
# Debate:
## Utilización de células CAR-T y anticuerpos biespecíficos en linfomas indolentes

## A favor de células CAR-T

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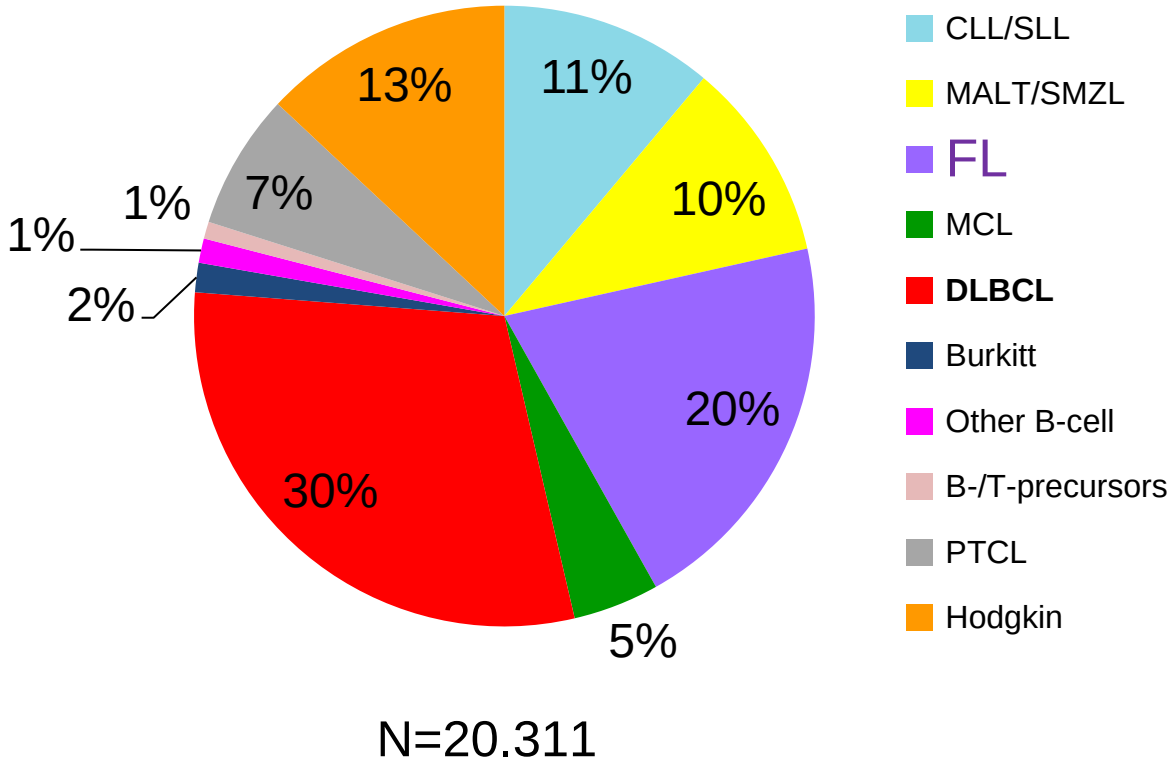
Clínic Barcelona | Universitat de Barcelona

# Disclosures

- Consulting: Roche, Gilead/Kite, Celgene/BMS, Novartis, Astra Zeneca, Abbvie, Morphosis, Takeda
- Research funding: Roche, Gilead/Kite, Celgene/BMS

# Histologic distribution of lymphomas

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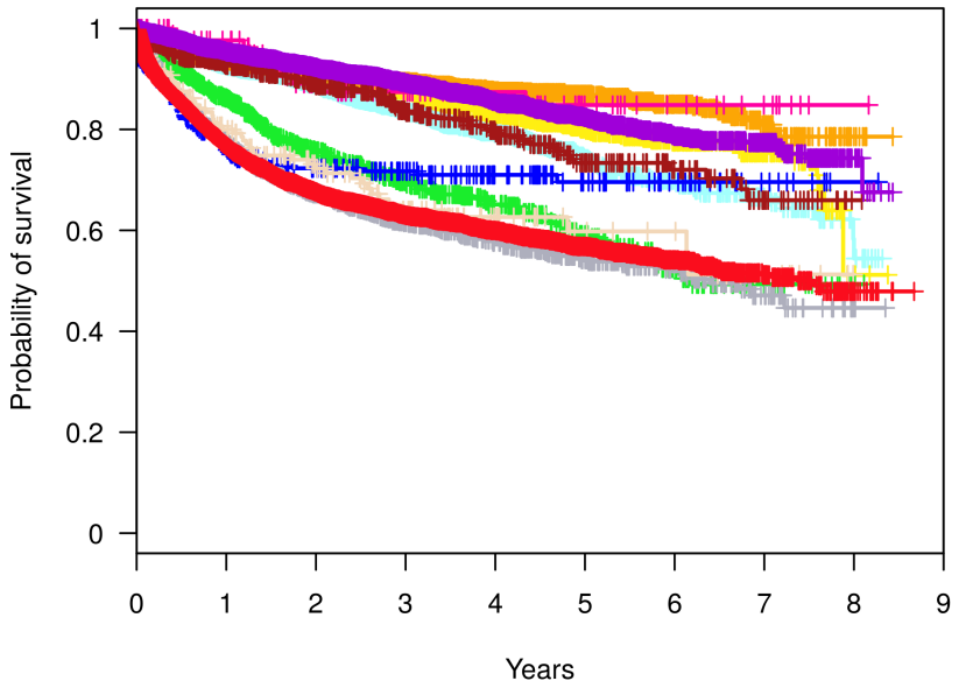



