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CHAIRPERSON'S PERSPECTIVE

This transcript has been edited for style and clarity and includes all slides from the presentation.

Core Concepts for Community-Based Practice:

The Evolving Role of Bispecific Antibody Therapy in Relapsed or Refractory Follicular Lymphoma

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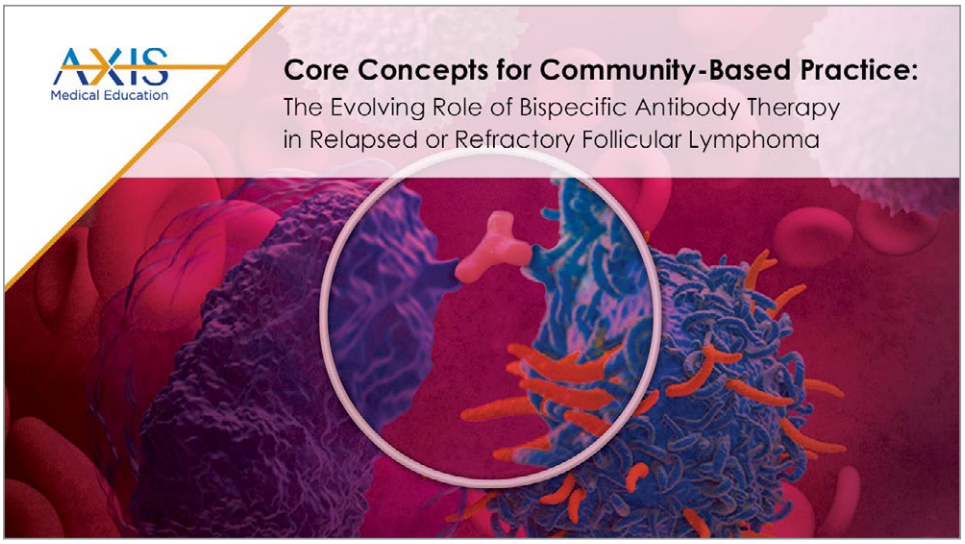
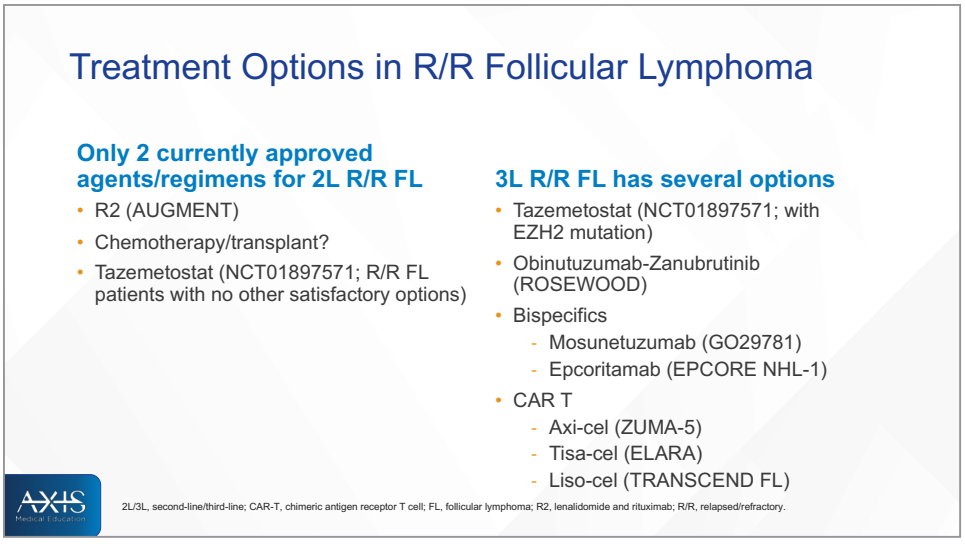
CHAIRPERSON'S PERSPECTIVE

Core Concepts for Community-Based Practice: The Evolving Role of Bispecific Antibody Therapy in Relapsed or Refractory Follicular Lymphoma

Tycel J. Phillips, MD

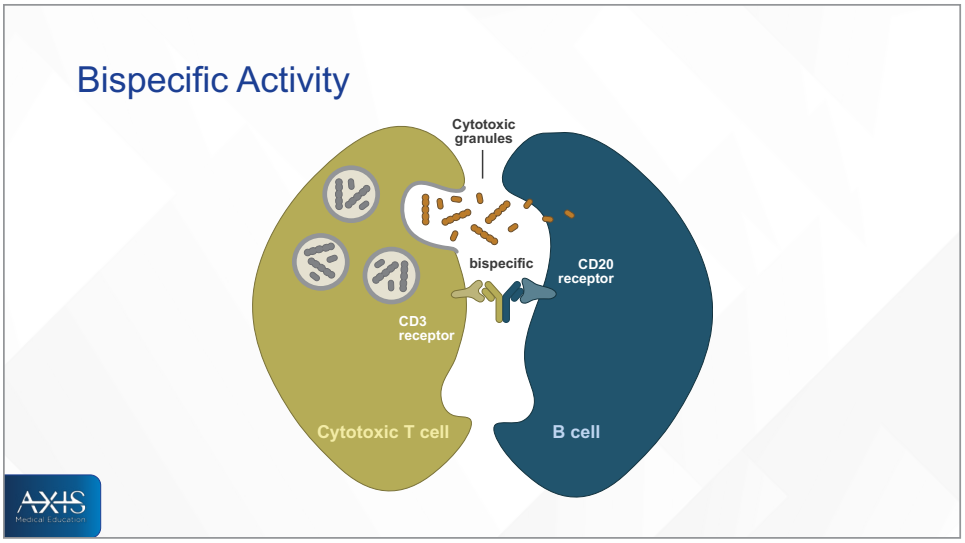


Tycel J. Phillips, MD: Hello. My name is Dr. Tycel Phillips. I'm coming from the City of Hope National Medical Center. And I want to thank you for joining this brief overview of core concepts for community-based practice, the evolving role of bispecific antibody therapy in relapsed or refractory follicular lymphoma.

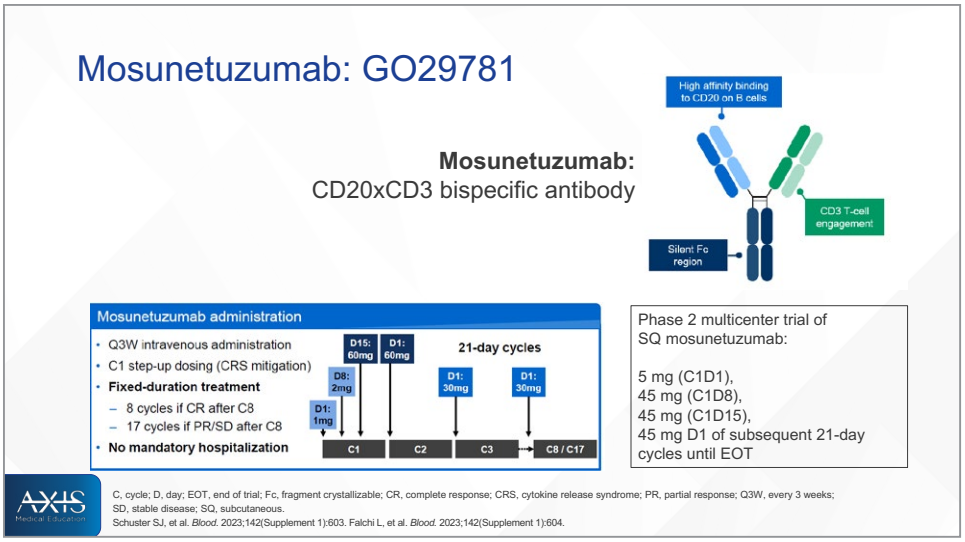


Currently, if we look at the current treatment options for relapsed/refractory follicular lymphoma, there are only two currently approved regimens for second-line relapsed/refractory follicular lymphoma. These are lenalidomide/rituximab based on the AUGMENT study. We do have chemotherapy and transplant, which has sort of fallen out of favor. And then we have tazemetostat for relapsed/refractory follicular lymphoma patients who have no other satisfactory options.

