Dr. James Armitage: Welcome to today's program. My name is Jim Armitage, and I'm a professor of medicine at the University of Nebraska Medical Center. Today I have the great pleasure to be joined by Dr. Andy Zelenetz, who is from Memorial Sloan Kettering, and a professor of medicine at Weill Cornell Medical College.

Faculty Disclosures

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

Dr. Andrew Zelenetz has relevant financial relationships related to consulting from AbbVie Inc., Adaptive Biotechnologies, AstraZeneca, BeiGene, Bristol-Myers Squibb Company, Celgene Corporation – A Bristol-Myers Squibb Company, Genentech - A Member of the Roche Group, Gilead, Janssen Pharmaceuticals, Inc., Juno Therapeutics, Kite Pharma, MEI Pharma Inc., MorphoSys, and Novartis AG, and has received research grant(s) from BeiGene, Genentech - A Member of the Roche Group, and MEI Pharma. He is a Data Monitoring Committee (DMC) member at Celgene Corporation – A Bristol-Myers Squibb Company and Juno.

These are our disclosures.

Learning Objectives

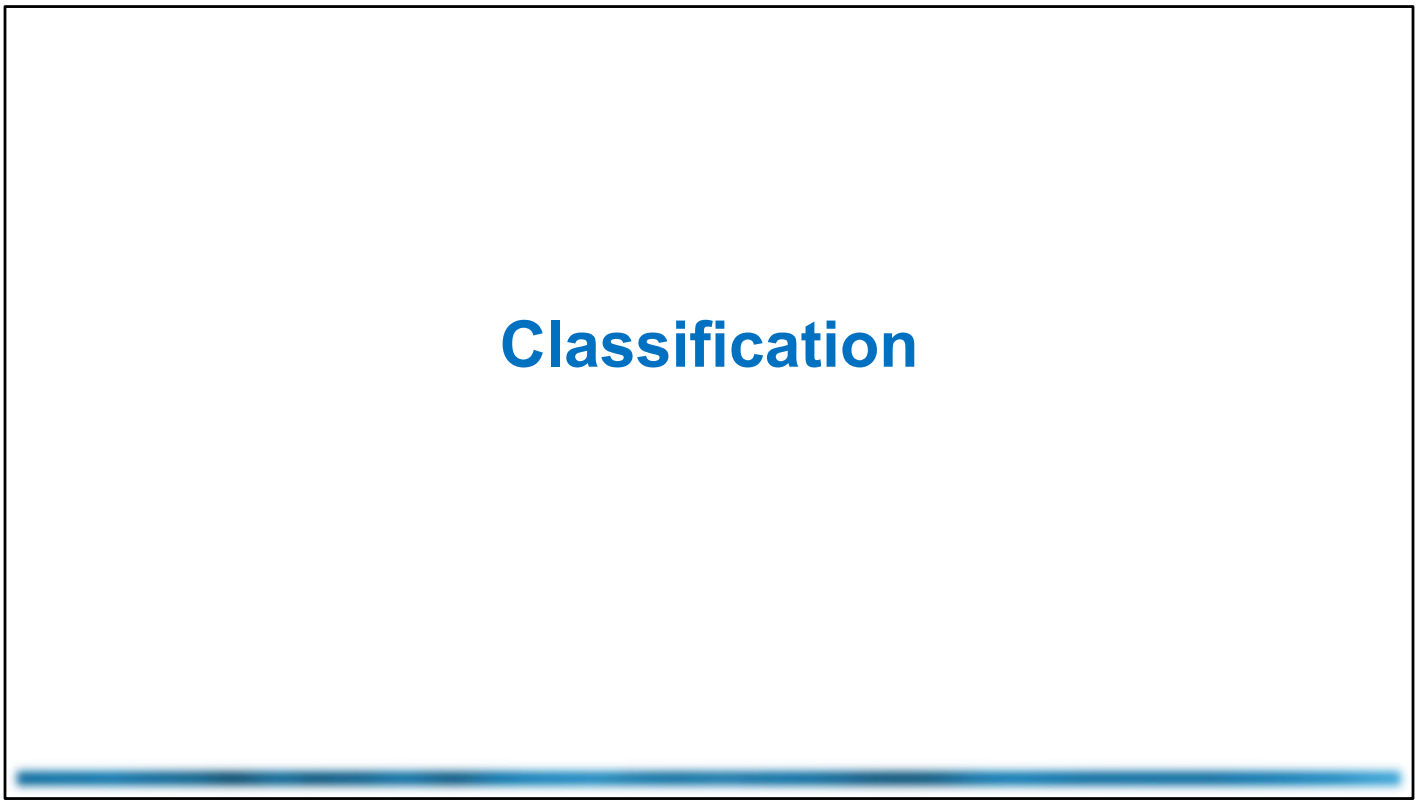
- Discuss key data from recent publications and conferences on emerging frontline approaches for the treatment of DLBCL
- Describe current and/or potential practice implications

All right. Today's program is going to address directions on the frontline treatment of patients with the most common lymphoma, diffuse large B-cell lymphoma.

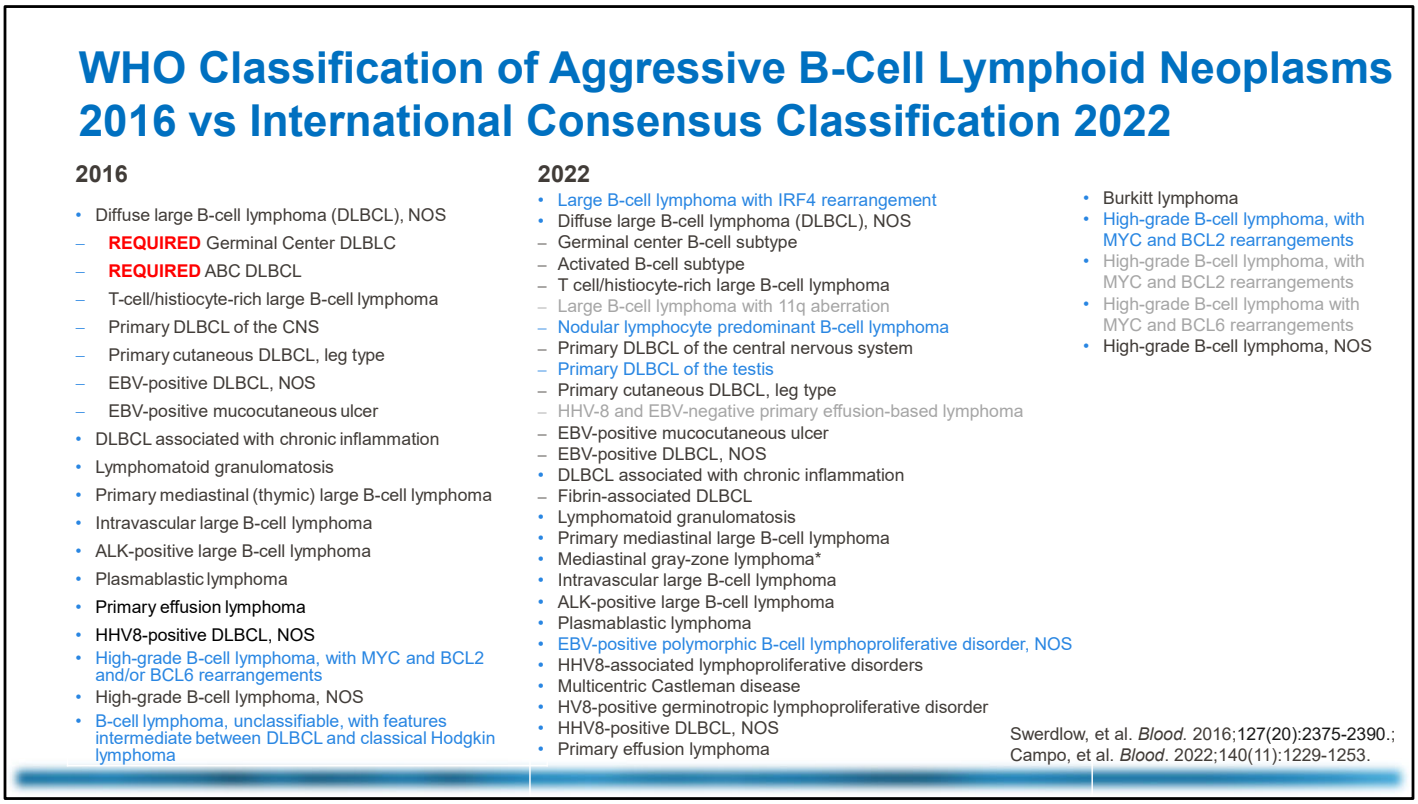
In this presentation, Dr. Zelenetz is going to discuss key data from recent publications and conferences, and emerging frontline approaches for the treatment of diffuse large B-cell lymphoma. He will discuss with us current and potential practice implications.

