Unmet challenges in high-risk hematological malignancies: from bench side to clinical practice – 3rd Edition
Torino, September 21-22, 2023

Indolent lymphoma

How I treat high-risk relapsed/refractory follicular lymphoma

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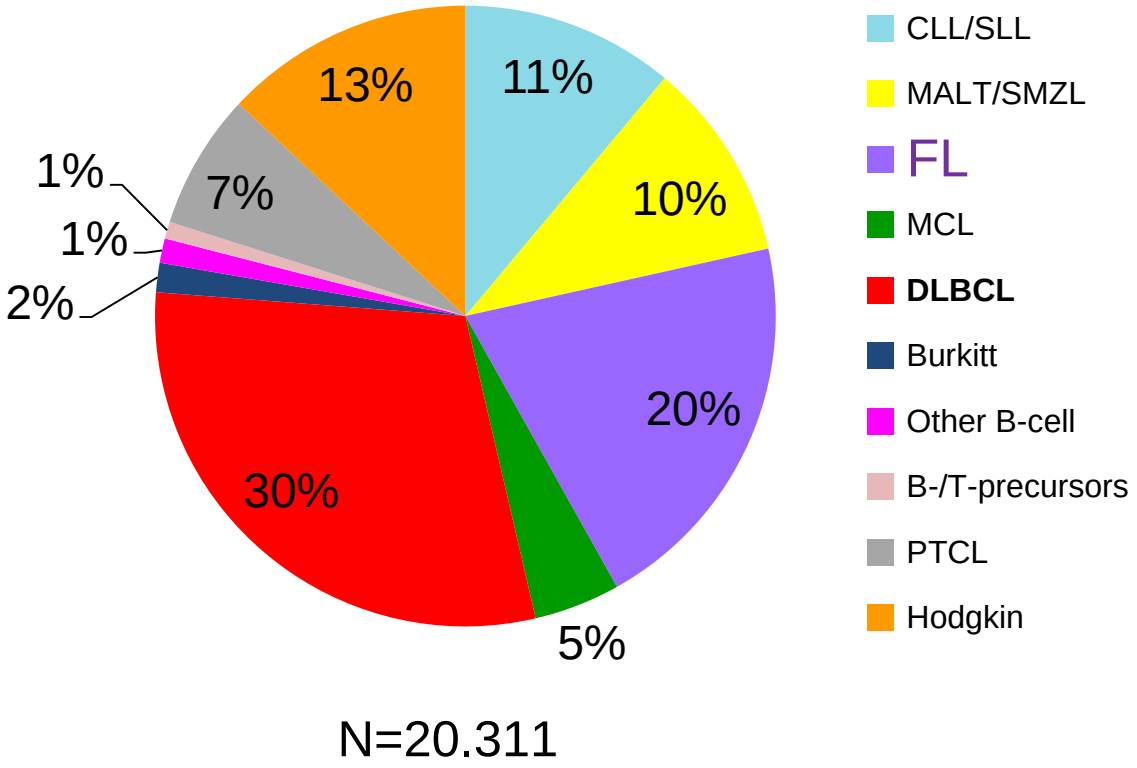
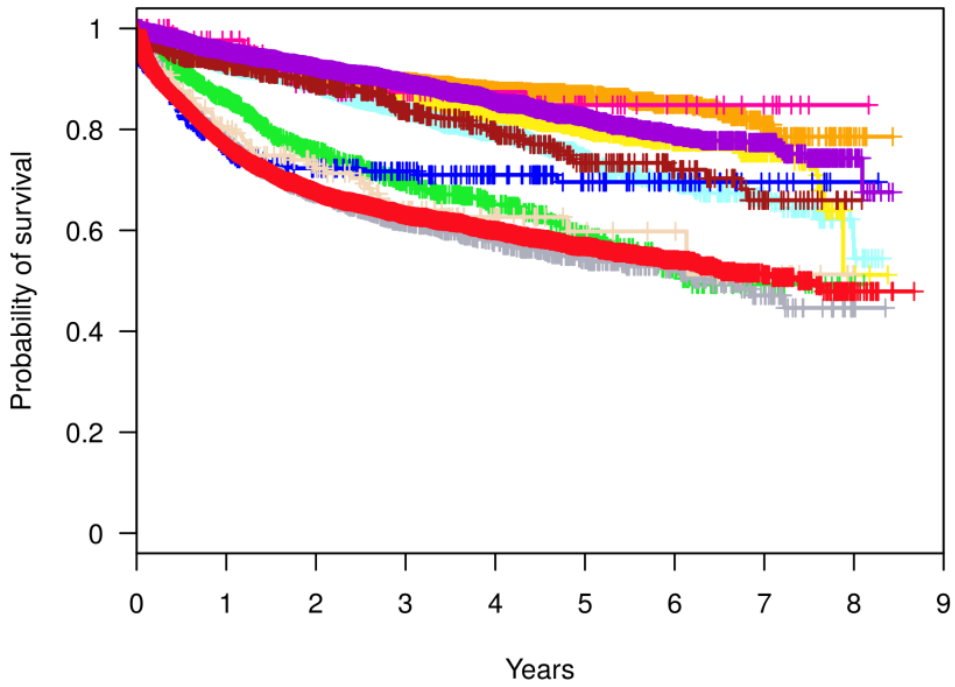
Disclosures

