ALGORITMO DI TRATTAMENTO

NEL LINFOMA FOLLICOLARE

MARIAGRAZIA MICHIELI
IRCCS CRO AVIANO

CAR-T:
e la storia continua...
migliorando

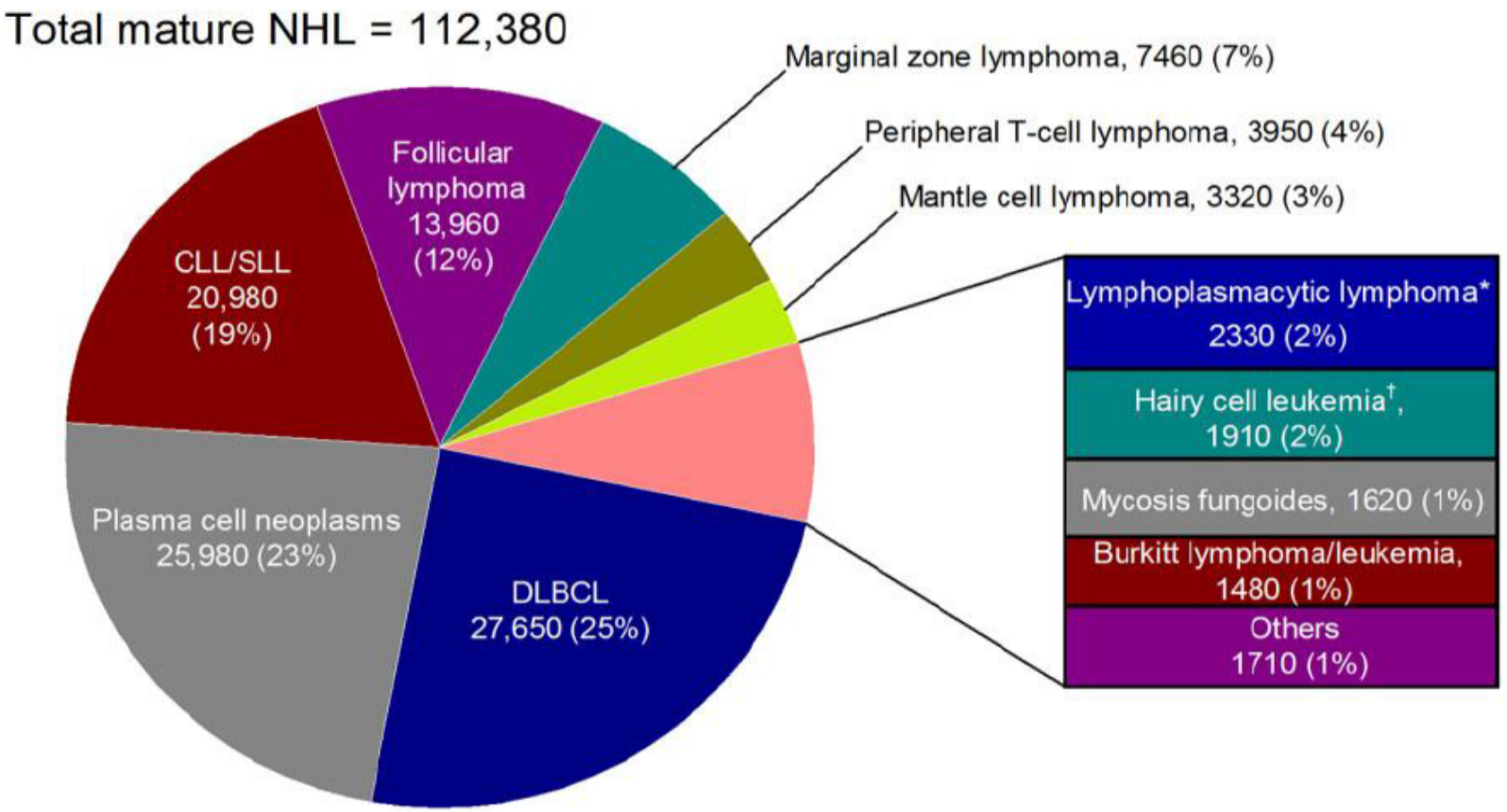
Verona, 11 novembre 2024
Hotel Indigo Verona – Grand Hotel Des Arts

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
nessuno							

Features of Follicular Lymphoma

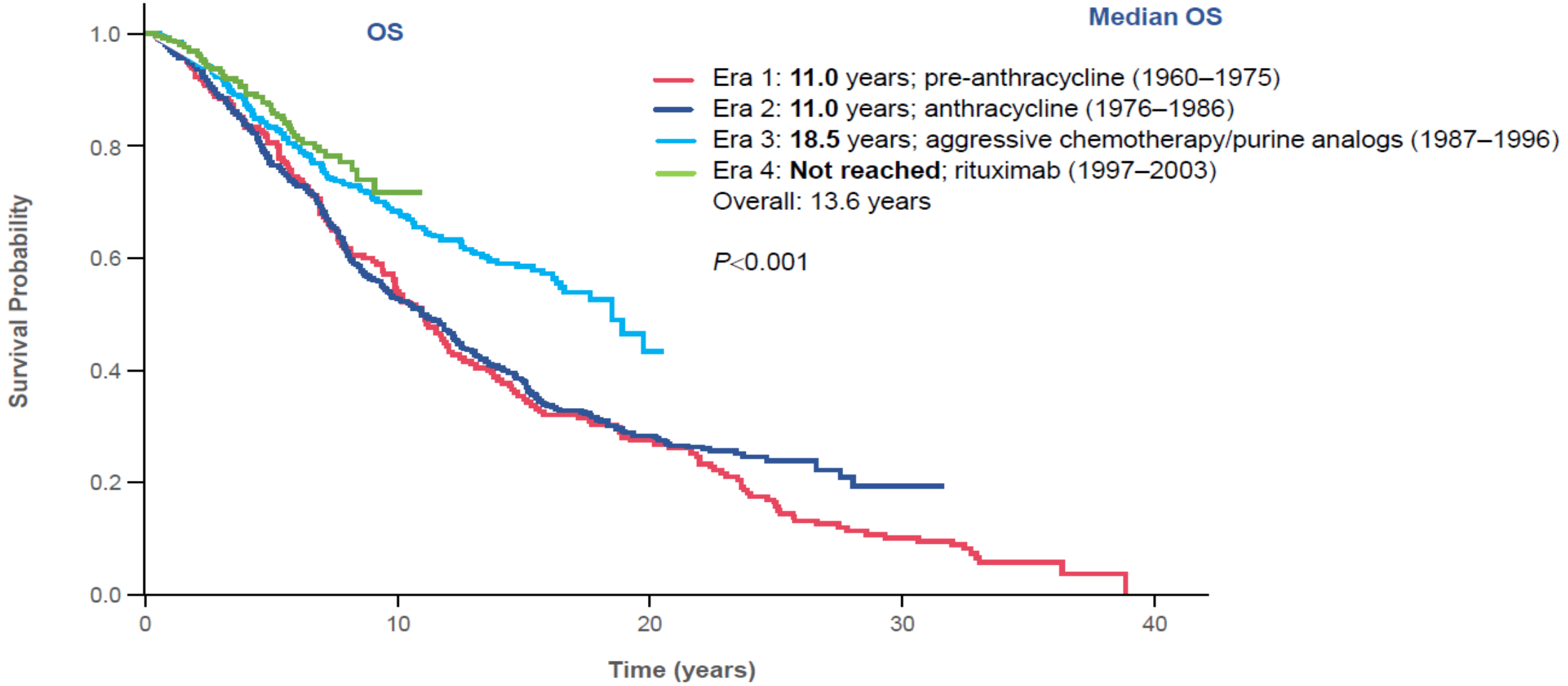
- Relapsing-remitting course with progression over several years[1]
- 80% diagnosed with advanced stage[1]
- Low impact on life expectancy with exceptions[2]
- Can transform into more aggressive lymphomas (2%–3% per year)[3]
- Continued improved survival in patients with FL is dependent on the tumor microenvironment[5]

Distribution of NHL Subtypes[4]



- DLBCL, diffuse large B-cell lymphoma; CLL, chronic lymphocytic leukemia; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; PTCL, peripheral T-cell lymphoma; SLL, small lymphocytic lymphoma. Adapted from: 1. Link BK, et al. Br J Haematol. 2019;184(4):660-663. 2. Maurer MJ, et al. Am J Hematol. 2016;91(11):1096-1101. 3. Link BK, et al. J Clin Oncol. 2013;31(26):3272-3278. 4. Teras LR, et al. CA Cancer J Clin. 2016;66(6):443-459. 5. Huet S, et al. Nat Rev Cancer.

Improving Survival in Patients With Follicular NHL

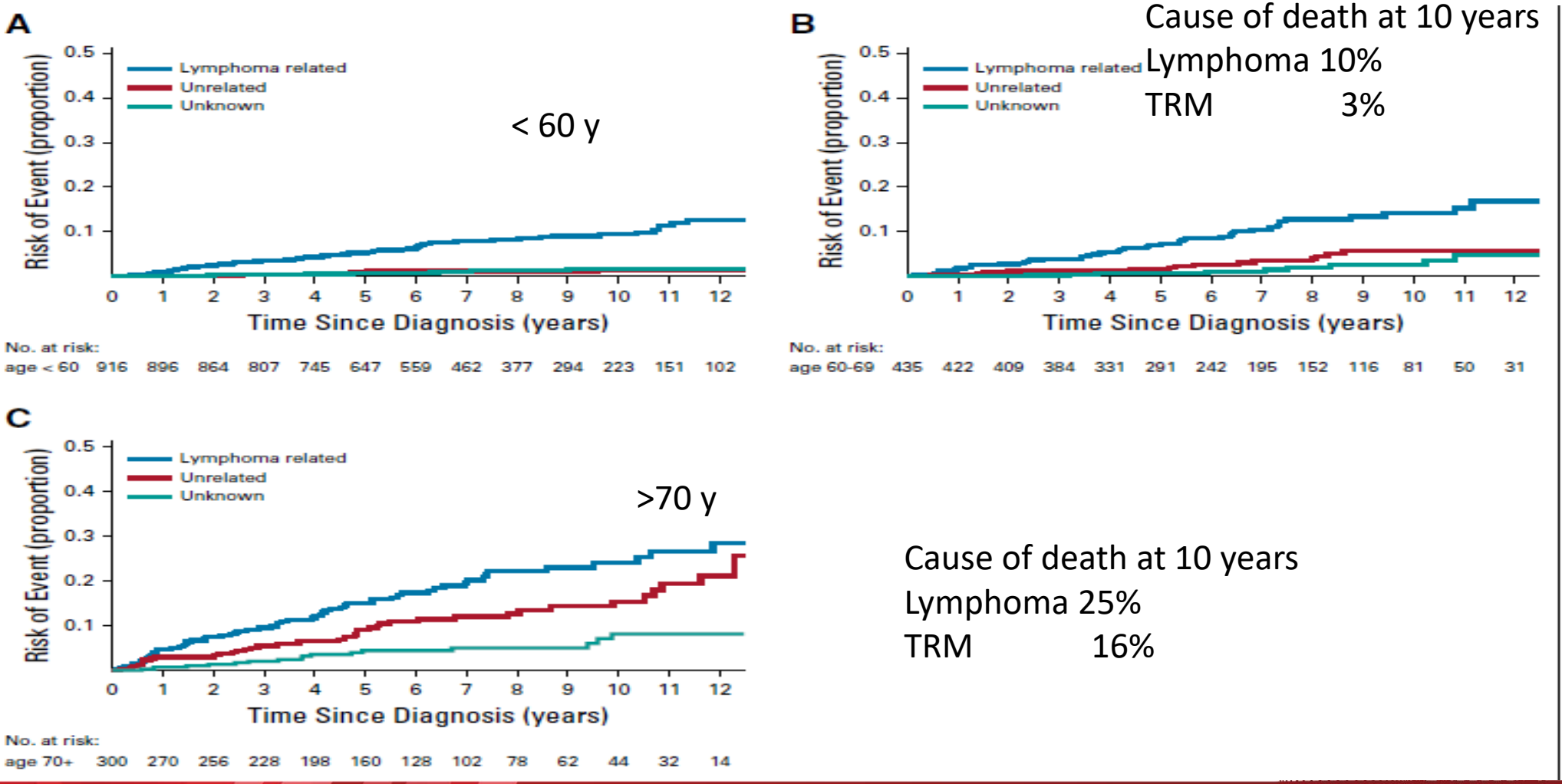


original report

Cause of Death in Follicular Lymphoma in the First Decade of the Rituximab Era: A Pooled Analysis of French and US Cohorts

Clémentine Sarkozy, MD[1]; Matthew J. Maurer, MS[2]; Brian K. Link, MD[3]; Hervé Ghesquieres, MD, PhD[1]; Emmanuelle Nicolas, MD[4]; Carrie A. Thompson, MD[2]; Alexandra Traverse-Glehen[1]; Andrew L. Feldman, MD[2]; Cristine Allmer[2]; Susan L. Slager[2]; Stephen M. Ansell, MD, PhD[2]; Thomas M. Habermann, MD[2]; Emmanuel Bachy[1]; James R. Cerhan, MD, PhD[2]; and Gilles Salles, MD, PhD[1]

2001-2013
N 920
Follow up di 84 months
Cause of death at 10 years
Lymphoma 10%
TRM 3%



Cause of death at 10 years
Lymphoma 25%
TRM 16%

original report

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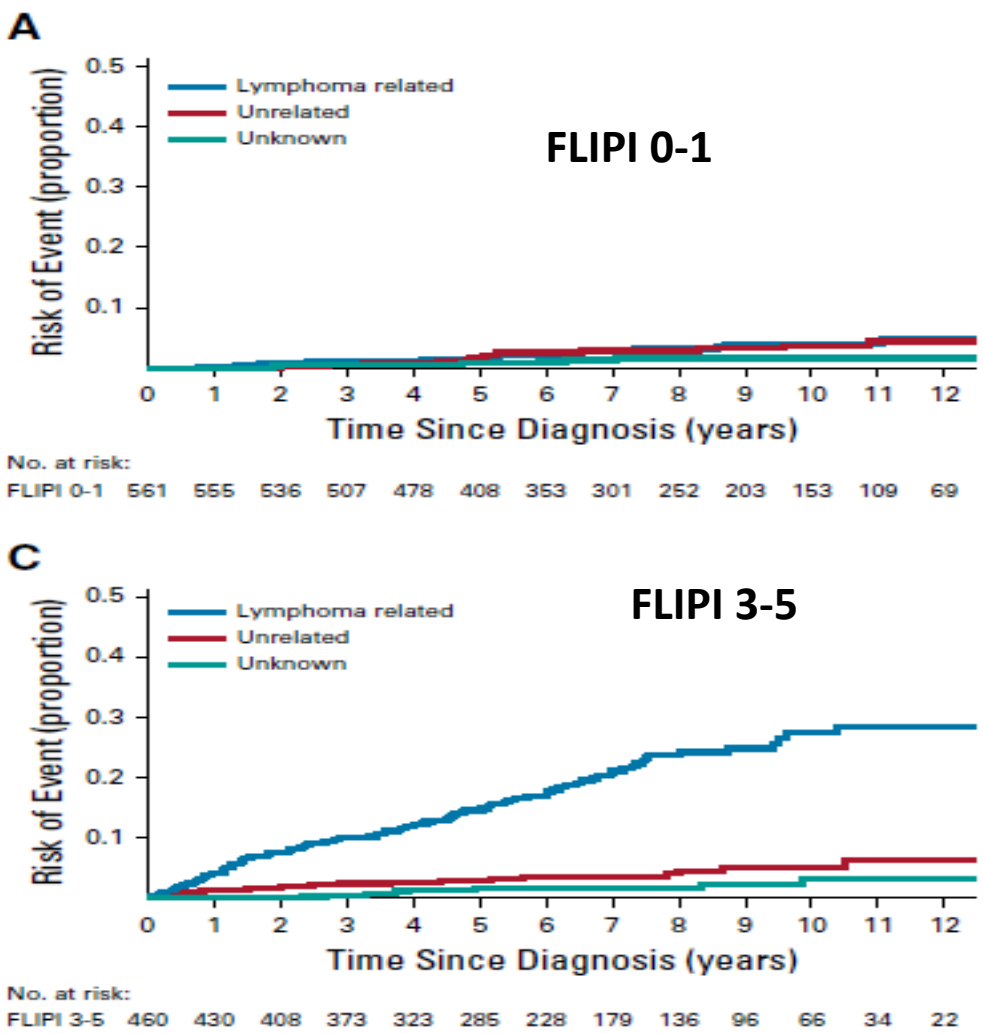
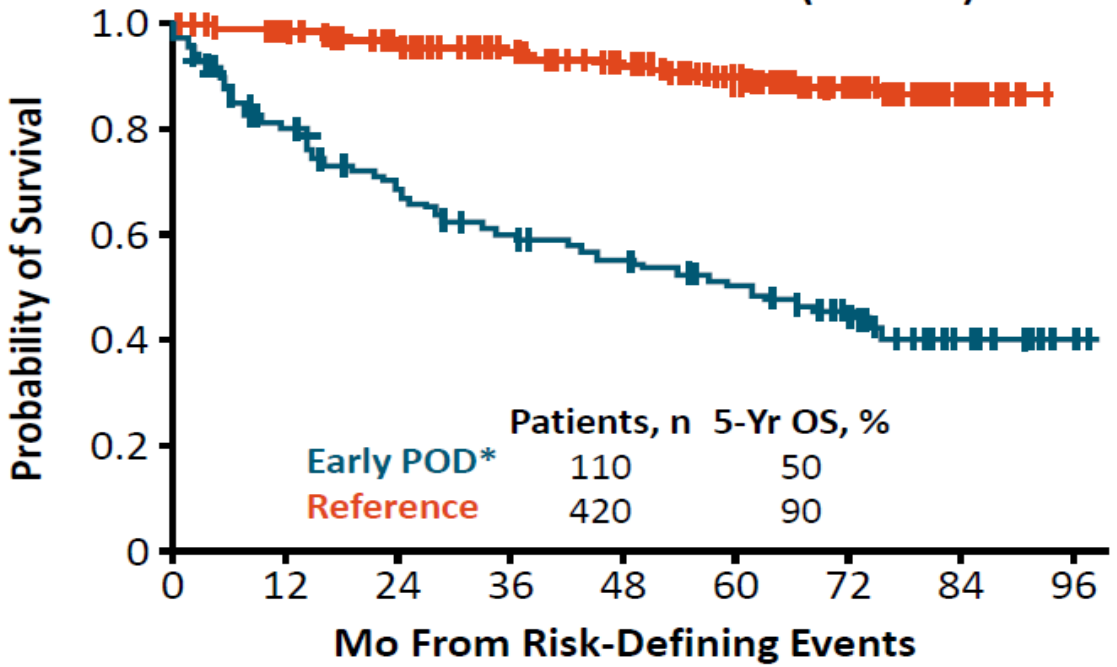


Overall 77/140 deaths as a result of lymphoma transformation

Early POD and PET Positivity at End of CIT Predicts Poor Prognosis in Patients With FL

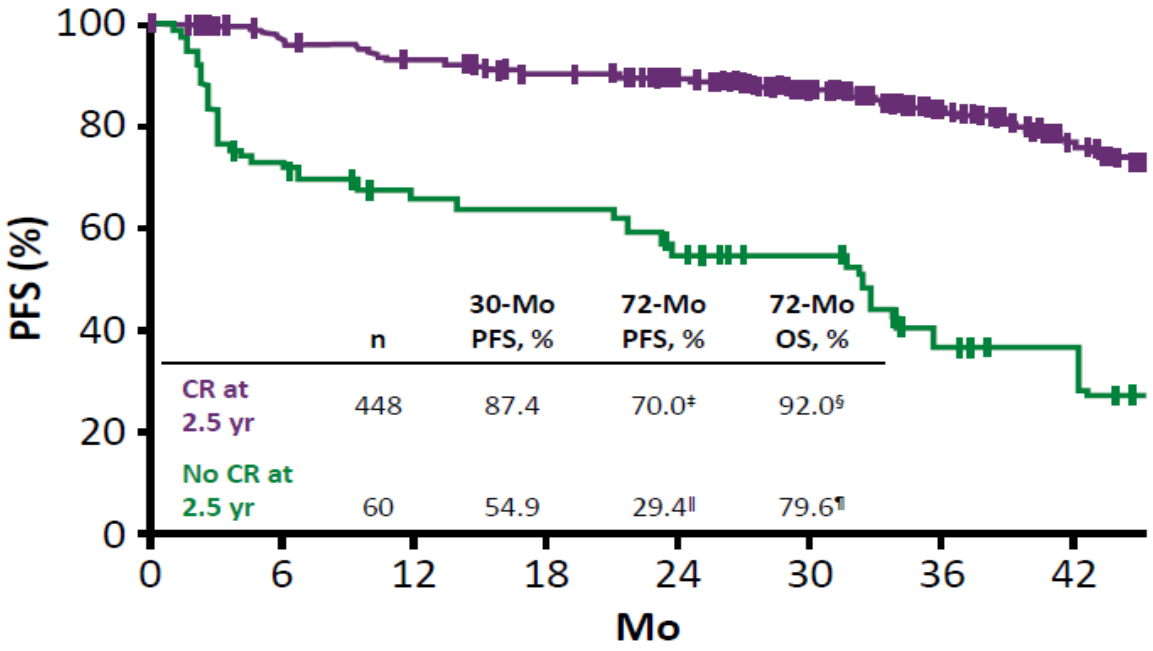
GELTAMO Cohort 162 POD
Multivariate analysis
HR FLIPI
Histological Transformation

OS of Patients With FL Treated With R-CHOP From NLCS (N = 588)



*Early POD: relapse within 2 yr. Similar results found for an independent validation set and for first-line R-CVP and R-fludarabine in exploratory analyses.

PFS of by PET Assessment† at End of CIT From GALLIUM (n = 595)



†According to Lugano 2014 criteria.
‡n = 449. §n = 450. ‖n = 56. ¶n = 69.

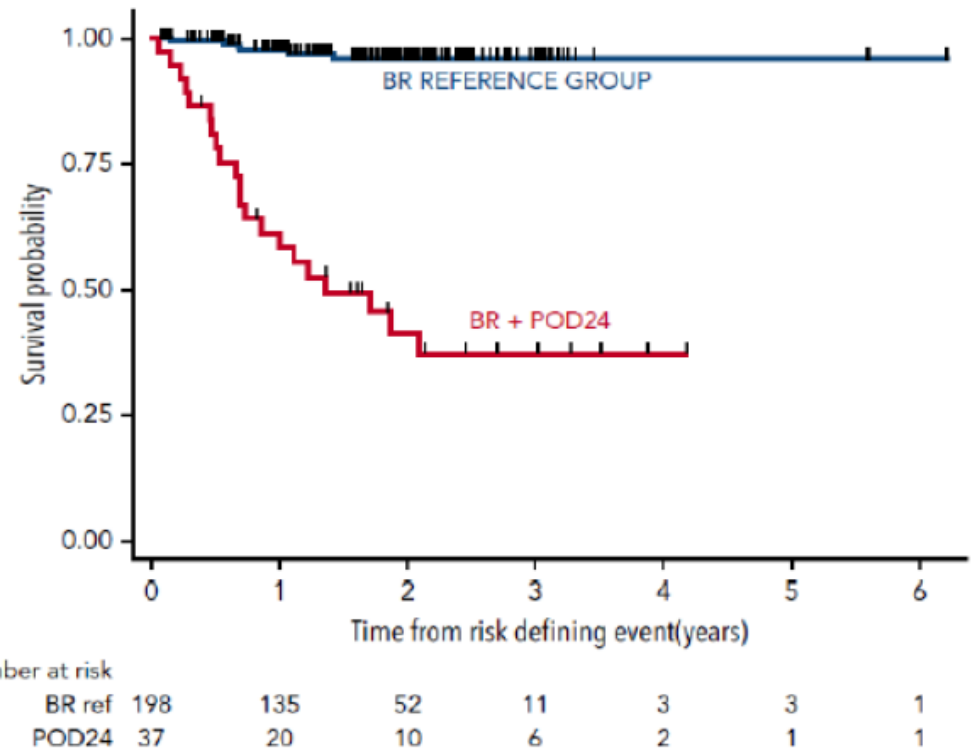
Casulo. JCO. 2015;33:2516. Trotman. Lancet Oncol. 2018;19:1530. Nielsen. ASCO 2020. Abstr 8025.

Slide credit: clinicaloptions.com

Early progression after bendamustine-rituximab is associated with high risk of transformation in advanced stage follicular lymphoma

Ciara L. Freeman,[1,2] Robert Kridel,[3] Alden A. Moccia,[4] Kerry J. Savage,[1,2] Diego R. Villa,[1,2] David W. Scott,[1,2] Alina S. Gerrie,[1,2] David Ferguson,[5] Fergus Cafferty,[5] Graham W. Slack,[1,2,6] Pedro Farinha,[1,2,6] Brian Skinnider,[1,2,6] Joseph M. Connors,[1,2] and Laurie H. Sehn[1,2]

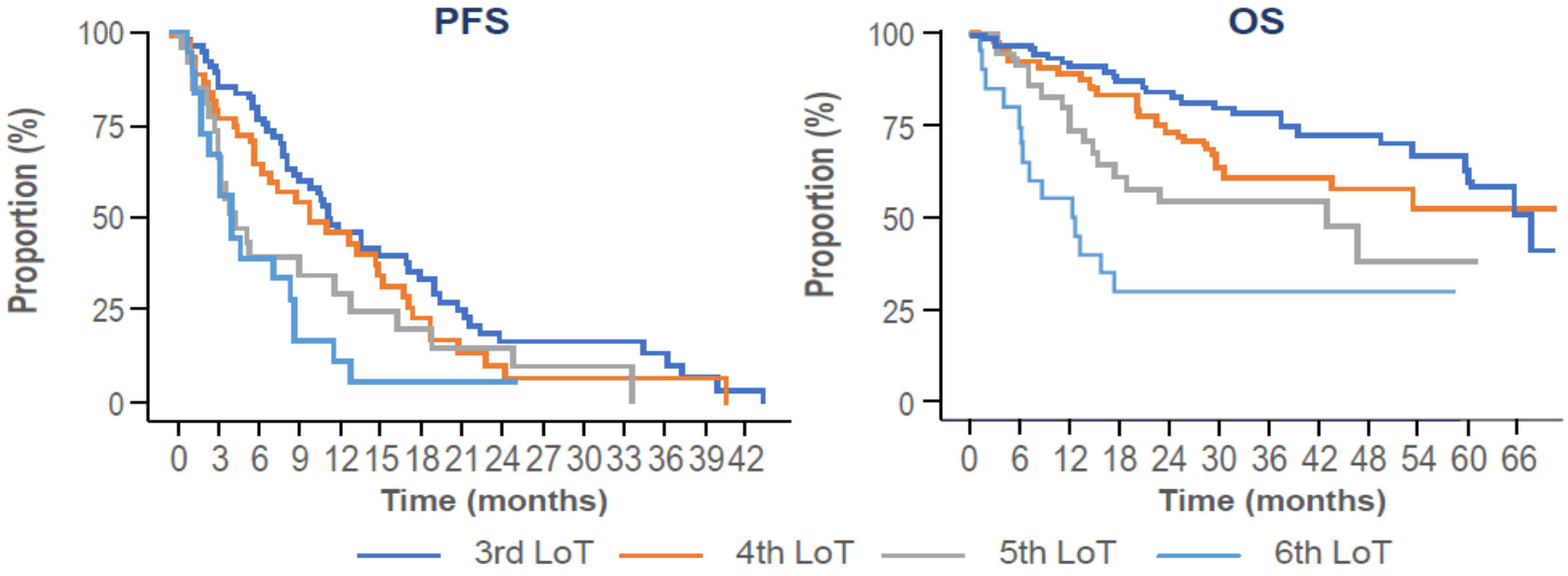
Progression of disease within 24 months (POD 24) occurred in 13% of patients and was associated with a significantly inferior outcome with 2year OS of 38% (95% CI 20-55)



Importantly, the majority of POD24 patients (76%) had transformed disease.

Worsening Outcomes With Additional Lines of Therapy: Results From the International SCHOLAR-5 Study

	Ghione, et al. (SCHOLAR-5)
N	128
Median age, years (range)	65 (36–86)
Stages 3–4	86%
FLIPI 3–5	39%
POD24	27%
Prior ASCT	18%
Prior anti-CD20+ alkylating agent	89%



	3rd LoT	4th LoT	5th+ LoT
ORR (%)	68	63	37
CRR (%)	44	27	22
5-year OS (%)	62	52	38
mPFS (median mo)	11	9.7	3.9
TTNT (median mo)	20.1	17.9	7.1

ASCT, autologous stem cell transplant; CRR, complete response rate; FLIPI, Follicular lymphoma international prognostic index; LoT, lines of therapy; mo, months; mPFS, median PFS; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; POD24, progression of disease within 24 months; TTNT, time to next treatment. Adapted from Ghione P, et al. *Haematologica*. 2023;108(3):822-832.

ESMO

ANNALS OF ONCOLOGY

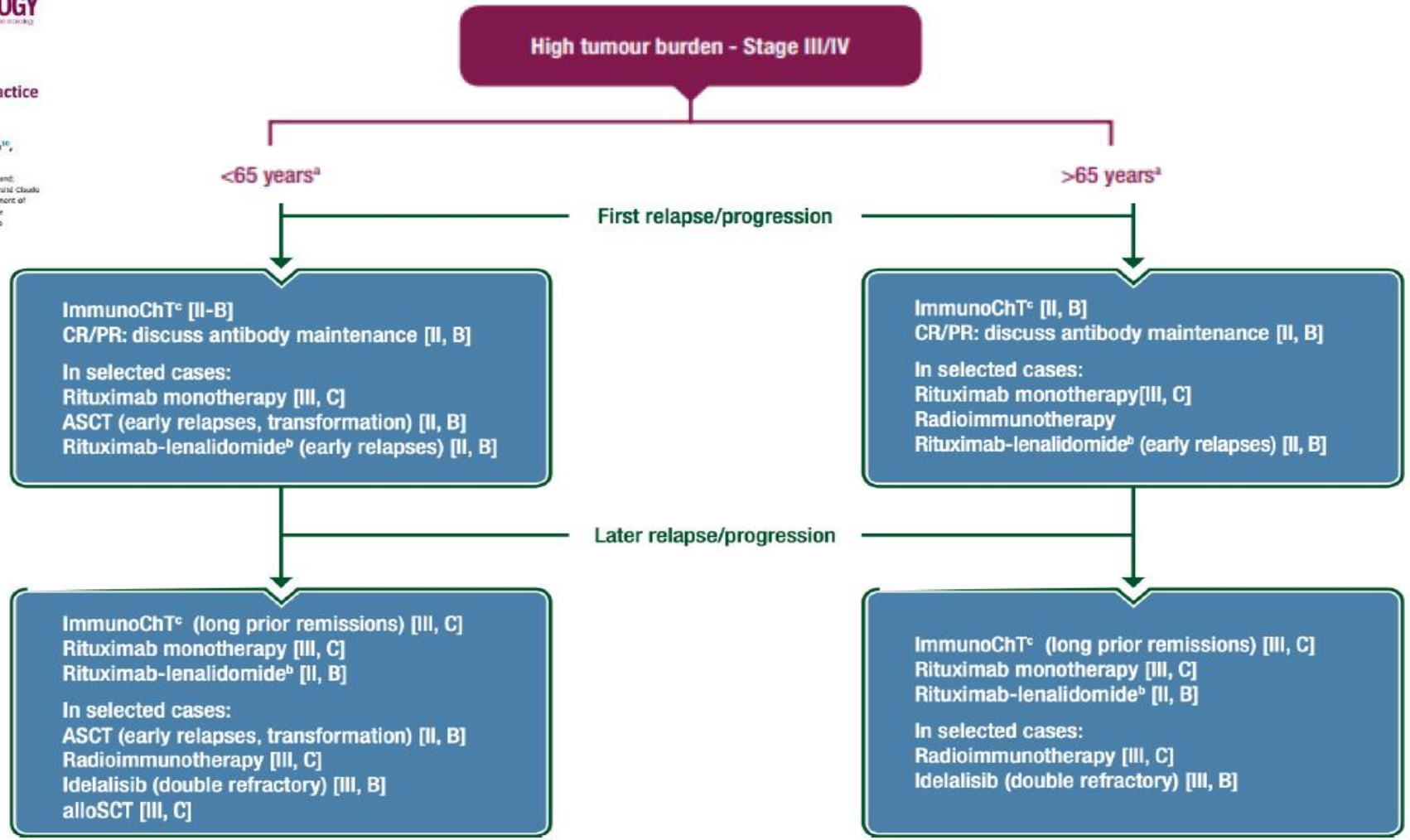
SPECIAL ARTICLE

Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up☆

M. Dreyling[1], M. Ghielmini[2], S. Rule[3], G. Salles[4,5], M. Ladetto[6], S. H. Tonino[7], K. Herfarth[8], J. F. Seymour[9] & M. Jerkeman[10], on behalf of the ESMO Guidelines Committee*

[1]Department of Medicine III, LMU Hospital Munich, Germany; [2]Oncology Institute of Southern Switzerland, Ospedale San Giovanni, Bellinzona, Switzerland; [3]Haematology, Peninsula School of Medicine, Plymouth, UK; [4]Service d'Hématologie, Hospices Civils de Lyon, Centre Hospitalier Lyon-Sud, Lyon; [5]Université Claude Bernard Lyon-1, Pierre-Bénite, France; [6]Divisione di Ematologia, Azienda Ospedaliera Sant Antonio e Biagio e Cesare Arrigo, Alessandria, Italy; [7]Department of Hematology, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands; [8]Department of Radiation Oncology, University of Heidelberg, Ge [9]Department of Haematology, Peter MacCallum Cancer Center & Royal Melbourne Hospital, Melbourne, University of Melbourne, Parkville, Australia; [10]Dep Oncology, Skåne University Hospital, Lund University, Lund, Sweden

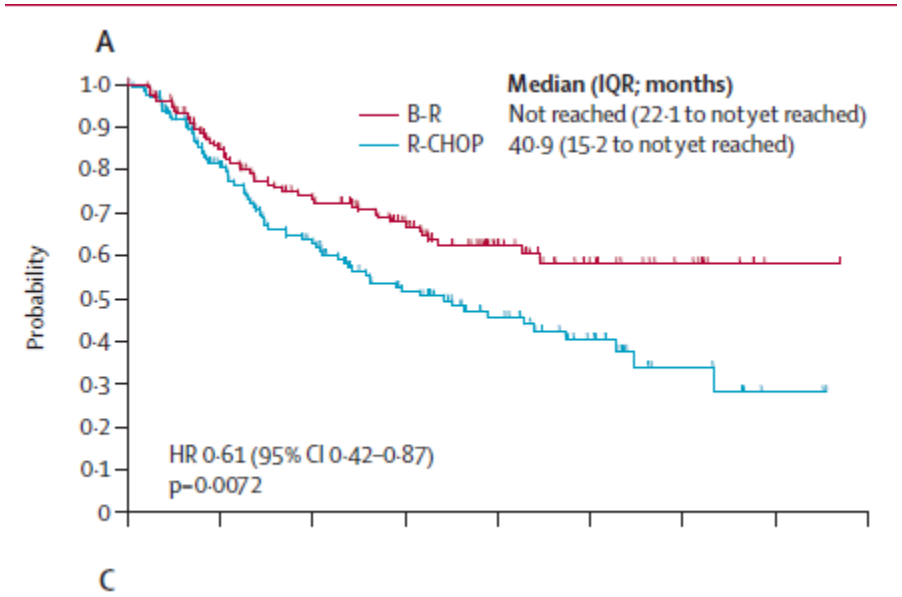
Available online 26 November 2020



Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial

Lancet 2013; 381: 1203–10

Mathias J Rummel, Norbert Niederle, Georg Maschmeyer, G Andre Banat, Ulrich von Grünhagen, Christoph Losem, Dorothea Kofahl-Krause, Gerhard Heil, Manfred Welslau, Christina Balser, Ulrich Kaiser, Eckhart Weidmann, Heinz Dürk, Harald Ballo, Martina Stauch, Fritz Roller, Juergen Barth, Dieter Hoelzer, Axel Hinke, Wolfram Brugger, on behalf of the Study group indolent Lymphomas (StiL)



	B-R (n=261)	R-CHOP (n=253)	p value
Alopecia	0	245 (100%)*	<0·0001
Paresthesia	18 (7%)	73 (29%)	<0·0001
Stomatitis	16 (6%)	47 (19%)	<0·0001
Skin (erythema)	42 (16%)	23 (9%)	0·024
Skin (allergic reaction)	40 (15%)	15 (6%)	0·0006
Infectious episodes	96 (37%)	127 (50%)	0·0025
Sepsis	1 (<1%)	8 (3%)	0·019

B-R=bendamustine plus rituximab. R-CHOP=CHOP plus rituximab. *Includes only patients who received three or more cycles.

