Dr. Jim Armitage: Welcome to today's program. My name is Jim Armitage, and I am from the University of Nebraska Medical Center. Today I'm joined by Dr. Reid Merryman from the Dana-Farber Center in Boston.

Faculty Disclosures

- **Dr. James Armitage** has relevant financial relationships related to advisory activities from Cardiff Oncology, Inc.
- **Dr. Reid Merryman** has relevant financial relationships related to consulting from AbbVie, Inc., Adaptive Biotechnologies, AlphaSights, Bristol Myers Squibb Company, Epizyme, Inc., Genmab A/S, and Intellia Therapeutics, Inc. He has received research grant(s) from Bristol Myers Squibb, Genentech – A Member of the Roche Group, Genmab, and Merck & Co., Inc.

These are our disclosures.

Learning Objectives

- Discuss recent evidence/publications on emerging therapies for relapsed/refractory follicular lymphoma treatment
- Describe implications for current/future practice of new clinical trial data in relapsed/refractory follicular lymphoma

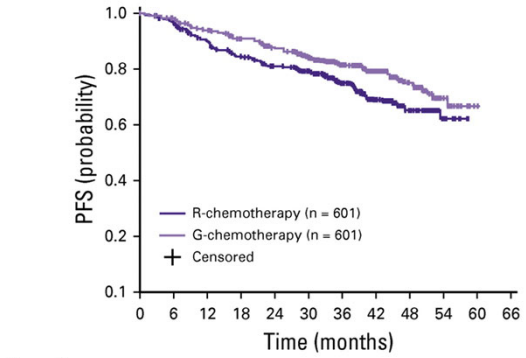
Today's presentation, we'll discuss recent evidence and publications on emerging therapies for relapsed or refractory follicular lymphoma. Dr. Merryman will also describe implications for current or future practice of new clinical data in these same clinical situations. We will conclude with a brief discussion on how he and I treat these patients and we'll have a little bit of dialogue.

But now, it's my pleasure to turn the presentation over to Dr. Merryman.

Spotlight on Relapsed/Refractory Follicular Lymphoma

Follicular Lymphoma

- Most common indolent NHL
- Standard approaches for first- and second-line therapy
  - Chemoimmunotherapy
  - Rituximab
  - Lenalidomide + rituximab (R^2)
- Treatment is not curative, but most patient have excellent outcomes
- Multiple novel agents tested and approved for third-line and later therapy



No. at risk

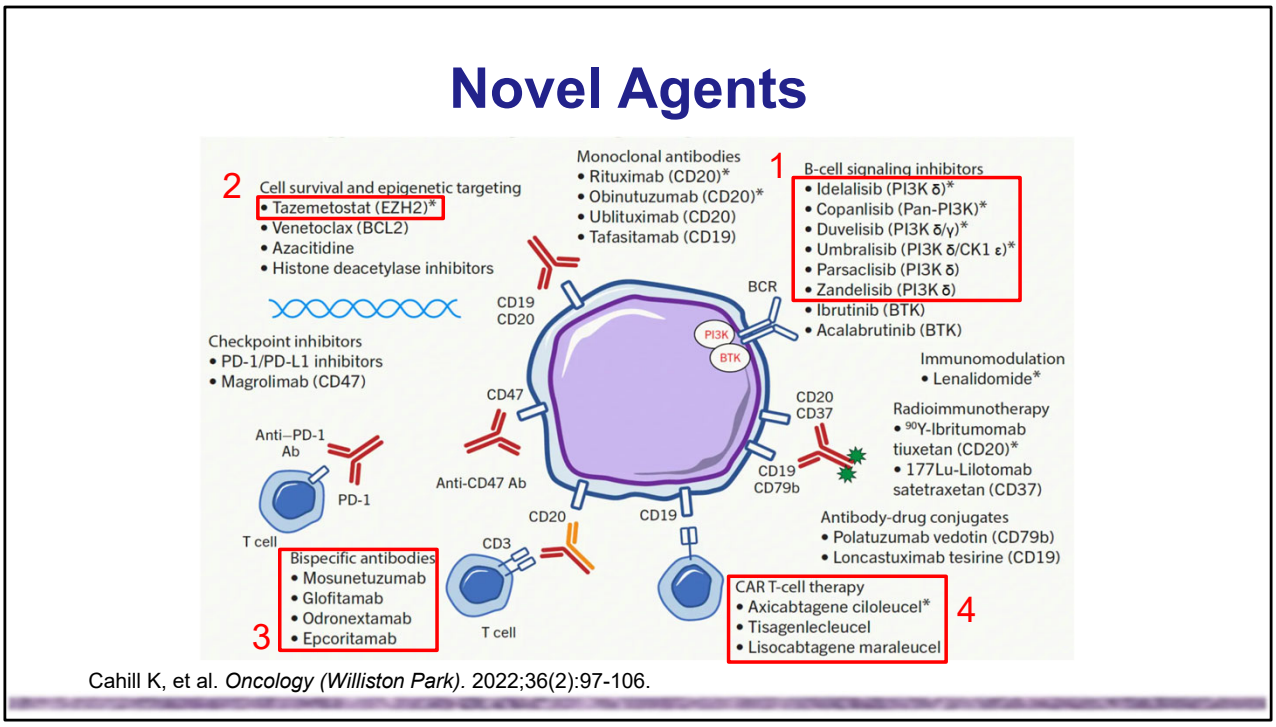
R-chemotherapy	601	561	505	464	438	396	267	149	77	18	0	0
G-chemotherapy	601	569	535	505	478	420	291	176	85	25	1	0

Hiddemann W, et al. *J Clin Oncol.* 2018;36(23):2395-2404.

Dr. Reid Merryman: I'm really excited to be here today to talk to you about follicular lymphoma management for relapsed and refractory patients. As you all know, follicular lymphoma is the most common indolent non-Hodgkin lymphoma. Standard first and second-line treatment options include chemoimmunotherapy, rituximab alone for select patients, and lenalidomide and rituximab is a common second-line therapy used.

While these treatments are not curative, most patients have excellent outcomes. On the right, you can see progression-free survival for patients treated with either rituximab or obinutuzumab-based chemoimmunotherapy in the GALLIUM study. Fortunately, there are multiple novel agents that are being tested or have been approved for treatment of third-line and later therapy.

Spotlight on Relapsed/Refractory Follicular Lymphoma



Cahill K, et al. *Oncology (Williston Park)*. 2022;36(2):97-106.

I want to focus on four different classes of drugs for today's talk.

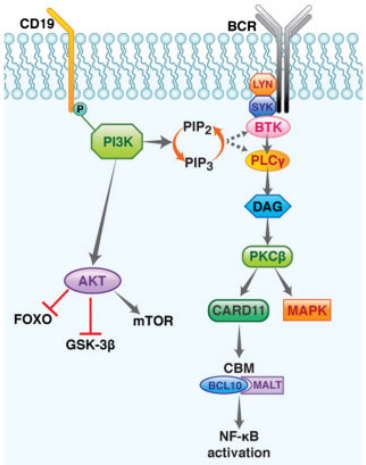
The first is PI3 kinase inhibitors. There have been significant changes in approvals in this area over the last year or so.

The second is tazemetostat which is an oral EZH2 inhibitor.

The third class of drugs is bispecific antibodies that target CD3 and CD20. None of these drugs have been approved yet, but we expect approval soon.

The last class of drugs is CAR T-cell therapy. There are two CAR T-cell products that are currently approved for relapsed or refractory follicular lymphoma.

PI3 Kinase Inhibitors



	Admin	α	β	α	γ
Idelalisib	PO	820	565	**2.5**	89
Copanlisib	**IV**	**0.5**	**3.7**	**0.7**	**6.4**
Duvelisib	PO	1600	85	**2.5**	**27**
Umbralisib	PO	>10,000	1120	**22**	1060
Parsaclisib	PO	>10,000	>10,000	**1**	>10,000
Zandelisib	PO	5491	335	**<5**	2533

von Keudell G, et al. *Curr Hematol Malig Rep.* 2019;14(5):405-413.; Roskoski R. *Pharmacol Res*. 2021;165:105463.; Shinn N, et al. *J Pharmacol Exp Ther*. 2020;374(1):211-222.