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

Histologic distribution of lymphomas



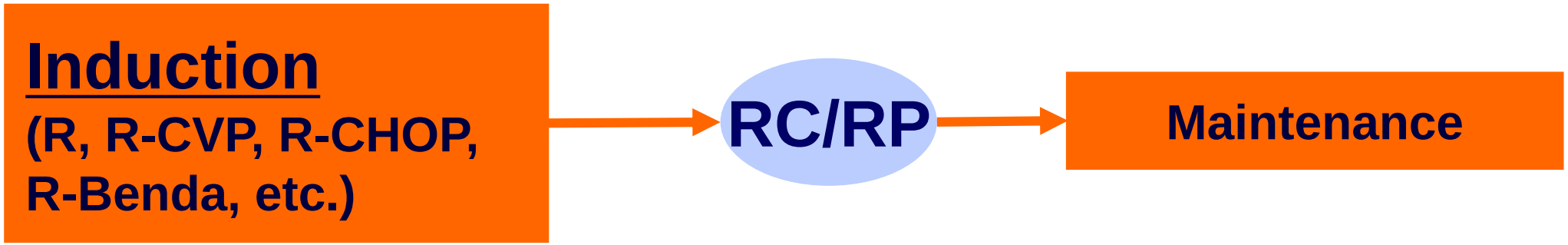
N=20.311



GELTAMO 2014/21

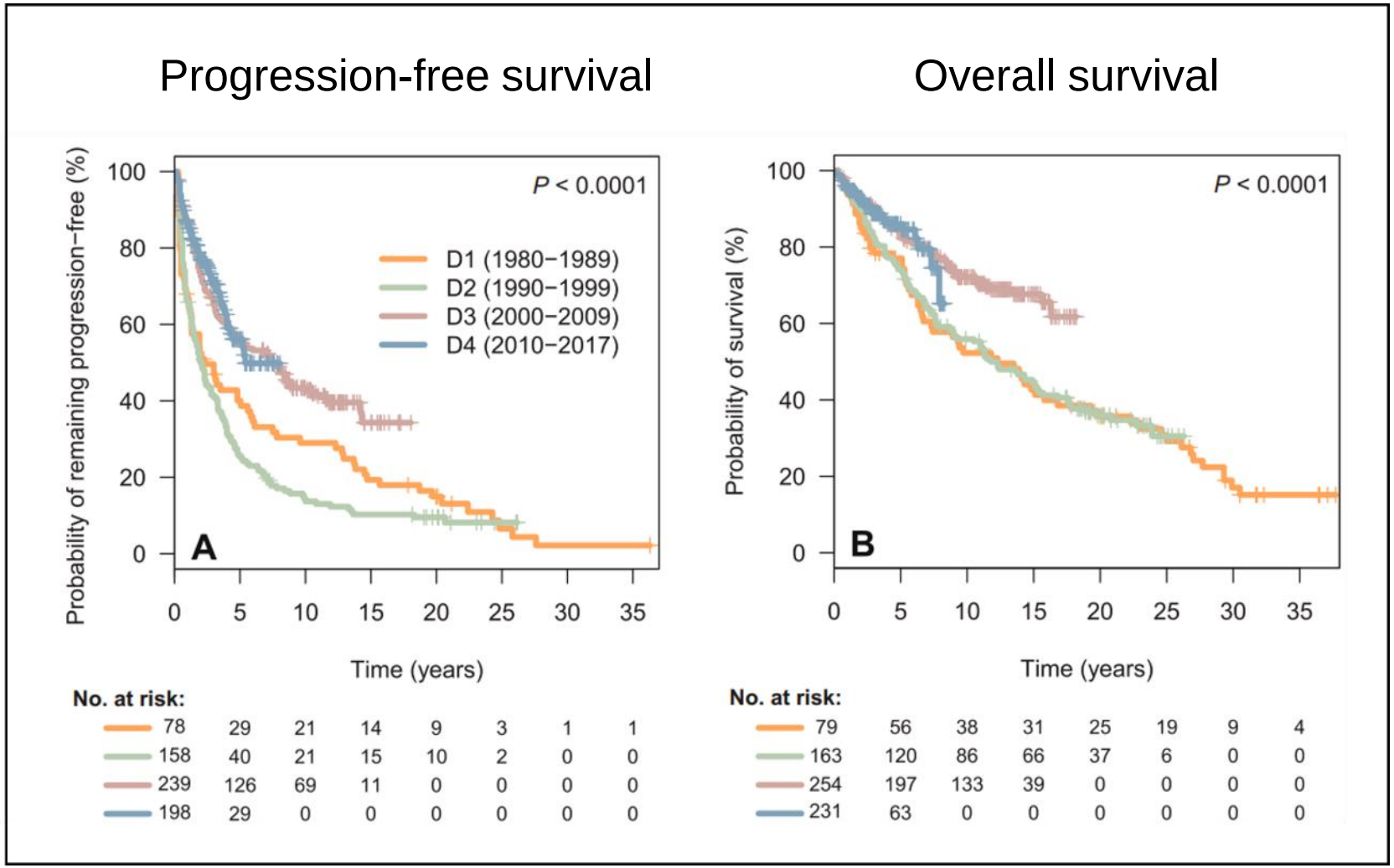
Bastos-Oreiro M, Ann Hematol 2020;99:799-808 (updated July 2022)

Treatment of follicular lymphoma



In absence of treatment criteria: observation (WW policy)

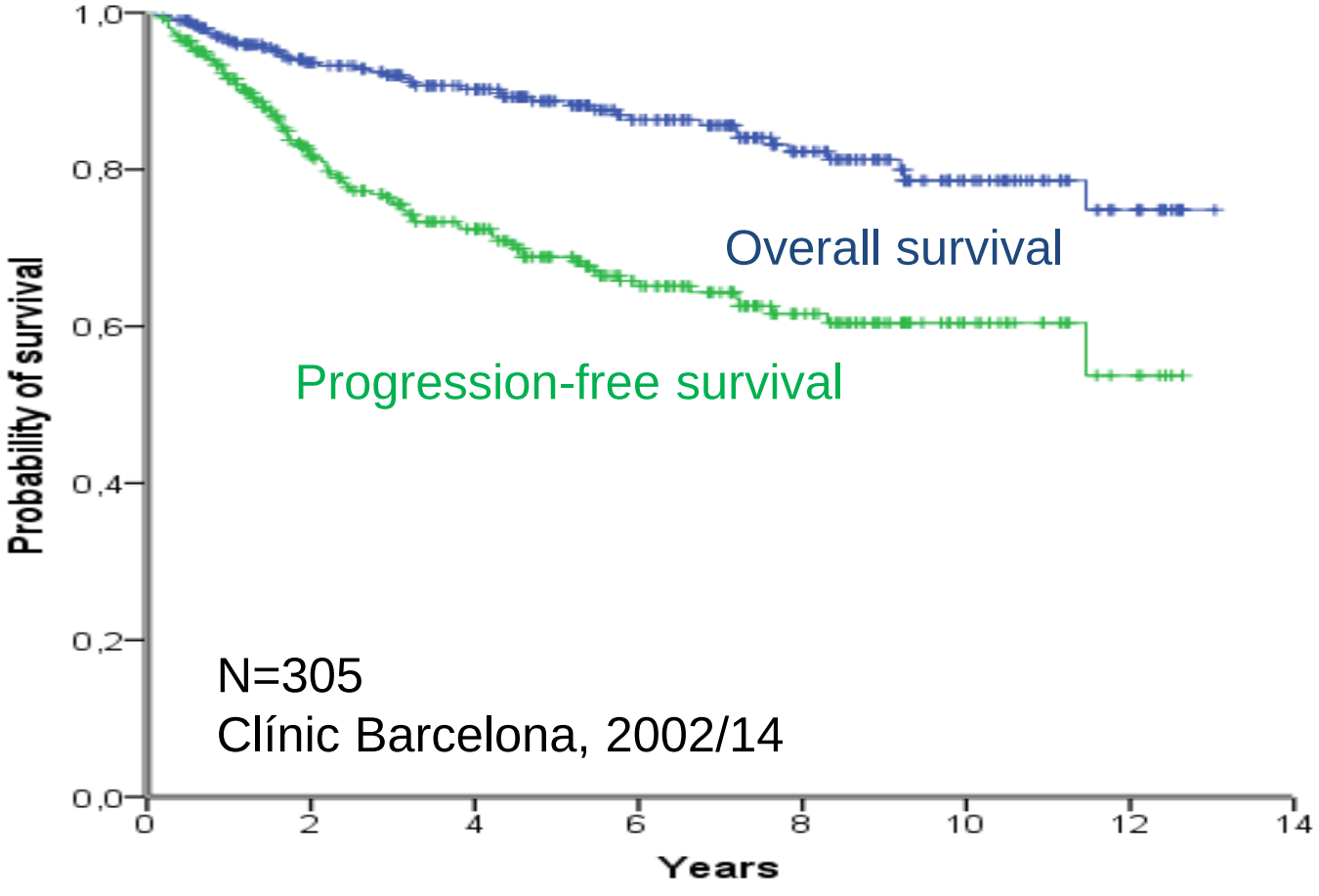
Follicular lymphoma: outcome over the past four decades



- Better prognosis in the last two decades
- “Current” median survival about 18-20 years

Mozas P, Blood Cancer J 2020;10:31

Follicular lymphoma treated with immunochemotherapy



- Very long survival (median: 15-¿20? years)
- But, high risk of relapse (often one or more relapses during the follow-up)
- Still poor risk:
  - Early relapses
  - Histological transformation

What does “high-risk” mean in the R/R setting?