Table 4: **All grades of non-haematological toxic events in patients receiving at least one dose of study treatment**

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

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Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†☆

M. Dreyling[1], M. Ghielmini[2], S. Rule[3], G. Salles[4,5], M. Ladetto[6], S. H. Tonino[7], K. Herfarth[8], J. F. Seymour[9] & M. Jerkeman[10], on behalf of the ESMO Guidelines Committee*

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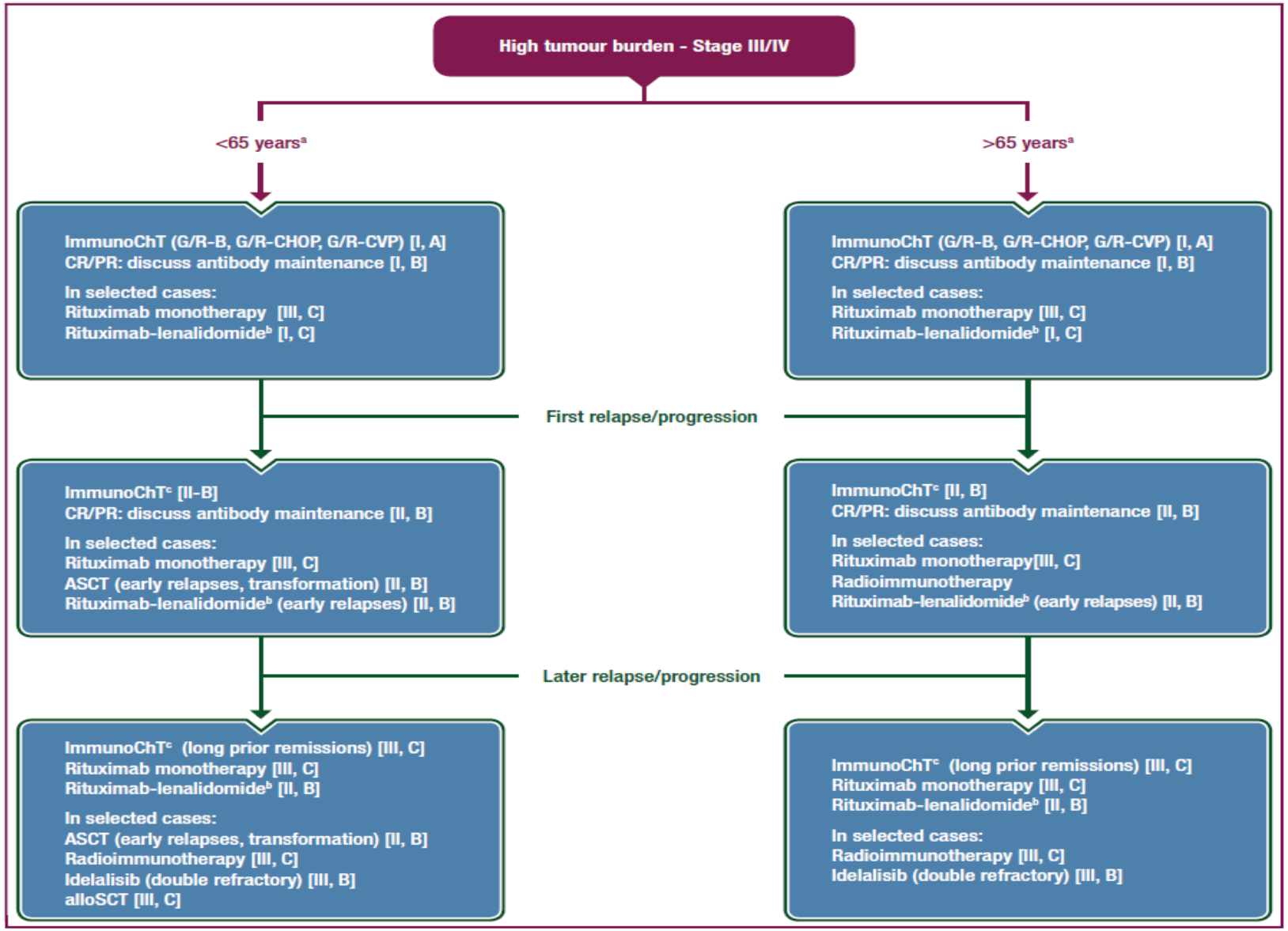


GADOLIN: Obinutuzumab Improved OS in Rituximab-Refractory iNHL When Added to Bendamustine

- Randomized, open-label, international phase III trial

Stratified by NHL subtype (FL vs other), prior therapies (≤2 vs >2), refractory type, and geographic region

Up to 6 28-day cycles

For 2 yr or until PD

Rituximab-refractory CD20-positive indolent NHL (N = 413)

Obinutuzumab* + Bendamustine

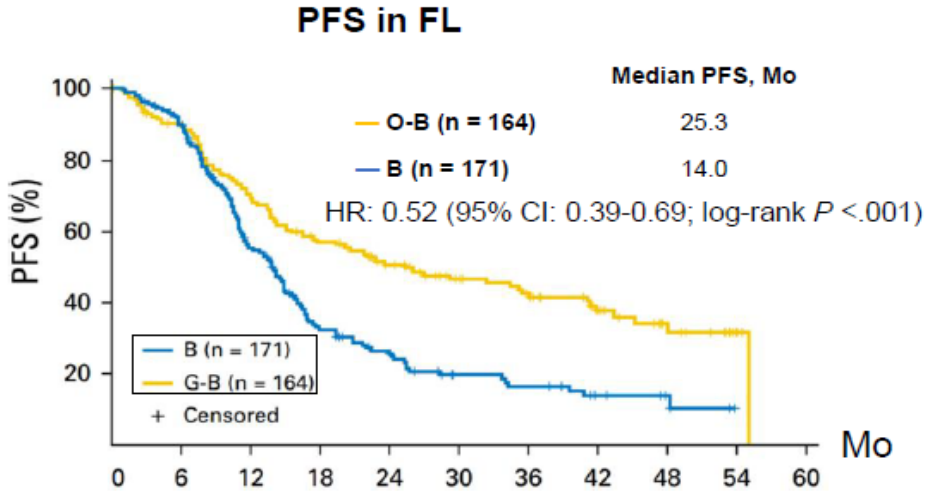
Bendamustine

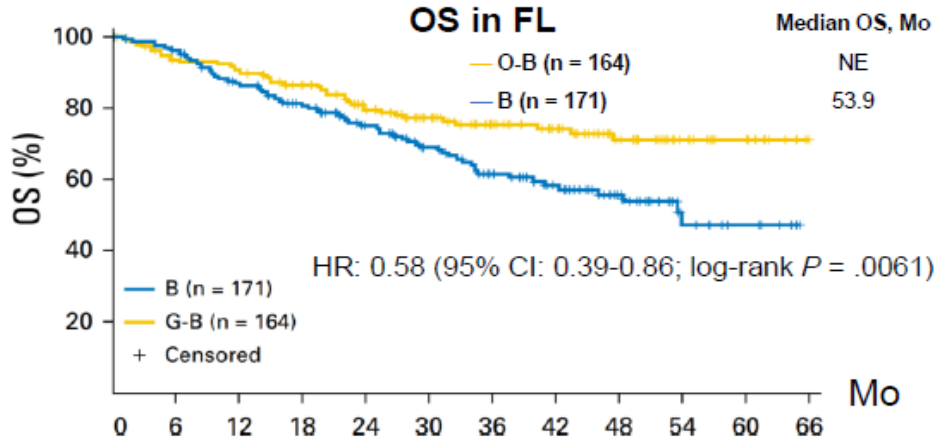
CR/ PR/ SD

Obinutuzumab maintenance 1000 mg IV Q2M

*1000 mg IV on Days 1, 8, 15 cycle 1; Day 1 cycles 2-6. Response monitored by CT scan post induction, then every 3 mo for 2 yr, then every 6 mo (modified Cheson criteria 2007).

- Primary endpoint: PFS

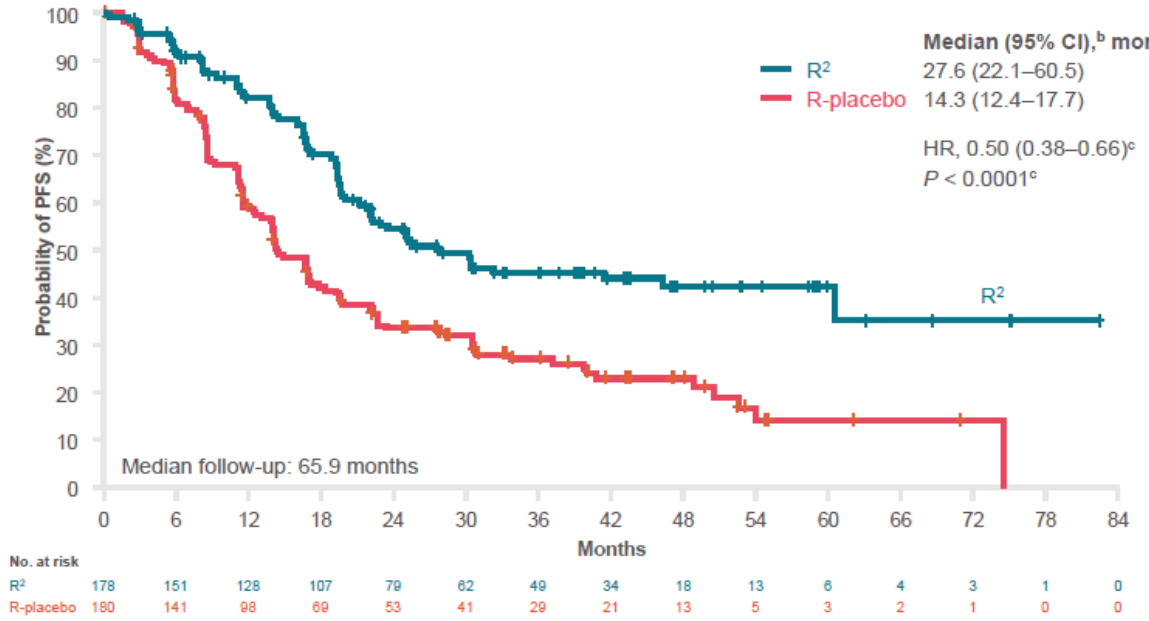




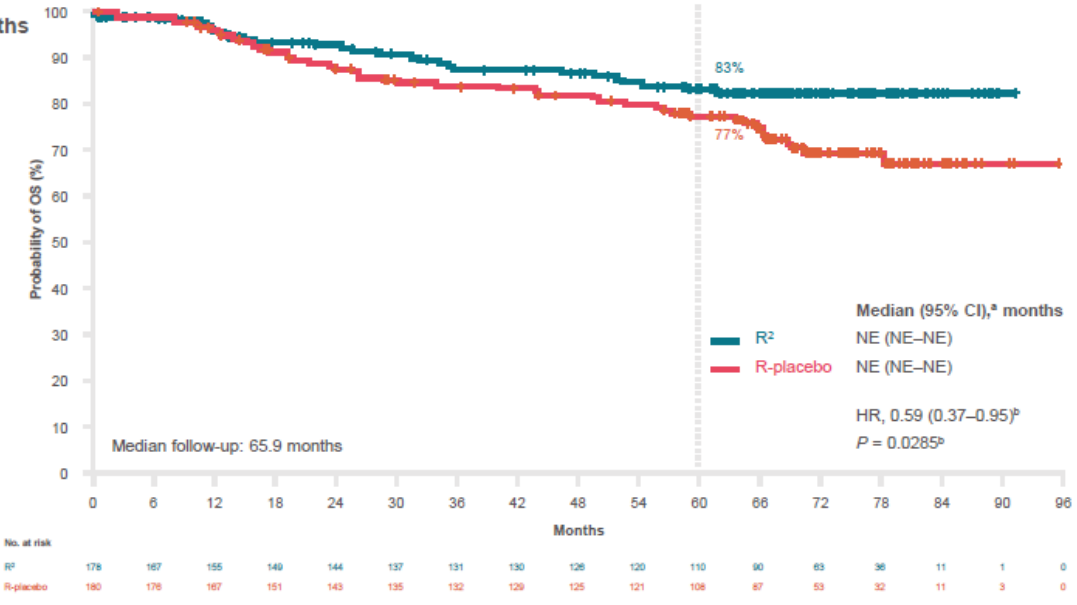
ırce: Sehn. Lancet Oncol. 2016;17:1081. Cheson. JCO. 2018;36:2259.

AUGMENT: PFS and OS advantage for R² in r/r FL

PFS (ITT, IRC)



OS (ITT, IRC)



ITT, intention to treat; NR, not reached

Source: Leonard JP, et al. AUGMENT: a phase III study of lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma. J Clin Oncol. 2019;37:1188-99. Updated aat ASH 2022

C’è ancora un ruolo per il trapianto in era di nuovi agenti immunologici?

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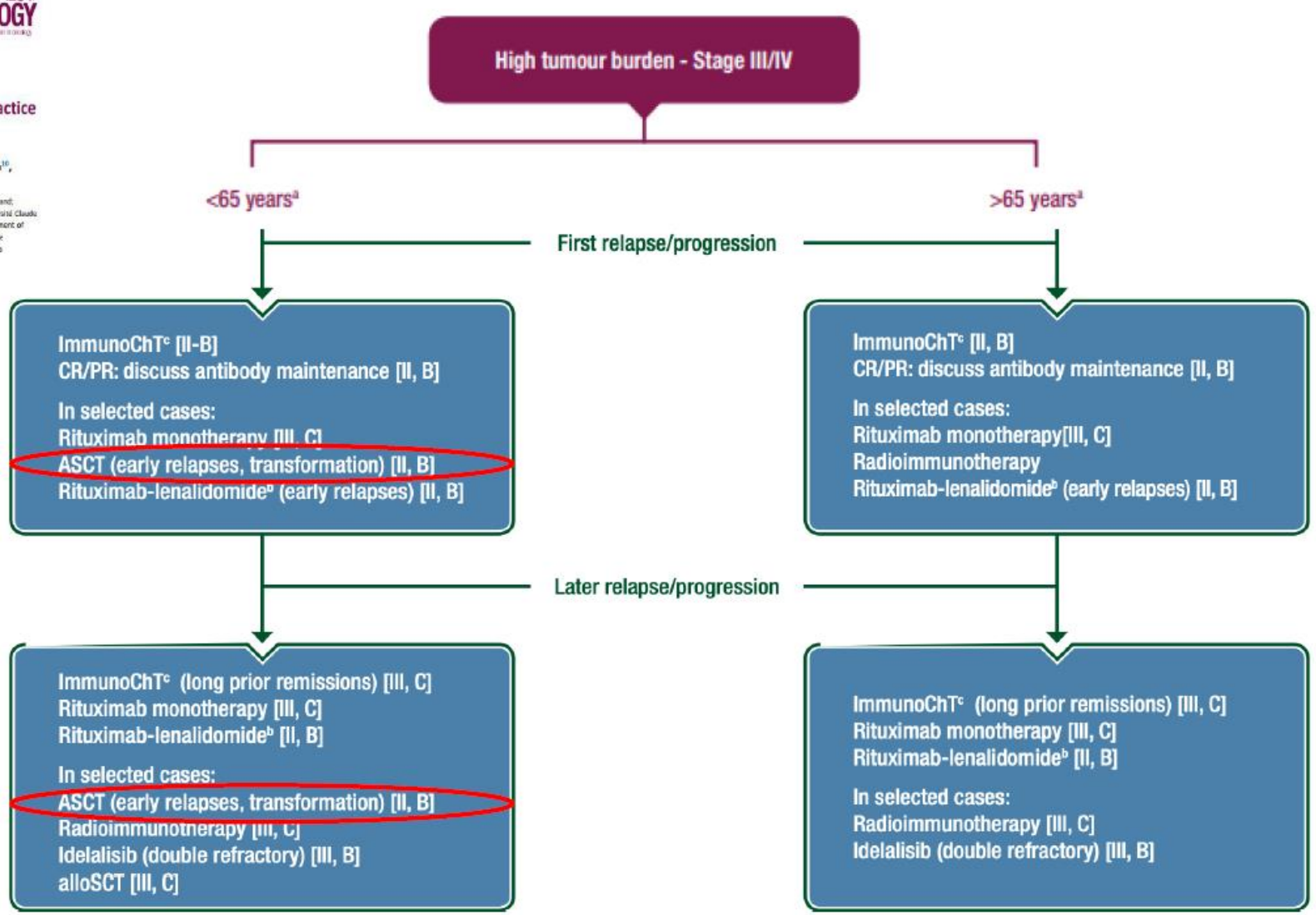
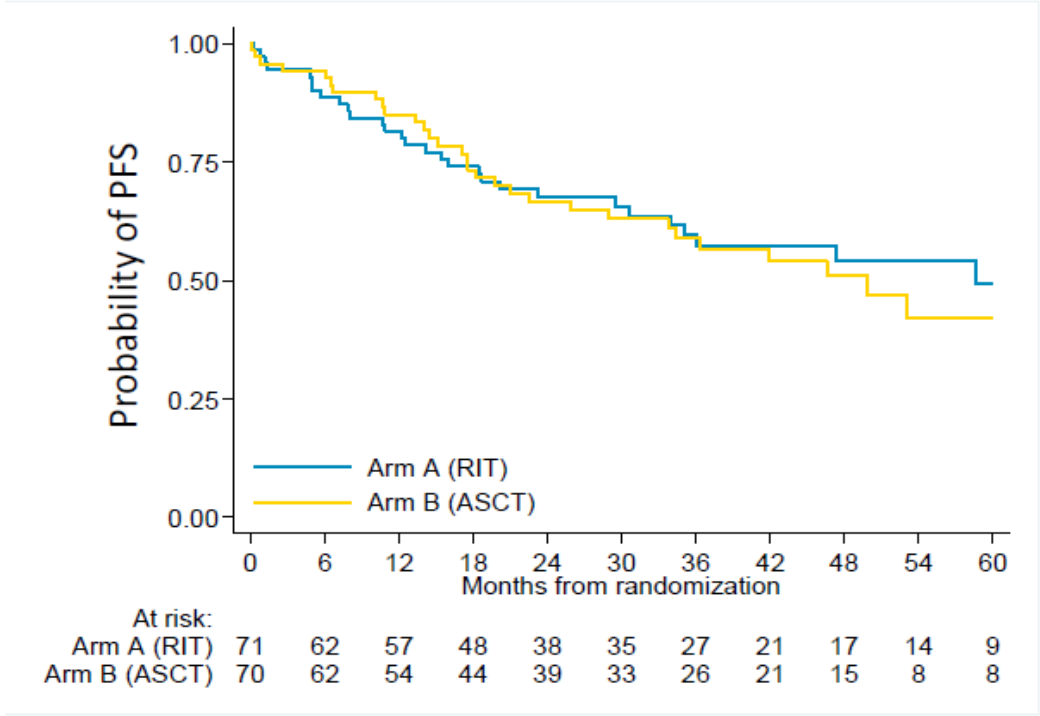
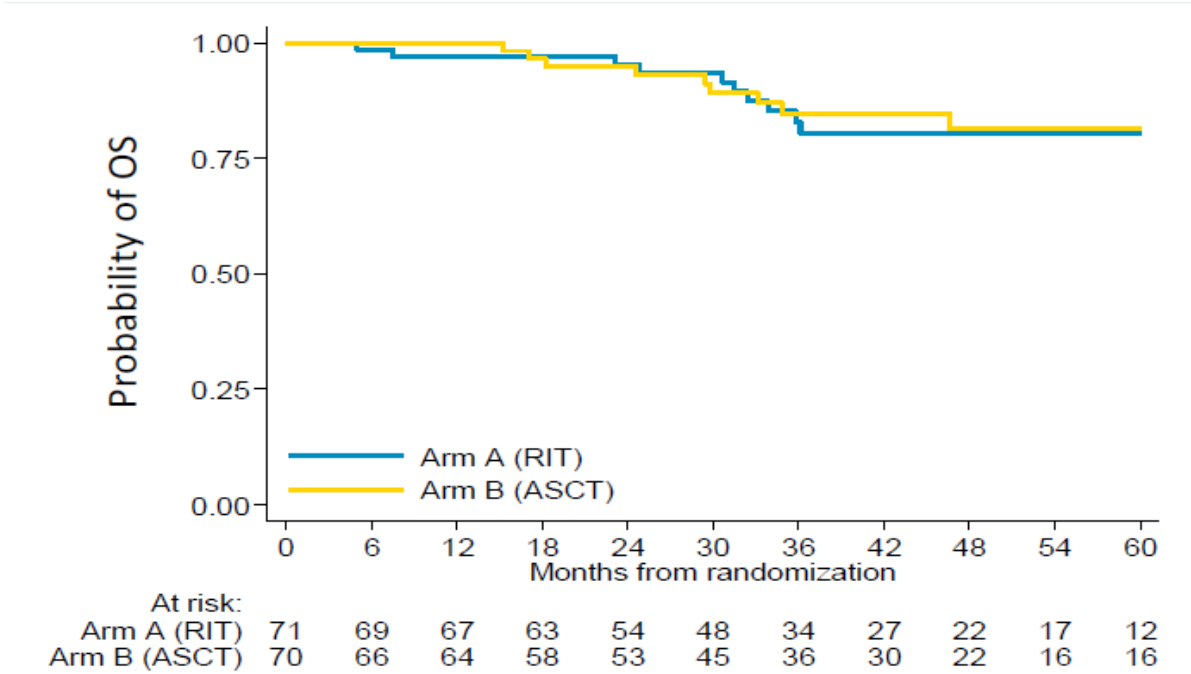


ASCT is not the best treatment fo RR FL, Lesson from the FIL FLAZ PhIII trial

Median follow-up time from enrollment 43 months PFS EVENTS 75; OS EVENTS 21





Source: Ladetto et al. Annals of Oncology 2023

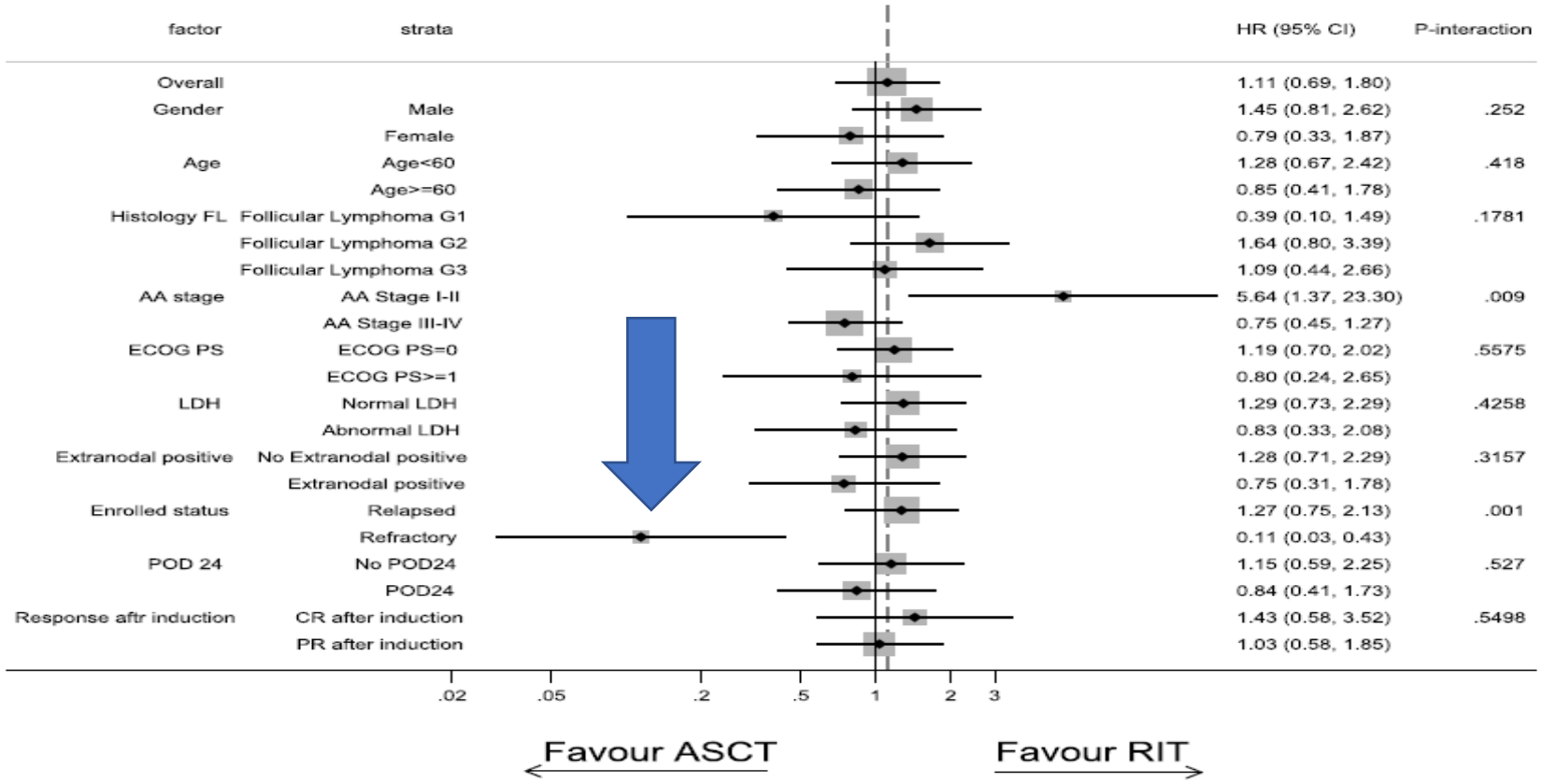
ORIGINAL ARTICLE | ARTICLES IN PRESS

PDF [1 MB]

Radioimmunotherapy versus autologous hematopoietic stem cell transplantation in relapse/refractory follicular lymphoma: a Fondazione Italiana Linfomi multicenter, randomized, phase 3 trial.

M. Ladetto † • R. Tavarozzi † • M. Zanni • ... C. Bottelli • G. Ciccone • U. Vitolo • Show all authors • Show footnotes

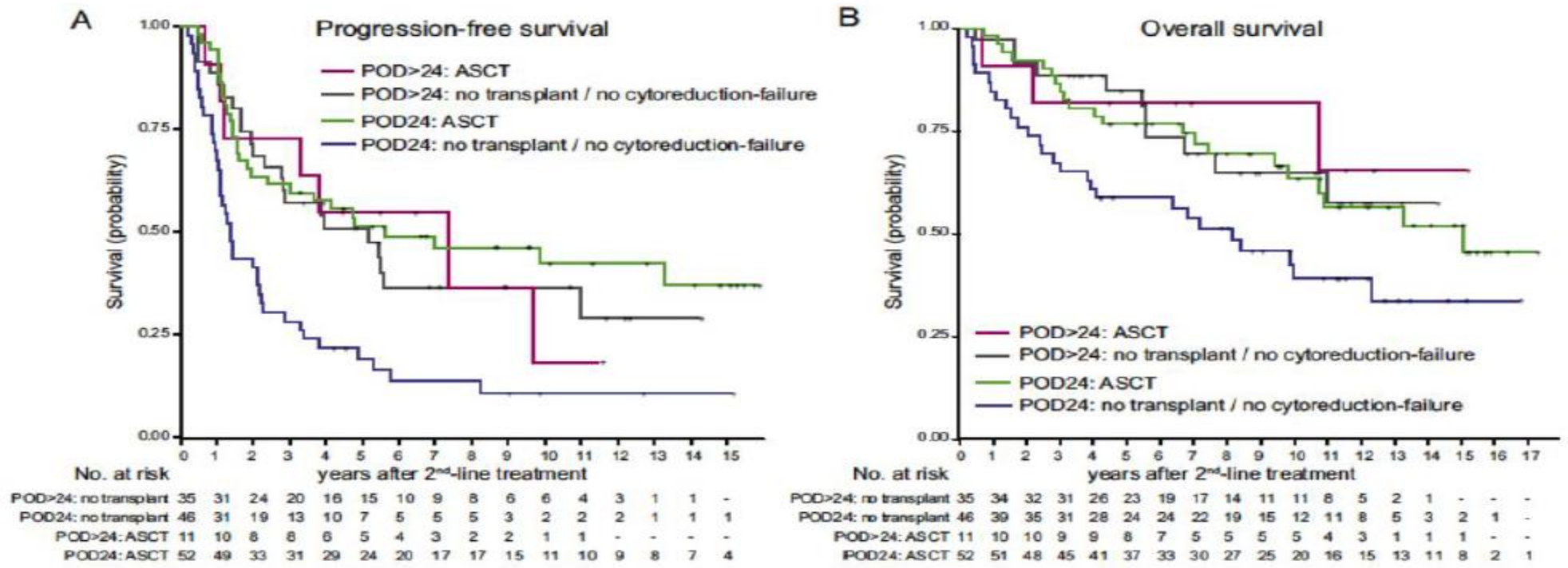
Open Access • Published: November 01, 2023 • DOI: https://doi.org/10.1016/j.annonc.2023.10.095



ASCT in POD24 patients

Autologous Stem Cell Transplantation for Patients with Early Progression of Follicular Lymphoma: A Follow-Up Study of 2 Randomized Trials from the German Low Grade Lymphoma Study Group

Vindi Jurinovic [1,2], Bernd Metzner [3], Michael Pfreundschuh [4], Norbert Schmitz [5], Hannes Wandt [6], Ulrich Keller [7], Peter Dreger [8], Martin Dreyling [1], Wolfgang Hiddemann [1,9,10], Michael Unterhalt [1], Eva Hoster [1,2], Oliver Weigert [1,9,10,*]



received no transplant (50%). In patients with POD24, a significant survival benefit was associated with ASCT with a 5-year second-line progression-free survival for ASCT versus no transplant of 51% versus 19% (hazard ratio, .38; 95% confidence interval, .24 to .62; $P < .0001$) and a 5-year second-line OS of 77% versus 59% (hazard ratio, .54, 95% confidence interval, .30 to .95; $P = .031$). Thus, ASCT is an effective treatment option for transplant-eligible patients with high-risk FL as identified by POD24 and should be evaluated in prospective clinical trials.

Jurinovic V, Biol Blood Marrow Transplant 2018

CIBMTR/NLCS study

Comparing 2 cohorts of patients aged ≤70 years with POD24 from the Center for International Blood and Marrow Transplant Research (CIBMTR) with AHCT and the National LymphoCare Study (NLCS)without AHCT

Among the entire CIBMTR cohort, no signif-i-cance difference in 5-year OS was seen in comparison to the NLCS cohort without AHCT.