The first class of drugs is PI3 kinase inhibitors. The PI3 kinase pathway is an important signaling pathway for B-cell lymphomas. That's essential for proliferation and survival. There are different isoforms of PI3 kinase that can be targeted and they're expressed differently.

The alpha and beta subunits are expressed widely on both hematopoietic and non-hematopoietic tissues, whereas delta and gamma tend to be preferentially expressed on hematopoietic cells. Here you can see some important differences for these six drugs. Copanlisib is unique in two ways. First, it's the only IV drug among these six, then second, it's a pan-PI3 kinase inhibitor.

The other drugs listed here are orally administered and they have specificity for the delta isoform with duvelisib being somewhat unique and that it also has some specificity for the gamma isoform.

Spotlight on Relapsed/Refractory Follicular Lymphoma

	N	ORR	CRR	Median PFS (mo)	Discontinuation rate due to AEs	FDA approval	Approval or application withdrawn	Citation
Idelalisib	72	56%	14%	11.0	25%	2014*	1/2022	Gopal, NEJM 2014; Salles Haem 2017
Copanlisib	104	59%	14%	11.2	16%	2017	NA	Dreyling JCO 2017
Duvelisib	83	42%	1%	9.5	31%	2018*	12/2021	Flinn, JCO 2019
Umbralisib	117	45%	5%	10.6	**15%**	2021	All trials on hold	Fowler, JCO 2021
Parsaclisib	126	75%	18%	14.0	24%	NA	2/2022	Lynch, ASH 2021
Zandelisib	91	70%	35%	NR	**10%**	NA	NA	*Press release

Parsaclisib is no longer being developed for follicular lymphoma

*Approval withdrawn

Here, I'm highlighting some important results from the phase II studies for these drugs among patients treated with follicular lymphoma.

You can see here that objective response rates range from about 40% up to 75%. There are pretty significant differences in the rate of complete responses ranging from 1% up to 35%. Then the progression-free survival for most of these drugs is around one year. You can see that the discontinuation rate is fairly high, up to 30% for these drugs, and that's been a significant concern and I think one of the reasons that these are not used more widely in practice.

As of about a year ago, there were four of these drugs that were available clinically, but a few of them have been pulled off the market just in the last year. Idelalisib, duvelisib, and umbralisib are no longer available and parsaclisib, the company has announced that they're no longer developing this drug for follicular lymphoma. Currently, there's only one PI3 kinase that's clinically available, which is copanlisib and the second, zandelisib, is still in clinical development.

PI3 Kinase Toxicity

α/β *(% grade 3+ AE)*	α/γ *(% grade 3+ AE)*
Hyperglycemia (40%)	Neutropenia (20-30%) Anemia (5-10%) Thrombocytopenia (5-10%)
Hypertension (25%)	Diarrhea/Colitis (5-15%)
	Hepatitis/Transaminitis (5-15%)
	Pneumonitis (2-7%)

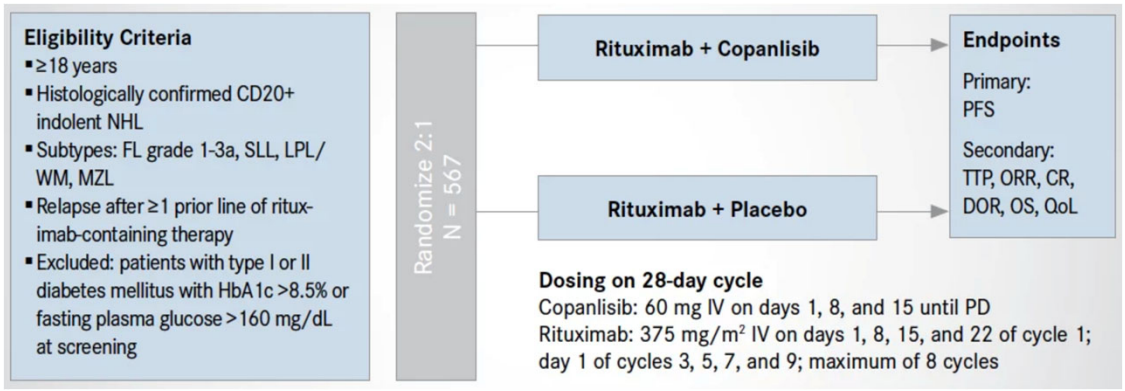
Strategies to Overcome Toxicity

- Less potent α inhibition (umbralisib)
- Intermittent dosing (duvelisib, zandelisib, parsaclisib)
- Lower doses (parsaclisib)

I mentioned that toxicity is a concern for these drugs and the toxicity that we see is dependent quite a bit on the different subunits that are targeted. If alpha and beta are targeted as in copanlisib, we see pretty significant rates of high-grade hyperglycemia and hypertension. Whereas for all the drugs delta is targeted, we see cytopenias, and then more concerningly, we can see severe diarrhea, colitis, hepatitis, transaminitis, and then less commonly, pneumonitis.

These toxicities have been a barrier for uptake of these drugs and different companies have explored strategies to try to mitigate toxicity, for example, using a less potent delta inhibitor, as in the case of umbralisib, using intermittent dosing, which has been used by a few different P13 kinase inhibitors and then trying lower dosing as well.

CHRONOS-3 – Copanlisib



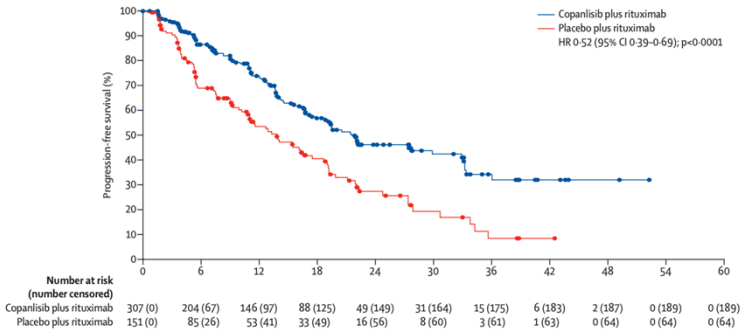
Matasar M, et al. *Lancet Oncol*. 2021;22(5):678-689.

I wanted to focus a little bit on copanlisib, which I mentioned is the only PI3 kinase inhibitor that's currently approved. CHRONOS-3 was a phase III trial comparing rituximab plus copanlisib to rituximab and placebo. This trial enrolled patients with indolent non-Hodgkin lymphoma. Follicular lymphoma was the most common subtype, but it also enrolled other indolent NHL subtypes as well. Patients had relapsed after at least one prior line of rituximab continuing chemotherapy and they excluded patients with poorly controlled diabetes.

I'll point out that copanlisib is administered IV and there's pretty frequent administrations as you can see here. The primary endpoint for this trial was progression-free survival.

Spotlight on Relapsed/Refractory Follicular Lymphoma

CHRONOS-3 – Copanlisib



	R-Copa	R-placebo
ORR	81%	48%
CRR	34%	15%
PFS (all pts)	21.5 m	13.8 m
PFS (FL only)	22.2 m	18.7 m

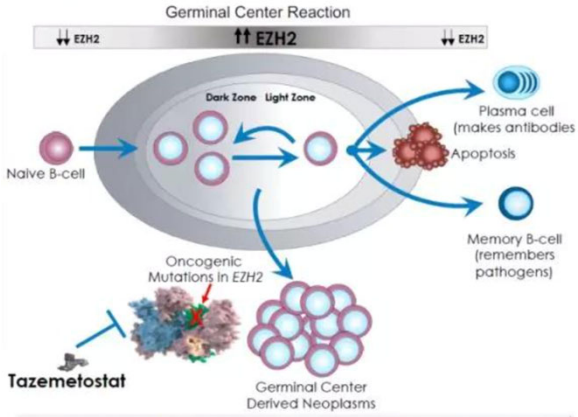
Matasar M, et al. *Lancet Oncol*. 2021;22(5):678-689.

Here I'm highlighting the important efficacy outcomes. You can see that the inclusion of copanlisib and treatment resulted in a higher objective response rate and complete response rate, and also improved progression-free survival in blue in the PFS curves here. When they look specifically at the follicular lymphoma subtypes, the subgroup of patients with follicular lymphoma, the progression-free survival benefits seem to be less significant, only about a four-month difference in the two groups.

