22nd INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM

CAR-T cells in Follicular Lymphoma

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Disclosure Summary

Role	Relationship	Company/ies
Advisory Board	Advisor	Gilead-Kite, BMS-Juno, Miltenyi Biomedicine, Lilly Oncology, Incyte, Abbvie, Cargo, Beigene, Kite, Allogene, Astrazeneca, Genentech, Ipsen, and Galapagos
Research Funding	Researcher	Miltenyi Biotec, Lilly Oncology, Genentech
Scientific Advisory Board	Founder	Tundra Therapeutics

Three CD19 CARs in Lymphoma 2025

	Axi-Cel/Brexu-Cel	Tisa-Cel	Lisa-Cel
Construct	CD28, CD3ζ, FMC63 binding domain	4-1BB, CD3ζ, FMC63 binding domain	4-1BB, CD3ζ, FMC63 binding domain Fixed 1:1 ratio of CD4: CD8 T-cells
Vector	retrovirus	lentiviral	lentiviral
Lympho-depletion	<u>Lymphoma</u> **Flu: 30 mg/m2 x 3D** **Cy: 500 mg/m2 x 3D**	<u>Lymphoma</u> **Flu: 25 mg/m2 x 3D** **Cy: 250 mg/m2 x 3D** **Or** **Bendamustine 90 mg/m2 x 2 days**	<u>Lymphoma</u> **Flu: 30 mg/m2 x 3D** **Cy: 300 mg/m2 x 3D**
Approval	DLBCL, PMBCL, FL, MCL, B-cell ALL	Pediatric ALL and adult DLBCL, FL	DLBCL, tFL, PMBCL, HGBL, FL, MCL, CLL

Multiply Relapsed Follicular Lymphoma

A litany of treatment options are available in the third line plus patient population

SUGGESTED TREATMENT REGIMENS[a,b,c]

THIRD-LINE AND SUBSEQUENT THERAPY **Subsequent systemic therapy options include second-line therapy regimens (FOLL-B 2 of 6) that were not previously given.**	
Preferred regimens (in alphabetical order) • T-cell engager therapy ▸ Bispecific antibody therapy[l,m] ◊ Epcoritamab-bysp ◊ Mosunetuzumab-axgb ▸ Chimeric antigen receptor (CAR) T-cell therapy[n] ◊ Axicabtagene ciloleucel (CD19-directed) ◊ Lisocabtagene maraleucel (CD19-directed) ◊ Tisagenlecleucel (CD19-directed)	**Other recommended regimens** • EZH2 inhibitor ▸ Tazemetostat[l] (irrespective of EZH2 mutation status) • BTK inhibitor (BTKi) ▸ Zanubrutinib[l] + obinutuzumab • Loncastuximab tesirine-lpyl + rituximab (category 2B)[k]

THIRD-LINE CONSOLIDATION THERAPY
Useful in Certain Circumstances • Allogeneic hematopoietic cell transplantation (HCT) in selected cases[o]

Axicabtagene ciloleucel

ZUMA-5 was a single-arm, multicenter phase II trial for axi-cel in patients with relapsed FL and MZL that had failed 2+ lines of therapy