**GELTAMO 2014/21**

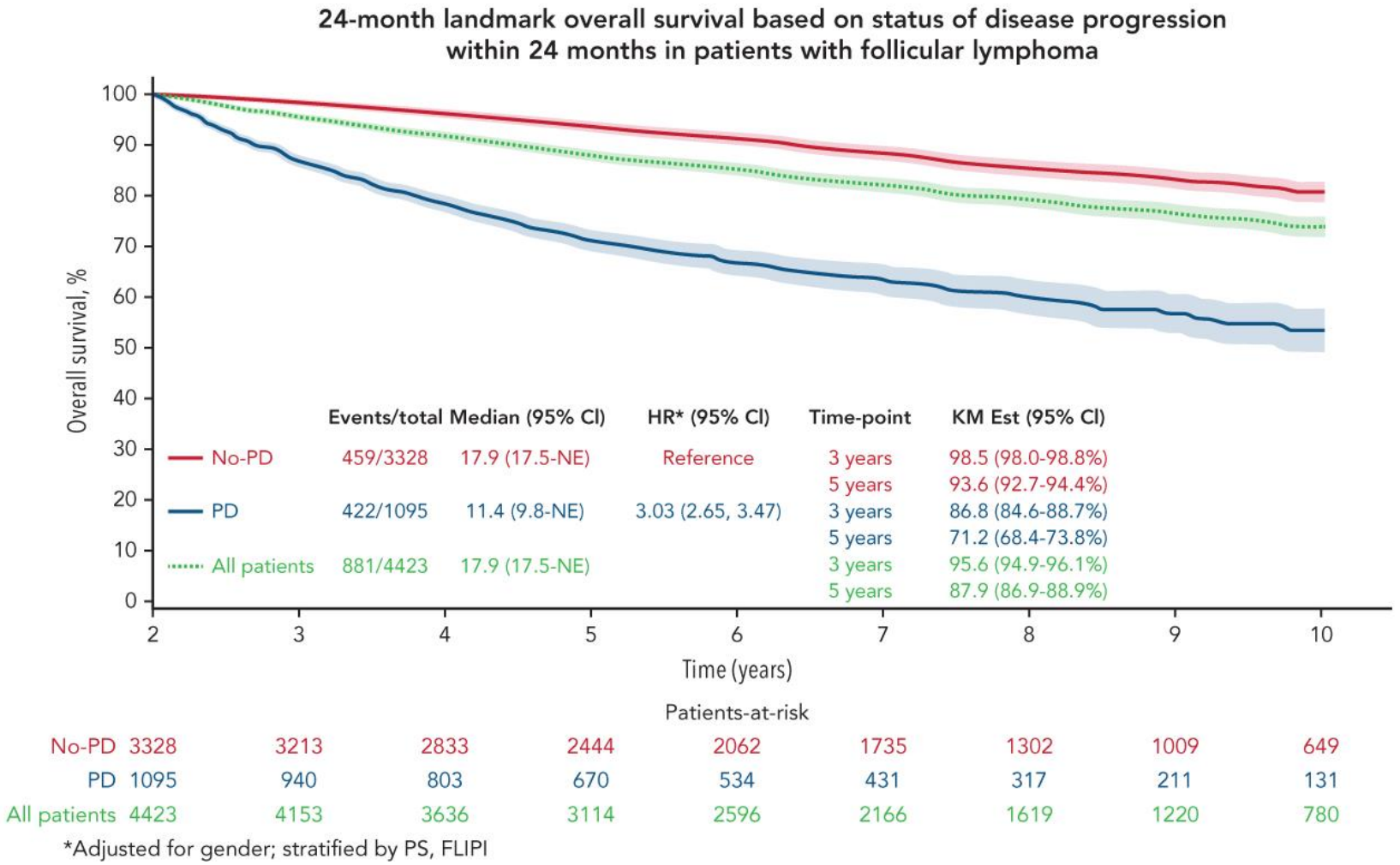
Bastos-Oreiro M, Ann Hematol 2020;99:799-808 (updated July 2022)

# Follicular lymphoma: prognosis at 2nd/3rd/… relapse

## (→ to select ”the best” treatment)

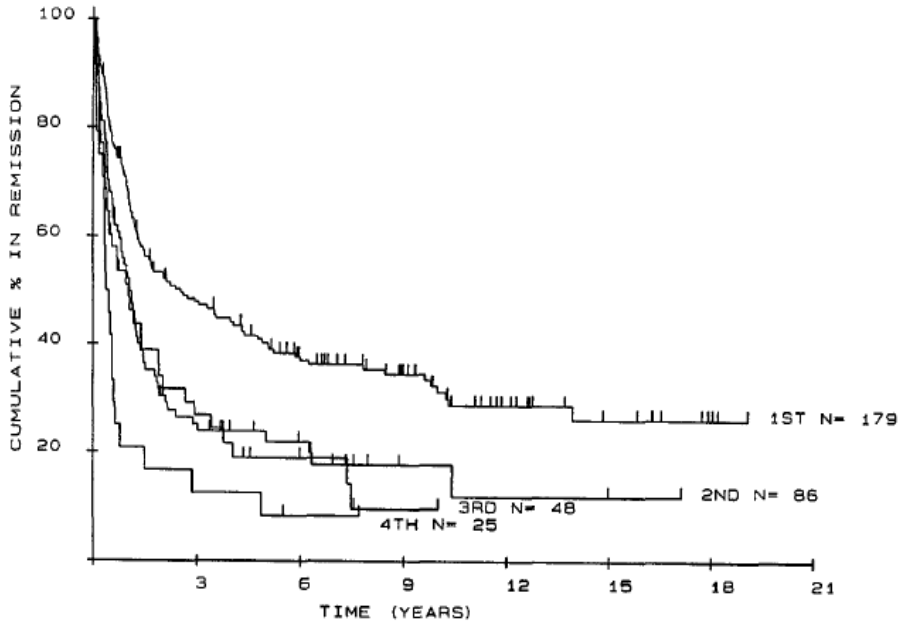
- Standard prognostic factors
  - Age, performance status, dissemination and tumor mass
  - FLIPI (or other scores)
- Previous treatment (R – R-CT …)
- Histology (histological transformation)
- Response duration
- No. of previous relapses (0, 1, 2, …)

# POD24 in follicular lymphoma



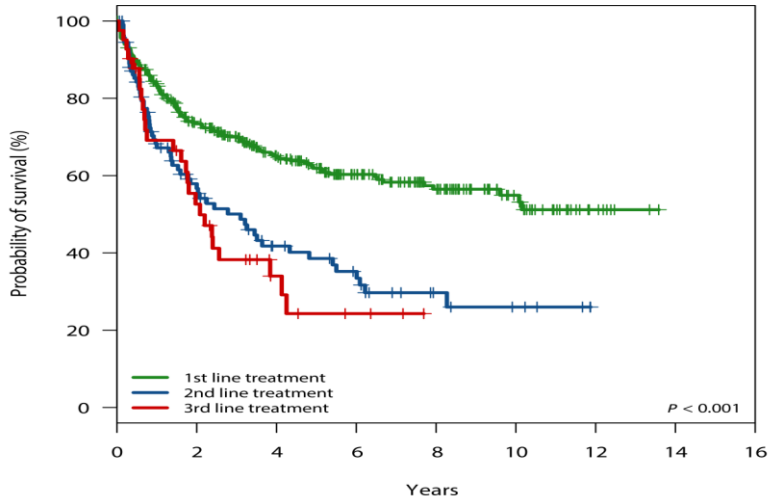

Casulo C, Blood 2022;139:1684-93

# Response duration progressively shortens with each relapse in FL

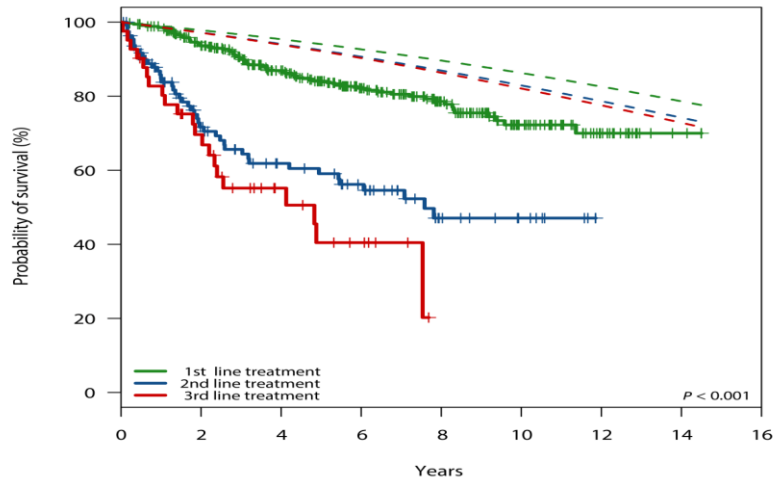



Johnson WM, J Clin Oncol *1995;13:140-7*

**Response duration after each line at Rituximab era**




**Overall survival after each line at Rituximab era**




Rivas A, Br J Haematol *2019;184:753-9*

*Lancet Haematol*. 2022 April ; 9(4): e289–e300. doi:10.1016/S2352-3026(22)00033-3.