Spotlight on Relapsed/Refractory Follicular Lymphoma

EZH2 in FL

- EZH2 is a histone methyltransferase, regulate germinal center formation
- EZH2 mutations can contribute to oncogenic transformation
- Gain-of-function mutations in the enzymatic domain of EZH2 are common (~20% of FL patients)
- Tazemetostat is an oral EZH2 inhibitor



Tazemetostat, an investigational, first-in-class, selective, oral inhibitor of EZH2 has shown antitumor activity in non-Hodgkin's lymphoma patients with either MT or WT EZH2[4,5]

Morschhauser F, et al. *Lancet Oncol*. 2020;21(11):1433-1442.

The next group of the next class of drugs I wanted to talk about are EZH2 inhibitors. EZH2 is a histone methyltransferase that regulates germinal center transformation. EZH2 mutations can contribute to oncogenic transformation by locking cells in a germinal center state and preventing terminal differentiation.

In total, about a fifth of patients with follicular lymphoma have a gain of function mutation in EZH2 and tazemetostat was the first EZH2 inhibitor that was tested widely in follicular lymphoma.

Tazemetostat – Phase 2 Trial

	$EZH2^{mut}$	$EZH2^{WT}$
N	45	54
Median lines of therapy (range)	2 (2-4)	3 (2-5)
Refractory to R	22 (49%)	32 (59%)
Refractory to R and chemotherapy induction	9 (20%)	15 (28%)
Prior stem cell transplant	4 (9%)	21 (39%)
POD24	18 (42%)	32 (59%)

Morschhauser F, et al. *Lancet Oncol*. 2020;21(11):1433-1442.

I'm going to highlight the results from the phase II study, which looked at about 100 patients, either with EZH2 mutated follicular lymphoma or EZH2 wild-type FL. You can see here that patients had received a median of two or three lines of prior treatment and patients in the wild-type group seem to be higher risk based on the number of lines of prior treatment, based on the frequency of prior stem cell transplant, and also a higher frequency of progression of disease within 24 months of initial therapy or POD24.

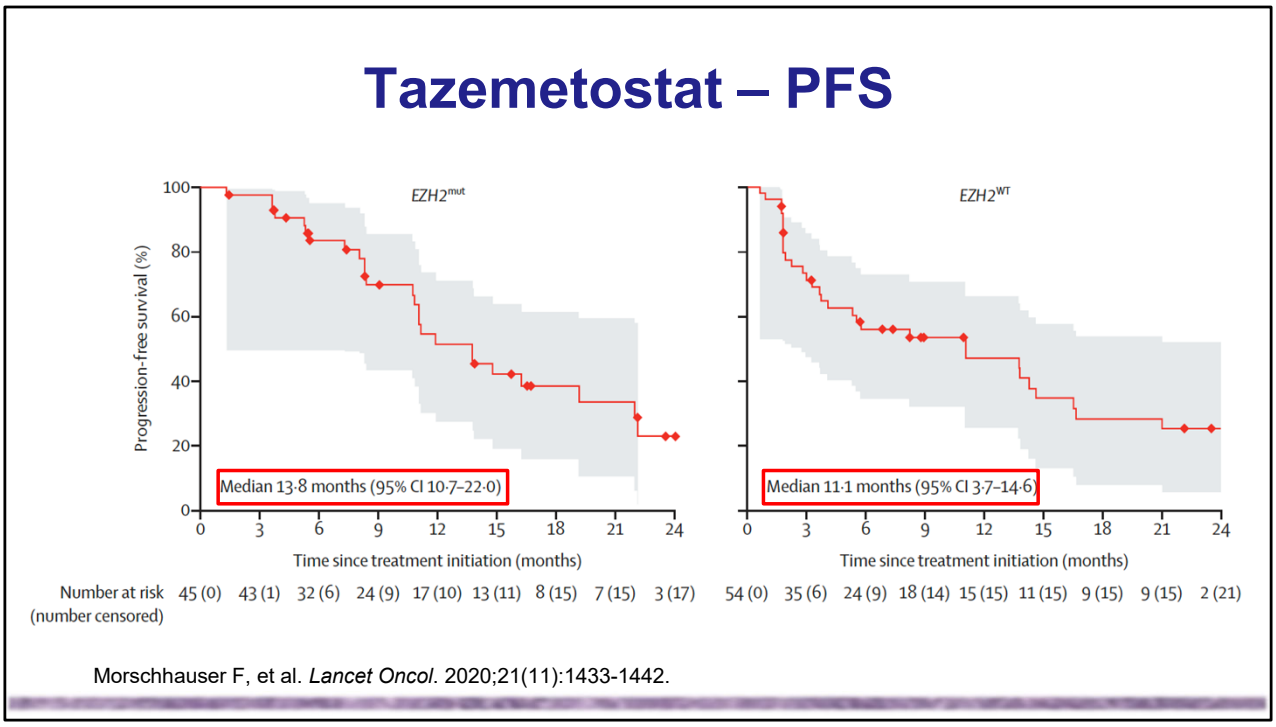
Tazemetostat – Responses

	EZH2^{mut} (n=45) IRC-assessed	*EZH2*^{wt} (n=54) IRC-assessed
Objective response rate	31 (69%; 53–82)	19 (35%; 23–49)
Overall disease control rate	44 (98%)	37 (69%)
Best overall response		
Complete response	6 (13%)	2 (4%)
Partial response	25 (56%)	17 (31%)
Stable disease	13 (29%)	18 (33%)
Progressive disease	1 (2%)	12 (22%)
Not estimable or unknown	0	5 (9%)

Morschhauser F, et al. *Lancet Oncol*. 2020;21(11):1433-1442.

Here are the response rates. It looks like at least based on response rates, that EZH2 mutation is a predictive biomarker, higher objective response rates were seen for EZH2 mutated patients, 69% versus 35% for wild-type patients. A low rate of complete responses were seen for patients regardless of EZH2 mutation status.

Spotlight on Relapsed/Refractory Follicular Lymphoma



Morschhauser F, et al. *Lancet Oncol*. 2020;21(11):1433-1442.

When you look at progression-free survival, the EZH2 mutations seemed to be maybe less significant predictive biomarker, about 14-month progression-free survival for mutated patients and 11 months for wild-type patients. This progression-free survival is pretty similar to what we're seeing for P13 kinase inhibitors.

Tazemetostat – Safety

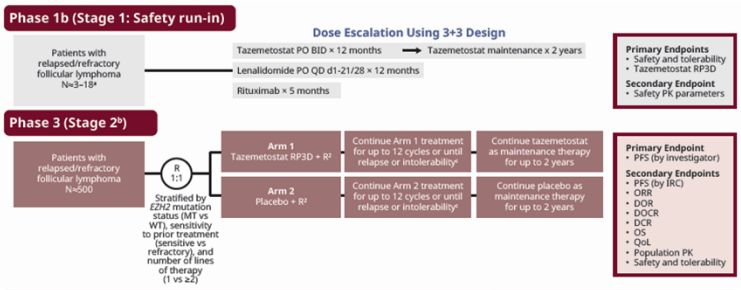
	Grade 1-2	Grade 3-4
Nausea	19%	0%
Alopecia	14%	0%
Asthenia	13%	1%
Diarrhea	12%	0%
Fatigue	11%	1%
Anemia	7%	2%
Thrombocytopenia	5%	3%
Neutropenia	3%	3%

Morschhauser F, et al. *Lancet Oncol*. 2020;21(11):1433-1442.

One of the things that sets this drug apart from PI3 kinase inhibitors is its tolerability. There were very low rates of Grade 3 or 4 side effects, and in general, this is a drug that is quite well tolerated and a good option for patients who have comorbidities and might not be good candidates for more intensive treatment options.

Spotlight on Relapsed/Refractory Follicular Lymphoma

Tazemetostat + R^2



Best Overall Response[a], n (%)	TAZ + R² (n=35)
Objective response rate	32 (91.4)
Complete response[b]	13 (37.1)
Partial response	19 (54.3)
Stable disease	3 (8.6)
Progressive disease	0

	N=40
Age	67 (39-83)
Elevated LDH	6 (15%)
B symptoms	6 (15%)
Prior lines	
1	19 (48%)
2	13 (32%)
3	3 (8%)
4+	5 (12%)
Prior therapy	
CD20+chemo	30 (75%)
CD20 mAb alone	10 (25%)

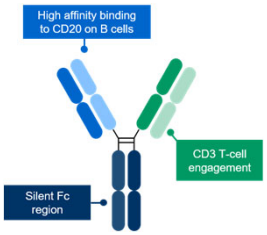
Batlevi CL. ASH 2021.