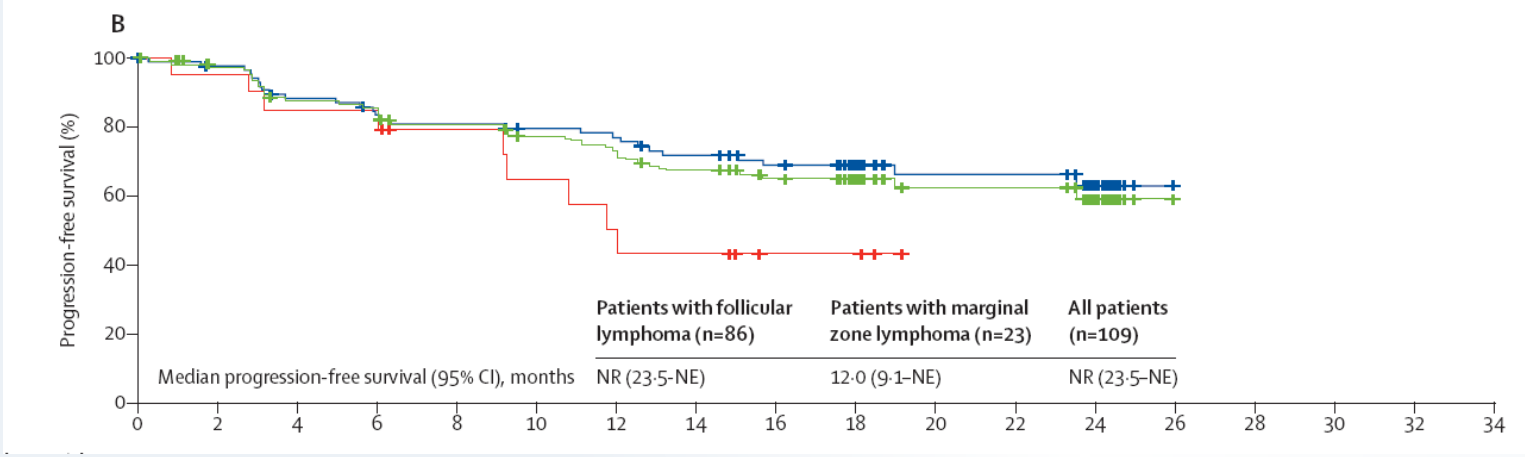
- 124 patients had Follicular lymphoma
- Median age was 60 years
- Majority of these patients had 3+ lines of therapy
- 52% had high tumor bulk by GELF criteria

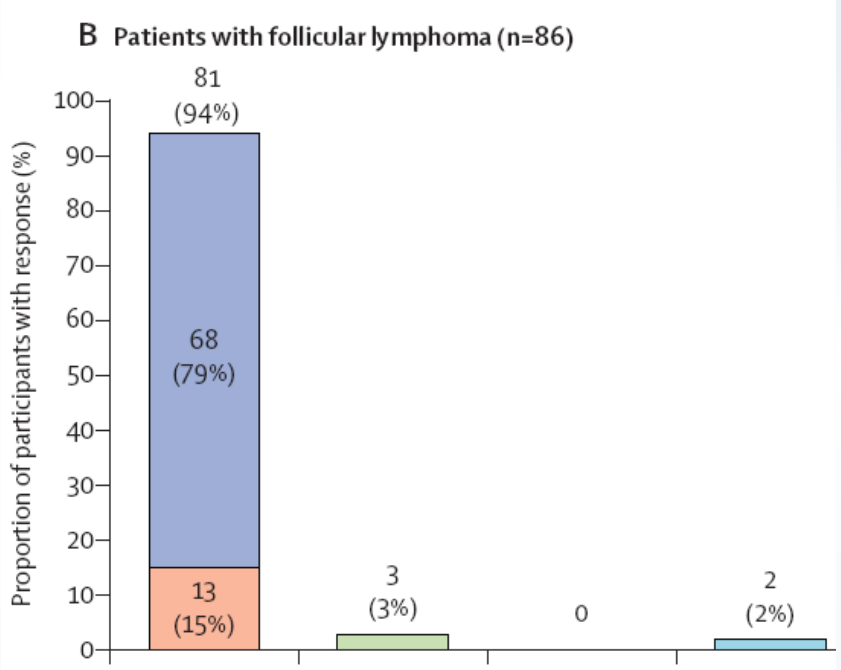
	Patients with follicular lymphoma (n=124)
(Continued from previous column)	
Previous lines of therapy	
Median†	3 (2–4)
≥3 previous lines of therapy	78 (63%)
Previous PI3K inhibitor	34 (27%)
Previous autologous stem-cell transplantation	30 (24%)
Previous anti-CD20 mAb and alkylating agent	123 (99%)
Previous anti-CD20 mAb single agent	39 (31%)
Previous alkylating single agent	16 (13%)
Previous lenalidomide	38 (31%)
Relapsed or refractory subgroup‡	
Refractory to last previous therapy	84 (68%)
POD24 from initiating first anti-CD20 mAb-containing therapy§	68 (55%)

Jacobson et al. Lancet Oncology 2022

ZUMA-5 Results

- ORR of 94% with CR rate of 79%
- 18 month PFS for the entire cohort was 65%
- Median PFS/OS/DOR were not met at the time of this publication