A real patient from our clinics …

- 62-year-old gentleman, with no relevant past medical history
- July 2014: grade 2 FL, asymptomatic, but with several enlarged lymph nodes, including abdominal bulky mass and bone marrow involvement

  Stage IV-"A", high-risk FLIPI (age, stage, #lymph node areas)
- August 2014: R-CHOPx6 → metabolic CR with residual mass
- January 2015: R maintenance
- February 2016: relapse

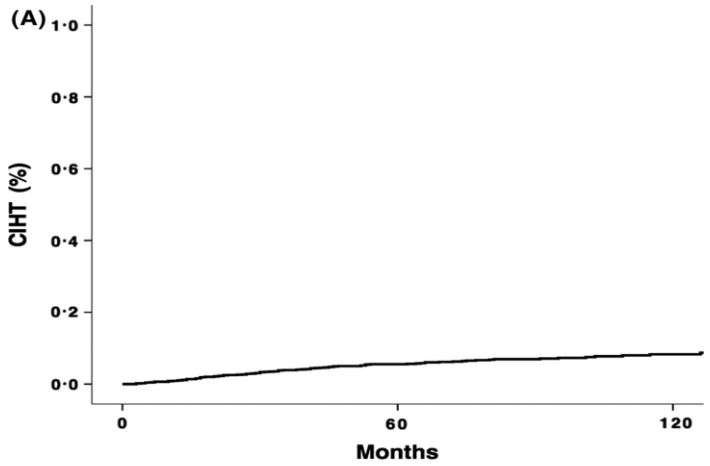
Follicular lymphoma: prognosis at 1st relapse

(→ to select ”the best” treatment)

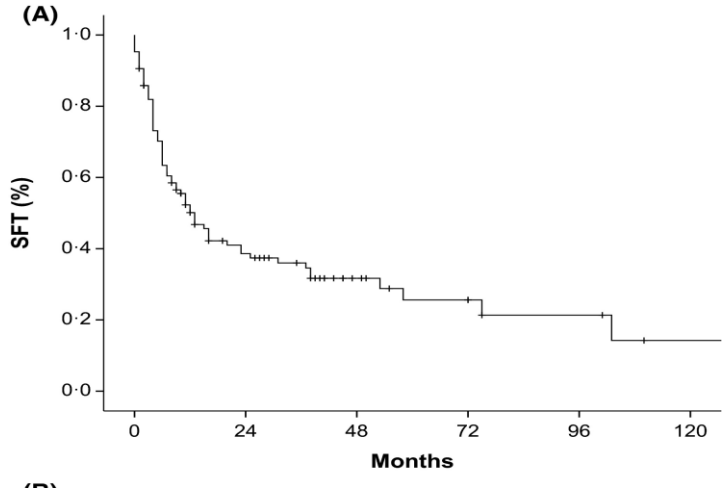
- Standard prognostic factors
  - Age, performance status, dissemination and tumor mass
  - FLIPI (or other scores)
- Previous treatment (R – R-CT …)
- Histology (histological transformation)
- Response duration

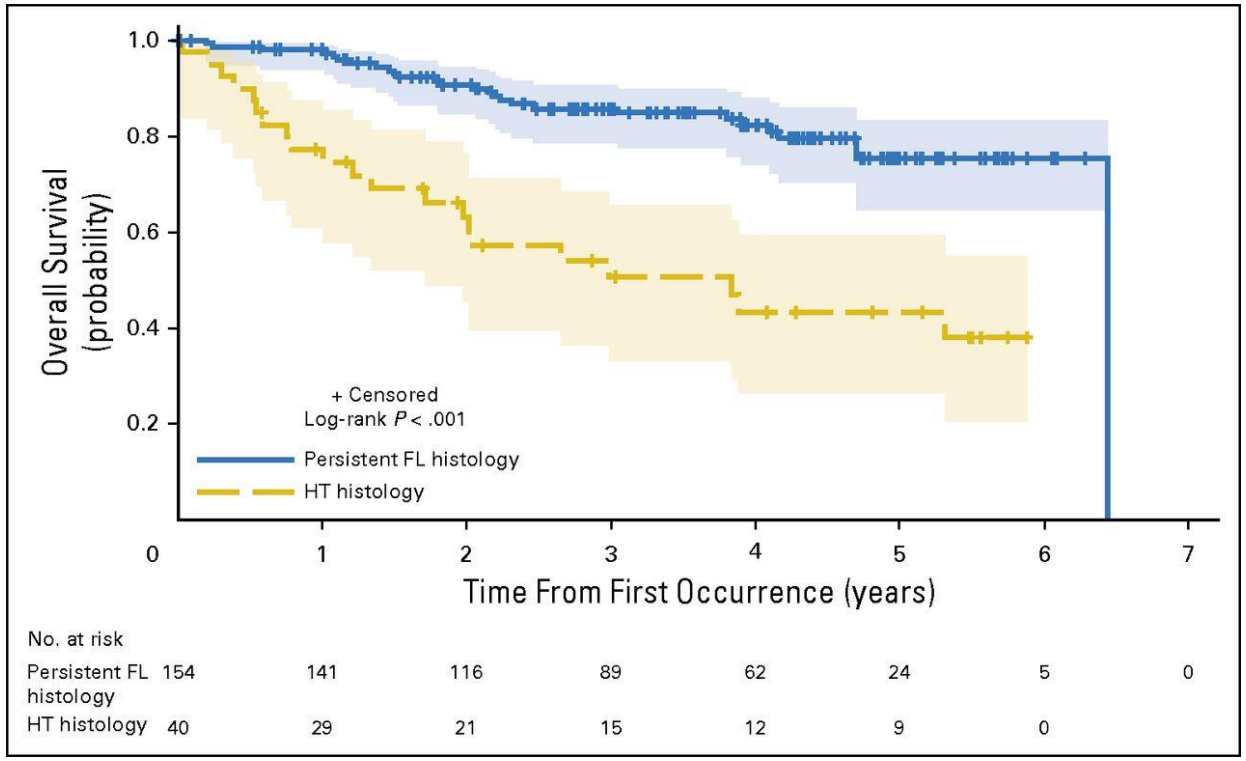
Cumulative incidence of histological transformation and survival from transformation. GELTAMO and PRIMA series

Risk of transformation



Survival from transformation



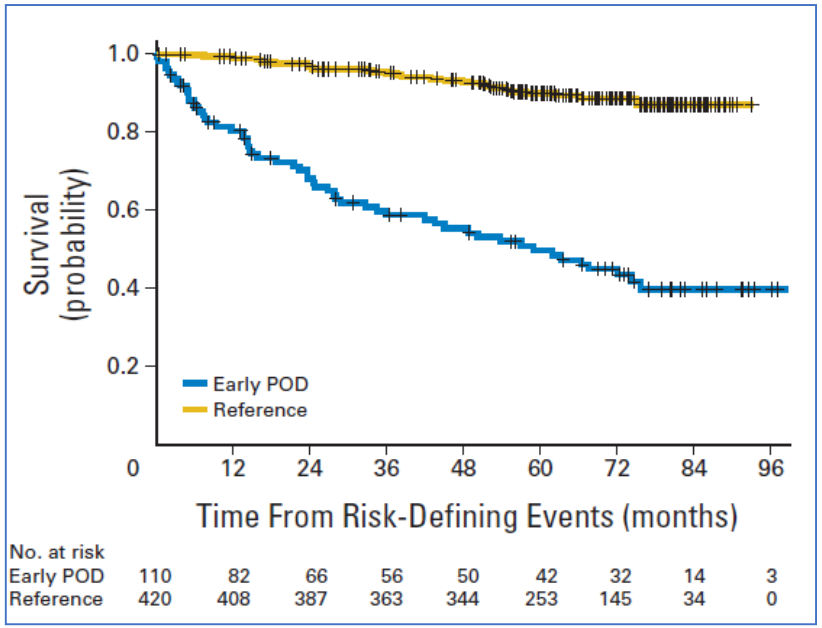


Alonso-Álvarez S, Br J Haematol 2017;178:699-708
Sarkozy C, J Clin Oncol 2016;34:2575-82