# Treatment Patterns and Outcomes of Patients with Relapsed/ Refractory Follicular Lymphoma Receiving Three or More Lines of Systemic Therapy: Results from a Lymphoma Epidemiology of Outcomes Consortium Observational Study

Carla Casulo, MD[1], Melissa C. Larson, MS[2], Julianne J. Lunde, MA[2], Thomas M. Habermann, MD[3], Izidore S. Lossos, MD[4], Yucai Wang, MD, PhD[3], Loretta J. Nastoupil, MD[5], Christopher Strouse, MD[6], Dai Chihara, MD, PhD[5], Peter Martin, MD[7], Jonathon B. Cohen, MD, MS[8], Brad S. Kahl, MD[9], Jean L. Koff, MD, MS[8], Yong Mun, PhD[10], Anthony Masaquel, PhD, MPH[10], Mei Wu, PharmD[10], Michael C. Wei, MD, PhD[10], Ashwini Shewade, MS, MSc[10], Jia Li, PhD[10], James Cerhan, MD, PhD[2], Christopher R. Flowers, MD, MS, FASCO[5], Brian K. Link, MD[6], Matthew J. Maurer, MS, DrMedSci[2]

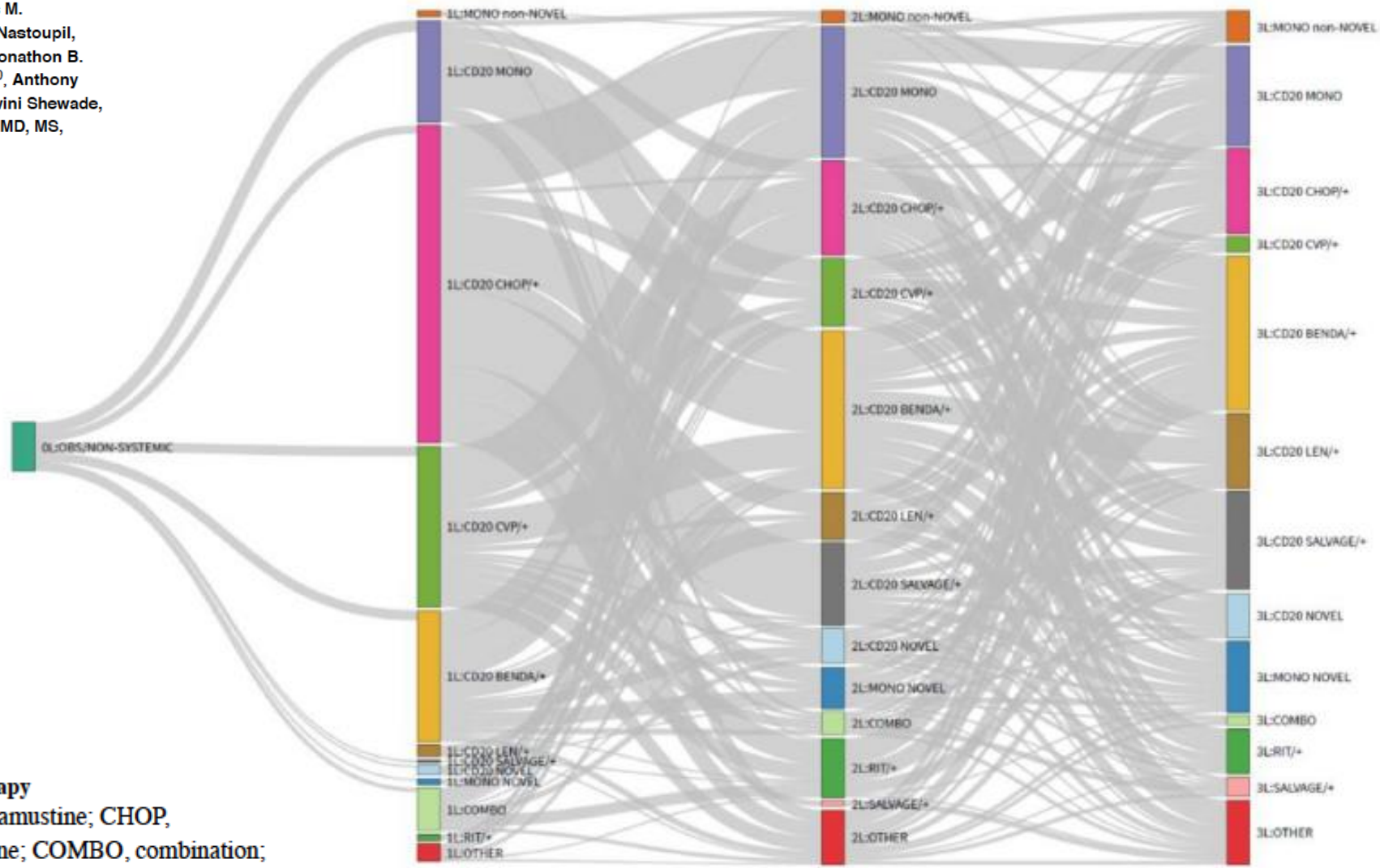
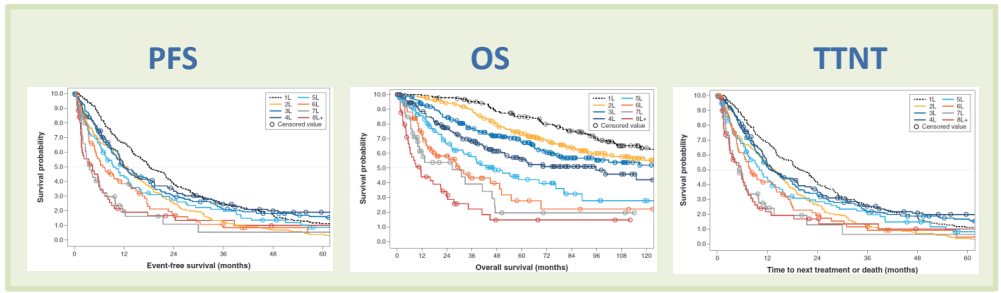



**Figure 1. Sankey plot of treatment patterns across lines of therapy**

1L, first-line; 2L, second-line; 3L, third-line; BENDA, bendamustine; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; COMBO, combination; CVP, cyclophosphamide, vincristine, and prednisolone; LEN, lenalidomide; MONO, monotherapy; RIT, rituximab.