There are additional options in third-line plus follicular lymphoma. Again, we have tazemetostat for patients with EZH2 mutations. We have obinutuzumab and zanubrutinib based on the ROSEWOOD study with its pending confirmatory phase 3 trial, MAHOGANY. And then we have the bispecific antibodies; mosunetuzumab based on the clinical trial GO29781, and epcoritamab from the EPCORE NHL-1 study. Additionally, there are three approved CAR T-cell products in this space, axicabtagene autoleucel from the ZUMA-5 study, tisagenlecleucel from the ELARA study, and lisocabtagene maraleucel from the TRANSCEND FL trial.



- So specifically, we will discuss bispecific antibodies. So, we have mosunetuzumab, odronextamab, and epcoritamab as agents being evaluated in patients with follicular lymphoma.



- Mosunetuzumab gained approval based on the GO29781 clinical trial. In this study, mosunetuzumab was given as an IV infusion every 3 weeks after initial step-up dosing. This study did not require any mandatory hospitalization. Mosunetuzumab is also being studied as a subcutaneous formulation.

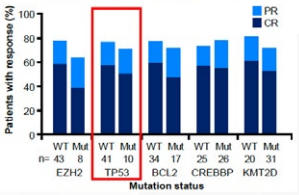
Mosunetuzumab Response

Response rates

Efficacy endpoint in the overall population by investigator assessment	N=90
ORR, % (95% CI)	78% (68-86)
CR, % (95% CI)	60% (49-70)
Median time to first response, months (range)	1.4 months (1.0–11)
Median time to first CR, months (range)	3.0 months (1.0–19)

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

Response by mutation status



CR, complete response; Mut, mutant; ORR, overall response rate; PR, partial response; WT, wild-type.
Bartlett NL, et al. ASH 2022. Abstract 610.
1. Budde LE, et al. *Lancet Oncol.* 2022;23(8):1055-1065.

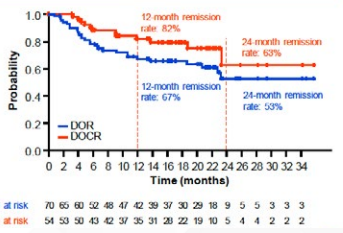
- So looking at the response rate from the initial pivotal study, we see the overall response rate is 78% and a complete response rate of 60%. Time to first response was 1.4 months, which corresponds with the first on-study disease assessment, and time the first CR was 3 months. If we look at high-risk subsets in this patient population, those are EZH2 mutations, TP53 mutations, BCL mutations, CREBBP, KMT2D. Again, we do see fairly equivalent rates of overall response and complete response rate in these high-risk subsets.

Mosunetuzumab Response

Durability of responses

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

DOR and DOCR



Durable responses: majority of patients in remission after 2 years

DOCR, duration of complete response; DOR, duration of response; NR, not reached; OS, overall survival; PFS, progression-free survival; TTNT, time to next therapy.
Bartlett NL, et al. ASH 2022. Abstract 610.

- Looking at durability of response, the median duration of response was not reached in these 90 patients with a 24-month duration of response of 53%. For those who obtained a complete response, again, median is not reached. And a 24-month duration of complete response of 63%.

Mosunetuzumab Safety

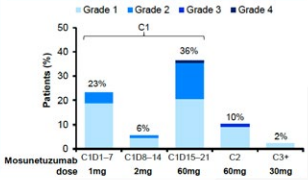
Safety profile

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%

CRS summary

CRS by ASTCT criteria	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)	5.2 (1.2–2.4)
C1D1	27 (0.1–391)
C1D15	
Median CRS duration, days (range)	3 (1–29)
Corticosteroids for CRS management	11%
Tocilizumab for CRS management	8%
Events resolved	100%

CRS by cycle and grade



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

ASTCT, American Society for Transplantation and Cellular Therapy; C, cycle; CRS, cytokine release syndrome; D, day; FL, follicular lymphoma
Bartlett NL, et al. ASH 2022. Abstract 610.

Now turning our attention to safety. The most important safety aspect in dealing with patients with bispecific antibodies is typically cytokine release syndrome. 44% of the patients had any grade cytokine release syndrome, with the majority of patients having grade 1 or grade 2. This is very important as we talk about management of patients with cytokine release syndrome, as typically grade 1 cytokine release syndrome does not require any hospitalization or introduction of tocilizumab. All patients with CRS had resolution of the event at the conclusion of study protocol.

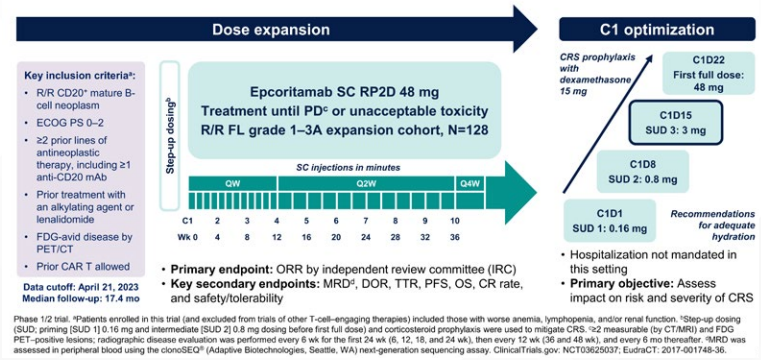
Mosunetuzumab FDA Approval

- On December 22, 2022, the FDA granted accelerated approval to mosunetuzumab-axgb, a bispecific CD20-directed CD3 T-cell engager for adult patients with relapsed or refractory follicular lymphoma after 2 or more lines of systemic therapy
- Mosunetuzumab-axgb was evaluated in GO29781, an open-label, multicenter, multi-cohort study
- The efficacy population consisted of 90 patients with relapsed or refractory follicular lymphoma who had received at least 2 prior lines of systemic therapy, including an anti-CD20 monoclonal antibody and an alkylating agent
- The prescribing information has a Boxed Warning for serious or life-threatening cytokine release syndrome
- Warnings and precautions include neurologic toxicity, infections, cytopenias, and tumor flare

FDA, US Food and Drug Administration.
FDA.gov. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-mosunetuzumab-axgb-relapsed-or-refractory-follicular-lymphoma

So, mosunetuzumab was approved for patients with relapsed/refractory follicular lymphoma based on the results of this open-label study. The boxed warning for this mentions cytokine release syndrome as one of the main concerns. But this does not require a mandatory hospitalization, as we did see with the bispecific antibodies approved in multiple myeloma, or any suggestion or requirement of hospitalization, as we see in the FDA approval for the bispecific antibodies in diffuse large B cell lymphoma.

