Faculty Roundtable on CAR T-cell Therapies, Bispecific Antibodies and Antibody-Drug Conjugates in Follicular Lymphoma

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Dr. Loretta Nastoupil: Hi, I'm Loretta Nastoupil from the Department of Lymphoma & Myeloma at the University of Texas MD Anderson Cancer Center. It is my great pleasure to welcome Dr. Catherine Diefenbach, also NYU Director of the Hematology Translational Research and Director of the Clinical Lymphoma Program in the Perlmutter Cancer Center. Today, we're going to do a *Faculty Roundtable on CAR T-cell Therapies, Bispecific Antibodies, and Antibody-Drug Conjugates in Follicular Lymphoma*.

Follicular Lymphoma Webinar

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I'm going to kick off this webinar and just give you an overview of follicular lymphoma. Then we'll spend a good portion of the time having Dr. Diefenbach walk us through some of the latest developments as it pertains T-cell engagers and antibody-drug conjugates.

Follicular Lymphoma Patients Have a Varied Clinical Spectrum

Limited Stage | Advanced Stage

Low Risk FL | High Risk FL

Asymptomatic | Symptomatic

Low Tumor Burden | High Tumor Burden

What are the goals of treatment?

- Maximize efficacy
- Reduce the risk of relapse/transformation
- Limit short-/long-term toxicities
- Reduce the impact on quality of life (QOL)

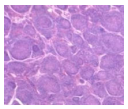
The first thing to recognize is follicular lymphoma is a very heterogeneous disease. Some patients will present with limited stage, so that's the minority. The majority will actually present with advanced stage. Some of those patients will be asymptomatic versus others may be grossly symptomatic. That does not always correlate with the amount of disease burden, in my experience.

What are the goals of our treatment and how do we put this into context, given the heterogeneity of presentation and the clinical course over time? I think it's important that we always want to maximize our efficacy while reducing the potential negative impact on quality of life as it pertains to toxicity. Obviously, we want patients to have a long normal lifespan.

What is going to potentially put them at risk for that not being true? Usually, it's disease progression, transformation, or potentially treatment-related toxicity. We balance that again with the efficacy of a given therapy, and hopefully, a reduced impact on quality of life.

FL: Histology and Grading

IMMUNOHISTOCHEMISTRY:



'follicle' growth pattern

Pan B cell markers:
CD19, CD20, CD22, CD79a

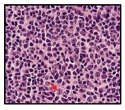
Germinal center markers:
BCL6, CD10

High BCL2 expression
Important neg: CD5/CD23/cyclin D1-ve

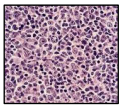
FISH: t(14;18) – not routinely done
- 85% of advanced FL
- 50% of early stage FL

GRADING:

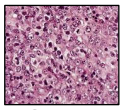
Grade	Description
1	≤5 centroblasts/HPF
2	6-15 centroblasts/HPF
3a	>15 centroblasts/HPF; centroblasts with intermingled centrocytes
3b	>15 centroblasts/HPF; pure sheets of centroblasts



Grade 1: Mostly Centrocytes



Grade 2: Mixed



Grade 3: Mostly Centroblasts

Treatment paradigms differ by grade: FL 1-3a (as FL); 3B (as DLBCL)

When we consider follicular lymphoma, there is also heterogeneity in terms of the histology and grading. You can see here the classic phenotype as described by immunohistochemistry or flow cytometry markers. This is a germinal center-derived B-cell lymphoma. The hallmark is translocation 14:18. Though this is generally present on the vast majority of cases, it's not necessary for all patients to be diagnosed with follicular, it is just a very common finding.

Grading is also somewhat controversial in that it's quite subjective. The difference between grade one and two is not clinically significant. Generally, we oftentimes will lump them together. Grade three A is designated by the number of centroblasts per high power field and distinguishing 3B from diffuse large B cell lymphoma requires a skilled hematopathologist.

Again, though it's relevant to understand the grading of follicular lymphoma, placing a large amount of decision based off of this finding, I think it's probably not well supported just based off of the subjectivity of this determination.

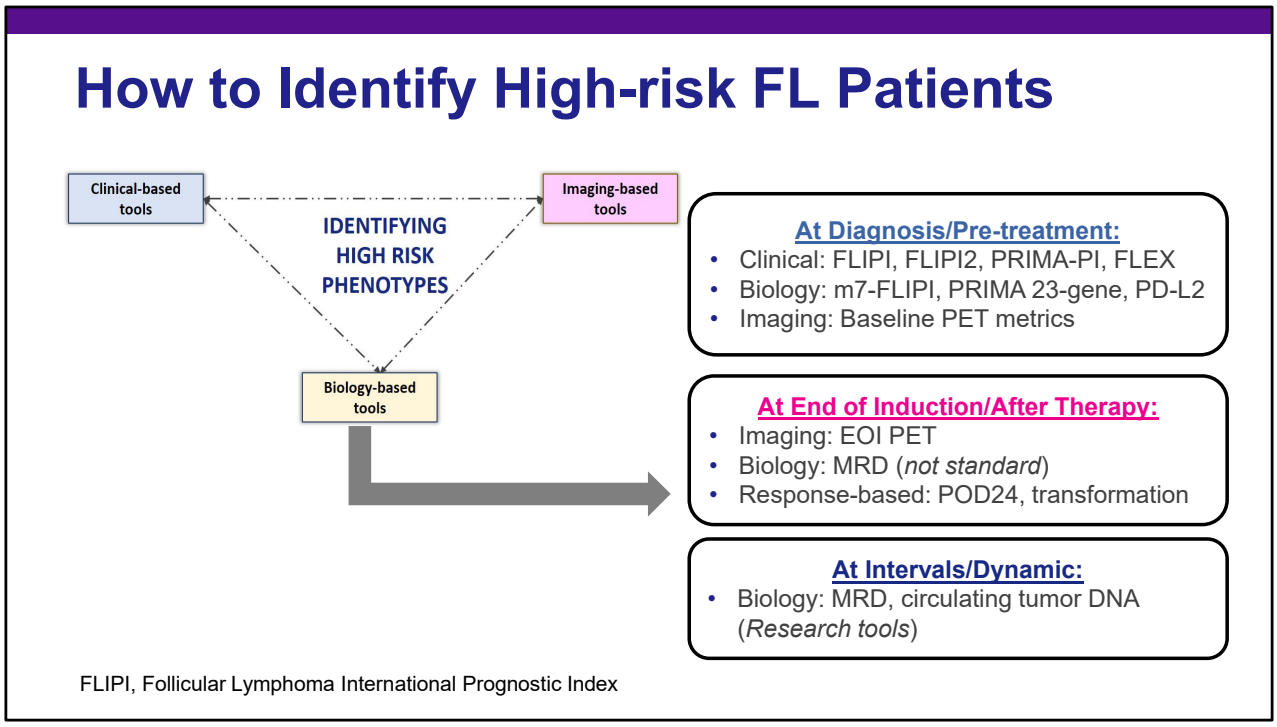
Indications for Initiating Treatment in FL: GELF and BNLI Criteria

GELF Criteria[1]	BNLI Criteria[2]
High Tumor Bulk defined by: • *Any tumor mass >7 cm in diameter* • *At least 3 nodes in 3 distinct areas, each >3 cm* • *Symptomatic splenic enlargement* • *Organ compression* • *Ascites or pleural effusion* • *Cytopenias or leukemia phase*	Rapid disease progression in the preceding three months
Presence of systemic symptoms (B-symptoms)	Life-threatening organ involvement
Elevated serum LDH or b2-macroglobulin	Renal or liver infiltration
	Bone lesions
	Systemic symptoms or pruritus
	Hb <10 g/dL or WBC <3.0 x 10^9/L or platelet count <100 x 10^9/L; related to marrow involvement

1. Brice P, et al. *J Clin Oncol.* 1997;15:1110-1117. 2. Ardeshna KM, et al. *Lancet.* 2003;362:516-522.

It's also important to spend some time talking about when do we start treatment because there's also heterogeneity in terms of clinical practice. For most of our prospective studies, it's pretty clear that, for frontline patients, having one of these criteria, either the GELF, modified GELF, as has been modified three times over the last few decades, or the BNLI criteria, having one of these criteria suggested it's probably no longer safe to observe patients.

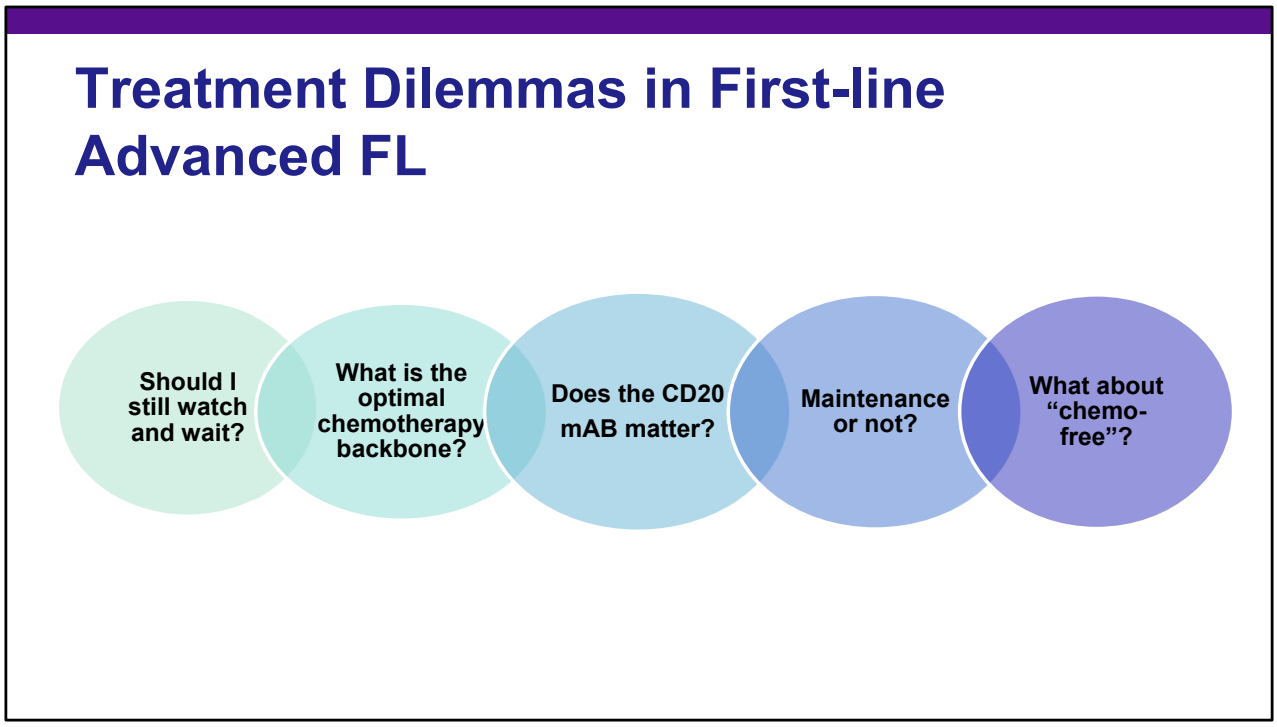
As seen here, those symptoms are included in both of these criteria. Again, in clinical practice, in my experience, it's not the majority of patients that have symptoms, so relying on that solely is probably not a good practice either. It would be really helpful to do a better job of risk-stratifying patients given the number of treatment options available. Not only to determining do they need treatment or are they appropriate for observation, but how aggressive should we be with that treatment.



There are a number of clinical tools available to us to try and risk-stratify patients. At diagnosis, there are a number of clinical prognostic models such as FLIPI, FLIPI2, the PRIMA-PI attempt to incorporate biology into these risk scores, include the m7-FLIPI or the PRIMA 23-gene. Though those can be helpful, they're not often readily available in the clinic, given some of that information may not be available to most clinicians. So PET-CT, for instance, in addition to the FLIPI score, is probably some of the more common tools used to try and identify who's appropriate for therapy and what does their 5 and 10-year survival rates look like.

The other time point to risk-stratify patients is the end of induction. PET-CR at the end of chemoimmunotherapy has been associated with prolonged PFS, and even improvement in overall survival. It's another time point that we may have a tool to help risk-stratify patients. Then a progression event within 24 months may designate higher-risk patients and currently identify as one of the greatest unmet needs.

Tools that are being studied, but not currently available to inform either risk or management strategies include circulating tumor DNA. Hopefully, in the next few years, these tools will also be included into this paradigm for how we might risk-stratify patients in informed treatment selection.



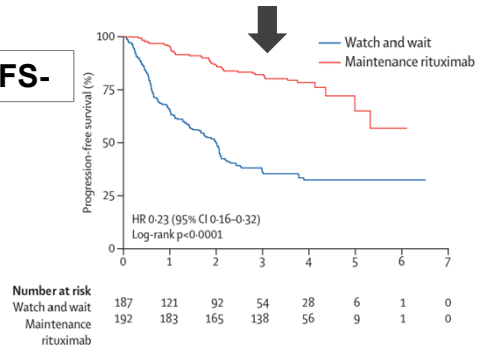
These are the current dilemmas in the frontline. Should I still watch weight in the modern era? If I'm going to use chemoimmunotherapy, what's the optimal chemotherapy backbone?

Does a CD20 matter such as rituximab or obinutuzumab? Now we have CD20/CD3 bispecific antibodies available in that third line or later setting that will likely move into earlier lines. Should you continue the CD20-directed therapy for an extended period of time in the form of maintenance? Then are there chemo-free options that are attractive for frontline follicular lymphoma?

Low Tumor Burden FL: Should I Still W&W?

Ardeshna Study[1]

PFS-



Improved PFS and TTNT:
Rituximab compared to Watch and Wait

Arguments for W&W

- Treatment does not impact OS
- 15-20% not received treatment after 10 years
- 12% spontaneous disease reduction

BUT:

- Median time to needing treatment: 2.5 years
- Psychological impact/QoL

W&W, watch and wait
Ardeshna KM, et al. *Lancet Oncol.* 2014;15:424-435.

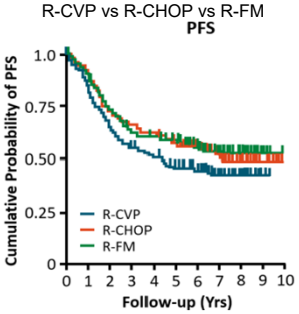
The first question about should we still observe patients in the modern era? The short answer is yes. That's based off of the Ardeshna study that demonstrated there's a good portion of patients at 10 years still have not been treated with follicular lymphoma if they were randomized to the observation arm.

On average, the median time to treatment is about two and a half years. Again, the overall survival in this group is still no different. Obviously, if you initiate treatment with single-agent rituximab, you're going to delay that first progression event. There are some patients where the psychology of having a cancer that's being observed may be more detrimental to them than not treating the lymphoma. If you're going to treat someone with low tumor burden, I think single-agent rituximab is a reasonable consideration, but it's still appropriate to observe patients in the modern era.

First-line FL Treatment: Is There an Optimal Chemotherapy Backbone?

FOLL05 Trial[1,2]

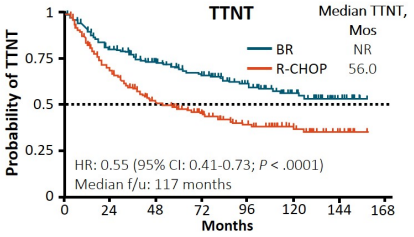
R-CVP vs R-CHOP vs R-FM



- R-CVP not as effective as R-CHOP/R-FM
- 3-fold 2° malignancies for R-FM-treated

STiL NHL1 Trial[3,4]

BR vs R-CHOP

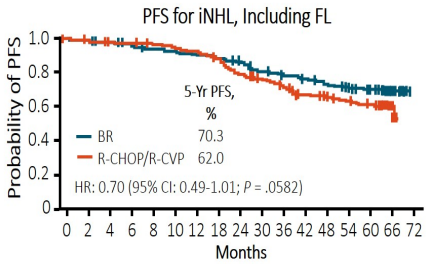


- STiL: Improved PFS and fewer toxicities with BR
- BRIGHT: Similar ORR, PFS; different toxicities

*No maintenance given in either study

BRIGHT Trial[5,6]

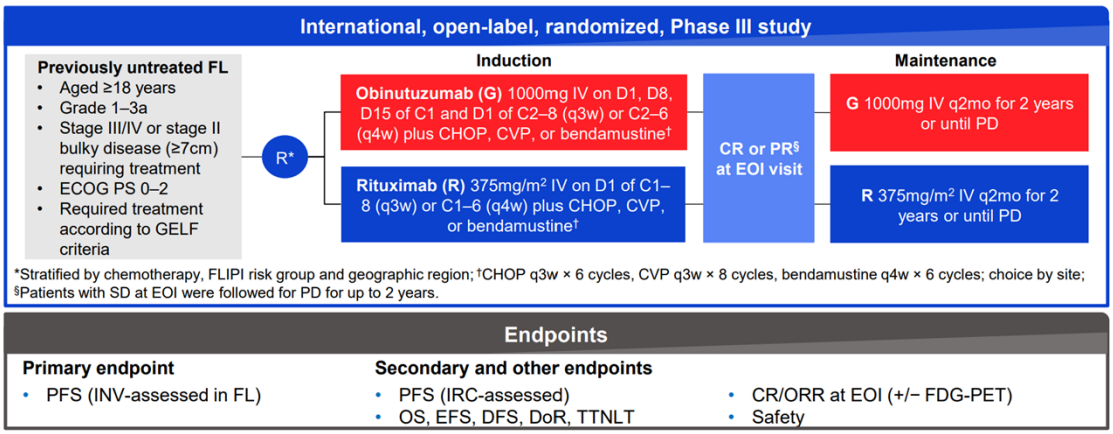
BR vs R-CHOP or R-CVP



1. Federico M, et al. *J Clin Oncol.* 2013;31:1506-1513. 2. Luminari S, et al. *J Clin Oncol.* 2018;36:689-696. 3. Rummel MJ, et al. *Lancet.* 2013;381:1203-1210. 4. Rummel MJ, et al. ASCO 2017. Abstract 7501. 5. Flinn IW, et al. *Blood.* 2014;123:2944-2952. 6. Flinn IW, et al. *J Clin Oncol.* 2019;37:984-991.

For patients who have high tumor burden or in need of systemic therapy, you have three chemotherapy backbone options that have been studied across a number of trials. The difference in the efficacy of the different chemo backbones, really probably about the only difference, is improvement in progression-free survival in the STIL study that looked at bendamustine, rituximab versus R-CHOP. Again, no difference in overall survival, and in the Bright study, bendamustine- rituximab was not inferior to R-CHOP or R-CVP. I think you need to use any of those options if you're considering chemotherapy.

Which Anti-CD20? Rituximab vs Obinutuzumab: Final Analysis of the GALLIUM Study



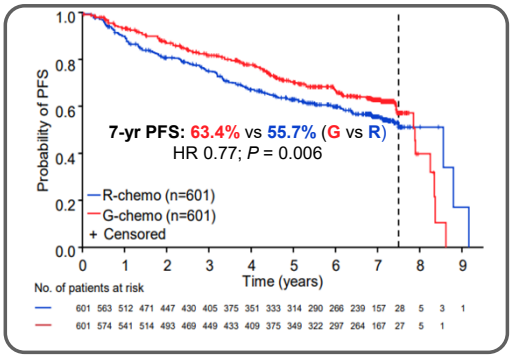
N =1202 previously untreated advanced FL patients

Marcus R, et al. *N Engl J Med*. 2017;377:1331-1344.; Townsend W, et al. EHA 2022. Abstract S206.

An important positive phase three study is the GALLIUM trial that set out to determine was obinutuzumab is superior antibody to rituximab. There's some important features of how the study was conducted and that, as a center, the chemotherapy backbone was established. It was not selected based off of patient specific characteristics, and that may have introduced some variables that impacted some of the findings.

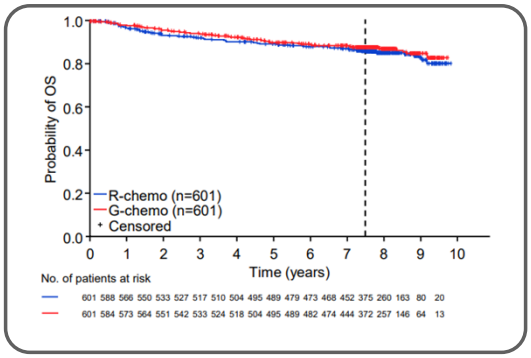
Final Analysis of the GALLIUM Study: PFS and OS

PFS: G-chemo vs R-chemo



PFS benefit maintained with G-chemo vs R-chemo

OS: G-chemo vs R-chemo



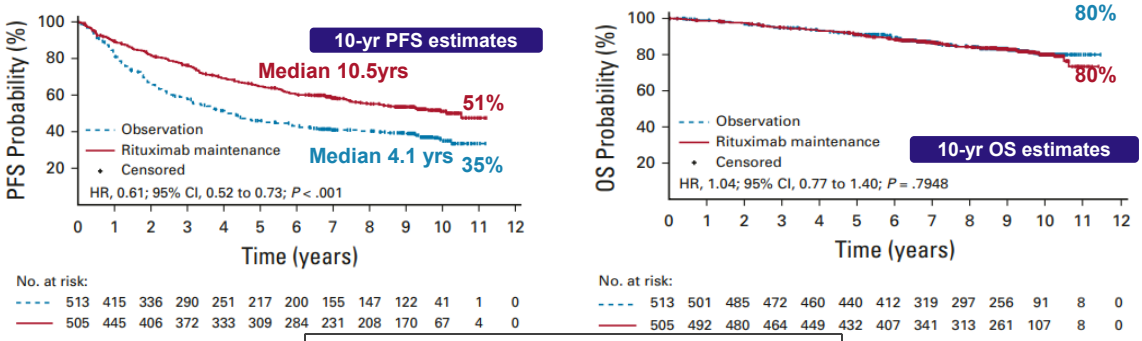
Overall survival similar between G-chemo vs R-chemo

Townsend W, et al. EHA 2022. Abstract S206.