FL: Prognosis after treatment

Early relapse: POD24

POD24 = progression or death within 24 months from starting treatment



5y-OS: 90% *vs.* 50% POD24

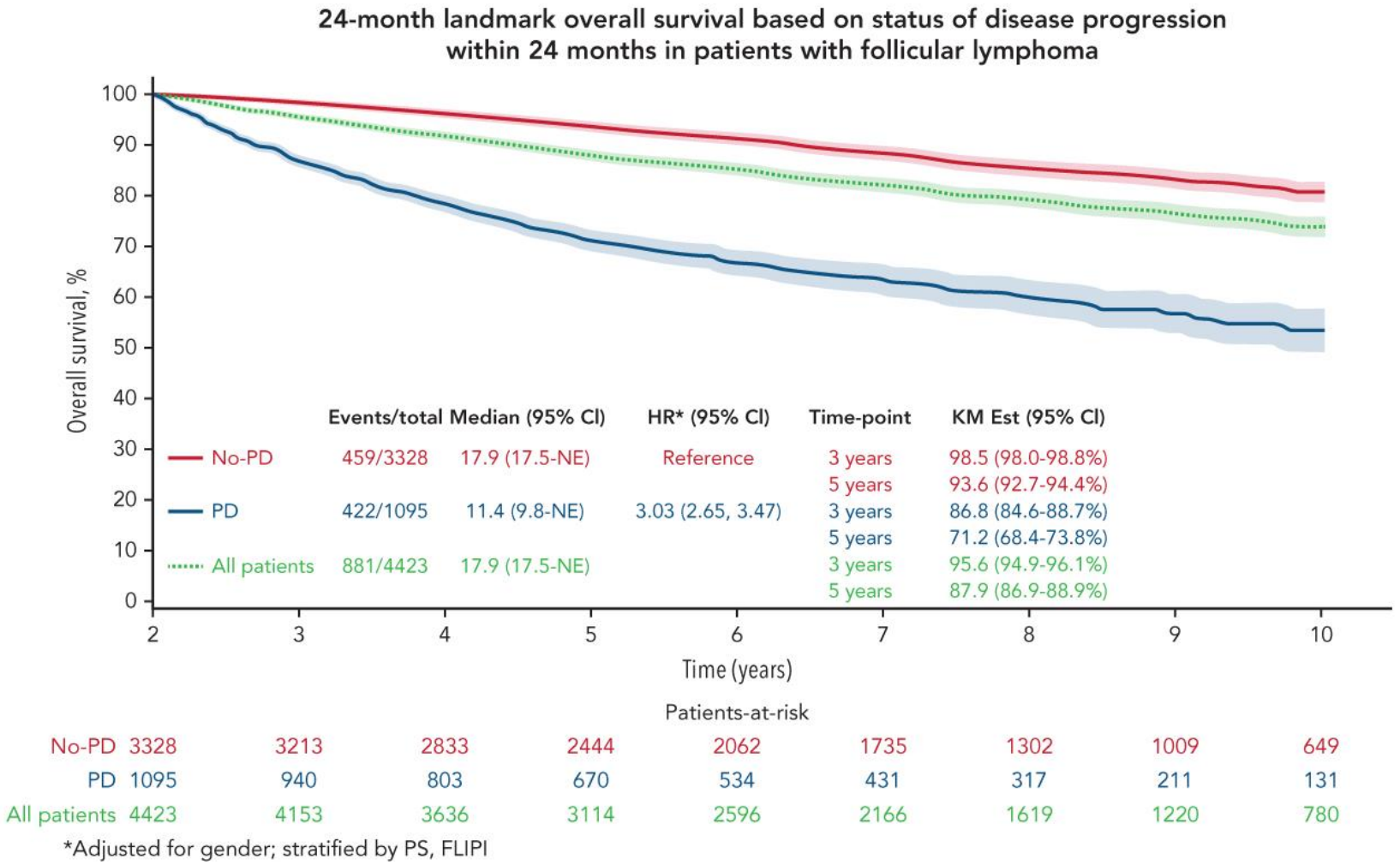
→ 1 out of 5 patients with FL (≈20%)

→ Similar incidence in most studies (exception: obinutuzumab)

→ Associated with high LDH, B-symptoms and high-risk FLIPI

Casulo C et al, JCO 2015; Murakami et al, Ann Hematol 2016

POD24 in follicular lymphoma

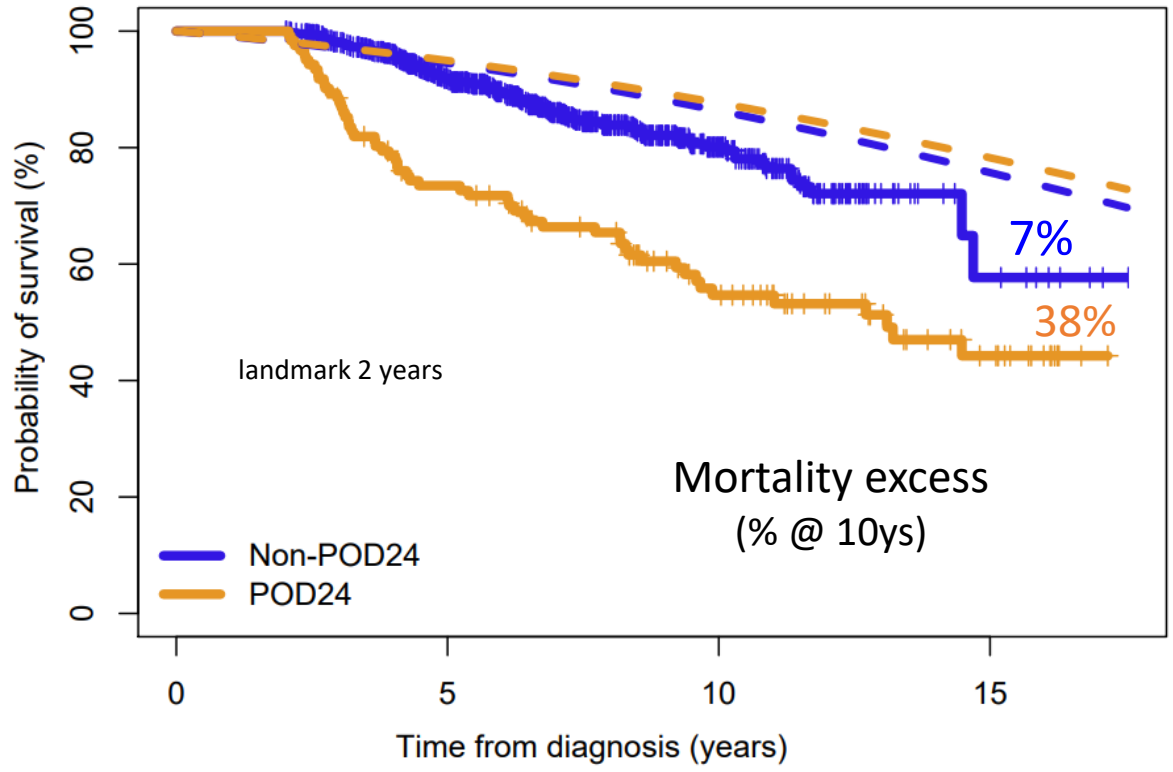


Casulo C, Blood 2022;139:1684-93

Global series N=1067

Overall survival

Patients POD24 vs. non-POD24



No. at risk				
Non-POD24	834	562	137	8
POD24	122	86	46	15

Relative survival

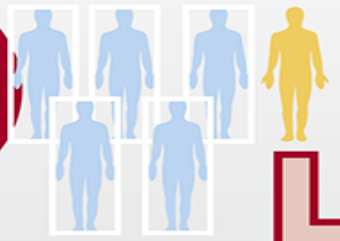
(compared with general population adjusted by sex and age)