A preplanned analysis restricted to patients undergoing AHCT within 12 months of first relapse demonstrated superior 5-year OS in comparison to the NLCS patients.

OS 5 yrs : 73% vs 60%, p=0.05.

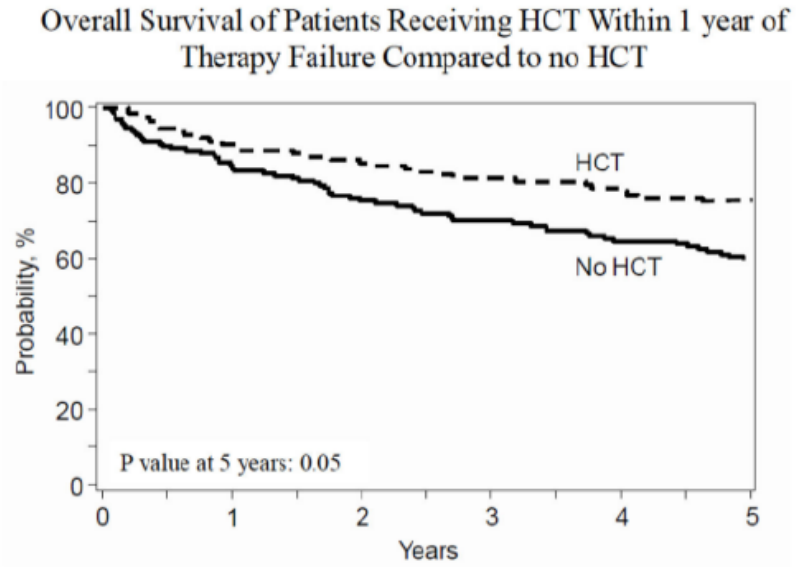


Figure 2.
Overall Survival for non-autoHCT cohort vs. autoHCT cohort patients receiving HCT within 1 year of ETF.

Casulo C, et al Biol Blood Marrow Transplant. 2018

Long-term follow-up demonstrates curative potential of autologo stem cell transplantation for relapsed follicular lymphoma

Robert Puckrin[1] | Neil Chua[2] | Kelly Chin[1] | Anthea Peters[2] | Peter Duggan[1] | Mona Shafey[1] | Jan Storek[1] | Kareem Jamani[1] | Carolyn Owen[1] | Douglas Stewart[1]

Received: 9 November 2022 | Accepted: 22 December 2022

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ORIGINAL PAPER

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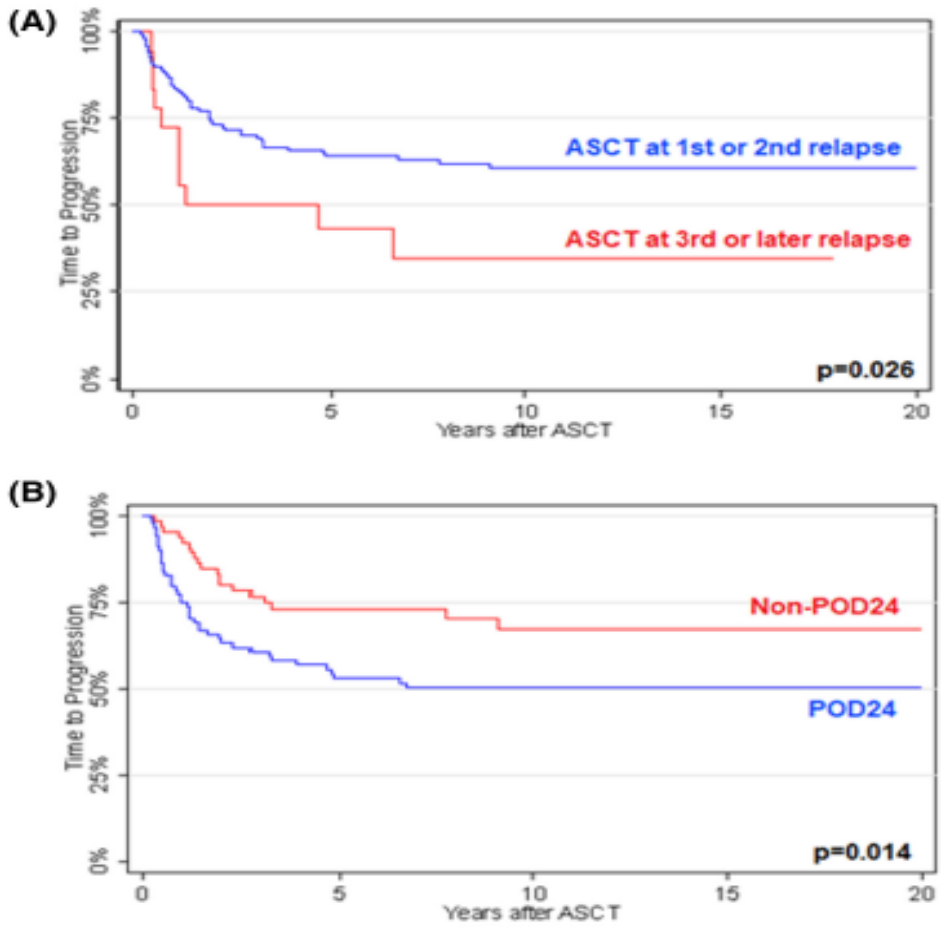


FIGURE 2 Time to progression by (A) timing of autologus stem cell transplantation (ASCT) and (B) progression of desease within 24 hours (POD24) status. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Causes of death of patients ($n = 49$)

Cause	No. of patients n (%)
Lymphoma	29 (5)
New malignancy	9 (18)
Infections	4 (8)
TRM before day +100	4 (8)
Cardiopulmonary disease	2 (4)
Dementia	1 (2)

Abbreviation: TRM, transplant-related mortality.

Final Clinical Practice Guidelines Consensus Statements for Transplantation and CAR T-Cell Therapy in Relapsed FL *(First Relapse Occurred Within Less Than 24 Months From Receiving Front Line Chemoimmunotherapy [POD24] and Without Evidence of Histological Transformation)*

ASTCT
American Society for Transplantation and Cellular Therapy

Question	Response* (N = 27)		Consensus Achieved†
	Agree N (%)	Disagree N (%)	
1. The panel **recommends** autologous transplant as an option for consolidation therapy in eligible, relapsed POD24 FL patients who have achieved complete or partial remission after second line therapies.	19 (70)	8 (30)	Yes
2. The panel **DOES NOT** recommend autologous transplant as consolidation therapy in eligible, relapsed FL patients who do not achieve complete or partial remission after second or subsequent line therapies.	26 (96)	1 (4)	Yes
3. The panel **DOES NOT** recommend allogeneic transplant as consolidation therapy in eligible, relapsed POD24 FL patients who have achieved complete or partial remission after second line therapies.	24 (89)	3 (11)	Yes
4. The panel **DOES NOT** recommend commercially available CAR T-cell therapy in eligible, relapsed FL patients who have achieved complete or partial remission after second line therapies.	21 (78)	6 (22)	Yes
5. The panel **considers** CAR T-cell therapy as a treatment option for patients who did not achieve complete or partial remission after second or subsequent line therapies.	26 (96)	1 (4)	Yes

Transplantation and Cellular Therapy 30 (2024) 832–843

Abbreviations: FL-follicular lymphoma, CAR-chimeric antigen receptor

* Statistical expert Dr. Ambuj Kumar did not participate in the voting process.

† A specific statement was defined as having achieved formal consensus, if >70% of the panel members voted to agree with the proposed statement

Clinical Guideline Recommendations for Third-line Relapsed Follicular Lymphoma

Chemo-IO or IMiD Therapy

- ***Preferred***
  - Lenalidomide + rituximab
  - Chemotherapy* + anti-CD20 mAb†
- ***Other***
  - Lenalidomide + obinutuzumab
  - Anti-CD20 mAb†
  - Lenalidomide‡
- ***Older Patients or Infirm***
  - Rituximab (preferred)
  - Chemotherapy§ ± rituximab

Small Molecule Inhibitor

- ***EZH2 inhibitor***
  - Tazemetostat (regardless of *EZH2*)

T-Cell–Mediated Therapy

- ***Anti-CD19 CAR T-Cell Therapy***
  - Axicabtagene ciloleucel
  - Tisagenlecleucel
- ***Bispecific T-Cell Engager Therapy***
  - Mosunetuzumab-axgb

*Bendamustine, CHOP, or CVP. †Rituximab or obinutuzumab. ‡If not a candidate for anti-CD20 mAb. §Chlorambucil or cyclophosphamide.

NCCN. Clinical practice guidelines in oncology: B-cell lymphomas. v6.2023.

Slide credit: clinicaloptions.com

Hematological ONCOLOGY

SUPPLEMENT ABSTRACTS | Free Access

ZANUBRUTINIB PLUS OBINUTUZUMAB VERSUS OBINUTUZUMAB IN PATIENTS WITH RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA: UPDATED ANALYSIS OF THE ROSEWOOD STUDY

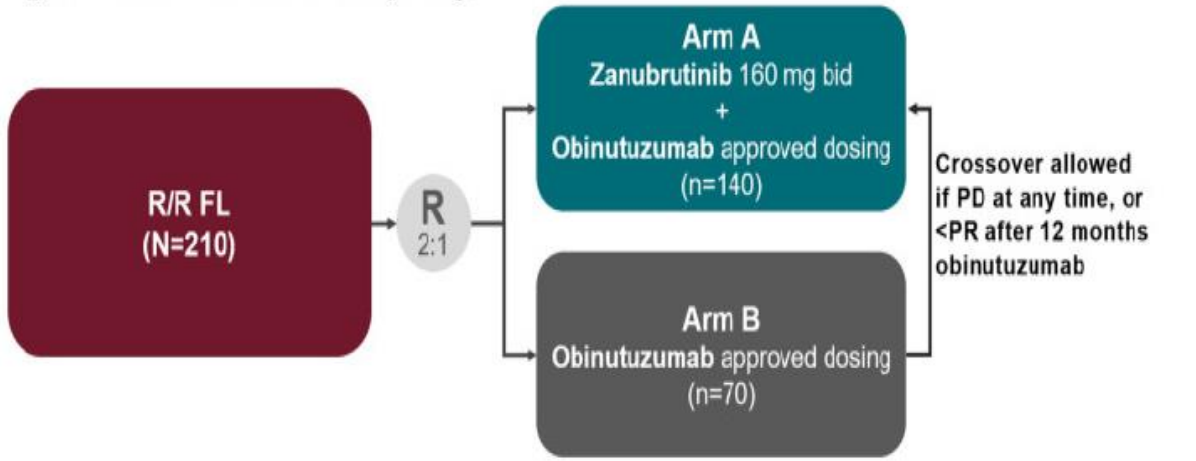
P. L. Zinzani, J. Mayer, J. Trotman, F. Bijou, A. C. de Oliveira, Y. Song, Q. Zhang, M. Merli, K. Bouabdallah, P. S. Ganly, H. Zhang, R. Johnson, A. M. Garcia-Sancho, M. Provencio Pulla, M. Trněný ... See all authors

First published: 09 June 2023 | https://doi.org/10.1002/hon.3163_81

Key eligibility criteria
- Age ≥18 years
- Grade 1-3A R/R FL
- Previous treatment with ≥2 lines of therapy, including an anti-CD20 antibody and an alkylating agent
- Measurable disease
- ECOG PS of 0-2
- Adequate organ function
- No prior BTK inhibitor

ZANUBRUTINIB + OBINUTUZUMAB

Figure: Phase 2 ROSEWOOD Study Design



bid, twice daily; FL, follicular lymphoma; PD, progressive disease; PR, partial response; R, randomized; R/R, relapsed/refractory.

Efficacy

- At the median study follow-up of 20.2 months, the difference in the ORR by independent review committee (IRC) was 22.7% (95% CI, 9.0%-36.5%) in favor of zanubrutinib plus obinutuzumab (**Table 2**)

Table 2. Efficacy Outcomes

Endpoint	Zanubrutinib + obinutuzumab (n=145)	Obinutuzumab (n=72)	2-sided *P* value
ORR by IRC (95% CI), %	69.0 (60.8-76.4)	45.8 (34.0-58.0)	.0012
CR	39.3	19.4	.0035
PR	29.7	26.4	–
DOR by IRC			
Median (95% CI), mo	NE (25.3-NE)	14.0 (9.2-25.1)	–
18-month DOR rate (95% CI), %	69.3 (57.8-78.2)	41.9 (22.6-60.1)	–
DOCR by IRC			
Median (95% CI), mo	NE (26.5-NE)	26.5 (2.7-NE)	–
18-month DOCR rate (95% CI), %	87.4 (73.8-94.2)	51.1 (21.0-74.9)	–

DOCR, duration of complete response; NE, not estimable.

- Across prespecified subgroups of patients, zanubrutinib plus obinutuzumab showed consistent benefit over obinutuzumab (**Figure 3**)

Hematological ONCOLOGY

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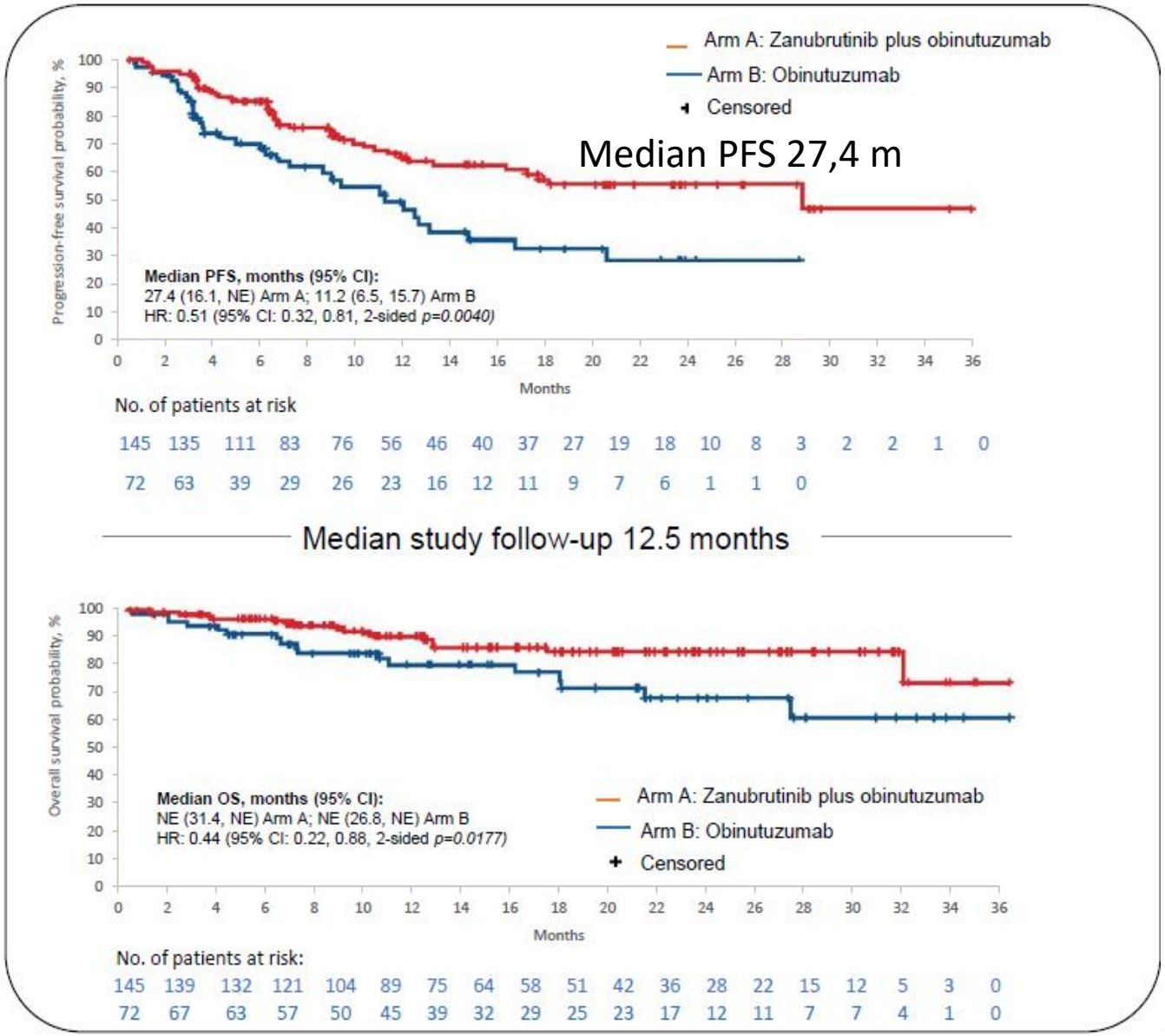
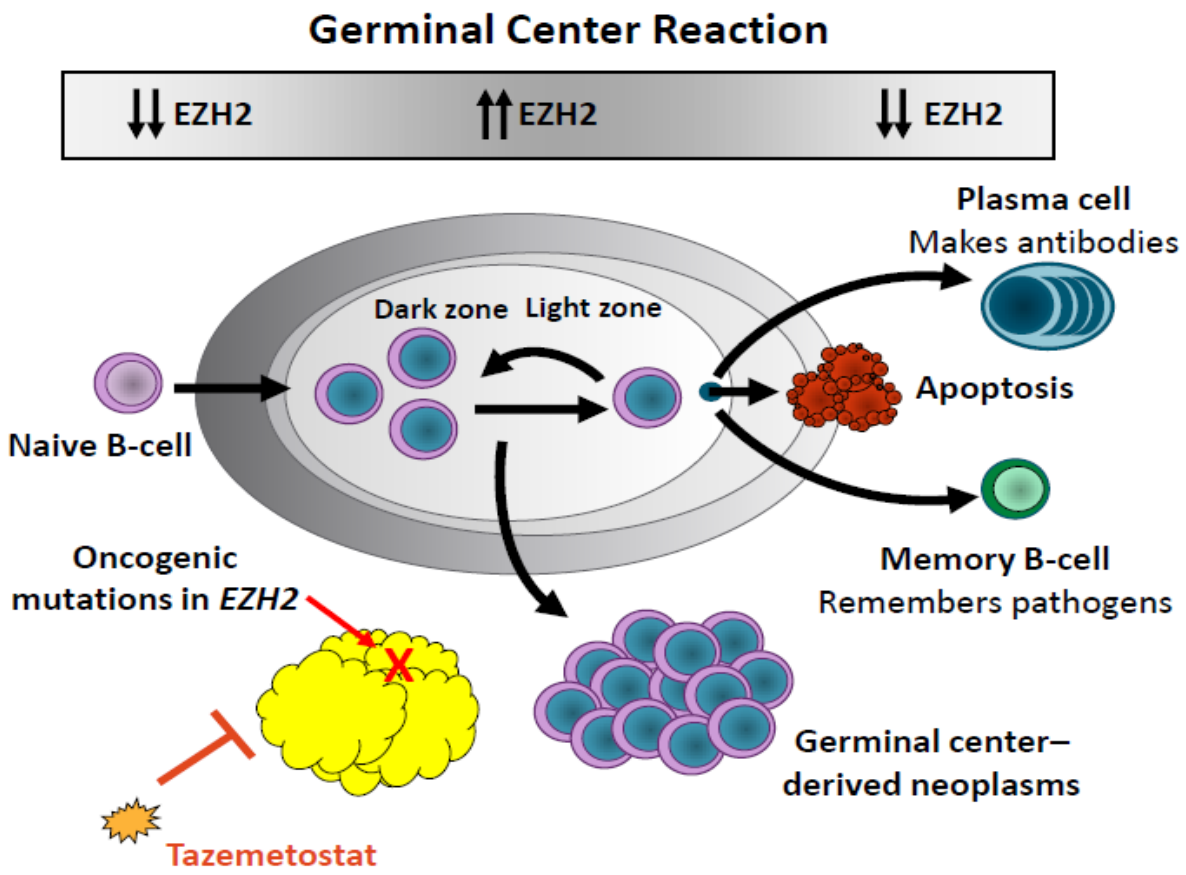
- Across prespecified subgroups of patients, zanubrutinib plus obinutuzumab showed consistent benefit over obinutuzumab (**Figure 3**)



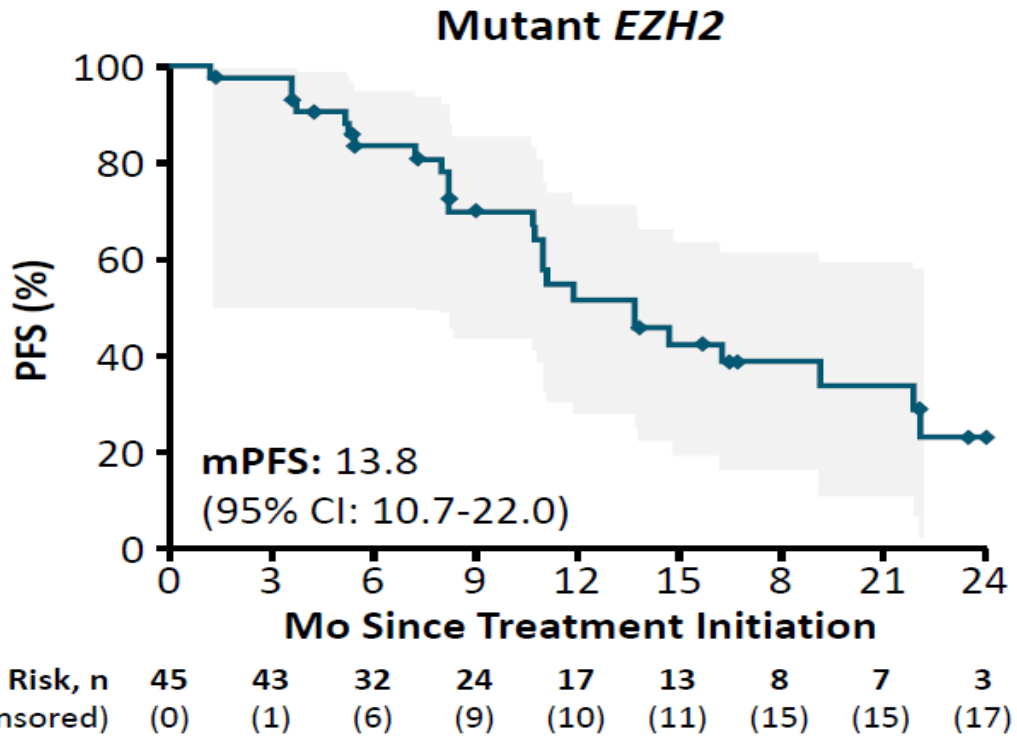
Slide credit: clinicaloptions.com

Tazemetostat: *EZH2* Inhibitor in FL

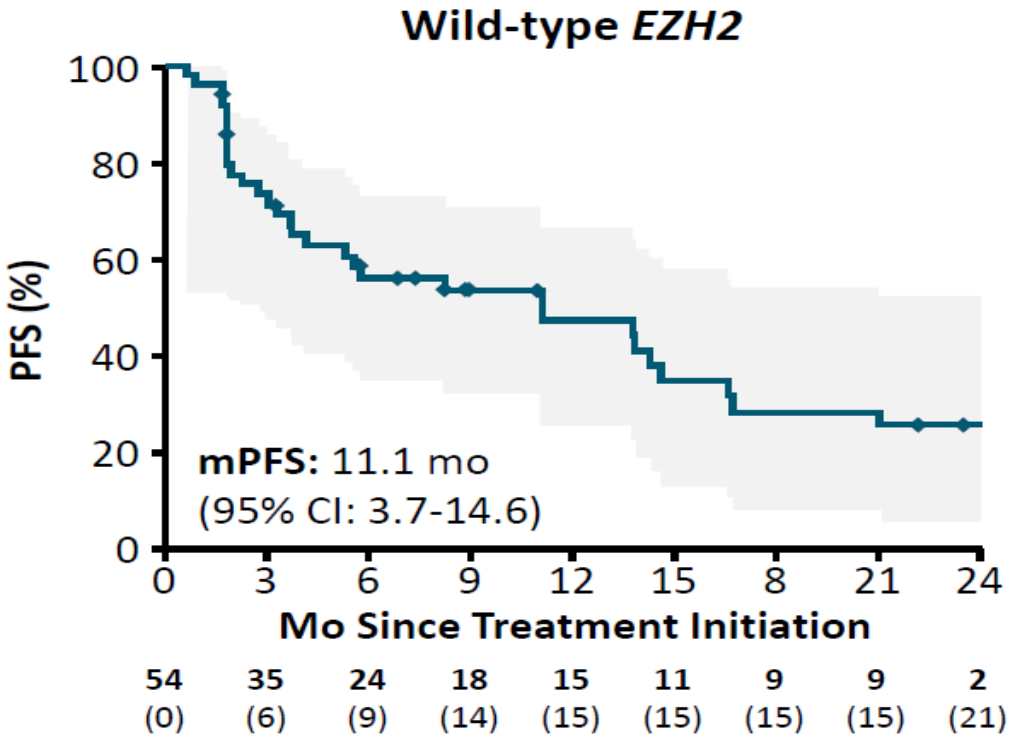
- In normal B-cell biology, EZH2 regulates germinal center formation[1]
- *EZH2* mutations can lead to oncogenic transformation by locking B-cells in germinal state and preventing terminal differentiation[1]
- *EZH2*-activating mutations found in ~25% of patients with FL[2]
- **Tazemetostat:** selective, oral, first-in-class EZH2 inhibitor[3]
- Whether WT or mutant, *EZH2* biology relevant to FL



Tazemetostat Phase II Study: PFS (by IRC)



Patients at Risk, n (number censored)	45 (0)	43 (1)	32 (6)	24 (9)	17 (10)	13 (11)	8 (15)	7 (15)	3 (17)



Patients at Risk, n (number censored)	54 (0)	35 (6)	24 (9)	18 (14)	15 (15)	11 (15)	9 (15)	9 (15)	2 (21)

Morschhauser. Lancet Oncol. 2020;21:1433.

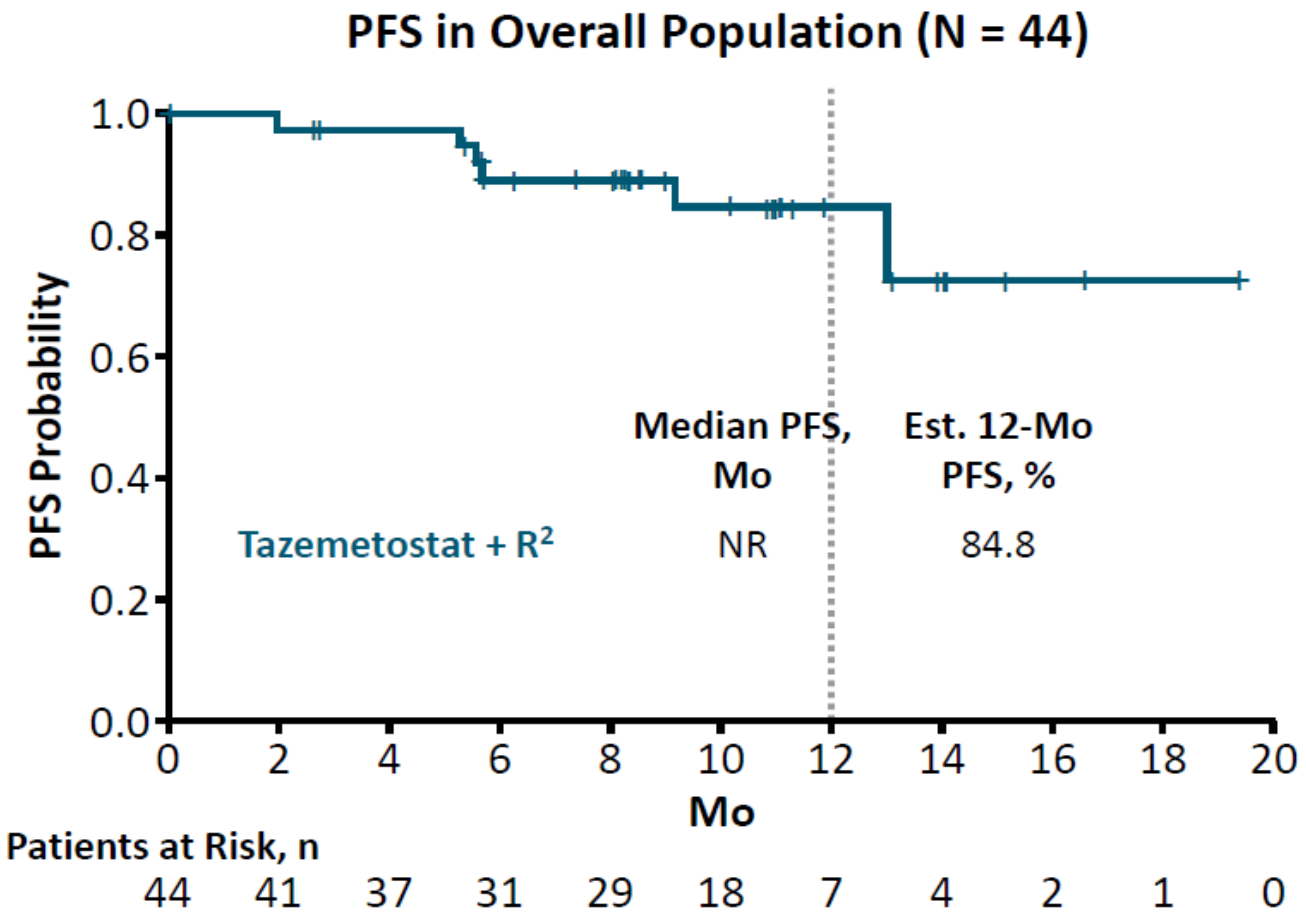
Slide credit: clinicaloptions.com

SYMPHONY-1: Tazemetostat + R^2 in R/R FL

- Phase Ib study anticipating randomized R^2 ± tazemetostat phase III trial
  - 83.3 % *EZH2* wild-type
  - No dose-limiting toxicities → recommended phase III dose is 800 mg BID

Response	Tazemetostat + R^2 (n = 41)
ORR, n (%)	40 (97.6)
▪ CR	21 (51.2)
Median DoR, mo	NR

- Most common toxicities: GI, headache, musculoskeletal, cytopenias (*similar to known profiles*)



Batlevi. ASH 2022. Abstr 954.

Slide credit: clinicaloptions.com

Clinical Guideline Recommendations for Third-line Relapsed Follicular Lymphoma

Chemo-IO or IMiD Therapy

- ***Preferred***
  - Lenalidomide + rituximab
  - Chemotherapy* + anti-CD20 mAb†
- ***Other***
  - Lenalidomide + obinutuzumab
  - Anti-CD20 mAb†
  - Lenalidomide‡
- ***Older Patients or Infirm***
  - Rituximab (preferred)
  - Chemotherapy§ ± rituximab

Small Molecule Inhibitor

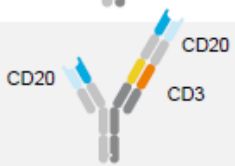
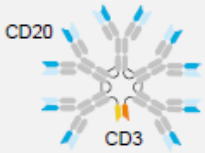
- ***EZH2 inhibitor***
  - Tazemetostat (regardless of *EZH2*)

T-Cell–Mediated Therapy

- ***Anti-CD19 CAR T-Cell Therapy***
  - Axicabtagene ciloleucel
  - Tisagenlecleucel
- ***Bispecific T-Cell Engager Therapy***
  - Mosunetuzumab-axgb

*Bendamustine, CHOP, or CVP. †Rituximab or obinutuzumab. ‡If not a candidate for anti-CD20 mAb. §Chlorambucil or cyclophosphamide.