Nonetheless, when we look at now a more mature follow-up of the GALLIUM study, obinutuzumab when combined with chemotherapy, either bendamustine, CHOP or CVP, did result in significant improvement in progression-free survival, albeit a modest improvement and no difference in overall survival. Slightly higher rates of grade three or higher infusion reaction or neutropenia in the obinutuzumab-containing arm. Again, it is a risk-benefit discussion.

Value in Adding Maintenance After First-line Rituximab Chemotherapy?

Yes, it Increases PFS: PRIMA Study Update



Comments:
- In PRIMA, no BR as induction
- No PET to assess EOI response
- Value in BR/OB-treated patients unclear

Salles G, et al. *Lancet.* 2011;377:42-51.; Bachy E, et al. *J Clin Oncol.* 2019;37:2815-2824.

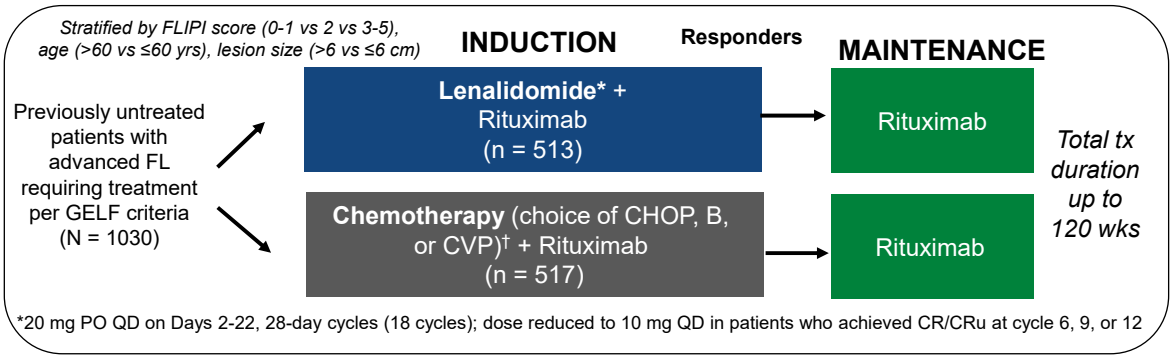
Should all patients get maintenance? That was not a question answered by the GALLIUM study. All patients that had at least a partial response after chemoimmunotherapy induction did go on to receive additional two years of maintenance.

The PRIMA study, which one of the limitations of this trial, there was no bendamustine in the induction, by continuing rituximab maintenance for two additional years after induction did result in a significant improvement in PFS of about 10 and a half years versus about four years of patients, were observed. Again, despite that dramatic difference, still no difference in overall survival.

In the era of COVID, I think it was a little bit harder to justify continuing CD20 exposure in patients that were in a response, particularly given the potential risk of infectious complications. Nonetheless, you can extend the PFS by quite a long time with maintenance rituximab.

Can We Improve Upon First-line: Chemo-Free Combination?
RELEVANCE trial – R^2 (Rituximab + Lenalidomide) vs R-Chemo

- International, randomized phase 3 study



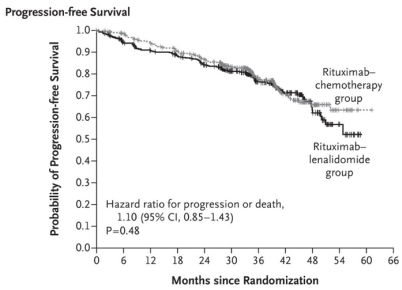
- Co-primary endpoints (superiority): CR/CRu at 120 wks, PFS

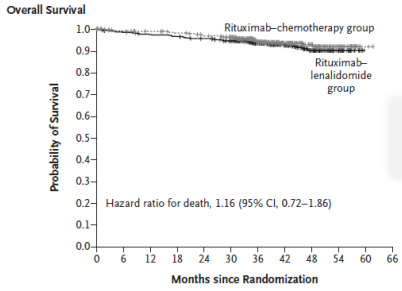
Morschhauser F, et al. *N Engl J Med.* 2018;379:934-947.

Is there a non-chemo option? The RELEVANCE study set out to answer that question. These were high tumor advanced-stage follicular lymphoma patients randomized to either lenalidomide and rituximab versus rituximab and chemo followed by two years of maintenance. The experimental arm had 18 cycles of the combination.

Now, there was a dose adjustment based off of response after the first six cycles where patients could be dose reduced if they were in a CR with lenalidomide down to 10 milligrams starting at 20 and then again rituximab after 18 cycles continued as monotherapy, so that the endpoint on both arms was similar.

Can We Improve Upon First-line: Chemo-Free Combination?
RELEVANCE trial – R^2 (Rituximab + Lenalidomide) vs R-Chemo





R^2 comparable to R-chemo

Safety

Higher grade 3-4 neutropenias in R-chemo (50% vs 32%)
Higher grade 3-4 cutaneous rxns in R^2 (7% vs 1%)

Outcomes

	R-chemo N = 517	R^2 N = 513
3-yr PFS % (95% CI)	78 (74-82)	77 (72-80)
CR rates (%)	33	28
3-yr OS %	94	94

Morschhauser F, et al. *N Engl J Med.* 2018;379:934-947.

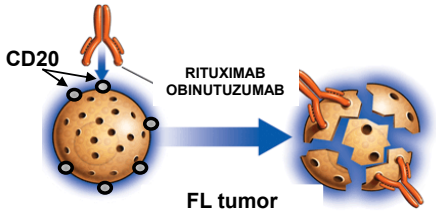
What we found, there was absolutely no difference in progression-free survival or overall survival. Though there was potentially some safety advantages in the lenalidomide-rituximab arm, less grade three or higher neutropenias, and a much lower rate of prophylactic growth factor use, there was higher cutaneous reactions such as rash in the lenalidomide-containing arm.

At the end of the day, this was a negative study, but it was at least intriguing that a non-chemo option had pretty similar efficacy in this large randomized phase-three study.

Summary of Frontline Treatment in Advanced FL in 2022

Anti-CD20 + chemotherapy remains the standard first-line therapy

- BR, R-CHOP, R-CVP – choice is patient-specific
- Rituximab maintenance improves PFS, but no difference in OS
- Obinutuzumab-chemo improves PFS, but no difference in OS compared to R-chemo
- R2 – not superior to R-chemo, but appears comparable, potential option if the goal is to avoid chemotherapy



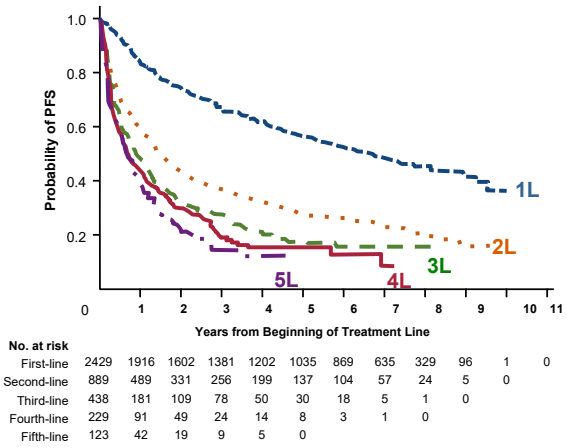
To summarize frontline, we have several options none of which have resulted in a significant difference in overall survival, so they're all reasonable options.
For low tumor-burden patients, observation is still appropriate. For high tumor-burden patients, chemoimmunotherapy is probably one of the most common approaches, and you can choose your chemo based off of patient-specific characteristics and their goals of treatment.

Relapsed/Refractory (R/R) FL

- Patients with FL will experience multiple relapses
- Sharply decreasing length of PFS after first relapse

Treatment Line	Median PFS, Years (95% CI)
First	6.62 (6.10-7.20)
Second	1.50 (1.35-1.70)
Third	0.83 (0.68-1.09)
Fourth	0.69 (0.50-0.97)
Fifth	0.68 (0.43-0.88)

Link BK, et al. *Br J Haematol*. 2019;184:660.

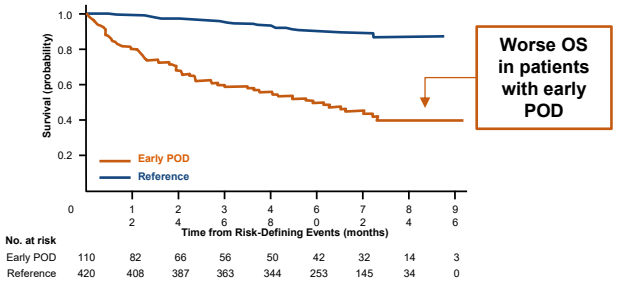


When we move into the relapse refractory setting, that's probably where more changes have emerged in the last few years. Historically, we have viewed this disease as one of a relapsing and remitting disease with remission durations getting shorter and shorter with subsequent lines of therapy. That was still true in the rituximab era.

This was an observational cohort reported on by Brian Link suggesting that yes, once we get into that second line and later, particularly third line and later, most PFS estimates are going to be around a year.

R/R FL: Important Considerations

- Biopsy recommended to detect histologic transformation of FL, which is reported to occur at a rate of 2% per year[1]
  - Treated as DLBCL[2]
- Early progression of disease (≤2 years) after frontline chemoimmunotherapy (POD24) occurs in approximately 20% of patients
  - Associated with a poor prognosis and represents an unmet medical need in FL[3]
  - Represents a population requiring novel intervention with non-chemo immuntherapeutic agents



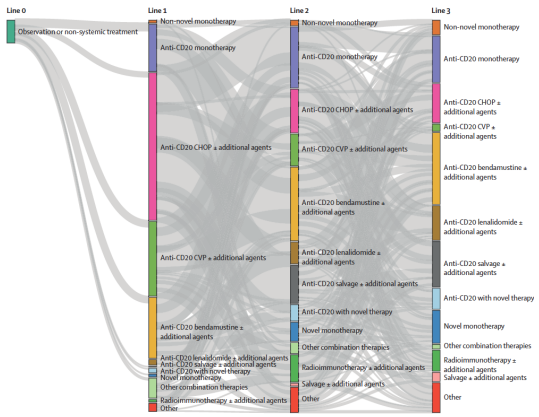
1. Link BK, et al. *J Clin Oncol.* 2013;31:3272. 2. Casulo C, Barr PM. *Blood.* 2019;133:1540. 3. Casulo C, et al. *J Clin Oncol.* 2015;33:2516.

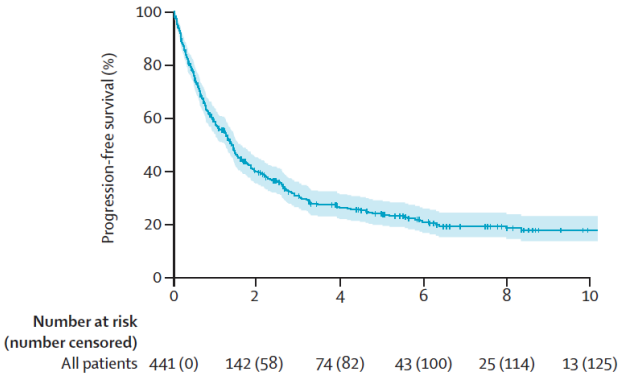
Can we do better at risk-stratifying other than just approaching all relapsed refractory patients equally? One way to potentially risk-stratify patients, as I alluded to, is a progression event within 24 months. This was an observational study reported by Carla Casulo suggesting that patients who had chemoimmunotherapy upfront, including R-CHOP, if they experienced a progression within two years, their median overall survival is about five years.

Whereas the other group of patients, which was about 80% of her cohort, if they experienced a progression event beyond that 24 month or not at all, their overall survival is the same as an age-sex match cohort of patients, suggesting those patients are going to do very well. Those that relapse early are going to be facing much far inferior outcomes.

One of the limitations of this study is that biopsies were not routinely done to confirm that this was still follicular not transformation, for instance. The vast majority had R-CHOP. How does this apply to the GALLIUM data, for instance, or have bendamustine cohort? There have been other data sets looking into this. In general, the outcomes are still poor for those with relapsed follicular lymphoma within 24 months.

Outcomes in FL: Third-line and Beyond



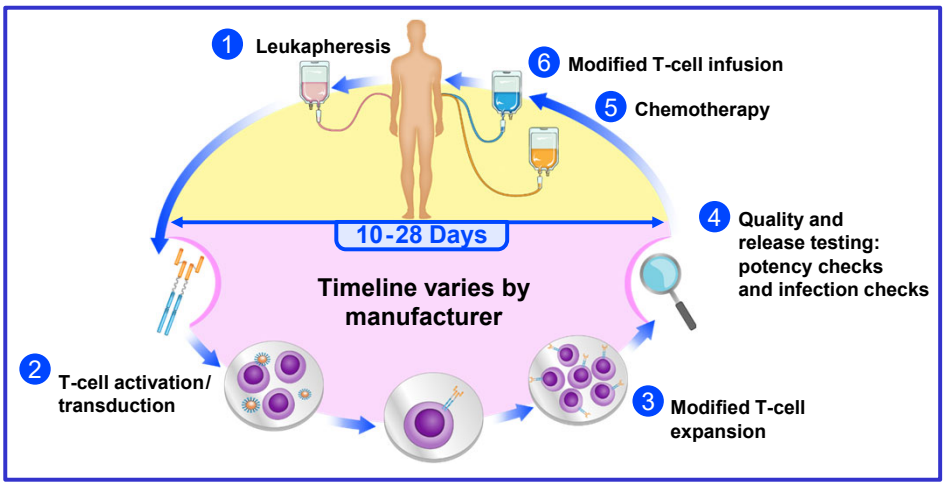


Casulo C, et al. *Lancet Haematol.* 2022;9:e289-e300.

Probably the greatest unmet need is third line and beyond. This just illustrates that the treatment can be so heterogeneous. Once we start walking you through some of the emerging data, recognize that how patients got to third line can be grossly different, some of which can be rituximab monotherapy, some may have had two different courses of chemoimmunotherapy.

Again, it's hard to generalize outcomes across all these studies, but it does-- at least I can conclude that the unmet need is for third line and beyond for follicular lymphoma.

Overview of CAR-T Therapy



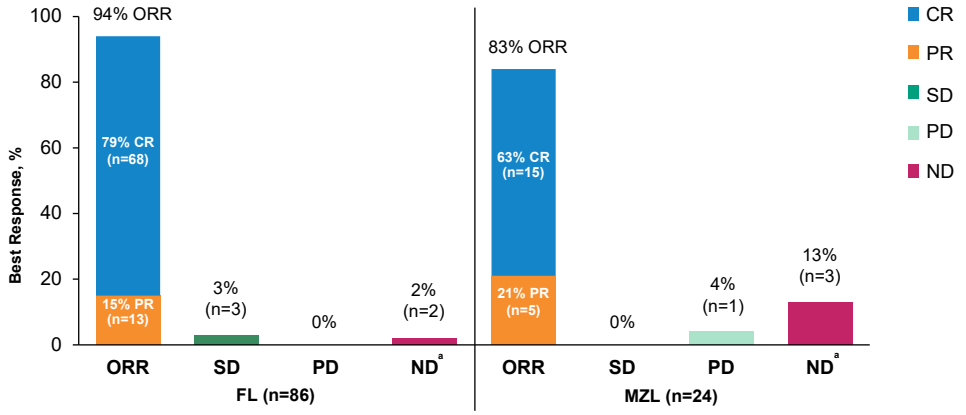
I'm going to start the discussion in this space by covering CAR T-cell therapy.

Just to remind everyone, this does require patients be identified as appropriate candidates for CAR because we use an autologous product. They have to undergo leukapheresis and then manufacturing occurs, currently using a viral vector to introduce the extracellular material that's going to bind CD19, which is on the surface of malignant B-cell and normal B-cells to grow up in culture.

There's an additional modification that they have two co-stimulatory domains, that once they engage their target, they're more primed to release cytokines, expand and bring in other immune cell reinforcement to that site.

Once they undergo a quality check, they're sent back to the originating site. Patients have to undergo lymphocyte-depleting chemotherapy and then cell infusion. Then they're monitored for the first 30 days for acute toxicity.

ZUMA-5 Outcomes: ORR and CR



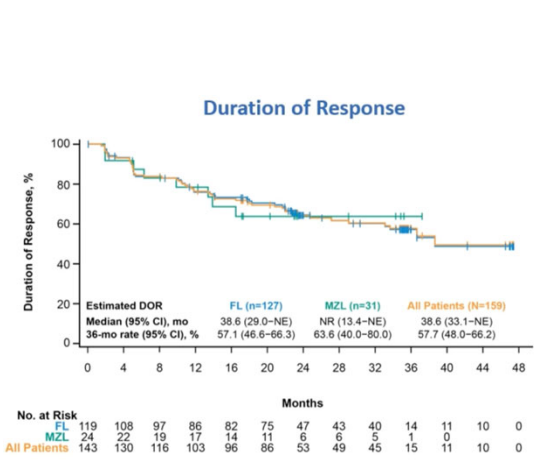
Neelapu SS, et al. ASH 2021. Abstract 93.

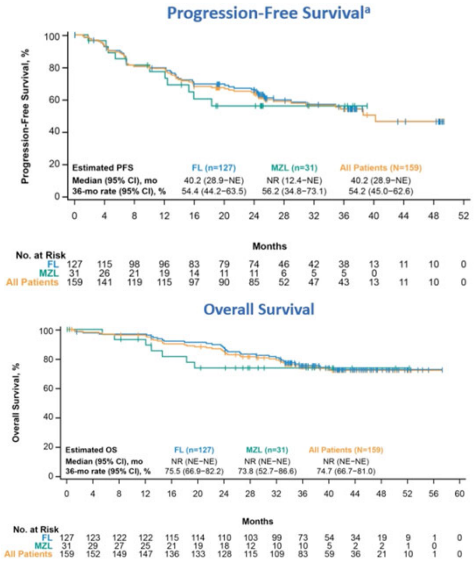
ZUMA-5 led to FDA approval of Axi-cel for relapse refractory follicular lymphoma after two prior lines of therapy. To qualify for the single-arm phase two study, patients had to have at least two prior lines of therapy that included an alkylator and CD20 antibody.

They were young for a follicular cohort, pretty heavily pre-treated. Most were refractory to their last line of therapy and over-rich for POD24 status. Suggesting again, for this more intensive approach, those were the types of patients with follicular lymphoma that were considered for this treatment.

Despite that, the response rates are quite high. You can see 79% of this cohort of a little over 100 patients achieved a complete response. Very few patients with stable disease.

ZUMA-5 Outcomes: DOR, PFS, OS - ASH 2022





Neelapu SS, et al. ASH 2022. Abstract 4660.

That did appear to be durable. We did see updates this year at ASH with three years of BDN follow-up now. Again, quite impressive progression-free survival duration response and overall survival for this heavily pre-treated cohort of patients.

If you look closely at the follicular lymphoma, it's about a median PFS of about 40 months for patients who received Axi-cel in that third line or later setting.

ZUMA-5 Outcomes by POD24 Status – ASH 2022

Parameter (95% CI)	Follicular Lymphoma (n=127)[a]	
	With POD24 (n=63)	Without POD24 (n=40)
Median DOR, months	NR (36.6–NE)	NR (24.7–NE)
36-month rate, %	64.6 (50.9–75.3)	52.7 (33.9–68.4)
Median PFS, months	40.2 (15.9–NE)	NR (25.4–NE)
36-month rate, %	59.2 (46.3–70.0)	52.2 (33.4–68.0)
Median OS, months	NR (NE–NE)	NR (NE–NE)
36-month rate, %	75.4 (63.4–83.9)	73.8 (56.5–85.0)

Neelapu SS, et al. ASH 2022. Abstract 4660.

When we look across subgroups, the POD24 patients, which is viewed to be a great unmet need, you can see the median PFS was about 40 months in that group, because again, that was the majority of patients included in the study. Those that didn't have this high risk or were not this high-risk designation did even better. median PFS not reached.