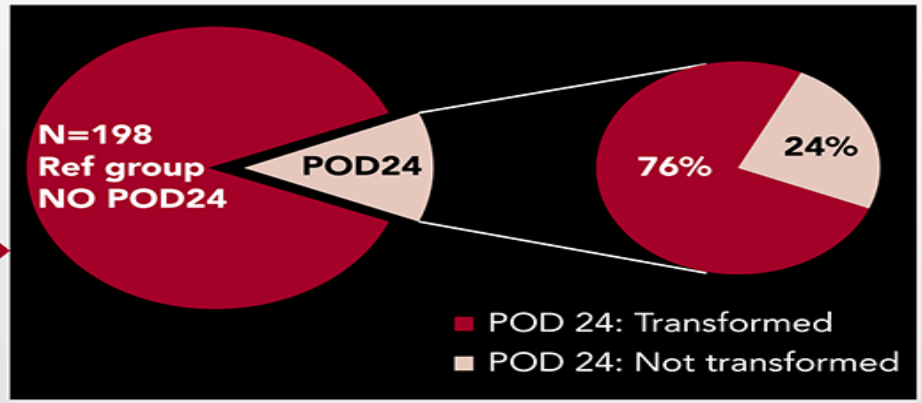
10-yr OS: 80% *vs* 54%

Muntañola A, Br J Haematol 2023;200:306-14

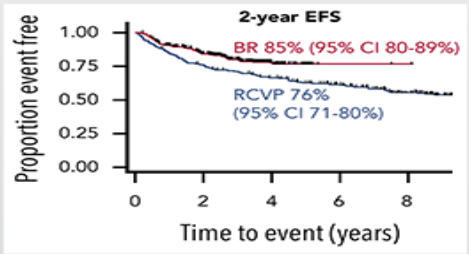
Early progression after BR is associated with high risk of transformation in advanced stage follicular lymphoma

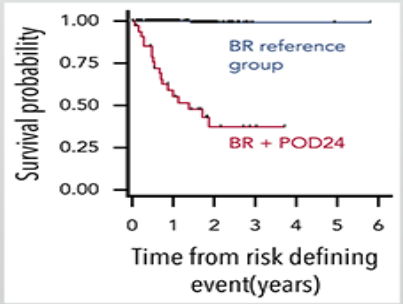
296 BR treated FL pts





Good outcomes vs historical controls





Poor OS in POD24 subgroup

The occurrence of early progression (POD24) may be decreasing following the introduction of BR, but the majority of POD24 patients have transformed lymphoma.

BC CANCER
Provincial Health Services Authority

CL Freeman, R Kridel, AA Moccia, KJ Savage, D Villa, DW Scott, AS Gerrie, D Ferguson, F Cafferty, GW Slack, P Farinha, B Skinnider, JM Connors, LH Sehn

Freeman CL, Blood 2019;134:761-4

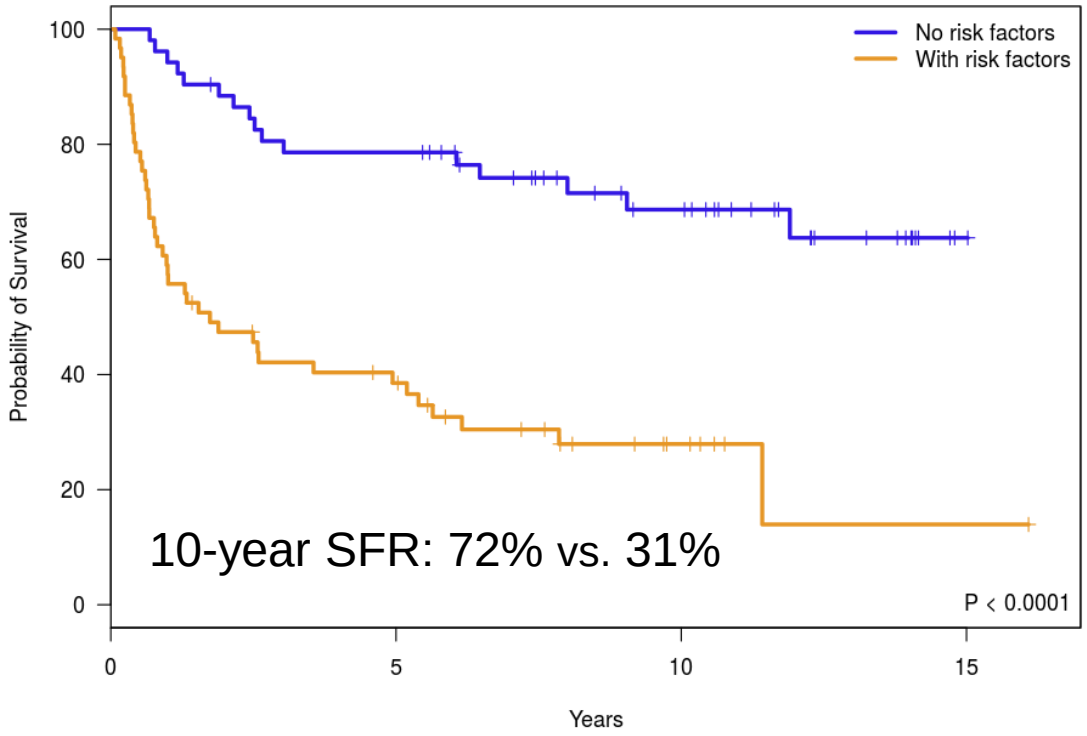
POD24 population N=162

Survival from relapse

Analyzed factors:

- Histological transformation
- High-risk FLIPI

No. of risk factors (110/162):
- None: 52 (47%)
- 1 factor: 10 (9%)
- 2 factors: 48 (44%)

