS rate, % (SE)	63.3 (5.77)	33.4 (5.30)
Two-sided 95% CI	52.0–74.7	23.0–43.8
12-month EFS rate, % (SE)	44.5 (7.72)	23.7 (5.28)
Two-sided 95% CI	29.4–59.6	13.4–34.1

One-sided *P* value significance threshold to reject the null hypothesis was < 0.012

EFS is defined as the time from randomization to death due to any cause, progressive disease, failure to achieve CR or PR by 9 weeks post-randomization or start of a new antineoplastic therapy due to efficacy concerns, whichever occurs first.
CI=confidence interval; HR=hazard ratio; NR=not reached; SE=standard error
Kamdar M, et al. ASH 2021. Abstract 91.

The primary endpoint of event free survival showed a significant improvement in events free survival of 10 months versus 2 months in the experimental arm of liso-cel versus standard of care.

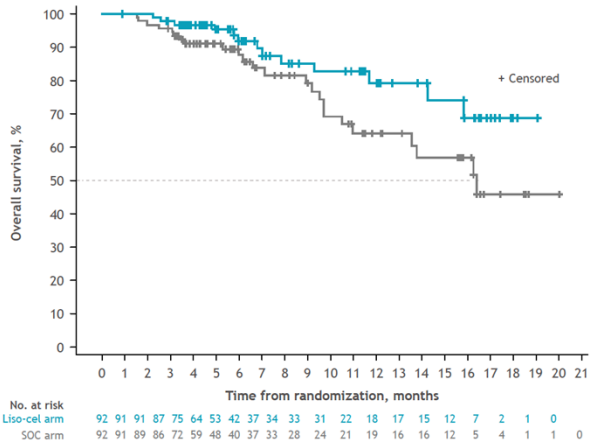
TRANSFORM: Complete and Objective Response Rates per IRC (ITT Set)



CR rate was defined as the proportion of patients achieving a best overall response of CR.
Kamdar M, et al. ASH 2021. Abstract 91.

The response rate is also dramatically better for the CAR T-cell, 86% overall response rate, 66% complete response rate in comparison to the standard of care high dose chemotherapy arm.

TRANSFORM: Overall Survival (ITT Set)



	Liso-cel arm (n = 92)	SOC arm (n = 92)
Patients with events, n	13	24
Stratified HR (95% CI)	0.509 (0.258–1.004)	
	P = 0.0257	
Median OS (95% CI), months	NR (15.8–NR)	16.4 (11.0–NR)
6-month OS rate, % (SE)	91.8 (3.29)	89.4 (3.36)
Two-sided 95% CI	85.4–98.2	82.9–96.0
12-month OS rate, % (SE)	79.1 (6.13)	64.2 (6.99)
Two-sided 95% CI	67.1–91.1	50.5–77.9

Patients in the SOC arm that crossed over to receive liso-cel continue to be followed for OS in the SOC arm

One-sided *P* value significance threshold to reject the null hypothesis was < 0.012

OS is defined as the time from randomization to death from any cause.
Kamdar M, et al. ASH 2021. Abstract 91.

Overall survival is quite immature in this dataset, which to date only has six months of median follow up, so difficult to interpret, but perhaps there could be an early separation of the curves with additional data to follow up.

Cross Trial Data Comparison

	CORAL		ORCHARRD		LY.12		Zuma 7		Belinda		Transform	
1L Refractory												
	NR (40% relapse <12m)		60%		30%		74%		66%		73%	
ORR												
	RDHAP	64%	RDHAP	42%	RDHAP	45%	Axi-cel	83%	Tisa-cel	46%	Liso-cel	86%
	RICE	63%	ODHAP	38%	RGDP	46%	SOC	50%	SOC	46%	SOC	48%
CR Rate												
	RDHAP	40%	RDHAP	22%	RDHAP	15%	Axi-cel	65%	Tisa-cel	28%	Liso-cel	66%
	RICE	36%	ODHAP	15%	RGDP	14%	SOC	32%	SOC	28%	SOC	39%
Received ASCT							Axi-cel	94%	Tisa-cel	96%	Liso-cel	98%
	RDHAP	55%	RDHAP	37%	RDHAP	49%	SOC	36%	SOC	33%	SOC	46%
	RICE	51%	ODHAP	33%	RGDP	53%	(Cross-over)	(56%)	(Cross-over)	(51%)	(Cross-over)	(51%)

In cross trial comparison, we have a lot of historical trials evaluating high dose chemotherapy with an intention for transplant, and then we have these three new randomized phase III trials looking at CAR T-cells.

Cross Trial Data Comparison

	CORAL		ORCHARRD		LY.12		Zuma 7		Belinda		Transform	
1L Refractory												
	NR (40% relapse <12m)		60%		30%		74%		66%		73%	
ORR												
	RDHAP	64%	RDHAP	42%	RDHAP	45%	Axi-cel	83%	Tisa-cel	46%	Liso-cel	86%
	RICE	63%	ODHAP	38%	RGDP	46%	SOC	50%	SOC	46%	SOC	48%
CR Rate												
	RDHAP	40%	RDHAP	22%	RDHAP	15%	Axi-cel	65%	Tisa-cel	28%	Liso-cel	66%
	RICE	36%	ODHAP	15%	RGDP	14%	SOC	32%	SOC	28%	SOC	39%
Received ASCT							Axi-cel	94%	Tisa-cel	96%	Liso-cel	98%
	RDHAP	55%	RDHAP	37%	RDHAP	49%	SOC	36%	SOC	33%	SOC	46%
	RICE	51%	ODHAP	33%	RGDP	53%	(Cross-over)	(56%)	(Cross-over)	(51%)	(Cross-over)	(51%)

The three new studies had an enrichment for refractory patients. These were a highly chemotherapy refractory group with either no response to first-line treatment here as refractory, or at best still progressing within 12 months.

Cross Trial Data Comparison

	CORAL		ORCHARRD		LY.12		Zuma 7		Belinda		Transform	
1L Refractory												
	NR (40% relapse <12m)		60%		30%		74%		66%		73%	
ORR												
	RDHAP	64%	RDHAP	42%	RDHAP	45%	Axi-cel	83%	Tisa-cel	46%	Liso-cel	86%
	RICE	63%	ODHAP	38%	RGDP	46%	SOC	50%	SOC	46%	SOC	48%
CR Rate												
	RDHAP	40%	RDHAP	22%	RDHAP	15%	Axi-cel	65%	Tisa-cel	28%	Liso-cel	66%
	RICE	36%	ODHAP	15%	RGDP	14%	SOC	32%	SOC	28%	SOC	39%
Received ASCT							Axi-cel	94%	Tisa-cel	96%	Liso-cel	98%
	RDHAP	55%	RDHAP	37%	RDHAP	49%	SOC	36%	SOC	33%	SOC	46%
	RICE	51%	ODHAP	33%	RGDP	53%	(Cross-over)	(56%)	(Cross-over)	(51%)	(Cross-over)	(51%)

The complete response rate on these trials, the new phase III randomized ones, in my mind, lines up generally with what we've seen in historical trials, with a complete response rate of around 30% for all the standard of care chemotherapy arms.