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5-year follow-up from ZUMA-5

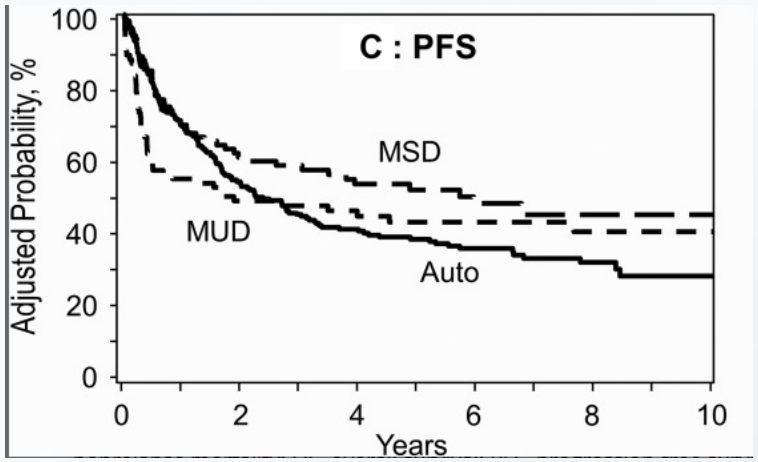
Presented at ASH 2024

- Median Follow-up of 65 months presented
- Median PFS for FL patients was 57 months
- Median OS not reached, and 5-year OS was 69%
- For FL patients, 60-month cumulative incidence of progression or lymphoma-related death was 35% and cumulative incidence of non-lymphoma death was 15%.
- Perhaps premature in FL; but abstract suggested curative potential of CAR-T in Follicular lymphoma

While these numbers are impressive: a counterpoint

CIBMTR data for FL patients with early treatment failure demonstrate 5-year PFS of 38% and 5-year OS of 70% (***yet no one will call auto-HCT curative***)

Progression-free survival	239	
1 y		70 (64-76)
3 y		45 (38-52)
5 y		38 (32-45)
Overall survival	240	
1 y		89 (85-93)
3 y		79 (74-85)
5 y		70 (64-76)



Neelapu et al ASH 2024
Smith et al Cancer 2018

Toxicity

Cytokine release syndrome occurred in 78% of patients with FL

- 6% had Grade 3+ CRS
- Median time to onset of CRS was 5 days after infusion
- 1 non-relapse mortality in high tumor burden FL patients who died of multi-organ failure

Neurological Events occurred in 56% of FL patients

- Grade 1-2 in 41% of patients
- Grade 3-4 in 15% of patients
- Median time to neurological event is 7 days and median duration of toxicity was 14 days

Grade 3+ infections occurred in 18% of patients overall.

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Tisagenlecleucel, CD19 CAR-T cell therapy in R/R FL

- ELARA Trial is a Phase II, multicenter trial in R/R FL that has failed 2+ lines of treatment
- Primary endpoint was CR rate
- 97/98 patients received infusion
- Included patients with Grade 1, 2, or 3A FL
- Median lines of therapy was 4
- 25% of patients were 65+ years old

Table 1 | Baseline demographic and disease characteristics of all treated patients

Parameter	Infused patients, *n* = 97
Median age (IQR), years	57.0 (49–64)
≥65 Years, *n* (%)	24 (24.7)
Male, *n* (%)	64 (66.0)
Female, *n* (%)	33 (34)
ECOG PS ≥1 before infusion, *n* (%)	41 (43.3)
Stage at study entry III–IV, *n* (%)	83 (85.6)
Bone marrow involvement at study entry, *n* (%)	37 (38.1)
Bulky disease at baseline, *n* (%)	62 (63.9)
FLIPI high (≥3) at study entry, *n* (%)	58 (59.8)
Median no. of previous therapies (range)	4 (2–13)
>4 lines of therapy, *n* (%)	27 (27.8)