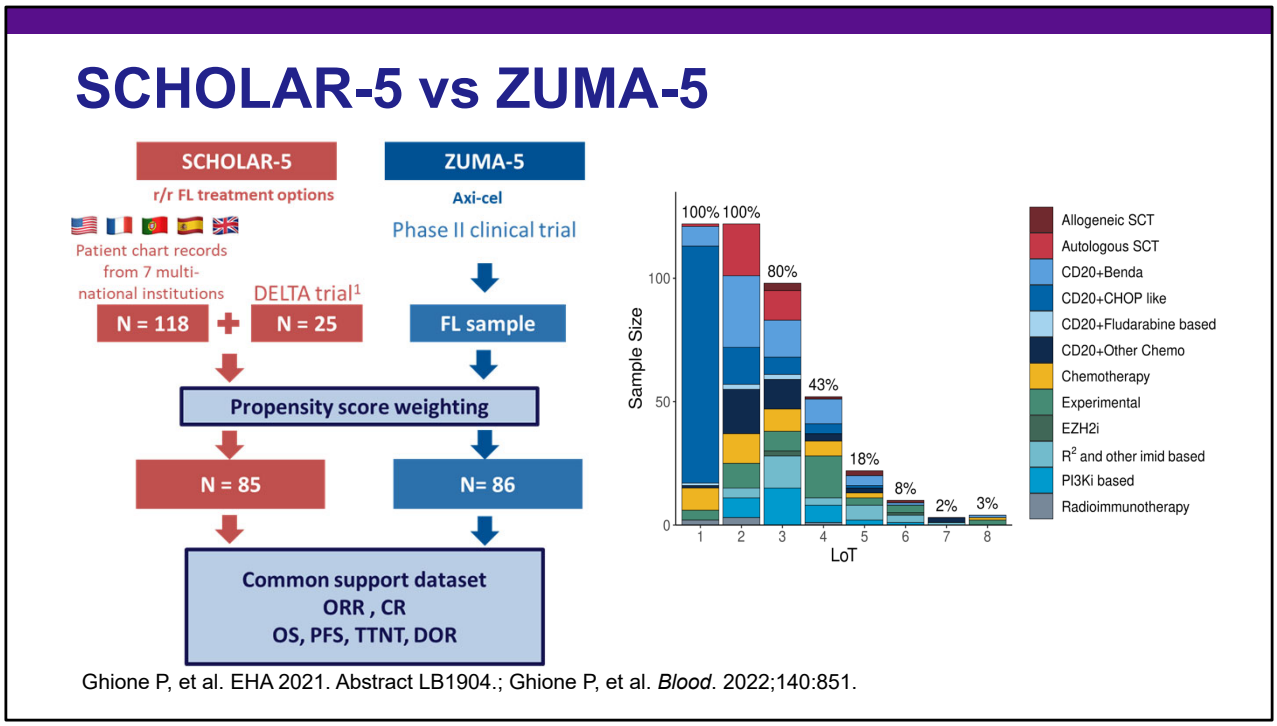
ZUMA-5 CRS and Neurologic Events

Parameter	CRS[a] FL (n=124)	CRS[a] MZL (n=22)	CRS[a] All Patients (N=146)	Neurologic Events[a] FL (n=124)	Neurologic Events[a] MZL (n=22)	Neurologic Events[a] All Patients (N=146)
Any grade	97 (78)	22 (100)	119 (82)	70 (56)	17 (77)	87 (60)
Grade ≥3	8 (6)	2 (9)	10 (7)	19 (15)	9 (41)	28 (19)
Most common CRS symptoms of any grade, n/n (%)						
Pyrexia	94/97 (97)	20/22 (91)	114/119 (96)	–	–	–
Hypotension	39/97 (40)	10/22 (45)	49/119 (41)	–	–	–
Most common neurologic events of any grade, n/n (%)						
Tremor	–	–	–	36/70 (51)	9/17 (53)	45/87 (52)
Confusional state	–	–	–	28/70 (40)	7/17 (41)	35/87 (40)
Tocilizumab use, n (%)	56 (45)	15 (68)	71 (49)	7 (6)	2 (9)	9 (6)
Corticosteroid use, n (%)	19 (15)	6 (27)	25 (17)	38 (31)	14 (64)	52 (36)
Median time to onset (range), days	4 (1–15)	4 (1–9)	4 (1–15)	7 (1–177)	7 (3–19)	7 (1–177)
Median duration of events (range), days	6 (1–27)	6 (2–14)	6 (1–27)	14 (1–452)	10 (2–81)	14 (1–452)
Patients with resolved events, n/n (%)	96/97 (99)[b]	22/22 (100)	118/119 (99)[b]	67/70 (96)	14/17 (82)	81/87 (93)

Jacobson CA, et al. ASH 2020. Abstract 700.

You can't talk about CAR-T and not at least recognize the acute toxicity cytokine release syndrome and ICANS or neurologic events, which are toxicities associated with cellular therapies that generally occur within the first one to two weeks.

You can see here, looking at specifically the follicular cohort in this study, you can't compare cross studies, but at least in my experience, a bit lower rates of grade three or higher CRS or ICANS with Axi-cel and follicular than what we might expect in more aggressive lymphoma subtypes. That being said, still 15% experienced grade three or higher ICANS. About a third of patients received corticosteroids to address these acute toxicities.



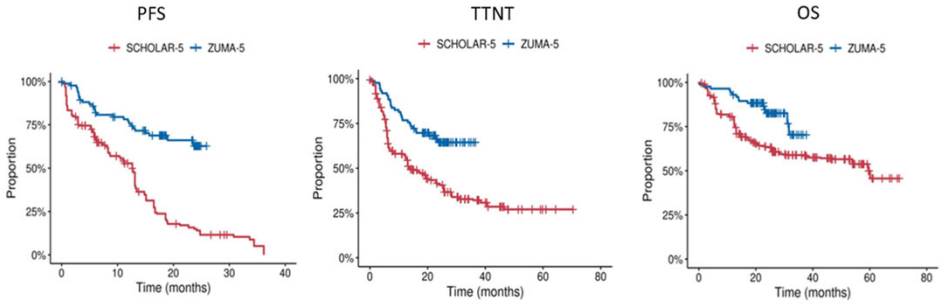
Ghione P, et al. EHA 2021. Abstract LB1904.; Ghione P, et al. *Blood*. 2022;140:851.

This was an attempt to try and identify how does this compare to the current treatment landscape. This was a retrospective cohort of patients treated with standard-of-care therapies, many of which were enrolled from outside of the US. There were patients treated in the US. I mention that because the treatment options are going to be so vastly different depending on where you recruit these patients.

You can see how many prior lines of therapy and what those lines of therapy, just illustrating how heterogeneous the treatment options are for patients with follicular lymphoma.

SCHOLAR-5 vs ZUMA-5

Among patients who failed ≥2 prior lines of therapy (LoT)		SCHOLAR-5	ZUMA-5	Odds Ratio (95% CI)	p-value
Overall response rate	Yes	42 (49.9%)	81 (94.2%)	16.24 (5.63, 46.85)	<0.0001
	No	43 (50.1%)	5 (5.8%)		
Complete response	Yes	25 (29.9%)*	68 (79.1%) **	8.86 (4.3, 18.25)	<0.0001
	No	60 (70.1%)	18 (20.9%)		



Ghione P, et al. EHA 2021. Abstract LB1904.

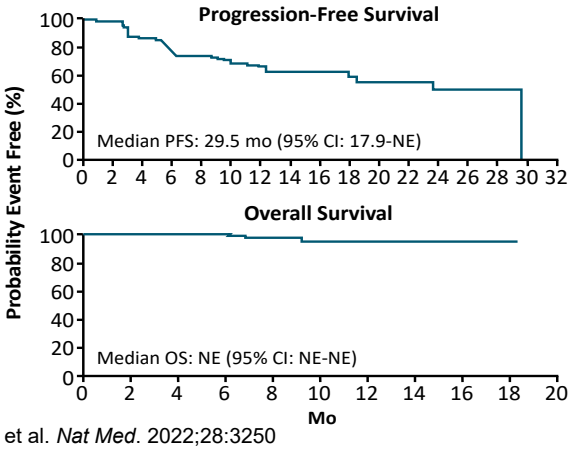
When you look at this retrospective comparison of the outcomes observed in the ZUMA-5 versus what was achieved with standard-of-care therapies for this patient group, you can see it does appear that Axi-cel can result in quite favorable outcomes and will likely compete quite favorably with the treatment landscape. A randomized study is underway currently looking at Axi-cel versus R-squared, BR, or R-CHOP.

ELARA: Tisagenlecleucel for Patients With Relapsed/Refractory FL

- Single-arm phase II study of tisagenlecleucel for patients with R/R FL (N = 97)

Outcome	Evaluable Patients (n = 94)
ORR (IRC), n (%)	81 (86.2)
▪ CR	65 (69.1)
▪ PR	16 (17.0)
▪ SD	3 (3.2)
▪ PD	9 (9.6)
▪ ND	1 (1.1)
Median DoR, mo (95% CI)	NE (15.6-NE)
9-mo DoR, % (95% CI)	76.0 (64.6-84.2)

- CRS, 49% (grade ≥3, 0%); neurotoxicity, 10% (grade ≥3, 1%)



Thieblemont C, et al. ASH 2021. Abstract 131.; Fowler NH, et al. *Nat Med*. 2022;28:3250

Here is a second FDA-approved CAR T-cell therapy, tisagenlecleucel, or tisa-cel for relapsed refractory follicular lymphoma. A similar eligibility criteria in that patients had to have had at least two prior lines of therapy that included an alkylator and CD20 antibody.

You can see here quite favorable progression-free survival media PFS of about 30 months, quite favorable overall survival, and quite notable complete response rate of about 69%. Most notable to me is that the toxicity looks to be very favorable. No grade three or higher CRS, and only 1% experienced a grade 3 or higher ICANS that did fully resolve.

ELARA Long-term Follow-up: ASH 2022

- No new safety signals
- Response rates in high-risk groups:

Characteristic	All Pts (N = 97)	CRR, %	ORR, %
POD24	61 (63)	59 (46-71)	82 (70-91)
High metabolic tumor volume	20 (21)	40 (19-64)	75 (51-91)
Bulky disease	62 (64)	65 (51-76)	86 (74-93)
Double refractory	65 (67)	66 (53-77)	85 (74-92)
High FLIPI (≥3)	57 (59)	61 (48-74)	81 (68-90)

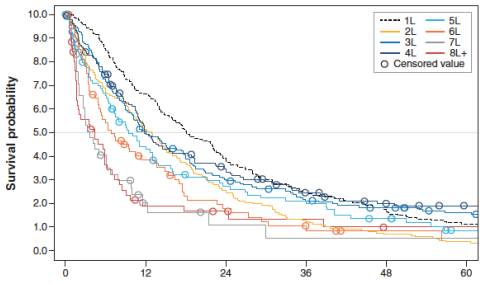
- Median DOR, PFS, OS, TTNT all not reached after median follow-up of 29 months

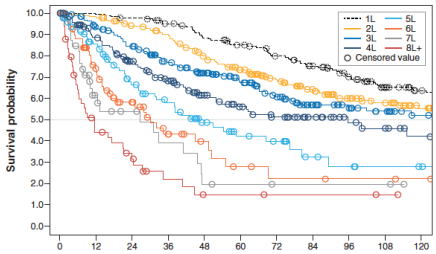
Clinical Outcome, %	All Pts (N = 81)	Pts in CR (n = 64)
DOR		
• 12-mo	74	87
• 24-mo	66	78
PFS		
• 12-mo	67	87
• 24-mo	57	75
OS		
• 12-mo	95	98
• 24-mo	88	95

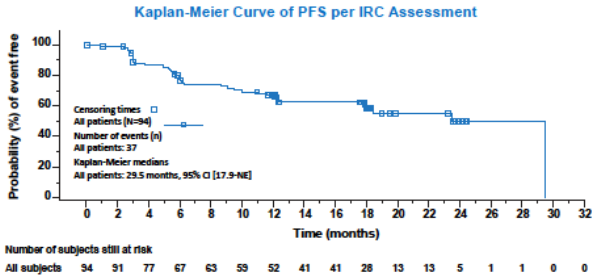
Dreyling M. ASH 2022. Abstract 608.

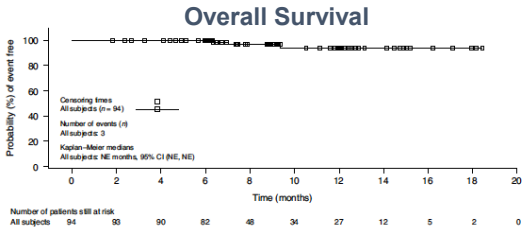
Again, when we saw updates this year at ASH across a number of poor risk subgroups including POD24, bulky disease, double refractory, high FLIPI score, you can see here we still see quite favorable responses. Maybe about the only outliers of the high metabolic tumor volume, maybe not quite as good a CR rate. Again, quite impressive given these high-risk features and high-risk population.

ReCORD-FL vs ELARA









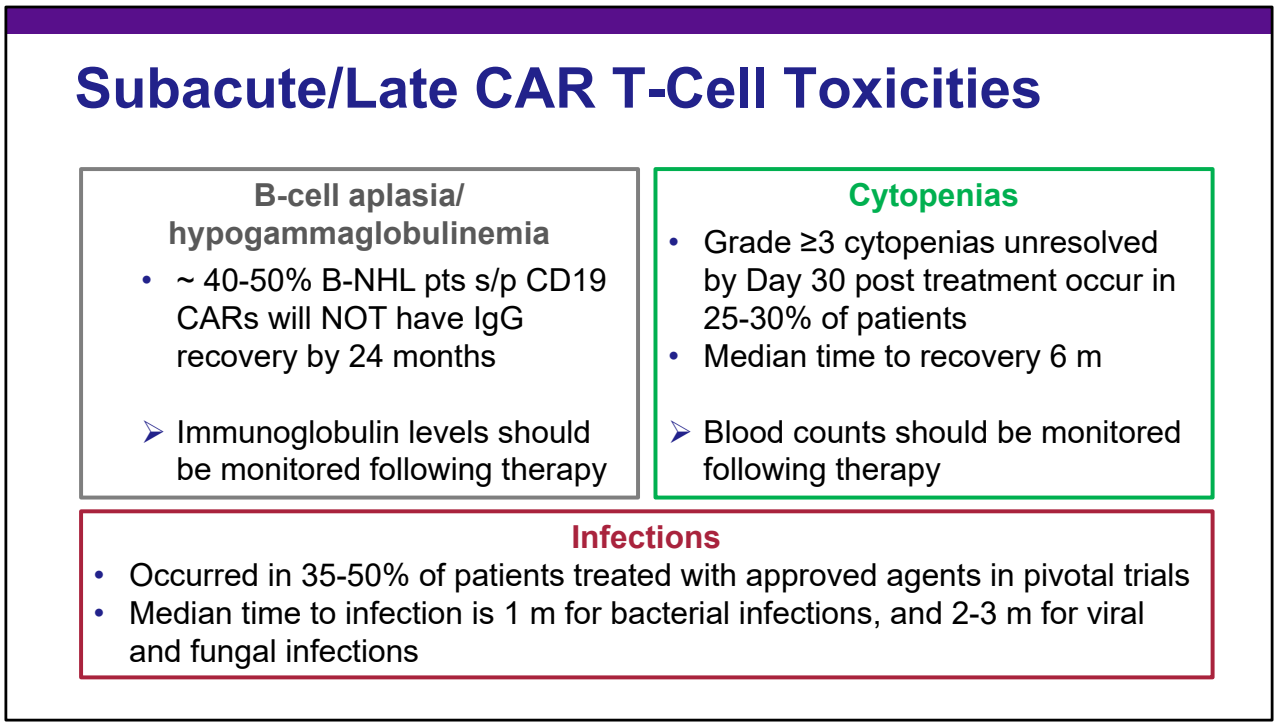
Fowler NH, et al. *Nat Med.* 2022;28:325-332.; Thieblemont C, et al. EHA 2021. Abstract 131.; Salles G. EHA 2022. Abstract S210.

Similar to what was done in SCHOLAR-5, an attempt to try and explore how tisa-cel might compete in the treatment landscape. Again, the outcomes look to be quite favorable with tisa-cel versus what may be achieved with other standard of care options.

Ongoing Clinical Trials of CAR T-Cell in FL

Trial	Design
TRANSCEND FL	Ph2 study of Liso-cel for FL or MZL in 2+L
ZUMA-22	Ph3 Randomized study of axi-cel in POD24 FL in 2L or all others in 3L vs SOC (BR, RCHOP, R^2)
ALLO501	Allogeneic CD19 CAR ALLO501 (+CD52 mAb ALLO647) in R/R LBCL and FL
NCT04007029	Ph 1 study of a CD19/CD20 CAR T-cell in R/R B-NHL
ADI-001	Ph 1 study of allogeneic anti-CD20 γδ CAR T-cells in R/R B-NHL

There are a number of ongoing clinical trials exploring CAR-T or cellular therapies, including allogeneic CAR, K-CARS for patients with relapsed or refractory follicular lymphoma, so stay tuned.



We have to also acknowledge the late toxicities associated with CAR-T as it pertains to eradicating CD19 positive cells, including B-cell aplasia or hypogammaglobulinemia that occurs in about half of patients that can extend well beyond one to two years.

Monitoring IgG levels, making sure patients are up to date on prophylactic strategies such as HSV, PJP prophylaxis for at least a year or until CD4 counts recover beyond 200. Then about a 25% to 30% of patients will have prolonged cytopenias that extend well beyond the first 30 days. Again, making sure that they're aware of potential bacterial and viral infections.

Practical Guidance for Late Toxicity

- Patients should be monitored for:
  - Prolonged cytopenias – transfusions as indicated; G-CSF as needed
  - B-cell aplasia (IgG levels) – replete with IVIG for levels <400, generally needed every 1-3 m
  - Infection
  - Relapse
  - Secondary malignancies
- Antibiotic (herpes and PJP) prophylaxis
  - Variable practices – we continue for at least 6 months; at which time we measure the CD4 count and only discontinue when >200
- Vaccination
  - Influenza – yearly
  - Post-transplant vaccines – resume 12 months after CAR T-cell therapy
    - Revaccination w/o prior transplant likely unnecessary for CD19 CARs; unclear with BCMA CARs
  - COVID vaccination – 3 months from CAR T-cell therapy (unknown)

The practical guidance on that is, again, somewhat controversial because we don't have a consensus on this, but some places will replace IVIG when IgG levels drop below 400. Again, it's our practice generally to maintain HSV and PJP prophylaxis until CD4 count is greater than 200 or a year, and then make sure patients are up to date on vaccinations.

Conclusions

- Outcomes for the majority of patients with FL are favorable
- Balancing the goals of therapy with patient specific characteristics generally informs treatment selection given the number of therapies available
- An unmet need is identifying optimal sequencing of therapy or predictive biomarkers
- The goal of treatment is to achieve a normal life expectancy without negatively impacting quality of life

Again, I'll conclude in terms of the heterogeneity and frontline. All the variable treatment options available to patients, so that generally requires an in-depth discussion about the potential risks and benefits, and personalizing the treatment choice based off of patient and disease characteristics, and balancing that with their goals of therapy.

Update on the Management of Follicular Lymphoma: Antibody Drug Conjugates and Bispecific Antibodies

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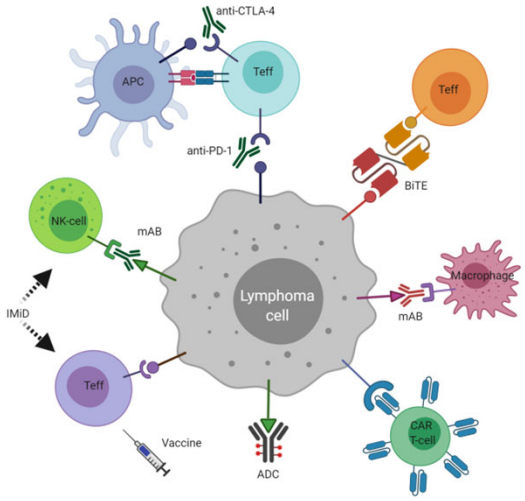
Director, Hematology Translational Research and
Director, Clinical Lymphoma Program
Perlmutter Cancer Center
New York, New York

Now I'm going to hand it over to Dr. Diefenbach to talk about some of the new emerging therapies that are quite exciting.

Thank you Dr. Nastoupil, and now I will go on. I'm going to talk to you about immune targets in lymphoma.

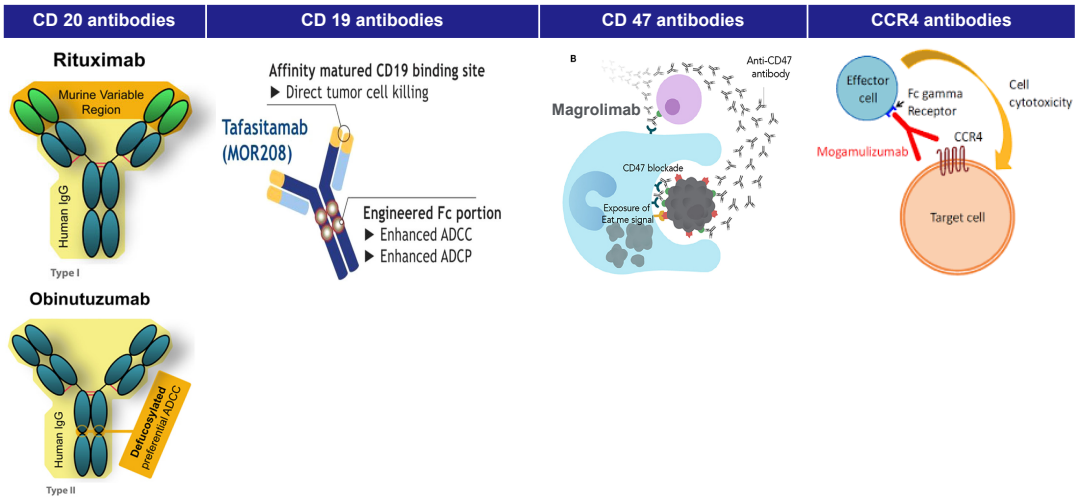
Overview of Immune Targets and Therapies in Lymphoma



I think Dr. Nastoupil has very artfully talked about CAR T cells, but there are many other targets on lymphoma cells that are worth targeting in an immunologic perspective. Here are some. Just to conceptualize what these therapies do. Bispecific antibodies are antibodies that have two arms rather than one. One arm, as you can see in this picture, grabs onto the antigen that's on the surface of the lymphoma cell.