Characteristics of bispecific antibodies

Product name	Schematic depiction	Format	Technology	CD20:CD3 ratio	CD3 clone	CD20 clone	Fc silencing mutations*
Mosunetuzumab		IgG1	Knobs-into-holes (different Fabs)	1:1	UCHT1v9 (CD3δε)	2H7 (type 1 epitope, identical to rituximab)	N297G (no FcγR binding)
Glofitamab		IgG1	Head-to-tail fusion	2:1	SP34-der.(CD3ε)	By-L1 (type 2 epitope, identical to obinutuzumab)	IgG1-P329G-LALA (no FcγR binding)
Epcoritamab		IgG1	Controlled Fab-arm exchange	1:1	huCACAO (SP34-der.)(CD3ε)	7D8 (type 1 epitope, shared by ofatumumab)	L234F, L235E, D265A (no FcγR,C1q binding)
Odronextamab		IgG4	Heavy chains with different affinity	1:1	REG1250 (CD3δε)	3B9-10 (type 1 epitope, shared by ofatumumab)	Modified IgG4 (no FcγRIII binding)
Plamotamab		IgG1	Fab-Fc x scFv-Fc	1:1	α-CD3_H1.30 (SP34-der.)(CD3ε)	C2B8_H1_L1 (type 1 epitope, shared by rituximab)	G236R, L328R (no FcγR binding)
IgM 2323		IgM	IgM + modified J chain	10:1	Not reported	Not reported	No

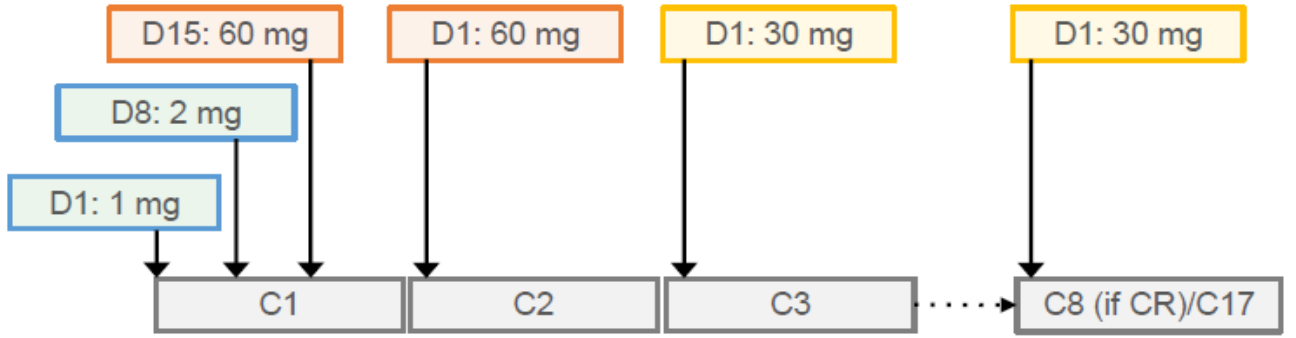
*These Fc-silencing mutations do not abolish the binding of bsAb to neonatal FcR

Mod. da Falchi L, et al. Blood 2023; 141: 467–480

Different Strategies for the Administration of BsAbs in FL

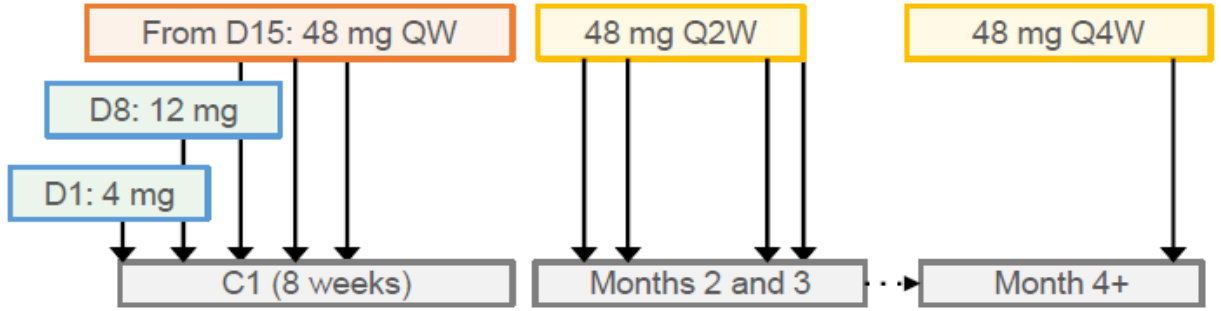
Mosunetuzumab

- IV mosunetuzumab administered weekly during C1 and then in 21-day cycles
- Step-up dosing in C1
- Fixed-duration treatment
- No mandatory hospitalization



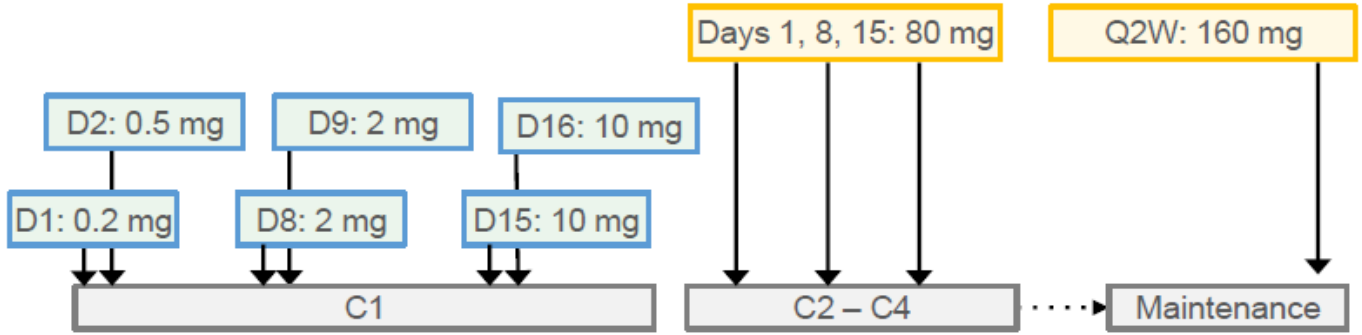
Epcoritamab

- SC epcoritamab administered weekly for 8 weeks then monthly
- Step-up dosing in C1 (4, 12, 48 mg)
- Treatment until progression
- Steroid prophylaxis
- Hospitalization at D15



Odronextamab

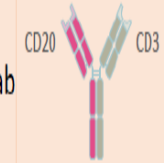
- IV odronextamab administered
- This was modified to 0.7/4/20 mg during C1 to further mitigate the risk of CRS
- Treatment until progression
- 48-hour hospital admission required at each split until nominal dose achieved



BsAb, bispecific antibody; C, cycle; CRS, cytokine release syndrome; D, day; FL, follicular lymphoma; IV, intravenous; Q2W, every 2 weeks; Q4W, every 4 weeks; QW, every week; SC, subcutaneous.

Adapted from: 1. Dreyling M, et al. *J Clin Oncol*. 2017;35(35):3898-3905. 2. Budde LE, et al. *Lancet Oncol*. 2022;23(8):1055-1065. 3. Kim T-M, et al. Presented at: ASH 2022.

Mosunetuzumab in relapsed/refractory follicular lymphoma

Mosunetuzumab		IgG1	Knobs-into-holes (different Fabs)

APPROVED FDA APPROVED EUROPEAN MEDICINES AGENCY APPROVED AIFA

Study overview

Single-arm, pivotal phase II expansion in patients with R/R FL and ≥2 prior therapies

Key inclusion criteria

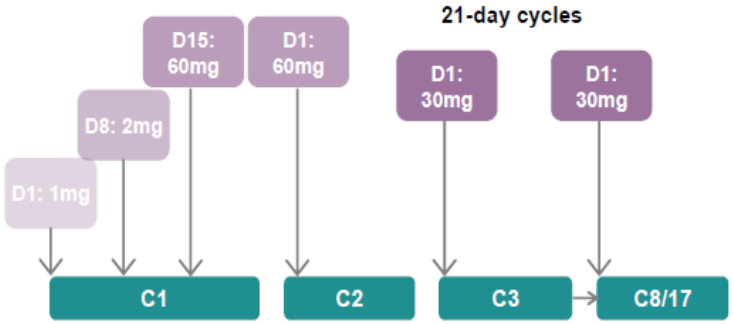
- FL (Gr 1–3a)
- ECOG PS 0-1
- ≥2 prior regimens, including
  - ≥1 anti-CD20 antibody
  - ≥1 alkylating agent

Endpoints

- Primary: CR (best response) rate by IRF* - assessed vs 14% historical control CR rate
- Secondary: ORR, DOR, PFS, safety and tolerability

Mosunetuzumab administration

- Q3W intravenous administration
- C1 step-up dosing for CRS mitigation
- **Fixed duration treatment**
  - 8 cycles if CR after C8
  - 17 cycles if PR/SD after C8
- **No mandatory hospitalization**



n, unless stated	N=90
Median age, years (range)	60 (29–90)
Male	55 (61%)
ECOG PS	
0	53 (59%)
1	37 (41%)
Ann Arbor stage	
I/II	21 (23%)
III/IV	69 (77%)
Median lines of prior therapy, (range)	3 (2–10)
Prior autologous stem cell transplant	28 (31%)
Refractory to last prior therapy	62 (69%)
Refractory to any prior anti-CD20 therapy	71 (79%)
POD24	47 (52%)
Double refractory to prior anti-CD20 and alkylator therapy	48 (53%)

Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study

Lihua E Budde, Laurie H Sehn, Matthew Matasar, Stephen J Schuster, Sarit Assouline, Pratyush Giri, John Kuruvilla, Miguel Canales, Sascha Dietrich, Keith Fay, Matthew Ku, Loretta Nastoupil, Chan Yoon Cheah, Michael C Wei, Shen Yin, Chi-Chung Li, Huang Huang, Antonia Kwan, Elicia Penuel, Nancy L Bartlett

Lancet Oncol 2022; 23: 1055–65

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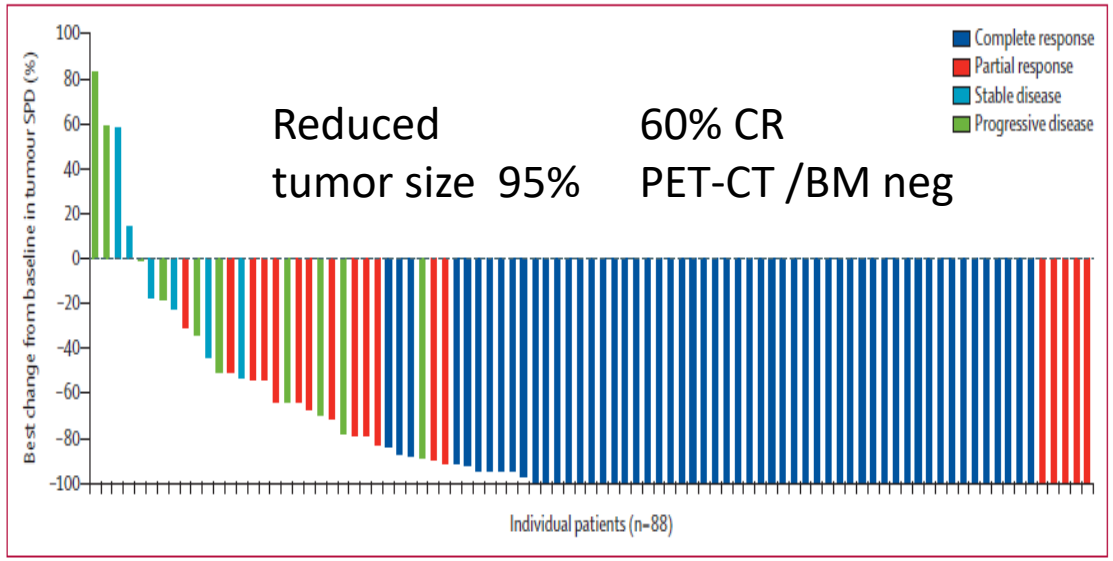
Median follow up 18 m

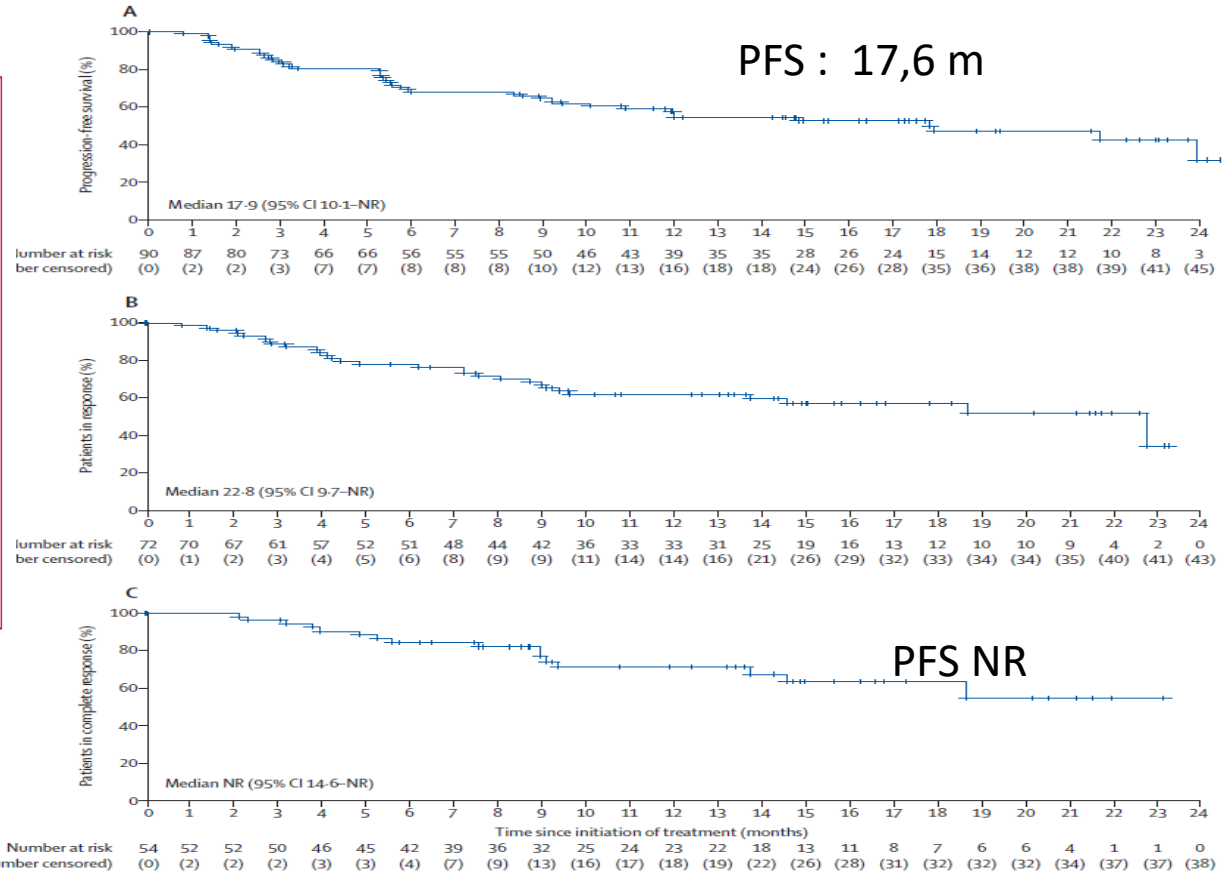


Reduced tumor size 95%

60% CR
PET-CT /BM neg

Figure 2: Waterfall plot of best percentage change in SPD
SPD=sum of the products of diameters.

Median number of cicles 8



PFS : 17,6 m

PFS NR

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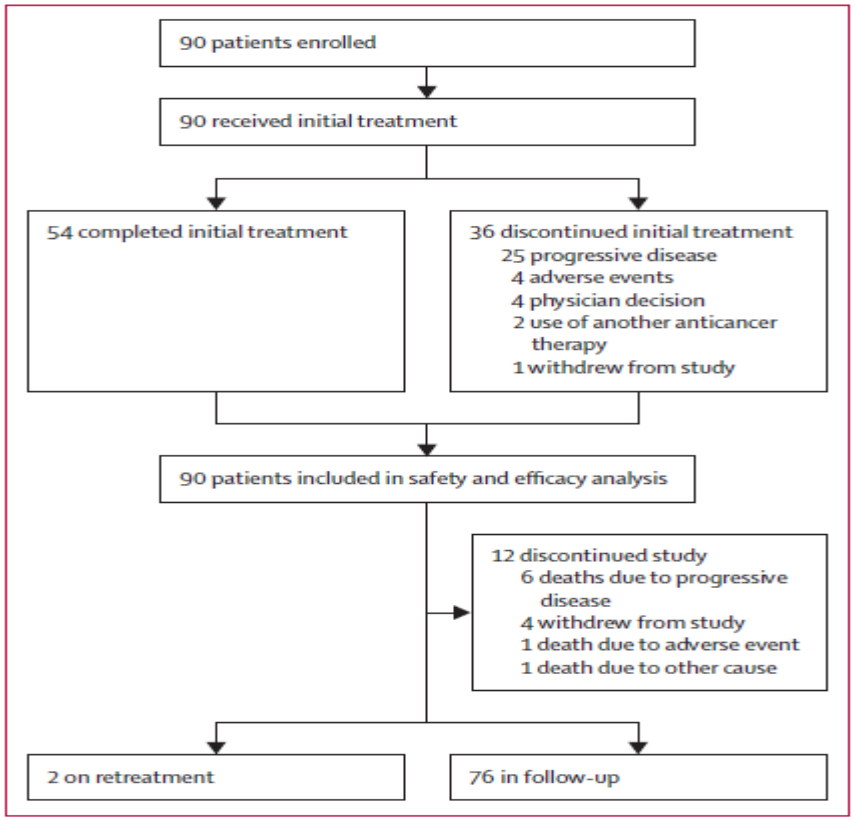


	Grade 1–2	Grade 3	Grade 4
Cytokine release syndrome	38 (42%)	1 (1%)	1 (1%)
Fatigue	33 (37%)	0	0
Headache	27 (30%)	1 (1%)	0
Neutropenia or decreased neutrophil count	2 (2%)	12 (13%)	12 (13%)
Pyrexia	25 (28%)	1 (1%)	0
Hypophosphataemia	9 (10%)	15 (17%)	0
Pruritus	19 (21%)	0	0
Hypokalaemia	15 (17%)	2 (2%)	0
Cough	16 (18%)	0	0
Constipation	16 (18%)	0	0
Diarrhoea	15 (17%)	0	0
Nausea	15 (17%)	0	0
Rash	13 (14%)	1 (1%)	0
Dry skin	14 (16%)	0	0
Anaemia	5 (6%)	7 (8%)	0
Chills	11 (12%)	1 (1%)	0
Hypomagnesaemia	11 (12%)	0	0
Increased alanine aminotransferase	6 (7%)	4 (4%)	1 (1%)
Insomnia	11 (12%)	0	0
Arthralgia	10 (11%)	0	0
Peripheral oedema	10 (11%)	0	0
Abdominal pain	8 (9%)	1 (1%)	0
Back pain	8 (9%)	1 (1%)	0
Dizziness	9 (10%)	0	0
Urinary tract infection	8 (9%)	1 (1%)	0
Skin exfoliation	9 (10%)	0	0
Thrombocytopenia or decreased platelet count	5 (6%)	0	4 (4%)

Data are n (%). Data are for all exposed patients (n=90) and the most common adverse events occurring in 10% or more of patients with one or more adverse events. No treatment-related grade 5 adverse events occurred.

Table 3: **Treatment-emergent adverse events**

Phase Ib/II Study: Mosunetuzumab + Lenalidomide in R/R FL

- Multicenter, open-label phase Ib/II study
  - Current analysis reports initial data from phase Ib (median follow-up: 5.4 mo)

Adults with CD20+ R/R FL (grades 1-3a) after ≥1 prior CIT regimen, including an anti-CD20 mAb; prior lenalidomide allowed; ECOG PS ≤2 (planned N = 169)

→

Cycle 1*: Step-up Dosing	Cycles 2-12
Mosunetuzumab IV D1: 1 mg > D8: 2 mg > D15: 30 mg (21-day cycle)	**Mosunetuzumab** 30 mg IV D1 + **Lenalidomide** 20 mg PO QD D1-21 (28-day cycle)

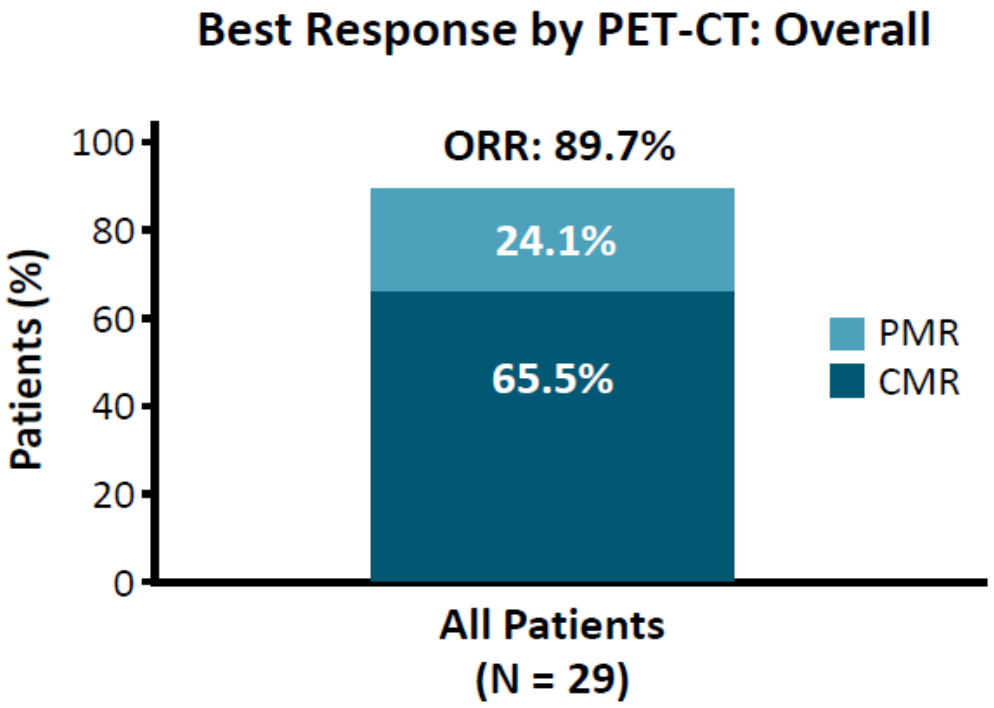
No mandatory hospitalization for treatment administration

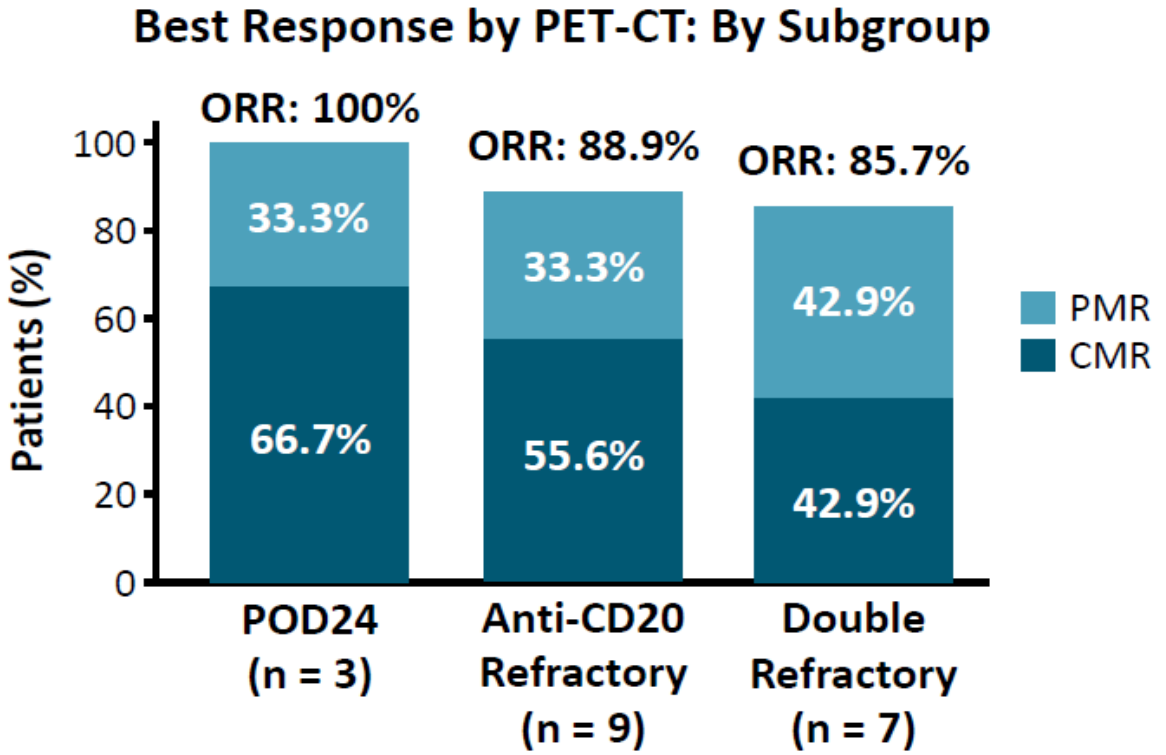
- **Primary endpoint:** safety/tolerability
- **Secondary endpoints:** efficacy (CR, ORR, DoR, DoCR), PK

Morschhauser. ASH 2021. Abstr 129. NCT04246086.

Slide credit: clinicaloptions.com

Phase Ib/II Study: Response With Mosunetuzumab + Lenalidomide in R/R FL





- Median time to first/best response: 2.5 mo (range: 1.4-5.3)/2.5 mo (range: 1.4-10.7)
- High ORR and CMR rate in overall population, including those with high-risk disease

Morschhauser. ASH 2021. Abstr 129. (Update: Morschhauser. ASH 2023. Abstr 605.)

Slide credit: clinicaloptions.com

CELESTIMO: Mosunetuzumab + Lenalidomide vs R² in R/R FL

- Multicenter, open-label, randomized phase III trial

Stratified by POD24 (yes v no), prior tx lines (1 v ≥2), refractory to anti-CD20 (yes v no)

Adults with R/R CD20+ FL (grade 1-3a) previously treated with ≥1 prior systemic tx (including prior IO or CIT); ECOG PS 0-2 (Planned N = 474)

	Cycle 1 (Step-up Dosing)	Cycles 2-12
	Mosunetuzumab IV D1: 1 mg, D8: 2 mg, D15: 30mg	**Mosunetuzumab** 30 mg IV D1 + **Lenalidomide** 20 mg D1-21
	Rituximab 375 mg/m² IV* + **Lenalidomide** 20 mg PO†	

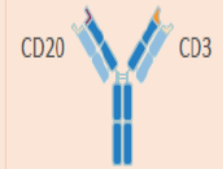
28-day cycles. *D1, D8, D15, D22 in cycle 1. D1 in cycles 3, 5, 7, 9, 11. †Day 1-21 in cycles 1-12.

- **Primary endpoint:** PFS by IRC
- **Secondary endpoints:** PFS by inv, ORR, CR, DoR, OS, safety, PRO

Nastoupil. ASCO 2022. Abstr TPS7588. NCT04712097.

Slide credit: clinicaloptions.com

EPCORE NHL-1: Epcoritamab in R/R B-Cell NHL

Epcoritamab		IgG1	Controlled Fab-arm exchange

- Phase I/II open-label, dose escalation/expansion study

Patients with R/R CD20+ B-cell NHL after ≥2 previous lines of tx and ≥1 anti-CD20 mAb; ECOG PS 0-2; FDG PET-avid; measurable disease by CT/MRI; previous CAR T-cell therapy allowed (planned N = 700)

→

Cycle 1 Step-Up Dosing*

Epcoritamab SC
D1: 0.16 mg
D8: 0.8 mg
D15: 48 mg
D22: 48 mg

*With corticosteroid prophylaxis. To mitigate CRS.

→

Epcoritamab 48 mg SC in 28-day cycles
QW cycles 2-3,
Q2W cycles 4-9,
Q4W cycles 10+

→ *Until PD or unacceptable toxicity*

FL (grade 1-3A) cohort, n = 128
Median lines of tx:
3 (range: 2-9);
31% with ≥4
POD24: 42%

122 cases

- **Primary endpoint:** ORR by IRC
- **Secondary endpoints:** DoR, TTR, PFS, OS, CR rate, safety

Linton. ASH 2023. Abstr 1655. NCT03625037.

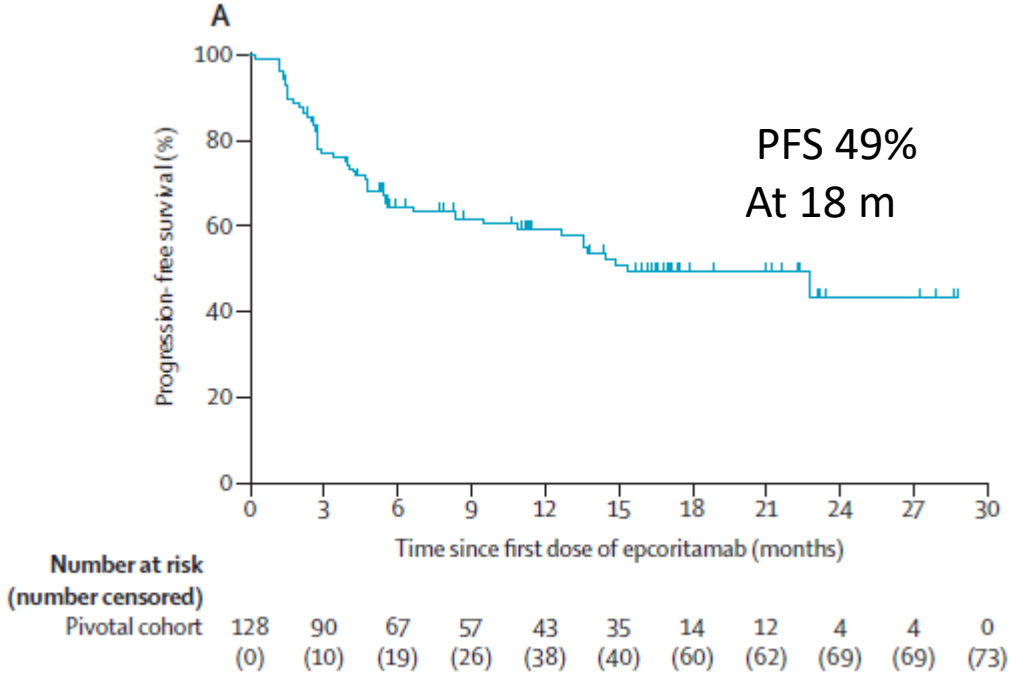
Slide credit: clinicaloptions.com

Epcoritamab monotherapy in patients with relapsed or refractory follicular lymphoma (EPCORE NHL-1): a phase 2 cohort of a single-arm, multicentre study

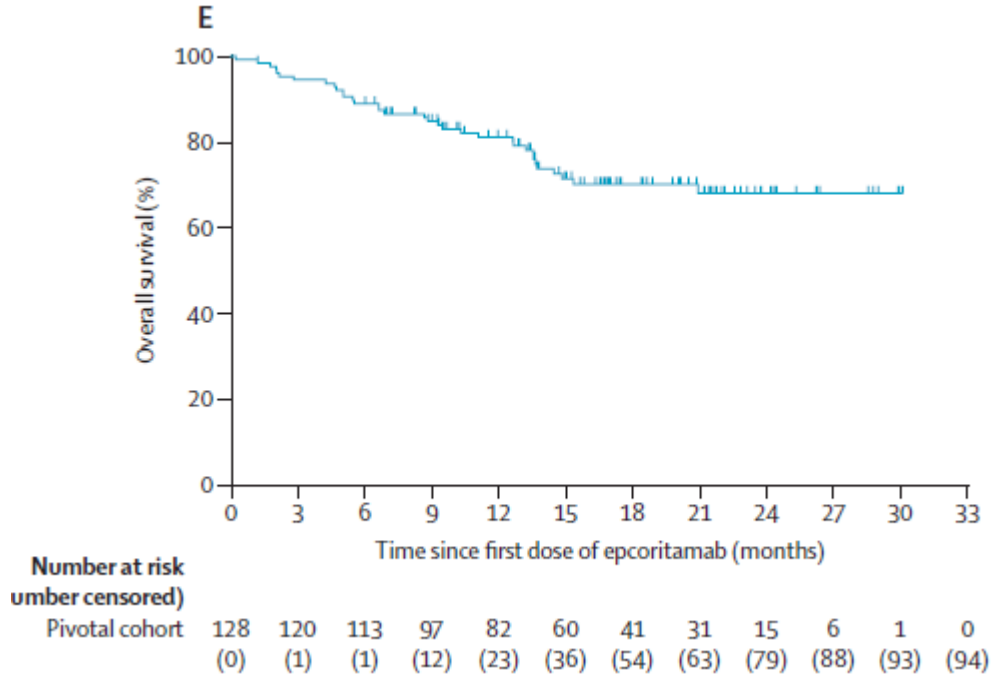
Lancet Haematol 2024; 11: e593–605

Kim M Linton, Umberto Vitolo, Wojciech Jurczak, Pieternella J Lugtenburg, Emmanuel Gyan, Anna Sureda, Jacob Haaber Christensen, Brian Hess, Hervé Tilly, Raul Cordoba, David John Lewis, Craig Okada, Martin Hutchings, Michael Roost Clausen, Juan-Manuel Sancho, Tara Cochrane, Sirpa Leppä, Martine E D Chamuleau, Diana Gernhardt, Işıl Altıntaş, Yan Liu, Tahamtan Ahmadi, Minh H Dinh, Daniela Hoehn, Elena Favaro, Brian Elliott, Catherine Thieblemont, Julie M Vose