Because this drug is well tolerated, it's an excellent possible combination partner so the company is pursuing a phase III trial that's comparing R^2 plus placebo to tazemetostat plus R^2. That trial is currently enrolling.

Before they opened the phase III trial, they ran a small phase IB trial looking at the safety and efficacy of that triad, tazemetostat, lenalidomide, and rituximab. Here you can see the baseline features of the 40 patients that were enrolled in that trial. Most patients had either one or two prior therapies. There were about 25% of patients who'd received only rituximab alone but the preliminary results look encouraging with an objective response rate of 91% and the complete response rate of 37%, which is a little bit higher than we would expect with R^2 alone.

CD3/CD20 Bispecific Antibodies

- BsAbs recognize two different antigens
- Prior clinical efficacy with CD3/CD19 BsAbs; limited by side effects in NHL
- CD3/CD20 BsAbs
  - Encouraging efficacy
  - Lower rates of CRS than CAR
  - Rare neurotoxicity



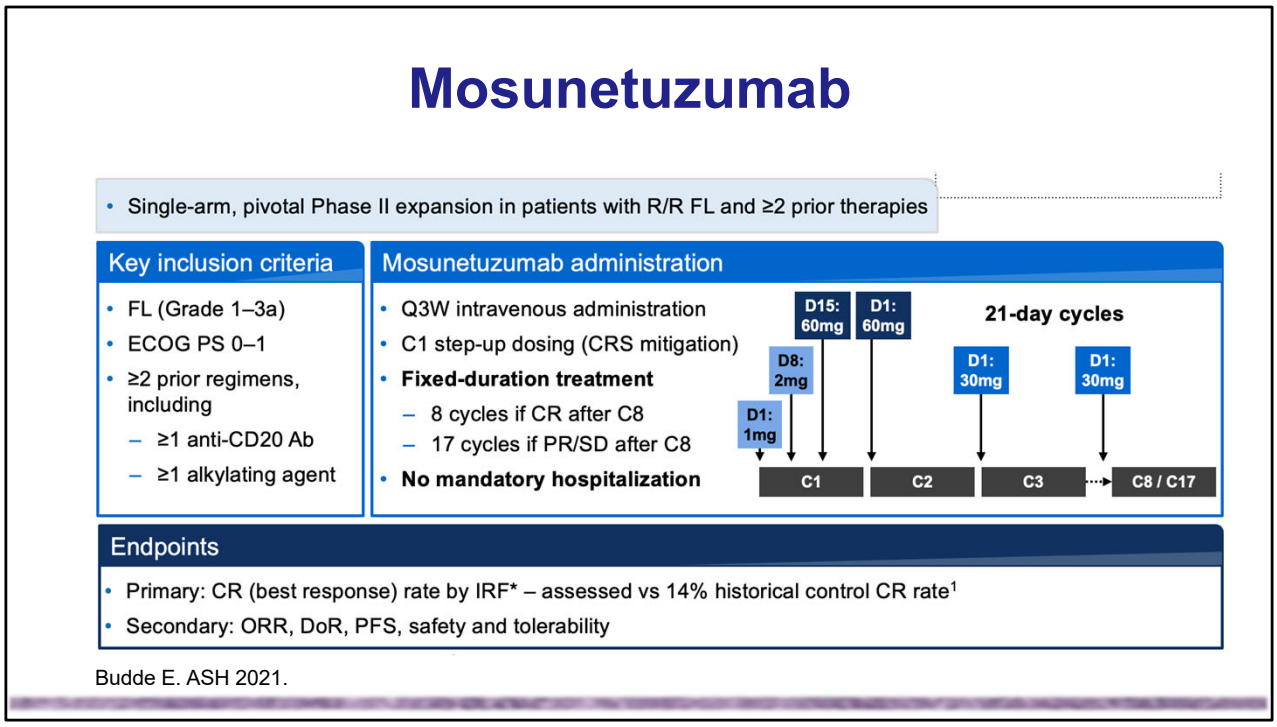
	Administration
Mosunetuzumab	IV (SC)
Glofitamab*	IV
Odronextamab	IV
Epcoritamab	SC

*Bivalent for CD20

The next class of drugs to highlight is CD3/CD20 bispecific antibodies. Bispecific antibodies (BsAbs) target two different antigens, in this case, CD3 on T-cells and CD 20 on follicular lymphoma cells. There has been some prior experience using bispecific antibodies in non-Hodgkin lymphoma using the CD3/CD19 bispecific blinatumomab and this actually showed encouraging efficacy results but its development was limited by side effects. So far, the data for CD3/CD20 bispecific antibodies looks very encouraging with high response rates and lower rates of toxicity compared to CAR T-cell. Lower rates of cytokine release syndrome and lower rates of neurotoxicity.

On the right here, I'm listing the four bispecifics that are furthest along in clinical development. Two of the drugs, mosuneduzumab and epcoritamab, are being studied as subcutaneous administration. Glofitamab is unique in that it has bivalency for CD20.

Spotlight on Relapsed/Refractory Follicular Lymphoma



Budde E. ASH 2021.

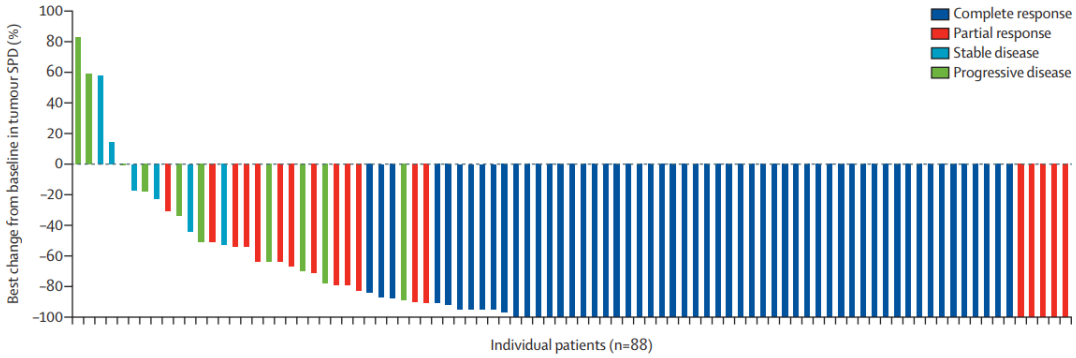
First, a phase II trial of mosuneduzumab, which is the farthest along in terms of clinical development. This trial enrolled patients with grade 1-3A follicular lymphoma, who had received two or more prior lines of treatment.

This drug was dosed using step-up dosing, which is a common strategy across all of the bispecifics. You start with a very low dose that's increased over three doses. The rationale for this is that there are some data suggesting that this can lower the rates of cytokine release syndrome with initial administration. This trial was time-limited therapy with eight cycles if patients achieved a CR or 17 cycles if they were in a partial response or stable disease after 8 cycles of treatment.

Importantly, this trial did not require mandatory hospitalization which is fairly unique among mosunetuzumab which seems to have a lower rate of cytokine release syndrome compared to some of the other bispecifics. The primary endpoint for this trial was complete response rate.

Spotlight on Relapsed/Refractory Follicular Lymphoma

Mosunetuzumab



ORR 80%, CRR 60%

Similarly high response rates for POD24 patients

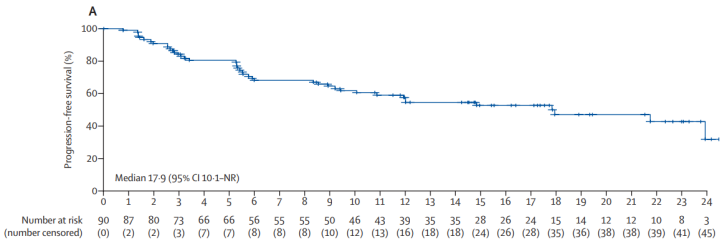
Budde L, et al. *J Clin Oncol.* 2022;40(5):481-491.