After that's over, Andy and I will talk for a little bit about some of the issues that we both think are interesting and important, and that you might want to hear his opinion about. Right now, I'm going to turn the presentation over to Dr. Andy Zelenetz.

Dr. Andrew Zelenetz: Thank you, Dr. Armitage. Thank you for the invitation to join you today.



Dr. Andrew Zelenetz: If we're going to talk about large cell lymphoma, I think an appropriate place to start is to discuss classification, particularly since we've recently updated the classification of non-Hodgkin lymphoma.

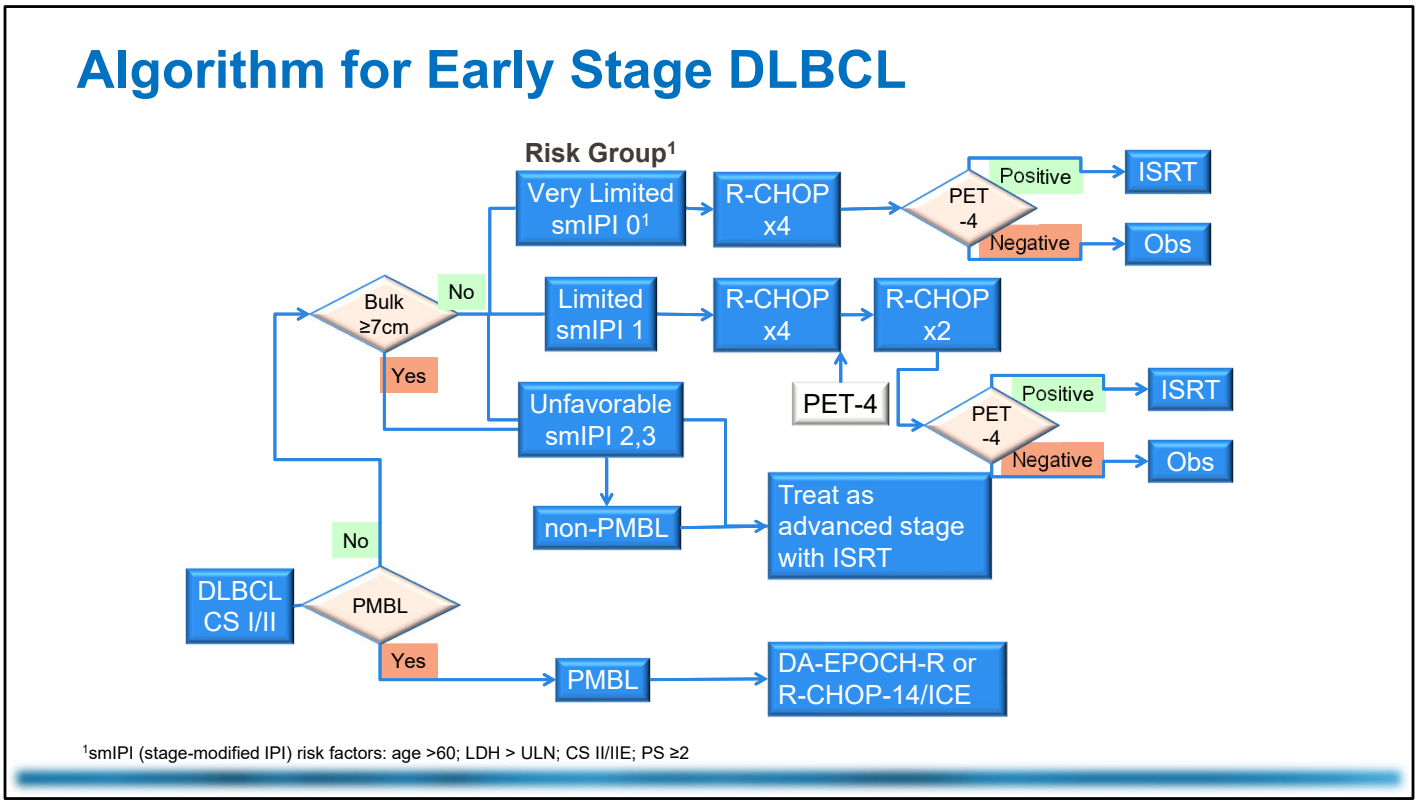


The WHO classification of lymphoid neoplasms was last updated in 2016. It has currently been undergoing an update. Unfortunately, we have a split in the updated classification. There is the International Consensus Classification that was recently published in *Blood*, which I show here. It's beyond the scope of today's discussion to discuss the differences between this International Consensus Classification and the new proposed WHO classification. They're not dramatically different. One of the things that you can see is that there are a number of new entities.

This is the aggressive large cell lymphoma. This is not all lymphomas. The entities entered in blue are considered provisional entities. One thing I do point out is that lymphocyte-predominant Hodgkin lymphoma has now been renamed to nodular lymphocyte-predominant B-cell lymphoma because it actually has no relationship to classical Hodgkin lymphoma. These are the entities. You can see that there's a wide variety of different aggressive lymphomas, so the fact that outcomes are heterogeneous are not that surprising.

First-line Therapy

Let's talk about first-line therapy. That's our topic today.



I'm not going to spend a lot of time on early stage disease. The early stage algorithm is pretty straightforward. First, you want to know is it PMBL or not, because if it's PMBL, then the treatment is going to be dose-adjusted EPOCH. At Memorial, we use a sequential regimen of R-CHOP, followed by ICE or R-ICE. The outcome of these two regimens is identical. If it's large cell lymphoma and it's not PMBL, then we want to know whether there's bulk, because if there's no bulk, patients can be treated without radiation therapy, particularly if their PET scan is negative.