At median FU of 17 m, 34% of 128 cases remained in treatment



PFS 49%
At 18 m



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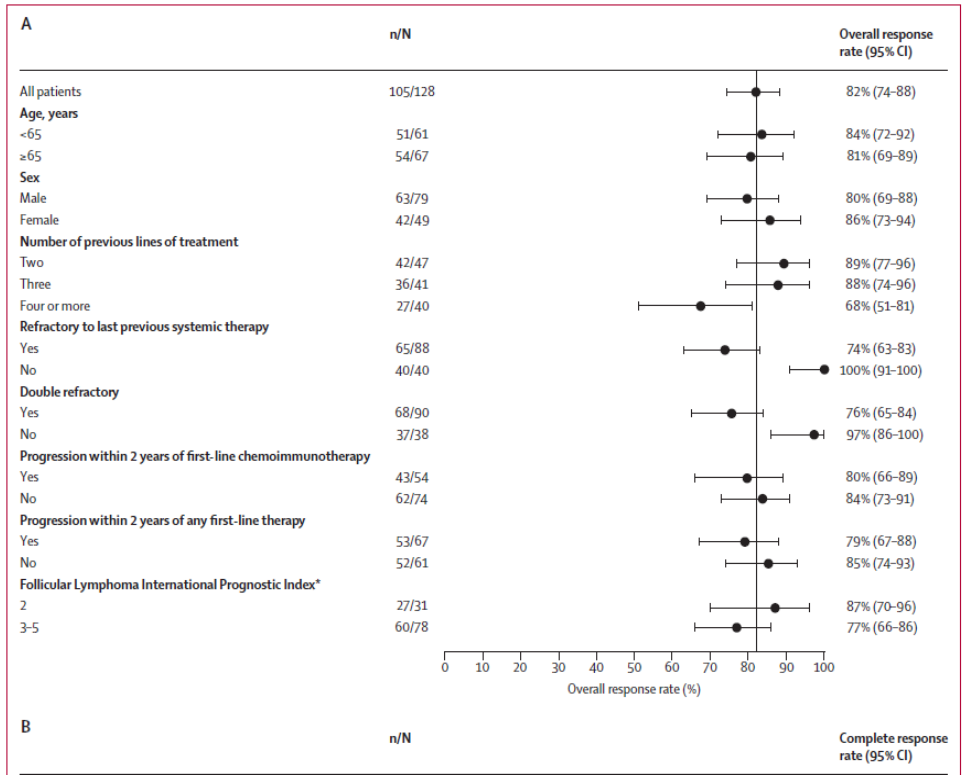
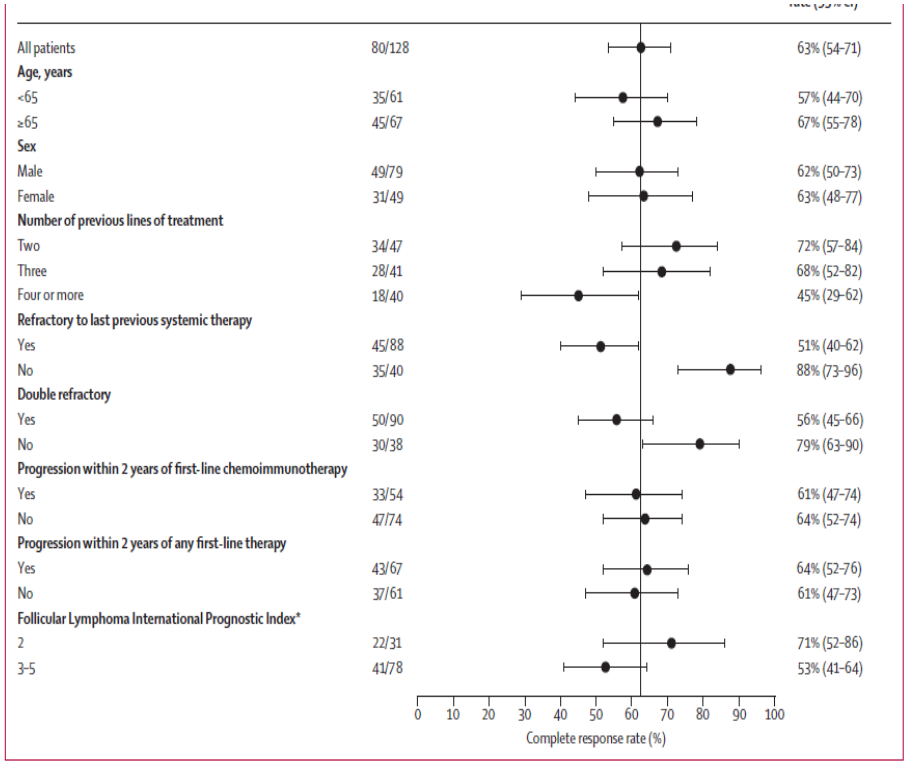
OS (82%) FU 17 m



CR (63%)

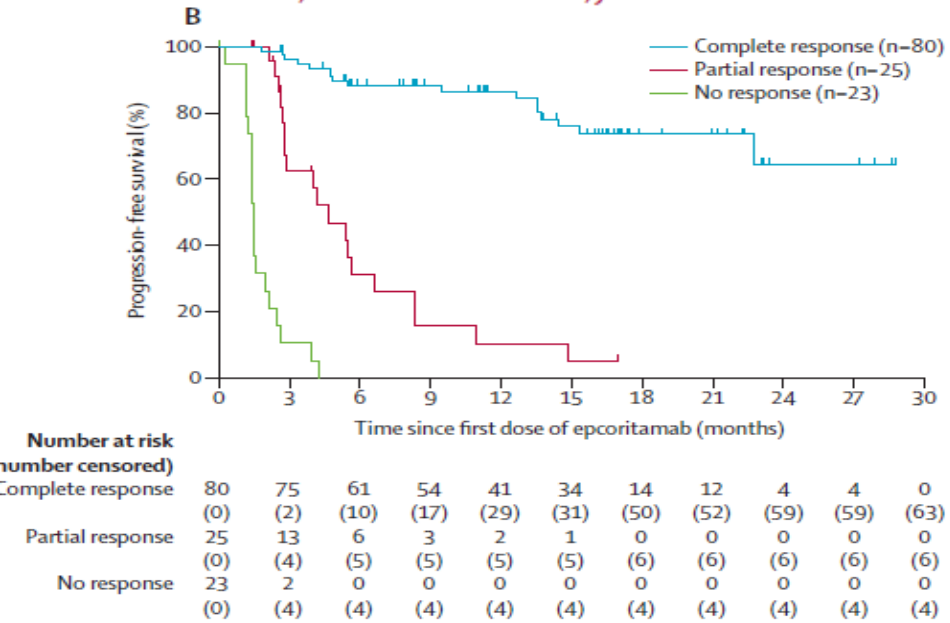


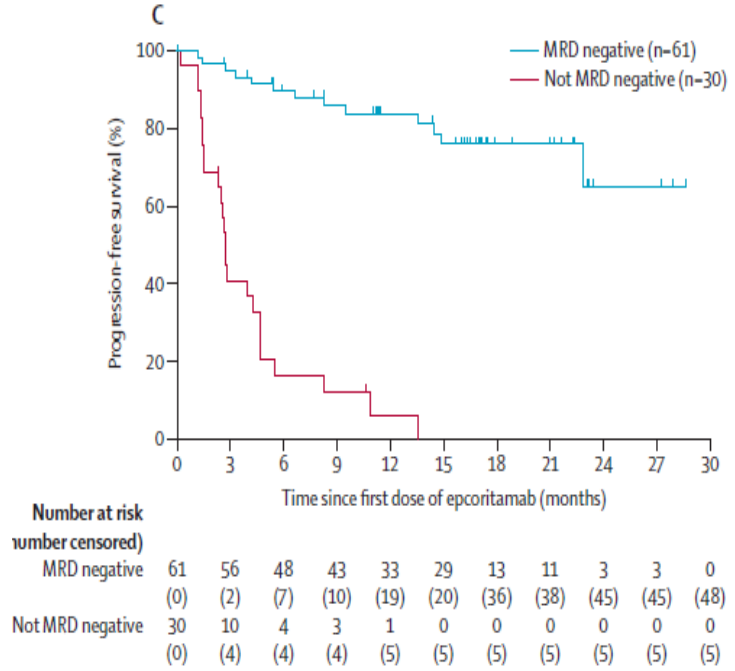
Subgroup analysis

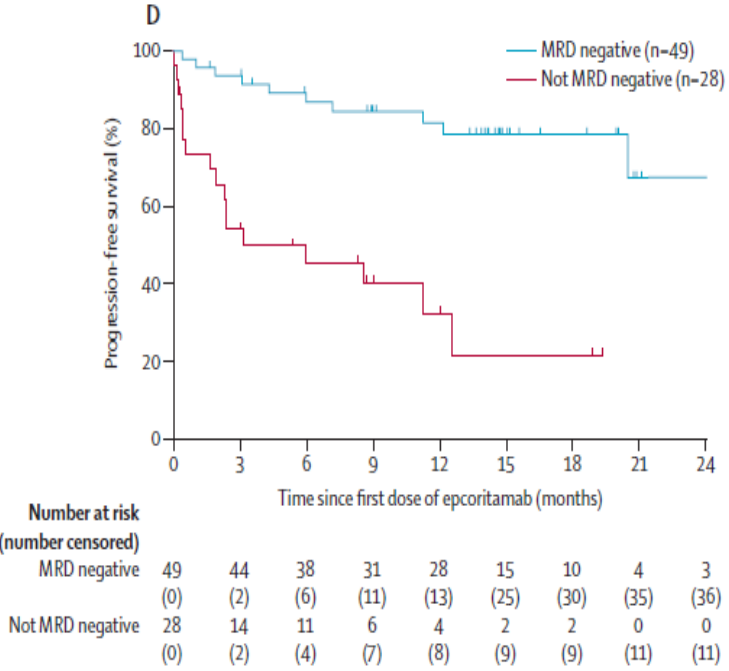
Epcoritamab monotherapy in patients with relapsed or refractory follicular lymphoma (EPCORE NHL-1): a phase 2 cohort of a single-arm, multicentre study

Lancet Haematol 2024; 11: e593–605

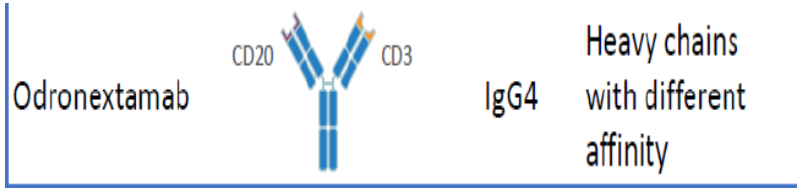
Kim M Linton, Umberto Vitolo, Wojciech Jurczak, Pieternella J Lugtenburg, Emmanuel Gyan, Anna Sureda, Jacob Haaber Christensen, Brian Hess, Hervé Tilly, Raul Cordoba, David John Lewis, Craig Okada, Martin Hutchings, Michael Roost Clausen, Juan-Manuel Sancho, Tara Cochrane, Sirpa Leppä, Martine E D Chamuleau, Diana Gernhardt, Işıl Altıntaş, Yan Liu, Tahamtan Ahmadi, Minh H Dinh, Daniela Hoehn, Elena Favaro, Brian Elliott, Catherine Thieblemont, Julie M Vose







ELM-2: Odronextamab Monotherapy in R/R FL



- Multicohort, open-label phase II study in R/R B-cell NHL
  - Current analysis reports FL cohort
  - Other disease-specific cohorts include DLBCL, MCL, MZL, other B-cell NHL subtypes

Adults with R/R FL (grades 1-3a) after ≥2 prior systemic tx including ≥1 anti-CD20 mAb and ≥1 alkylating agent; ECOG PS ≤1 (N = 131)

Cycle 1:* Step-up Dosing†‡	Cycle 2-4*	Cycles 5+:* Maintenance
Odronextamab IV D1,2: 0.7 mg > D8,9: 4 mg > D15,16: 20 mg	**Odronextamab** IV 80 mg D1, D8, D15	**Odronextamab** IV 160 mg Q2W

→ *Until PD or unacceptable toxicity*

*21-day cycles. †Cycle 1 step-up dosing at study initiation was 1/20/80 mg but was modified to further mitigate CRS risk.
‡Each step-up dose delivered as split infusions and is accompanied with premedication to further mitigate CRS risk.

- **Primary endpoint:** ORR by ICR per Lugano criteria
- **Secondary endpoints:** ORR by investigator, CR rate, DoR, PFS, OS, safety/tolerability

Kim. ASH 2022. Abstr 949. NCT03888105.

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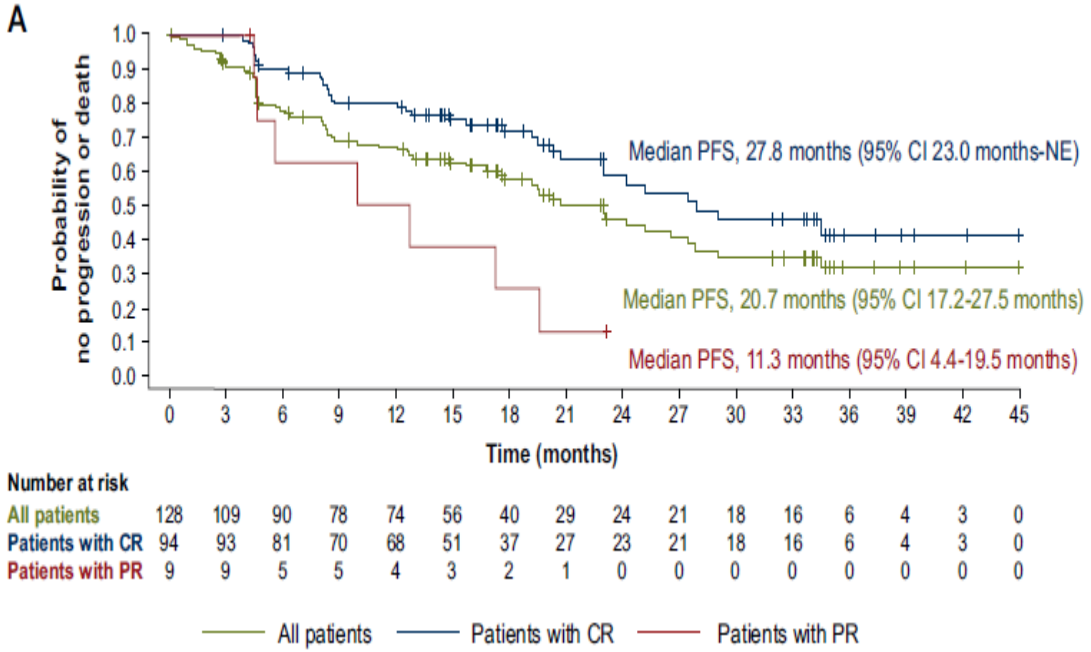
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

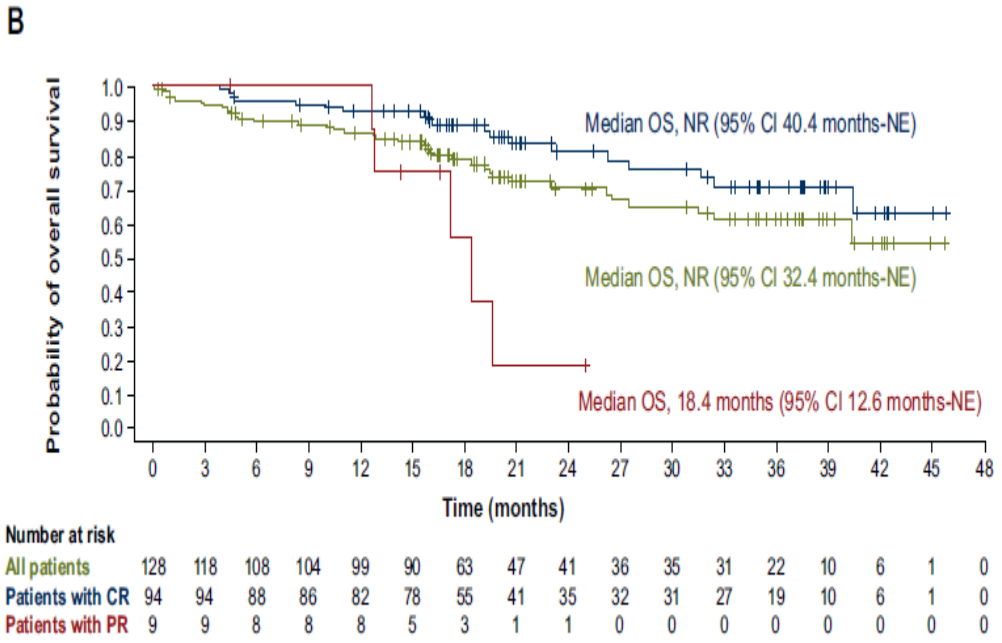
ESMO ANNALS OF ONCOLOGY DRIVING INNOVATION IN ONCOLOGY

ORIGINAL ARTICLE

Safety and efficacy of odronextamab in patients with relapsed or refractory follicular lymphoma☆

T. M. Kim[1*], M. Taszner[2], S. Novelli[3], S-G. Cho[4], J. C. Villasboas[5], M. Merli[6], A. Jiménez-Ubieto[7], B. Tessoulin[8], L. M. Poon[9], D. Tucker[10], J. Walewski[11], S. Yi[12], Y. Song[13], G. Chong[14], E. Bachy[15,16], S. Guidez[17], A. Alonso[18], D. Jagadeesh[19], W. Zhang[20], L. Magnano[21,22], E. Iskierka-Jażdżewska[23], M. Tani[24], B. Shen[25], A. Uppala[25], M. Zhu[25], S. Shariff[26], J. Brouwer-Visser[25], A. Chaudhry[25], H. Mohamed[25], S. Ambati[25] & S. Luminari[27], on behalf of ELM-2 Investigators





BiTEs for the treatment of R/R follicular lymphoma

BiTEs (CD20xCD3) - single agent

Agent and trial	Phase	Administration	Pts, n	POD24, %	Prior tx, median	ORR (CR), %	Follow-up, median mo	PFS, median mo	OS, median mo	CRS-ICANS (any/gr ≥3), %	Infections gr ≥3, %
Mosunetuzumab (GO29781)[1,2]	II	IV, fixed duration	90	52	3 (2–4)	78 (60)	37.4	24	NR	44/2 5/0	18
Odronextamab (ELM-2)[3,4]	II	IV, Until PD	131	48	3 (2–13)	80 (72)	22.4	20.2	NR	56/4 1/0	32
Epcoritamab[5]	I/II	SC, Until PD	128	42	4.5 (2.5–8)	82 (63)	17.4	15.4	NR	59/2 6/2	NA
Glofitamab[6,7]	I	IV, Fixed duration	53	36	3 (1–12)	81 (70)	NA	NA	NA	67/5 NA	NA

BiTEs (CD20xCD3) - combinations regimen

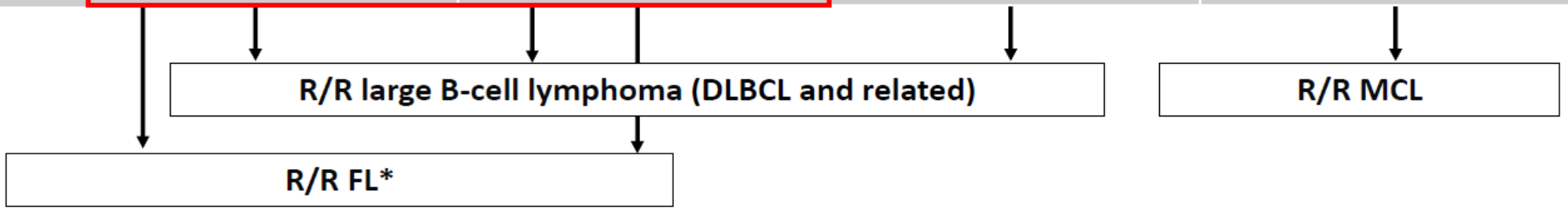
Agent and trial	Phase	Administration	Pts, n	POD24, %	Prior tx, median	ORR (CR), %	Follow-up, median mo	PFS, median mo	OS, median mo	CRS-ICANS (any/gr ≥3), %	Infections gr ≥3, %
Epco + lena + rit (EPCORE NHL-2)[8]	I/II	SC+OS+IV/SC Fixed duration	109	36	2 (1–9)	97 (86)	8.8	6mo: 93%	NA	46/2 2/0	NA
Mosu + lena[9]	Ib	IV+OS Fixed duration	27	11	1 (1–4)	92 (77)	NA	NA	NA	30/0 NA	NA

PD: progressive disease; POD24: progression of disease within 24 months; tx: treatment; R/R: relapsed/refractory; ORR: objective response rate; CR: complete response; PFS: progression-free survival; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome

Mod. da 1. Schuster SJ, et al. Blood 2023; 142 (Supplement 1): 603; 2. Bartlett NL, et al. Blood 2022; 140: 1467–1470; 3. Villasboas JC, et al. Blood 2023; 142 (Supplement 1): 3041; 4. Taszner M, et al. EHA 2024. Abstract S232; 5. Linton KM, et al. Lancet Haematol 2024; S2352-3026(24)00166-2; 6. Morschhauser F, et al. Blood 2021; 138 (Supplement 1): 128; 7. Hutchings M, et al. J Clin Oncol 2021; 39: 1959–1970; 8. Merryman R, et al. J Clin Oncol 2023; 41: (Supplement 16): 7506; 9. Morschhauser F, et al. Blood 2021; 138 (Supplement 1): 129

CD19-Directed CAR T-Cell Products for NHL

	Axicabtagene Ciloleucel[1]	Tisagenlecleucel[2]	Lisocabtagene Maraleucel[3]	Brexucabtagene Autoleucel[4]
Construct	Anti–CD19-**CD28**-CD3z	Anti–CD19-**41BB**-CD3z	Anti–CD19-**41BB**-CD3z	Anti–CD19-**CD28**-CD3z
Dose	2 x 10^6/kg (max 2 x 10^8)	0.6-6.0 x 10^8/kg	In 2L: 90-110 x 10^6 In 3L+: 50-110 x 10^6	2 x 10^6/kg (max 2 x 10^8)
Lympho-depletion	Flu/Cy **30/500** mg/m^2 x 3 days	Flu/Cy **25/250** mg/m^2 x 3 days, or **bendamustine x 2 days**	Flu/Cy **30/300** mg/m^2 x 3 days	Flu/Cy **30/500** mg/m^2 x 3 days



*Adult patients with R/R FL after ≥2 or more lines of systemic therapy.

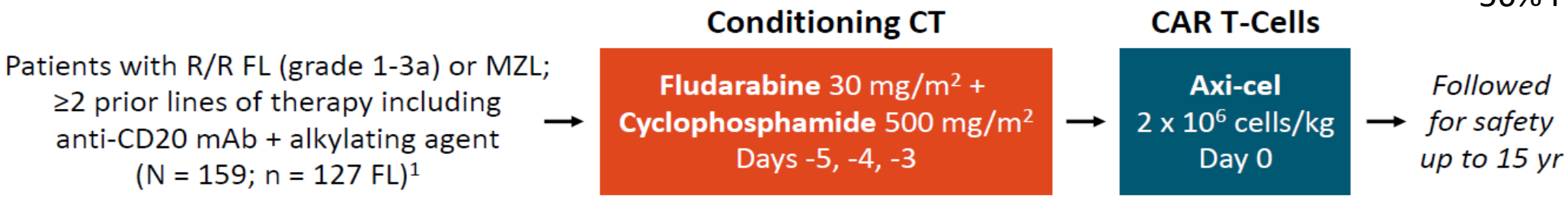
1. Axicabtagene ciloleucel PI. 2. Tisagenlecleucel PI. 3. Lisocabtagene maraleucel PI. 4. Brexucabtagene autoleucel PI.

Slide credit: clinicaloptions.com

ZUMA-5: Axicabtagene Ciloleucel in FL and MZL

31% age <65
44% H FLIPI
24% previous ASCT
69% refractory
44 double refractory
56% POD

- Multicenter, single-arm phase II trial[1,2]



Patients with SD but no relapse >1 yr from completion of last therapy ineligible. Single-agent anti-CD20 mAb not counted as line of therapy for eligibility. Median time to delivery of axi-cel: 17 days following leukapheresis.

- **Primary endpoint:** ORR (CR and PR) by IRC per Lugano classification
  - In primary analysis, ORR was 94% for 84 patients with FL after 17.5 mo follow-up[2]
- **Key secondary endpoints:** CR rate (IRRC assessed), ORR (investigator assessed), DoR, PFS, OS, AEs, CAR T-cell and cytokine levels

1. Neelapu. ASH 2022. Abstr 4660. 2. Jacobson. Lancet. 2022;23:91.

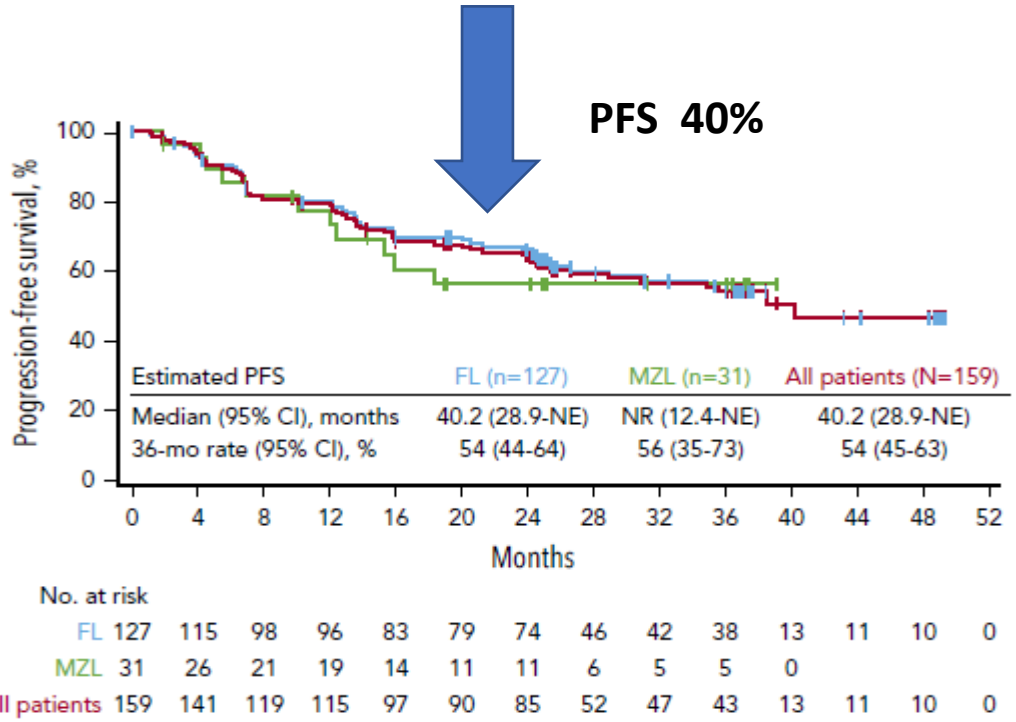
Slide credit: clinicaloptions.com

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]

A



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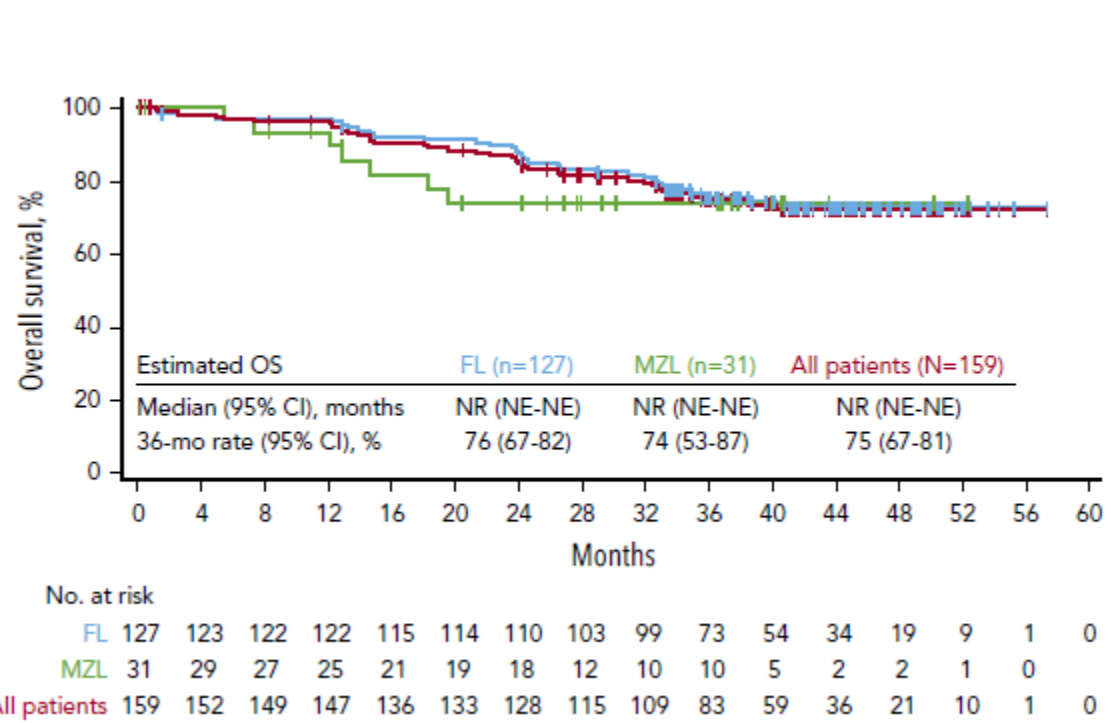


ZUMA-5: Safety of Axi-cel in R/R FL

Adverse Events	FL (n = 124)	MZL (n = 22)	All (N = 148)
Any AE, %	99	100	99
▪ Any grade infection	52	63	53
Grade ≥3 AEs, %	85	96	86
▪ Neutropenia	60	67	61
▪ Anemia	23	29	24
▪ Thrombocytopenia	23	21	23
▪ Infection	15	29	18
Serious AEs, %	46	71	50
CRS, %	78	100	82
▪ Grade ≥3	6	8	7
Neurologic events, %	56	71	59
▪ Grade ≥3*	15	38	19
▪ Median duration, days (IQR)	14 (5-43)	10 (5-28)	--

*No grade 5.

- Most common grade ≥3 AEs were cytopenias (70%) and infections (18%)
  - Grade ≥3 infections included pneumonia (n = 10), opportunistic (n = 4), URTI (n = 1)
- All CRS events resolved except 1 event of multisystem organ failure in a patient with FL and bulky disease
- No new safety signals observed in 3-yr follow-up analysis

Jacobson. Lancet Oncol. 2022;23:91. Neelapu. ASH 2022. Abstr 4660.

Slide credit: clinicaloptions.com

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

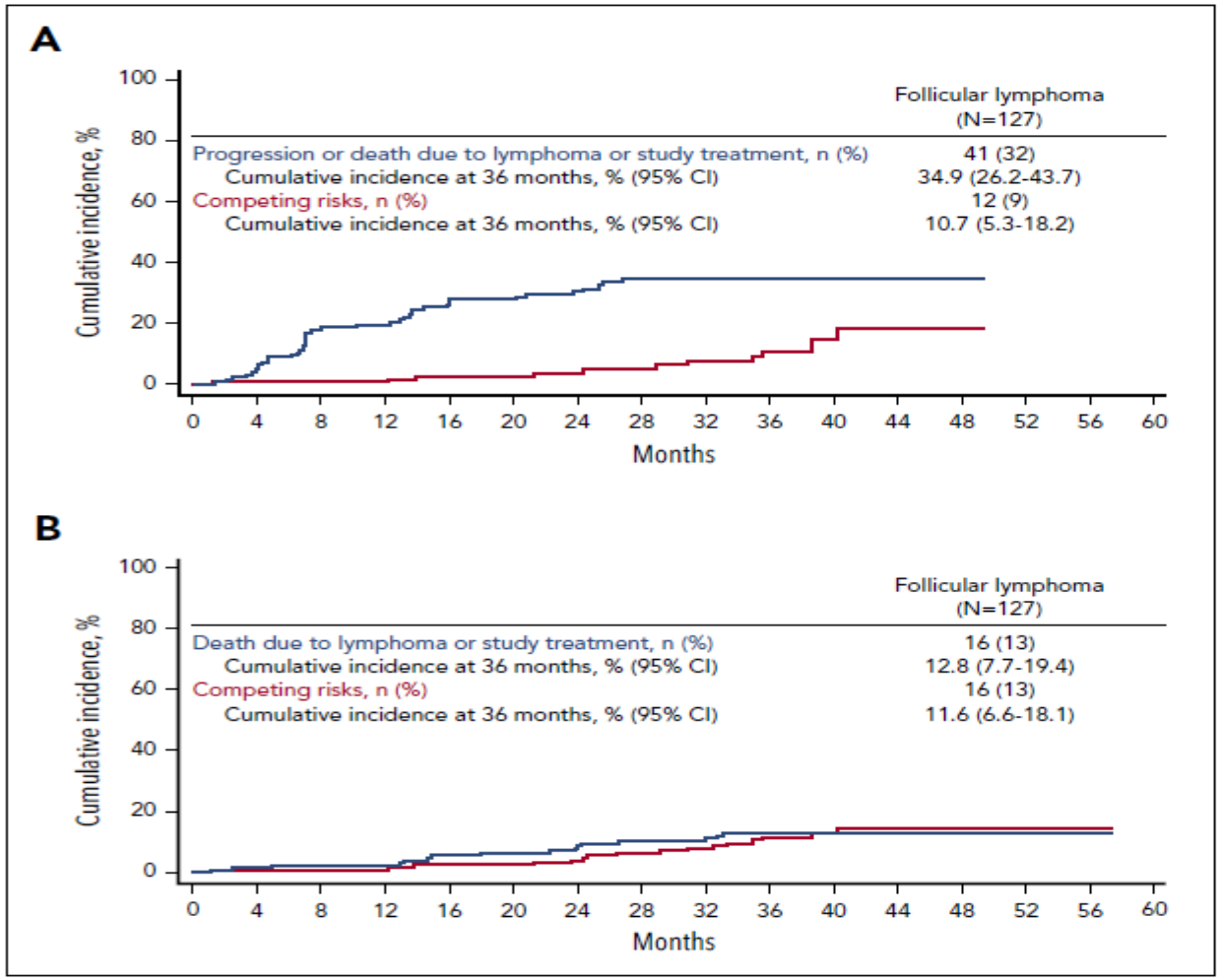


Figure 2. Lymphoma-specific survival outcomes of patients with FL based in cumulative incidence and competing risk. Cumulative incidence plots of competing risk lymphoma-specific (A) PFS and (B) OS by investigator assessment for enrolled patients with FL. Main events included those due to lymphoma or study treatment complications. Events due to reasons other than lymphoma or study treatment complications were considered competing risks.