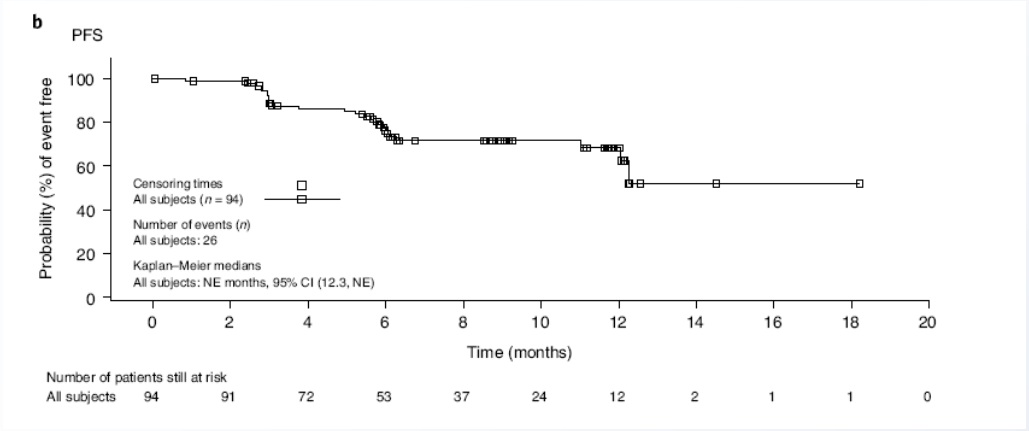
Fowler et al. Nature Medicine 2022

Outcomes for Tisa-cel in R/R FL

- Primary Endpoint of CR rate was 65.5%
- Overall response rate was 81%
- Among 31 patients who achieved a PR, 15 converted to a CR'
- Patients with POD24 had low CR rate of 59% versus 88%
- 12-month PFS was 67%
- Among patients who achieved a CR, estimated 12-month PFS was 67%

Table 2 | Best overall response in the EAS and per-protocol population[a]

Parameter	Per-protocol set, $n = 85$		EAS, $n = 94$	
	Local assessment	IRC assessment	Local assessment	IRC assessment
Best overall response, *n* (%)				
CR	64 (75.3); 95% CI, 64.7–84.0	62 (72.9); 95% CI, 62.2–82.0	68 (72.3); 95% CI, 62.2–81.1	65 (69.1); 95% CI, 58.5–78.3
PR	14 (16.5)	12 (14.1)	17 (18.1)	16 (17.0)
SD	2 (2.4)	3 (3.5)	3 (3.2)	3 (3.2)
PD	5 (5.9)	8 (9.4)	6 (6.4)	9 (9.6)
UNK				1 (1.1)
Overall response rate (CR + PR), *n* (%)	78 (91.8); 95% CI, 83.8–96.6	74 (87.1); 95% CI, 78.0–93.4	85 (90.4); 95% CI, 82.6–95.5	81 (86.2); 95% CI, 77.5–92.4



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Tisa-cel Toxicity

Cytokine release syndrome occurred in 49% of patients

- Grade 3+ CRS in NO patients(Lee Scale)
- Median time to onset of CRS was 4 days after infusion
- 34% received tocilizumab and only 6% received steroids
- 4 patients admitted to ICU and needed vasopressor support

Neurological Events occurred in 37% of FL patients

- Grade 1-2 in 33% of patients
- Grade 3-4 in 4% of patients
- Median time to neurological event is 9 days

Events, n (%)	Infused patients N=97
CRS	47 (48.5)
Grade 1 or 2	47 (48.5)
Grade ≥3	0
In patients with CRS (n=47)	
Tocilizumab use during CRS	16 (34.0)
1 dose	8 (17.0)
2 doses	5 (10.6)
3 doses	3 (6.4)
Corticosteroids	3 (6.4)
Median time to onset, days (IQR)	4.0 (2–7)
Admitted to ICU, n (%)	4 (8.5)
Median total duration of ICU stay during CRS, days (range)	4.0 (2.5–5)
Patients with resolved events, n (%)	47 (100)