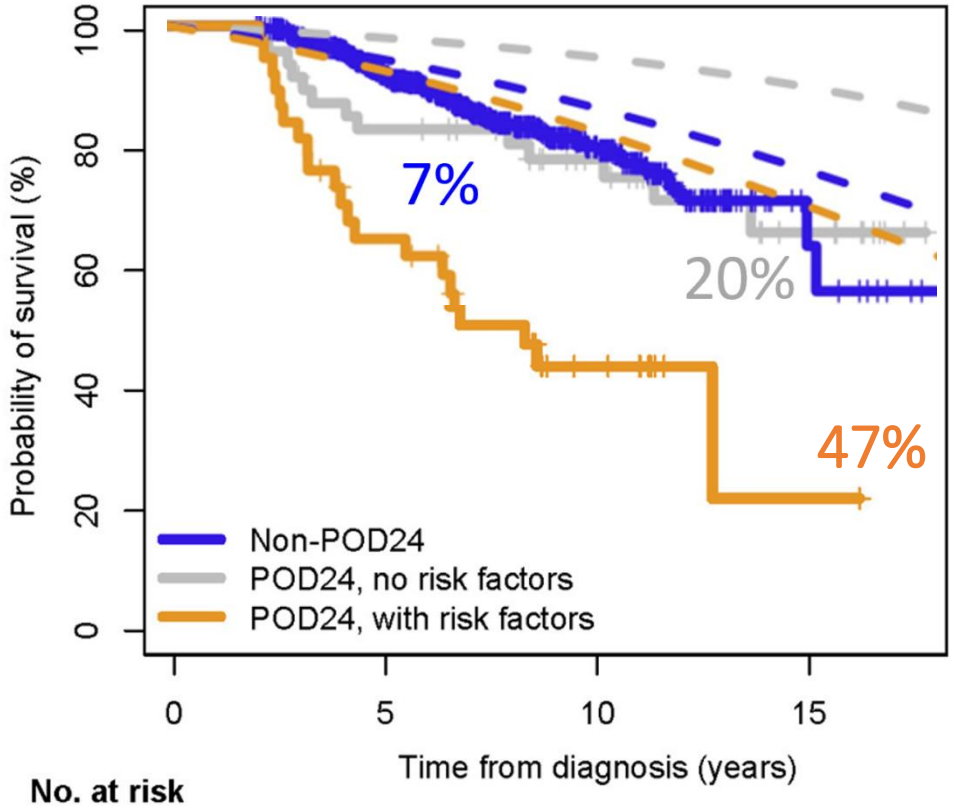


Muntañola A, Br J Haematol 2023;200:306-14

Global series N=1067

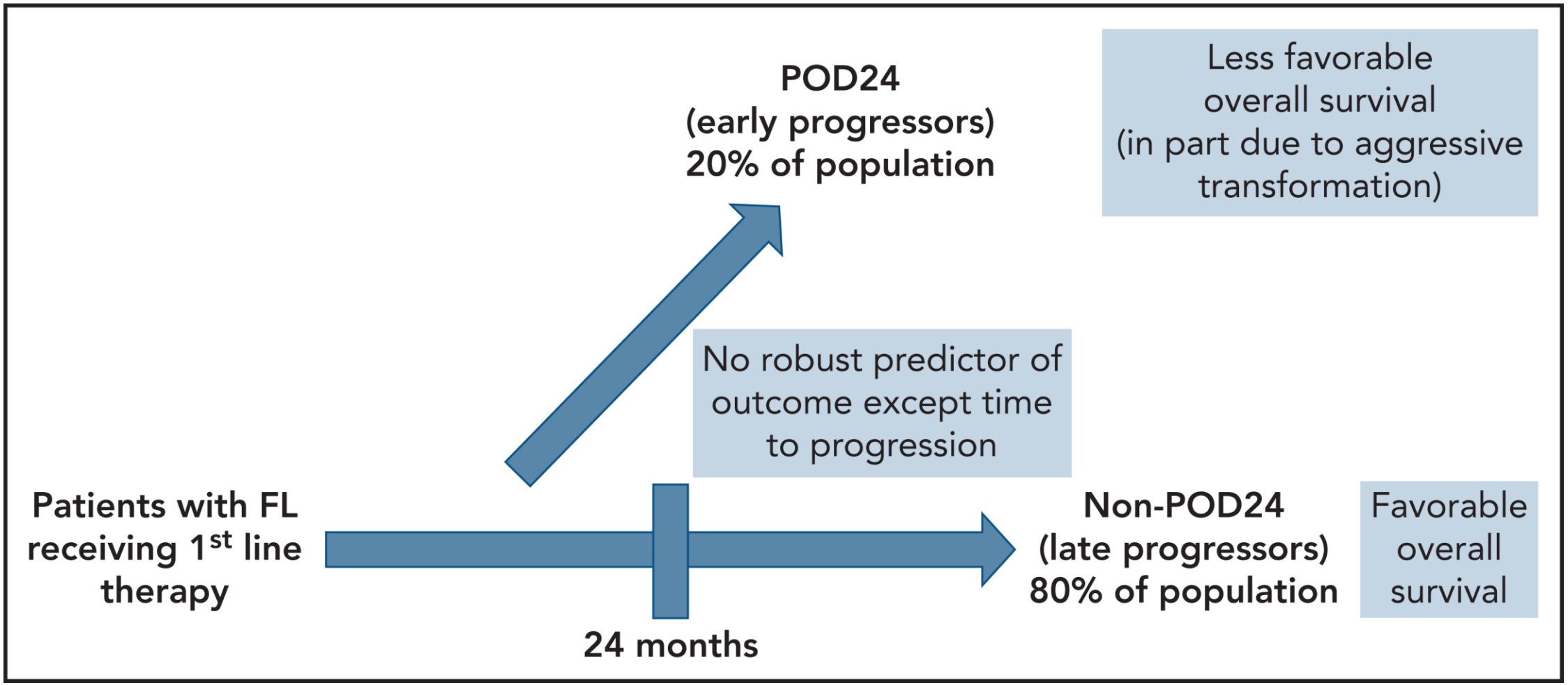
Overall survival

"low-risk" POD24 *vs.* "high-risk" POD24 *vs.* non-POD24



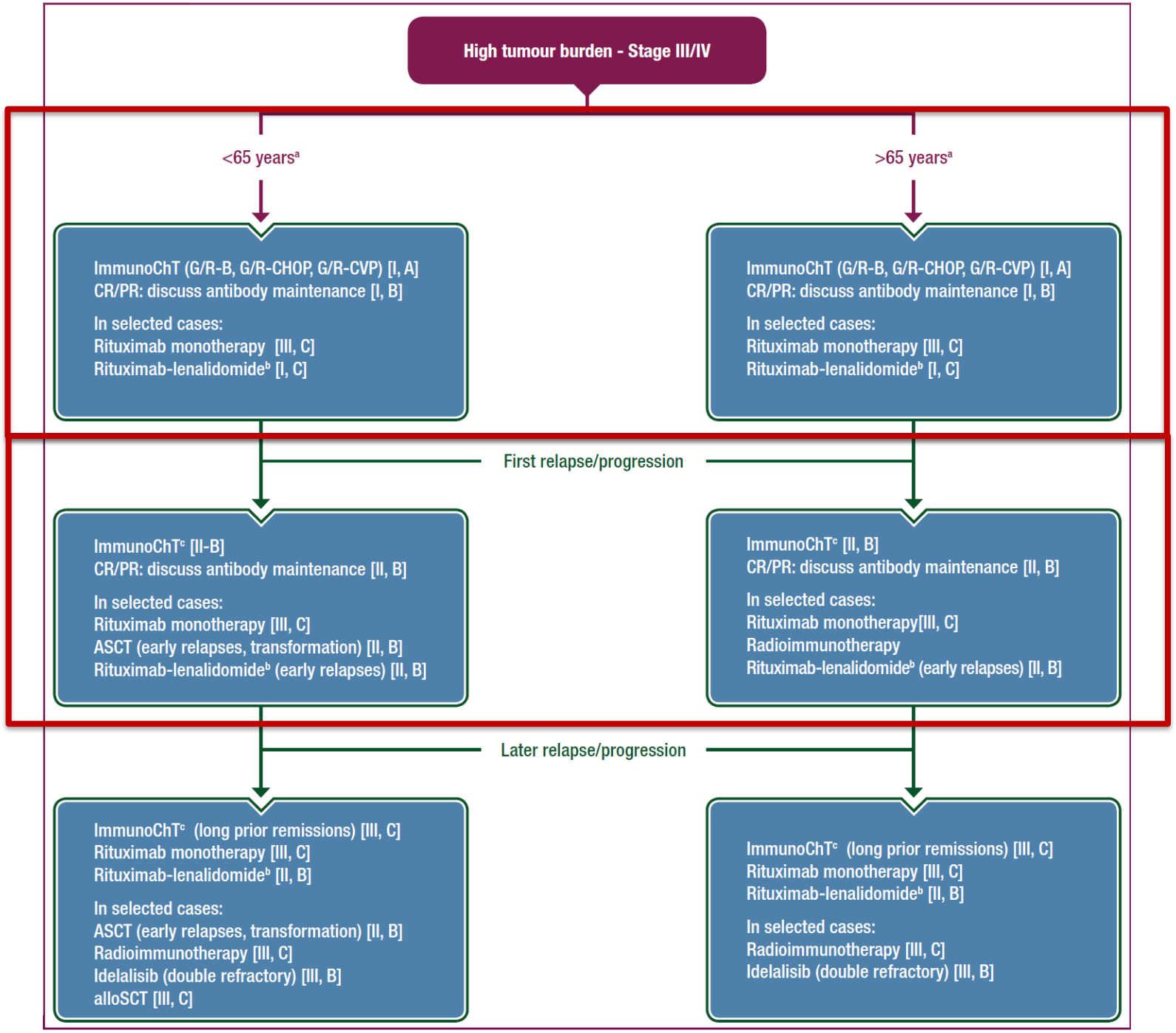
No. at risk				
Non-POD24	834	562	137	8
POD24, no risk factors	49	40	26	9
POD24, with risk factors	39	24	9	1