Table 4. Second primary malignancies

	FL (n = 124)
Any second primary malignancy, n (%)	13 (10)
Nonmelanoma skin cancer	3 (2)
Melanoma	1 (1)
t-MDS/t-AML	5 (4)
Colorectal cancer	1 (1)
B-ALL/AML	1 (1)
Anal/rectal cancer	1 (1)
Prostate cancer	1 (1)
Neuroendocrine tumor	0
Breast cancer	0

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

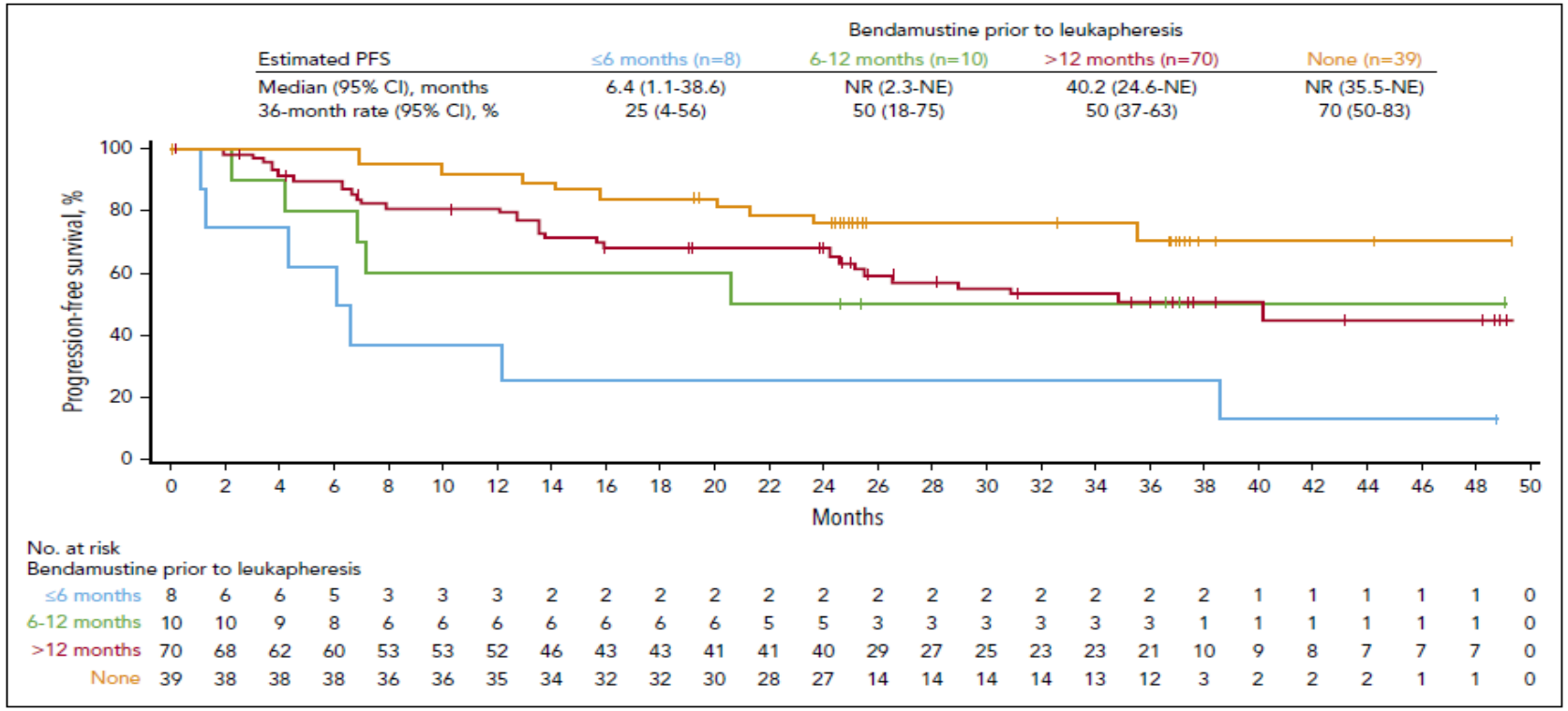
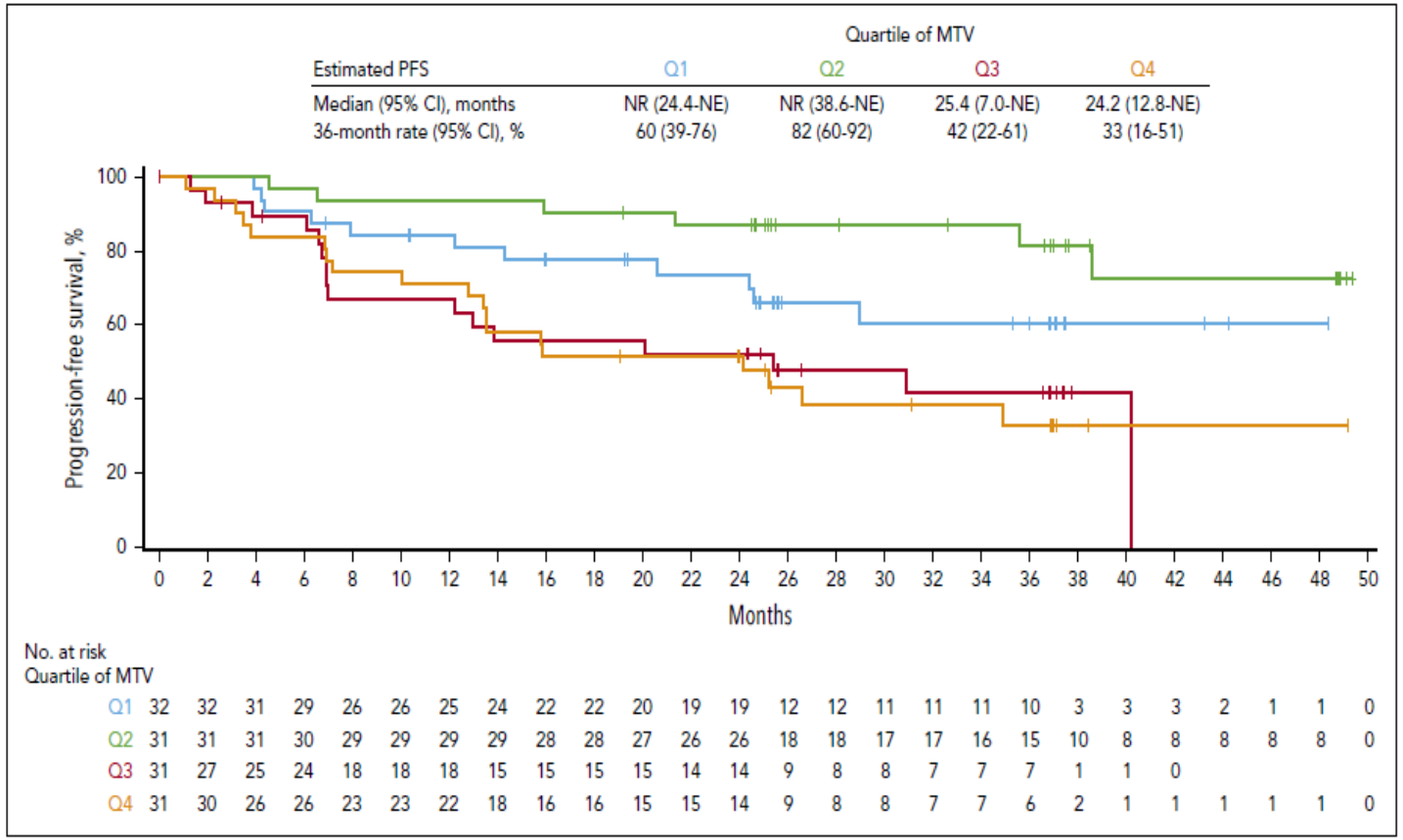


Figure 3. PFS of patients with FL based on the time point of bendamustine use before axi-cel infusion. Kaplan-Meier estimates of PFS among enrolled patients with FL by investigator assessment in those who had no prior bendamustine exposure, received bendamustine within 6 months of leukapheresis, received bendamustine between 6 and 12 months of leukapheresis, and received bendamustine >12 months before leukapheresis.

recente exposure to BENDAMUSTINE correleted negatively with outcome

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



Clinical outcome corretaleted negatively with high metabolic volume

Figure 4. PFS of patients with FL based on the quartile of baseline metabolic tumor volume. Kaplan-Meier plot of PFS per investigator assessment based on the quartile of baseline metabolic tumor volume of evaluable enrolled patients with FL. MTV, metabolic tumor volume.

REGULAR ARTICLE

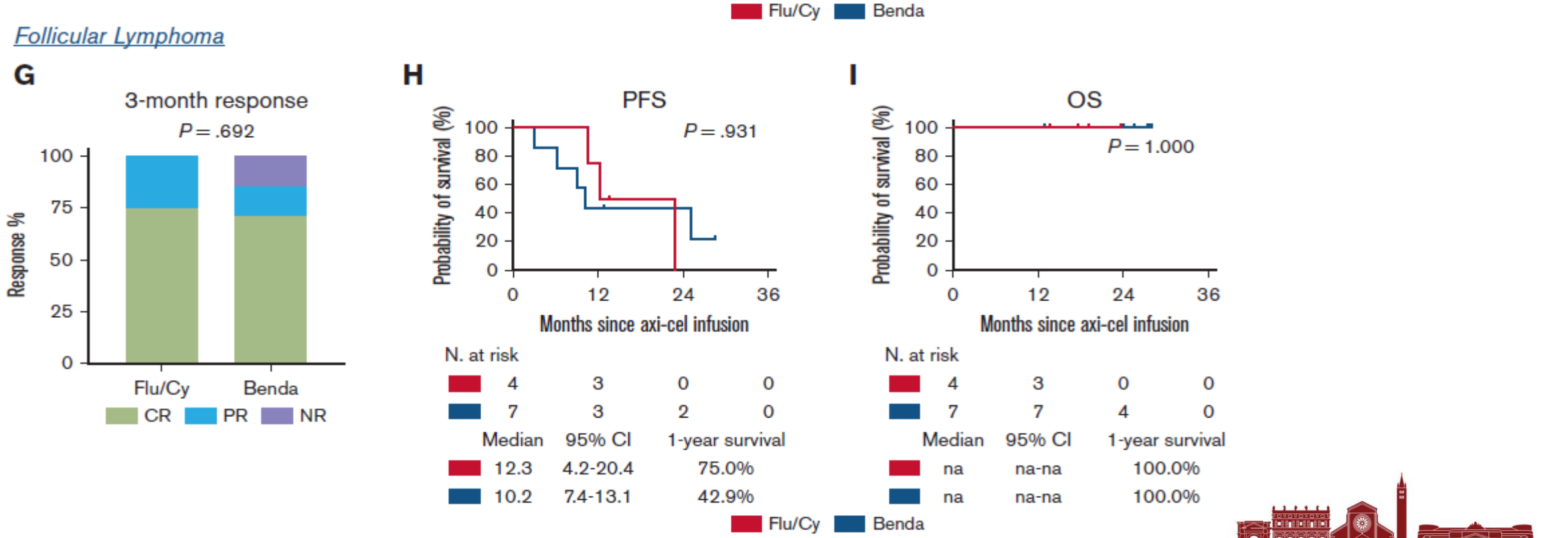
blood advances

Bendamustine lymphodepletion before axicabtagene ciloleucel is safe and associates with reduced inflammatory cytokines

Guido Ghilardi,[1-3] Luca Paruzzo,[1-4] Jakub Svoboda,[1-3] Eise A. Chong,[1-3] Alexander A. Shestov,[2,5] Linhui Chen,[1-3] Ivan J. Cohen,[1-3] Giulia Gabrielli,[1-3,6] Sunita D. Nasta,[1-3] Patrizia Porazzi,[1-3] Daniel J. Landsburg,[1,3] James N. Gerson,[1,3] Jordan Carter,[1-3] Stefan K. Barta,[1-3] Rebecca Yelton,[1-3] Raymone Pajarillo,[1-3] Vrutti Patel,[1-3] Griffin White,[1,3] Hatcher J. Ballard,[1,3] Elizabeth Weber,[1,3] Ellen Napier,[1,3] Emeline R. Chong,[1-3] Joseph A. Fraietta,[2] Alfred L. Garfall,[2,3] David L. Porter,[1,3] Michael C. Milone,[2,5] Roderick O'Connor,[2,5] Stephen J. Schuster,[1-3,*] and Marco Ruella[1-3,5,*]

[1]Lymphoma Program, Abramson Cancer Center and [2]Center for Cellular Immunotherapies, University of Pennsylvania, Philadelphia, PA; [3]Division of Hematology-Oncology, Hospital of the University of Pennsylvania, Philadelphia, PA; [4]Department of Oncology, University of Turin, Turin, Italy; [5]Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; and [6]Department of Molecular Biotechnology and Health Sciences, University of Turin, Turin, Italy

Follicular Lymphoma



REGULAR ARTICLE

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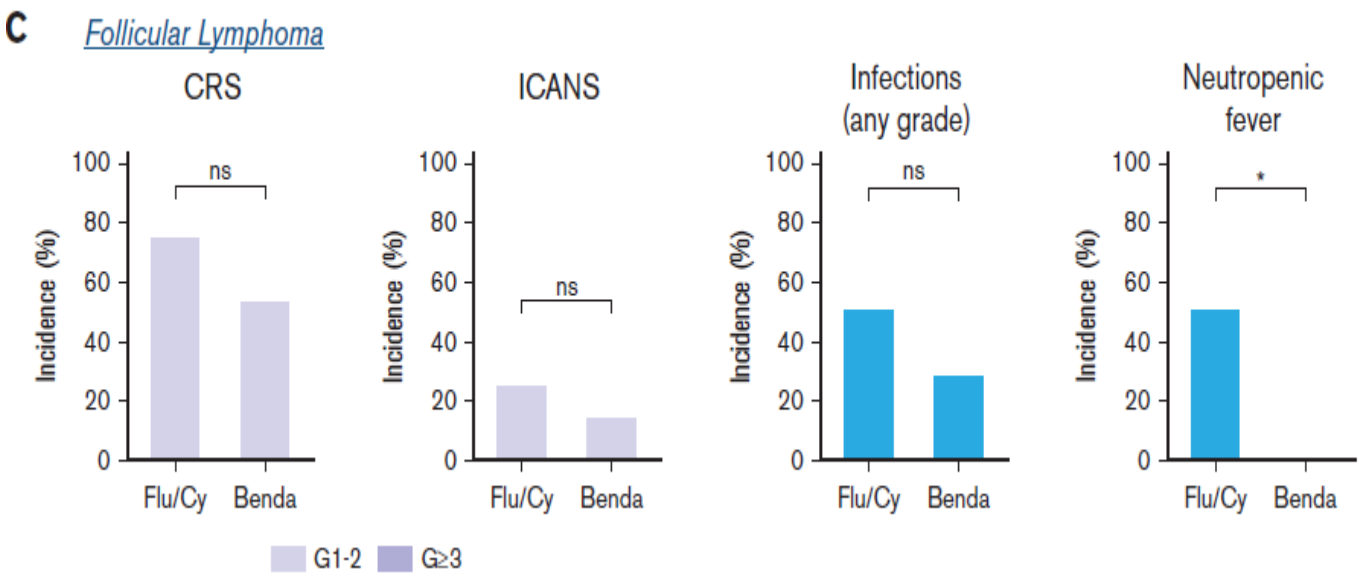
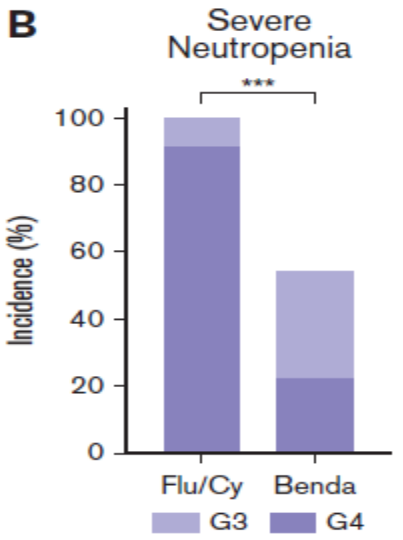
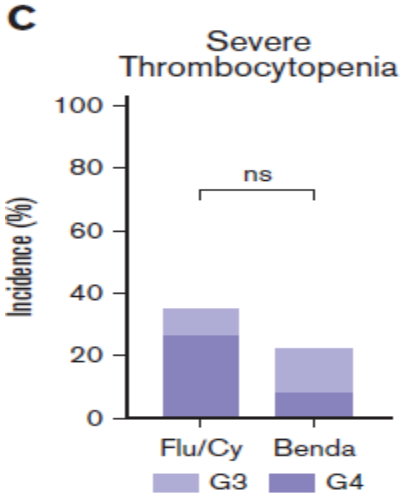
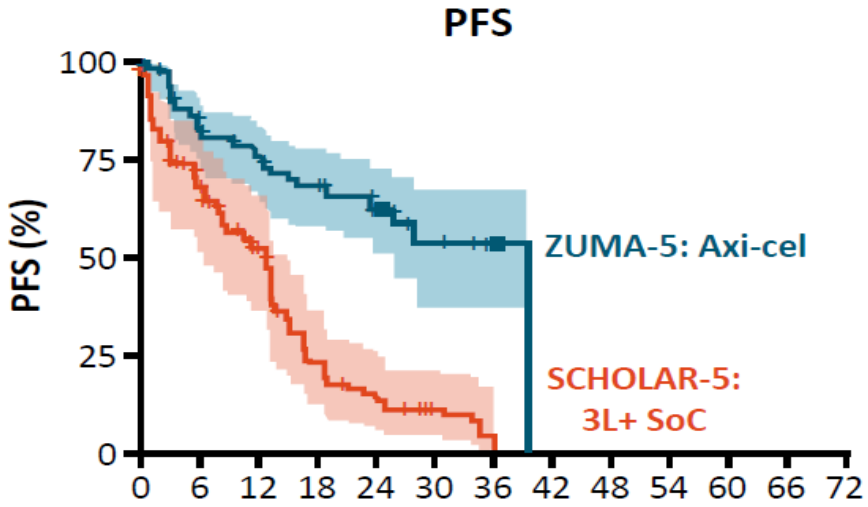




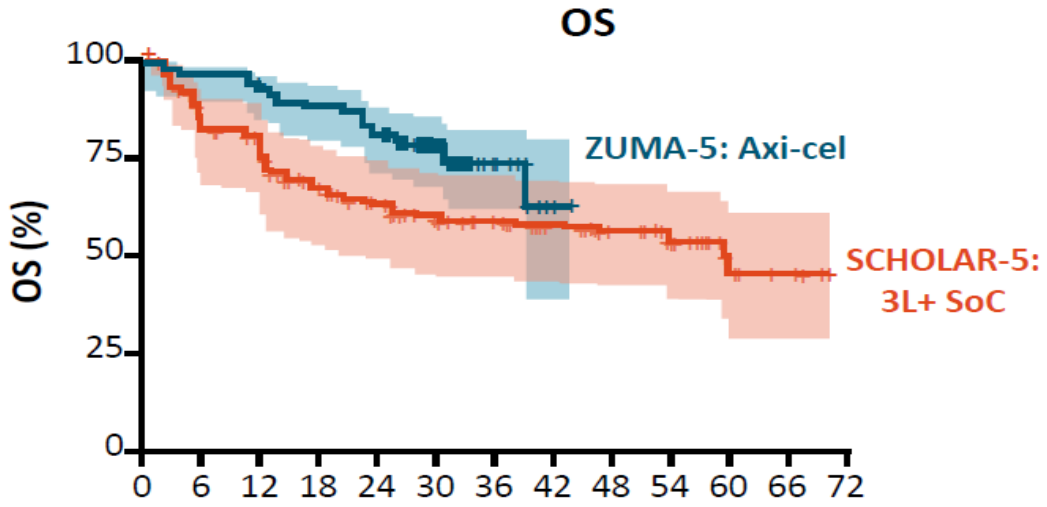


ZUMA-5 vs SCHOLAR-5 External Control 24-Mo Update: Axi-cel vs 3L+ SoC Therapies in R/R FL

- Weighted comparative analysis of phase II ZUMA-5 evaluating axi-cel in patients with R/R FL (N = 86) vs SCHOLAR-5 evaluating 3L+ therapy in similar group of patients as ZUMA-5 (N = 86)



Patients at Risk, n													
ZUMA-5	86	69	60	53	27	11	7	0	0	0	0	0	0
SCHOLAR-5	56	28	15	6	4	1	1	0	0	0	0	0	0



Patients at Risk, n													
ZUMA-5	86	83	80	75	69	40	15	2	0	0	0	0	0
SCHOLAR-5	85	70	66	49	44	37	32	28	21	18	5	1	0

Palomba. Exp Rev Anticancer Therapy. 2023;23:199.

Shaded area in curves is 95% CI.

Slide credit: clinicaloptions.com

Full Length Article
Cellular Therapy

Matching-Adjusted Indirect Comparisons of Axicabtagene Ciloleucel to Mosunetuzumab for the Treatment of Relapsed/Refractory Follicular Lymphoma

Markqayne D. Ray[1], Steve Kanters[2], Sara Beygi[1], Timothy Best[1], Jacob Wulff[1], Eve Limbrick-Oldfield[2], Anik R. Patel[1], Olalekan O. Oluwole[3,*]

[1] *Kite, A Gilead Company, Santa Monica, California*
[2] *RainCity Analytics, Vancouver, British Columbia, Canada*
[3] *Vanderbilt University Medical Center, Nashville, Tennessee*

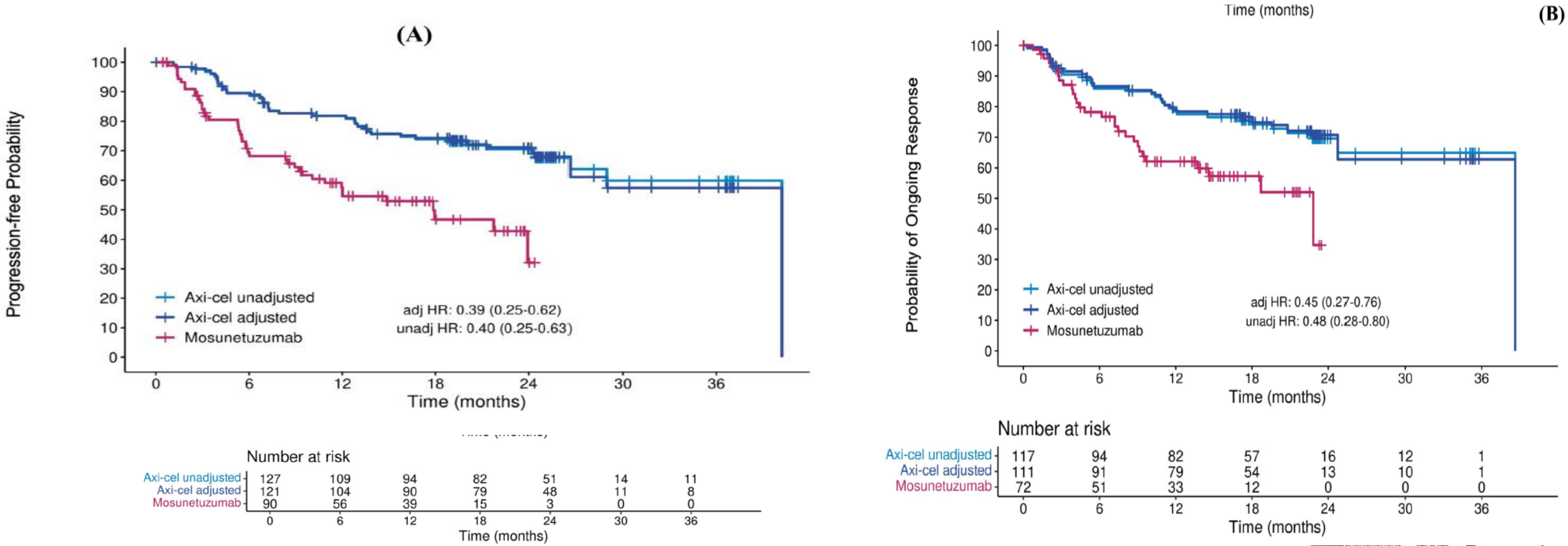


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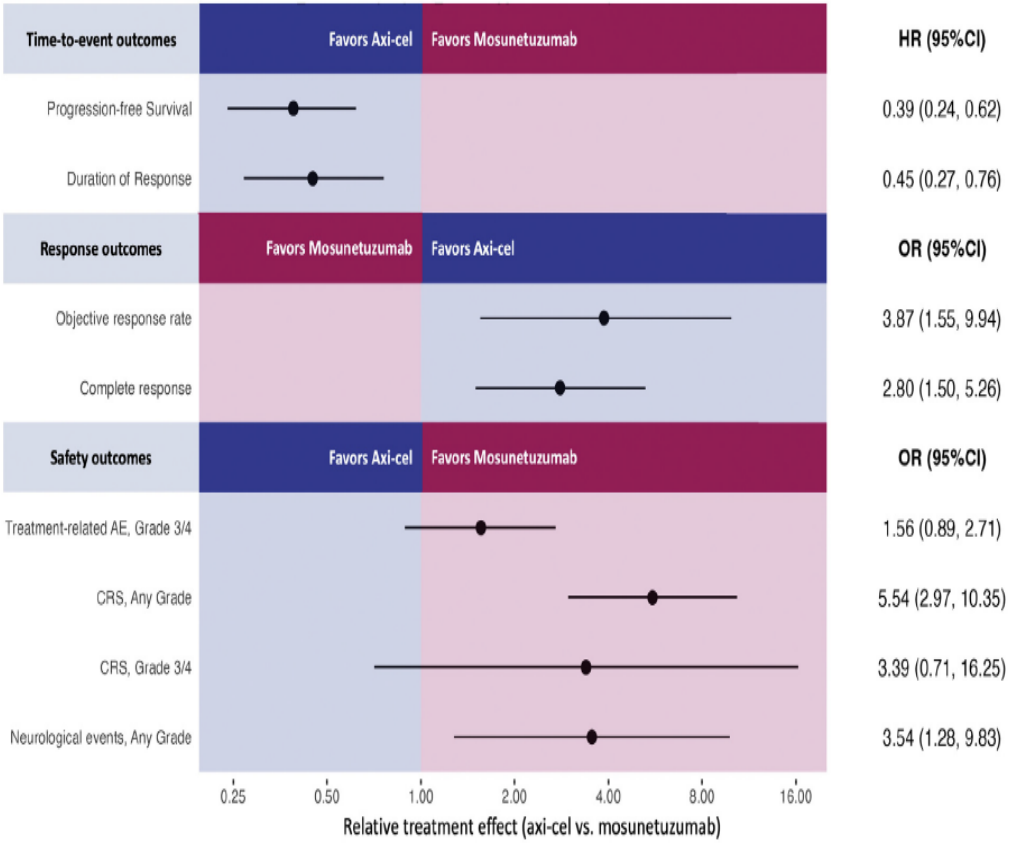
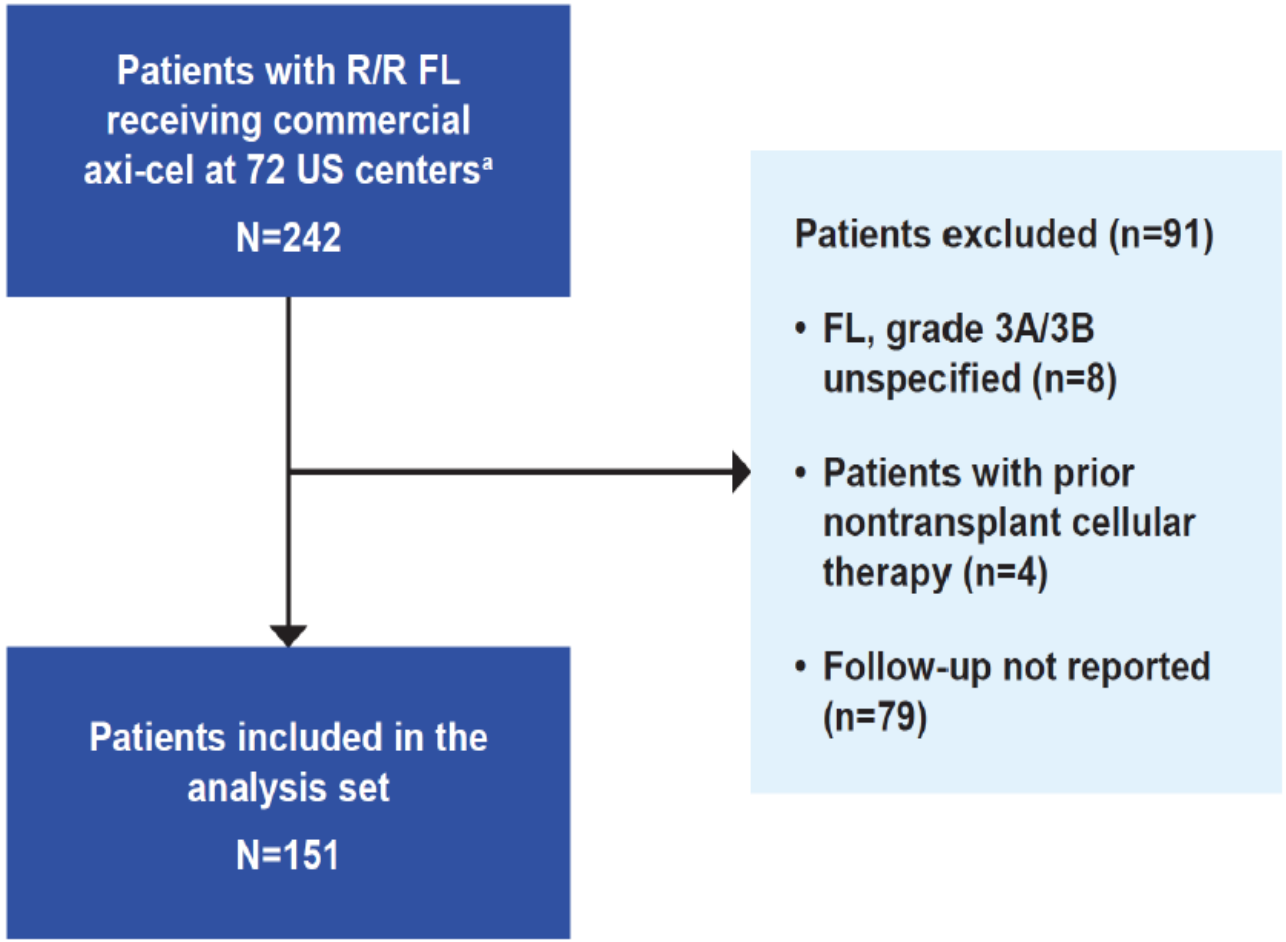
Table 1
Patient Characteristics by Analysis Set, ZUMA-5 vs GO29781

Variable	ZUMA-5[†] (n = 127)	GO29781 (n = 90)
Age, median (IQR)	60 (53-67)	60 (53-67)
Age, ≥65 years	31.5%	33.3%
Male, (%)	59.1%	61.1%
Caucasian (%)	92.1%	82.2%
Time since diagnosis, median (IQR)	58.0 m (32.0-76.5 m)	–
Number of prior lines of therapy, median	3	3
Number of prior lines of therapy ≥ 3, %	69.3%	62%
Histological Grade 3A, %	23.6%	–
Prior ASCT, (%)	23.6%	21.1%
Refractory to prior line, (%)	68.5%	68.9%
ECOG performance, (%)		
0	62.2%	58.9%
1	37.8%	41.1%
Disease stage III/IV, (%)	85.8%	76.7%
Size of largest nodal mass (Tumor bulk)—cm, median (IQR)	4.0 (3.2-6.0)	–
Bulky disease % (>6 cm)	24.4%	34.4%
FLIPI Score—high/≥3, (%)	44.1%	44.4%
POD24, (%)	65.3%	52.2%
Double refractory, %	58.3%	53.3%

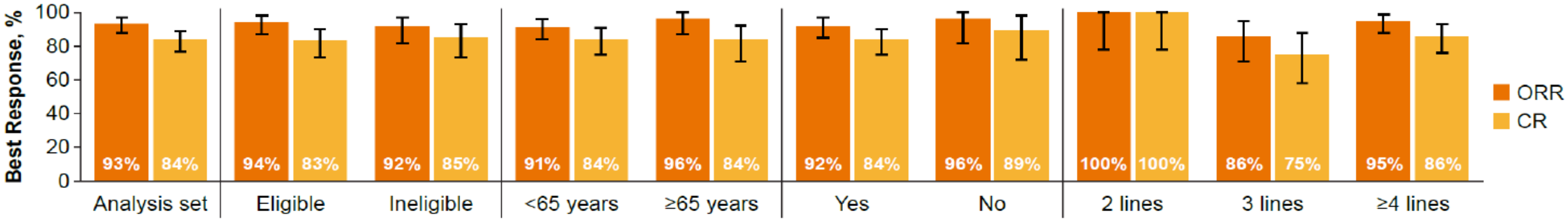
[†] ZUMA-5 statistics were for the FAS population. ASCT: Autologous stem cell transplant; ECOG: Eastern Cooperative Oncology Group; IQR: Interquartile range; PS: Performance status; FLIPI: Follicular Lymphoma International Prognostic Index; POD24: Progression of disease within 24 months, LDH: Lactase dehydrogenase.