# Treatment outcomes of R/R FL: **real-world studies**

| | **ReCORD-FL**(n=187)<br>Median follow-up: 9 years<br>**Salles *et al*. HemaSphere 2022** | | **SCHOLAR-5** (n=128)<br>Median follow-up: 7 years<br>**Ghione *et al*. Haematologica 2023** | |
|---|---|---|---|---|
| | **3 L** | **5L** | **3L** | **5L** |
| **ORR, n(%)** | **70%** | **46%** | **68%** | **37%** |
| **CR, n (%)** | **37%** | **22%** | **44%** | **22%** |
| **PFS**<br>Median, mo (95% CI)<br>18-mo PFS rate | **12** (10.1-16.6)<br>**40%** | **9** (6.8-13)<br>**33%** | **11** (9-17.9)<br>**34%** | **3.9** (3-8.5)<br>**10%** |
| **OS**<br>Median, mo (95% CI)<br>18-mo PFS rate | **128** (78-232)<br>**94%** | **46** (32-76.5)<br>**86%** | **68** (60-1-ne)<br>**87%** | **43** (15-3-ne)<br>**60%** |
| **TTNT**<br>Median, mo (95% CI) | **13** (10.9-17.6) | **10** (7.3-13) | **20** (15.7-40) | **7** (4.3-17.4) |




# Recommendations – Treatment in 2nd or later relapse

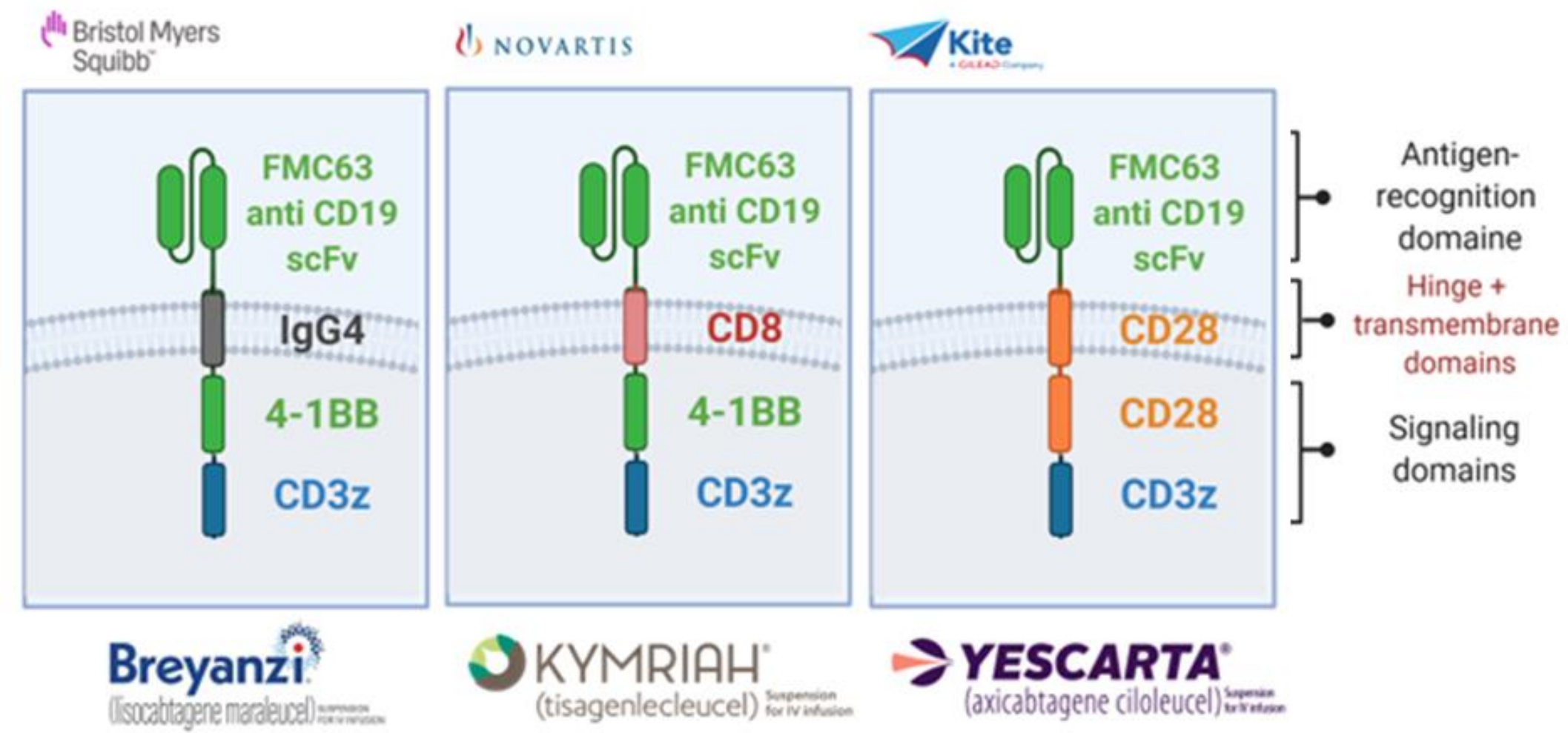
For 2nd or later relapse the following possibilities have been pointed out (only those with positive opinión by the EMA):

| | |
|---|---|
| ▪ Inmunochemotherapy | 1C |
| ▪ Idelalisib (double refractory) | 2B |
| ▪ Rituximab/lenalidomide $R^2$ | 1B |
| ▪ Mosunetuzumab | 1B |
| ▪ CAR-T therapy (tisacel in ≥3rd line*; axicel in ≥4th line) | 1B |
| ▪ Palliative care | 1C |

GELTAMO FL guidelines 2023

* This recommendation although approved by the EMA has not yet reimbursement by the health public system in Spain

# CAR-T cell therapy in R/R follicular lymphoma




Approved in 3rd or later line

Approved in 4th or later line
Con precio de reembolso en España (febrero 2024)

# Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial

Caron A Jacobson, Julio C Chavez, Alison R Sehgal, Basem M William, Javier Munoz, Gilles Salles, Pashna N Munshi, Carla Casulo, David G Maloney, Sven de Vos, Ran Reshef, Lori A Leslie, Ibrahim Yakoub-Agha, Olalekan O Oluwole, Henry Chi Hang Fung, Joseph Rosenblatt, John M Rossi, Lovely Goyal, Vicki Plaks, Yin Yang, Remus Vezan, Mauro P Avanzi, Sattva S Neelapu

## Summary

**Background** Most patients with advanced-stage indolent non-Hodgkin lymphoma have multiple relapses. We assessed axicabtagene ciloleucel autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy in relapsed or refractory indolent non-Hodgkin lymphoma.