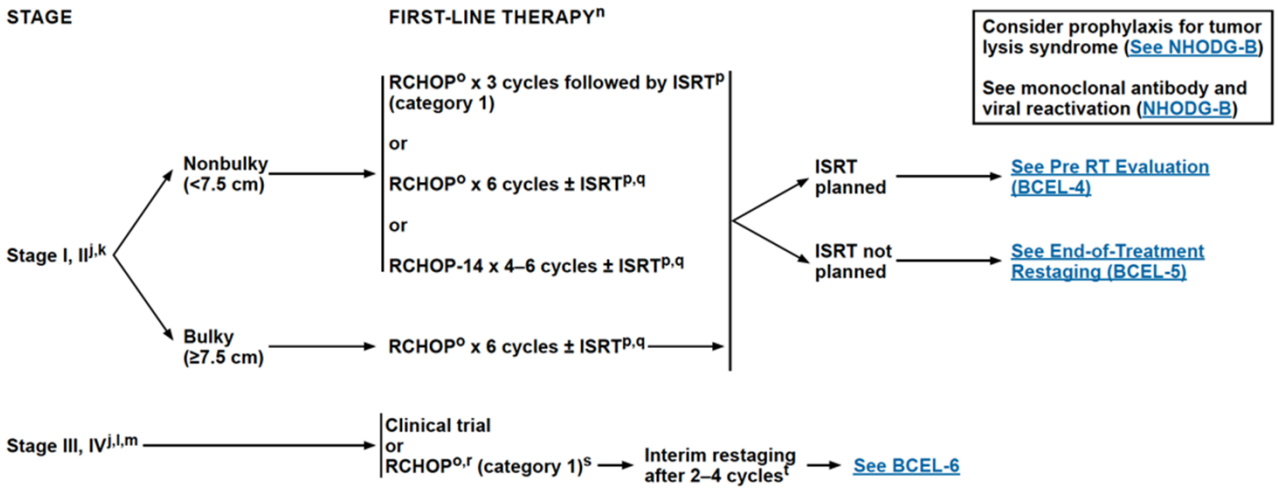
After treatment, observation is appropriate. If the PET scan is positive, we're going to do involved site radiation. For patients who have slightly less favorable disease, they are older age, their LDH is elevated, they have stage two disease, not stage one disease, their performance status is two or greater, then we're going to treat those patients with four cycles of R-CHOP, get a PET scan, do two more cycles of R-CHOP. Then again, based on that PET 4, if the PET four is positive, we're going to consolidate with radiation, but we can avoid the radiation if the PET 4 is negative.

For patients with bulky disease, or have multiple unfavorable risk factors, those patients should be treated as if they have advanced stage disease, though with involved site radiation therapy.

DLBCL: Advanced Stage

Let's talk about the more common presentation, that is with advanced stage disease.

NCCN Guideline for 1L DLBCL



Zelenetz, et al. *J Natl Compr Canc Netw*. 2019;17(6):650-661.

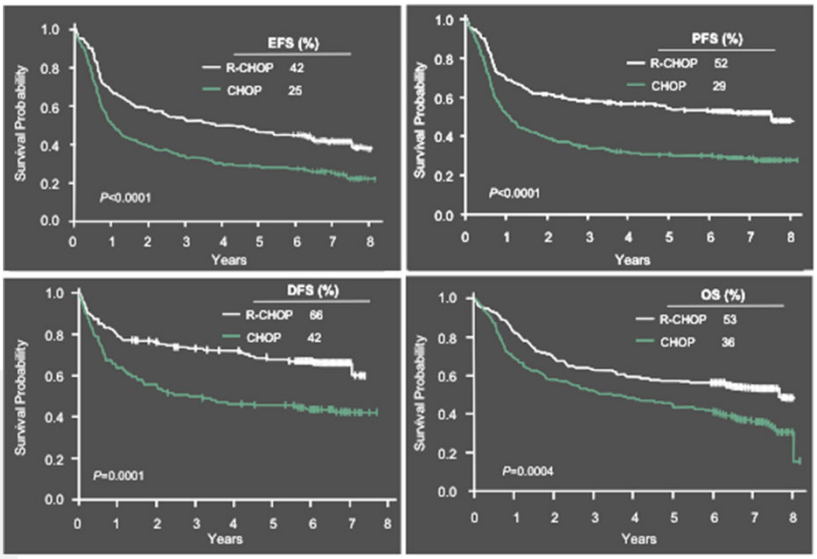
This is the NCCN guidelines, and this is about the simplest NCCN guideline we have. Advanced stage disease, give R-CHOP.

Where does this come from?

International Standard of Care: R-CHOP

- Rituximab 375 mg/m^2 day 1
- Cyclophosphamide 750 mg/m^2 day 1
- Doxorubicin 50 mg/m^2 day 1
- Vincristine 1.4 mg/m^2 day 1 (2 mg max)
- Prednisone 40 mg/m^2 (or 100 mg) daily x 5
  - Age >60 pegfilgrastim 6 mg SQ day 2
  - Original Gela LNH 98-5 confirmed in multiple studies

- Caveat: this standard does not apply to
  - PMBL
  - HGL with translocation of MYC and BCL2 and/or BCL6
  - PCNS



Coiffier, et al. ASCO 2007. Abstract 8009.

This comes from the original GELA study, which has been confirmed in multiple randomized studies, but with very long-term follow-up.

We know that R-CHOP provides superior event-free survival and long-term overall survival advantage. I'm always amazed by this curve because the curves continue to separate even many years after the completion of therapy. This is the international standard of care. It's good. Clearly, we improved the outcome of patients. We're curing close to 60% of patients with advanced stage large cell lymphoma, but 40% of patients aren't being cured. Obviously, we want to try to improve things.

Improving on R-CHOP-21: Alternative Dosing and Regimens

Investigational Arm	PFS HR (*P*-value)	OS HR (*P*-value)	Comments	Ref.
R-CHOP	NR (0.571)	NR (0.257), IPI 1±bulk		Pfreundschuh, et al. *Lancet Oncol.* 2011;12:1013-1022.
R-ACVBP	0.48 (0.0015)	0.44 (0.0071)	Age 18-59, IPI 1	Récher, et al. *Lancet.* 2011;378:1858-1867.
R-CHOP-14	0.99 (0.8983)	0.96 (0.7487)		Delarue, et al. *Lancet Oncol.* 2013;14:525-533.
	0.94 (0.5907)	0.90 (0.3763)		Cunningham, et al. *Lancet.* 2013;381:1817-1826.
G-CHOP	0.92 (0.3868)	1.00 (0.9982)		Vitolo, et al. *J Clin Oncol.* 2017;35:3529-3537.
DA-EPOCH-R	0.93 (0.6519)	1.09 (0.6414)		Bartlett, et al. *J Clin Oncol.* 2019;37(21):1790-1799.

How do we do that? We've tried alternative chemotherapy.

We've tried adding etoposide to CHOP. That did not improve either progression or your overall survival. We tried an alternative chemotherapy program, RACVBP, which is actually sequential chemo immunotherapy program. That also includes cytarabine and anti-phosphamide. Interestingly, this is one of the most ignored results because there was not only a progression-free survival, but an overall survival advantage in this prospective randomized trial. However, there's a major caveat. Only patients 18 to 59 were included, and only patients with an international prognostic score of one were included.

This is why this has never really been adopted. There's also this concern that it includes vindesine, though most patients, actually even in France, were not treated with a vindesine, but were treated with vincristine. R-CHOP-14, so let's just give it more frequently. Unfortunately, two different studies, negative for both progression-free and overall survival. Let's change the antibody. Let's give obinutuzumab rather than rituximab. Again, no difference. Dose-adjusted EPOCH. What was thought to be a very promising regimen, prospective randomized trial from the alliance, no difference in progression-free or overall survival.

Improving on R-CHOP-21: Maintenance After Induction with R-CHOP-like Therapy

If we can't improve by rearranging the deck chairs or adding a drug. What about adding maintenance? That seems to have been beneficial in indolent lymphoma and mantle cell lymphoma, so what about large cell lymphoma?