Here's the waterfall plot. You can see that nearly all patients had reduction in the size of their lymphoma. The objective response rate was 80% and the complete response rate was 60% and prior chemo resistance or chemo refractoriness did not seem to be predictive of response in this case. High response rates were seen for patients with POD24.

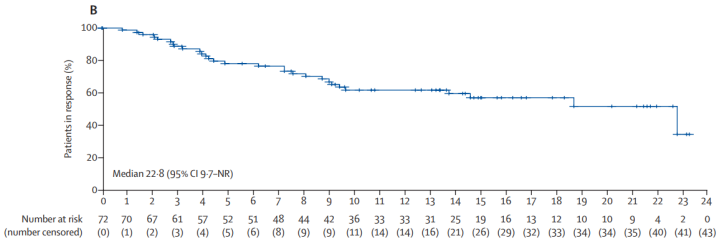
Spotlight on Relapsed/Refractory Follicular Lymphoma

Mosunetuzumab

PFS



DOR



Budde L, et al. *Lancet Oncol*. 2022;23(8):1055-1065.

Here's the progression-free survival and the duration of response, both of which look quite encouraging in a patient population that was heavily pretreated, although I'll point out that it doesn't seem like there's a tail on these curves.

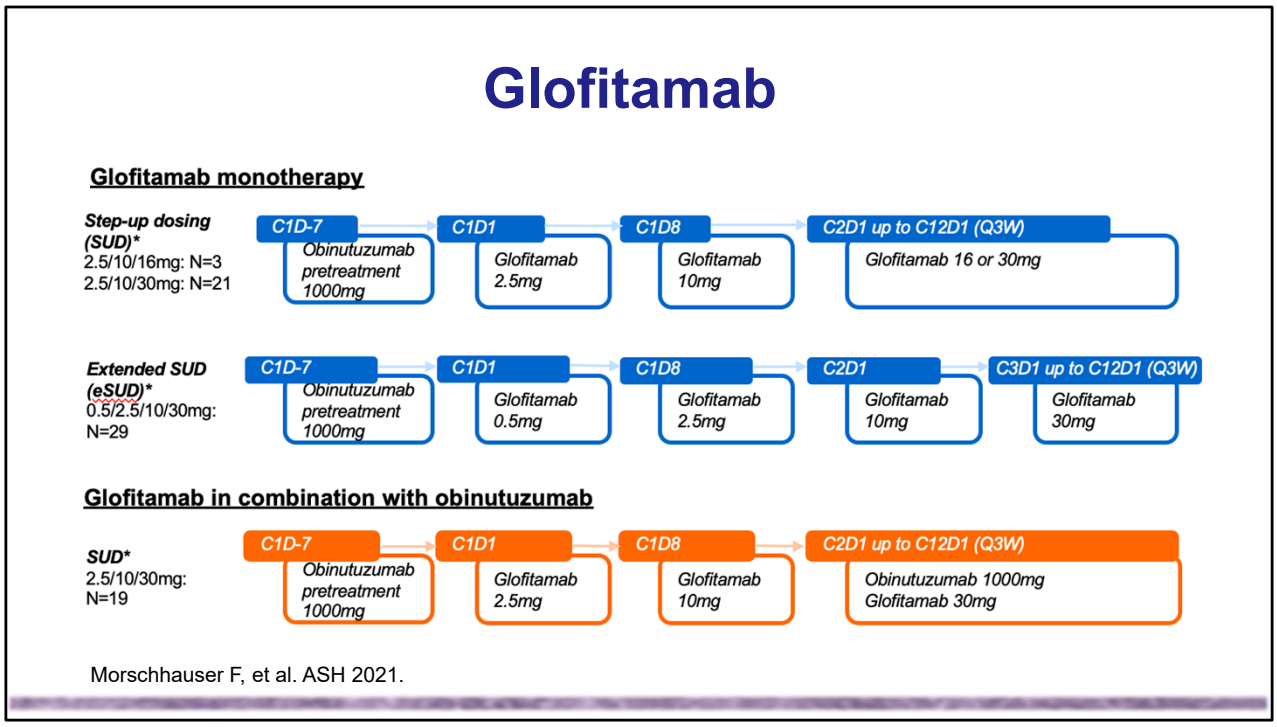
CD3/CD20 Bispecific Antibodies

	N	ORR	CRR	PFS	CRS	ICANS
Mosunetuzumab	**88**	**80%**	**60%**	**17.9 months**	**44% (any grade) 2% (grade 3+)**	**4% (grade 1-2) 0% (grade 3+)**

Budde L, et al. *Lancet Oncol*. 2022;23(8):1055-1065.

Here I'm highlighting the toxicity profile. About 44% of patients had any grade CRS and rates of high-grade CRS were quite low at 2% and neurotoxicity was rarely seen and tended to be low grade.

Spotlight on Relapsed/Refractory Follicular Lymphoma



The next bispecific is glofitamab.

Next, I'm going to highlight results of the phase II study. This drug is also using step-up dosing to try to mitigate CRS but it's also using an additional strategy pretreatment with the CD20 monoclonal antibody obinutuzumab with the goal that that can either provide some debulking or remove any circulating B cells and further reduce the risk of CRS.

CD3/CD20 Bispecific Antibodies

	N	ORR	CRR	PFS	CRS	ICANS
Mosunetuzumab	88	80%	60%	17.9 months	44% (any grade) 2% (grade 3+)	4% (grade 1-2) 0% (grade 3+)
Glofitamab (+ obinutuzumab)	**72**	**81%**	**70%**	**NR**	**69% (any grade) 1% (grade 3+)**	**0% (any grade)**

Budde L, et al. *Lancet Oncol*. 2022;23(8):1055-1065.; Morschhauser F, et al. ASH 2021. Abstract 2417.

This trial also had very encouraging results. High objective response rate, high complete response rate, slightly higher than seen with mosunetuzumab. Follow-up was brief so we don't have a good estimate for progression-free survival yet. It seems like the rate of CRS, particularly low-grade CRS, is higher for glofitamab than for some of the other bispecifics, but the rate of more severe CRS was also very low and no neurotoxicity was seen in this trial.

Spotlight on Relapsed/Refractory Follicular Lymphoma

CD3/CD20 Bispecific Antibodies

	N	ORR	CRR	PFS	CRS	ICANS
Mosunetuzumab	88	80%	60%	17.9 months	44% (any grade) 2% (grade 3+)	4% (grade 1-2) 0% (grade 3+)
Glofitamab (+ obinutuzumab)	72	81%	70%	NR	69% (any grade) 1% (grade 3+)	0% (any grade)
Epcoritamab	**10**	**90%**	**50%**	**NR**	**59% (any grade)* 0% (grade 3+)**	**6% (any grade)* 2% (grade 3)**

*AE rates for mixed NHL population

Budde L, et al. *Lancet Oncol*. 2022;23(8):1055-1065.; Morschhauser F, et al. ASH 2021. Abstract 2417.; Hutchings M, et al. *Lancet*. 2021;398(10306):1157-1169.

Epcoritamab is a subcutaneously administered bispecific smaller body of evidence so far, but the early evidence also looks promising. High response rates and similar rates of CRS and neurotoxicity.

CD3/CD20 Bispecific Antibodies

	N	ORR	CRR	PFS	CRS	ICANS
Mosunetuzumab	88	80%	60%	17.9 months	44% (any grade) 2% (grade 3+)	4% (grade 1-2) 0% (grade 3+)
Glofitamab (+ obinutuzumab)	72	81%	70%	NR	69% (any grade) 1% (grade 3+)	0% (any grade)
Epcoritamab	10	90%	50%	NR	59% (any grade)* 0% (grade 3+)	6% (any grade)* 2% (grade 3)
Odronextamab	**40**	**91%**	**72%**	**17.1 months**	**63% (any grade)* 7% (grade 3+)**	**2% (grade 1-3)***

*AE rates for mixed NHL population

Budde L, et al. *Lancet Oncol*. 2022;23(8):1055-1065.; Morschhauser F, et al. ASH 2021. Abstract 2417.; Hutchings M, et al. *Lancet*. 2021;398(10306):1157-1169.; Bannerji R, et al. *Lancet Haematol*. 2022;9(5):e327-e339.