**Methods** ZUMA-5 is a single-arm, multicentre, phase 2 trial being conducted at 15 medical cancer centres in the USA and two medical cancer centres in France. Patients were eligible if they were aged 18 years or older, with histologically confirmed indolent non-Hodgkin lymphoma (follicular lymphoma or marginal zone lymphoma), had relapsed or refractory disease, previously had two or more lines of therapy (including an anti-CD20 monoclonal antibody with an alkylating agent), and an Eastern Cooperative Oncology Group performance score of 0 or 1. Patients underwent leukapheresis and received conditioning chemotherapy (cyclophosphamide at 500 mg/m² per day and fludarabine at 30 mg/m² per day on days −5, −4, and −3) followed by a single infusion of axicabtagene ciloleucel (2× 10⁶ CAR T cells per kg) on day 0. The primary endpoint was overall response rate (complete response and partial response) assessed

Lancet Oncol 2022; 23: 91–103
Published Online December 8, 2021
https://doi.org/10.1016/S1470-2045(21)00591-X

See Comment page 6

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Regular Article

CLINICAL TRIALS AND OBSERVATIONS

# Three-year follow-up analysis of axicabtagene ciloleucel in relapsed/refractory indolent non-Hodgkin lymphoma (ZUMA-5)

Sattva S. Neelapu,[1,*] Julio C. Chavez,[2,*] Alison R. Sehgal,[3] Narendranath Epperla,[4] Matthew Ulrickson,[5] Emmanuel Bachy,[6] Pashna N. Munshi,[7] Carla Casulo,[8] David G. Maloney,[9] Sven de Vos,[10] Ran Reshef,[11] Lori A. Leslie,[12] Olalekan O. Oluwole,[13] Ibrahim Yakoub-Agha,[14] Rashmi Khanal,[15] Joseph Rosenblatt,[16] Ronald Korn,[17] Weixin Peng,[18] Christine Lui,[18] Jacob Wulff,[18] Rhine Shen,[18] Soumya Poddar,[18] A. Scott Jung,[18] Harry Miao,[18] Sara Beygi,[18] and Caron A. Jacobson[19]

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nature medicine
ARTICLES
https://doi.org/10.1038/s41591-021-01622-0



# Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial

Nathan Hale Fowler[1,2] ✉, Michael Dickinson[3], Martin Dreyling[4], Joaquin Martinez-Lopez[5], Arne Kolstad[6], Jason Butler[7], Monalisa Ghosh[8], Leslie Popplewell[9], Julio C. Chavez[10], Emmanuel Bachy[11], Koji Kato[12], Hideo Harigae[13], Marie José Kersten[14], Charalambos Andreadis[15], Peter A. Riedell[16], P. Joy Ho[17], José Antonio Pérez-Simón[18], Andy I. Chen[19], Loretta J. Nastoupil[1], Bastian von Tresckow[20,21], Andrés José María Ferreri[22], Takanori Teshima[23], Piers E. M. Patten[24,25], Joseph P. McGuirk[26], Andreas L. Petzer[27], Fritz Offner[28], Andreas Viardot[29], Pier Luigi Zinzani[30,31], Ram Malladi[32], Aiesha Zia[33], Rakesh Awasthi[34], Aisha Masood[35], Oezlem Anak[33], Stephen J. Schuster[36,38] and Catherine Thieblemont[37,38]

**Tisagenlecleucel is an autologous anti-CD19 chimeric antigen receptor-T cell therapy with clinically meaningful outcomes demonstrated in patients with relapsed/refractory (r/r) B-cell lymphoma. In a previous pilot study of tisagenlecleucel in r/r follicular lymphoma (FL), 71% of patients achieved a complete response (CR). Here we report the primary, prespecified interim analysis of the ELARA phase 2 multinational trial of tisagenlecleucel in adults with r/r FL after two or more treatment lines or who relapsed after autologous stem cell transplant (no. NCT03568461). The primary endpoint was CR rate (CRR). Secondary endpoints included overall response rate (ORR), duration of response, progression-free survival, overall survival, pharmacokinetics and safety. As of 29 March 2021, 97/98 enrolled patients received tisagenlecleucel (median follow-up, 16.59 months; interquartile range, 13.8–20.21). The primary endpoint was met. In the efficacy set ($n = 94$), CRR was 69.1% (95% confidence interval, 58.8–78.3) and ORR 86.2% (95% confidence interval, 77.5–92.4). Within 8 weeks of infusion, rates of cytokine release syndrome were 48.5% (grade ≥3, 0%), neurological events 37.1% (grade ≥3, 3%) and immune effector cell-associated neurotoxicity syndrome (ICANS) 4.1% (grade ≥3, 1%) in the safety set ($n = 97$), with no treatment-related deaths. Tisagenlecleucel is safe and effective in extensively pretreated r/r FL, including in high-risk patients.**

nature medicine

Article

https://doi.org/10.1038/s41591-024-02986-9

# Lisocabtagene maraleucel in follicular lymphoma: the phase 2 TRANSCEND FL study

Received: 12 January 2024

Accepted: 10 April 2024

Published online: 3 June 2024

Check for updates

A list of authors and their affiliations appears at the end of the paper

An unmet need exists for patients with relapsed/refractory (R/R) follicular lymphoma (FL) and high-risk disease features, such as progression of disease within 24 months (POD24) from first-line immunochemotherapy or disease refractory to both CD20-targeting agent and alkylator (double refractory),

This table does not intend to compare trials that are intrinsically different

## Cellular therapy in R/R FL

# Differences in the design of the trials

| | ZUMA-5[1-2] (Axicel) | ELARA[3-4] (Tisacel) | TRANSCEND FL[5] (Lisocel) |
|---|---|---|---|
| Inclusion criteria | FL 1-3a<br>R/R to ≥2 lines (including anti-CD20 and alkylants)<br>ECOG 0,1-Age ≥18 yrs | | FL 1-3a<br>R/R to ≥2 lines or ≥1 line+POD24<br>ECOG 0,1-Age ≥18 yrs |
| N | 124* | 98 | 130 |
| Design | Phase 2 single arm | Phase 2 single arm | Phase 2 single arm |
| Planned treatment | CART: Axicel (1 infusion) | CART: Tisacel (1 infusion) | CART: Lisocel (1 infusion) |
| Main end-point | IRC assessed ORR** | IRC-assessed CRR** | IRC-assessed ORR** |

*Plus other 24 patients with marginal zone lymphoma; **Best response

1) Jacobson, Lancet 2022; 2) Neelapu, Blood 2024; 3) Fowler, Nat Med 2022;28:325-32; 4) Dreyling ASH 2022 #608; 5) Morschhauser, Nat Med 2024

This table does not intend to compare trials that are intrinsically different

## Cellular therapy in R/R FL

# Initial characteristics

| | ZUMA-5[1-2] (Axicel) | ELARA[3-4] (Tisacel) | TRANSCEND FL[5] (Lisocel) |
|---|---|---|---|
| N | 124 | 98 | 130 |
| Median age (years) | 60 | 57 | 62 |
| ECOG 1 (%) | 37 | 43 | 37 |
| FLIPI 3-5 (%) | 44 | 60 | 57 |
| #Previous lines<br>Median (range)<br>≥3 (%) | <br>3 (2-4)<br>63 | <br>4 (2-13)<br>≥5: 28 | <br>2 (1-10)<br>- |
| ASCT (%) | 24 | 36 | 25 |
| Refractory to previous therapy (%) | 68 | 78 | 32 |
| POD24 (%) | 55 | 63 | 45 |

*plus other 24 patients with marginal zone lymphoma

1) Jacobson, Lancet 2022; 2) Neelapu, Blood 2024; 3) Fowler, Nat Med 2022;28:325-32; 4) Dreyling ASH 2022 #608; 5) Morschhauser, Nat Med 2024

