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<br>Fixed 1:1 ratio of CD4: CD8 T-cells |
| Vector | retrovirus | lentiviral | lentiviral |
| Lympho-depletion | <u>Lymphoma</u><br>**Flu: 30 mg/m2 x 3D**<br>**Cy: 500 mg/m2 x 3D** | <u>Lymphoma</u><br>**Flu: 25 mg/m2 x 3D**<br>**Cy: 250 mg/m2 x 3D**<br><br>**Or**<br>**Bendamustine 90 mg/m2 x 2 days** | <u>Lymphoma</u><br>**Flu: 30 mg/m2 x 3D**<br>**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<br>**Subsequent systemic therapy options include second-line therapy regimens (FOLL-B 2 of 6) that were not previously given.** | |
|---|---|
| **Preferred regimens (in alphabetical order)**<br>• T-cell engager therapy<br>▸ Bispecific antibody therapy[l,m]<br>◊ Epcoritamab-bysp<br>◊ Mosunetuzumab-axgb<br>▸ Chimeric antigen receptor (CAR) T-cell therapy[n]<br>◊ Axicabtagene ciloleucel (CD19-directed)<br>◊ Lisocabtagene maraleucel (CD19-directed)<br>◊ Tisagenlecleucel (CD19-directed) | **Other recommended regimens**<br>• EZH2 inhibitor<br>▸ Tazemetostat[l] (irrespective of EZH2 mutation status)<br>• BTK inhibitor (BTKi)<br>▸ Zanubrutinib[l] + obinutuzumab<br>• Loncastuximab tesirine-lpyl + rituximab (category 2B)[k] |

| THIRD-LINE CONSOLIDATION THERAPY |
|---|
| **Useful in Certain Circumstances**<br>• 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

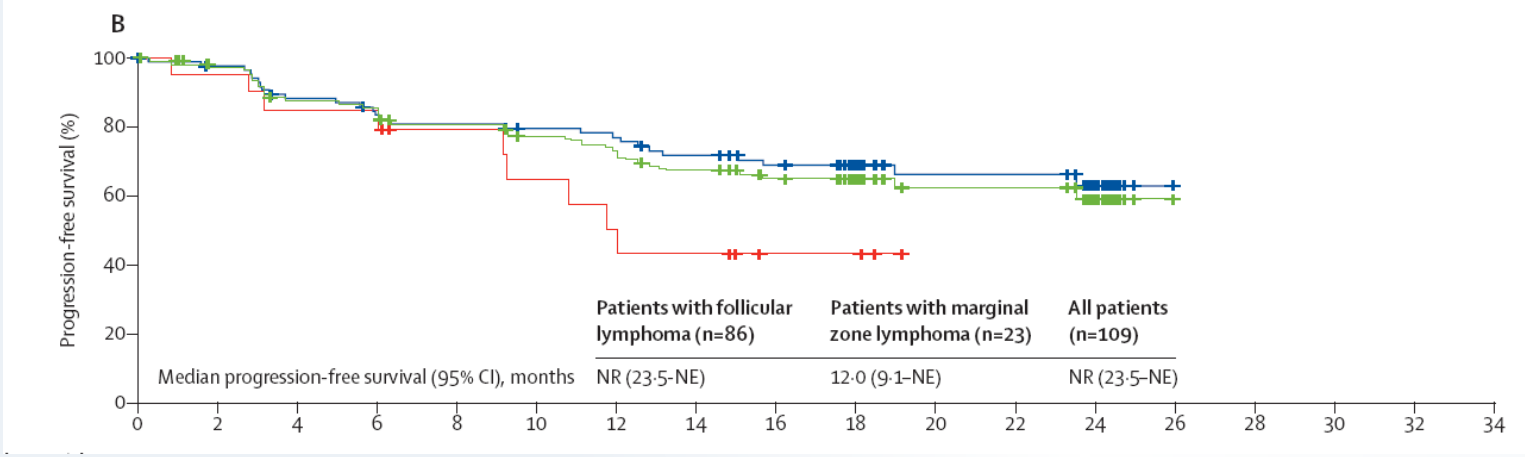
- 124 patients had Follicular lymphoma
- Median age was 60 years
- Majority of these patients had 3+ lines of therapy
- 52% had high tumor bulk by GELF criteria