Real-World Early Outcomes of Axicabtagene Ciloleucel for Relapsed or Refractory Follicular Lymphoma



Overall Response in the Analysis Set, by ZUMA-5 Eligibility, by Age, by Prior Exposure to Bendamustine, and by Prior Lines of Therapy

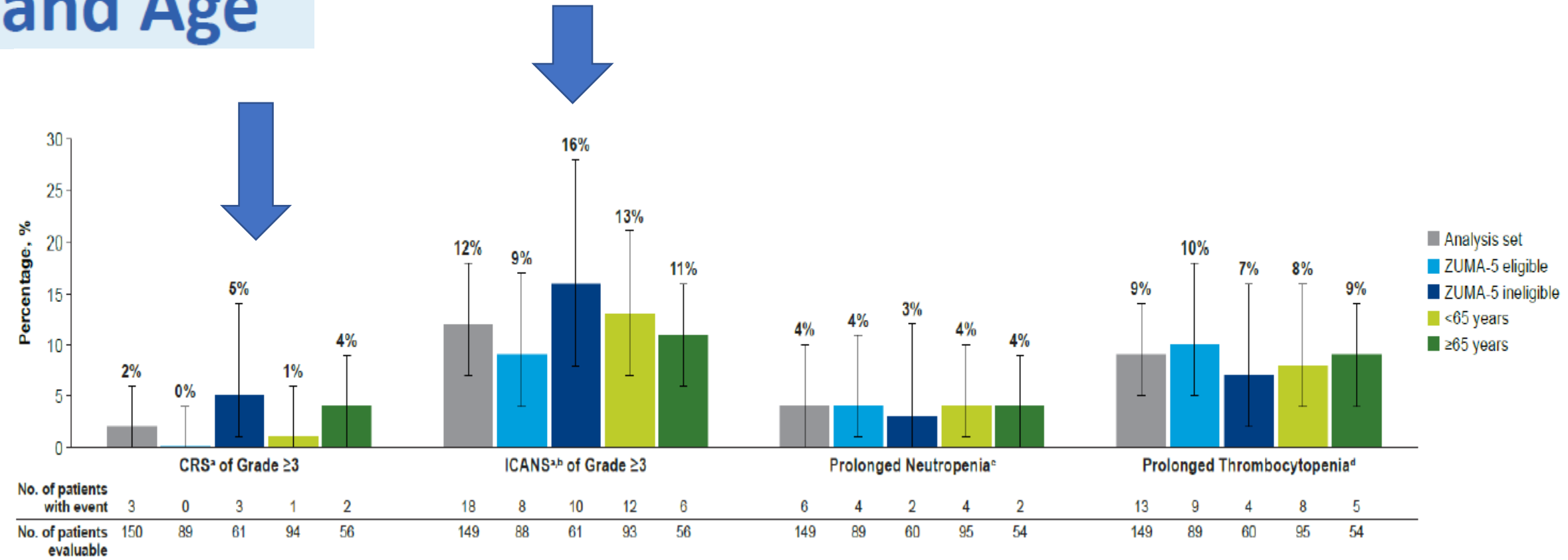


No. of patients	138	124	83	73	55	51	85	78	53	46	96	87	27	25	15	15	31	27	75	68
N	148	148	88	88	60	60	93	93	55	55	104	104	28	28	15	15	36	36	79	79

- Among 148 patients evaluable for response, for whom the median follow-up was 6.2 months, **138 (93%; 95% CI, 88-97) had an overall response, with 124 patients (84%; 95% CI, 77-89) achieving a CR**
- Overall response was comparable regardless of ZUMA-5 eligibility, age, prior exposure to bendamustine, and prior lines of therapy

Efficacy and survival – Jacobson ASCO 2023 abs *#7509*

Grade ≥3 CRS, Grade ≥3 ICANS, and Prolonged Cytopenias in the Analysis Set, ZUMA-5 Eligibility, and Age



nature medicine

ARTICLES

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

Check for updates

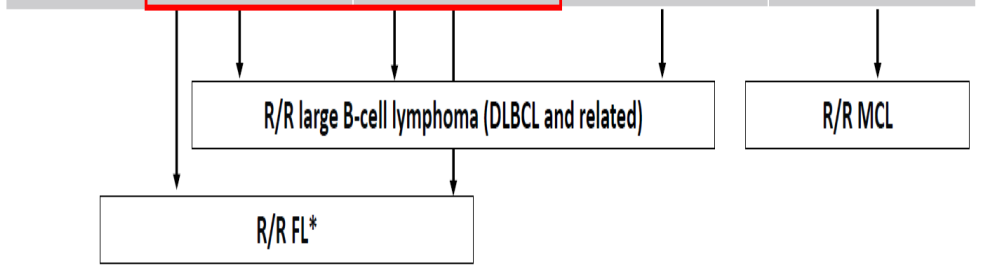
Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial

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.

CD19-Directed CAR T-Cell Products for NHL

	Axicabtagene Ciloleucel[1]	Tisagenlecleucel[2]	Lisocabtagene Maraleucel[3]	Brexucabtagene Autoleucel[4]
Construct	Anti–CD19-**CD28**-CD3z	Anti–CD19-**41BB**-CD3z	Anti–CD19-**41BB**-CD3z	Anti–CD19-**CD28**-CD3z
Dose	2 x 10^6/kg (max 2 x 10^8)	0.6-6.0 x 10^8/kg	In 2L: 90-110 x 10^6 In 3L+: 50-110 x 10^6	2 x 10^6/kg (max 2 x 10^8)
Lympho-depletion	Flu/Cy **30/500** mg/m^2 x 3 days	Flu/Cy **25/250** mg/m^2 x 3 days, or **bendamustine x 2 days**	Flu/Cy **30/300** mg/m^2 x 3 days	Flu/Cy **30/500** mg/m^2 x 3 days



*Adult patients with R/R FL after ≥2 or more lines of systemic therapy.

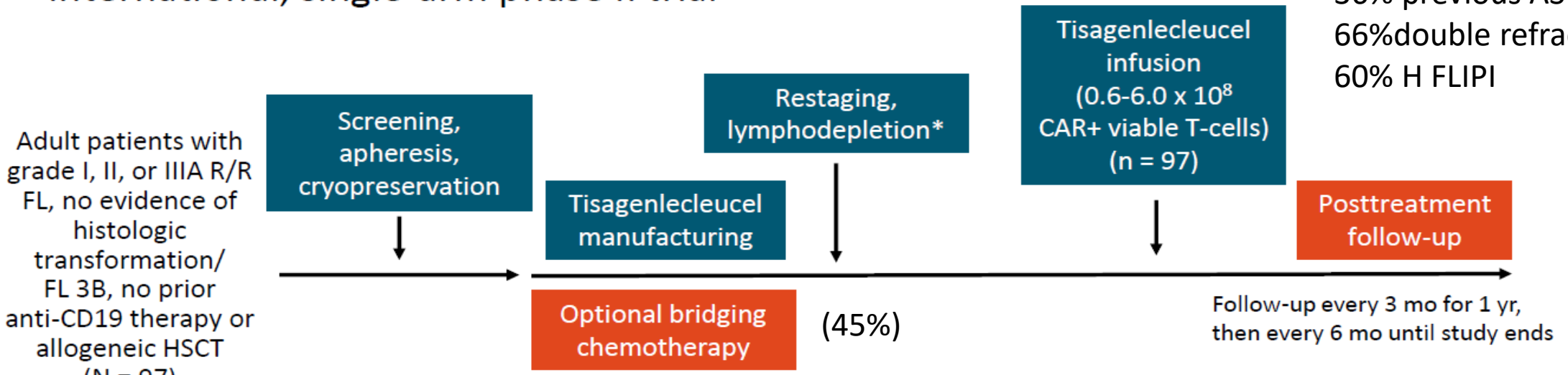
1. Axicabtagene ciloleucel PI. 2. Tisagenlecleucel PI. 3. Lisocabtagene maraleucel PI. 4. Brexucabtagene autoleucel PI.

Slide credit: clinicaloptions.com

ELARA: Tisagenlecleucel in R/R FL

Age>65 25%
63% POD
78% refractory
36% previous ASCT
66%double refractory
60% H FLIPI

- International, single-arm phase II trial



*Lymphodepleting therapy: fludarabine 25 mg/m^2/day IV for 3 days + cyclophosphamide 250 mg/m^2/day IV for 3 days or bendamustine 90 mg/m^2/day IV for 2 days.

- Primary endpoint: CRR by IRC
- Secondary endpoints: ORR, DoR, PFS, OS, safety, cellular kinetics

Fowler. Nat Med. 2022; 28:325.

Slide credit: clinicaloptions.com

ELARA: Efficacy of Tisagenlecleucel in R/R FL

Response, %	Efficacy Analysis Set (n = 94)	
	IRC	Investigator
ORR	86.2	90.4
▪ CR	69.1	72.3
▪ PR	17.0	18.1

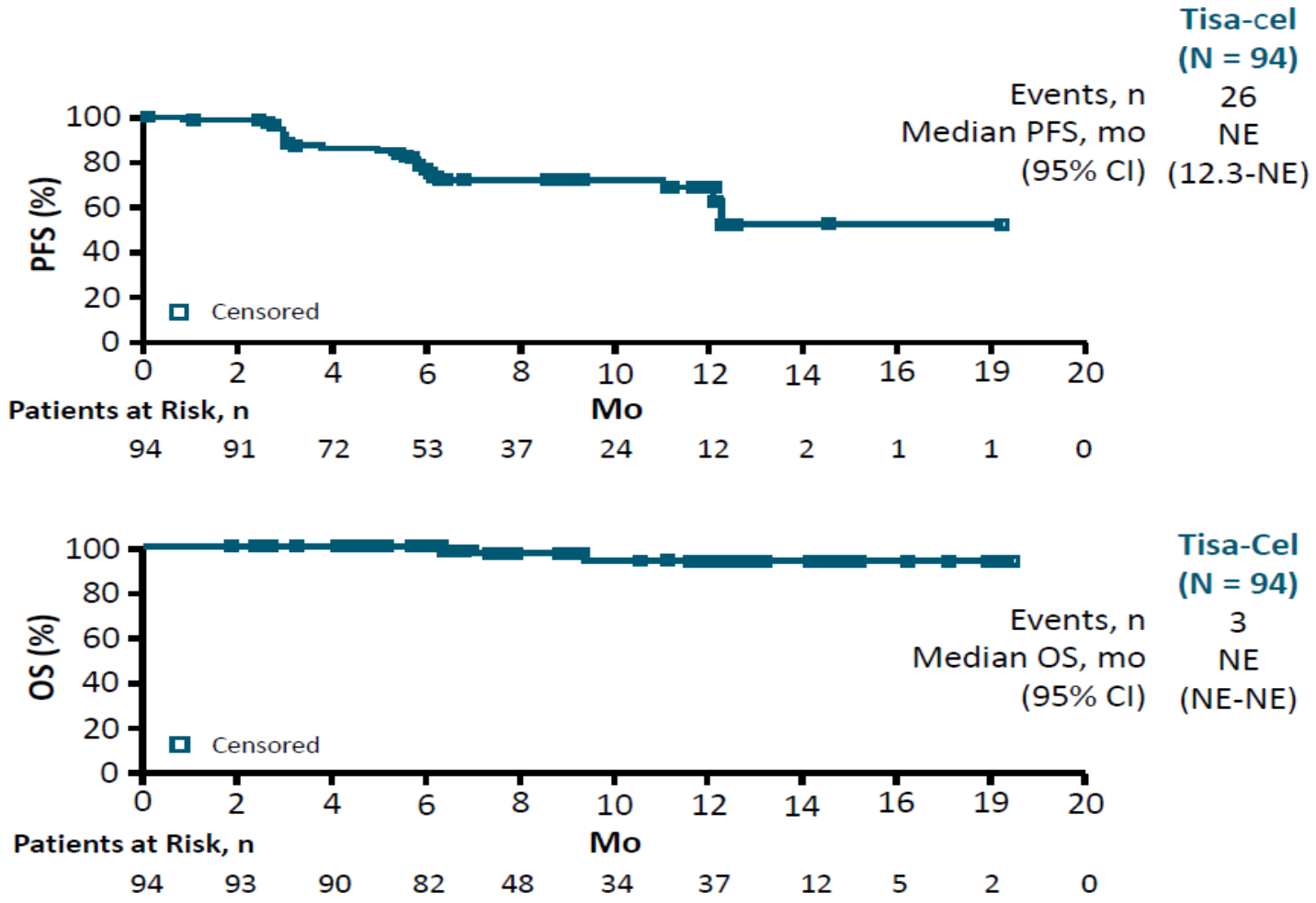
- Median f/u for efficacy: 29 mo
- Median DoR, PFS, OS not reached
  - Est. 9-mo DoR: 86.5% (95% CI: 74.7%-93.1%)
  - 12-mo PFS: 67% (95% CI: 56%-76%)

- 15/31 of patients achieving PR converted to CR
  - 11 occurred between Mo 3 and 6
- CR rate consistent across majority of subgroups examined including age, sex, grade, use of PI3K inhibitors, prior HSCT, disease status to last line of therapy

Fowler. Nat Med. 2022;28:325.

Slide credit: clinicaloptions.com

ELARA: Survival With Tisagenlecleucel in R/R FL



Fowler. Nat Med. 2022;28:325.

Median follow-up: 17 mo.

Slide credit: clinicaloptions.com

ELARA: Safety of Tisagenlecleucel in R/R FL

AEs, n (%)	Patients (N = 97)
Any AE, n (%)	96 (99.0)
Grade 3/4 AE, n (%)	76 (78.4)
Death, n (%)	7 (7.2)
▪ Due to study indication	5 (5.1)
▪ Due to CRS	1 (1)
▪ Due to general disorders	1 (1)
▪ Within 30 days post infusion	0

AEs of Special Interest,* %	All Grades	Grade ≥3
▪ CRS	48.5	0
▪ Neurologic events	37.1	3.1
▪ Infections	18.6	5.2
▪ Hypogammaglobulinemia	9.3	0
▪ Neutropenia	33	32
▪ Febrile neutropenia	10.3	10.3
▪ Anemia	24.7	13.4
▪ Thrombocytopenia	16.5	9.3

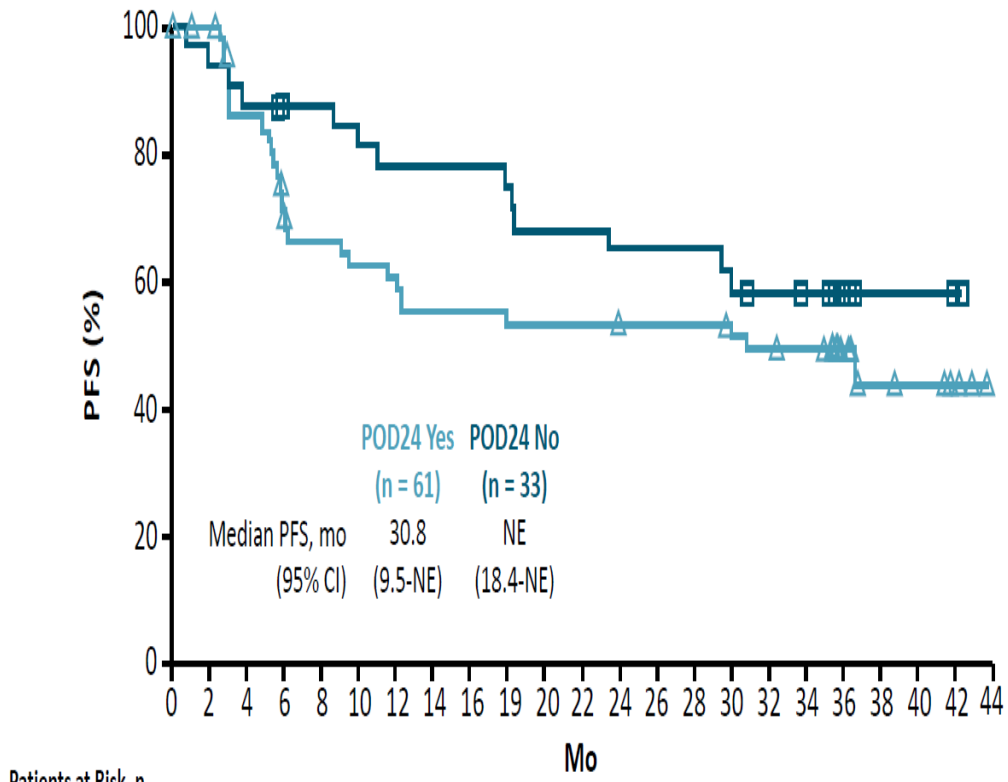
*8 wk post infusion.

- AE management required:
  - Tocilizumab in 34%
  - Corticosteroids in 6.4%
- Median onset of CRS: 4 days (IQR: 2-7)
- Median onset of serious NE: 9 days
- ICANS in 4.1% within 8 wk

Fowler. Nat Med. 2022; 28:325.

Slide credit: clinicaloptions.com

ELARA Update: PFS by POD24 Status With Tisa-Cel at 3 Yr (ASH 2023)



Patients at Risk, n

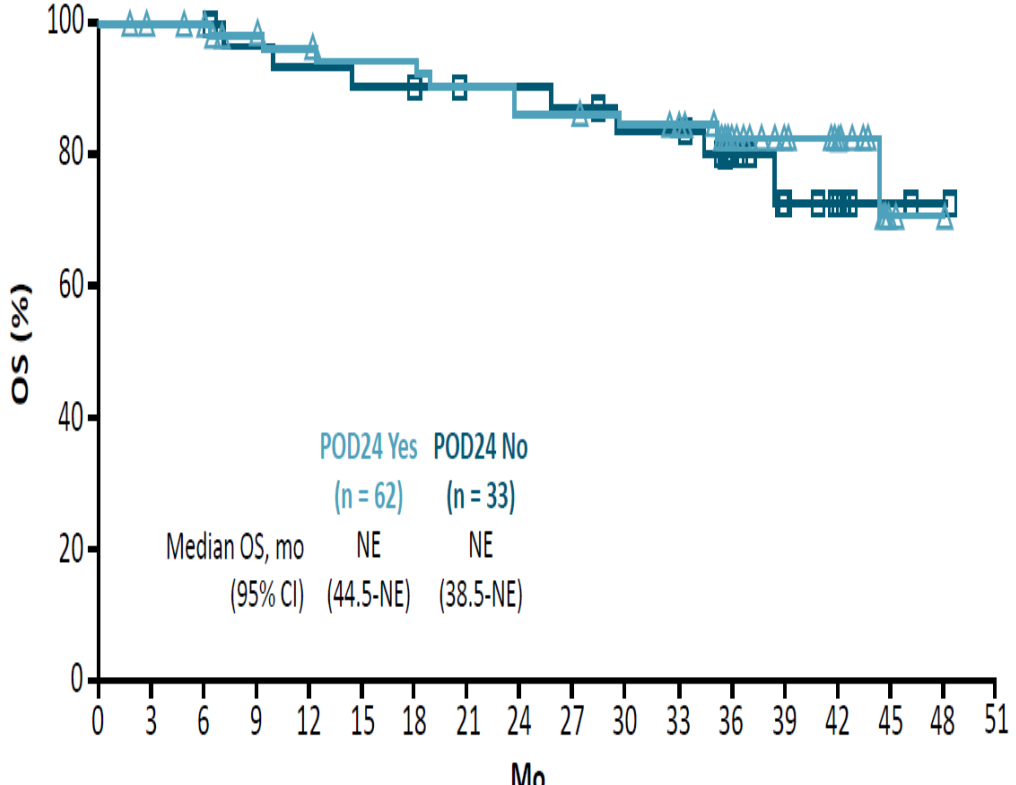
POD24 Yes	61	59	49	40	36	34	33	30	30	29	29	29	28	28	28	27	25	24	14	7	6	3	0
POD24 No	33	32	29	27	27	25	24	24	24	23	21	21	20	20	20	18	17	16	8	3	3	1	0

Schuster. ASH 2023. Abstr 601.

Median follow-up: 41 mo.

Slide credit: clinicaloptions.com

ELARA Update: OS by POD24 Status With Tisa-Cel at 3 Yr (ASH 2023)



Patients at Risk, n

POD24 Yes	61	59	58	53	51	49	49	47	45	45	43	42	30	19	15	3	1	0
POD24 No	33	33	33	31	30	29	29	27	27	26	24	24	17	9	5	2	1	0

Schuster. ASH 2023. Abstr 601.

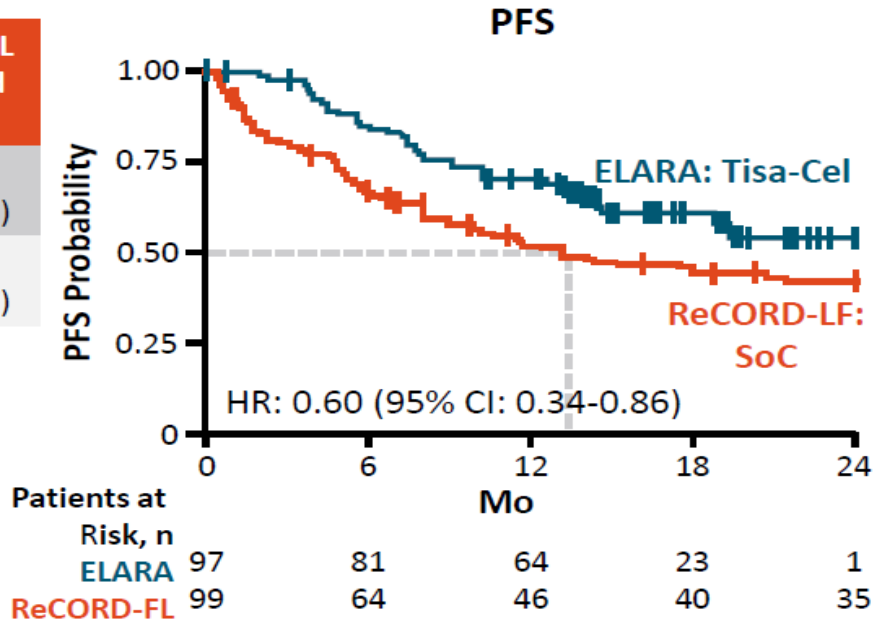
Median follow-up: 41 mo.

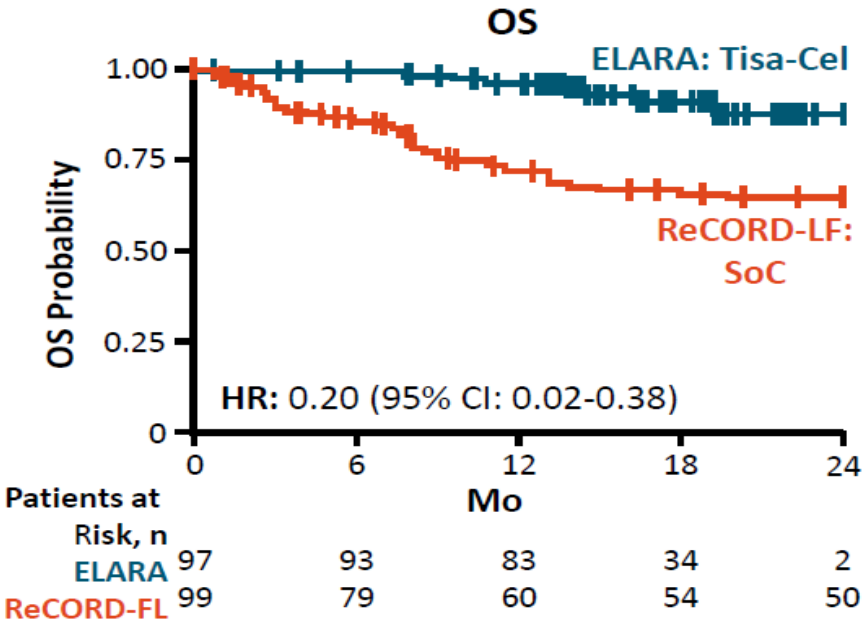
Slide credit: clinicaloptions.com

ELARA vs ReCORD-FL Chart Review: Tisagenlecleucel vs 4L SoC Therapies in R/R FL

- Weighted comparative analysis of phase II ELARA evaluating tisa-cell in patients with R/R FL (N = 98) vs ReCORD-FL chart review evaluated SoC in similar group of patients as ELARA (N = 187)

Best Response	ELARA (n = 97)	ReCORD-FL (weighted n = 99)
CRR, % (95% CI)	69.1 (59.8-78.3)	37.3 (26.4-48.3)
ORR, % (95% CI)	85.6 (78.7-92.5)	63.6 (52.5-74.7)





Salles. Blood Adv. 2022;6:5835.

Slide credit: clinicaloptions.com

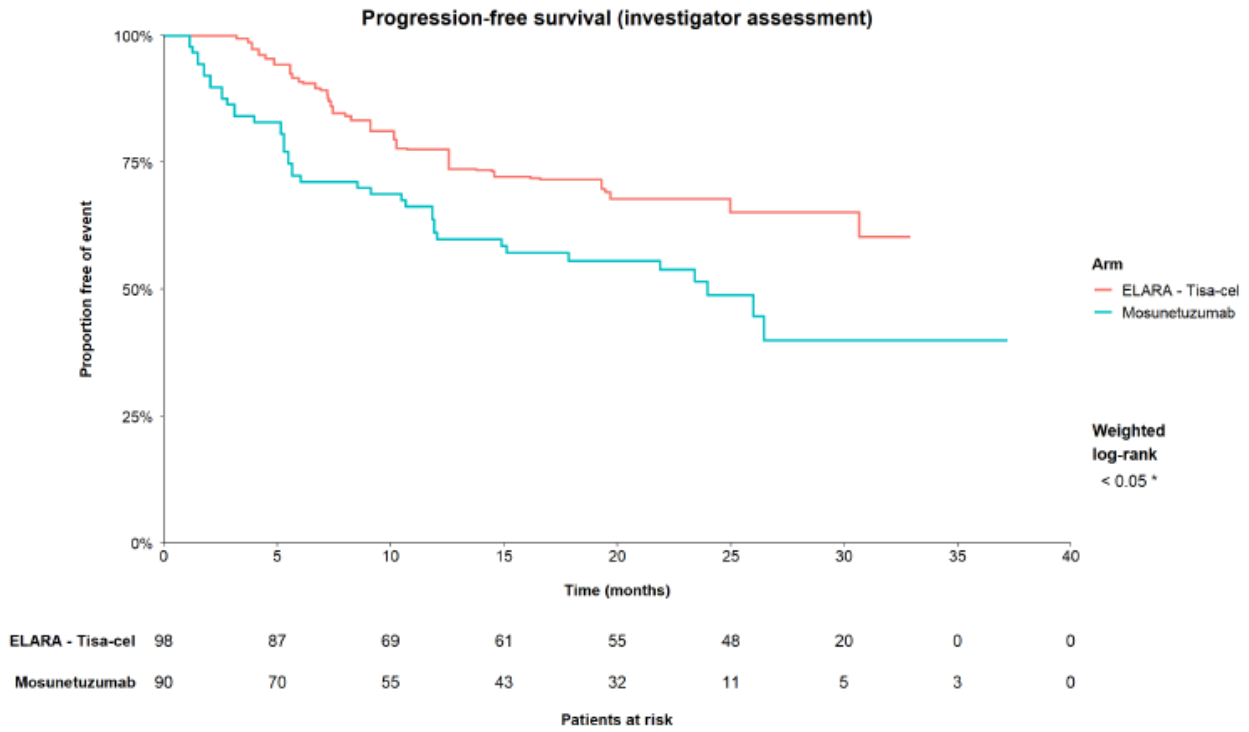
Matching-adjusted indirect comparison of efficacy and safety for tisagenlecleucel and mosunetuzumab in patients with relapsed/refractory follicular lymphoma (r/r fl)

ELARA VS Mosunetuzumab

To **indirectly compare** efficacy (ORR, CRR, and PFS*) and key safety outcomes between **Tisa-cel and Mosunetuzumab** in patients with r/r FL using **matching-adjusted indirect comparison (MAIC)**.

Safety outcomes with regards to CRS and ICANS **were not statistically different** between Tisagenlecleucel and Mosunetuzumab in patients with r/r FL.

PFS from enrolment after weighting



Fowler et al. Meetings of ASTCT and CIBMTR 2023

LEUKEMIA & LYMPHOMA
2024, VOL. 65, NO. 3, 323–332
https://doi.org/10.1080/10428194.2023.2289854

Taylor & Francis
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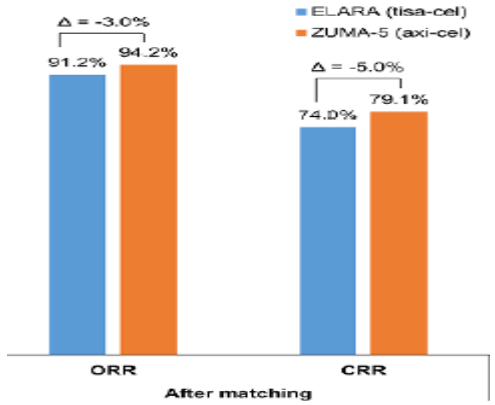
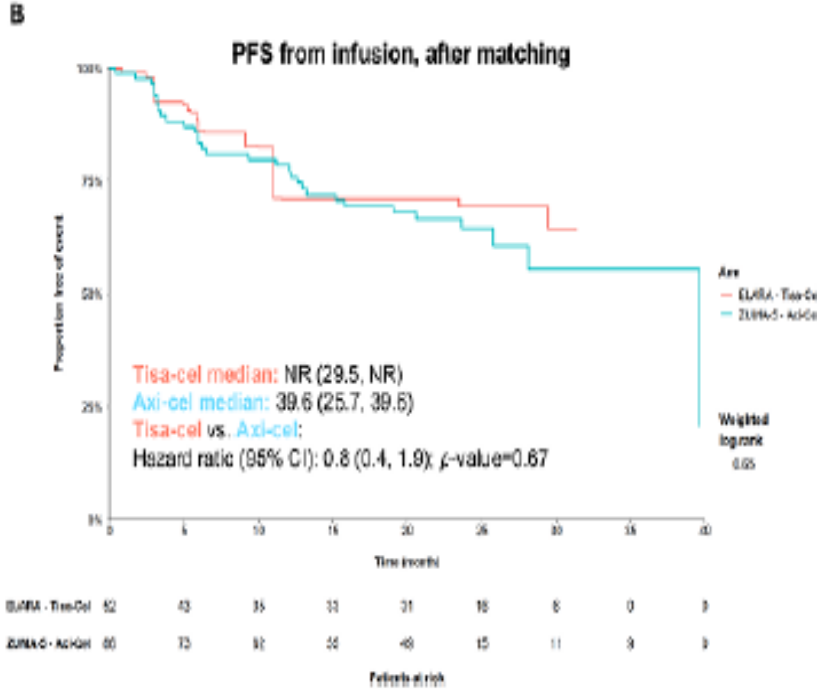
ORIGINAL ARTICLE

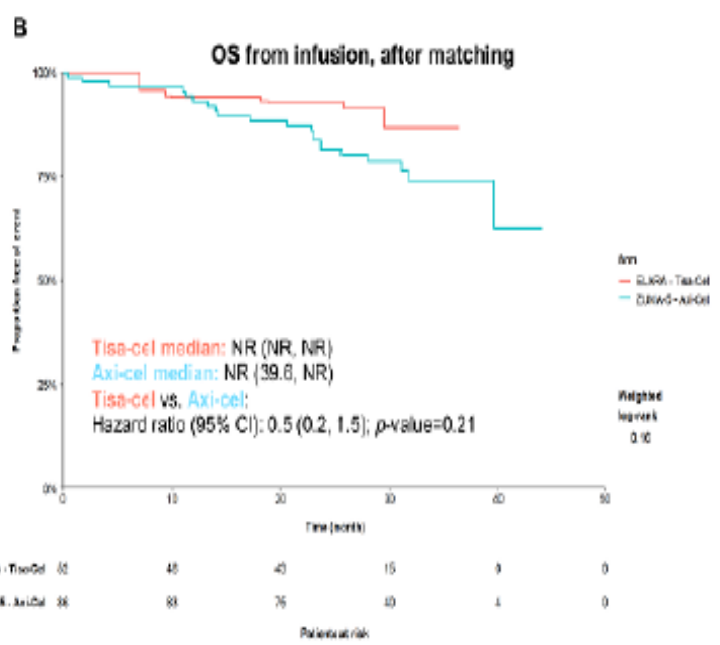
Comparative efficacy and safety of tisagenlecleucel and axicabtagene ciloleucel among adults with r/r follicular lymphoma

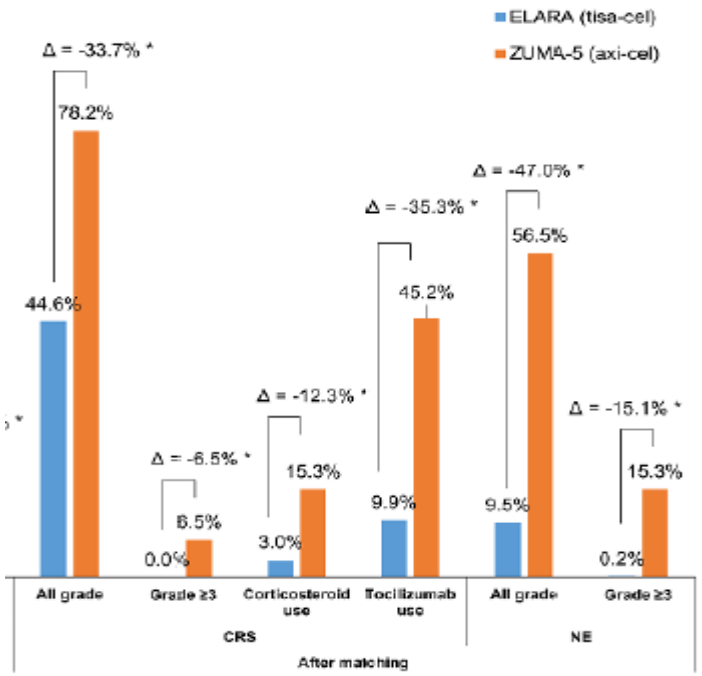
Michael Dickinson[a], Joaquin Martinez-Lopez[b], Etienne Jousseaume[c], Hongbo Yang[d], Xinglei Chai[d], Cheryl Xiang[d], Travis Wang[d], Jie Zhang[e], Roberto Ramos[e], Stephen J. Schuster[f] and Nathan Fowler[g]

[a]Peter MacCallum Cancer Centre, Royal Melbourne Hospital and the University of Melbourne, Melbourne, Australia; [b]Department of Medicine, School of Medicine, Hospital Universitario 12 de Octubre, Complutense University, CNIO, Centro de Investigación Biomédica en Red Cáncer (CIBERONC), Madrid, Spain; [c]Novartis Pharmaceuticals AG, Basel, Switzerland; [d]Analysis Group Inc., Boston, MA, USA; [e]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [f]Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [g]The University of Texas MD Anderson Cancer Center, Houston, TX, USA









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Article

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

Received: 12 January 2024

Accepted: 10 April 2024

Published online: 3 June 2024

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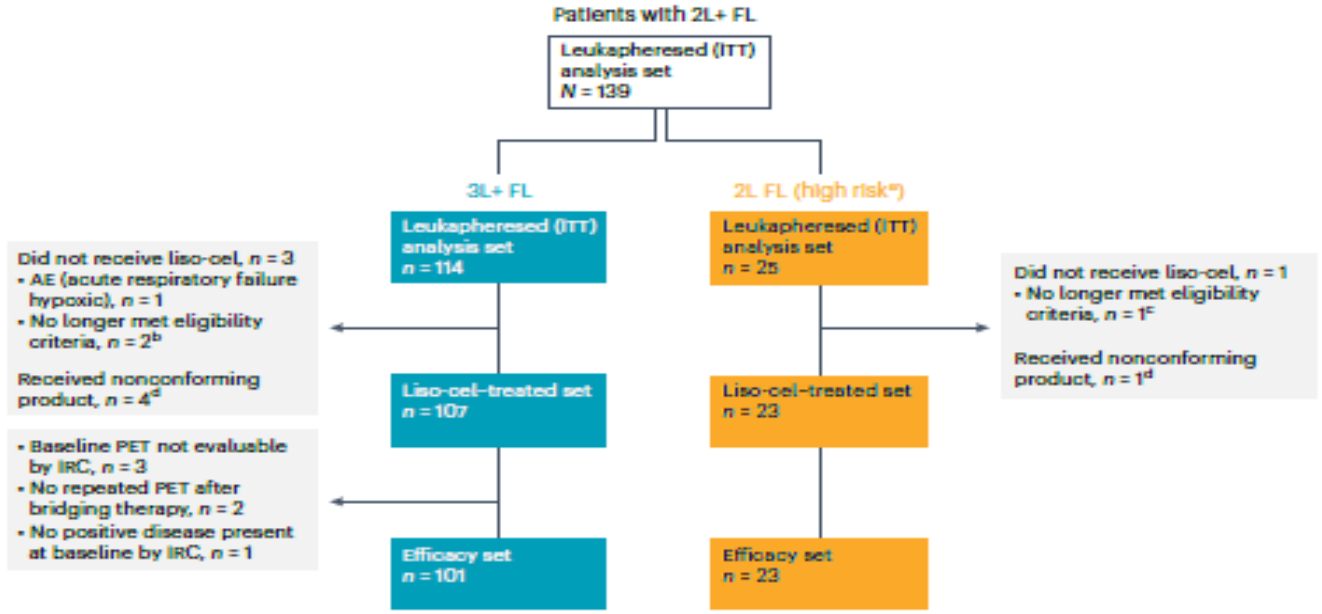

Fig. 1 | CONSORT diagram for patients with 3L+ FL and patients with high-risk 2L FL. [a]The high-risk 2L FL cohort included patients with POD24 from diagnosis and/or who met mGELF criteria. [b]One patient had history of transformed FL, and one patient had PET-negative disease at pre-treatment assessment. [c]Reached CR after bridging therapy per investigator assessment and had PET-negative disease at pre-treatment assessment. [d]Non-conforming product was defined as any product wherein one of the CD8 or CD4 cell components did not meet one of the requirements to be considered liso-cel but was considered appropriate for infusion.