This table does not intend to compare trials that are intrinsically different

## Cellular therapy in R/R FL

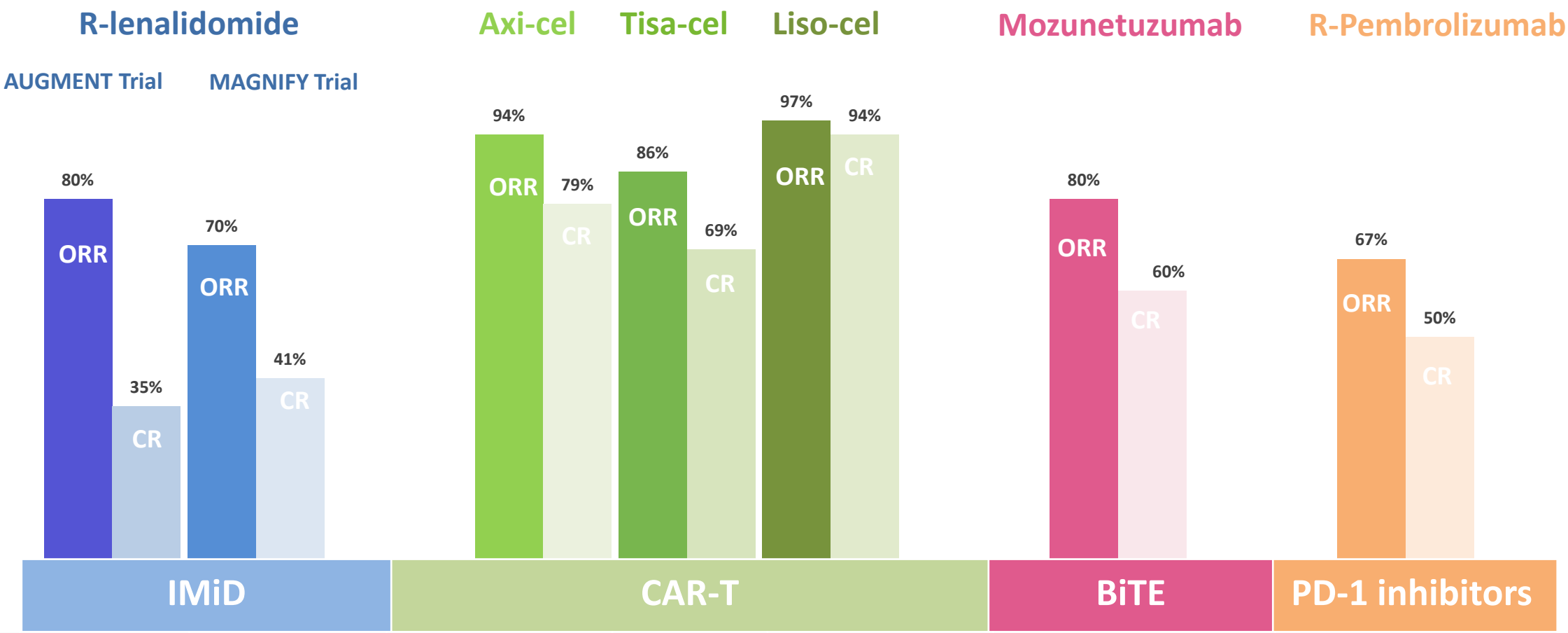
# Efficacy results

| | ZUMA-5[1-2] (Axicel) | ELARA[3-4] (Tisacel) | TRANSCEND FL[5] (Lisocel) |
|---|---|---|---|
| ORR (%) | 94 | 86 | 97 |
| CR (%) | 79 | 69 | 94 |
| Time to CR (mo.) | 1 | 1 | 1 |
| Median follow-up (mo.) | 41.7 | 23 | 18.9 |
| CR duration (at 1 yr) | 74% | ≈75% | 71% |
| PFS | | | |
| Median (mo.) | 40.2 | NR | NR |
| 12-mo. (%) | ≈74 **(54% at 36 mo.)** | 67 | 83 |
| OS | | | |
| Median (mo.) | NR | NR | NR |
| 12-mo. (%) | ≈95 **(76% at 36 mo.)** | 95 | 93 |

mo.: months; NR: not reached

1) Jacobson, Lancet 2022; 2) Neelapu, Blood 2024; 3) Fowler, Nat Med 2022;28:325-32; 4) Dreyling ASH 2022 #608; 5) Morschhauser, Nat Med 2024

# Summary of immunotherapy in follicular lymphoma




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Prior lines** | 1 (1-12) | 2 (1-8) | 3 (1-10) | 4 (2-13) | 3 (2–10) | 3 (2-4) | 1 (1-4) |
| **DOR** | 39mo | NR | 39 | NR | NR | 23 mo | 17.5 mo |

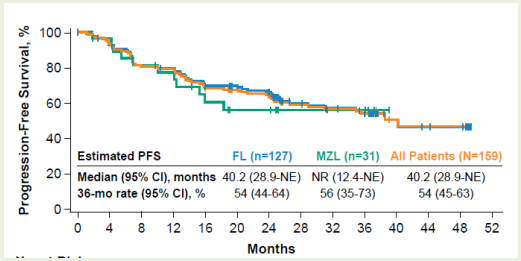
Courtesy of Dr. L. Magnano

# CAR-T cell therapy in R/R follicular lymphoma

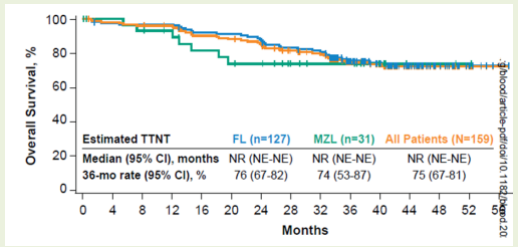
## ZUMA-5 (axi-cel)