Odronextamab was targeted in 40 patients with follicular lymphoma. Again, very high response rates. Subjective response rate of 91%, complete response rate of 72%, and a similar progression-free survival compared to that seen for mosunetuzumab. Maybe slightly higher rates of cytokine release syndrome and higher grade CRS here, but again, low rates of neurotoxicity.

Bispecific-based Combinations

Key inclusion criteria

- CD20+ FL Grade 1–3a
- R/R to ≥1 prior chemo-immunotherapy regimen including an aCD20 antibody; prior lenalidomide allowed
- ECOG PS 0–2

Objectives

- Primary: safety and tolerability of M-Len
- Other: efficacy (response, durability of response) and pharmacokinetics

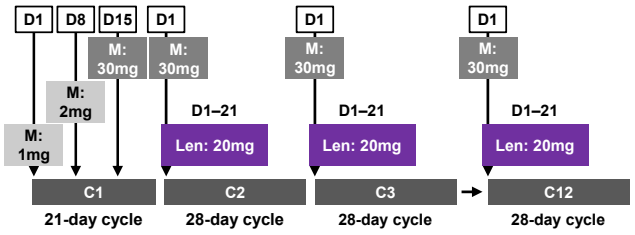
M-Len administration

Mosunetuzumab

- IV administration for 12 cycles (C1: Q3W; C2–12: Q4W)
- C1 step-up dosing (CRS mitigation)
- No mandatory hospitalization

Lenalidomide

- Oral administration for 11 cycles (C2–12)



Morschhauser F, et al. ASH 2021.

Given the early success with bispecific monotherapy, there are a number of trials that are looking at bispecific-based combinations. I wanted to highlight two of those. This first trial is a combination of mosunetuzumab and lenalidomide. Patients are treated for 12 cycles, about a year, with this combination. Again, step-up dosing was used initially with the bispecific.

I'll point out that the final dose of the bispecific here, 30 milligrams is lower than what was tested with mosunetuzumab monotherapy. This is a similar cohort of patients, people who are relapsed or refractory to at least one prior line of chemoimmunotherapy.

CD3/CD20 Bispecific Antibodies

	N	ORR	CRR	PFS	CRS	ICANS
Mosunetuzumab	88	80%	60%	17.9 months	44% (any grade) 2% (grade 3+)	4% (grade 1-2) 0% (grade 3+)
Glofitamab (+ obinutuzumab)	72	81%	70%	NR	69% (any grade) 1% (grade 3+)	0% (any grade)
Epcoritamab	10	90%	50%	NR	59% (any grade)* 0% (grade 3+)	6% (any grade)* 2% (grade 3)
Odronextamab	40	91%	72%	17.1 months	63% (any grade)* 7% (grade 3+)	2% (grade 1-3)*
Mosunetuzumab + Lenalidomide**	**29**	**90%**	**66%**	**NR**	**28% (any grade) 0% (grade 3+)**	**3% (grade 3)**

** Lower dose of mosunetuzumab (30 mg vs 60 mg in monotherapy trial)

Budde L, et al. *Lancet Oncol*. 2022;23(8):1055-1065.; Morschhauser F, et al. ASH 2021. Abstract 2417.; Hutchings M, et al. *Lancet*. 2021;398(10306):1157-1169.; Bannerji R, et al. *Lancet Haematol*. 2022;9(5):e327-e339.

You can see that again, there were very high response rates, an objective response rate of 90%, a complete response rate of 66%. With the lower dose of mosunetuzumab, it seemed like there were lower rates of any grade CRS and no high-grade CRS was seen.

CD3/CD20 Bispecific Antibodies

	N	ORR	CRR	PFS	CRS	ICANS
Mosunetuzumab	88	80%	60%	17.9 months	44% (any grade) 2% (grade 3+)	4% (grade 1-2) 0% (grade 3+)
Glofitamab (+ obinutuzumab)	72	81%	70%	NR	69% (any grade) 1% (grade 3+)	0% (any grade)
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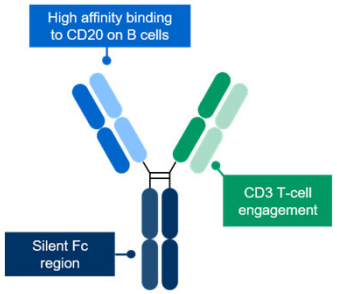
Odronextamab	40	91%	72%	17.1 months	63% (any grade)* 7% (grade 3+)	2% (grade 1-3)*
Mosunetuzumab + Lenalidomide**	**29**	**90%**	**66%**	**NR**	**28% (any grade) 0% (grade 3+)**	**3% (grade 3)**
Epcoritamab + R-Lenalidomide	**30**	**100%**	**93%**	**NR**	**50% (any grade) 7% (grade 3+)**	**3% (grade 2)**

Budde L, et al. *Lancet Oncol*. 2022;23(8):1055-1065.; Morschhauser F, et al. ASH 2021. Abstract 2417.; Hutchings M, et al. *Lancet*. 2021;398(10306):1157-1169.; Bannerji R, et al. *Lancet Haematol*. 2022;9(5):e327-e339.; Falchi L, et al. *Clin Lymphoma Myeloma Leuk*. 2015;15 Suppl(0):S27-33.

Epcoritamab has also been studied in combination with lenalidomide plus rituximab. Among the 30 patients, the preliminary results look very encouraging with an objective response rate of 100% and CR rate of 93% with similar rates of CRS and neurotoxicity.

Bispecific Antibodies

- Important questions to be answered
  - Is there a difference in efficacy?
  - Difference in safety?
  - Can these agents be administered safely in the outpatient setting? In community practices?
- How to optimally combine with other FL treatments? Many ongoing trials in
  - First-line setting
  - Second-line setting



I think these data are very exciting, but there are some important questions that still need to be answered. Is there a difference in efficacy across these different bispecifics? It seems like they're probably more similar than different but there may be slight differences that emerge with longer follow-up. Are there differences in safety perhaps higher rates of CRS for some of the bispecifics compared to others? Can these be safely administered in the outpatient setting and in community practices?

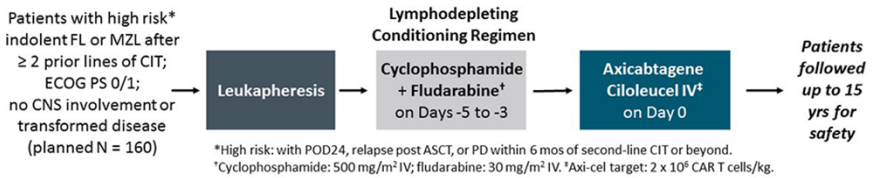
I think the answer to both of those questions is likely yes but I think there's still a learning curve and we're still working on best practices to safely administer these drugs in different settings and ideally in the outpatient setting. Then, given the very encouraging results, I think a key question is how do we optimally combine these treatments with other FL treatments that are effective? There are many trials ongoing in the first and second-line setting and I think in five years we may be seeing these drugs even earlier in the FL treatment paradigm.

Spotlight on Relapsed/Refractory Follicular Lymphoma

CAR T-Cells

ZUMA-5: Phase II Trial of Axicabtagene Ciloleucel (Axi-Cel) in High-Risk R/R Indolent NHL

- Multicenter, single arm, open-label phase II study
  - Axi-cel: autologous second-generation CD19-directed CAR T-cell therapy FDA approved for R/R DLBCL after ≥2 prior lines of systemic therapy



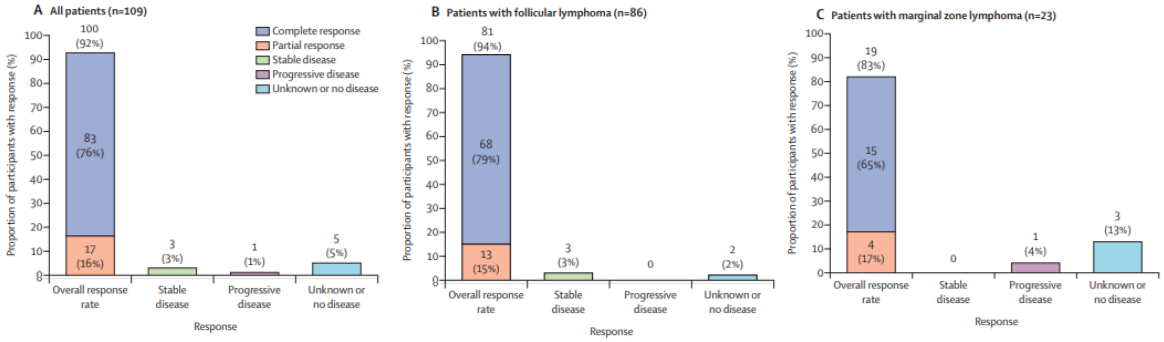
- Primary endpoint: ORR (CR + PR per Lugano criteria)
- Secondary endpoints: CR, DoR, PFS, OS, AEs

Then finally, to highlight CAR T-cells, which are probably the most active drugs for patients with relapsed or refractory follicular lymphoma, there are two CAR T-cell products that are approved.