Improving on R-CHOP-21: Maintenance

Investigational Arm	PFS HR (*P*-value)	OS HR (*P*-value)	Comments	Ref.
Rituximab	0.73 (0.27)	1.28 (0.48)	R-CHOP treated subset age >60, PR/CR randomized	Habermann, et al. *J Clin Oncol.* 2006;24:3121-3127.
Rituximab	0.62 (0.0120)	0.81 (0.4145)	Age >18, CR or CRu	Jaeger, et al. *Haematologica.* 2015;100:955-963
Enzastaurin	EFS 0.92 (NS)	1.04 (NS)	Stage II bulky, III/IV, IPI 3-5, CR or Cru	Crump, et al. *J Clin Oncol.* 2016;34:2484-2492.
Lenalidomide	0.708 (0.0135)	1.218 (0.2640)	Age 60-80; PR and CR patients randomized	Thieblemont, et al. *J Clin Oncol.* 2017;35:2473-2481.
Everolimus	0.92 (0.276)	0.75 (NS)	Stage II bulky, III/IV, IPI 3-5, CR	Witzig, et al. *Ann Oncol*. 2018; 29:707-714.

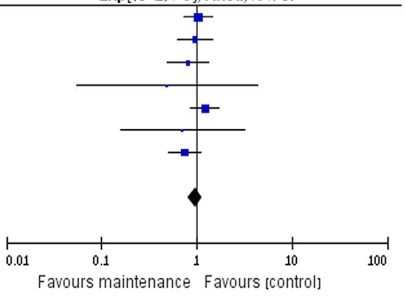
It has been studied. Rituximab has been used in a couple of different trials. In the US Intergroup trial, there was no progression-free overall survival benefit for the addition of rituximab maintenance. This was somewhat of a difficult trial because of interaction between the arms, but still statistically no difference between the two treatments.

There was a European study that looked at rituximab maintenance. There was a statistically significant improvement with a 32% reduction in risk of progression. Unfortunately, this did not translate to a statistically significant difference in overall survival. Enzastaurin has been looked at based on the work of Margaret Shipp, and that was negative. Lenalidomide, like the European rituximab study, was positive for progression-free survival, but there was actually close to a trend for a negative overall survival. So, a survival disadvantage, and that was because these were older patients and there was a lot of cumulative toxicity from the lenalidomide maintenance. Everolimus has been tested. There are a couple of trials that suggest some may be improvement in progression-free. What about doing a meta-analysis, and that has been done.

Improving on R-CHOP-21: Meta-analysis of Maintenance After R-CHOP

Study or Subgroup	Maintenance Events	Maintenance Total	Observation/Placebo Events	Observation/Placebo Total	O-E	Variance	Weight	Peto Odds Ratio Exp[(O-E) / V], Fixed, 95% CI
Crump et al 2016	0	0	0	0	1.29	32.88	25.3%	1.04 [0.74, 1.46]
Habermann 2006	0	0	0	0	-0.88	21.47	16.5%	0.96 [0.63, 1.47]
Jaeger et at 2015	0	0	0	0	-3.2	15.18	11.7%	0.81 [0.49, 1.34]
Li et at 2010	0	0	0	0	-0.58	0.8	0.6%	0.48 [0.05, 4.33]
Thieblemont et at 2016	0	0	0	0	6.32	32.04	24.6%	1.22 [0.86, 1.72]
Witzens-Harig et al 2015	0	0	0	0	-0.59	1.71	1.3%	0.71 [0.16, 3.17]
Witzig 2016	0	0	0	0	-7.48	26.01	20.0%	0.75 [0.51, 1.10]
Total (95% CI)		0		0			100.0%	0.96 [0.81, 1.14]
Total events	0		0					

Heterogeneity: $Chi^2 = 4.58$, $df = 6$ ($P = 0.60$); $I^2 = 0\%$
Test for overall effect: $Z = 0.45$ ($P = 0.65$)



Rozenthal, et al. *Hematol Oncol.* 2019;37:27-34,

If we look at a meta-analysis of maintenance after R-CHOP for large cell lymphoma, unfortunately there's no suggestion of a improvement in overall survival.

Improving on R-CHOP-21: R-CHOP + X

If you can't beat them, what about joining them?

Improving on R-CHOP-21: R-CHOP + X

Investigational Arm (X)	PFS HR (*P*-value)	OS HR (*P*-value)	Comments	Ref
Bortezomib	0.82 (0.160)	0.85 (0.400)	Randomization after cycle 1 R-CHOP	Davies, et al. *Lancet Oncol.* 2019;20(5):649-662.
Ibrutinib	0.934 (0.5906)	0.991 (0.9593)	OS benefit for patients <60	Younes, et al. *J Clin Oncol.* 2019;37(15):1285-1295.
Lenalidomide	NS	NR		ICML 2019
	0.66 (0.03 one-sided)	0.69 (0.08 one-sided)	ECOG 1412	ICML 2019
Polatuzumab	0.73 (0.02)	0.94 (0.75 one-sided)	POLARIX ~6% improvement in PFS @ 2y	Tilly, et al. *N Engl J Med.* 2022;386:351-363.
Venetoclax			Phase I/II Only	Zelenetz, et al. *Blood.* 2019.; Morschhauser, et al. *Blood.* 2020.

Let's take R-CHOP-21, but add something to it. This has been a well-studied approach. Bortezomib, based on molecular studies, should have been superior for patients with activated B-cell tumors. In this trial, patients received one cycle of R-CHOP while their tumors were tested. Then if they were activated B-cell, they were randomized to receive bortezomib or not. Unfortunately, no difference in progression-free or overall survival.

The PHOENIX trial took a different approach. Everyone was tested before they went on study, but based on the Hans algorithm. Then they were tested molecularly. This trial was negative for both progression-free and overall survival. However, there was an unplanned subset analysis, and I'm going to talk more about this in a moment, that there was a clear overall survival advantage for patients under the age of 60. The question was whether it was a biological basis or toxicity in older patients. I'll give you my takeaway, I think it's toxicity, and I'll show you some data. Lenalidomide also was supposed to be preferential for non-germinal center tumors.

A large randomized study showed no difference in progression-free overall survival. In a slightly different design, the ECOG did a phase two randomized study where they took all comers and they showed a small advantage in progression-free survival with a p value of 0.03. I caution that this was a one-sided p value, so if you use a two-sided p value, it's 0.06 and not statistically significant. Unfortunately, it did not translate to an overall survival advantage. The most recent addition was the addition of polatuzumab to CHOP.

Improving on R-CHOP-21: R-CHOP + X (continued)

Investigational Arm (X)	PFS HR (*P*-value)	OS HR (*P*-value)	Comments	Ref
Bortezomib	0.82 (0.160)	0.85 (0.400)	Randomization after cycle 1 R-CHOP	Davies, et al. *Lancet Oncol.* 2019;20(5):649-662.
Ibrutinib	0.934 (0.5906)	0.991 (0.9593)	OS benefit for patients <60	Younes, et al. *J Clin Oncol.* 2019;37(15):1285-1295.
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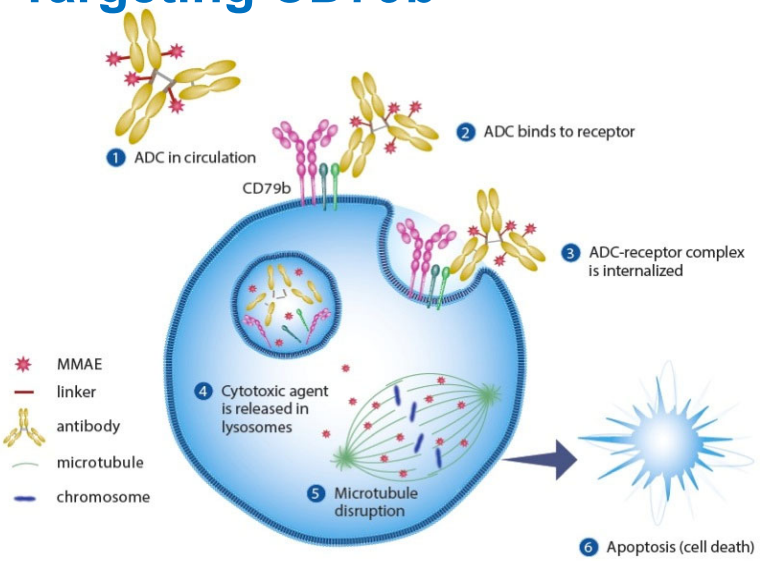
Venetoclax			Phase I/II Only	Zelenetz, et al. *Blood.* 2019.; Morschhauser, et al. *Blood.* 2020.