Neelapu *et al.* Blood 2024

### PFS



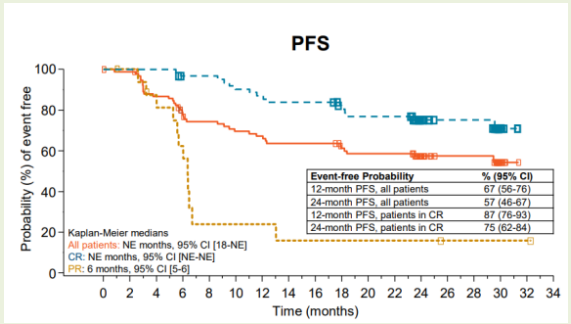

### OS



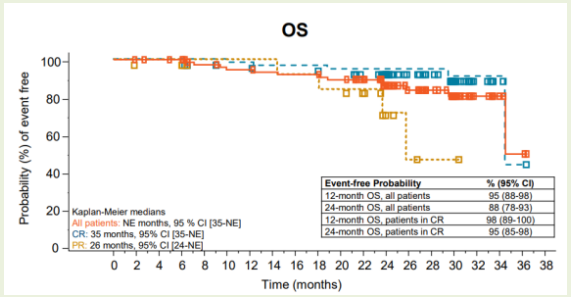

## ELARA (tisa-cel)

Dreyling *et al.* ASH 2022
Abstract #608

### PFS



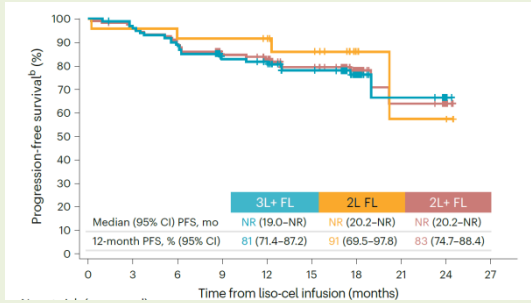

### OS



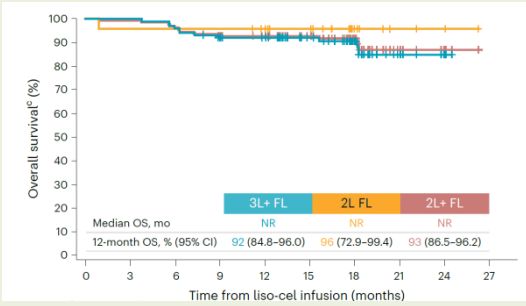

## TRANSCEND FL (liso-cel)

Morschhauser et al. Nat Med 2024

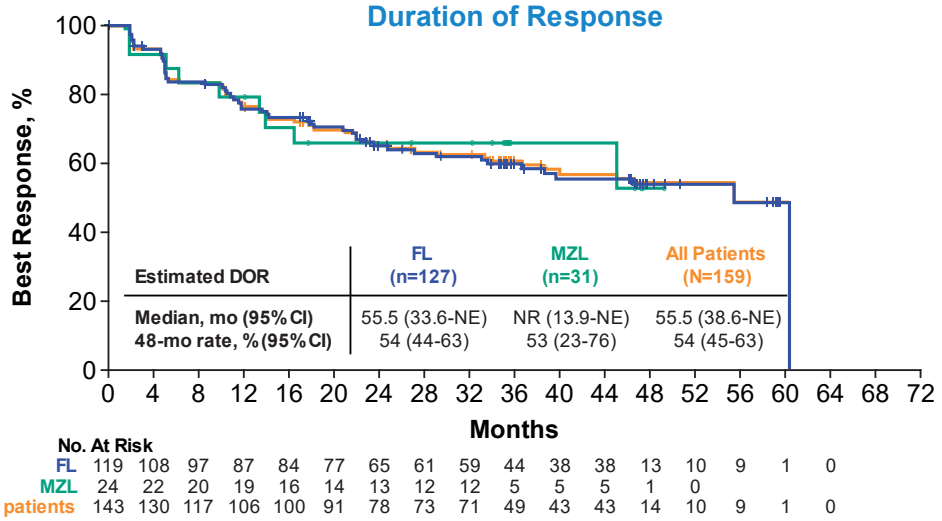
### PFS

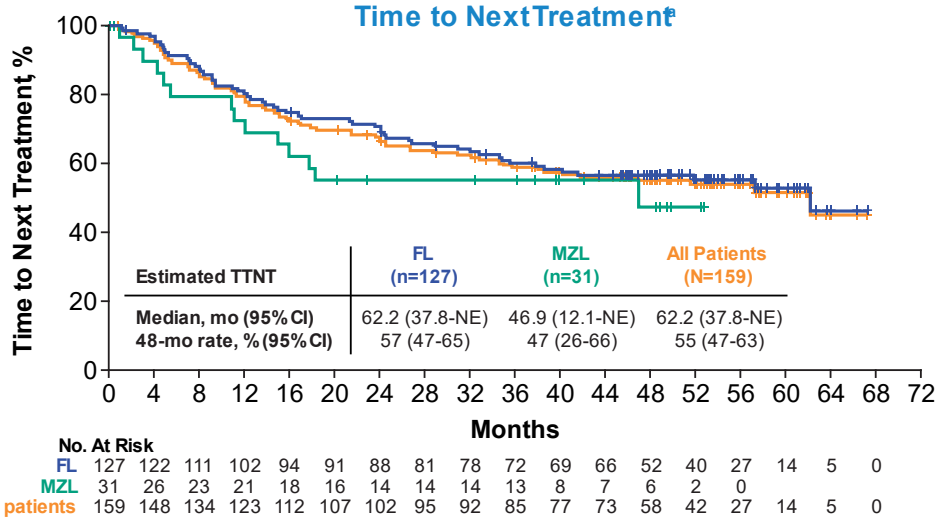


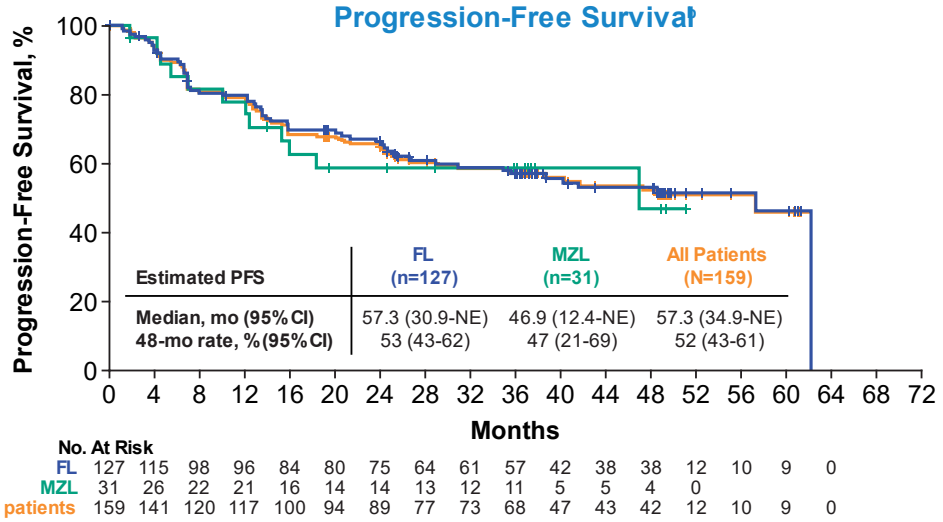

### OS

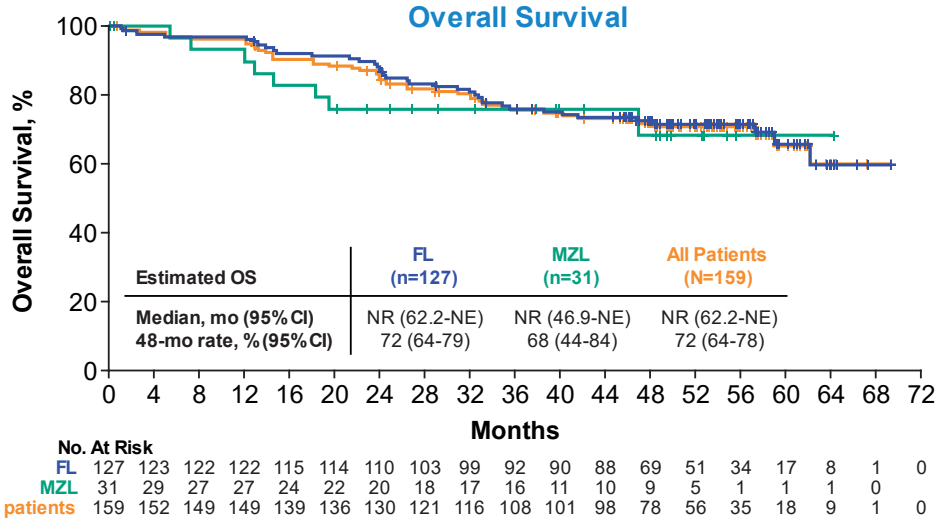


# ZUMA 5 - DOR, TTNT, PFS, and OS




[a]Time to next treatment is defined as the time from the leukapheresis date to the start of subsequent anticancer therapy or death from any cause. [b]Progression events were determined by the investigator.
DOR, duration of response; FL, follicular lymphoma; MZL, marginal zone lymphoma; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival; TTNT, time to next treatment.