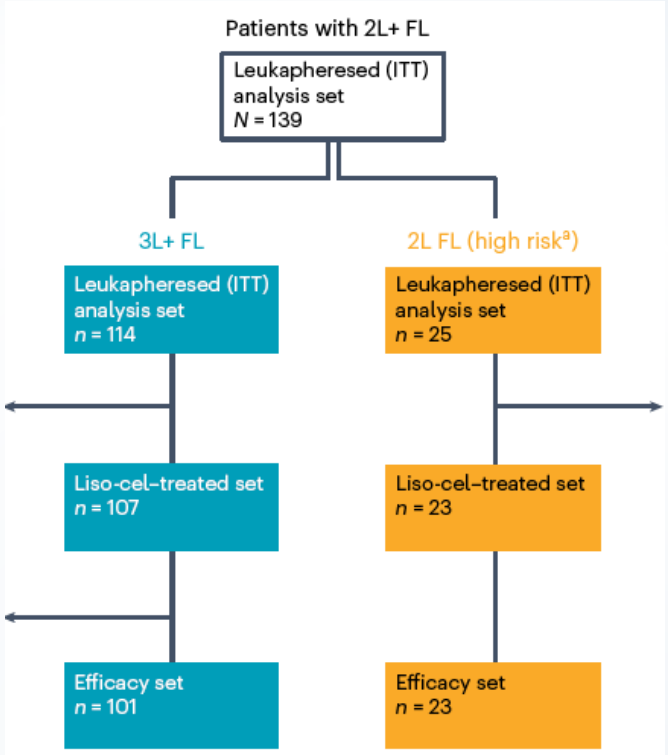
Grade 3+ infections occurred in 5.2% of patients overall.

7 deaths on trial, 5 of progressive lymphoma and 1 due to CRS

Fowler et al. Nature Medicine 2022

Lisocabtagene maraleucel in follicular lymphoma

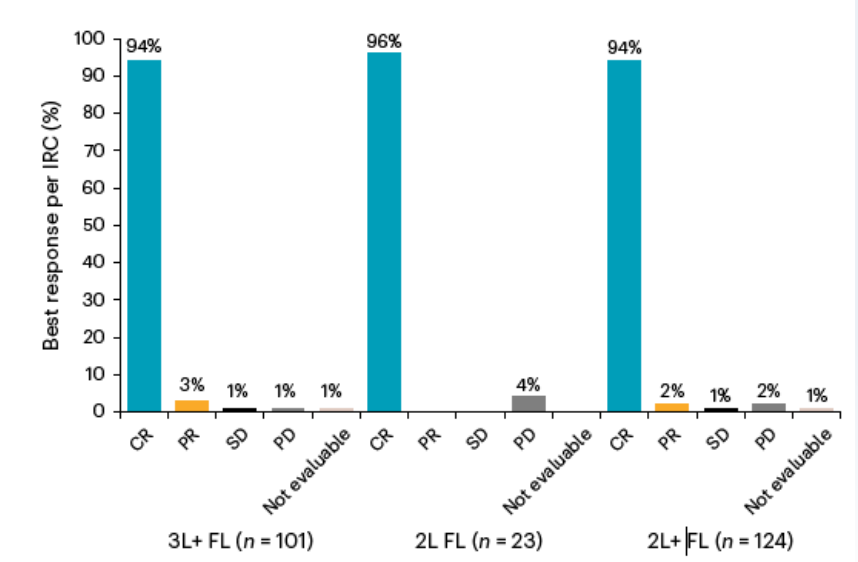
- Phase 2 TRANSCEND FL study of liso-cel CAR-T product
- Enrolled 3rd line + FL patients and small subset of high-risk 2nd line FL patients
- Key Demographics for 3+ line cohort
  - Median age 62 years
  - POD24=43%
  - Prior HSCT=31%
  - Bridging Chemotherapy=41%



Morschhauser et al. Nature Medicine 2024

Response to Liso-cel

	ORR	CR rate
3L+ FL (n = 101)	97% (95% CI: 91.6–99.4) P < 0.0001[a]	94% (95% CI: 87.5–97.8) P < 0.0001[a]
2L FL (n = 23)	96% (95% CI: 78.1–99.9) P < 0.0001[b]	96% (95% CI: 78.1–99.9) P < 0.0001[b]
2L+ FL (n = 124)	97% (95% CI: 91.9–99.1)[c]	94% (95% CI: 88.7–97.7)[c]