The other arm grabs onto an antigen on the surface of a T-cell, often CD3, and basically brings the T-cell into proximity of the lymphoma cell and says, "Look T-cell, here's a foreign lymphoma cell. Eat this cell, get rid of it, destroy it." Thus the proximity is more stimulating to the T-cell than if they're just floating around in the milia and not recognizing the lymphoma cells. Then we have monoclonal antibodies such as rituximab, which are just antigen-antibody single conjugation. That usually will stimulate something like cytotoxicity through ADCC. Bispecific antibodies in consequence are very interesting because what they do is they use the antigen-antibody binding of a monoclonal antibody as a mechanism for delivery of a chemotherapy moiety.

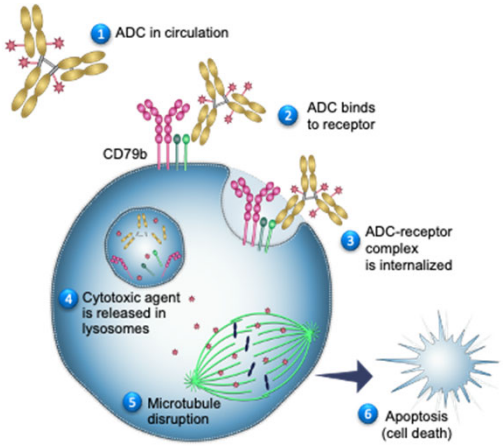
Monoclonal Antibodies



Ag, Biocom. "Incyte Licenses Morphosys' Tafasitamab." European Biotechnology - First and Foremost in European Biotech. Pierpont T, et al. *Front Oncol.* 2018;4;8:163.;Chao M, et al. *Front Oncol.* 2020;9:1380.

Here are some monoclonal antibodies that you know, such as rituximab or tafasitamab.

Polatuzumab

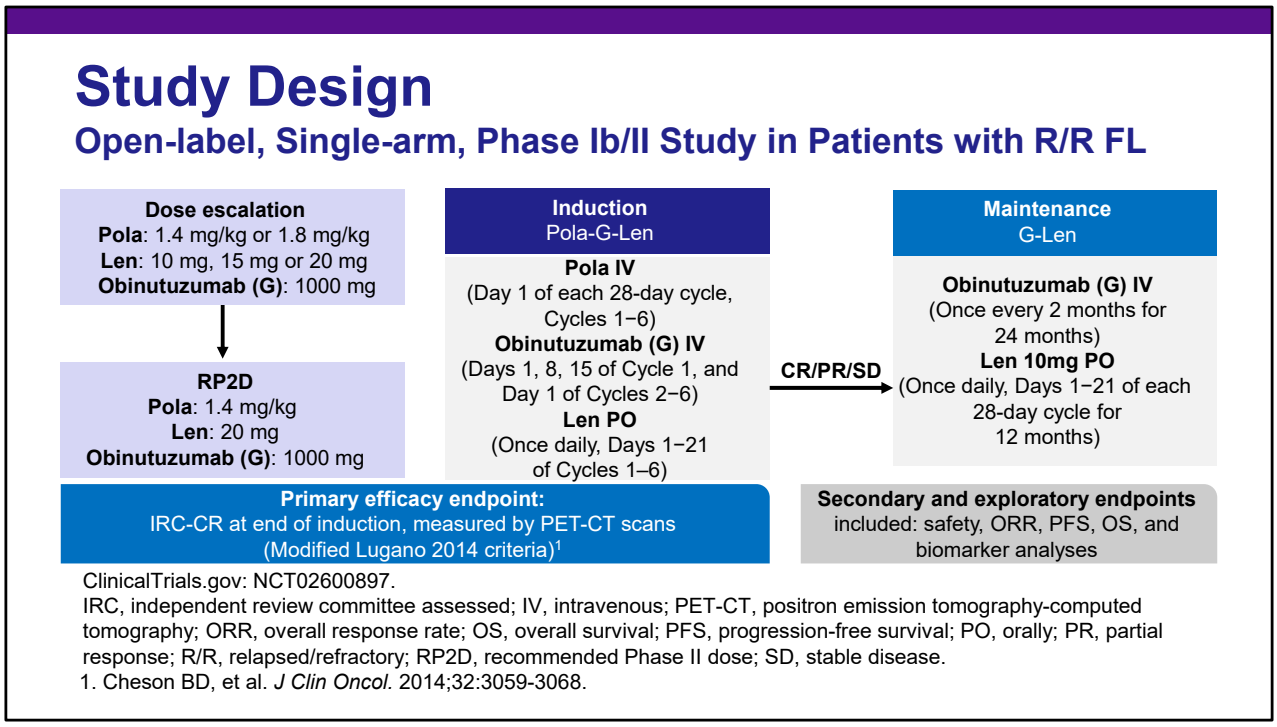


- Polatuzumab vedotin (Pola) is an ADC targeted to CD79b expressed on B-cell receptors, which delivers a potent microtubule-disrupting agent (MMAE) directly to tumor cells[1,2]
- In a heavily pre-treated and refractory FL population, Pola-G-Len demonstrated a CR rate of 63% (95% CI: 50–75, median follow-up 26.7 months)[3]
  - The novel triplet combination had a safety profile consistent with the known profiles of the individual drugs[3]
- Here, we report the **final safety and efficacy results from this Phase Ib/II study**

ADC, antibody-drug conjugate; CI, confidence interval; CR, complete response; FL, follicular lymphoma; G, Obinutuzumab; Len, lenalidomide; MMAE, monomethyl auristatin E; Pola, polatuzumab vedotin.
1. Polson AG, et al. *Blood*. 2007;110:616-623. 2. Francisco JA, et al. *Blood*. 2003;102:1458-1465. 3. Diefenbach C, et al. *Lancet Haematol*. 2021;8:e891-e901.

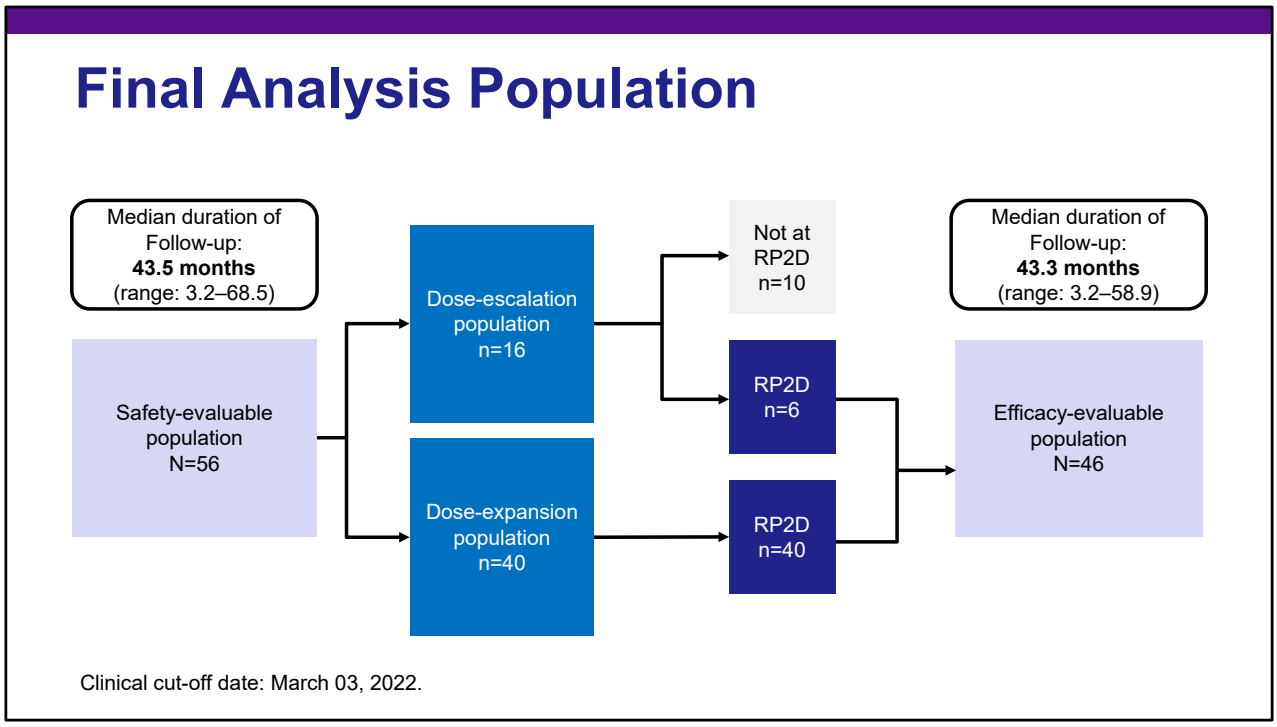
Antibody-drug conjugates such as polatuzumab which I'm going to talk to you about today, target an antigen that's on the surface of the T-cell or the B-cell in this case, CD79b, which is on the surface of the B-cell, and uses this antigen-antibody binding to deliver a microtubule disrupting toxin in this case, MMAE directly to the tumor cells. It is, if you will, a Trojan horse, it is not itself the antigen-antibody binding that causes the therapeutic effect, but the byproduct of the antigen-antibody binding, which is the opsonization of the chemotherapy moiety.

Polatuzumab was looked at in combination with bendamustine in large cell lymphoma. This is now a combination in the follicular population of polatuzumab with obinutuzumab, the monoclonal antibody and lenalidomide in combination in follicular lymphoma. I'll report to you the final safety and efficacy results from the phase one B2 study that were reported in ASH this year.



This was a single-arm phase one B2 study in which patients received polatuzumab at either 1.4, 1.8 mg/kg, lenalidomide in escalating doses, and obinutuzumab at standard dose of a thousand mg. The recommended phase two dose was 20 of Len and 1.4 of Pola with a thousand mg of Len.

In induction, patients received six cycles of therapy. Patients who then had a CR/PR/SD clinical benefit were able to move on to maintenance where they got obinutuzumab once every two months for 24 months and lenalidomide daily for 21 of 28 days. The primary endpoint was IRC-CR assessed at the end of induction measured by PET-CT scans. Secondary endpoint included overall response, PFS, OS, and biomarker analysis.



In the final analysis population, the efficacy evaluable population was 46 patients with a median duration of follow up now of 43.3 months.

Baseline Characteristics

Characteristic, n (%) unless otherwise stated	Safety-evaluable population N=56
Median age, years (range)	62 (32–87)
Male	33 (59)
ECOG PS 2	1 (2)
Ann Arbor Stage III/IV	49 (88)
Bulky disease (≥7cm)	9 (16)
Bone marrow involvement	24 (43)
High FLIPI (≥3)	31 (55)
No. of prior lines of therapy	
1	13 (23)
2	14 (25)
≥3	29 (52)
Median prior lines of therapy (range)	3 (1–7)
Refractory to last prior therapy*	33 (59)
Refractory to any line of anti-CD20 therapy†	40 (71)
POD24 on first-line treatment‡	15 (27)

Clinical cut-off date: March 03, 2022.

*Defined as no response or progression or relapse within 6 months of last anti-lymphoma therapy end date; †Defined as no response or progression or relapse within 6 months of therapy with an anti-CD20 agent at any prior line of treatment; ‡Defined as progression of disease within 24 months of initiation of first anti-lymphoma treatment with chemoimmunotherapy.
No, number; POD24, progression of FL within 24 mos of diagnosis.

Similar to the patients that Dr. Nastoupil described, these were extremely heavily pretreated patients. A full one-third of them were POD24 positive and 71% of them were refractory at any line of CD20 therapy. They had a median of three prior lines of therapy with a range of three to seven. Almost 60% were refractory to their last prior therapy. I think what is different about this in the CAR T population is that these were older patients, so their median age was 62, with patients as old as 87 being treated on this study.

Safety Summary

Any Grade AE Observed in ≥12.5% of Patients

n (%)	Safety-evaluable population N=56
Infections and infestations*	42 (75)
Neutropenia	36 (64)
Thrombocytopenia	30 (54)
Diarrhea	24 (43)
Anemia	23 (41)
Infusion-related reaction	22 (39)
Pyrexia	21 (38)
Peripheral neuropathy†	16 (29)
Cough	15 (27)
Fatigue	14 (25)
Rash‡	14 (25)
Nausea	12 (21)

n (%)	Safety-evaluable population N=56
ALT increased	11 (20)
Arthralgia	11 (20)
Asthenia	11 (20)
Constipation	10 (18)
Decreased appetite	10 (18)
Blood creatinine increased	8 (14)
Abdominal pain	7 (13)
AST increased	7 (13)
Dyspnea	7 (13)
Hypokalemia	7 (13)

Clinical cut-off date: March 03, 2022.
*Presented as System Organ Class term – all other AEs are reported by Preferred Terms; †Peripheral neuropathy standard MedDRA query included: peripheral motor neuropathy, peripheral sensory neuropathy, neuropathy peripheral, paresthesia, hypoesthesia, and neuralgia; ‡Rash includes maculopapular rash and erythematous rash.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; MedDRA, medical dictionary for regulatory activities.

In terms of any grade - any grade AEs were observed in 12.5% of patients. The primary AEs that were seen were hematologic AEs, primarily neutropenia thrombocytopenia, which are known toxicities of lenalidomide, particularly anemia. There were also infusion reactions primarily to the obinutuzumab peripheral neuropathy, which is a known toxicity of the polatuzumab.

Safety Summary: Grade 3-4 AEs and AESIs

n (%)	Safety-evaluable population N=56
Grade 3–4 AEs	48 (86)
Hematologic AEs	
Neutropenia	31 (55)
Thrombocytopenia	14 (25)
Anemia	8 (14)
Febrile neutropenia	6 (11)
Non-hematologic AEs	
Infections and infestations*	14 (25)
Hypokalemia	3 (5)
ALT increased	2 (4)
Diarrhea	2 (4)
Hypophosphatemia	2 (4)
Lipase increased	2 (4)
Laboratory tumor lysis syndrome	2 (4)
Syncope	2 (4)

- **Filgrastim (GCSF) use:**
  - 31 (55%) patients during induction
  - 20 (36%) patients during maintenance
- **Platelet transfusions:**
  - 2 (4%) patients during induction

AESI, n (%)	Safety-evaluable population N=56
Second malignancy	4 (7)
Squamous cell carcinoma	2 (4)
Lung neoplasm malignant	1 (2)
Myelodysplastic syndrome	1 (2)

Clinical cut-off date: March 03, 2022.
*Presented as Systems Organ Class term – all other AEs are reported by Preferred Terms.
AESI, adverse event of special interest; GCSF, granulocyte colony stimulating factor.

With regard to Grade 3 and 4 AEs, the primary Grade 3 and 4 AEs were either hematologic or infections. Once we instituted prophylaxis with GCSF, the number of infections went down substantially and 55% of patients received GCSF during induction and 36% then required it during maintenance.

Despite the fact that 14 patients had Grade 3 thrombocytopenia, only two patients needed platelet transfusions and only eight patients had Grade 3 anemia.
In terms of secondary malignancies, these were patients who were on maintenance therapy. We had two patients who had squamous cell carcinoma. One patient who had a prior history of lung cancer had a likely relapse. One patient who was very heavily pre-treated ended up developing myelodysplastic syndrome.

Efficacy: EOI Response Analysis

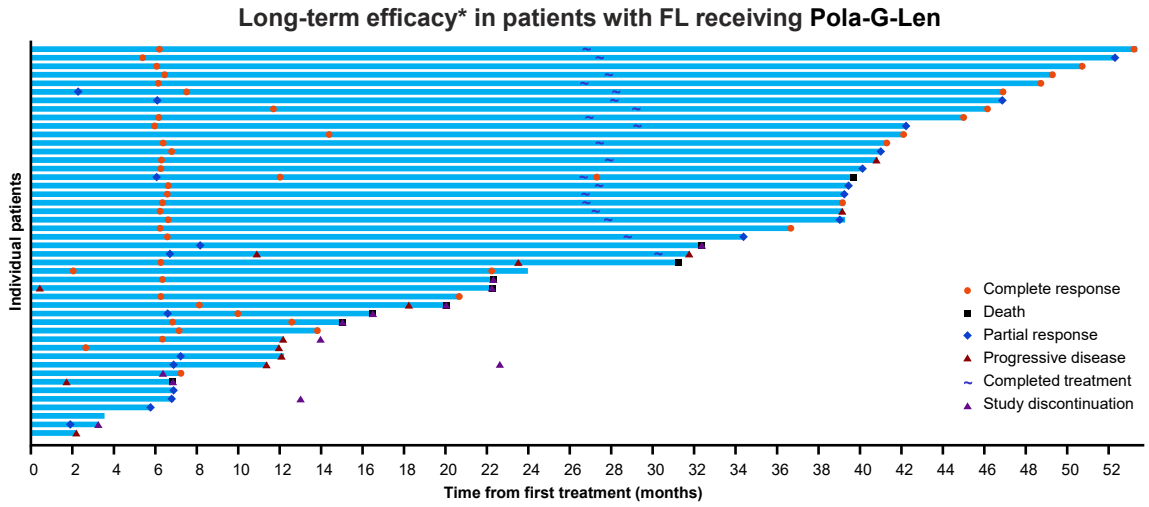
EOI response, n (%)	Efficacy-evaluable population (N=46)			
	Modified Lugano 2014*[1]		Lugano 2014	
	INV	IRC	INV	IRC
Objective response	38 (83)	35 (76)	38 (83)	35 (76)
Complete response	28 (61)†	28 (61)†	34 (74)	33 (72)
Partial response	10 (22)	7 (15)	4 (9)	2 (4)
Stable disease	3 (7)	4 (9)	3 (7)	4 (9)
Disease progression	2 (4)	1 (2)	2 (4)	1 (2)
Missing/not evaluable/not available	3 (7)	6 (13)‡	3 (7)	6 (13)‡

Clinical cut-off date: March 03, 2022.
*Modified Lugano requires a negative bone marrow biopsy to confirm PET-CR and PET-PR; †CR downgraded to PR due to missing bone marrow biopsy in 6 patients by INV and 5 patients by IRC; ‡Three patients did not have EOI scans completed (missing by INV and IRC); for two patients who experienced early disease progression, scans were not sent to IRC and therefore were classified as missing; one patient had stable disease by INV but was not evaluable by IRC.
EOI, end of induction; INV, investigator assessed.
1. Cheson BD, et al. *J Clin Oncol.* 2014;32:3059-3068.

With our end of response analysis by Lugano 2014, which did not require bone marrows, the complete response rate was 74% with a overall response rate of 83%.

We had several patients who were downgraded because they didn't have a follow-up bone marrow, which gave still a very impressive overall response rate of 76% by IRC with a CR rate of 61%.

Efficacy: EOI Response Analysis

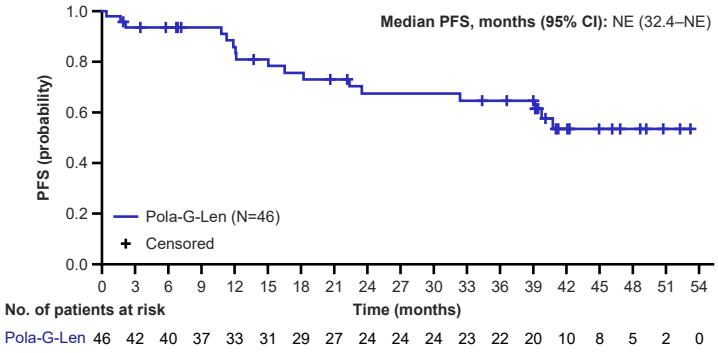


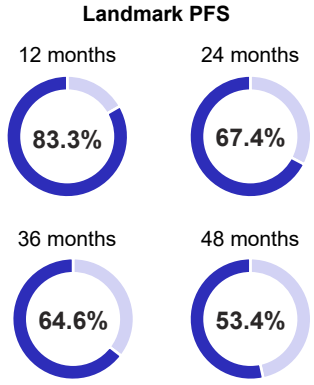
*Modified Lugano criteria.
Clinical cut-off date: March 03, 2022.

This was our waterfall plot.

Progression-free Survival

Median Not Reached with 3.6 Years of Follow-up*



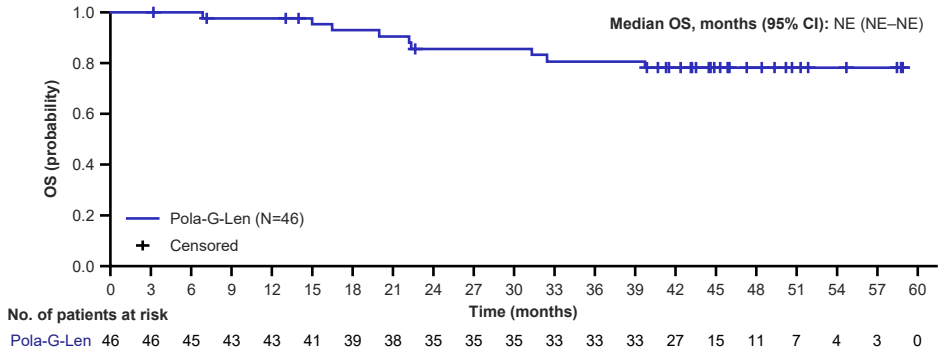


- Clinical cut-off date: March 03, 2022. PFS was INV assessed.
- *Median duration of follow-up.
NE, not evaluable.

Progression-free survival now with 3.6 years of follow-up has not been reached in the landmark PFS at 48 months is 53.4%. A therapy that is effective in heavily pretreated patients with really minimal toxicity given completely outpatient with the PFS now at more than three years. More than half of patients remain in remission.

Overall Survival

Median Not Reached with 3.6 Years of Follow-up*



Clinical cut-off date: March 03, 2022.

*Median duration of follow-up.

Overall survival was excellent.