Cross Trial Data Comparison

	CORAL		ORCHARRD		LY.12		Zuma 7		Belinda		Transform	
1L Refractory												
	NR (40% relapse <12m)		60%		30%		74%		66%		73%	
ORR												
	RDHAP	64%	RDHAP	42%	RDHAP	45%	Axi-cel	83%	Tisa-cel	46%	Liso-cel	86%
	RICE	63%	ODHAP	38%	RGDP	46%	SOC	50%	SOC	46%	SOC	48%
CR Rate												
	RDHAP	40%	RDHAP	22%	RDHAP	15%	Axi-cel	65%	Tisa-cel	28%	Liso-cel	66%
	RICE	36%	ODHAP	15%	RGDP	14%	SOC	32%	SOC	28%	SOC	39%
Received ASCT							Axi-cel	94%	Tisa-cel	96%	Liso-cel	98%
	RDHAP	55%	RDHAP	37%	RDHAP	49%	SOC	36%	SOC	33%	SOC	46%
	RICE	51%	ODHAP	33%	RGDP	53%	(Cross-over)	(56%)	(Cross-over)	(51%)	(Cross-over)	(51%)

In contrast, the two CAR T-cells that performed well in these studies showed almost a doubling of complete response rate in the mid 60s. We have two thirds of patients responding complete response to CAR T versus one third responding completely to chemotherapy and then receiving the transplant.

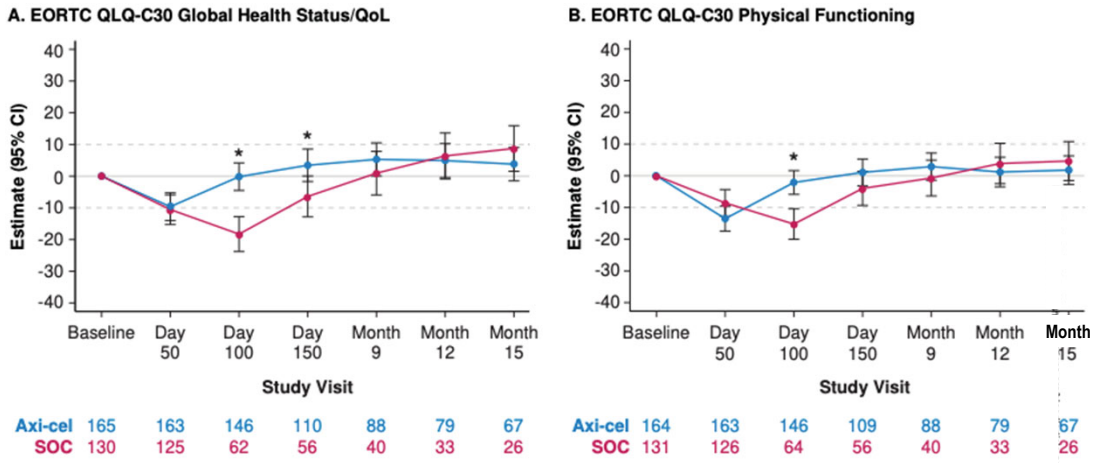
Cross Trial Data Comparison

	CORAL		ORCHARRD		LY.12		Zuma 7		Belinda		Transform	
1L Refractory												
	NR (40% relapse <12m)		60%		30%		74%		66%		73%	
ORR												
	RDHAP	64%	RDHAP	42%	RDHAP	45%	Axi-cel	83%	Tisa-cel	46%	Liso-cel	86%
	RICE	63%	ODHAP	38%	RGDP	46%	SOC	50%	SOC	46%	SOC	48%
CR Rate												
	RDHAP	40%	RDHAP	22%	RDHAP	15%	Axi-cel	65%	Tisa-cel	28%	Liso-cel	66%
	RICE	36%	ODHAP	15%	RGDP	14%	SOC	32%	SOC	28%	SOC	39%
Received ASCT							Axi-cel	94%	Tisa-cel	96%	Liso-cel	98%
	RDHAP	55%	RDHAP	37%	RDHAP	49%	SOC	36%	SOC	33%	SOC	46%
	RICE	51%	ODHAP	33%	RGDP	53%	(Cross-over)	(56%)	(Cross-over)	(51%)	(Cross-over)	(51%)

In these studies, 30% to 40% receive transplant. That's not too different from what we've seen historically.

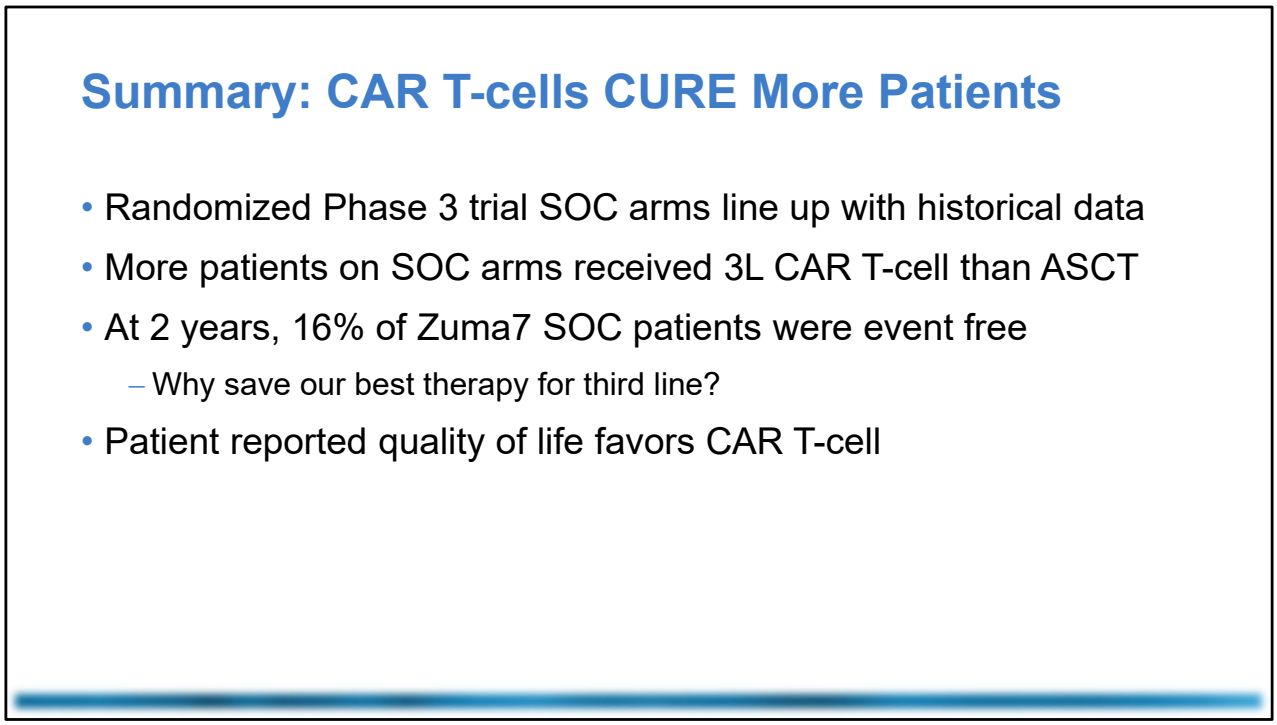
These trials, the standard of care arm performed as well as it could, but the CAR T-cell arm outperformed it and therefore, the new standard of care, in my opinion, is to consider a CAR T-cell of axi-cel or liso-cel for patients who are early relapsed or refractory from frontline treatment.