There was a difference in progression-free survival that was statistically significant, meeting the primary endpoint. The study is still relatively early, so no difference in overall survival to date. Then there was a phase ½ study in which venetoclax was added to R-CHOP. When done as a matched case control to historical data from the GOYA study, we showed that there was an overall survival advantage of adding venetoclax in BCL2-expressing tumors, though this needs to be confirmed in a prospective randomized study.

Polatuzumab Vedotin is an Antibody Drug Conjugate Targeting CD79b



Dornan D, et al. *Blood.* 2009;114:2721-2729.; Polson AG, et al. *Expert Opin Invest Drugs.* 2011;20:75-85.; Doronina SO, et al. *Nat Biotechnol.* 2003;21:778-784; Tilly H, et al. *Lancet Oncol.* 2019;20:998-1010.

Let's talk about the POLARIX study, which was a positive study. Polatuzumab is a antibody-drug conjugate. It targets the B cell protein called CD79B. It delivers auristatin, or MMAE to the tumor. It binds to the CD79B protein. It's endocytosed. The drug is then released from the antibody, and it is a very potent microtubular disruption.

BR ± Polatuzumab Vedotin for Relapsed/Refractory DLBLC

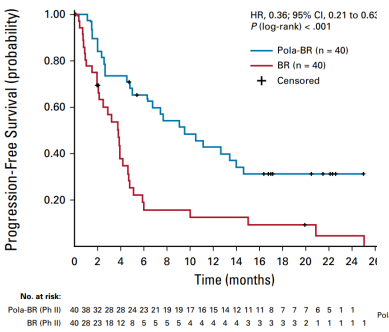
Results (Pola-BR v BR):

- CR rate (40.0% v 17.5%)
- PFS (median, 9.5 v 3.7 months)
- OS (median, 12.4 v 4.7 months)
- Median follow-up 22.3 months

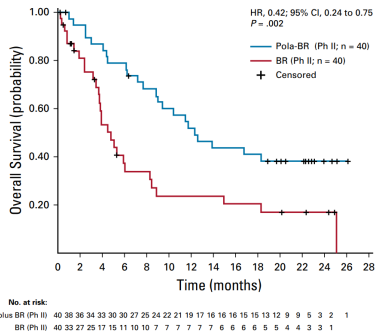
Pola-BG and pola-BR had a tolerable safety profile:

- Grade 3-4 neutropenia (46.2% v 33.3%)
- Similar grade 3-4 infections (23.1% v 20.5%)
- Peripheral neuropathy associated with polatuzumab vedotin (43.6% of patients) was grade 1-2 and resolved in most patients.

PFS



OS

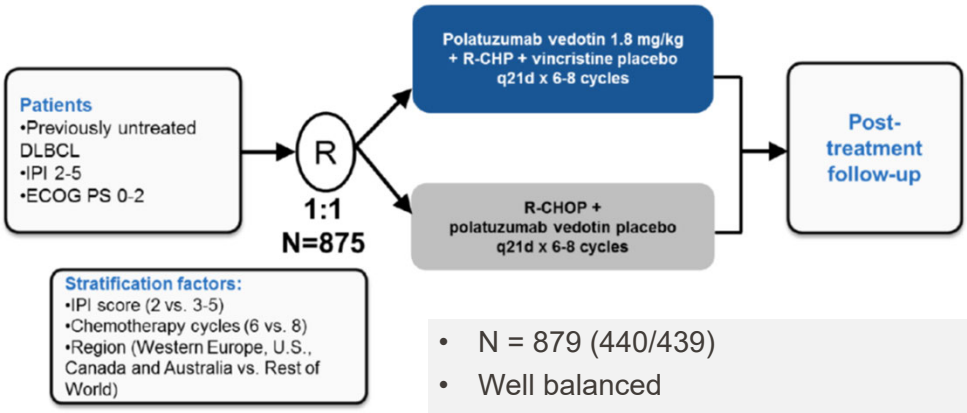


Sehn LH, et al. *J Clin Oncol.* 2020;38:155-165.

This was initially studied in relapsed/refractory disease with bendamustine or rituximab with or without polatuzumab, and there was both a progression-free and overall survival advantage. This actually led to the approval of polatuzumab for the relapsed/ refractory setting.

POLARIX: R-CHOP vs R-CHP+ Polatuzumab Vedotin in First-line DLBLC

Randomized and double-blind international phase 3 trial

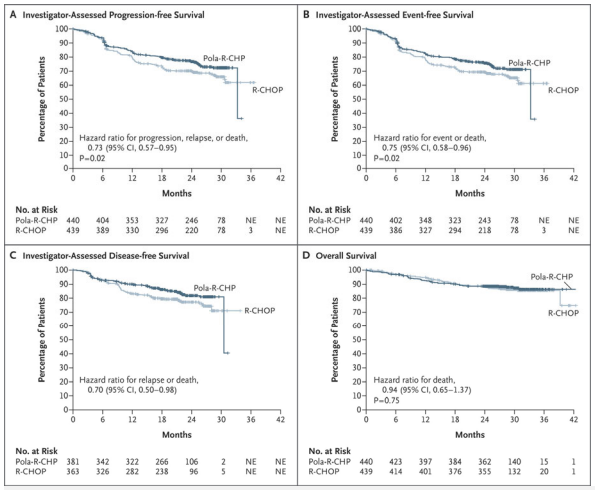


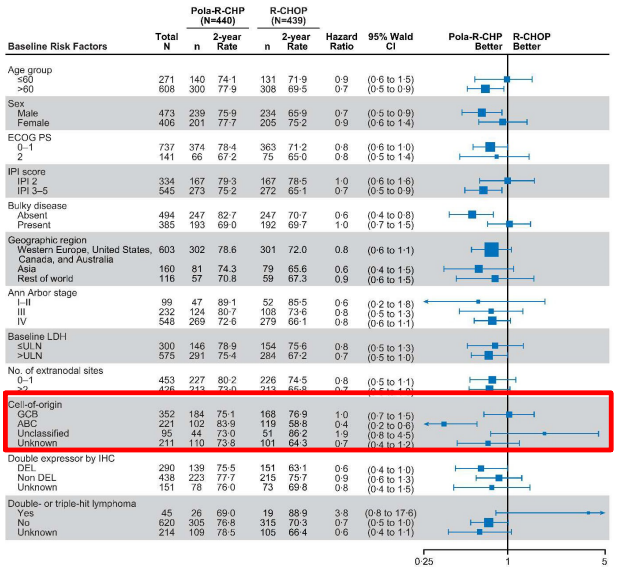
- N = 879 (440/439)
- Well balanced
- Med FU = 28.2 m
- **Primary endpoint**: Investigator-assessed PFS

Tilly F, et al. *N Engl J Med*. 2022;386:351-363.

It also led to the upfront study of R-CHOP versus R-CHP polatuzumab, using polatuzumab as a substitute for vincristine because they both have similar mechanisms of action, both are microtubular drugs. A large study with almost 900 patients, well-balanced, and the median follow-up was 28 months at time of publication.