Conclusions Polatuzumab

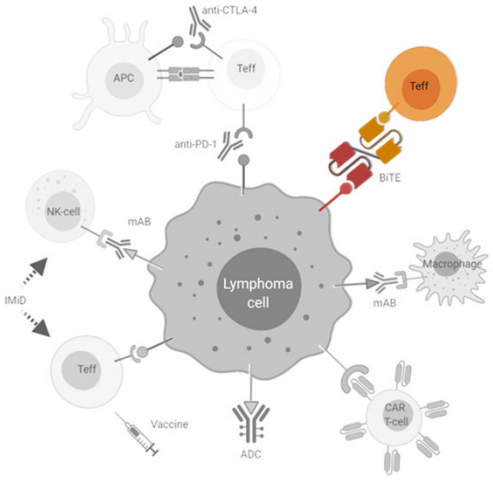
- With extended follow-up, Pola-G-Len continued to demonstrate a safety profile consistent with the known profiles of the individual drugs
- This novel triplet combination elicited high CR rates at EOI in a heavily pre-treated and refractory population, which compares favorably with currently available R/R FL therapies
- After a median follow-up of 3.6 years, median PFS was not reached; **53% of patients remain progression free at 48 months**

These findings confirm the ongoing benefit of this triplet combination in patients with R/R FL and support further exploration of the optimal sequencing in this treatment landscape

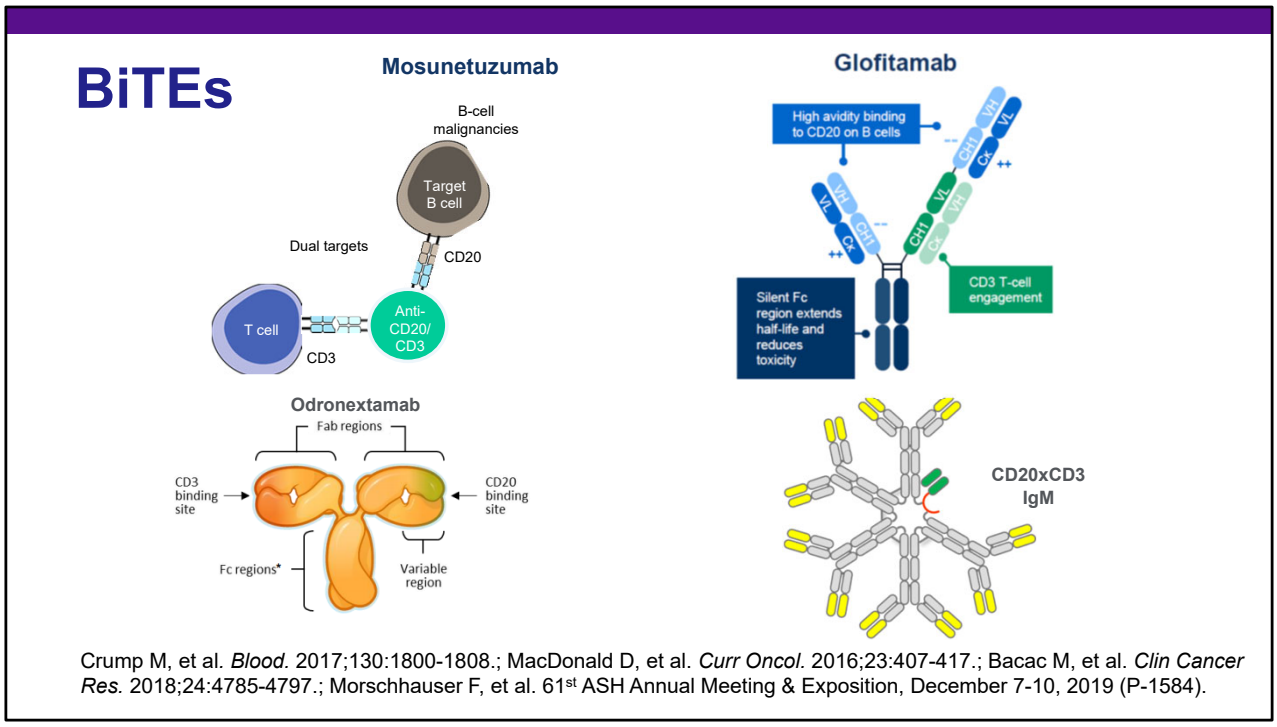
With extended follow up, the safety profiles continued to be consistent with the known profiles of individual drugs and there were no new safety signals.

The novel triplet combination elicited high CR rates at end of induction in a heavily pretreated and refractory population, and PFS was not reached with 53% of patients remaining progression-free now at 48 months.

Bispecific T-cell Engagers (BiTEs) – Mechanism of Action



Let's talk now about bispecific T-cell engagers or BiTEs.



Crump M, et al. *Blood.* 2017;130:1800-1808.; MacDonald D, et al. *Curr Oncol.* 2016;23:407-417.; Bacac M, et al. *Clin Cancer Res.* 2018;24:4785-4797.; Morschhauser F, et al. 61st ASH Annual Meeting & Exposition, December 7-10, 2019 (P-1584).

There are really four BiTEs that are commercially under investigation, at least. These are the first four.

Mosunetuzumab was engineered to bind into CD20 on B-cell and CD3 on T-cells. which is used primarily for large cell lymphoma, is a novel T-cell engaging bispecific with unique two to one molecular configuration that has superior potency, but also, higher toxicity. The dual targeting results in T-cell activation proliferation and CD20 bearing, T-cell killing, B-cell killing.

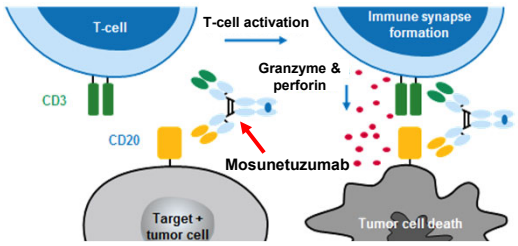
Mosunetuzumab

- Mosunetuzumab **(first-in-class)** is approved in the EU and is under Priority Review by the FDA, for the treatment of **relapsed/refractory follicular lymphoma (R/R FL)** after ≥2 prior systemic therapies[1,2]
  - **ORR 80%, CR 60%,** majority maintaining response after 18 months[3]
  - Consistent benefit in patients with double-refractory disease and POD24[3]
  - **Off-the-shelf, fixed-duration** treatment that can be administered in the **outpatient** setting[3]

On 12/22/2022 the FDA granted accelerated approval to Mosunetuzumab for 3L+*

*3L+ = third line or later

Mosunetuzumab: CD20xCD3 T-cell-engaging bispecific antibody that redirects T cells to engage and eliminate malignant B cells[4,5]



We present updated results after a median 28.3 months of follow-up (cut-off: July 8, 2022)

1. Lunsumio SmPC: https://www.ema.europa.eu/en/medicines/human/EPAR/lunsumio; 2. Lunsumio Filing Acceptance: https://www.roche.com/media/releases/med-cor-2022-07-06; 3. Budde LE, et al. *Lancet Oncol.* 2022;23:1055-1065. 4. Sun LL, et al. *Sci Transl Med.* 2015;7:287ra70; 5. Hernandez G, et al. ASH 2019; poster presentation (P-1585).

Mosunetuzumab is a first in class. It's now been granted accelerated approval to third-line follicular lymphoma. In a single-agent study, the overall response rate was 80% with 60% CR rate, with the majority maintaining their response after 18 months. There was consistent benefit in patients with double refractory disease who were POD24 positive. Mosunetuzumab is a fixed duration treatment that can be administered in the outpatient setting. This is now some updated results now after 28.3 months of follow up.

Pivotal Phase II Study Design

Pivotal, single-arm, multicenter, Phase II expansion in patients with R/R FL and ≥2 prior therapies

Key inclusion criteria

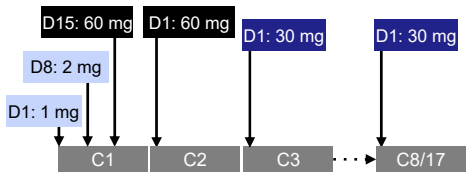
- FL Grade 1–3a
- ECOG PS 0–1
- ≥2 prior therapies including an anti-CD20 antibody and an alkylator

Data analysis

- Study met its primary endpoint: 60% CR rate versus 14% historical control (P<0.0001)[1,2]
- Updated efficacy and safety analysis with median 28.3 months of follow up (10 months after the previous report)

Mosunetuzumab administration

- IV mosunetuzumab administered in 21-day cycles with step-up dosing in C1
- Fixed-duration treatment: 8 cycles if CR after C8; 17 cycles if PR/SD after C8
- Re-treatment with mosunetuzumab permitted at relapse for patients who achieved CR
- No mandatory hospitalization



1. Dreyling M, et al. *J Clin Oncol*. 2017;35:3898-3905; 2. Budde LE, et al. *Lancet Oncol*. 2022;23:1055-1065.

This was their pivotal phase two design. Again, more than two prior therapies required. Mosunetuzumab is administered in step up dosing. This is actually very important because I think you saw Dr. Nastoupil described some of the toxicities of CAR T-cells, particularly, the CRS and the neurotox that requires them to be in the hospital. We found that when you give small doses of these bispecifics and ramp up to a full dose, you can mitigate a lot of the CRS toxicity that was previously associated with them.

You start at one milligram and then you give two milligrams and then you give full dose. When this was done, then patients received fixed-duration treatment. They got eight cycles if a CR, if no CR, they were able to be treated for up to 17 months and they did not need to be hospitalized.

Baseline Characteristics

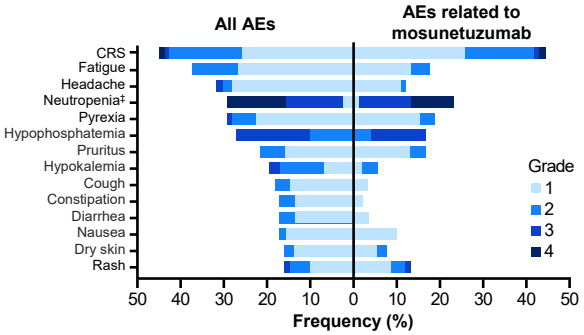
	N=90
Median age, years (range)	60 (29–90)
Male	61%
ECOG PS	
0	59%
1	41%
Ann Arbor stage	
I/II	23%
III/IV	77%
Median lines of prior therapy, n (range)	3 (2–10)
Refractory to last prior therapy	69%
Refractory to any prior anti-CD20 therapy	79%
Progression of disease within 24 months from start of first-line therapy (POD24)	52%
Double refractory to prior anti-CD20 and alkylator therapy	53%
Prior autologous stem cell transplant	21%

Again, these were very refractory patients on the elderly side with the oldest patient being 90 years old, at a median age of 60, and 52% POD24 positive.

Safety Profile

Adverse events (AEs)	N=90
AE	100%
Mosunetuzumab related	92%
Grade 3/4 AE	70%
Mosunetuzumab related	51%
Serious AE	47%
Mosunetuzumab related	33%
Grade 5 (fatal) AE	2%*
Mosunetuzumab related	0
AE leading to treatment discontinuation	4%†
Mosunetuzumab related	2%

AEs (≥15%) by grade *and relationship with* mosunetuzumab



No new serious AEs, Grade ≥3 AEs, or treatment-related AEs were reported with 10 additional months of follow-up

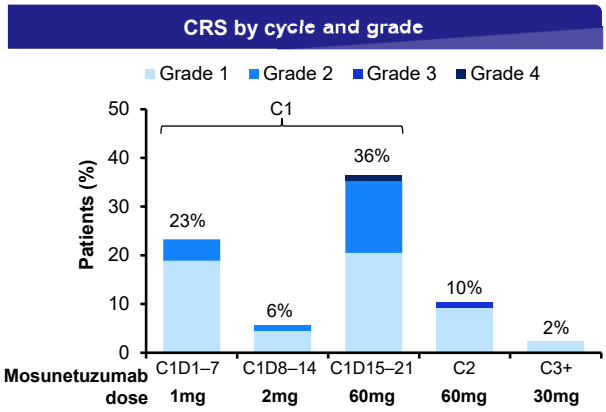
*Malignant neoplasm progression (n=1) and unexplained death (n=1). †Mosunetuzumab related: CRS (2 patients); mosunetuzumab unrelated: Esptein-Barr viremia and Hodgkin's disease (1 patient each). ‡Grouped term including preferred term 'neutropenia' and 'neutrophil count decreased'.

The safety profile, and I think it's interesting to contrast this really with CAR Ts as they're really the other very potent therapy.

There were 2% Grade 5 AEs. One was progression of disease and one was an unexplained death.

CRS Summary

CRS by ASTCT criteria[1]	N=90
CRS (any grade)	44%
Grade 1	26%
Grade 2	17%
Grade 3	1%
Grade 4	1%
Median time to CRS onset, hours (range)	
C1D1	5.2 (1.2–24)
C1D15	27 (0.1–391)
Median CRS duration, days (range)	3 (1–29)
Corticosteroids for CRS management	11%
Tocilizumab for CRS management	8%
Events resolved	100%



CRS was predominantly low grade and during Cycle 1
All CRS events resolved; no new events were reported with 10 months of additional follow-up

1. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625–638.

Here's the CRS summary. CRS, any grade. Grade 1 is 26% and Grade 2 is 17%. You can see that only 1% of patients had a higher CRS. The median time to CRS is short. The median CRS duration is also short. 11% of patients required corticosteroids, but only 8% of patients required tocilizumab and all events resolved. There's quite a few CRS events at cycle one day 15. After cycle 2 and beyond, there really are almost no CRS events.

Response Rates

Efficacy endpoint in the overall population by investigator assessment; % (95% CI)	N=90
ORR	**78%** (68–86)
CR	**60%** (49–70)

Time to first response (median [range]): **1.4 months** (1.0–11)
Time to first CR (median [range]): **3.0 months** (1.0–19)

High ORR and CR rate were consistent with published results[1]

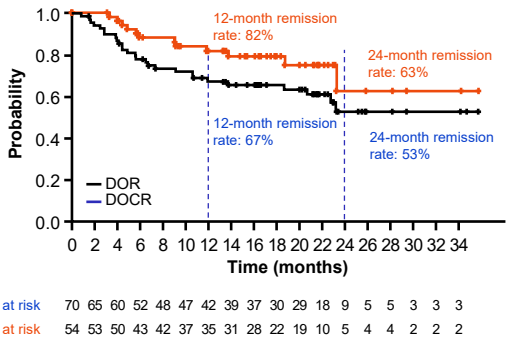
1. Budde LE, et al. *Lancet Oncol*. 2022;23(8):1055–1065.

The response rate in this larger study was 78% with a CR rate of 60% with a very fast time to response.

Durability of Responses

Efficacy endpoint by investigator assessment	N=90
Median DOR, months (range), n=70	NR (21–NR)
24-month DOR (95% CI)	53% (38–68)
Median DOCR, months (range), n=54	NR (23–NR)
24-month DOCR (95% CI)	63% (38–88)
Median PFS, months (range)	24 (12–NR)
24-month PFS (95% CI)	48% (36–60)
Median TTNT, months (range)	NR (18–NR)
24-month TTNT (95% CI)	56% (45–67)
Median OS, months (range)	NR (NR–NR)
24-month OS (95% CI)	87% (80–94)

DOR and DOCR



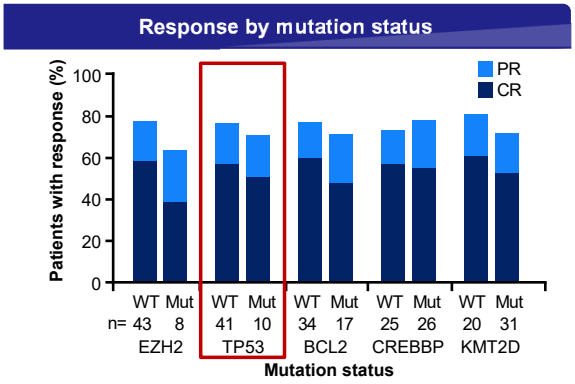
Durable responses: majority of patients in remission after 2 years

DOCR, duration of complete response; TTNT, time-to-next therapy.

In terms of the durability of response, the median PFS, the 24-month PFS is 48%. The median overall survival is 87%.

Best Overall Response by Baseline Tumor Mutation Status

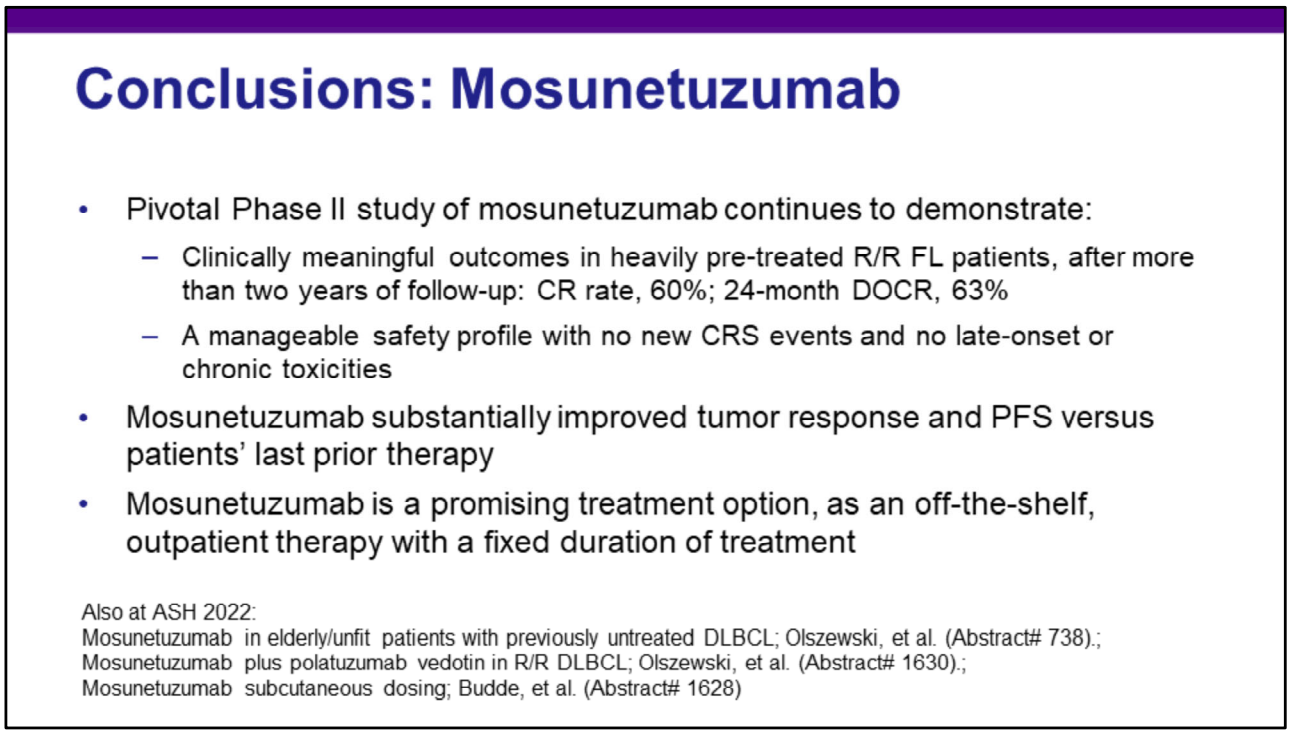
- Whole exome sequencing performed in 51 available baseline biopsy samples to assess activity of mosunetuzumab in patients with known prognostic variants
- Single nucleotide variants were found at a similar frequency to reported prevalence rates[1]



Clinically meaningful response rates were observed in patients with common mutations, including those associated with poor prognosis

1. Pastore A, et al. *Lancet Oncol.* 2015;16:1111–1122.

Patients were evaluated by tumor mutation status by whole exome sequencing to assess whether patients with known prognostic variants were more or less sensitive to mosunetuzumab and single nucleotide variants were found to have similar frequency to reported prevalence rates. Clinically meaningful responses to mosunetuzumab were basically observed in patients who had common mutations including those, such as T53 that are associated with a poor prognosis or BCL-2 or CREBBP.



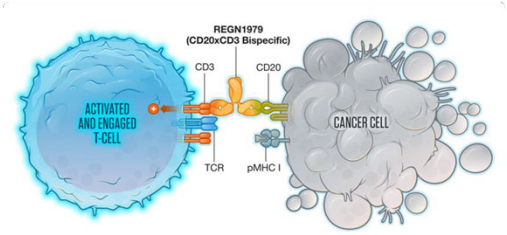
In conclusion, mosunetuzumab continued to demonstrate high activity and a very manageable safety profile with no new CRS events and no later chronic toxicities, which is really striking. Dr. Nastoupil showed you how remissions tend to be shorter and shorter as you have more and more therapy in follicular lymphoma. Well, in these heavily pretreated patients, mosunetuzumab improved the PFS, though they had a better PFS than they had to their therapy before mosunetuzumab. Mosunetuzumab is now approved.