Quality of Life – ZUMA7



Elsawy M, et al. *Blood.* 2022;blood.2022015478.

Further supporting that is that quality of life data is now being presented from a couple of these trials showing that the patients who received axi-cel had an earlier return to their quality of life pre-treatment, and actually an improvement in quality of life over their baseline, versus the standard of care patients had a longer time to recover. Not only is it more effective, but patients quality of life appears to be improved based on these CAR T-cell data.



In summary, CAR T-cells cure more patients. The randomized phase III trials do line up with historical data and the standard of care arms.

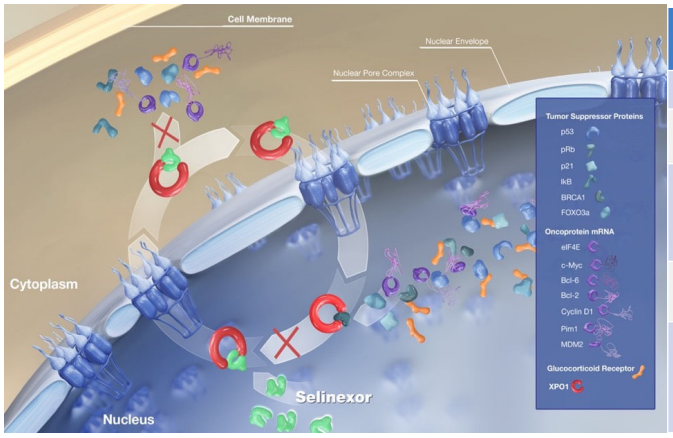
More patients on the standard of care arms actually received a third-line CAR T-cell than they did transplant.

I think quite provocatively for our field at two years, despite an intensive chemotherapy program, only 16% of patients on the ZUMA-7 clinical trial with median follow-up of 24 months were event free, implying that we are giving high dose chemotherapy historically to these patients, and one out of five, one out of six patients are receiving long-term benefit. That's not great. I would argue why save our best therapy for third-line?

In my practice, CAR T-cells have now moved into second-line for these early relapsing patients.

Moving on to the next subjects, the selective inhibitors of nuclear export are led by this compound called Selinexor.

Selinexor



Select Targets	Outcome
TP53	Tumor suppressor
IkB	Inhibitor of NFkB signaling pathway
FOXO	Tumor suppressor (upregulate factors which inhibit cell proliferation)
CDKN1A/1B	Inhibitors of cell cycle progression
eIF4E	Regulates passage of mRNA of a number of oncoproteins (MYC, Cyclin D1)

This is a clever idea of blocking a nuclear export protein which effectively traps tumor suppressors within the nucleus which preferentially should be toxic to cancer cells.

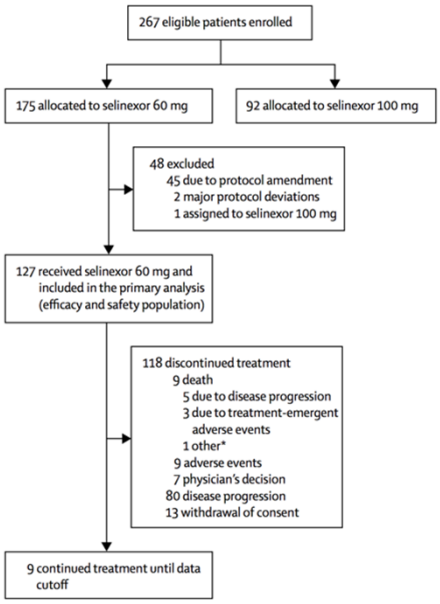
Improving the Spectrum of Care for Patients with Diffuse Large B-cell Lymphoma

Selinexor

Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicentre, open-label, phase 2 trial

Nagesh Kalakonda, Marie Maerevoet*, Federica Cavallo, George Follows, Andre Goy, Joost S P Vermaat, Olivier Casasnovas, Nada Hamad, Josée M Zijlstra, Sameer Bakhshi, Reda Bouabdallah, Sylvain Choquet, Ronit Gurion, Brian Hill, Ulrich Jaeger, Juan Manuel Sancho, Michael Schuster, Catherine Thieblemont, Fátima De la Cruz, Miklos Egyed, Sourav Mishra, Fritz Offner, Theodoros P Vassilakopoulos, Krzysztof Warzocha, Daniel McCarthy, Xiwen Ma, Kelly Corona, Jean-Richard Saint-Martin, Hua Chang, Yosef Landesman, Anita Joshi, Hongwei Wang, Jatin Shah, Sharon Shacham, Michael Kauffman, Eric Van Den Neste, Miguel A Canales*

- Patients whose most recent systemic anti-DLBCL therapy induced a partial response or complete response had to have at 60 days or more elapsed since the end of that therapy.
- All other patients, had to have at least 14 weeks (98 days) elapsed since the end of their most recent systemic anti-DLBCL therapy



Kalakonda N, et al. *Lancet Haematol.* 2020;7(7):e511-e522.

Selinexor was evaluated in the SADAL trial, which was a single arm phase II study. The eligibility criteria for this trial were somewhat unique in that patients were required to either have a complete or partial response and have had 60 days elapsed since their most recent therapy, or if they didn't have a complete response, have to have waited 14 weeks since their most recent therapy. That is not a hyper-proliferative group, that's a relatively slow growing version of large B-cell lymphoma.

The CONSORT diagram shows that this is a subset of a subset that we're analyzing here. 200 some odd patients were initially enrolled, but the primary efficacy was at a certain dose level, and that only was 127 patients that were evaluable in this trial.