POLARIX: R-CHOP vs R-CHP-Polatuzumab





- **PFS** R-CHP-Pola 76.7% vs. R-CHOP 70.2% at 2 years
  - Stratified hazard ratio for 0.73 by Cox regression; *P*=0.02
- Overall survival at 2 years: 88.7% vs 88.6%
- The safety profile was similar in the two groups

Tilly F, et al. *N Engl J Med*. 2022;386:351-363.

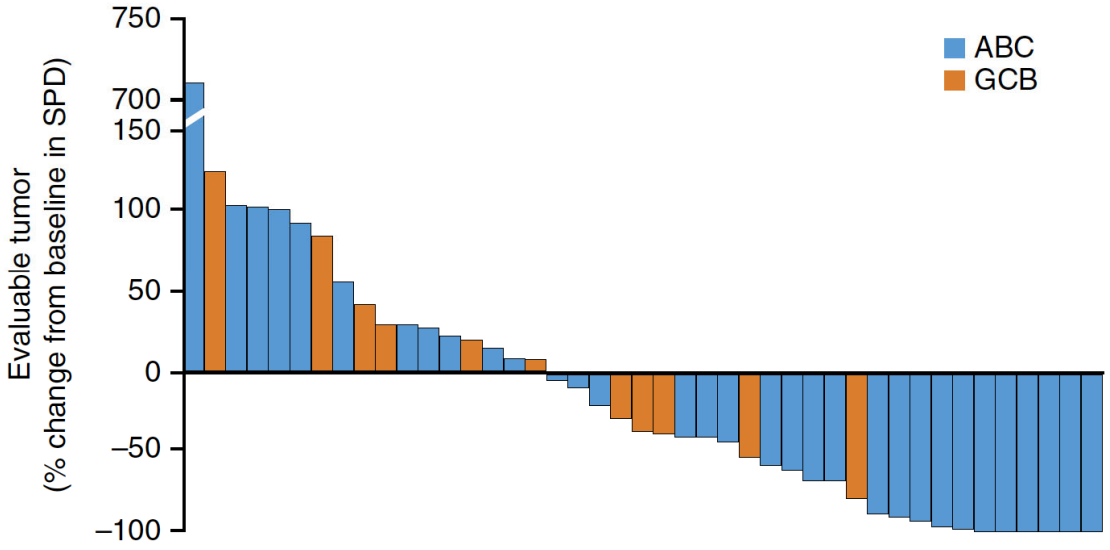
Here are the results. This was the primary endpoint in investigator-assessed progression-free survival showing a 6% improvement in progression-free survival. To date, no improvement in overall survival.

The question will become how do we use this? I think one of the things is, gee, is there a subgroup where there is bigger benefit or not? In the forest plots, there's a very interesting observation, this needs more follow-up, and we need to understand it better. Shockingly, and this was a big surprise to everyone, that all of the benefit of adding polatuzumab to CHOP was for the activated B-cell tumors. Molecularly, I can't explain this, but we actually have several sets of data to suggest that this is probably correct. It seems that all of the benefit is in this subgroup that was unexpected. We would have expected it to benefit everybody, if it had benefited anybody.

Applied Biology: BTKi in DLBCL

I want to turn back a little to the BTK inhibitor because this had such strong biology for it.

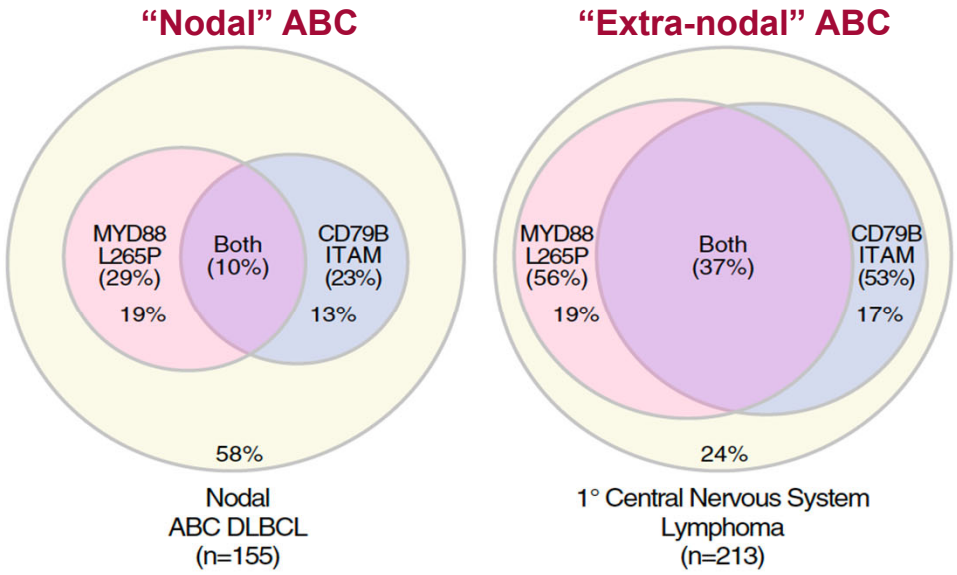
Ibrutinib Activity Specific for ABC DLBCL



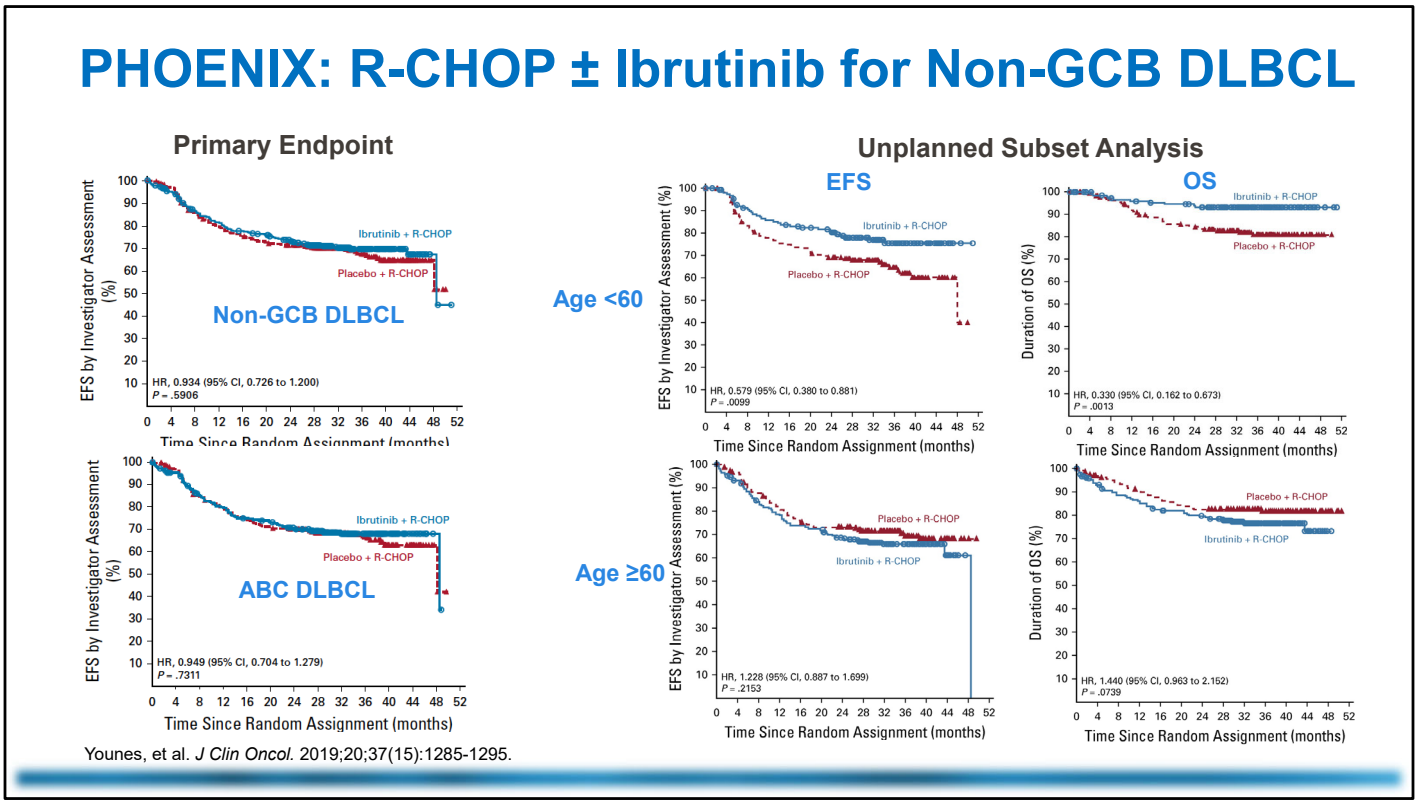
Wilson, et al. *Nat Med.* 2015;21(8):922-926.