Odronextamab

- FL is an incurable disease, and PFS reduces with each relapse[1]
  - By third line, median PFS is ~1 year
  - High unmet medical need for effective treatments that can improve tumor control and extend survival
- Odronextamab, a CD20 × CD3 bispecific antibody, was investigated in the Phase 1 trial (ELM-1, NCT02290951)[2]
  - Encouraging efficacy and manageable safety observed in heavily pre- treated patients with R/R FL
    - 91% ORR; 72% CR; median PFS 17.1 months
- Here we report the first, interim results of the pivotal Phase 2 trial ELM-2 in patients with R/R FL (NCT03888105)

Odronextamab

Hinge-stabilized CD20 × CD3 bispecific antibody

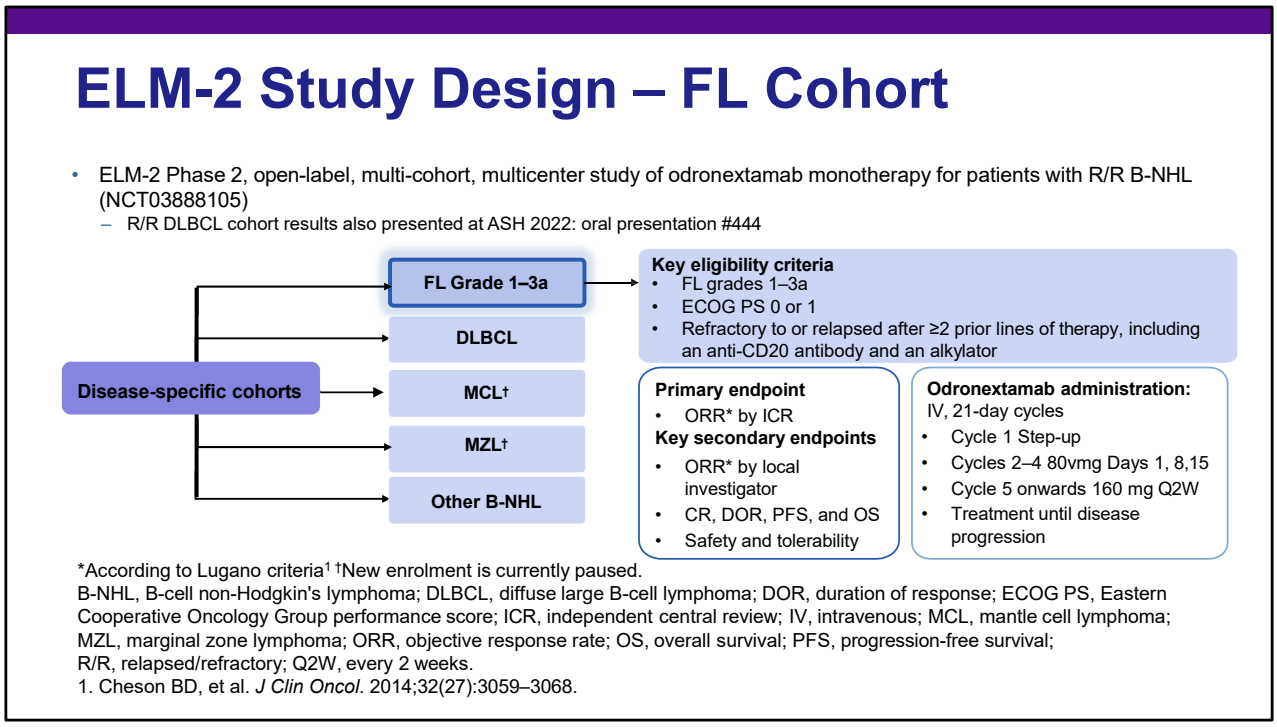


Binds CD20 on malignant B-cells and CD3 on T cells, to elicit T-cell-mediated cytotoxicity

CD, cluster of differentiation; FL, follicular lymphoma; ORR, objective response rate; R/R, relapsed/refractory; pMHC I, peptide major histocompatibility complex type I; TCR, T-cell receptor.

1. Batlevi CL, et al. *Blood Cancer J.* 2020;10(7):74. 2. Bannerji R, et al. *Lancet Haematol.* 2022;9(5):e327–e339.

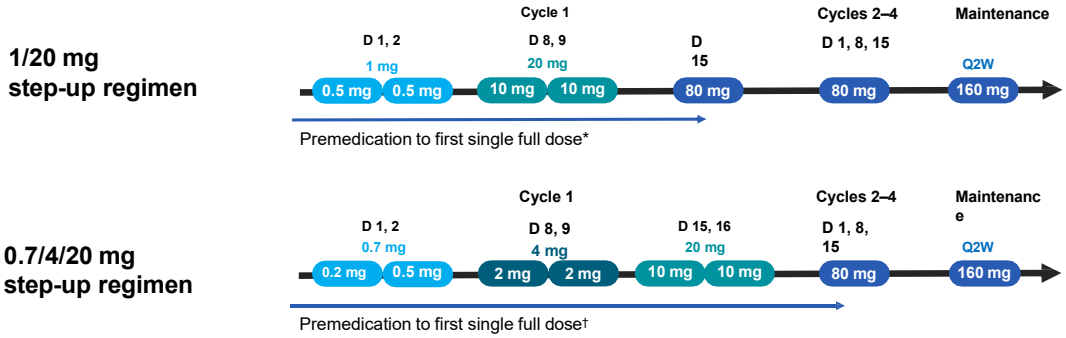
Another bispecific antibody that's being explored in the follicular cell space is odronextamab, which is another CD20 CD3 biospecific. It was investigated in a phase one trial called the ELM trial, where it had a very high, response rate, 91% with a CR rate of 72%, and the median PFS that was a little shorter than that of mosunetuzumab at 17.1 months.



This is the phase two data of ELM, which looked at, this bispecific antibody in multiple cohorts. We'll talk about the follicular cohort today. These patients also received step up dosing as is common really for all bispecifics.

Cycle 1 Step-up Regimen Optimized During the Course of the Study to Further Mitigate the Risk for Cytokine Release Syndrome

- The study initiated with a Cycle 1 step-up regimen of 1/20/80 mg
- This was modified to 0.7/4/20 mg during Cycle 1 to further mitigate the risk of CRS



Updated guidelines for tocilizumab and steroids introduced with 0.7/4/20 mg regimen.
*20 mg IV dexamethasone 1 to 3 hours prior to each split or initial single infusion; †10 mg dexamethasone orally 12 to 24 hours prior to the first split infusion. On each day of split or single infusion: dexamethasone 20 mg IV 1 to 3 hours before infusion; diphenhydramine 25 mg IV or orally and acetaminophen 650 mg orally 30 to 60 minutes before infusion.
CRS, cytokine release syndrome; D, day; IV, intravenous; Q2W, every 2 weeks.

There were two step up regimens. This step up was really optimized to mitigate CRS.

Baseline Characteristics

- Heavily pretreated, highly refractory patient population

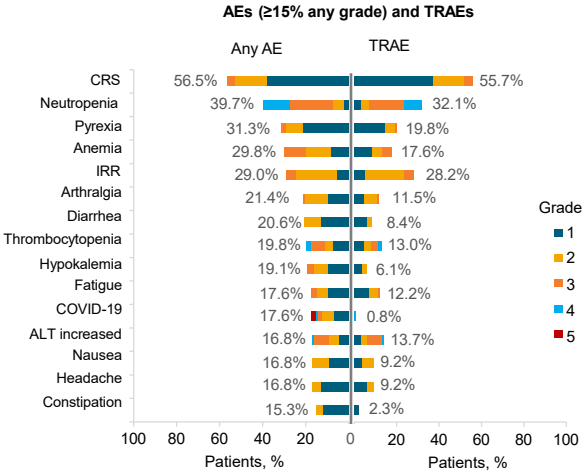
Patient and disease characteristics		N=131
Median age, years (range)		61 (22–84)
Age ≥65		38.9%
Male		53.4%
ECOG performance status	0 / 1 / 2	51.1% / 48.1% / 0.8%
Ann Arbor stage	I–II / III–IV	15.3% / 84.7%
FLIPI risk score	0–1 / 2 / 3–5	14.5% / 26.7% / 58.8%
Bulky disease (investigator assessment)		13.7%
Median no. of prior lines, n (range)		3.0 (2–13)
Prior ASCT		30.5%
Prior PI3K inhibitor		13.7%
Prior R^2 (lenalidomide + rituximab)		13.7%
Refractory to last line of therapy		71.0%
Refractory to anti-CD20 antibody		74.8%
Double refractory to alkylator/anti-CD20 Ab		43.5%
POD24		48.1%

Data cut-off date: Sep 15, 2022.
Ab, antibody; ASCT, autologous stem cell transplant; ECOG, Eastern Cooperative Oncology Group; PI3K, phosphoinositide 3-kinase; POD24, progression of disease within 24 months of starting first-line therapy.

In terms of baseline characteristics. Again, 48% POD24 positive median age, again, 61, 30% prior auto transplant, 71 refractory to last line of therapy.

Odronextamab Safety Profile

Treatment-emergent adverse events, n (%)	Patients N=131 All events	TRAEs
Any TEAE	131 (100%)	118 (90.1%)
Grade ≥3 TEAE	102 (77.9%)	73 (55.7%)
Serious AE	81 (61.8%)	53 (40.5%)
Grade 5 TEAE	17 (13.0%)	3 (2.3%)
Related to COVID-19	7 (5.3%)	0
Other grade 5 events	10 (7.6%)	3 (2.3%)
TEAE leading to treatment discontinuation	15 (11.5%)	10 (7.6%)



- TRAEs leading to treatment discontinuation: IRR (n=2); IRR and tremor (n=1); ALT increase; arthralgia; CRS; epilepsy; PML; viral bronchitis; weight decrease (n=1 each)
- Grade 5 TRAEs: pneumonia, PML, systemic mycosis (n=1 each)

Data cut-off date: Sep 15, 2022.
AEs per NCI-CTCAE v5.0. CRS per Lee 2019.
AE, adverse event; ALT, alanine aminotransferase; CRS, cytokine release syndrome; IRR, infusion related reaction; PML, Progressive multifocal leukoencephalopathy; TEAE, treatment-emergent adverse event; TRAE, treatment-related AE.

You can see the safety profile is very similar to mosunetuzumab, with the CRS primarily Grade 1 and 2, neutropenia up to Grade 4.

Adverse Events: Cytokine Release Syndrome

n, (%)	1/20 regimen (N=68)	0.7/4/20 regimen (N=63)
CRS any	38 (55.9%)	36 (57.1%)
Grade	22 (32.4%)	28 (44.4%)
Grade 1		
Grade 2	12 (17.6%)	7 (11.1%)
Grade 3	4 (5.9%)	1 (1.6%)
Grade 4	0	0
Grade 5	0	0
Received corticosteroids	11 (16.2%)	17 (27.0%)
Received tocilizumab	9 (13.2%)	12 (19.0%)
Received vasopressors	4 (5.9%)	1 (1.6%)

- 0.7/4/20 mg step-up regimen reduced the incidence of grade 2 and grade 3 CRS
- Approximately half of patients with R/R FL had CRS, mostly grade 1
- Only 1 case of grade 3 CRS with 0.7/4/20 mg step-up regimen and no grade 4 or higher CRS events
- All CRS events resolved with a median time to resolution of 2 days (range 1–51)
- No patients required mechanical ventilation or ICU admission for the management of CRS

Data cut-off date: Sep 15, 2022. CRS per Lee 2019.
CRS, cytokine release syndrome; R/R FL, relapsed/refractory follicular lymphoma; ICU, intensive care unit.

Here are the cytokine release events. You can see, on the second regimen, the Grade 2 CRS was only seven patients or 11%, and there was only, one Grade 3 CRS. The primary CRS events were Grade 1.

All CRS events resolved with a median time to resolution that was quite short, two days and no patients needed a mechanical ventilation or ICU admission.

Adverse Events of Interest

n (%)	1/20 regimen (N=68)	0.7/4/20 regimen (N=63)	All patients (N=131)
ICANS, any grade	1 (1.5%)	0	1 (0.8%)
Grade ≥3	0		0
Infusion related reaction, any grade	21 (30.9%)	16 (25.4%)	37 (28.2%)
Grade ≥3	4 (5.9%)	2 (3.2%)	6 (4.6%)
Infection, any grade	51 (75.0%)	35 (55.6%)	86 (65.6%)
Grades 1–2	23 (33.8%)	21 (33.3%)	44 (33.6%)
Grades 3–4	19 (27.9%)	11 (17.5%)	30 (22.9%)
Grade 5	9 (13.2%)	3 (4.8%)	12 (9.2%)
Tumor lysis syndrome, any grade	1 (1.5%)	0	1 (0.8%)
Grade ≥3	1 (1.5%)		1 (0.8%)

Data cut-off date: Sep 15, 2022.
ICANS, immune effector cell-associated neurotoxicity syndrome.

These are just, ICANS again, extremely low. Really low, almost no neurologic events. There were infections which are related primarily to these patients being quite immunocompromised. Some of these were COVID infections. The Grade 5 infections, several of these were COVID infections, but there were infections that these patients had.

Odronextamab Efficacy: ORR

Best overall response	Independent central review N=121*	Investigator evaluation N=121*
Objective response rate (ORR)†	**81.8%** [95% CI: 73.8–88.2%]	81.8% [95% CI: 73.8–88.2%]
Complete response	**75.2%**	70.2%
Partial response	6.6%	11.6%
Stable disease	5.8%	2.5%
Progressive disease	4.1%	5.8%

Week 12 response assessment by independent central review	1/20 step-up regimen N=68	0.7/4/20 step-up regimen N=53
ORR	72.1% [95% CI: 59.9–82.3%]	75.5% [95% CI: 61.7–86.2%]
Complete response	61.8%	71.7%

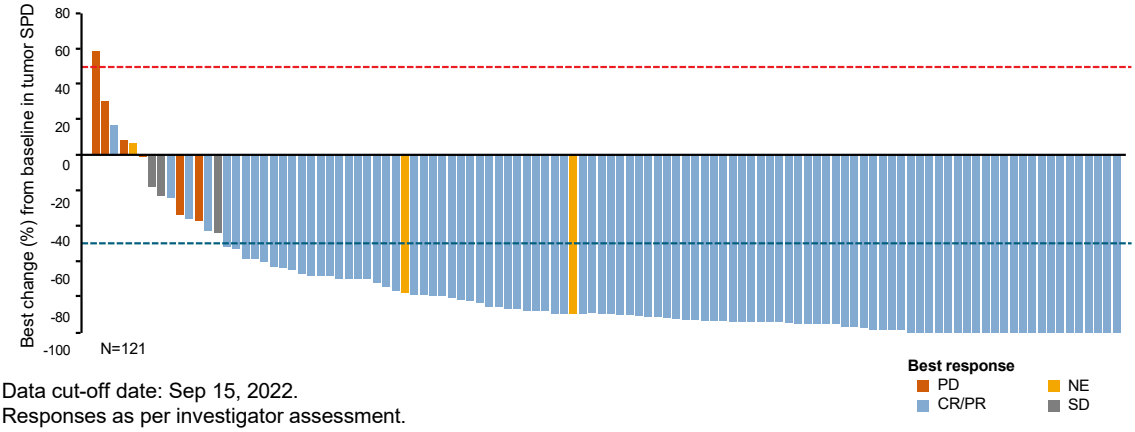
- Majority of R/R FL patients achieved a complete response
- 92% of responders were complete responders
- Consistent efficacy observed at Week 12 regardless of Cycle 1 step-up regimen

Median opportunity of follow-up: 22.4 months (range 2.6–33.0)
*Partial responses. FL, follicular lymphoma; ORR, objective response rate; R/R relapsed/refractory
Data cut-off date: Sep 15, 2022.
*Efficacy evaluable (with an opportunity for assessment at 12 weeks); †ORR = Complete responses

Then the overall response in this phase II study was 81% with a CR of 75%.

Odronextamab Efficacy

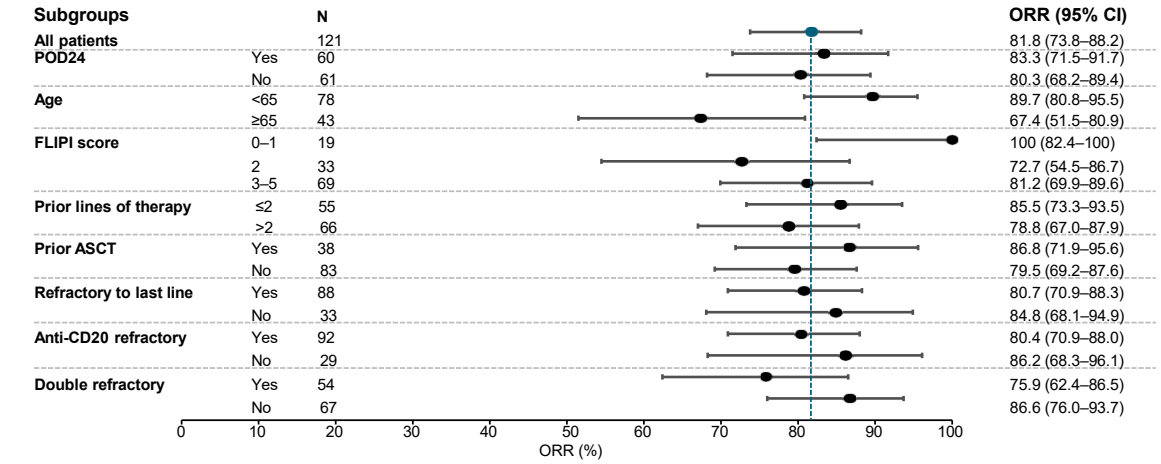
- Majority of R/R FL patients had substantial tumor shrinkage



Data cut-off date: Sep 15, 2022.
Responses as per investigator assessment.
CR complete response; FL, follicular lymphoma; NE, not evaluable; R/R relapsed/refractory; PD, progressive disease; PR, partial response; SD, stable disease; SPD, sum of the products of diameters

You can see that almost all patients benefited

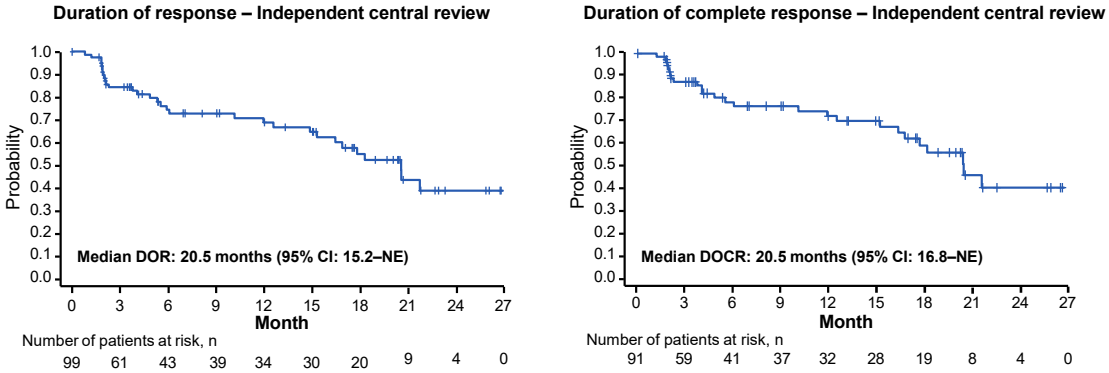
Odronextamab Efficacy: Consistent Efficacy in High-risk Subgroups



Data cut-off date: Sep 15, 2022.; Responses as per independent central review.
ORR, objective response rate; POD24, progression of disease within 24 months of starting first-line therapy.

and that the responses were consistent across high risk subgroups

Odronextamab Duration of Response



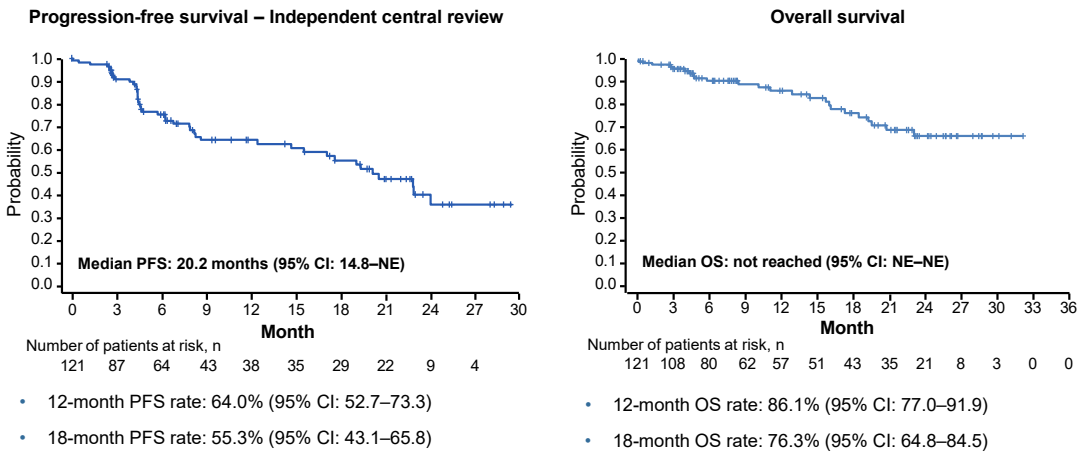
- 12-month DOR: 68.8% (95% CI: 55.9–78.7)
- 18-month DOR: 55.0% (95% CI: 40.6–67.3)

- 12-month DOCR: 72.2% (95% CI: 58.7–81.9)
- 18-month DOCR: 59.1% (95% CI: 43.6–71.6)

Data cut-off date: Sep 15, 2022.
CI, confidence interval; DOCR, duration of complete response; DOR, duration of response; NE, not estimable.

with the duration of response at 18 months, that was 55% by Independent Central Review. Their median DOR is 20 months.

Progression-free Survival and Overall Survival



- 12-month PFS rate: 64.0% (95% CI: 52.7–73.3)
- 18-month PFS rate: 55.3% (95% CI: 43.1–65.8)
- 12-month OS rate: 86.1% (95% CI: 77.0–91.9)
- 18-month OS rate: 76.3% (95% CI: 64.8–84.5)

Data cut-off date: Sep 15, 2022.
CI, confidence interval; NE, not estimable; OS, overall survival; PFS, progression-free survival.