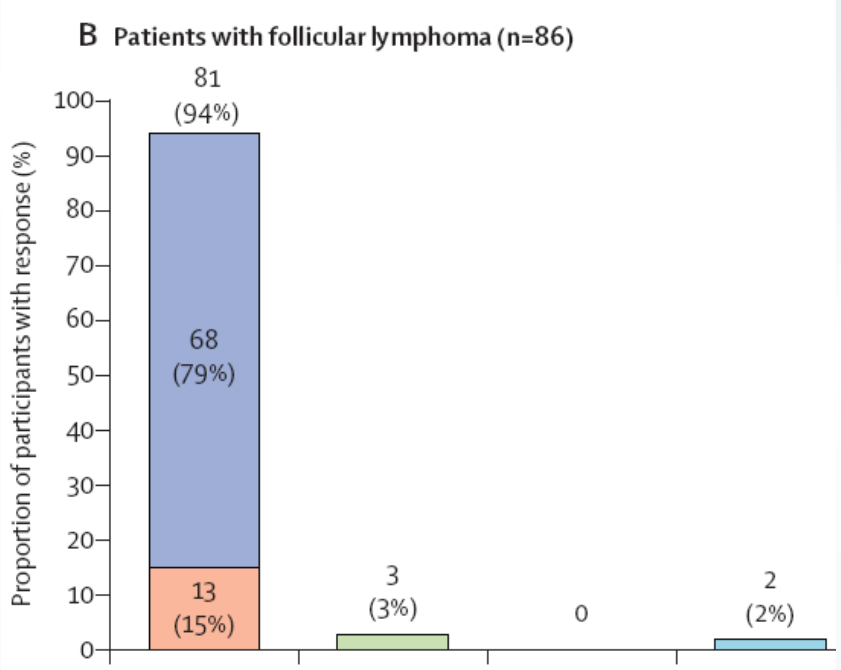
| | Patients with follicular lymphoma (n=124) |
|---|---|
| (Continued from previous column) | |
| Previous lines of therapy | |
| Median† | 3 (2–4) |
| ≥3 previous lines of therapy | 78 (63%) |
| Previous PI3K inhibitor | 34 (27%) |
| Previous autologous stem-cell transplantation | 30 (24%) |
| Previous 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

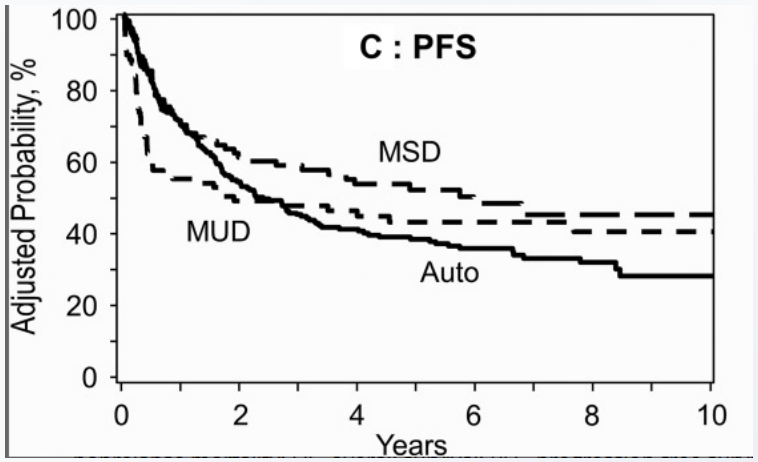
Presented at ASH 2024

- 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) |

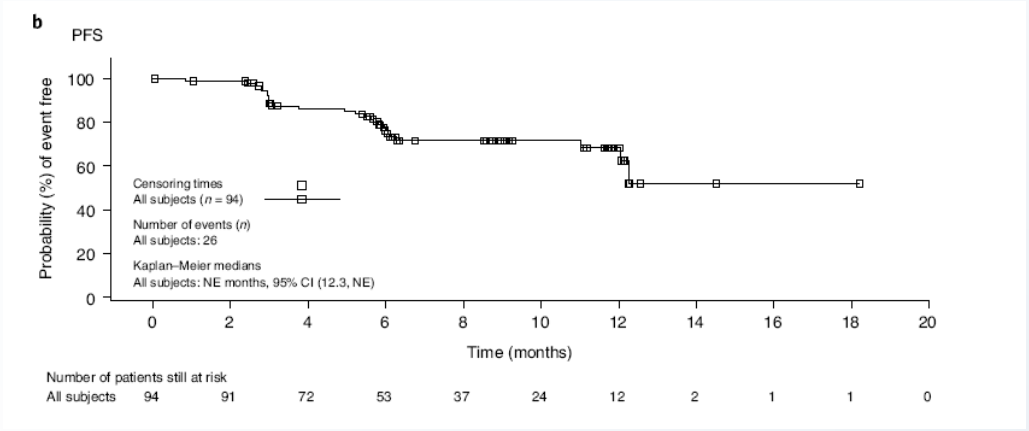
Fowler et al. Nature Medicine 2022

# 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**

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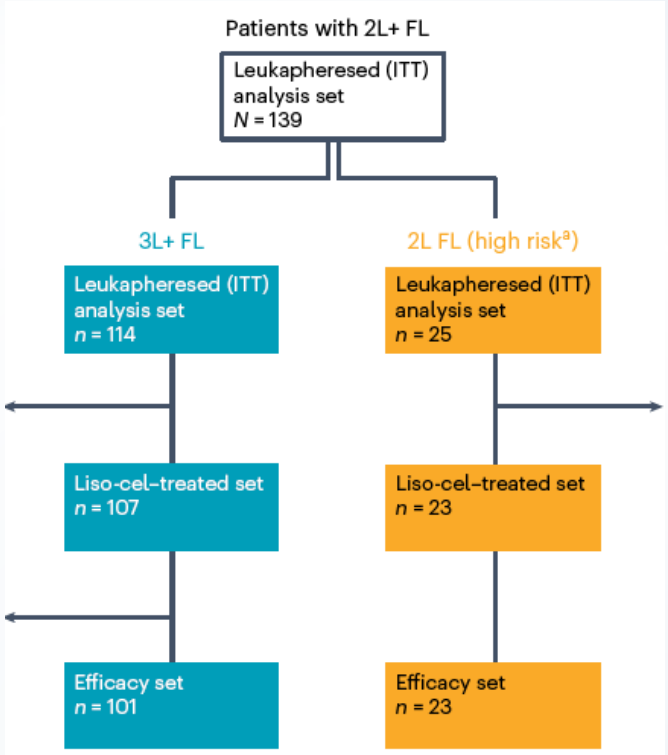
# Lisocabtagene maraleucel in follicular lymphoma