Muntañola A, Br J Haematol 2023;200:306-14



Leonard JP, Blood 2022;139:1609-10

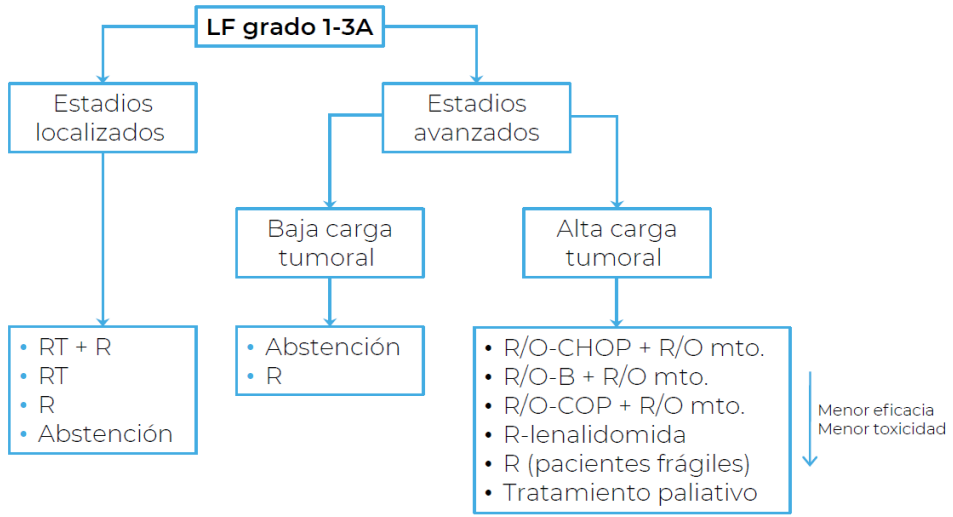
Follicular lymphoma
ESMO guidelines



Dreyling M, Ann Oncol 2021;32:298-308

www.geltamo.es

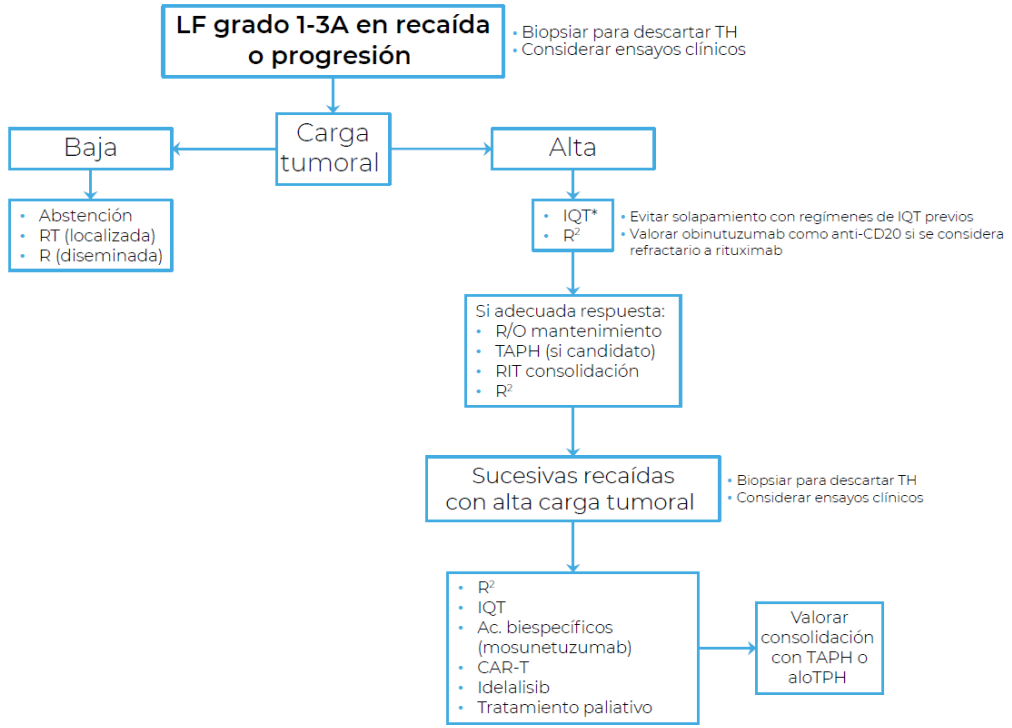
Figura 1. Algoritmo terapéutico en primera línea para pacientes con linfoma folicular



El orden de las opciones terapéuticas no pretende reflejar la preferencia de uso: ver las recomendaciones de la guía.

LF: linfoma folicular; **RT:** radioterapia; **R:** rituximab; **O:** obinutuzumab; **C(H)OP:** ciclofosfamida, (doxorrubicina), vincristina y prednisona; **B:** bendamustina; **RP:** respuesta parcial; **RC:** respuesta completa.

Figura 2. Algoritmo terapéutico para pacientes con linfoma folicular en recaída/refractariedad



LF: linfoma folicular; **TH:** transformación histológica; **TAPH:** trasplante autólogo de progenitores hematopoyéticos; **IQT:** inmunoquimioterapia; **R:** rituximab; **O:** obinutuzumab; **R²:** rituximab-lenalidomida; **RIT:** radioinmunoterapia; **RT:** radioterapia; **CAR-T:** linfocitos T con receptor de antígeno quimérico; **Ac:** anticuerpos; **Alo-TPH:** trasplante alogénico de progenitores hematopoyéticos.

Recommendations – Treatment in 1st R/R

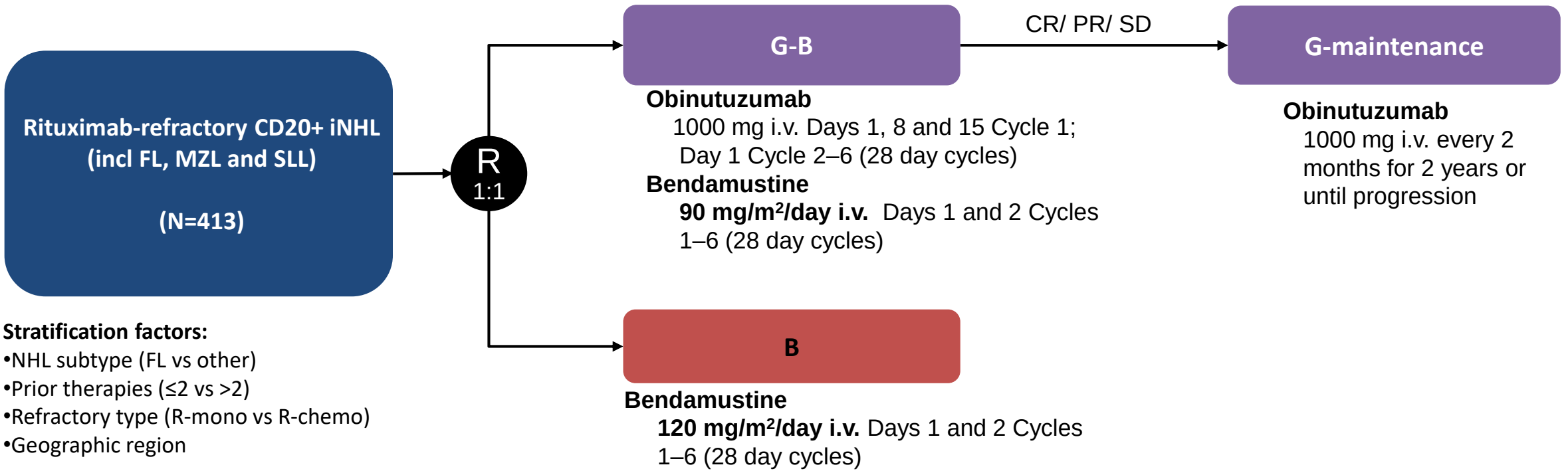
Patients treated with immunochemotherapy at induction who show early relapse needing therapy:

▪ Immunochemotherapy régimen different from the induction.	1C
▪ If refractory to rituximab, consider obinutuzumab*.	1B
▪ Rituximab / lenalidomida (R2) is an option.	1A
▪ Radioimmunotherapy might be an option in highly selected patients.	2C
▪ These patients could be candidates to clinical trial	1C