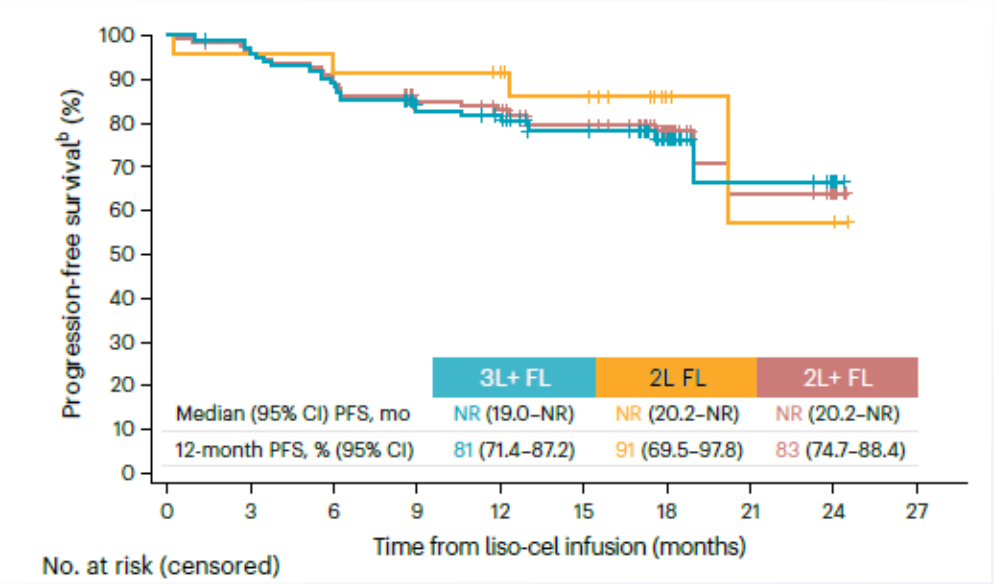


3rd Line+ FL

- Among 107 patients with 3rd line+ FL the ORR was 97% with CR rate of 94%
- Median PFS of patients was not reached
- 12-month PFS rate was 81%

2nd Line FL

- Similar ORR in 2L FL patients with ORR of 96%
- Median PFS not reached
- 12-month PFS rate was 91%



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Liso-Cel Toxicity Profile

- Low-rates of Grade 3+ Toxicities outside of cytopenias
- 1 patient with Grade 3+ CRS
- Two patients required vasopressors
- 15% of patients had any grade neurotoxicity event. All grade 1-2 except 3 patients (grade 3=2%) with no Grade 4-5 events
- Grade 3+ infections in 5% of patients
- 12 deaths after Liso-cel, 4 due to disease progression, rest were non-relapse mortality events

Table 2 | Most common TEAEs[a] (≥10%) in patients with 2L+ FL (liso-cel–treated set)

	2L+ FL (*n*=130)	
TEAE, *n* (%)	**Any grade**	**Grade ≥3**
Neutropenia	85 (65)	76 (58)
CRS	75 (58)	1 (1)
Anemia	49 (38)	13 (10)
Headache	38 (29)	0
Thrombocytopenia	33 (25)	13 (10)
Constipation	26 (20)	0
Pyrexia	23 (18)	0
Diarrhea	22 (17)	0
Lymphopenia	20 (15)	17 (13)
Fatigue	19 (15)	0
Tremor	18 (14)	0
Leukopenia	18 (14)	15 (12)
Asthenia	16 (12)	0

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Conclusions

- Three different CAR T products are available for relapsed, refractory follicular lymphoma
- CD19 CAR-T offers a one-time treatment with now durable responses 5+ years after therapy.
- Is CAR-T curative? Likely for a subset of patients with FL, functional cures are likely.
- Need to weigh toxicity/efficacy balance in choosing among CAR-Ts and between CAR-T cell therapies and bispecific antibodies

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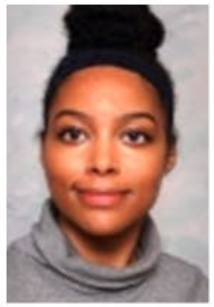

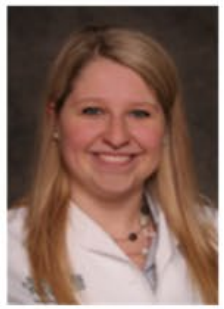

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