Epcoritamab: EPCORE NHL-1



Phase 1/2 trial. [a]Patients enrolled in this trial (and excluded from trials of other T-cell–engaging therapies) included those with worse anemia, lymphopenia, and/or renal function. [b]Step-up dosing (SUD; priming [SUD 1] 0.16 mg and intermediate [SUD 2] 0.8 mg dosing before first full dose) and corticosteroid prophylaxis were used to mitigate CRS. [c]≥2 measurable (by CT/MRI) and FDG PET–positive lesions; radiographic disease evaluation was performed every 6 wk for the first 24 wk (6, 12, 18, and 24 wk), then every 12 wk (36 and 48 wk), and every 6 mo thereafter. [d]MRD was assessed in peripheral blood using the clonoSEQ® (Adaptive Biotechnologies, Seattle, WA) next-generation sequencing assay. ClinicalTrials.gov: NCT03625037; EudraCT: 2017-001748-36.

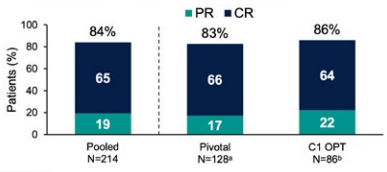
C, cycle; CAR T, chimeric antigen receptor T cells; CR, complete response; CRS, cytokine release syndrome; CT, computed tomography; D, day; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FDG, fluorodeoxyglucose; FL, follicular lymphoma; mAb, monoclonal antibody; MRD, minimal residual disease; NHL, non-Hodgkin lymphoma; ORR, overall response rate; OS, overall survival; PET, positron emission tomography; PD, progressive disease; PFS, progression-free survival; R/R, relapsed/refractory; RP2D, recommended phase II dose; SC, subcutaneous; SUD, step-up dose; TTR, time to relapse; wk, week.

Linton KM, et al. *Trans Cell Ther.* 2024;30(2):S33-S34.

- So next we will look epcoritamab, which was approved in the EPCORE NHL-1 study. This was given as a subcutaneous injection. The initial study proceeded with step-up dosing at 0.16, 0.8, and then 48 mg. Due to rates of CRS, there was a Cycle 1 optimization introduced to reduce the rates of CRS and hopefully prevent these patients from requiring hospitalization. And so in this situation, patients were given prophylaxis with dexamethasone. But also there was an introduction of an intermediary dose of 3 mg with Cycle 1 Day 15, and thus pushing the full dose back to Cycle 1 Day 22 in this cohort of patients.

Epcoritamab Response

High Rates of Complete Response and MRD Negativity



MRD-Negativity Rate	n (%)
Pooled (n=135)	89 (66)
Pivotal (n=91)	61 (67)
C1 OPT (n=44)	28 (64)

Based on MRD-evaluable population per clonoSEQ® PBMC assay with 10^{-6} cutoff.

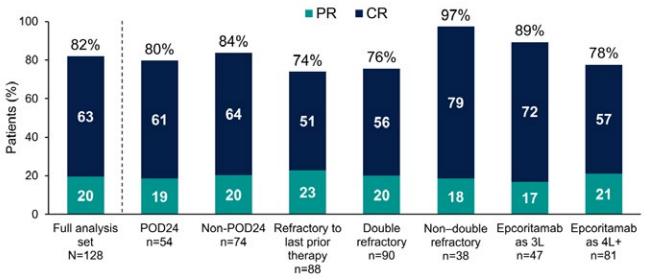
- At 6 months in C1 OPT, an estimated 86% of patients with CR remained in CR
- No impact on time to response in C1 OPT
  - **Median time to response** was 1.4 months in both cohorts[c]
  - **Median time to complete response** was 1.5 months in both cohorts[d]

CR was complete metabolic response (ie, PET negativity).
[a]Three patients (2%) were not evaluable. [b]Five patients (6%) were not evaluable. [c]Range: 1.2-4.4 in C1 OPTS, 1.0-3.0 in pivotal. [d]Range: 1.2-4.7 in C1 OPT, 1.2-11.1 in pivotal.
C, cycle; CR, complete response; MRD, minimal residual disease; OPT, optimization; PBMC, peripheral blood mononuclear cell; PR, partial response.
Linton K, et al. ASH 2023. Abstract 1655.

- So taking all patients together, even the optimization cohort and those treated traditionally with the three step-up dosing mechanism, you see high overall response rate of 84%, complete response rate of 65%. Again, between the two cohorts, the optimization and the pivotal trial, you see equivalent CR rates and overall response rate; thus, the introduction of the intermediate dose did not add any sort of detriment to the overall response in this patient population.

Epcoritamab Detailed Response

ORRs and CR Rates Were High Regardless of Subgroup

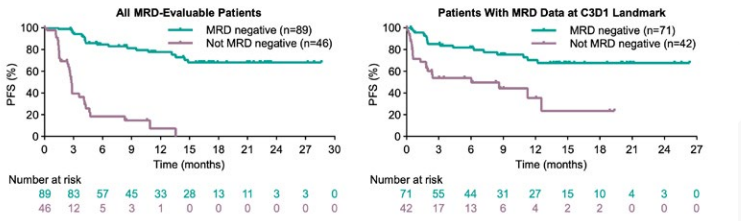


CR, complete response; ORR, overall response rate; POD24, progression of disease within 2 years; PR, partial response; 3L, third-line; 4L, fourth-line.
Linton K, et al. ASH 2023. Abstract 1655.

- So looking at some high-risk subsets, and you can see equivalency in this patient population of high overall response rate and complete response rates, with the highest being 97% overall response rate and complete response rate of 79% in those who were considered to be non-double refractory. But, even in the double refractory patients, we have a high overall response rate of 76% and a complete response rate of 56%. This all compares very favorably with mosunetuzumab.