The first approval came for axi-cel, and it was based on ZUMA-5, which was a phase II study that tested axi-cel among patients with relapsed or refractory follicular lymphoma or marginal zone lymphoma that had relapsed after at least two prior lines of treatment. Patients received standard cyclophosphamide and fludarabine lymphoid depletion, followed by axi-cel. The primary endpoint in this study was objective response rate.

Spotlight on Relapsed/Refractory Follicular Lymphoma

ZUMA-5: Axi-cel in iNHL

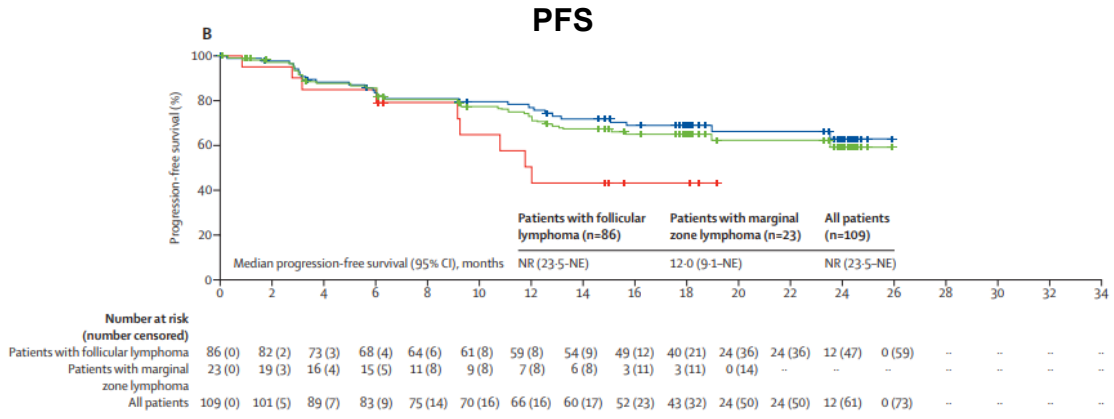


Jacobson C, et al. *Lancet Oncol*. 2022;23(1):91-103.

Here in the middle, you can see response rates for patients with follicular lymphoma, which were the largest group in this study. The objective response rate was 94%. The complete response rate was 79%. Very high response rates, higher than seen with marginal zone lymphoma patients in this study, and quite a bit higher than seen for patients with diffuse large B-cell lymphoma.

Spotlight on Relapsed/Refractory Follicular Lymphoma

ZUMA-5: Axi-cel in iNHL



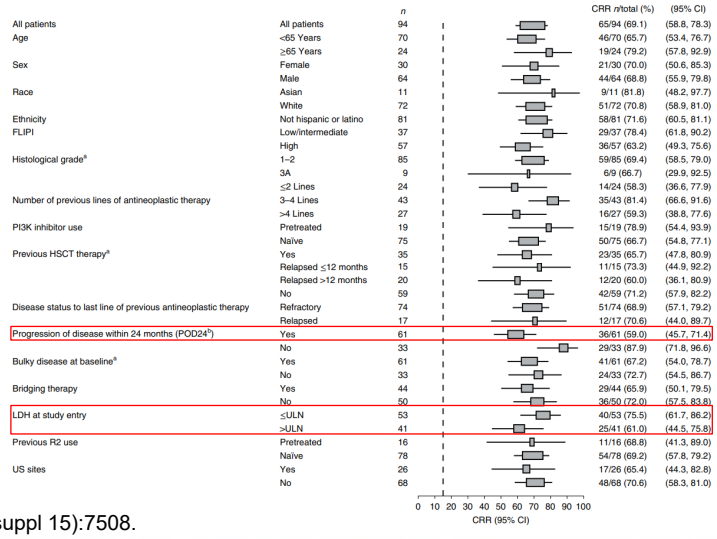
Jacobson C, et al. *Lancet Oncol*. 2022;23(1):91-103.

Here's the progression-free survival for all patients. Patients with follicular lymphoma are in blue. So durable remissions, but again, unclear if there's a tail on this curve, unclear if some patients may be cured with CAR T-cell therapy in this setting.

Spotlight on Relapsed/Refractory Follicular Lymphoma

ELARA 5 – Tisa-cel in FL

-	N=97
ORR	69.1%
CRR	86.2%
12-month PFS	67%



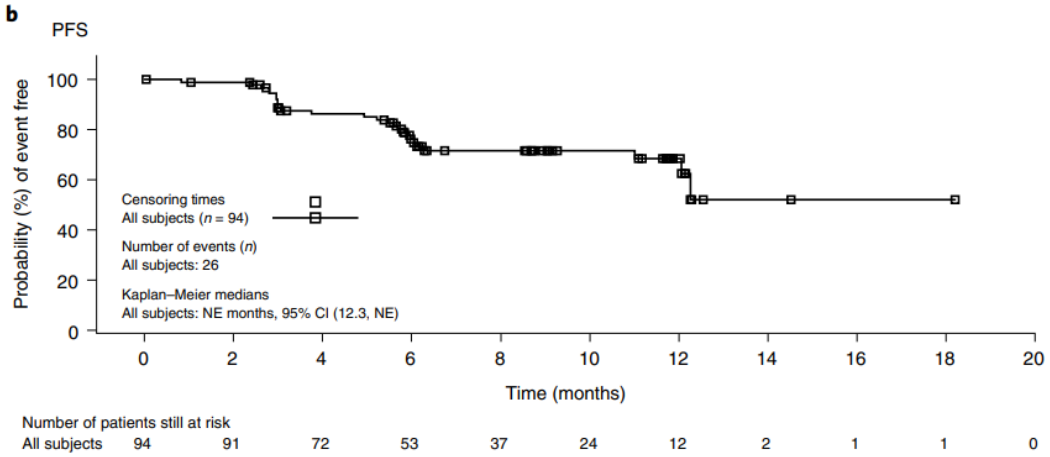
Schuster S, et al. *J Clin Oncol*. 2021;39(suppl 15):7508.

Here's data for the phase II study for tisa-cel, which is the second CAR T-cell product that's approved for relapsed or refractory follicular lymphoma patients. The objective response rate here was 86%, a complete response rate of 69%. At 12 months, about two-thirds of patients were still alive and in remission.

It looks like different subtypes of follicular lymphoma benefited, although there may be a trend that higher risk patients like POD24 patients or patients with an elevated LDH at study entry may have had lower rates of complete response shown here in red.

Spotlight on Relapsed/Refractory Follicular Lymphoma

ELARA 5 – Tisa-cel in FL



Schuster S, et al. *J Clin Oncol*. 2021;39(suppl 15):7508.

Again, encouraging response duration for these patients, although I think it's unclear if some patients may be cured with tisa-cel as well, and follow-up here is shorter than we had with axi-cel.

Comparison of CAR Products in FL

	Axi-cel	Tisa-cel
CRS **Any grade** **Grade 3+**	 **78%** **7%**	 **49%** **0%**
ICANs **Any grade** **Grade 3+**	 **56%** **15%**	 **4%** **1%**
ORR	94%	86%
CRR	79%	69%
12-month PFS	75-80%	67%

Then, to compare safety, there are important differences in safety between these two products similar to differences that were seen in diffuse large B-cell lymphoma. Axi-cel is associated with a higher rate of any grade CRS and higher rates of severe CRS and a similar pattern is seen for neurotoxicity. It may be that the slightly higher efficacy response rates and more durable remissions likely come at the cost of increased toxicity.