SADAL: Response Rates

(N=127)	Response per IRC, n (%)	Median DoR per IRC, months (95% CI)
ORR [95% CI]	36 (28.3) [20.7, 37.0]	9.3 months (4.8, 23.0)
CR	15 (11.8)	23.0 months (10.4, 23.0)
PR	21 (16.5)	4.4 months (2.0, NE)
SD	11 (8.7)	N/A
PD/NE	80 (63.0)	N/A

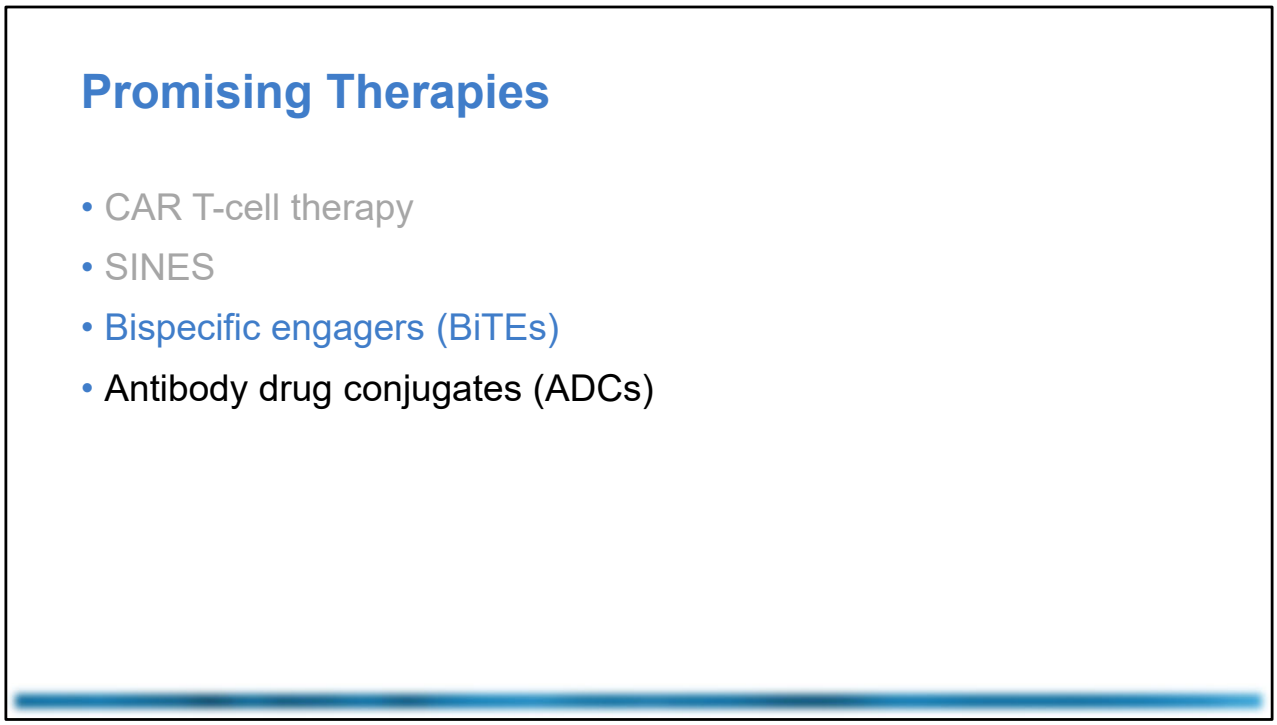
Median time to response: 1.8 months (range: 1.5 – 6.4)

CI=confidence interval; CR=complete response; DoR=duration of response; IRC=independent review committee; N/A=not applicable; Ne=Not evaluated; ORR=overall response rate; PD=progressive disease; PR=partial response; SD=stable disease

Kalakonda N, et al. *Lancet Haematol*. 2020;7(7):e511-e522.; Maerevoet M, et al. EHA 2020. Abstract EP1260.; Zijlstra JM, et al. EHA 2020. Abstract EP1226.

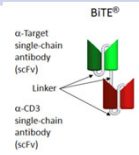
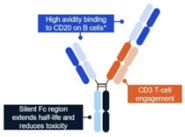
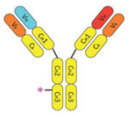
This was approved by the FDA based upon these response rates with an overall response rate of 28% and a complete response rate of 11.8%. Now, that seems relatively low, however, for those patients who did achieve a complete response, their duration of response median was 23 months.

There is a subset of patients who do extremely well with this Selinexor approach, an oral agent which may be attractive for those that aren't wanting to receive IV therapy or travel to a specialized center.



Moving on to what I think is an exciting new advance, not yet approved by the FDA, but I'd say stay tuned because this will change soon, are the so-called bispecific antibodies.

Bispecific Antibodies in Non-Hodgkin Lymphomas

The Original: Proof of Concept	The Emerging: Viable Future Therapies?			
Blinatumomab[1]	**Epcoritamab[2]**	**Mosunetuzumab[3]**	**Glofitamab[4]**	**Odronextamab[5]**
				
CD3 (scFV) x CD19 (scFV)	DuoBody- CD3 x CD20 BsAb	CD3 x CD20 Knobs-in-hole Fc BsAb	CD3 (Fab) x CD20 (Fab x2) Fc BsAb	CD3 x CD20 Common LC Fc BsAb

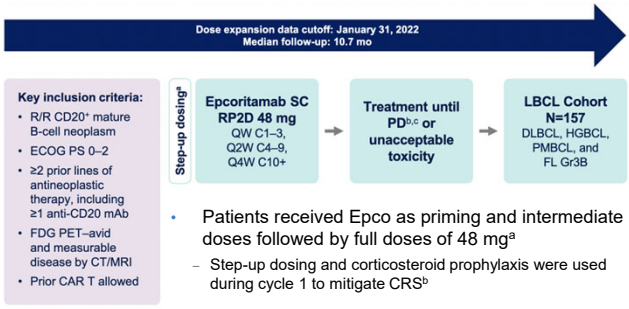
- Numerous bispecific antibody structures exist
- Properties of the BsAbs vary by construct
- Distinguishing features of BsAbs include:
  - **Off-the-shelf** – rapid access, relative ease of delivery[6,7]
  - **Adaptable** – lack of persistence and ability to modulate dosing may improve tolerability[6]

[1]Queudeville M, et al. *Onco Targets Ther*. 2017;10:3567-3578. [2]Clausen MR, et al. *J Clin Oncol*. 2021;39(suppl 15):7518. [3]Budde LE, et al. *Blood*. 2018;132(suppl 1):399. [4]Hutchings M, et al. *Blood*. 2020;136(suppl 1):45-46. [5]Bannerji R, et al. *Blood*. 2020;136(Suppl_1):42-43. ASH 2020. Abstract 400. [6]Husain B, et al. *BioDrugs*. 2018;32(5):441-464. [7]Schuster S. SurvivorNet. Bispecific antibodies: an off-the-shelf approach to treating lymphoma. Accessed June 23, 2022. https://www.survivornet.com/articles/bispecific-antibodies-an-off-the-shelf-approach-to-treating-lymphoma/

The original shot on goal in this field was an antibody called blinatumomab targeting CD19 and CD3, but the new emerging kids on the block are targeting CD20 and CD3. I'll highlight three of these today, epcoritamab, mosunetuzumab and glofitamab. Glofitamab is slightly unique in that it has two antigen binding epitopes for CD20 and one for CD3, the others are one and one of CD20 and CD3.