- 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%

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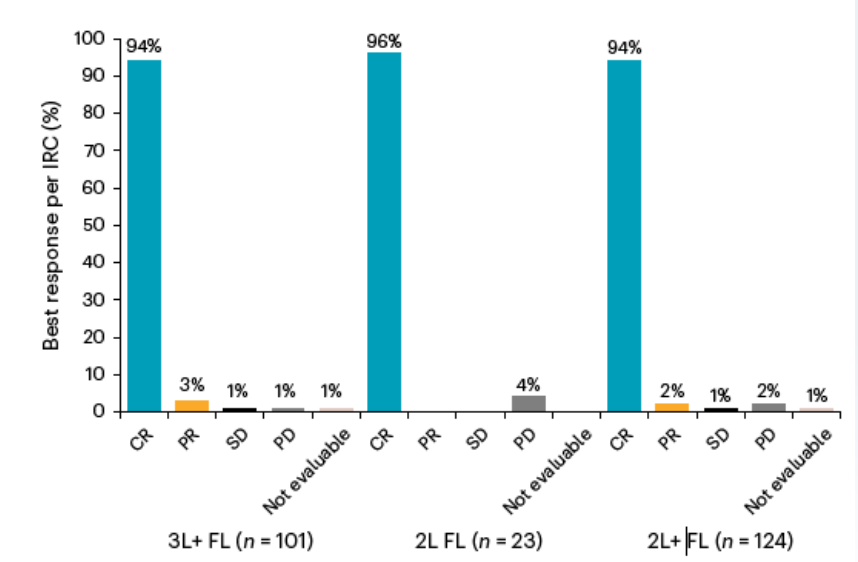
# Response to Liso-cel

| | 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] |

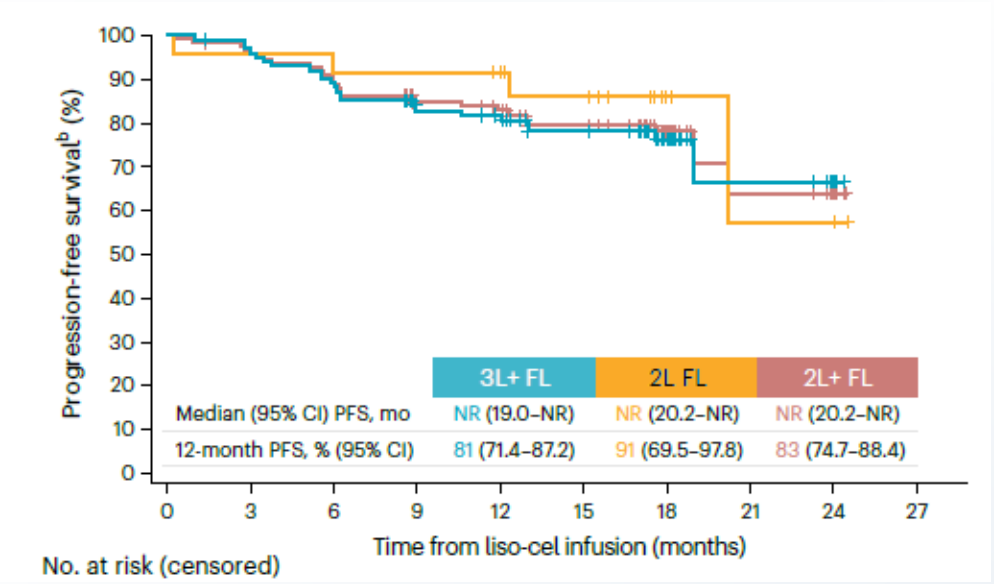



## 3rd Line+ FL

- 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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# CAR-T versus Bispecifics in R/R Follicular Lymphoma

In the ERA of bispecific therapies, the question is when should CAR-T be used?

There is an adage from my time as a medical student at the University of Illinois at Chicago that applies to this debate:

Beer Before Liquor,
Never Been Sicker!

Liquor before Beer
Now you're in the clear

Beer=Bispecifics

Liquor=CAR-T

CAR-T before TCE we know what to expect!

TCE before CAR-T, nobody knows the answer!

# 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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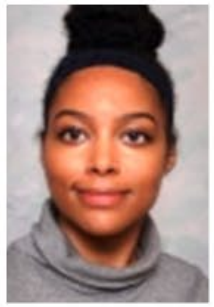

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