We did an initial study. This was a multi-center study. What we found is that single-agent ibrutinib was largely beneficial for people with activated B-cell tumors, and in particular, people who had mutations of CD79D or MYD88.

Some DLBCLs Are Hyper-addicted to BTK Driven Pathway

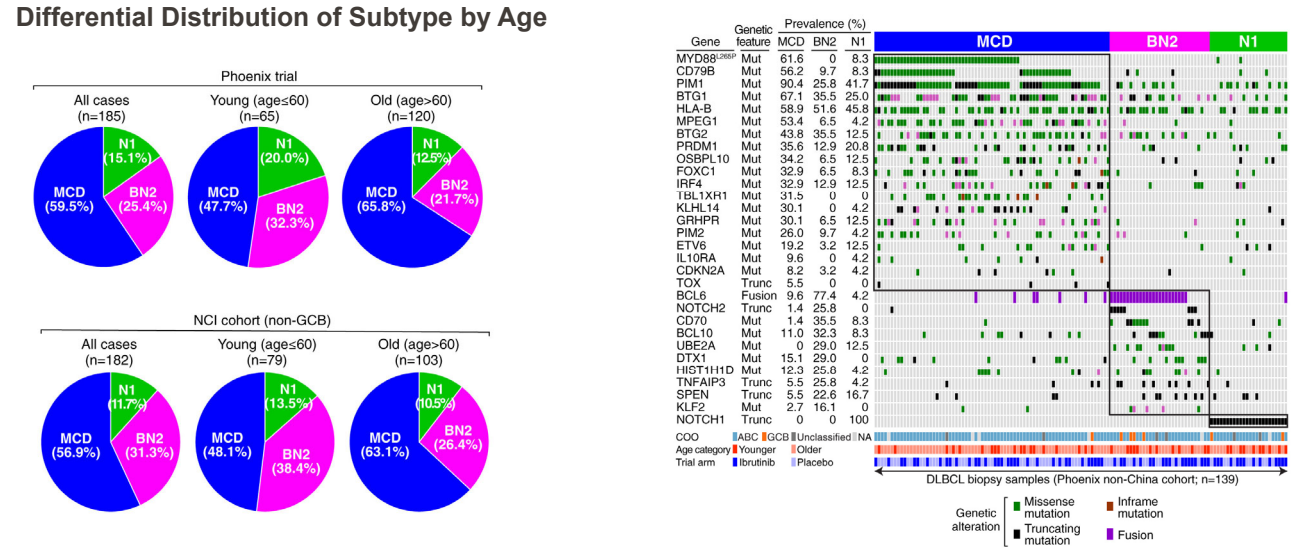


Interestingly, those which we consider hyper-addicted to BTK-driven pathway represent about 10% of nodal-activated B-cell lymphomas, but interestingly, about 37% of primary central nervous system lymphomas, a large proportion of testicular lymphomas, and of diffuse large B-cell lymphoma, leg type, these, somewhat unusual, extranodal lymphomas.



Let's go back to the PHOENIX trial. As I told you, the primary endpoint, which was progression-free survival. There was no difference in non-germinal center of ibrutinib versus placebo. This is by Hans, done by NanoString using gene expression profiling. Again, no difference. Here's that unplanned subset analysis that I mentioned. A big difference in event-free survival, and interestingly, an important difference in overall survival. If we look at the older patients, they actually had a survival decrement. I believe they did have higher toxicity. I actually think that is the explanation. I'll explain why I think that's the explanation in the next couple of slides.

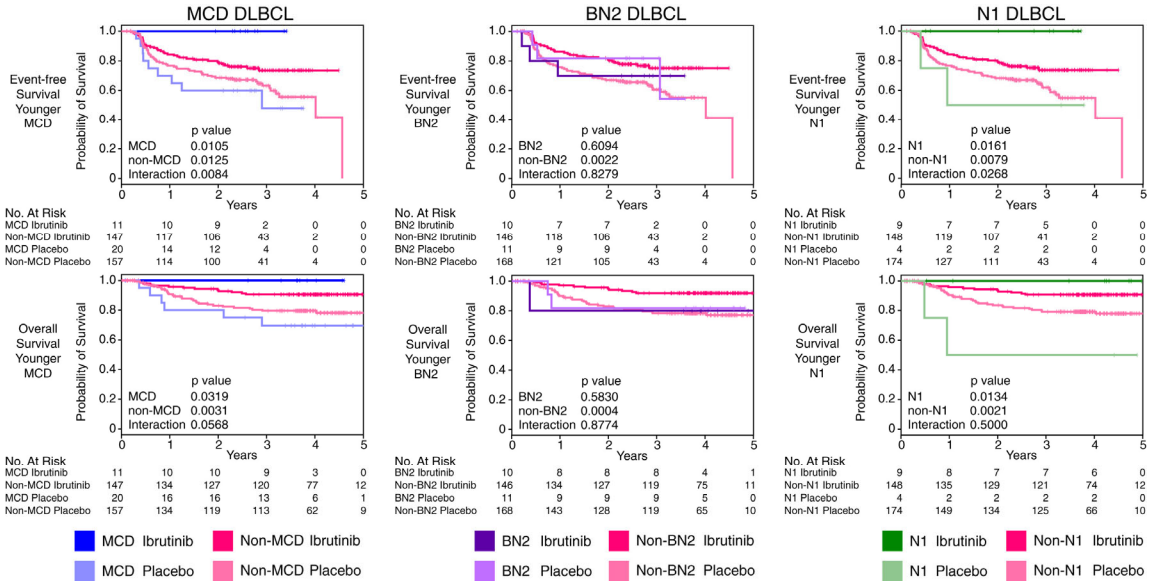
PHOENIX: DLBCL Subtypes



Wilson, et al. *Cancer Cell*. 2021;39:1643-1653.

If we look at the PHOENIX trial and we go back to not just ABC versus GCB, but we dive a little deeper into the molecular subtypes, interestingly, what we find is that younger patients have slightly different distribution of lymphomas than older patients. Older patients are more likely to have MCD tumors, they're less likely to have N1 tumors, and they're a little bit less likely to have the BN2 tumors.

Benefit of Ibrutinib in Younger Patients is Subtype Specific



No benefit in any subset in older patients. Trend for poorer outcome for ibr-R-CHOP in MCD DLBCL

Wilson, et al. *Cancer Cell*. 2021;39:1643-1653.