Improving the Spectrum of Care for Patients with Diffuse Large B-cell Lymphoma

Phase 2 EPCORE NHL-1: Epcoritamab Monotherapy in R/R DLBCL



- Patients received Epco as priming and intermediate doses followed by full doses of 48 mg[a]
  - Step-up dosing and corticosteroid prophylaxis were used during cycle 1 to mitigate CRS[b]

Baseline Characteristics	N=157
Median age, years (range)	64 (20-83)
Primary refractory disease, n (%)	96 (61)
Median prior lines of therapy, n (range)	3 (2-11)
Refractory to last line of therapy, n (%)	130 (83)
Prior CAR T-cell therapy, n (%)	61 (39)
Prior ASCT, n (%)	31 (20)

- Primary results of subcutaneous epcoritamab dose expansion in patients with relapsed or refractory large B-cell lymphoma

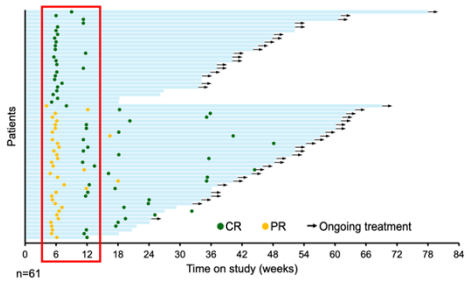
Data cutoff: January 31, 2022.
[a] Patients received Epco until disease progression or unacceptable toxicity. [b] Patients were hospitalized for 24 hours following the first full dose for observation.
Thieblemont C, et al. EHA 2022. Abstract LB2364.

The first data set to explore is epcoritamab in the EPCORE trial targeting patients with relapse refractory large B-cell lymphoma. What's common to all three of these bispecific antibodies is a way to try and mitigate toxicities, including cytokine release syndrome, is a step-up dosing, starting off with a very low dose, then a medium dose, and then the full dose to try and effectively temper cytokine release syndrome by gently exposing the patient to the drug over time.

Epcoritamab is treatment until progression or unacceptable toxicity. In this cohort, the patients, 61% were primary refractory and 20% had prior CAR T-cell therapy.

Phase 2 EPCORE NHL-1: Epcoritamab Monotherapy in R/R DLBCL

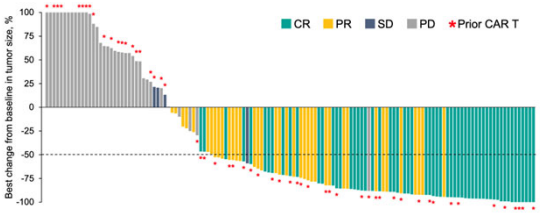
Durability of responses



Follow-Up and Disposition

- Median follow-up was 10.7 months
- Of the patients achieving CR, 89% were still in CR at 9 months[b]

Best overall change in size of tumor

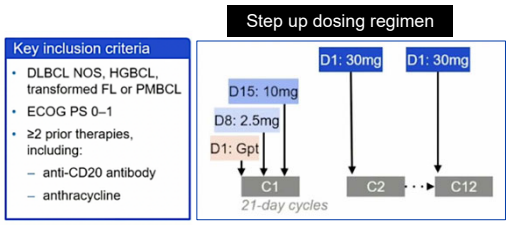


Efficacy		N=157
ORR,[a] n (%)		99 (63)
CR		61 (39)
Median DOR, months		12
Patients with prior CAR T-cell therapy, %	ORR	54
	CR	34
Patients without prior CAR T-cell therapy, %	ORR	69
	CR	42

Data cutoff: January 31, 2022.
[a] ORR was assessed by IRC using PET-CT and Lugano criteria. [b] This is based on a Kaplan-Meier estimate.
Thieblemont C, et al. EHA 2022. Abstract LB2364.

Here are the results. It's a very impressive overall response rate of 63%, and a complete response rate of 39%. You can see the waterfall plot. The majority of patients derive clinical benefit. On the left-hand side, the swimmers plot shows that the durability of responses appears to be very promising with many patients now more than 30 weeks on study, again, still on treatment until progression but nonetheless, in this refractory population appears very attractive, and many studies are ongoing evaluating this bispecific.

Phase 2 Glofitamab Monotherapy IV in Patients With R/R DLBCL



- Phase 2 expansion results in patients with R/R DLBCL and ≥2 prior therapies[a]
  - Primary endpoint was CR rate[b]

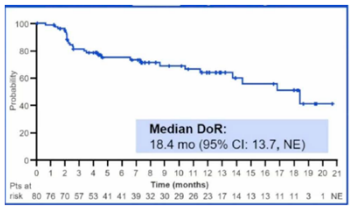
Baseline Characteristics	N=154
Median age, years (range)	66 (21-90)
Ann Arbor stage III-IV, n (%)	116 (75)
Median prior lines of therapy, n (range)	3 (2-7)
≥3 prior therapies, n (%)	92 (60)
Prior CAR T-cell therapy, n (%)	51 (33)
Refractory to prior regimens	
Refractory to last prior regimen, n (%)	132 (86)
Refractory to prior anti-CD20 antibody, n (%)	128 (83)
Refractory to prior CAR T-cell therapy, n (%)	46 (30)

Data cutoff: March 14, 2022.
[a] Includes ≥1 anti-CD20 antibody and ≥1 anthracycline. [b] Assessed by IRC using Lugano 2014 criteria.
Gpt, obinutuzumab pretreatment.
Dickinson M, et al. ASCO 2022. Abstract 7500.

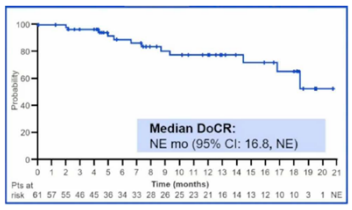
The next bispecific to review is glofitamab. In this clinical trial looking at glofitamab monotherapy, the step-up dosing, as we've heard before, up to a total of 12 cycles of therapy, so a fixed duration of therapy. Patients on this trial had refractory disease to their most recent treatment of 86%, and 30% were refractory to prior CAR T-cell treatment.