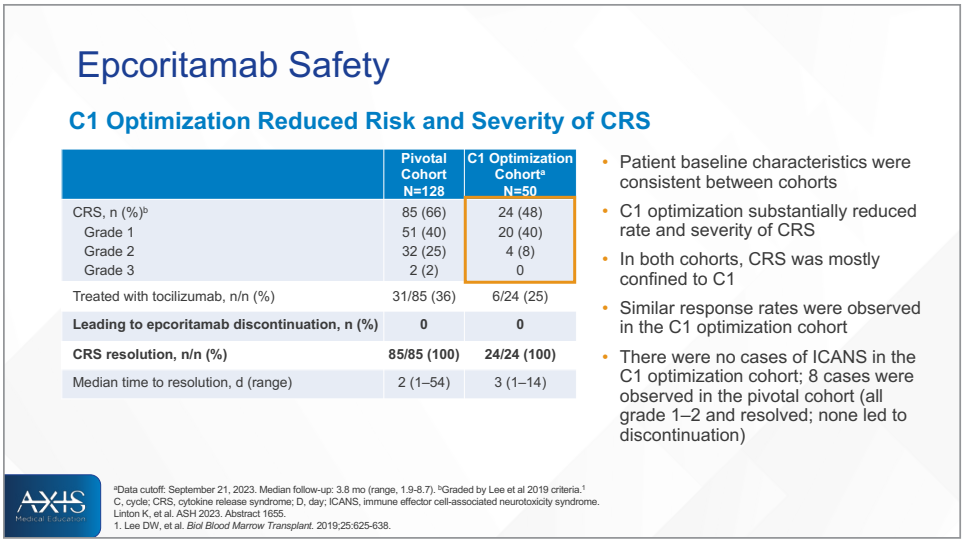
Epcoritamab Response

MRD Negativity (Overall and at C3D1) Associated With Favorable PFS

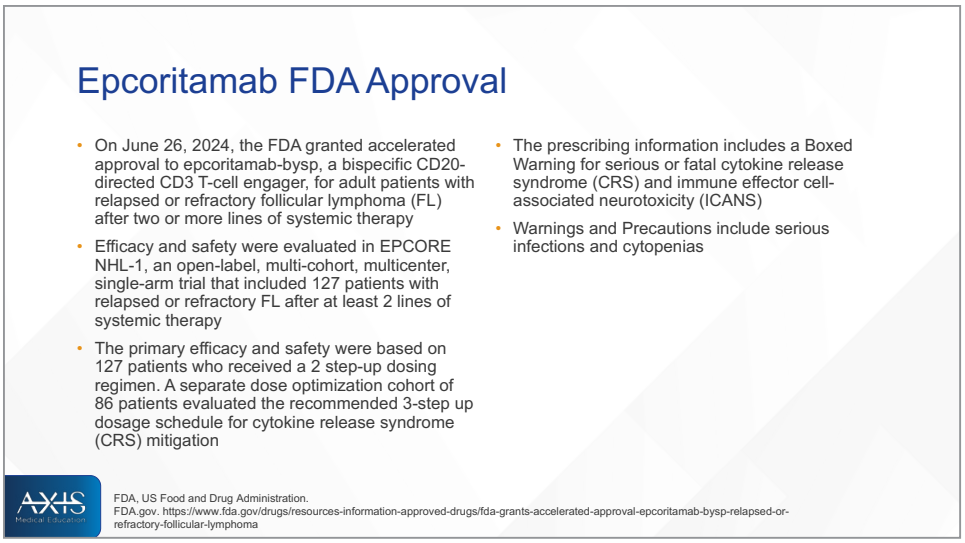


PFS assessed by investigator, MRD based on PBMC assay with 10^{-6} cutoff. MRD negative was defined as having MRD negativity at any time point.
C, cycle; D, day; MRD, minimal residual disease; PFS, progression-free survival.
Linton K, et al. ASH 2023. Abstract 1655.

- So they did look at some rates of MRD negativity. Those who were MRD undetectable in this protocol tend to have very prolonged and durable responses.



As I mentioned with the introduction of the C1 optimization, you can see a marked reduction in the rates of cytokine release syndrome, specifically a reduction in rates of Cycle 2 and above cytokine release syndrome, or CRS. Again, reduction in the use of tocilizumab. None of these events led to discontinuation epcoritamab. All patients had resolution Overall, the C1 optimization cohort and the safety profile compares very favorably to mosunetuzumab, again, suggesting that with this optimization, patients can be treated in an outpatient setting without the need for hospitalization or heavy utilization of tocilizumab.

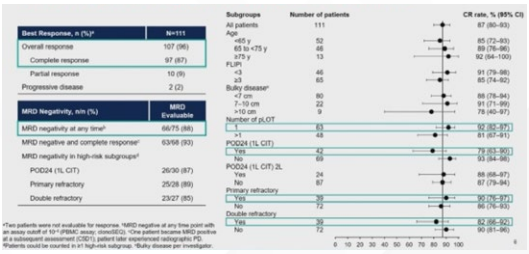


And so, based on this, epcoritamab was approved in June of 2024 thus providing a second sort of CD20/CD3 bispecific in this patient protocol. And again, we do have some concern and warnings for CRS, of an immune effector cell-associated neurological syndrome. This is minor compared to what we see with chimeric antigen receptor therapy. This did not require hospitalization for epcoritamab with the additional step-up dosing in this optimization cohort. So, epcoritamab and mosunetuzumab both can be given in an outpatient setting without the need for 24-hour hospitalization monitoring.

Epcoritamab: EPCORE NHL-2

- Fixed-duration epcoritamab plus lenalidomide + rituximab (R2) in adult patients with R/R FL
- Among 111 patients with a median follow-up of over two years, ORR was 96%, and CR rate was 87%
- MRD analysis from blood samples showed that 88% of patients were MRD negative, indicating no detectable disease at 10-6 threshold
- The FDA recently granted BTD for epcoritamab plus R2 for the treatment of adult patients with R/R FL who have received at least one prior line of therapy
- Epcoritamab in combination with R2 vs R2 in R/R FL is being studied further in the ongoing, randomized, Phase 3 EPCORE FL-1 trial (NCT05409066)

Deep Responses Regardless of High-Risk Features



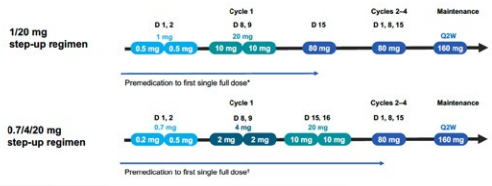
1L, first-line; BTD, breakthrough therapy designation; CIT, chemoimmunotherapy; CR, complete response; FDA, U.S. Food and Drug Administration; FL, follicular lymphoma; FLIPI, The Follicular Lymphoma International Prognostic Index; MRD, minimal residual disease; ORR, overall response rate; pLOT, prior lines of therapy; POD24, progression of disease within 24 months; R/R, relapsed/refractory.
Falchi L, et al. ASH 2024. Abstract 342. Soong D, et al. *Cancer Res*. 2024;84(6_Supplement):5071. Abbvie. https://news.abbvie.com/2024-12-07-Investigational-Epcoritamab-DuoBody-R-CD3xCD20-Combination-Therapy-Shows-High-Response-Rates-in-Clinical-Trial-of-Patients-With-Relapsed-or-Refractory-R-R-Follicular-Lymphoma-FL

So, if we look at some more information with epcoritamab in follicular lymphoma, we have the EPCORE NHL-2 study, which looked at epcoritamab plus the immunomodulatory drug lenalidomide. This drug is a currently approved agent in patients with relapsed/refractory follicular lymphoma, based on the AUGMENT study. In this study, they did add epcoritamab to the R2 backbone in this situation. In this phase 2 trial, there is a very high overall response rate of 96%, a complete response rate at 87%. This was given breakthrough designation for patients with relapsed/refractory follicular lymphoma, who have received at least one prior line of therapy. This is being studied in a phase 3 randomized study, EPCORE FL-1, which will randomize R2 versus R2 plus epcoritamab.

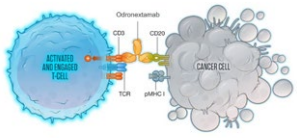
Odronextamab: ELM-2

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



Odronextamab
Hinge-stabilized CD20×CD3 bispecific antibody



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

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; FL, follicular lymphoma; IV, intravenous; Q2W, every 2 weeks.
Kim TM, et al. *Blood*. 2022;140(1):2280-2282. Kim TM, et al. *Ann Oncol*. 2024;35(11):1039-1047. Chong G, et al. *Cancer Res*. 2024;84(7_Suppl):CT243.