Now, if we look at the outcome in the PHOENIX trial of these different tumors, these are the younger patients.

MCD, clearly an enormous benefit for adding ibrutinib in the MCD tumors. BN2 tumors, no difference. N1 tumors, again, a big difference in favor of adding ibrutinib in the younger patients.

Both of these groups, MCD and N1 are more frequent in the older patients, but when we do the same analysis for older patients, we actually see a poor outcome for ibrutinib in the MCD patients. I think it's toxicity, not biology. We have to figure out how to give these treatments safer to derive the benefit for older patients.

Revisiting BTKi + R-CHOP in DLBCL

- REMoDL-A: Randomized Phase II
  - R-CHOP cycle 1
  - 1/3 continue with R-CHOP; 2/3 continue with R-CHOP + acalabrutinib
- Response-adapted Acalabrutinib Window Study
  - DLBCL, ABC, GCB, unclassified and HGBL-DH get acalabrutinib x 14 days
  - <25% reduction continue with R-CHOP or DA-EPOCH-R
  - >25% reduction continue with R-CHOP or DA-EPOCH-R with acalabrutinib for 10 days/cycle
- Smart Stop
  - Cohort 1: rituximab (1), acalabrutinib (1-21), lenalidomide (1-10), tafasitamab (1,8, 15) x 4
  - Cohort 2: CR patients from cohort 1 get 2 additional cycles with CHOP x 6
- ESCALADE
  - R-CHOP ± acalabrutinib for non-GCB DLBCL <70 years of age

This has been explored in a number of trials trying to ask the question, how can we incorporate BTK inhibition to improve outcome in large cell lymphoma? Because this is one of the most intriguing leads that we have.

Conclusions

- R-CHOP is the international standard of care in the 1L treatment of DLBCL
- Substitution of polatuzumab-vedotin for vincristine improves PFS by 6%
  - With follow-up to date, there is no impact on OS
  - In the subset analyses, there is the curious observation that the benefit is restricted to the ABC DLBCL
- Though the Phoenix trial was negative, younger patient has superior OS
  - Addition of ibrutinib to R-CHOP was not tolerable in older patients
  - Several trials are underway to determine if there is a subset of ABC DLBCL that should be treated with BTKi

To sum up, R-CHOP remains the international standard of care in first-line treatment of large cell lymphoma.

Substitution of polatuzumab improved progression-free survival by 6%. So far, no difference in overall survival. A curious observation that the benefit is in activated B-cell tumors only.

Though the PHOENIX trial was negative, younger patients had this intriguing benefit for overall survival. There are a number of trials that are undergoing to try to answer this question, how do we integrate BTK inhibitors into activated B-cell tumors to improve outcomes for all patients?

With that, I'll stop. Dr. Armitage, I'm happy to have a discussion about large cell lymphoma.

Dr. James Armitage: Dr. Zelenetz, or Andy since we've been friends for longer than most of the people watching have been alive probably, but anyway, I have some questions for you because I think we have here in you a real-life expert with huge experience in studying this disease. I'm going to ask you some things that I think people would like to know about how you actually do stuff.

You have a patient that for whatever reason, either doesn't want to be on or isn't eligible to be on a clinical trial with a new diffuse large B-cell lymphoma. Would you today take into account that information you so nicely discussed about subgroups in the new classifications, into account when you make a treatment recommendation?

Dr. Andrew Zelenetz: Though we clearly see this benefit on this post hoc analysis of PHOENIX with a big improvement for the MCD tumors and the N1 tumors in younger patients, the problem is we have not yet reduced this to routine clinical determination. To make that diagnosis in real time, in a time frame that's appropriate for clinical care, we're not quite there yet.

Would I take a non-GCB because that's the best we have? Non-GCB by Hans, a younger patient, would I be tempted to include ibrutinib? The answer is yes, I would be tempted to. The problem is I pretty much can't get it approved, because I actually have tried in a number of cases. Most of the time, because the trial was negative, an insurance company is not going to give us access to the drug.

Dr. James Armitage: That's the problem that I anticipated that we ran into, that these drugs are so expensive. If we can't get it paid for, it's a relatively small proportion of patients who could afford to pay for it themselves. Next question. Same thing, how you approach a patient that isn't otherwise going to be on a trial where the treatment would be determined by that. Are there any subgroups other than mediastinal or people with a very, very high case 67, a Burkitt-like proliferative faction, where you would consider either R-EPOCH or the regimen that you all have developed at Memorial as opposed to R-CHOP?

Dr. Andrew Zelenetz: What we call high grade lymphoma with translocation of MIK and BCL2, or MIK and BCL6, those tend to be treated without randomized data, I will point out, with dose-adjusted R-EPOCH, there is not universal consensus that that is the correct approach because of the absence of randomized data. The one group that I treat a little differently and it's based on data that has been reported, and you will see in publication form hopefully soon, that our regimen of R-CHOP times four cycles followed by RICE for three cycles, has been particularly effective for non-GCB diffuse large B-cell lymphoma. In fact, our outcomes in the non-GCB patients are superior with that regimen than they are for germinal center tumors. That's the one group that outside the setting of a clinical trial, I would use our R-CHOP RICE regimen.

Dr. James Armitage: You do it all as an outpatient?

Dr. Andrew Zelenetz: We do the R-CHOP obviously is an outpatient. The ICE is usually we admit for one day, we do part of the ICE as an outpatient, but we do admit for one night simply because the infusional ifosfamide can be tricky as an outpatient.

Dr. James Armitage: Another practical point. As I think you and I do in Hodgkin lymphoma and certain other situations, the interim PET scan has become a really useful tool in a number of things. In a disease where the thing that matters here is the PET scan at the end of therapy, does it make any sense to do interim PETs routinely in patients with diffuse large B-cell lymphoma with the exception that you showed us of localized disease?

Dr. Andrew Zelenetz: This is a controversial area. My opinion is no. We're not going to-- we have no evidence that changing treatment based on interim PET is necessary. We know from prospective data that we published that was biopsy-controlled. We took essentially 200 patients that were on a trial. Every interim-positive PET scan got biopsied. There were 70 positive PET scans, 7 positive biopsies. The positive interim PET did not really predict outcome, and so I actually use the end of treatment PET.

There is an exception, of course there's always an exception. The exception is if someone has largely osseous-based disease that's CT-invisible, then I will get that interim PET, but that's really just to make sure that they're responding to treatment. If someone has CT-occult disease, then those patients should have an interim PET. In terms of the way we use it in Hodgkin lymphoma to make decisions, no, I think an end of treatment PET is adequate.

Dr. James Armitage: I really appreciate you doing all this. I want to pick on you, one last thing. We'll pick your brain one more time. Other than CNS, mediastinal, and testicular, are there other primary sites that you think that people listening to you today should consider an alternative approach?

Dr. Andrew Zelenetz: The diffuse large B-cell lymphoma leg type has a poor outcome. There's a high risk of CNS involvement. They are like testicular and CNS hyper-addicted to the BTK pathway frequently with MYD88 and CD79 mutations. Those are patients who I would actually consider using dose-adjusted EPOCH. Those are the patients, if they came to me because we have it open, I would put them on the ESCALADE trial which is one of the trials revisiting the question of the role of BTK inhibitors in large cell lymphoma.

Dr. James Armitage: Andy, that was a wonderful clear presentation. You just gave people all sorts of things, if they bothered to listen to the things you have said for the last 5 or 10 minutes, all sorts of things they can use to improve practice. Thank you so much for doing that for us. You take care of yourself.

Dr. Andrew Zelenetz: Thanks for having me, this was fun.