Phase 2 Glofitamab Monotherapy IV in Patients With R/R DLBCL

Duration of overall response[a]



Duration of complete response[a]



- Similar CR rates in patients with and without prior CAR T-cell therapy (35% vs 42%)
- Most CRs were ongoing at time of data cutoff (80%)

Efficacy	R/R DLBCL (N=155)
ORR, n (%) CR, n (%)	80 (52) 61 (39)
Median time to CR, days (95% CI)	42 (42-44)
Median duration of follow-up, months (range)	12.6 (0-22)
Median OS, months (95% CI)	11.5 (7.9-15.7)

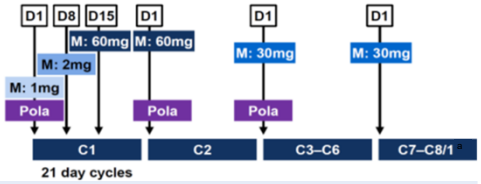
Data cutoff: March 14, 2022.
[a] Assessed by an independent review committee.
Gpt, obinutuzumab pretreatment; ORR, overall response rate.
Dickinson M, et al. ASCO 2022. Abstract 7500.

Here are the results. An overall response rate at 52%, complete response rate at 39%, and the duration of overall response now at 18 months, duration of complete response not yet reached.

Now, granted, patients are on treatment for 12 cycles of about 9 months. Time will tell what will happen is patients who are off therapy, what is their long term response? Are we seeing a plateau or are these patients having late relapses? We don't yet know, but there are hints there may be patients who remain in remission for a durable time after treatment.

Phase 1b/2 Mosunetuzumab + Polatuzumab Vedotin in Patients With R/R DLBCL

- Open-label, phase 1b/2, dose-escalation and dose-expansion study of IV mosunetuzumab + polatuzumab vedotin in patients with R/R B-NHL



Key Eligibility Criteria
- DLBCL (including trFL or grade 3b FL): phase 1b/2
- FL grade 1-3a: phase 1b only

M-Pola administration in phase 2 expansion
- Mosunetuzumab
  - Q3W IV infusions at RP2D (C1-8/17)[a]
  - C1 step-up dosing for CRS mitigation
  - No mandatory hospitalization
- Polatuzumab vedotin
  - Q3W IV infusion (1.8 mg/kg) (D1 C1-6)

Primary objectives: Efficacy, safety and tolerability

Patient Characteristics		All Patients (N=63)	DLBCL (n=60)
Median age, years (range)		68 (20-83)	68 (20-83)
ECOG PS, n (%)	0-1	59 (93.7)	56 (93.3)
	2	4 (6.3)	4 (6.7)
Histology, n (%)	**DLBCL**	**60 (95.2)**	60 (100)
	de novo	44 (69.8)	44 (73.3)
	Transformed FL	12 (19.0)	12 (20.0)
	Grade 3b FL	4 (6.3)	4 (6.7)
	FL grade 1-3a	3 (4.8)	0
Bulky disease (≥10 cm), n (%)		6 (9.5)	6 (10.0)
Ann Arbor stage III-IV, n (%)	I-II	13 (20.6)	12 (20.0)
	III-IV	50 (79.4)	48 (80.0)
Median prior lines of therapy, n (range)		3 (1-10)	3 (1-8)
Prior CAR T-cell therapy, n (%)		25 (39.7)	24 (40.0)
Refractory to last prior therapy, n (%)		48 (76.2)	46 (76.7)

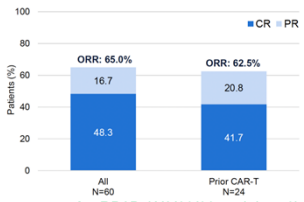
[a] Mosunetuzumab discontinuation after C8 if patient achieved CR or after C17 if patient achieved PR or SD.
NE=not estimable; ORR=overall response rate
Budde E, et al. ASH 2021. Oral Presentation 533.

Lastly, mosunetuzumab and polatuzumab, now, polatuzumab we'll talk about the next section an antibody drug conjugate.

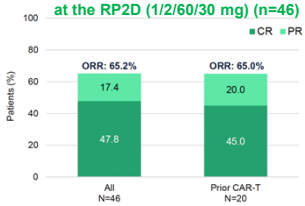
Step-up dosing, concurrent doublet therapy here with mosunetuzumab and polatuzumab in patients with 40% prior CAR T-cell therapy.

Phase 1b/2 Mosunetuzumab + Polatuzumab Vedotin in Patients With R/R DLBCL

Response in Patients With DLBCL Receiving Mosunetuzumab at 1/2/9 mg to 1/2/60/30 mg (n=60)

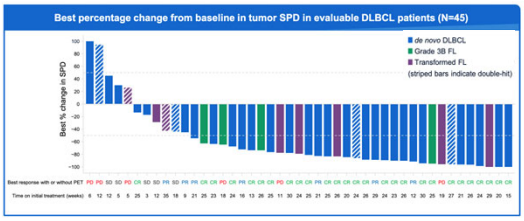


at the RP2D (1/2/60/30 mg) (n=46)



NE=not estimable; ORR=overall response rate
Budde E, et al. ASH 2021. Oral Presentation 533.

Best percentage change from baseline in tumor SPD in evaluable DLBCL patients (N=45)



Other Efficacy Data

- Median DOR in all patients with DLBCL: NR (95% CI: 6.3, NE)
- Median PFS in all patients with DLBCL: (data immature) 8.9 months (95% CI: 3.5, NE)
- Of 29 patients who achieved CR, 28 (96.6%) remained in CR and 1 (3.4%) had PD (later received retreatment and achieved CR)

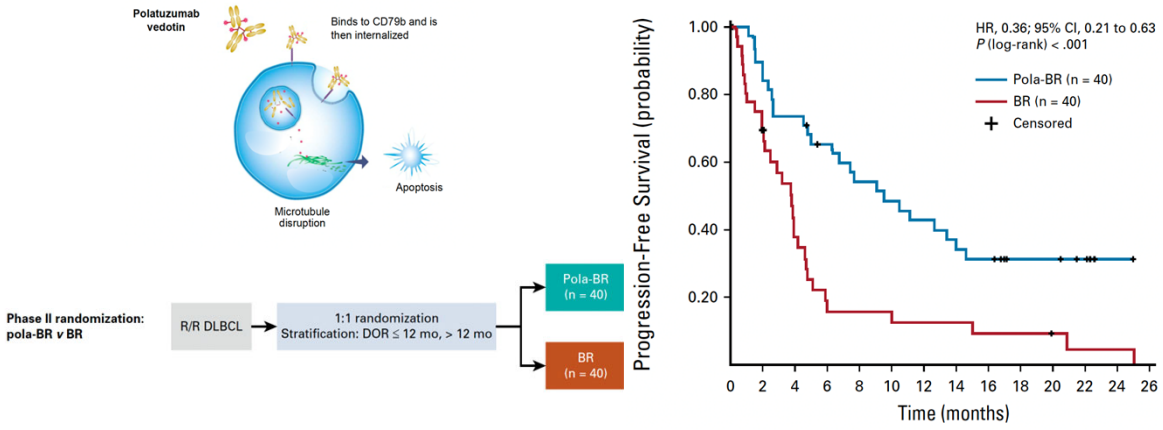
Showed a very impressive waterfall plot with an overall response rate of nearly 60%, a little bit above 60%, and a complete response rate in the 40% range, both in CAR T naïve and CAR T-cell relapse patients. Very impressive combination here in this hard to treat patient population.