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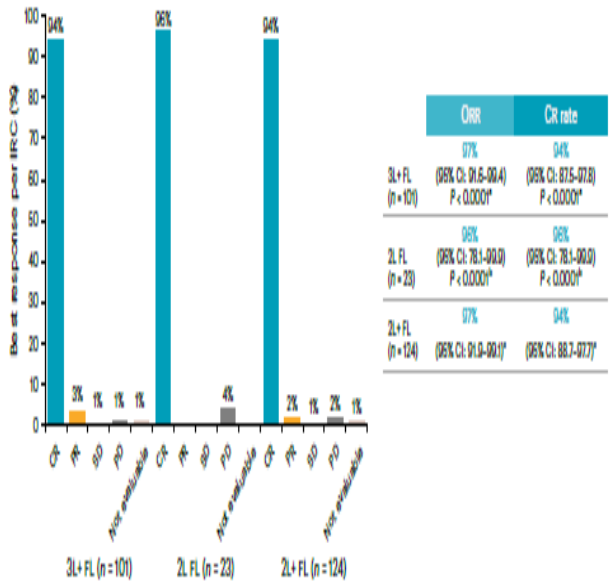
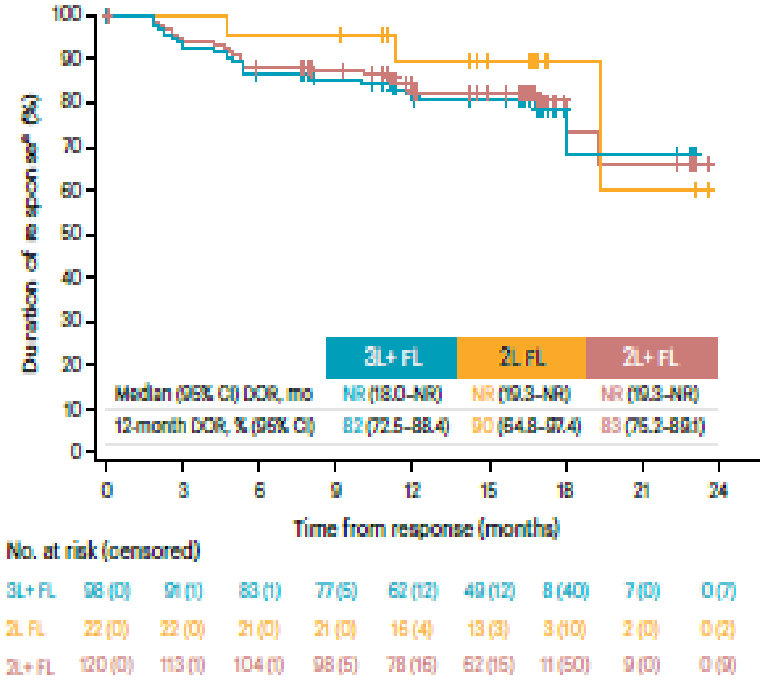


	ORR	CR rate
3L+ FL (n = 101)	97% (95% CI: 91.6–99.4) P < 0.0001*	94% (95% CI: 87.5–97.8) P < 0.0001*
2L FL (n = 23)	96% (95% CI: 78.1–99.9) P < 0.0001*	96% (95% CI: 78.1–99.9) P < 0.0001*
2L+ FL (n = 124)	97% (95% CI: 91.9–99.1)*	94% (95% CI: 88.7–97.7)*

Fig. 2 | ORR by best overall response per IRC assessment. *One-sided *P* value using exact binomial test (H_0 of ORR ≤ 60%; H_0 of CR rate ≤ 30%). †One-sided *P* value using exact binomial test (H_0 of ORR ≤ 50%; H_0 of CR rate ≤ 19%). ‡Not statistically tested (descriptive). H_0, null hypothesis; PR, partial response; SD, stable disease.



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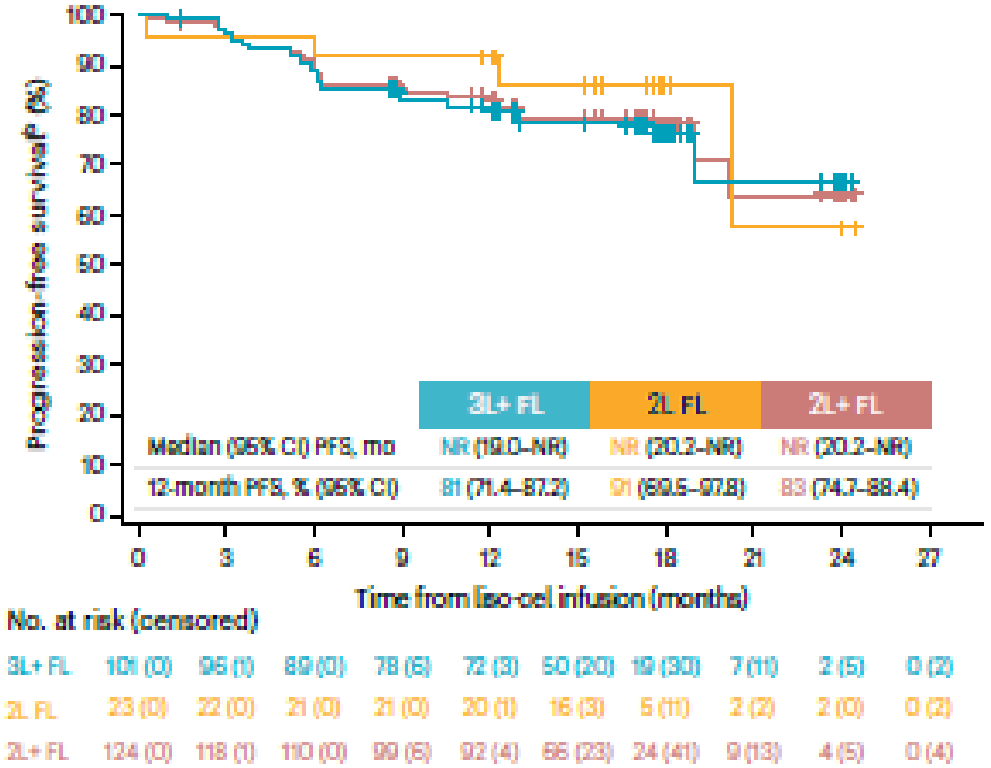

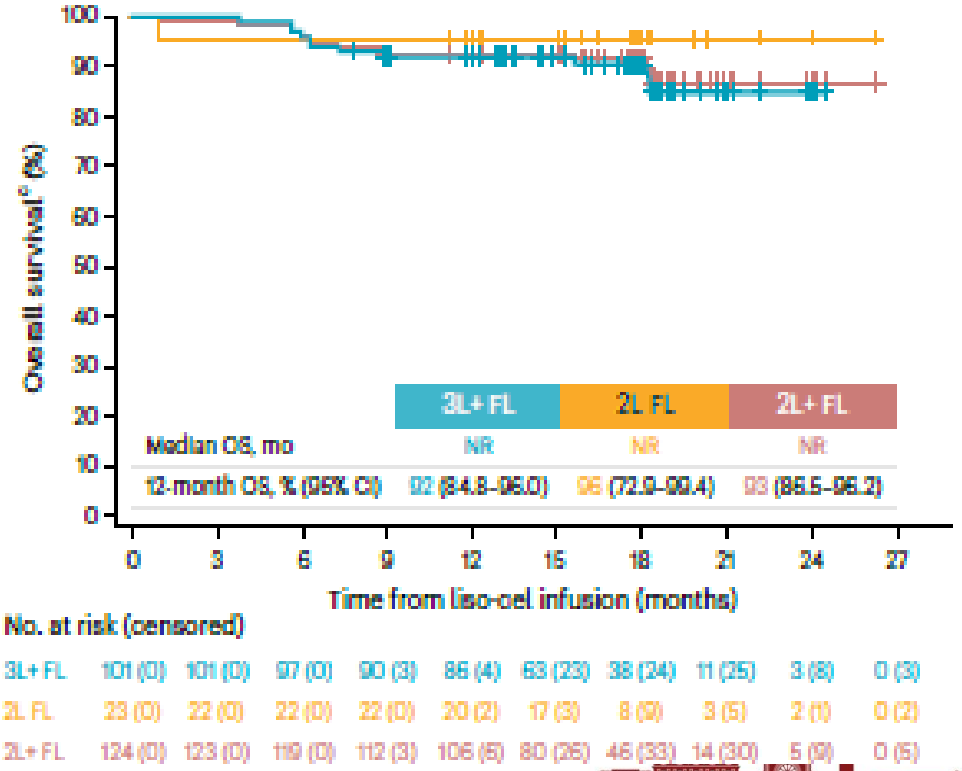

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Article

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

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

[a] TEAE period was defined as the time from initiation of liso-cel administration through and including study day 90.

Table 3 | AEs of special interest (liso-cel–treated set)

	2L+ FL (n=130)
CRS[a], n (%)	
Any grade	75 (58)
Grade 1	55 (42)
Grade 2	19 (15)
Grade 3[b]	1 (1)
Grade 4/5	0
Prolonged cytopenia[f], n (%)	29 (22)
Grade ≥3 neutropenia at day 29 visit, n (%)	20 (15)
Recovered to grade ≤2 by day 60[g], n/N (%)	12/20 (60)
Recovered to grade ≤2 by day 90[g], n/N (%)	18/20 (90)
Grade ≥3 anemia at day 29 visit, n (%)	6 (5)
Recovered to grade ≤2 by day 60[g], n/N (%)	2/6 (33)
Recovered to grade ≤2 by day 90[g], n/N (%)	5/6 (83)
Grade ≥3 thrombocytopenia at day 29 visit, n (%)	19 (15)

Table 3 (continued) | AEs of special interest (liso-cel–treated set)

	2L+ FL (n=130)
Second primary malignancy[j,k], n (%)	4 (3)
MAS/HLH, n (%)[b,l]	1 (1)
NEs[d], n (%)	
Any grade	20 (15)
Grade 1	15 (12)
Grade 2	2 (2)
Grade 3[e]	3 (2)
Grade 4/5	0
Median time to first onset of NE (range), d	8.5 (4-16)
Median time to resolution of first NE (range), d	3.5 (1-17)

12deaths , 2 progression,
1 PML, 1MAS/HLH

BiTEs (CD20xCD3) - single agent

Agent and trial	Phase	Administration	Pts, n	POD24, %	Prior tx, median	ORR (CR), %	Follow-up, median mo	PFS, median mo	OS, median mo	CRS-ICANS (any/gr ≥3), %	Infections gr ≥3, %
Mosunetuzumab (GO29781)[1,2]	II	IV, fixed duration	90	52	3 (2–4)	78 (60)	37.4	24	NR	44/2 5/0	18
Odronextamab (ELM-2)[3,4]	II	IV, Until PD	131	48	3 (2–13)	80 (72)	22.4	20.2	NR	56/4 1/0	32
Epcoritamab[5]	I/II	SC, Until PD	128	42	4.5 (2.5–8)	82 (63)	17.4	15.4	NR	59/2 6/2	NA
Glofitamab[6,7]	I	IV, Fixed duration	53	36	3 (1–12)	81 (70)	NA	NA	NA	67/5 NA	NA

CAR-T

Agent and trial	Phase	Infused pts, n	POD24, %	Prior tx, median	BT, %	Median time for infusion, days	ORR (CR), %	Follow-up, median mo	PFS, median mo	OS, median mo	CRS-ICANS (any/gr ≥3), %
Tisa-cel (ELARA)[1,2]	II	97	62	4 (2–13)	45	46*	86 (68)	29	NR	NR	48/0 4/1
Axi-cel (ZUMA-5)[3,4]	II	124	55	3 (2–4)	4	17**	94 (79)	40.5	40.2	NR	97/8 56/15
Liso-cel[5] (TRANSCEND-FL)	I/II	101	43	3 (2–10)	NA	NA	97 (94)	16.6	NR	NR	58/1 15/2

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†☆

M. Dreyling[1], M. Ghielmini[2], S. Rule[3], G. Salles[4,5], M. Ladetto[6], S. H. Tonino[7], K. Herfarth[8], J. F. Seymour[9] & M. Jerkeman[10], on behalf of the ESMO Guidelines Committee*

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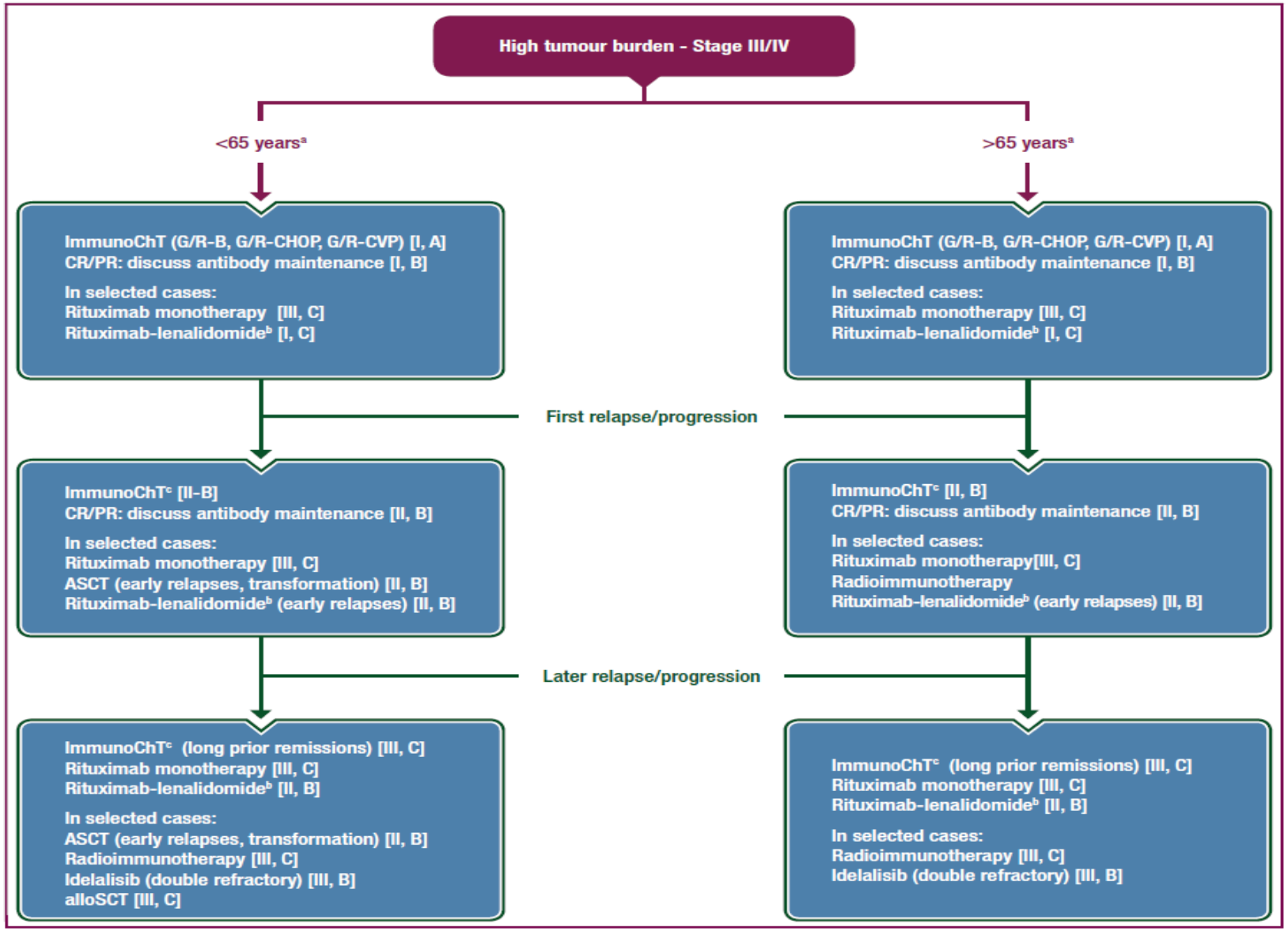
Available online 26 November 2020

Ab Bispecifici / CAR T
Nuove Combinazioni



CAR-T: e la storia continua...migliorando

Verona, 11 novembre 2024

Bispecific Antibodies in R/R FL: Considerations

- Currently, bispecific antibodies appear to be among the most active agents available for 3L+ FL, with the possible exception of CAR T-cell therapy
- Bispecific antibodies have some practical advantages over CAR T-cell therapy in terms of tolerability, administration, and availability
- **HOWEVER**, bispecific antibodies may still incur serious adverse events
  - Training and preparation of all staff, as well as patient education, are required to use bispecific antibodies safely
    - RNs, house staff, APPs, infusion center, whoever answers your phones (day or night), etc

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Future Oncology

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ifon20

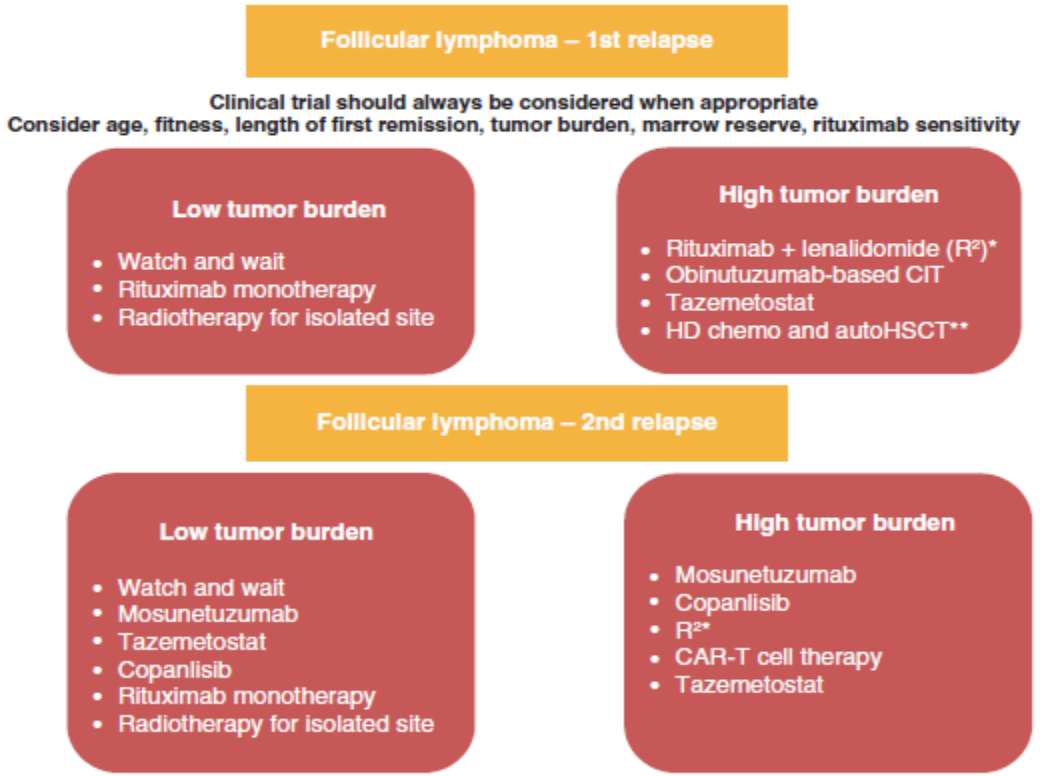


Figure 1. Proposed algorithm for treatment of relapsed/refractory follicular lymphoma at first and second relapse.
*If lenalidomide-naive.
**For younger, fit, chemo-sensitive patients with POD24.
CIT: Chemoimmunotherapy; HSCT: Hematopoietic stem cell transplantation.

Transplantation and Cellular Therapy 30 (2024) 832–843

Transplantation and Cellular Therapy

journal homepage: www.astctjournal.org

Guideline

Clinical Practice Recommendations for Hematopoietic Cell Transplantation and Cellular Therapies in Follicular Lymphoma: A Collaborative Effort on Behalf of the American Society for Transplantation and Cellular Therapy and the European Society for Blood and Marrow Transplantation

Madiha Iqbal[1,*], Ambuj Kumar[2], Peter Dreger[3], Julio Chavez[4], Craig S. Sauter[5], Anna M. Sureda[6], Veronika Bachanova[7], Richard T. Maziarz[8], Martin Dreyling[9], Sonali M. Smith[10], Caron Jacobson[11], Bertram Glass[12], Carla Casulo[13], Olalekan O. Oluwole[14], Silvia Montoto[15], Ranjana Advani[16], Jonathon Cohen[17], Gilles Salles[18], Nada Hamad[19], John Kuruvilla[20], Brad S. Kahl[21], Mazyar Shadman[22], Abraham S. Kanate[23], Lihua Elizabeth Budde[24], Manali Kamdar[25], Christopher Flowers[26], Mehdi Hamadani[27,#], Mohamed A. Kharfan-Dabaja[1,#]

Final clinical practice guidelines consensus statements for transplantation and CAR T-cell treatments for late first relapse, second relapse and beyond FL

Question	Response* (N = 27)		Consensus Achieved†
	Agree N (%)	Disagree N (%)	
1. The panel **DOES NOT** recommend autologous transplant as consolidation therapy in eligible, relapsed FL patients who did not achieve complete or partial remission after second or subsequent line therapies.	26 (96)	1 (4)	Yes
2. The panel **recommends** considering CAR T-cell therapy in relapsed FL patients who did not achieve complete or partial remission after second line of therapy.	24 (89)	3 (11)	Yes
3. The panel **recommends** considering CAR T-cell therapy in relapsed FL patients who did not achieve complete or partial remission after third or subsequent lines of therapies.	25 (93)	2 (7)	Yes
4. The panel **recommends** considering CAR T-cell therapy in eligible, relapsed FL patients who have relapsed after an autologous transplant and did not achieve complete or partial remission to most recent anti-lymphoma treatment.	25 (93)	2 (7)	Yes
5. The panel **DOES NOT** recommend autologous transplant as consolidation therapy in eligible, relapsed FL patients who have relapsed after CAR T-cell therapy and did not achieve complete or partial remission to most recent anti-lymphoma treatment.	26 (96)	4 (1)	Yes

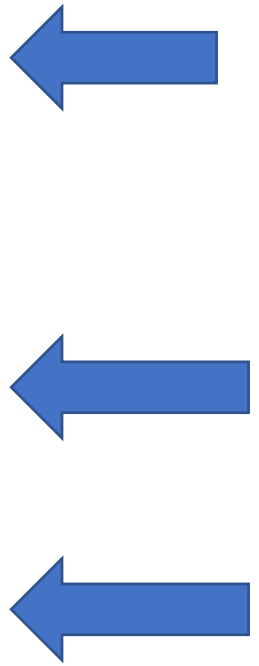
ASTCT
American Society for Transplantation and Cellular Therapy

Transplantation and Cellular Therapy 30 (2024) 832–843

Final clinical practice guidelines consensus statements for transplantation and CAR T-cell treatments for late first relapse, second relapse and beyond FL

ASTCT
American Society for Transplantation and Cellular Therapy

6. The panel **recommends** considering allogeneic transplant as consolidation therapy in eligible, relapsed FL patients who have received 3 or more lines of systemic therapy and are in one of the following clinical scenarios: i. Develop disease relapse early post autologous transplant and do not have access to CAR T-cell therapy ii. Develop disease relapse post CAR T-cell therapy iii. Develop therapy related myeloid neoplasm or bone marrow failure syndrome.	22 (81) 24 (89) 25 (93)	5 (19) 3 (11) 2 (7)	Yes Yes Yes
7. The panel **recommends** that allogeneic transplant be considered as a salvage/consolidation therapy only in patients who have achieved complete or partial remission to the most recent anti-lymphoma treatment. Candidacy for allogeneic transplant is dependent on good performance status and adequate organ function.	21 (78)	6 (22)	Yes
8. The panel **recommends** CAR T-cell therapy in eligible, relapsed FL patients who have relapsed after allogeneic transplant and are untreated or did not achieve complete or partial remission to most recent anti-lymphoma treatment.	25 (93)	2 (7)	Yes

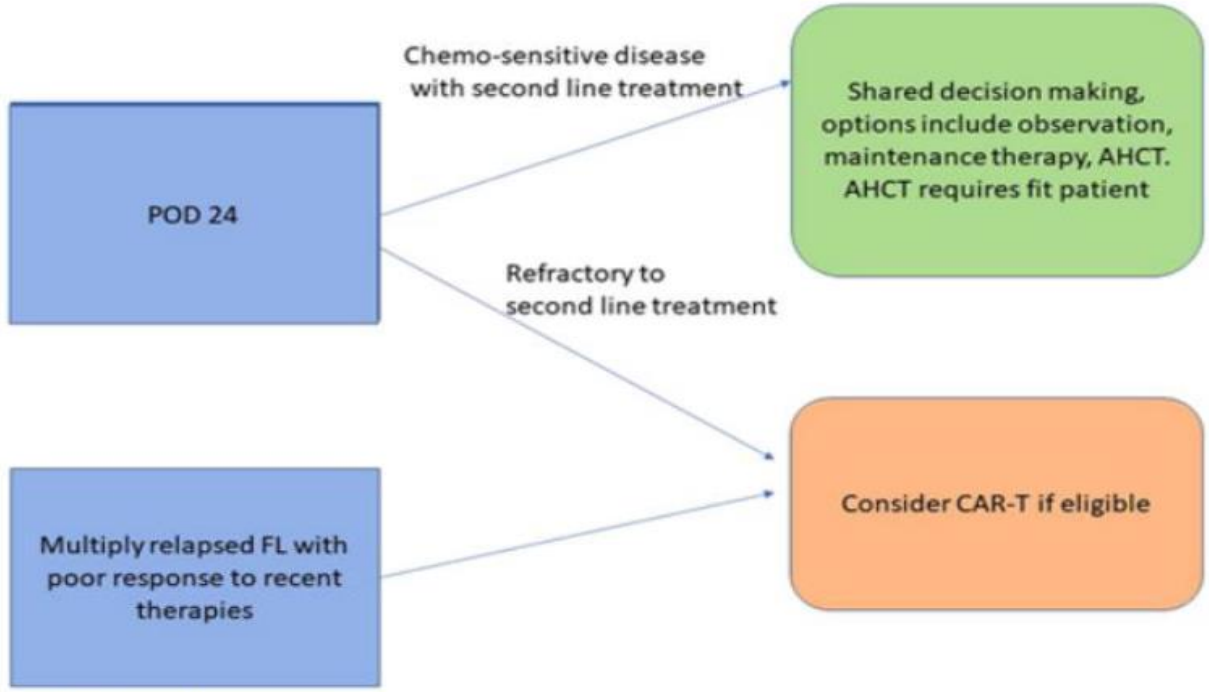


Transplantation and Cellular Therapy 30 (2024) 832–843

When should autologous transplant or cellular therapy be considered for follicular lymphoma?

Recommendations

1. AHCT in first remission does not improve OS in FL and should not be performed—strong recommendation based on moderate certainty to the evidence of effects.
2. AHCT in second or third remission may be considered for select very high-risk patients with FL with chemosensitive disease, ideally achieving complete metabolic response—conditional recommendation based on low certainty of the evidence of effects.
3. CAR-T therapy in the third or later line of therapy for FL offers high response rates and should be considered in high-risk patients with a short expected duration of response to alternative available therapies or lack of complete response to chemotherapy—conditional recommendation based on moderate certainty to the evidence of effects.



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Regular Article

LYMPHOID NEOPLASIA

Loss of CD20 expression as a mechanism of resistance to mosunetuzumab in relapsed/refractory B-cell lymphomas

Stephen J. Schuster,[1] Ling-Yuh Huw,[2] Christopher R. Bolen,[2] Victor Maximov,[2] Andrew G. Polson,[2] Katerina Hatzi,[2] Elisabeth A. Lasater,[2] Sarit E. Assouline,[3] Nancy L. Bartlett,[4] L. Elizabeth Budde,[5] Matthew J. Matasar,[6] Hartmut Koeppen,[2] Emily C. Piccione,[2] Deanna Wilson,[2] Michael C. Wei,[2] Shen Yin,[2] and Elicia Penuel[2]

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KEY POINTS

- We identified CD20 loss at progression in the phase 1/2 GO29781 trial of mosunetuzumab monotherapy in B-cell NHL.
- Reduced transcription or gain of truncating mutations explained most but not all cases of CD20 loss with mosunetuzumab.

CD20 is an established therapeutic target in B-cell malignancies. The CD20 × CD3 bispecific antibody mosunetuzumab has significant efficacy in B-cell non-Hodgkin lymphomas (NHLs). Because target antigen loss is a recognized mechanism of resistance, we evaluated CD20 expression relative to clinical response in patients with relapsed and/or refractory NHL in the phase 1/2 GO29781 trial investigating mosunetuzumab monotherapy. CD20 was studied using immunohistochemistry (IHC), RNA sequencing, and whole-exome sequencing performed centrally in biopsy specimens collected before treatment at predose, during treatment, or upon progression. Before treatment, most patients exhibited a high proportion of tumor cells expressing CD20; however, in 16 of 293 patients (5.5%) the proportion was <10%. Analyses of paired biopsy specimens from patients on treatment revealed that CD20 levels were maintained in 29 of 30 patients (97%) vs at progression, where CD20 loss was observed in 11 of 32 patients (34%). Reduced transcription or acquisition of truncating mutations explained most but not all cases of CD20 loss. In vitro modeling confirmed the effects of CD20 variants identified in clinical samples on reduction of CD20 expression and missense mutations in the extracellular domain that could block mosunetuzumab binding. This study expands the knowledge about the occurrence of target antigen loss after anti-CD20 therapeutics to include CD20-targeting bispecific antibodies and elucidates mechanisms of reduced CD20 expression at disease progression that may be generalizable to other anti-CD20 targeting agents. These results also confirm the utility of readily available IHC staining for CD20 as a tool to inform clinical decisions. This trial was registered at www.ClinicalTrials.gov as #NCT02500407.