So the third bispecific antibody being explored in follicular lymphoma is odronextamab from the ELM-2 study. There is a little bit more complicated step-up dosing with odronextamab compared to epcoritamab and mosunetuzumab. So we have split dosing of 0.2/0.7 mg on Cycle 1 Day 1 and Day 2. We do then have on Cycle 8 Day 9, 2 and 2, for a total of 4 mg. Split dosing on cycle Day 15 and 16, 10 and 10. And then thereafter you get to work your way toward the full dose. But from Cycles 2 to 4, patients get weekly doses of 80 mg, and thereafter they get, every 2 weeks at 160 mg. This increase in optimization was sort of introduced initially during the early parts to reduce the rates of CRS with odronextamab.

Odronextamab Response

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)

FL, follicular lymphoma; R/R, relapsed/refractory.
Kim TM, et al. *Blood.* 2022;140(1):2280-2282.

So looking at the response rate, we still see high overall response rate, complete response rate with odronextamab, 81.8% and 75.2%. With investigator evaluation, there was a slight decrease in the complete response rate, but overall, relatively stable. And again, with the change in step-up dosing, you do see that there is no detriment in patients' overall and complete response rate. And you actually see a higher complete response rate with the additional step-up dosing, with the improvement in safety.

Odronextamab Safety

n, (%)	1/20 regimen (N=68)	0.7/4/20 regimen (N=63)
CRS any Grade	38 (55.9%)	36 (57.1%)
Grade 1	22 (32.4%)	28 (44.4%)
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%)

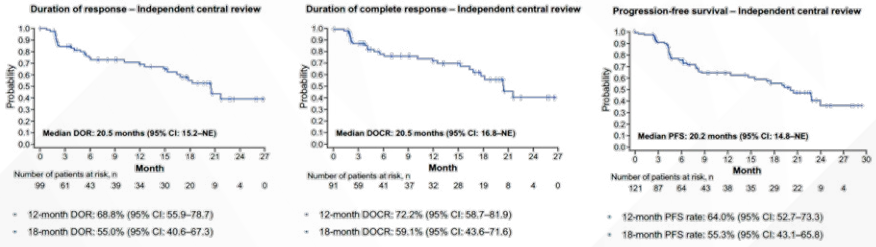
n (%)	1/20 regimen (N=68)	0.7/4/20 regimen (N=63)	All patients (N=131)
ICANS, any grade	1 (1.5%)	0	1 (0.8%)
Grade ≥3	0		0
Infusion related reaction, any grade	21 (30.9%)	16 (25.4%)	37 (28.2%)
Grade ≥3	4 (5.9%)	2 (3.2%)	6 (4.6%)
Infection, any grade	51 (75.0%)	35 (55.6%)	86 (65.6%)
Grades 1–2	23 (33.8%)	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%)

- 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; FL, follicular lymphoma; ICANS, immune effector cell-associated neurotoxicity syndrome; ICU, intensive care unit; R/R, relapsed/refractory.
Kim TM, et al. *Blood.* 2022;140(1):2280-2282.

You do see a decrease in the rates of grade 2 and grade 3 cytokine release syndrome, with the improvement with the extra dose and expansion of the step-up dose in this patient population in fairly equivalent patients, Overall, the cytokine release syndrome rate was fairly similar, but again, more patients had grade 1 CRS, and, a marked reduction in grade 2 and grade 3. Very important as you try to transition this drug into an outpatient setting. Looking at ICANS, there was no ICANS reported with the additional prolonged step-up dosing regimen. There were some reports of infusion-related reaction, but this was fairly equivalent and then what we would expect with this treatment cohort.

Odronextamab 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)
- 12-month PFS rate: 64.0% (95% CI: 52.7–73.3)
- 18-month PFS rate: 55.3% (95% CI: 43.1–65.8)

Data cut-off date: Sep 15, 2022.
DOCR, duration of complete response; DOR, duration of response; NE, not evaluable; PFS, progression-free survival.
Kim TM, et al. *Blood.* 2022;140(1):2280-2282.

So looking at response, the 12-month duration of response of 68.8%, 18-month duration of response at 55%, 12-month duration of complete response of 72.2%, and 18-month duration of complete response at 59.1%. And this study is ongoing with more maturation of the data expected in the relatively near future.