Promising Therapies

- CAR T-cell therapy
- SINES
- Bispecific engagers (BiTEs)
- Antibody drug conjugates (ADCs)

Lastly, moving into the antibody drug conjugates.

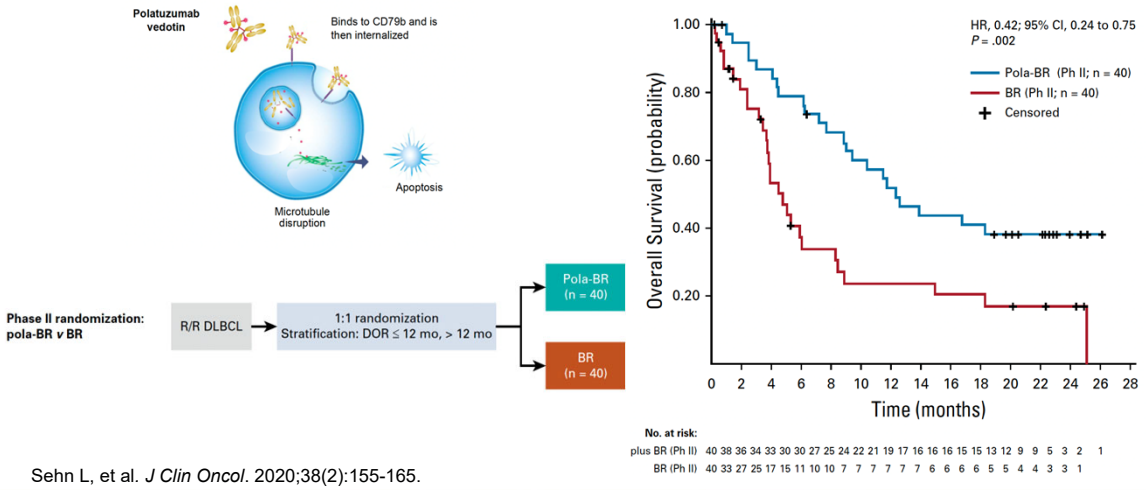
Polatuzumab in R/R LBCL



Sehn L, et al. *J Clin Oncol*. 2020;38(2):155-165.

We heard a little bit about this from Dr. Leonard in his talk, including the POLARIX trial. Polatuzumab vedotin is an anti-CD-79B antibody drug conjugate, and was originally improved based on a trial led by Dr. Laurie Sehn and colleagues randomizing patients to receive either polatuzumab with bendamustine rituximab, or bendamustine rituximab alone, 40 patients per arm, and these were the results.

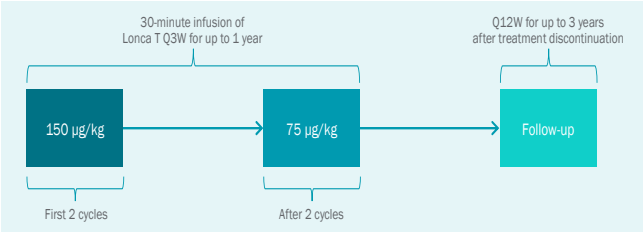
Polatuzumab in R/R LBCL



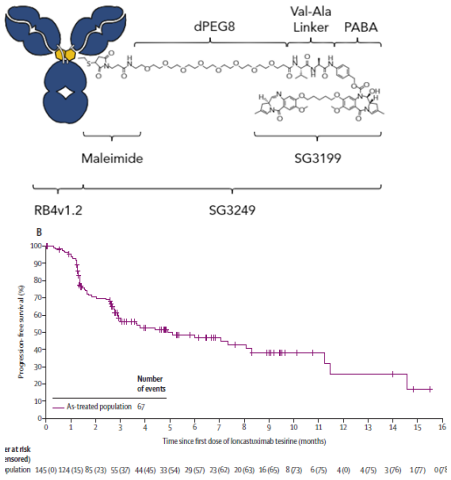
Sehn L, et al. *J Clin Oncol*. 2020;38(2):155-165.

A dramatic difference between the two groups for progression free survival and notably for overall survival leading to additional studies including that POLARIX trial. This is certainly a live option for patients in third-line therapy today.

LOTIS-2: Loncastuximab Tesirine in R/R DLBCL



- Lonca T comprises a humanized anti-CD19 antibody conjugated to a potent PBD dimer toxin



PBD=pyrrolobenzodiazepine
Caimi PF, et al. ASH 2020. Abstract 1183.

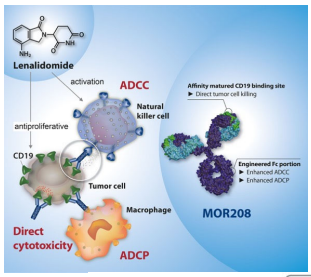
Loncastuximab tesirine is another antibody drug conjugate recently approved by the FDA for third-line plus for diffuse large B-cell lymphoma targeting CD19.

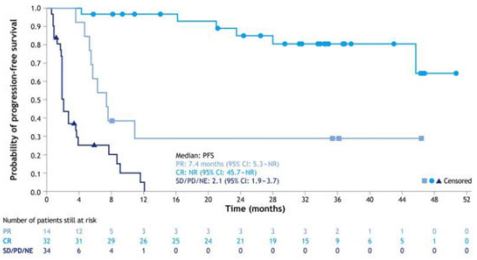
Here, there are two cycles of a higher dose, a loading dose, if you will, and then patients drop down to 75 micrograms per kilogram and can continue therapy for up to 3 years based upon the schedule shown here on the screen.

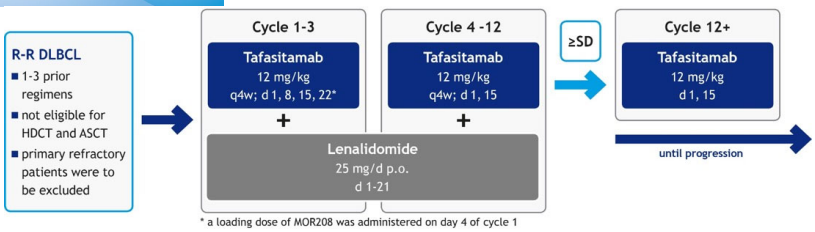
On the LOTIS-2 trial, the overall response rate was around 48%, complete response rate of around 25%. You can see this unique dimer that's added, the PBD (pyrrolobenzodiazepine) dimer toxin. This is not something that we typically see with the other antibody drug conjugates often using MMAE technology. PBD is a unique dimer which has unique toxicities to learn about if you're going to use this therapy.