This table does not intend to compare trials that are intrinsically different

# Cellular therapy in R/R FL

# Toxicities

| | ZUMA-5[1-2] (Axicel) | ELARA[3-4] (Tisacel) | TRANSCEND FL[5] (Lisocel) |
|---|---|---|---|
| G3-5 AE (%) | | | |
| G3-5 Neutropenia (%) | 33 | 15 | 27 |
| G3-5 Infections (%) | 18 | 5 | 5 |
| CRS | | | |
| Any grade (%) | 78 | 48 | 52 |
| G3-5 (%) | 6 | 0 | 1 |
| ICANS | | | |
| Any grade (%) | 56 | 37 | 5 |
| G3-5 (%) | 15** | 1*** | 2 |
| Related deaths | 1 (5) | 0 | 2 (2) |

*grade 3; **No grade 5; ***Neurotoxicity 3%

1) Jacobson, Lancet 2022; 2) Neelapu, Blood 2024; 3) Fowler, Nat Med 2022;28:325-32; 4) Dreyling ASH 2022 #608; 5) Morschhauser, Nat Med 2024

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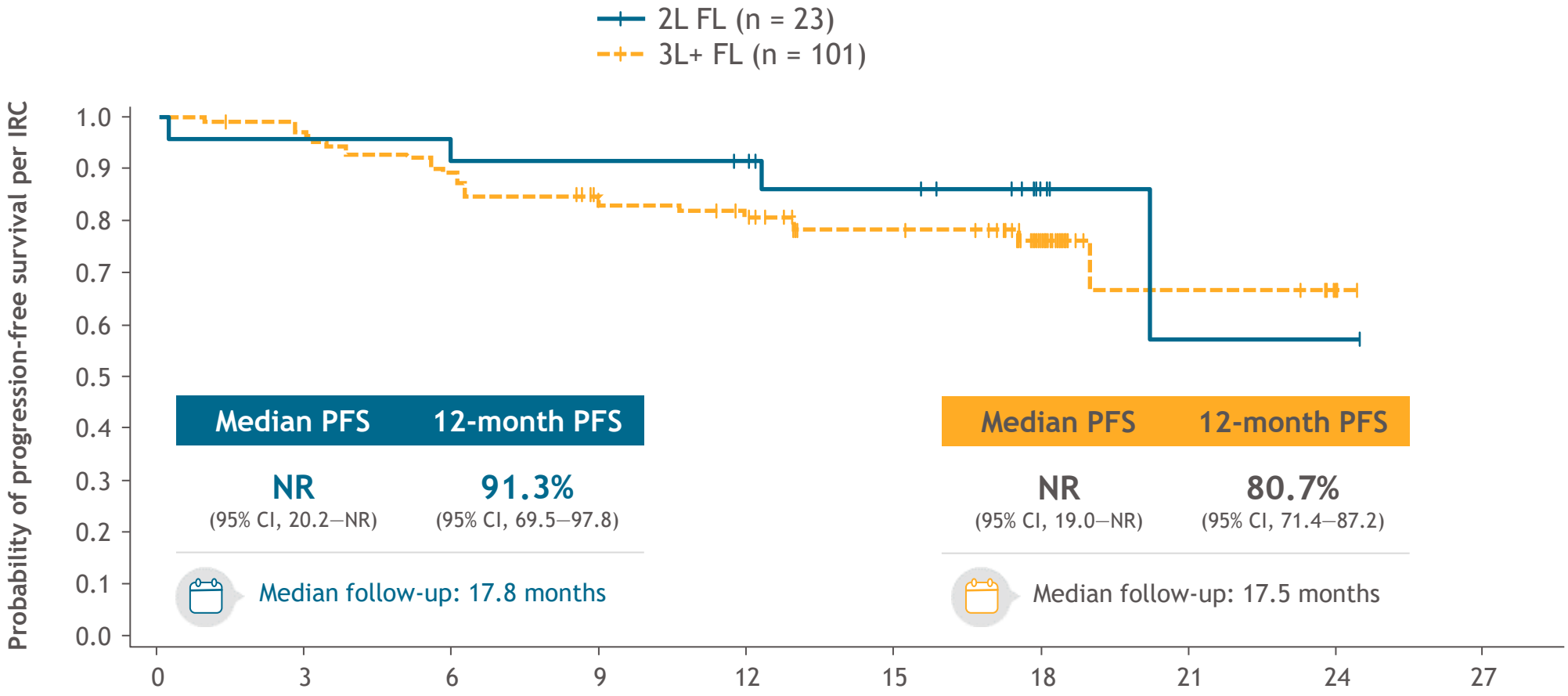
| ICANS | | | |
| Any grade (%) | 56 | 37 | 5 |
| G3-5 (%) | 15** | 1*** | 2 |
| Related deaths | 1 (5) | 0 | 2 (2) |

*grade 3; **No grade 5; ***Neurotoxicity 3%

1) Jacobson, Lancet 2022; 2) Neelapu, Blood 2024; 3) Fowler, Nat Med 2022;28:325-32; 4) Dreyling ASH 2022 #608; 5) Morschhauser, Nat Med 2024

# Progression-free survival per IRC in efficacy set




No. at risk (censored)

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 2L FL | 23 (0) | 22 (0) | 21 (0) | 21 (0) | 20 (1) | 16 (3) | 5 (11) | 2 (2) | 2 (0) | 0 (2) |
| 3L+ FL | 101 (0) | 96 (1) | 89 (0) | 78 (6) | 72 (3) | 50 (20) | 19 (30) | 7 (11) | 2 (5) | 0 (2) |

Morschhauser F, et al. ASH 2023 [Presentation #602]

# Recommendations – Treatment in 2nd or later relapse

For 2nd or later relapse the following possibilities have been pointed out (only those with positive opinión by the EMA):

| | |
|---|---|
| ▪ Inmunochemotherapy | 1C |
| ▪ Idelalisib (double refractory) | 2B |
| ▪ Rituximab/lenalidomide $R^2$ | 1B |
| ▪ Mosunetuzumab | 1B |
| ▪ CAR-T therapy (tisacel in ≥3rd line*; axicel in ≥4th line) | 1B |
| ▪ Palliative care | 1C |

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* This recommendation although approved by the EMA has not yet reimbursement by the health public system in Spain

# Conclusiones

- La inmunoterapia y la terapia celular son los tratamientos más prometedores en el LF en recaída o refractariedad.
- Con la terapia CART se logran las mayores tasas de respuesta global y completa de todos los tratamientos de rescate, respuestas que parecen mantenerse en el tiempo.
- No han aparecido toxicidades inesperadas.
- ... *Ergo* la terapia CART sería la de elección en esta situación.