The progression-free survival is 20 months as well, with the median overall survival not reached.

Conclusions: Odronextamab

- Odronextamab is an off-the-shelf, investigational CD20 × CD3 bispecific antibody
- First results from the pivotal Phase 2 trial of odronextamab demonstrate a new benchmark for efficacy in heavily pretreated, R/R FL
  - ORR 81.8%, CR 75.2%; 92% of responders were complete responders
  - Reponses were deep and durable with a mPFS of 20.2 months
- Odronextamab has a generally manageable safety profile with the optimized step-up regimen
  - CRS was mostly grade 1 and generally occurred with Cycle 1 step-up
  - No cases of ICANS or TLS
  - Treatment-related adverse events leading to treatment discontinuation occurred infrequently (7.6%)
- Phase 3 randomized controlled studies will be initiating in follicular lymphoma in earlier lines of therapy

CRS, cytokine release syndrome; FL, follicular lymphoma; ICANS, immune effector cell-associated neurotoxicity syndrome; mPFS, median progression-free survival; TLS, tumor lysis syndrome; ORR, objective response rate; R/R, relapsed/refractory.

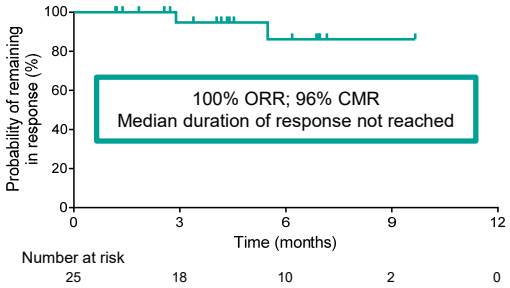
In conclusion, similar to mosunetuzumab, odronextamab, these are both off the shelf, so you can basically just take them out of your pharmacy and give them to your patient. This is not FDA approved yet, but like mosunetuzumab, it has a high overall response rate with quite durable responses for many patients.

With its step up regimen, it has a very manageable safety profile with CRS, primarily Grade 1, and no cases of ICANS or TLS. There will be phase three studies that will, I'm sure lead to this drugs registration.

Epcoritamab, a Subcutaneous Bispecific Antibody

- Epcoritamab binds to CD3 on T cells and CD20 on B cells to induce killing of malignant B cells[1-6]
- **Evidence for single-agent epcoritamab**
  - Substantial antitumor activity observed in patients with R/R FL (dose escalation in EPCORE NHL-1)[3]
- **Rationale for epcoritamab + R² in R/R FL**
  - Epcoritamab and R² may synergize and have nonoverlapping toxicities[1,5,6]
  - Previously reported data from EPCORE NHL-2, arm 2a, show that epcoritamab + R² led to high ORR and CMR rates with manageable safety[6]

ASCO 2022
EPCORE NHL-2, Arm 2a: Duration of Response



Data cutoff: March 25, 2022. Median follow-up: 8.6 mo.[6]
CMR, complete metabolic response; ORR, overall response rate.

Here we present arm 2b, with a less intense and more convenient dosing schedule

1. Engelberts PJ, et al. *EBioMedicine*. 2020;52:102625. 2. van der Horst HJ, et al. *Blood Cancer J*. 2021;11:38. 3. Hutchings M, et al. *Lancet*. 2021;398:1157-69. 4. Thieblemont C, et al. EHA 2022. Abstract LB2364. 5. Chiu CW, et al. AACR 2021. Abstract 1574. 6. Falchi L, et al. ASCO 2022. Abstract 7524.

Epcoritamab is a little different than the other two drugs in that epcoritamab is a subcutaneous bispecific while the other two drugs are intravenous bispecific. Epcoritamab has single agent activity in follicular lymphoma, but it's also being explored in combination with R squared or lenalidomide and rituximab.

There has been already a study called EPCORE NHL-2 Arm 2A, which showed that this combination was safe and led to high response rates.

You can see here that the median duration response is not reached with a hundred percent overall response rate and 96% CMR.

Study Design: EPCORE NHL-2, Arm 2b

A phase 1b/2, open-label trial evaluating the safety and antitumor activity of epcoritamab + R² in adults with R/R FL[a]

Key inclusion criteria

- R/R CD20+ FL
  - Grade 1, 2, or 3A
  - Stage II–IV
- Need for treatment based on symptoms or disease burden, as determined by GELF criteria[1]
- ECOG PS 0–2
- Measurable disease by CT or MRI
- Adequate organ function

Data cutoff: September 16, 2022
Median follow-up: 6.4 mo

	Treatment Regimen Epcoritamab SC 48 mg + R²						
Agent	**C1**	**C2**	**C3**	**C4**	**C5**	**C6–C12**	**C13+**
Epcoritamab SC 48 mg	QW	QW	Q4W	Q4W	Q4W	Q4W	Q4W Up to 2 years
R² Rituximab IV 375 mg/m²	QW	Q4W	Q4W	Q4W	Q4W		
R² Lenalidomide oral 20 mg	Daily for 21 d (for 12 cycles)						

Primary objective: Safety and antitumor activity[b]

[a]Patients received SC epcoritamab with step-up dosing (ie, priming and intermediate doses before first full dose), corticosteroid prophylaxis to mitigate CRS, and protocol-mandated hospitalization for 24 h after the first full dose. Epcoritamab was administered in 28-d cycles as shown. In arm 2a, epcoritamab schedule was QW in C1–3, Q2W in C4–9, and Q4W in C10+. Dose escalation evaluated 24 and 48 mg epcoritamab + R². [b]Tumor response was evaluated by PET-CT obtained at 6, 12, 18, 24, 36, and 48 wk, and every 24 wk thereafter, until disease progression.

1. Brice P, et al. *J Clin Oncol*. 1997;15:1110-1117.

Then, this is further data in the EPCORE. You can see that patients get rituximab, for five cycles. They take lenalidomide per standard and they get epcoritamab subcutaneously every cycle. Prior to this step-up dosing of epcoritamab as is now standard for all bispecifics.

Patient Characteristics

Demographics and Disease Characteristics	Total N=76
Median age, y (range)	64 (30–79)
Female, n (%)	37 (49)
Ann Arbor stage, n (%)	
II	12 (16)
III	19 (25)
IV	45 (59)
Histologic grade, n (%)[a]	
1	6 (8)
2	37 (49)
3A	24 (32)
FLIPI, n (%)[b]	
0–1	7 (9)
2	24 (32)
3–5	39 (51)
ECOG PS, n (%)	
0	48 (63)
1	25 (33)
2	3 (4)

Treatment History	Total N=76
Median time from diagnosis to first dose, mo (range)	59 (4–331)
Median time from end of last line of therapy to first dose, mo (range)	16 (0.2–198)
Median number of prior lines of therapy (range)	1 (1–9)
1 prior line, n (%)	41 (54)
2 prior lines, n (%)	21 (28)
≥3 prior lines, n (%)	14 (18)
Primary refractory[c] disease, n (%)	29 (38)
Double refractory[d] disease, n (%)	30 (39)
POD24[e], n (%)	32 (42)
Refractory[c] to last line of therapy, n (%)	29 (38)
Prior ASCT, n (%)	8 (11)
Prior CAR T, n (%)	2 (3)

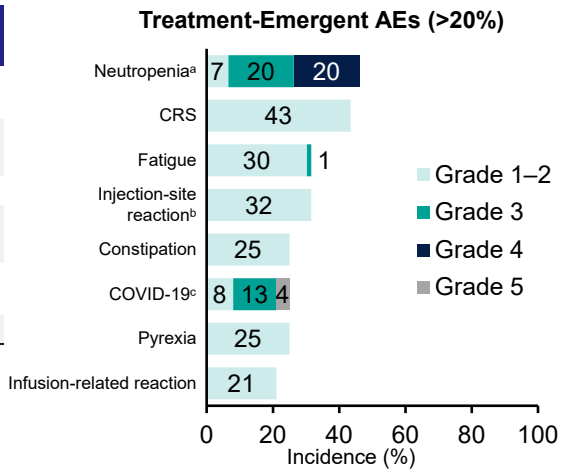
[a]Histologic grade was unknown or missing for 9 patients. [b]FLIPI was unknown for 6 patients. [c]Refractory indicates no response or relapse within 6 mo after prior therapy. [d]Double refractory indicates refractory to both anti-CD20 and an alkylating agent. [e]Progression within 2 y of initiating first-line treatment that included immunochemotherapy.

Again, very similar patient population, older, in their 60s, heavily pretreated, double refractory and, high number of POD24 positive patients.

Safety Profile

	Total N=76
Median number of epcoritamab cycles initiated (range)	6 (1–11)
Grade ≥3 TEAE, n (%)	53 (70)
Related to epcoritamab	29 (38)
Fatal TEAE (all COVID-19), n (%)	3 (4)
Epcoritamab dose delay due to TEAE, n (%)	40 (53)
Related to epcoritamab	19 (25)
Epcoritamab discontinuation due to TEAE, n (%)	5 (7)
Related to epcoritamab	0

- No clinical tumor lysis syndrome was observed
- One patient experienced ICANS (grade 1), which resolved in 7 days



[a]Combined term includes neutropenia and neutrophil count decreased; 3 patients (4%) had febrile neutropenia (grade 3). [b]Combined term includes injection-site reaction and erythema. [c]Combined term includes COVID-19, COVID-19 pneumonia, and post-acute COVID-19 pneumonia.

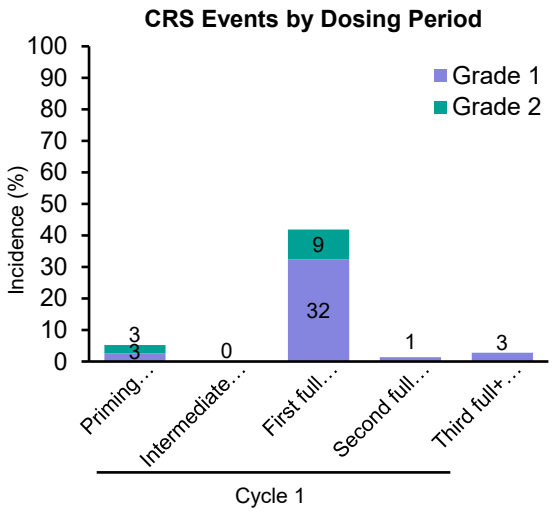
Safety profile. No, tumor lysis was observed. There was one patient who had ICAN Grade 1, which took seven days to resolve. You can see that neutropenia was the primary toxicity. COVID 19 was also a significant toxicity. CRS although frequent was primarily Grade 1 to 2.

CRS Events

	Total, N=76
CRS, n (%)[a]	33 (43)
Grade 1	25 (33)
Grade 2	8 (11)
Median time to onset after first full dose, d (range)	2 (1–9)
CRS resolution, n (%)	33 (100)
Median time to resolution, d (range)[b]	2 (1–23)
Treated with tocilizumab, n (%)	8 (11)
Leading to treatment discontinuation, n (%)	**0**

[a]Graded by Lee et al 2019 criteria. [b]Median is Kaplan–Meier estimate based on longest CRS duration in patients with CRS.

- CRS occurrence was predictable, with most cases occurring following the first full dose
- No grade ≥3 CRS events
- These data support fully outpatient administration



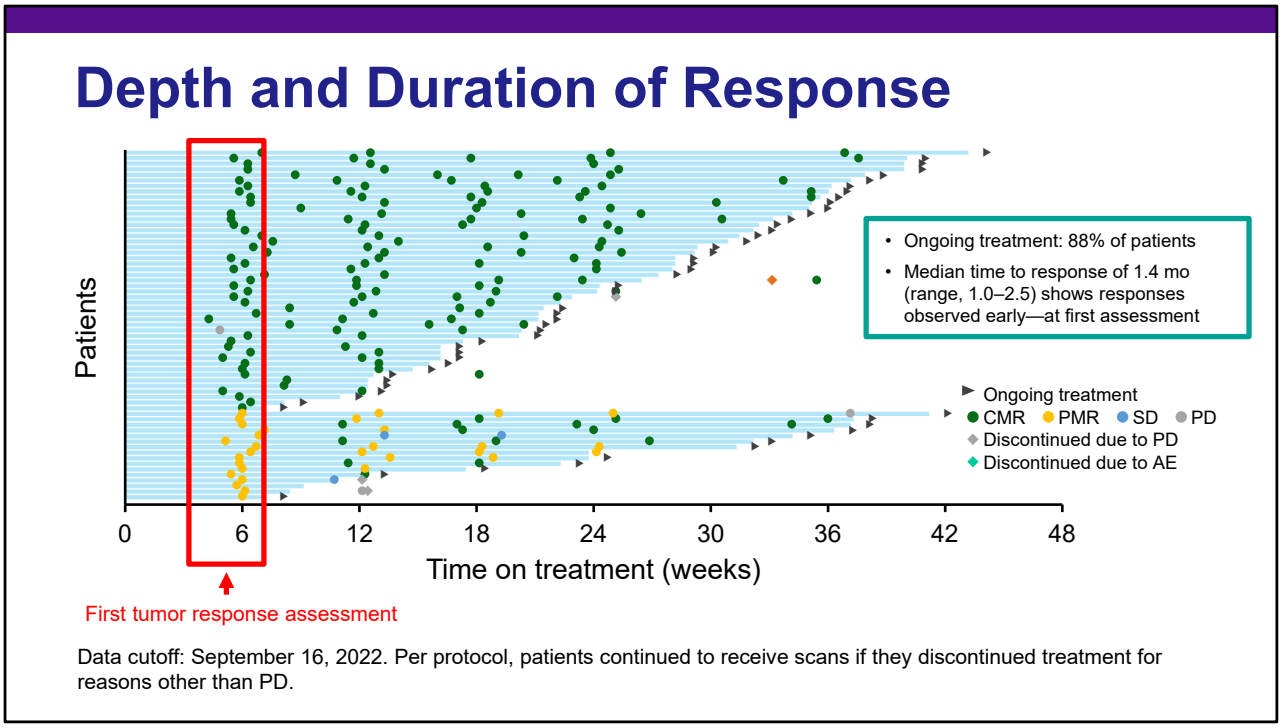
Here's the CRS events. CRS Grade 1 is 33%, very low number of Grade 2, no Grade 3. All CRS resolved again with two days of onset, and the only eight patients required treatment with tocilizumab. No patients needed to discontinue. Again, this data fully supports outpatient administration of this Sub-Q therapy,

High Overall and Complete Metabolic Response Rates

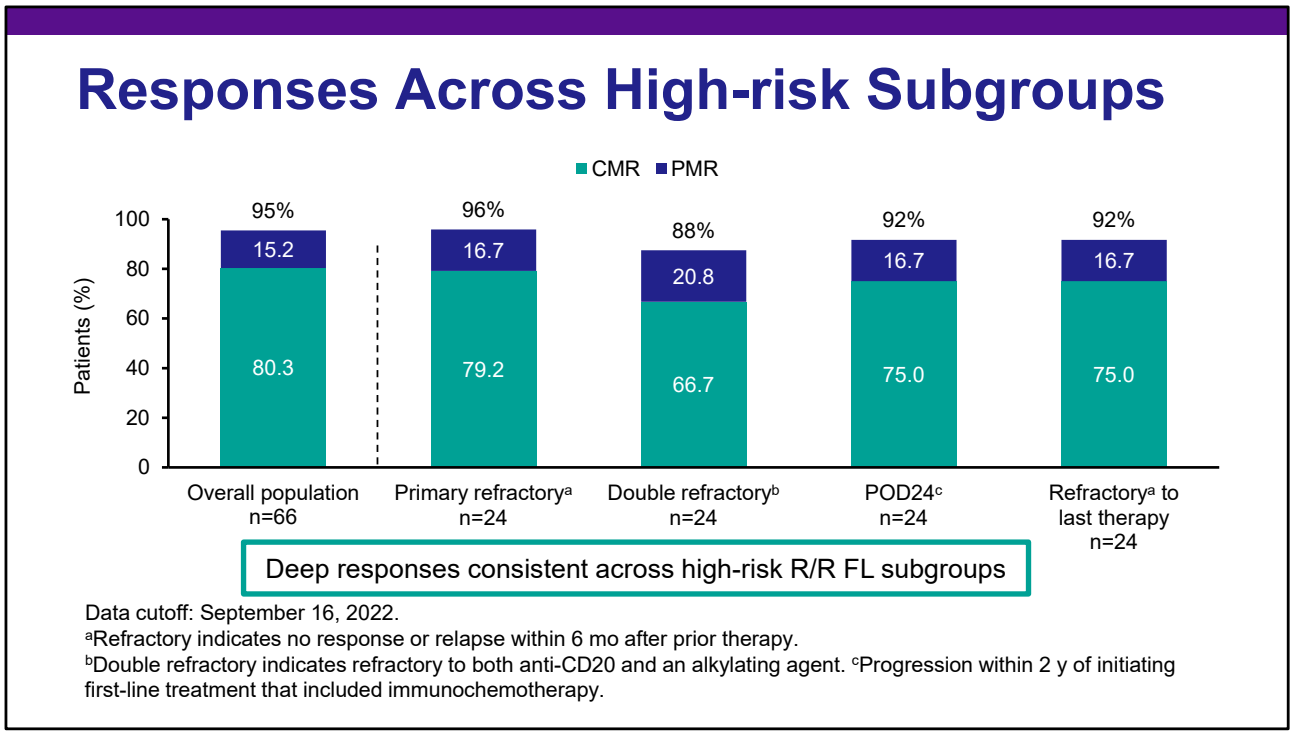
Response[a]	Efficacy Evaluable n=66
Overall response	**95%**
CMR	80%
PMR[b]	15%
Stable disease	3%
Progressive disease	2%

Data cutoff: September 16, 2022. Median follow-up was 6.4 mo (range, 0.5–9.9). [a]Based on modified response-evaluable population, defined as patients with ≥1 target lesion at baseline and ≥1 postbaseline response evaluation and patients who died within 60 d of first dose. [b]Ongoing PMR in 3 patients.

which has high response rates similar to the others 95% with an 80% CMR.

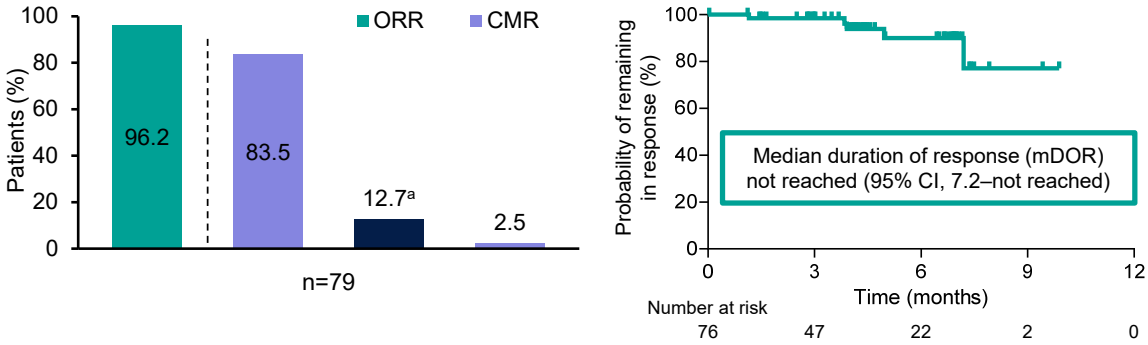


Ongoing treatment here in 88% of patients with a short median time to respond of 1.4 months. Patients benefit quickly and continue to benefit for a long period of time.



They just show nice responses across all high-risk subgroups that were consistent

Updated Response Data



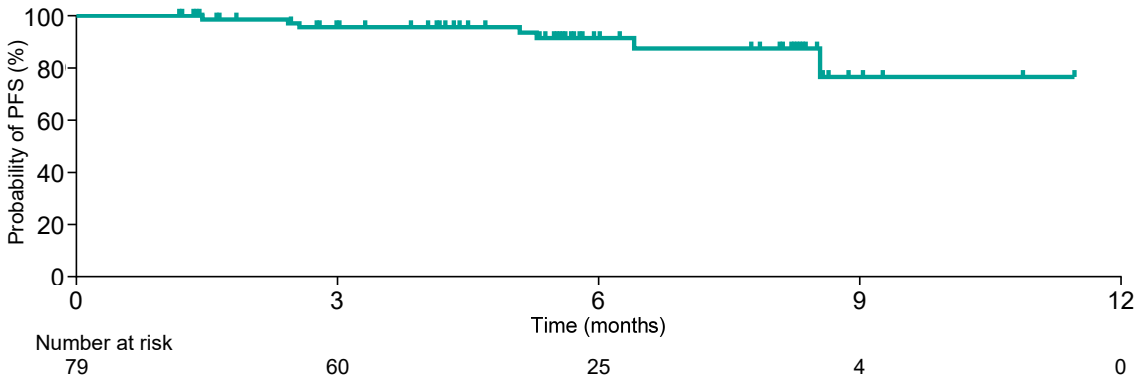
Data cutoff: October 31, 2022

Median follow-up: 5.6 mo (range, 1.2+ to 11.5+)

[a]Ongoing PMR in 6 patients.

and median response duration now not reached, with a median follow-up that's still short 5.6 months.

Progression-free Survival



Median PFS not reached (95% CI, 8.5–not reached)

Data cutoff: October 31, 2022. Median follow-up: 5.6 mo (range, 1.2+ to 11.5+).