The reason you may want to use it is the responses do appear to be quite promising, with many patients deriving benefit lasting more than six months.

L-Mind: Tafasitamab + Lenalidomide in R/R LBCL







Salles G, et al. *Lancet Oncol*. 2020;21(7):978-988.; Duell J, et al. *Haematologica*. 2021;106(9):2417-2426.

Lastly, not an antibody drug conjugate, but one I wanted to mention nonetheless, because it's also a CD19 targeting agent, tafasitamab.

This in combination with lenalidomide, the immunomodulatory drug, has been evaluated in the L-MIND trial, which led to FDA approval in second-line plus therapy for diffuse large B-cell lymphoma. Here the overall response rate was 60% with a complete response rate of 40 plus percent in patients with heavily pretreated disease.

The schema is shown here on the slide, and with an update to the responses, we now are seeing patients who've achieved a complete response, having a median duration of response not yet reached, but many patients are now more than three years out without a progression event, implying the possibility that some of these patients may not have disease anymore, that perhaps they could in fact be cured, not with a cell therapy-based approach, which would be a remarkable advance for our field.

Conclusion

- An incredible number of promising therapies in development or approved
- How to sequence?
- How to select?
- How to combine?

In conclusion, we have a great problem. We have an incredible number of promising therapies in development or approved, and now our challenge in the next era is how to sequence these therapies, how to select patients for a specific therapy, and I would argue the biggest challenge is how to successfully combine these treatments going forward and to change practice for our patients. Thank you very much for your attention.

Improving the Spectrum of Care for Patients with Diffuse Large B-cell Lymphoma

Dr. Jim Armitage: Jason. Thank you for that wonderful concise, clear presentation. I have a few questions for you.

I'm just going to run through several of them. I'm actually really quite interested to hear what you think. Outside of a study, do you have a particular approach that would match up to a certain group of patients, either biologically or clinically? Do you have in your mind, now we're talking of salvage therapy, which group for which patients, what groups require a particular approach?

Dr. Jason Westin: I think to me the salvage approach that would line up with a particular group are in those chemorefractory patients, those that never responded to initial treatment. We now know with these large randomized trials that more chemotherapy is throwing good money after bad. It doesn't work. If a patient is refractory to frontline treatment, they will very likely not respond to second-line chemotherapy. That's a big unmet need because not a lot of our patients will have access to CAR T-cells quite yet. CAR T-cells are administered in specialized centers.

Although I argue that is the new standard of care for those patients, for patients who can't reach a CAR T-cell or have a difficult time doing so, we clearly need to have better options than platinum-based chemotherapy for those that are refractory to initial disease. The clinical trial I just showed for L-MIND looking at tafasitamab lenalidomide actually did not enroll patients who were primary refractory. That was an eligibility exclusion.

We don't yet have a great standard option in second-line for those who are not going to be able to get to a transplant despite intention because of being refractory to chemotherapy. I think some of the agents we just talked about, the new promising ones, including the bispecifics, have great potential to expand our ability to treat those patients with a targeted approach.

Dr. Jim Armitage: Thank you. Are bispecifics going to replace CAR T-cell therapy?

Dr. Jason Westin: I don't think that they will. CAR T-cells have a durable response, which is now evaluated out as long as five years, showing that about 30% of patients who receive a CAR T-cell for what was a refractory patient population are likely cured, in my words, at least, cured with their diffuse large B-cell lymphoma. Now, 30% is not as good as we'd like, but many of those patients would not have been alive anywhere close to five years if CAR T-cells didn't exist.

Dr. Jason Westin: Bispecific therapies have some advantages in that they're off the shelf and the toxicities may be a little bit less or a little bit more predictable, but they are still requiring an expert management strategy of how to deal with cytokine release syndrome. That may be a challenge in the community for this to have a widespread adoption, plus we don't yet know if patients who achieve a complete response to a bispecific are eradicated from their disease.

Is their disease eradicated or is it just suppressed in the way that we've seen with some other targeted therapies and may eventually relapse? If we had a scenario where we had a plateau for a bispecific treatment that was in the ballpark of what we see for CAR T-cells, then perhaps we would see a shift. I think for now, knowing that patients can be cured with CAR T-cells, that's a pretty strong argument that if you had them both on the table and had to pick one, most people who have access to both would say that CAR T-cells would be the preferred option.

Bispecifics perhaps fix that by jumping ahead of CAR T-cells and moving in their frontline therapy, and perhaps that could be a reality in the coming years, but I think as of now the durability of response would be the deciding factor for me.

Dr. Jim Armitage: All right. Showing that you don't forget about old things, which one of these patients that you treat with one of these new therapies should also get radiotherapy?

Dr. Jason Westin: We think that radiotherapy still plays a role especially for patients that have very bulky disease. There's always a concern that the tumor penetrance of the treatment is not great if there's necrosis or poor blood flow.

I still in my practice do use radiotherapy for people that have a bulky site of disease. Obviously, the other considerations would be for someone has a testicular diffuse large B-cell lymphoma to radiate the contralateral testicle, and then select situations for somebody who had a mediastinal large B-cell lymphoma and received a CHOP-based regimen. Sometimes we use radiotherapy for folks who are going for CAR T-cells as a bridging strategy. Radiation treatment still does play an active role in large B-cell lymphoma here in 2022.

Dr. Jim Armitage: Finally Jason, are there any people today, you just reviewed a bunch of hopeful approaches, who your recommendation for palliative care rather than going this route?

Improving the Spectrum of Care for Patients with Diffuse Large B-cell Lymphoma

Dr. Jason Westin: Well, certainly, the patients who are very elderly, very frail, very unfit it's a difficult situation for newly diagnosed disease and for relapse disease. Many of these treatments appear very promising, but they do have the potential for side effects. There's a population of frontline patients who based upon geriatric assessments, may not be fit to receive chemotherapy.

There's been a lot of clinical trials trying to evaluate that space, taking some of these great therapies from relapsed disease settings and trying to evaluate them in frontline therapy, including bispecifics or antibody-drug conjugates, looking specifically at that "chemo unfit or chemo frail patient population."

As of now, some of those patients might be recommended for palliative care. I don't think that'll be the case in the coming years if we can use some of these relatively non-toxic targeted therapies and achieve good long-term responses.

Dr. Jim Armitage: Wonderful presentation and a fun discussion. I want to thank all of our listeners and watchers to this program. I hope that you gain from it like I did. Thank you very much.