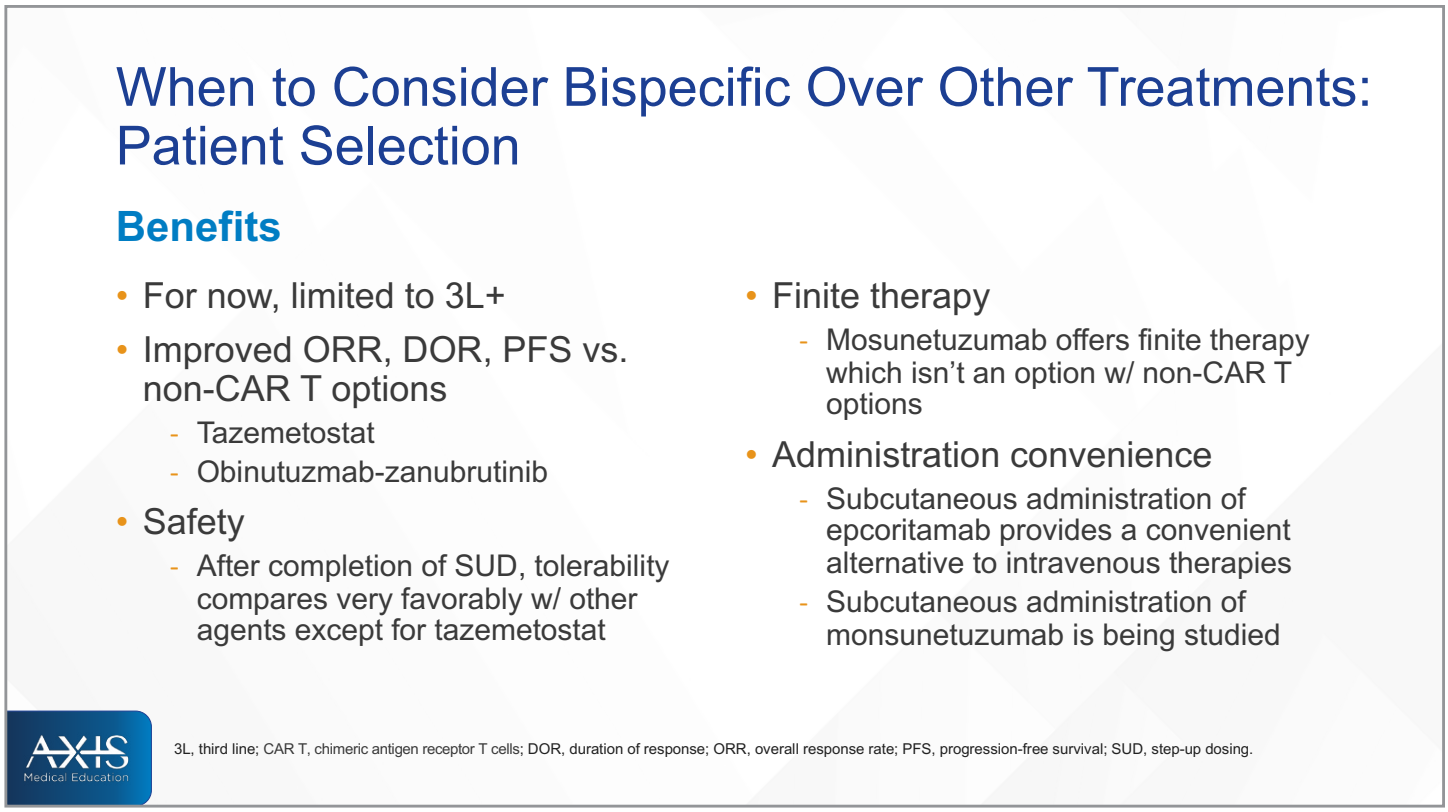
Summary of Response FL

Drug	N	ORR	CR	PFS 36 m	OS 36 m	mOS
Mosunetuzumab	90	78%	60%	43.2%	82.4%	NR
Epcoritamab	128	82%	63%	49.4%*	70.2%*	N/A
Odronextamab	121	81.8%	75.2%	55.3%*	70.1%[24m]	NR

Drug	DOR 12 m	DOCR 12 m	DOR 30 m	DOCR 30 m	mDOR	mDOCR
Mosunetuzumab	67%	82%	56.6%*	72.4%	35.9 m	NR
Eporitamab	58.4%*	72.2%	N/A	N/A	NR	N/A
Odronextamab	68.8%	75%	55%*	59.1%*	22.6 m†	25.1 m†

*18 months
†20.1 months
CR, complete response; DOCR, duration of complete response; DOR, duration of response; FL, follicular lymphoma; m, months; mDOCR, median DOCR; mDOR, median DOR; mOS, median OS; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
1. Sehn LH,, et al. *Blood.* 2025;145(7):708-719. 2. Linton KM, et al. *Lancet Haematol.* 2024;11(8):e593-e605. 3. Kim TM, et al; ELM-2 Investigators. *Ann Oncol.* 2024;35(11):1039-1047.

So just summarizing what we have with follicular lymphoma, there is equivalency for the most part, with the overall response rate, complete response rate, and the progression-free survival of all three of these drugs. Again, the top two agents are currently FDA approved. The third one is being evaluated for FDA approval, thus cementing the sort of efficacy of these bispecific antibodies in patients with relapsed/ refractory follicular lymphoma, even as single agents.



So, when to consider bispecifics over other treatments? So, we're looking at patient selection for now, these drugs are limited to third-line and beyond. And so the benefits we have here, they have an improved overall response rate, duration of response, and progression-free survival versus non-CAR-T options, which include tazemetostat, and obinutuzumab-zanubrutinib. And specifically with mosunetuzumab, that is a finite treatment option, meaning that treatment will stop, as compared to these other options, which are given to progression or intolerance. Again, safety with these agents, again, after completion of step-up dosing, the tolerability of bispecific antibodies compares very favorably with other agents, except for possibly tazemetostat, which has a very safe and sort of patient-friendly patient profile. If we look at administrative convenience, we have subcutaneous options with epcoritamab and potentially in the future, mosunetuzumab, as well as the IV options with mosunetuzumab currently and if odronextamab gets an approval.

When to Consider Bispecific Over Other Treatments: Patient Selection

Limitations

- Although risk of serious CRS/ICANS is low, some management structure is still required to address these side effects
  - Champion to guide team
  - SOP would be beneficial
  - Tocilizumab needs to be on formulary
- Risk of viral infections
- Comfort
  - Limited experience of some providers…learning curve

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CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; SOP, standard operating procedure.

So there are some limitations. The risk of CRS and ICANS was low, but they still require some sort of structure to be in place to help manage those who might have this event. Again, it's not a zero-sum situation, even with these optimizations that we've implemented. So there needs to be some sort of plan in place when things do go bad. Typically, we'll have a champion to guide a team of support staff, whether that's a physician or nurse, to help sort of coordinate with the other team. A standard operating procedure would be beneficial for most academic centers or clinical facilities to help manage these patients. Tocilizumab needs to be sort of accessible in case patients do have grade 2 and beyond CRS, as you do a sort of mitigation of this will be very important to prevent any sort of severe adverse events. Outside of that, there's risk of viral infections with bispecific antibodies. So, monitoring IgG levels is important, and sometimes supplementation on IVIG is needed. And then as far as comfort, there is limited experience of some providers with bispecifics so there will be a learning curve not too dissimilar from what we saw with the introduction of monoclonal antibodies, and some of these other agents, such as venetoclax, into the community setting.

Considerations in Choosing Between Bispecifics and CAR T-Cells in FL

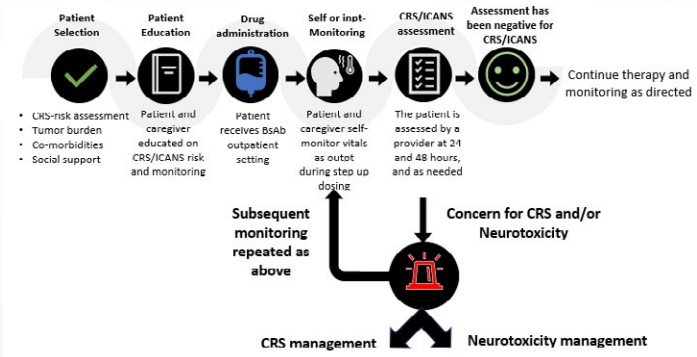
CAR T-cells	Mosunetuzumab/Epcoritamab
Excellent efficacy with longer follow up	Excellent efficacy, but with shorter follow up
Requires 3-4 weeks of manufacturing	Off-the-shelf
Logistically more complex	Logistically less complex
"One and done" for life at this time	8-17 cycles (can be repeated [mosunetuzumab only])
Needs lymphodepleting chemotherapy	No lymphodepleting chemotherapy
Higher risk of CRS and neurotoxicity	Lower risk of CRS and neurotoxicity
Usually inpatient	Usually outpatient

- They are not mutually exclusive, though we do not have data on optimal sequencing
- Decision will be personalized for most patients between bispecifics and CAR T-cells
- CAR T-cells for those with concern of tDLBCL

axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; FL, follicular lymphoma; tDLBCL, transformed diffuse large B-cell lymphoma; tisa-cel, tisagenlecleucel.