Novel Agents in FL

- Numerous options for R/R FL:
  - PI3 kinase inhibitors
  - Tazemetostat
  - CD3/CD20 BsAbs
  - CD19 CAR T-cell therapy
- Key differences in safety, ease of administration, and efficacy
- Sequencing of these agents depends on individual patient
- Shifting landscape - numerous trials in earlier lines of therapy

We're in a fortunate place for patients with relapsed or refractory follicular lymphoma. We have a number of good treatment options. PI3-kinase inhibitors, I think there are still concerns about toxicity and we have fewer options available, but there still is a place, I think, for copanlisib for carefully selected patients who maybe don't mind frequent infusions. Tazemetostat is a very well-tolerated option. That's a good option for patients who have comorbidities and aren't good candidates for more intensive therapies. CD3/CD20 bispecific antibodies are not yet approved, but I think we'll see our first approval soon. I think these drugs are going to be an important part of our treatment armamentarium for this disease. Then, of course, CD19 CAR T-cell therapy is an extremely active disease, but one that requires in most cases hospitalization and does have a higher risk of side effects.

There are key differences in safety, ease of administration, and efficacy, as I pointed out. Really, the sequencing of these agents depends on the individual patient on the aggressiveness of their follicular lymphoma, on their comorbidities, on their wishes. To emphasize, once again, this is a shifting landscape. I think the treatment landscape will look quite a bit different in the years to come as there are numerous trials and earlier lines of therapy that could change our current standard approach.

Spotlight on Relapsed/Refractory Follicular Lymphoma

Dr. Jim Armitage: Reid, thank you for that very nice and thorough and very clear presentation on increasingly complicated clinical situation. A disease where we're getting too many treatments, where we have all these things we can do and it's hard to choose. I'll ask you about that in a minute. What I'd like to do to spend the next few minutes is to go back and forth with you. I'll try to be asking the questions that I can imagine our viewers who get to view this might want to be able to ask of you because they've got a chance here to find this international expert in this disease.

I'm going to ask you the questions that I think the clinicians might want to know and a couple of these aren't specifically about therapy, but just how you practice. One, when you have a patient that's referred to you or one of your patients who has a recurrent relapsed follicular lymphoma. When do you do a biopsy? I assume sometimes you want to rule out diffuse large B-cell lymphoma. What are your rules for a biopsy before you treat?

Dr. Reid Merryman: It's a great question. It's a really important question. I think I try to biopsy as much as possible. I try to, basically in every circumstance, do a biopsy because I think we do see fairly high rates of transformation. The lifetime risk is probably on the order of 20% to 30% and it's higher in patients with higher-risk disease, for example, POD24 patients.

I will try to biopsy after each line of therapy, and particularly, if patients have a high SUV over 10 or 15 on a restaging PET scan, I'll definitely try to biopsy those patients because many of our traditional follicular lymphoma treatments are not effective or not as effective for diffuse large B-cell lymphoma so we really want to know if a patient is transformed before we subject them to a new treatment.

Dr. Jim Armitage: Anytime you're treating somebody with follicular lymphoma, watch and wait after Saul Rosenberg showed that it can be a very useful clinical approach, sometimes. You always think about that and I would like to know-- I'm sure all of us would like to know if you have rules where you would always observe without therapy or you would never observe without therapy. What are the rules you follow?

Dr. Reid Merryman: That's a good question. It's hard to say always. I feel like there are almost always exceptions.

Dr. Jim Armitage: I often tell patients, if physicians use the words always and never very often, you probably should get rid of them. Medicine's not like that. Anyway, I'm sorry.

Dr. Reid Merryman: I agree. I think patients with a small tumor burden who are asymptomatic, I think you have to think of a good reason to treat those patients. I try to encourage watchful waiting for those patients, even if patients are initially reluctant, which many patients are, especially at first diagnosis. Then, obviously, anytime a patient is symptomatic, I will start treatments. Patients have bulky disease or disease that really puts at risk important organs. Patients who have lymphadenopathy that's pushing on liver or kidneys, for example, I encourage those patients to start treatment even if they don't have symptoms at that time.

Dr. Jim Armitage: Thank you. Now, there are a number of old treatments here and I'm going to ask you about a few of them and whether you think about them or you just don't ever think about them anymore at all. How about radio antibodies?

Dr. Reid Merryman: To be honest, radio antibodies I think the data for it came along before I started treating patients with lymphoma. I think the efficacy in those trials looks really encouraging, but there is a risk of MDS. At our center, I think we've really stopped using them. This one setting where we were still using them some was as bridging therapy to ALLO transplant where you worry a little bit less about the long-term risk of MDS, but I think we're fortunate to have, as you said at the beginning, almost too many options for follicular lymphoma. I think things like radioimmunotherapy or to some degree autologous stem cell transplant, which has higher risk of long-term side effects. As we get better and better options, we're using those treatments less frequently.

Dr. Jim Armitage: And us, by the way. Radio antibodies or even hard radioimmuno-therapy is hard to be able to get to treat a patient with, but I have to say, both I have a patient treated many, many years ago with the radio antibody who got a remission and has never relapsed decades later. With autologous transplants, your institution and the group in London, and we have all reported a fairly large series where people stay well for a really long time. My longest patient now is about 38 years. I'm not sure ignoring those like we tend to do, especially the auto-transplant is the right thing, but it's become much, much less popular. ALLO transplants, you implied that you still do those.

Dr. Reid Merryman: We do. I think ALLO transplants actually a really important treatment, particularly for young patients with follicular lymphoma. Our data right now suggests an overall survival for IFL that's probably close to or over 20 years, but for patients who are diagnosed in their 40s or 50s we'd like them to live longer than 20 years. I think ALLO transplant is an important option for those patients. It can be

curative. The rates of long-term survival after ALLO are really quite good for follicular lymphoma better than for other lymphoma subtypes. That seems that the graft versus lymphoma effect is probably better for FL than for other lymphoma subtypes. I have referred patients to ALLO when you're running out of treatment options with more conventional treatments.

Dr. Jim Armitage: The last one of the old ones I'd like you to comment, I'm sure all everybody would like to hear what you say, is when do you use traditional external beam radiotherapy?

Dr. Reid Merryman: I think that is the standard for patients with early-stage follicular lymphoma at diagnosis, where the long-term data suggests that we can probably cure 40% or 50% of patients with radiation. Then in other settings, I use it for palliation. If a patient has one lymph node that's causing issues, but otherwise their disease is well controlled and they're not having symptoms, I'll use oftentimes two by two, two gray times two fractions to treat those symptoms and hopefully delay systemic therapy some amount of time.

Dr. Jim Armitage: Me too. I'm shocked about how efficacious that can be. Seems like it's just a CT scan, but it has sometimes an amazingly good effect. All right, before we quit, there really are a lot of choices and you just reviewed for us the future, these new exciting therapies. Today, outside of a study, if you could get the drugs, which would you use in which situations? Which one of those do you favor? Of the new things you said, which are you most excited by?

Dr. Reid Merryman: I think for our highest risk follicular lymphoma patients where you're really worried about them, where their disease is behaving aggressively, where maybe you haven't been able to prove transformation, but clinically, you have a suspicion for transformation. I think those are the patients where CAR T-cell really is the optimal treatment. I think there aren't a lot of patients with follicular lymphoma where you need CAR T-cell at least where you need it right now, but those are the patients where I've been using CAR T-cell therapy. I think for other patients who maybe have a disease that's a little bit better behaved; I'm really excited about bispecific antibodies.

I think they're really effective drugs. They're generally well tolerated, particularly after the first one or two cycles. Most of the CRS that we see is within that first cycle or two,

and afterwards, these tend to be quite well tolerated and I think they're good combination partners. I think going forward, we're going to be using these more frequently and probably earlier in treatment. I think tazemetostat is a good option, particularly for patients, old frail patients who aren't good candidates for chemo or for CAR T-cell therapy, for example. I think that's how I think about these drugs that I mentioned today.

Dr. Jim Armitage: Reid, thank you. That was both a wonderful talk and I'm sure everybody enjoyed the insights you just provided about how to actually apply these approaches to these patients. Thank you very much.

Dr. Reid Merryman: Thank you.