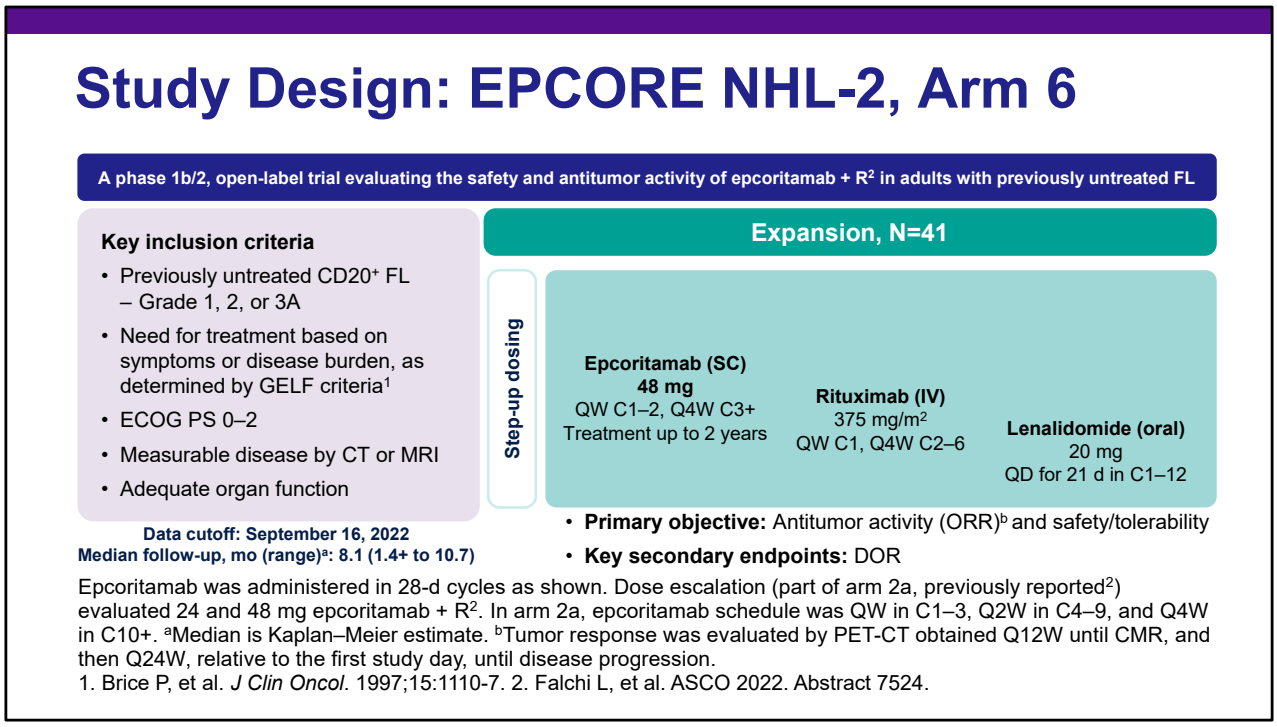
and median PFS is not reached.

Conclusions

- **Epcoritamab + R^2 showed potent antitumor activity**
  - High response rates: ORR 96.2%, CMR 83.5%; majority achieved at first assessment
  - Deep responses observed across high-risk subgroups
  - Durable responses have been observed
- **Safety remained consistent with previous reports**
  - No grade ≥3 CRS observed; CRS events mostly occurred after the first full dose
- **Ongoing phase 3 trial, EPCORE FL-1, is evaluating fully outpatient epcoritamab + R^2 in patients with R/R FL**
  - Trial-in-progress poster 4206 (Monday, December 12, 2022, 6:00 PM–8:00 PM)

Similar to the other bispecifics, epcoritimab plus R^2, now you see a bispecific in combination that plays well in the sandbox. It combines very well with an existing therapy for follicular lymphoma that Dr. Nastoupil showed you.

Remember the RELEVANCE trial of R^2 versus chemo? Well, now think about if you added a bispecific to R^2 how that would compare to chemo. Well, this is a question that's actually being asked, especially when you see such high response rates and high CR rates. Can you move this earlier into earlier lines of treatment? That is something that is actively being explored with all three bispecifics.



This is now a study of epcoritamab, although the other two bispecifics have similar studies in patients who are untreated, combined with R^2.

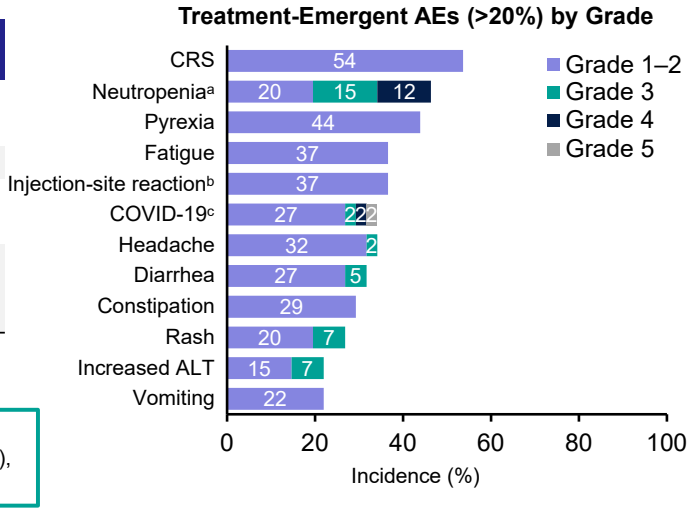
0

Safety Profile

Patients, n (%)	Total N=41
Grade ≥3 TEAE	30 (73)
Related to epcoritamab	14 (34)
Fatal TEAE	2 (5)[a]
Epcoritamab dose delay due to TEAE	22 (54)
Related to epcoritamab	7 (17)
Epcoritamab discontinued due to TEAE	4 (10)
Related to epcoritamab	3 (7)[b]

[a]COVID-19 pneumonia and septic shock (n=1 each) unrelated to epcoritamab. [b]COVID-19 pneumonia, pneumonitis, and toxic skin eruption (n=1 each).

- No clinical tumor lysis syndrome was observed
- One patient (2%) experienced ICANS (grade 1), which resolved in 2 days



[a]Combined term includes neutropenia and neutrophil count decreased. [b]Combined term includes injection-site reaction, erythema, rash, and hypersensitivity. [c]Combined term includes COVID-19, COVID-19 pneumonia, and post-acute COVID-19 pneumonia.

That study showed similar tolerability with no clinical tumor lysis syndrome. Only one patient had ICANs. You can see that the CRS is all Grade 1 to 2.

0

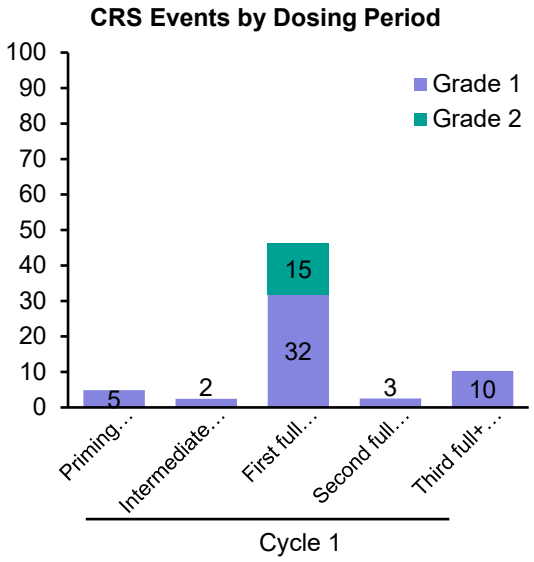
CRS Events

	Total, N=41
CRS, n (%)[a]	22 (54)
Grade 1	16 (39)
Grade 2	6 (15)
Median time to onset after first full dose, d (range)	3 (1–6)
CRS resolution, n (%)	22 (100)
Median time to resolution, d (range)[b]	4 (1–10)
Treated with tocilizumab, n (%)	4 (10)
Leading to treatment discontinuation, n (%)	**0**

Incidence (%)

[a]Graded by Lee, et al 2019 criteria. [b]Median is Kaplan–Meier estimate based on longest CRS duration in patients with CRS.

- No grade ≥3 events
- All CRS events resolved
- Timing was predictable, with most cases occurring after the first full dose



Again, no Grade 3 CRS, primarily Grade 1 to 2 CRS

High Rates of Overall and Complete Metabolic Response

Best Overall Response[a]	Total Efficacy Evaluable n=36
Overall response	**94%**
CMR	86%
PMR	8%
Progressive disease	3%

Median follow-up, mo (range): 8.1 (1.4+ to 10.7). [a]Based on modified response-evaluable population, defined as patients with ≥1 target lesion at baseline and ≥1 postbaseline response evaluation and patients who died within 60 d of first dose. One patient died within 60 d of first dose without assessment (COVID-19).

and very, very high rates of overall and complete metabolic response

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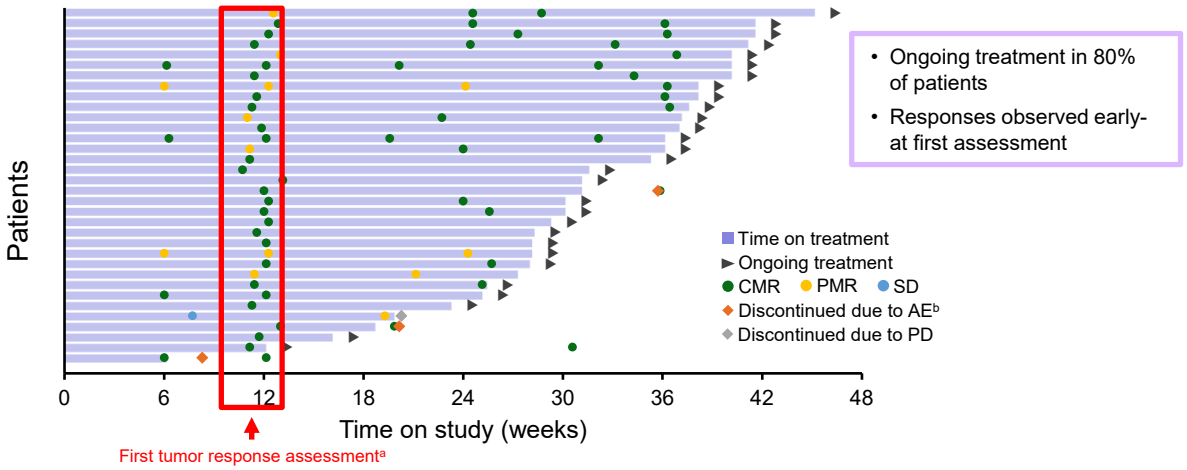
Depth and Duration of Response



Median follow-up, mo (range): 8.1 (1.4+ to 10.7). Per protocol, patients continued to receive scans if they discontinued treatment for reasons other than PD. [a]Most patients had first assessment at week 12, per protocol; some were assessed at week 6 based on investigator's discretion. [b]Two patients discontinued treatment due to COVID-19; 1 discontinued treatment due to pneumonitis.

with deep responses and high duration of response.

Conclusions

- **In first-line FL therapy, epcoritamab + R^2 showed promising efficacy**
  - ORR: 94%; CMR: 86%
  - Responses were observed early, with nearly all patients achieving a response at their first assessment
  - Almost all responses were maintained at the time of this analysis
- **Combination therapy showed a consistent safety profile**
  - No new safety findings
  - CRS had predictable timing, was of low grade, and resolved in all cases
  - One ICANS event (resolved)
- **These data support further clinical evaluation of epcoritamab + R^2 as a chemo-free treatment option in previously untreated FL**

In this early study, epcoritimab R^2 showed promising efficacy and a good safety profile. This is certainly going to be explored as a chemo-free option in previously untreated follicular lymphoma.

Conclusions

- Harnessing the immune system to target follicular lymphoma is yielding exciting novel therapies and combinations
  - Bispecific antibodies combine well with other agents and appear to have additive or synergistic effects
    - High ORR and long DOR for responders
  - Bispecific antibodies have high activity as a class with minimal toxicity – especially compared to CAR-T
    - DOR for responders is extremely long across this class: optional placement in treatment paradigm?
    - Biomarkers to stratify patients to optimal therapy?

In conclusion, harnessing the immune system to target follicular lymphoma is yielding exciting novel therapies and combinations. Bispecific antibodies combine well with other agents and appear to have additive or synergistic effects such as epcoritamab, lenalidomide, and rituximab. There's high overall response rate and responders tend to have a very long duration of response.

Bispecific antibodies have high activity as a class with minimal toxicity compared to CAR T, especially now with step-up dosing. They are all appropriate to give in outpatient a setting except for glofitamab, which is a unique bispecific with a two-to-one, rather than a one-to-one design. It's not really used in the follicular lymphoma space.

I think across this class, the duration of response to respond is extremely long. The question really is what is the optimal placement in the treatment paradigm? Should these drugs be given earlier in combination with R^2 or other things?
It's not clear that patients who have bendamustine, despite the fact that their T-cells are less fit, are having suboptimal responses to bispecific antibodies which is interesting because there's emerging data that bendamustine too close to CAR may actually impair response to CAR. I think more data is going to have to be explored in terms of the relationship of T-cell bendamustine bispecific antibodies.

Finally, I think it will be really important going forward to have biomarkers to stratify patients to optimal therapy. Who should get a bispecific upfront? Who is this overkill for? Who would benefit in relapse from a CAR versus device-specific? How should these be sequenced? These are some of the important questions I think that are going to move the field forward over the next 10 years or so.

Questions?

I'll now move to your questions.

If I have a patient who I believe is a candidate for CAR T therapy, are there guidelines to guide decisions on which approved agent to use?

Dr. Diefenbach: I have a question for Dr. Nastoupil.

If I have a patient who I believe is a candidate for CAR T therapy, are there guidelines to guide decisions on which approved agent to use?

Dr. Nastoupil: That's a good question. The short answer is no. I think each center that's a designated CAR delivery site makes that decision. There are patient-specific characteristics in a center like ours, where we have the opportunity to prescribe either axi-cel or tisa-cel. It's going to have to do with the performance status of the patient, the comorbidities given that the tisa-cel construct is a little bit better in terms of toxicity. That's how we might approach that, but in general, it's going to again, be center-specific, and there are no national guidelines to help answer that question.

Is CRS toxicity only a concern at time of initial treatment?

Dr. Diefenbach: Here is one about bispecifics, I'll answer two because one is very short.

Is CRS toxicity only of concern at time of initial treatment?

I think this is a very important question, particularly as eventually these therapies will be given in the community as well. All of the CRS appears to occur really in cycle one, often at this first high dose, but sometimes at the first dose of the step up dose. All three of those initial doses in cycle one, the day 1, day 8, and day 15, you need to watch very carefully the patient, after that the risk of CRS is exceedingly small. A patient who hasn't had CRS in cycle one will not have CRS in cycles two or later. In fact, the only patients who have CRS in cycle two are more patients who had a Grade 2 CRS in cycle one.

Are steroids always given preemptively prior to starting a bispecific? Are there other management strategies that can be employed to decrease the risk of CRS at the start of treatment?

Dr. Diefenbach: The next question, which is also I think, related to CRS:

Are steroids always given preemptively prior to starting a bispecific? Are there other management strategies that can be employed to decrease the risk of CRS at the start of treatment?

That's a very good question. I think step-up dosing is really the primary way that we mitigate toxicity with bispecifics. On clinical trials, patients are always required to receive steroids. For my patients who are in later cycles and I feel like this is not really clinically indicated, I take them down to 12.5 milligrams of . I give them as little steroid as I can. I think there are now guidelines that you can-- if your patient has tolerated the bispecific that after cycle two, you do not need to give steroids.

For a patient who I think follow the guidelines, but I think steroids are certainly something you would need to give in the first two cycles. After that, if you have the latitude, you probably don't need to give.

Which patient would benefit most from mosunetuzumab? Where does this treatment option fit in the current treatment paradigm?

Dr. Diefenbach: *Which patient would benefit most for most in mosunetuzumab? Where does this treatment option fit in the current treatment paradigm?*

Mosunetuzumab is an extremely well-tolerated therapy that is highly active. I would say any patient who currently fits the label, and who has relapsed after– who is in the third line, who doesn't have a clinical trial option should be offered mosunetuzumab. It's easy to give, it doesn't interrupt your life, you can basically get it and go back to work the next day.

Who would I not give mosunetuzumab to? A patient who was a trial candidate in a trial that had a bispecific in combination like Epco R^2 trial or Mosu or Pola trial. Because I think, our trials are how we've developed these exciting drugs that Dr. Nastoupil and I have brought to you today. Without trials to move the field forward and bring these drugs to patients before they're approved, we wouldn't have any more advances. There are so many exciting drug combinations of drugs we know are safe that I would probably offer a patient clinical trial before mosunetuzumab.

Let's say, they weren't a trial candidate. I think the question then becomes bispecific or CAR. For most patients, I would probably offer bispecific before CAR. The exception might be someone who was very young with very aggressive lymphoma or someone who I was concerned had transformed lymphoma because remember that these therapies are only approved for patients with follicular lymphoma Grade 1 to 3A. If I had any concern for transformation, I would probably not feel that that patient could benefit from mosunetuzumab.

How would you address CRS in patients, not on trials for BiTE?

Dr. Diefenbach: *As many more BiTEs get approved even though CRS is minimal, there is a risk. Toci is still only approved for CAR T products. How would you address CRS on patients, not on trials for BiTE?*

Dr. Nastoupil: I think it's important first to recognize where is the patient in that treatment scheme? Meaning, is it their first exposure? Are they at full dose? Have they had prior CRS before? For instance, if this is a patient who just had their first cycle one day one at a low dose and they're having their first onset of fever, do you want to know if they are high risk for developing Grade 2 or higher? Most are going to have fever and that's it. Those patients, I think you could potentially manage with something like an antipyretic, such as the acetaminophen, for instance.

If, however, this is a patient who is getting full dose, they may have had Grade 1 CRS previously, they may have high tumor burden, and I'm worried they're going to progress from Grade 1 to Grade 2. Those are patients I might be on the ready to have corticosteroids available to them with their first onset of fever. If I have a patient that they have CRS, they are in our facility either inpatient or in our infusion center, and they also have hypoxia or hypotension, now we're in the Grade 2 or higher arena. That's when I'm going to reach for tocilizumab.

How would you address CRS in patients, not on trials for BiTE?

Dr. Nastoupil (continued): Though, yes, it's FDA approved for CAR T cell therapy, in all of our trials for the management of CRS I should specify, in all of our trials, there was the option of using institutional standards that you could apply to the bispecific CRS that's already in place for your CRS management for CAR T. In most centers, I say tocilizumab is utilized in Grade 2 or higher CRS.

I think the tricky thing for all of us is as we roll out these treatment algorithms for our standard-of-care patients, anticipating they're going to be a little bit sicker and frailer than what was seen on the prospective study is when will people react to that fever and utilize things like corticosteroids and/or tocilizumab.

I suspect at first, we'll probably react a little bit more strongly, and then as we gain more experience and have our workflow sorted out for how to transition patients that need to be hospitalized from an outpatient to inpatient setting, I think we'll get more comfortable with utilizing less aggressive measures. That's what happened with CAR T.

What was the overall age of the patients in the polatuzumab study?

Dr. Diefenbach: One very quick one. Someone asked the overall age of the patients in the polatuzumab study, it was 64. There was a range from young to in the late 80s, so it was a very well-tolerated therapy as well.

Given the rapid advances in treatment modalities, how would you treat Pod 24 disease and what would govern your sequence regimen?

Dr. Diefenbach: Now, the next one, I think--*Given the rapid advances in treatment modalities, how would you treat Pod 24 disease and what would govern your sequence regimen?*

I think this is very similar to the mosunetuzumab question, just phrased differently. I think the first question really is, has the patient relapsed with follicular lymphoma or do they have transformed disease?

By that, I mean transformed into an aggressive large cell lymphoma, because that takes you down two different treatment paradigms. All of these therapies we're talking about the pola, obinutuzumab, rituximab, the R^2, the bispecific antibodies, for patients with Grade 1 to 3A disease. These are not therapies for patients with transformed follicular lymphoma. If the patient has transformed follicular lymphoma, they should be treated as a DLBCL patient and taken down a DLBCL treatment paradigm, which in second line would most likely be CAR T therapy.

If the patient is Pod 24 positive but continues to have follicular lymphoma histology, you have many options at this time, including R^2. If they got R chemo to start, R chemo. If they got R^2 to start, clinical trial, polatuzumab combinations, bispecifics alone, bispecifics in combination, and CAR T. I think all of those are excellent options. I'll ask Dr. Nastoupil if she wants to add anything.

Given the rapid advances in treatment modalities, how would you treat Pod 24 disease and what would govern your sequence regimen?

Dr. Nastoupil: I think, as you said earlier, I think for the field, the most important thing we need to do right now is support trials for these patients because this is the unmet need. I'm going to choose a trial first and foremost for these patients. If a trial is not an option, or if I'm practicing in a setting where clinical trial is just not feasible, then I think it does depend a little bit on what their prior treatment was. How worried am I that they have aggressive histology concurrently?

If, for instance, the most common scenario is a patient had bendamustine-rituximab front line, they're relapsing early, I've biopsied them and proven that there's no signs of large cell lymphoma, then your question in my mind is, do you give R-CHOP or do you give something like lenalidomide and rituximab? It depends a little bit on the age and frailty of the patient. If there's someone I'm worried is not going to tolerate an anthrocycline-based approach, I'm going to prefer R^2 in that setting.

If, however, it is someone that's young and fit, and I really am concerned they have occult transformation, I just didn't prove it on the biopsy, meaning LDH is high. They may even have hypercalcemia. They have the B symptoms. SUVs are higher on PET, then I'm going to proceed with R-CHOP in my second line.

Dr. Diefenbach: That is all the time we have today. Thank you very much for your attention. On behalf of Dr. Nastoupil and myself, thank you so much for joining us.