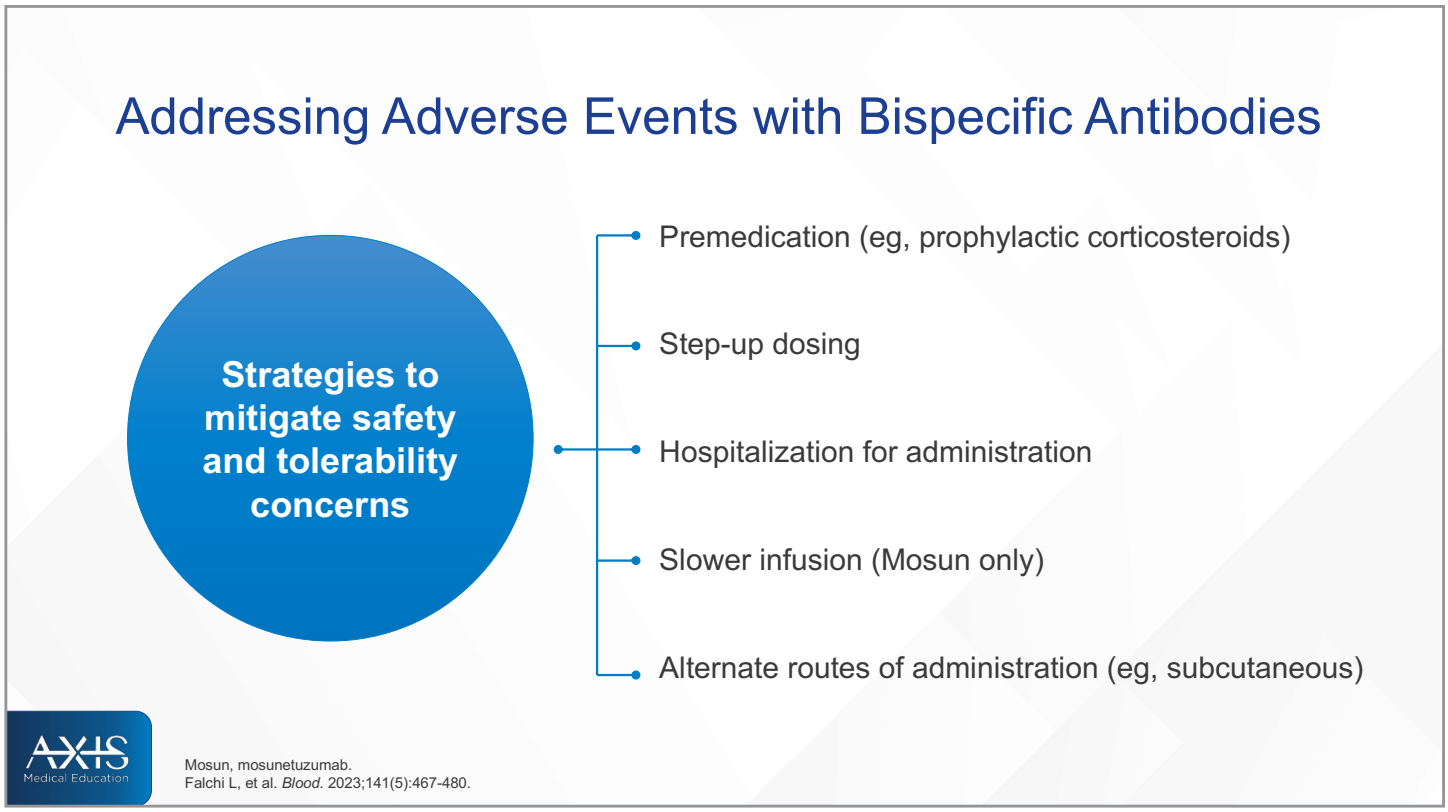
So when comparing CAR T-cell therapy and a bispecific in this space, again, the agents are very similar. The benefits to bispecifics, excellent efficacy, shorter follow-up, they are off the shelf, logistically less complex than what we need with CAR T-cell therapy. With mosunetuzumab, you do have a one and done therapy. Epcoritamab, as of right now, as a treat to progression, but there are some studies evaluating limited therapy. You don't require lymphodepleting chemotherapy, lower risk of CRS and neurotoxicity, usually outpatient, and likely to be less cumbersome and burdensome to a hospital system due to less cost over time, especially for the finite treatment options.

When to Consider Bispecific: Plan is to Have a Plan



BsAb, bispecific antibodies; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; inpt, inpatient.
Crombie JL, et al. *Blood*. 2024;143(16):1565-1575.

So plan to have a plan in place. Again, patient selection, patient education. Educating the patient is very important, as some of these events may happen outside of the time of an office being open, so patients should know what to do. Drug administration, in an outpatient setting, are you equipped to manage this in case of any adverse reactions happen. Self or inpatient monitoring, none of these bispecific antibodies in follicular lymphoma require in-hospital stay so education of the patient, having the patient make sure they have a thermometer, in some cases, a blood pressure cuff is important for monitoring and having a plan in place of what to happen when they have a fever, or if they have other events that may occur related to cytokine release syndrome. And continue therapy as directed if no issues occur. And a management plan in place, an SOP for CRS management and neurotoxicity management in these patients.



- So premedication, prophylactic corticosteroids, are recommended with both agents to help prevent sort of cytokine release syndrome. Epcoritamab does have a little bit longer duration of corticosteroid, usually Days 1 through 4, where mosunetuzumab is typically given at the time of the infusion. Step-up dosing has been implemented with all these agents based on our experience with blinatumomab. Hospitalization can be considered for some patients, but again, it's not required with any of these bispecific antibodies in follicular lymphoma. A slower infusion, so you can slow down the infusion rate with mosunetuzumab. That will eventually go away with the subcutaneous injection. But subcutaneous injections themselves typically have a longer sort of uptake. So you don't get as quick of a peak with a T-cell expansion in these patient populations with these bispecific antibodies, as we just mentioned on the last point.

BsAbs Management Strategies: CRS

- Occurs mostly within the first 24 hours following treatment initiation with continuous administration
- CRS events are typically confined to the step-up doses or first full dose with intermittent administration
- Typically occurs on the day of IV infusion and the day after SC administration
- SC formulations may reduce the risk of severe CRS
  - More gradual increase in serum concentration and reduce the peak plasma levels of the antibodies

Prevention

- Step-up dosing and premedication
- Educate patients and caregivers on the signs and symptoms of CRS
- Coordinate with local emergency departments and clinics

Supportive care

- Prompt administration of IL-6 receptor-blocking antibodies (tocilizumab) or steroids
- Antipyretics (acetaminophen)
- Intravenous fluid administration
- Oxygen supplementation
- Withhold drug or permanently discontinue

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BsAbs, bispecific antibodies; CRS, cytokine release syndrome; IL, interleukin; IV, intravenous; SC, subcutaneous.

So looking at cytokine release syndrome, for the most part, these typically occur within the first 24 hours around the treatment initiation. The events are typically confined to step-up dosing, so once you get out of step-up dosing, the risk of this is generally very minimal, if at all. Subcutaneous formulations may reduce the risk of CRS, given a slow uptake, but it may also cause a delay at the occurrence of CRS, so you have to be aware that this may not occur within the first 24 hours, and something you should keep in mind through the first 48 to 96 hours. With supportive care, prompt administration of IL-6 receptor blocking antibodies such as tocilizumab; steroids, sometimes a pill in the pocket to send patients home with; antipyretics or anti-fever medications, acetaminophen; IV fluid administration; support of blood pressures; oxygen supplementation when needed. And then with severe cytokine release syndrome, then you would typically want to withhold the drug or permanently discontinue in this situation.

BsAbs Management Strategies: Neurotoxicity/ICANS

- Lower incidence compared with CD19-directed agents (CAR T)
- Typically develops concurrently or shortly after CRS
  - Can also occur independently
- Characterized by headaches, tremors, ataxia, aphasia, confusion, hallucinations, and seizures

Prevention

- Step-up dosing and premedication
- Monitor patients for neurological signs or symptoms during treatment

Supportive care

- Tocilizumab if concurrent with CRS
- Steroids (dexamethasone)
- Anti-epileptic drugs
- Withhold drug or permanently discontinue

BsAbs, bispecific antibodies; CAR T, chimeric antigen receptor T cells; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; IV, intravenous; SC, subcutaneous.
van de Donk NWCJ, Zweegman S. *The Lancet*. 2023;402(10396):142-158. ACTEMRA (tocilizumab). Prescribing information. Genentech; 2022.

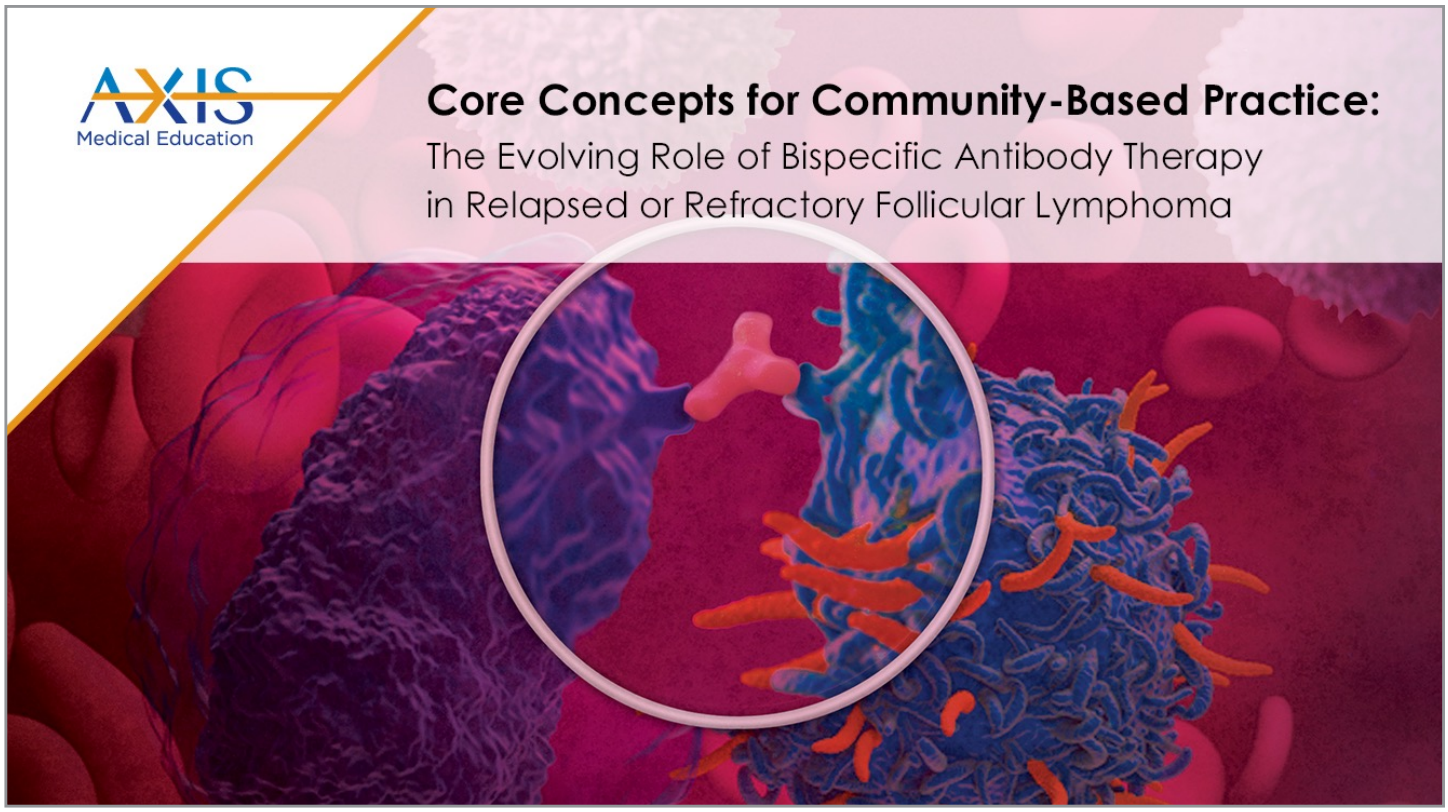
Although neurotoxicity is a very low incidence in this patient population, it can occur. So some of the same mechanisms that actually prevent CRS are there, except that in neurological toxicity, the main agent to utilize to prevent this will be corticosteroids. So steroids are far more important for management of immune effector cell associated neurological syndrome than tocilizumab. And depending on the severity of ICANS or neurotoxicity, you would withhold or permanently discontinue the drug.

Bispecific Antibodies in Phase 3 Clinical Trials

Treatment	Trial	Phase	Setting
epcoritamab + R2 (rituximab + lenalidomide) Vs. R2	EPCORE FL-1 NCT05409066	3	R/R FL
epcoritamab + R2 Vs. chemoimmunotherapy	EPCORE FL-2 NCT06191744	3	Previously untreated FL
odronextamab + lenalidomide Vs. R2	OLYMPIA-5 NCT06149286	3	R/R FL
odronextamab Vs. rituximab + chemotherapy	OLYMPIA-1 NCT06091254	3	Previously untreated FL
odronextamab + chemotherapy Vs. rituximab + chemotherapy	OLYMPIA-2 NCT06097364	3	Previously untreated FL
mosunetuzumab + lenalidomide vs. anti-CD20 monoclonal antibody + chemotherapy	MorningLyte NCT06284122	3	Previously untreated FL FLIPI 2-5
mosunetuzumab + lenalidomide Vs. R2	Celestimo NCT04712097	3	R/R FL

FL, follicular lymphoma; FLIPI, The Follicular Lymphoma International Prognostic Index; R2, lenalidomide and rituximab; R/R, relapsed/refractory.
Falchi L, et al. *Blood*. 2023;142(Supplement 1):3053.

So lastly, we'll cover some bispecific antibodies in clinical trials. There are several phase 3 studies ongoing, looking at bispecific antibodies versus what we consider to be standard of care. Epcoritamab and R2 versus R2 in a relapsed/refractory setting, and versus chemoimmunotherapy in previously untreated follicular lymphoma patients. Odronextamab has several clinical trials. And mosunetuzumab plus zanubrutinib for relapsed/refractory follicular lymphoma.



So with that, we'll shift to key takeaways, which is that bispecific antibodies are an important addition to the armamentarium for patients with relapsed/refractory follicular lymphoma. I would highly anticipate these agents will move up beyond where they're currently situated in the third-line plus follicular lymphoma. And we eventually see these agents being utilized in untreated patients with follicular lymphoma. These antibodies do allow the option of retreatment depending on the duration of treatment that the patients will get with the initial therapy. So very exciting future as we move forward in bispecifics in follicular lymphoma. As we are shifting into the community space, comfort with these agents are very important. Having a plan in place is very important. All these will improve the experience of both the physician and the patient with use of these bispecific antibodies.

And with that, I'd like to thank you for participating in this activity.

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