GELTAMO FL guidelines 2023

Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial

Laurie H Sehn, Neil Chua, Jiri Mayer, Gregg Dueck, Marek Trněný, Kamal Bouabdallah, Nathan Fowler, Vincent Delwail, Oliver Press, Gilles Salles, John Gribben, Anne Lennard, Pieternella J Lugtenburg, Natalie Dimier, Elisabeth Wassner-Fritsch, Günter Fingerle-Rowson, Bruce D Cheson



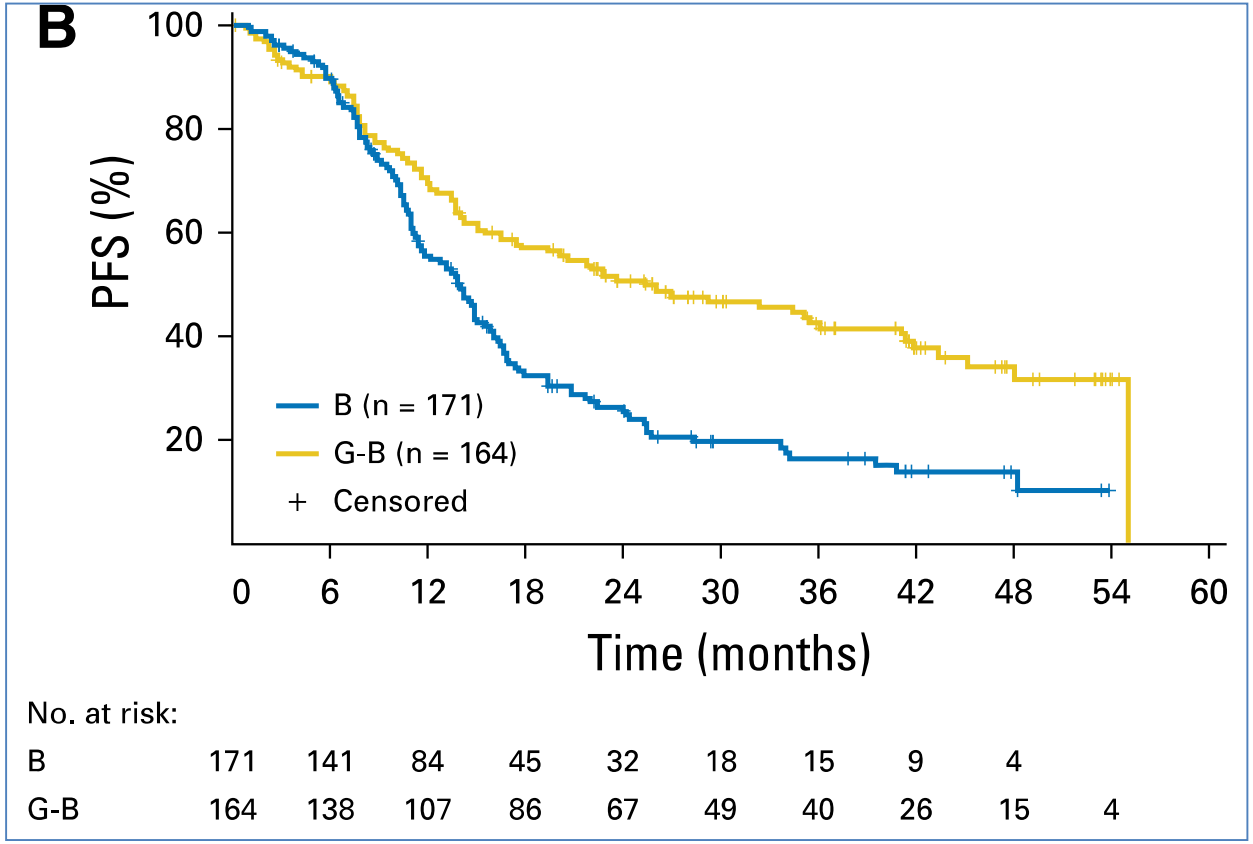
Primary endpoint: PFS as assessed by an Independent Radiology Facility (IRF)

Secondary endpoints:

PFS by investigator, OS, end of induction response, best OR, DOR, EFS DFS, safety, PK, Pharmacoeconomics, patient-reported outcomes (PROs)

Sehn et al
Lancet Oncol 2016

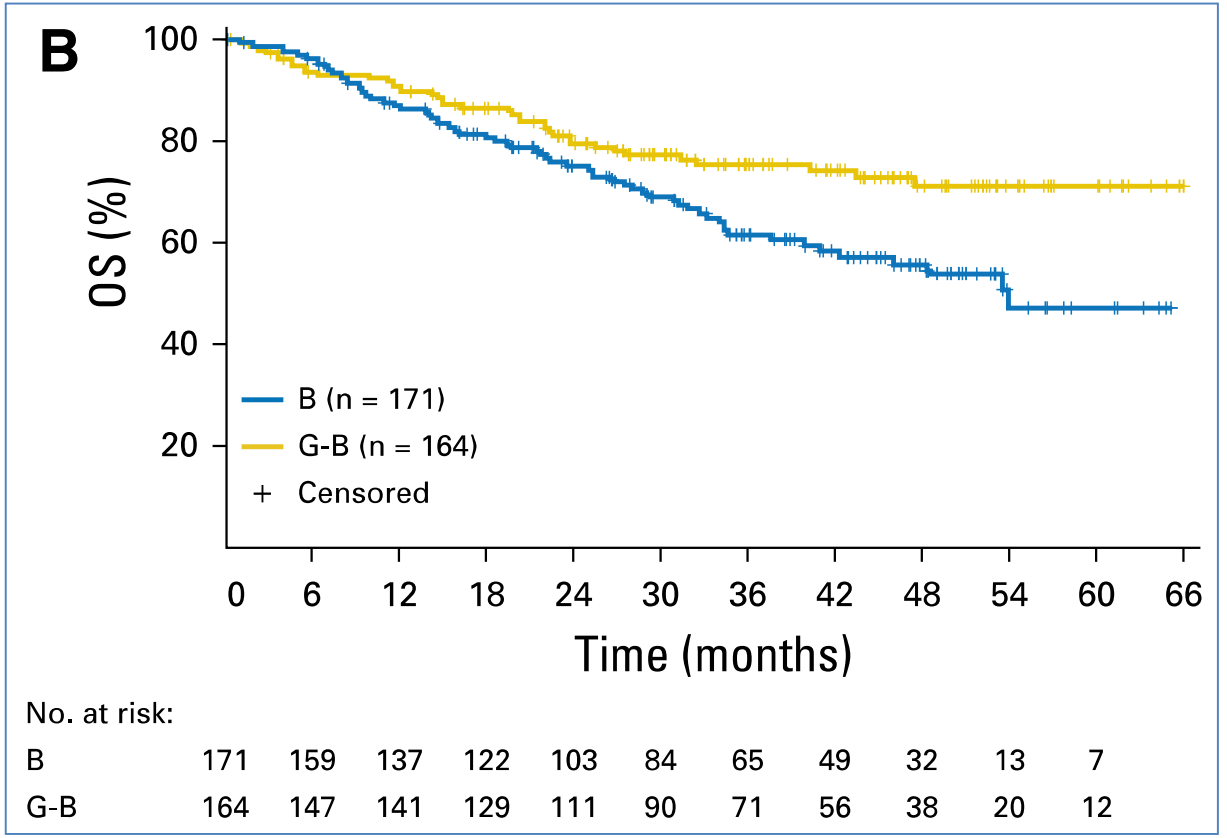
Supervivencia libre de progresión en LF



25.3 m (17.4, 36.0) vs 14.0 m (11.3, 15.3)

HR 0.52 (0.39, 0.69), p<0.001

Supervivencia global en LF



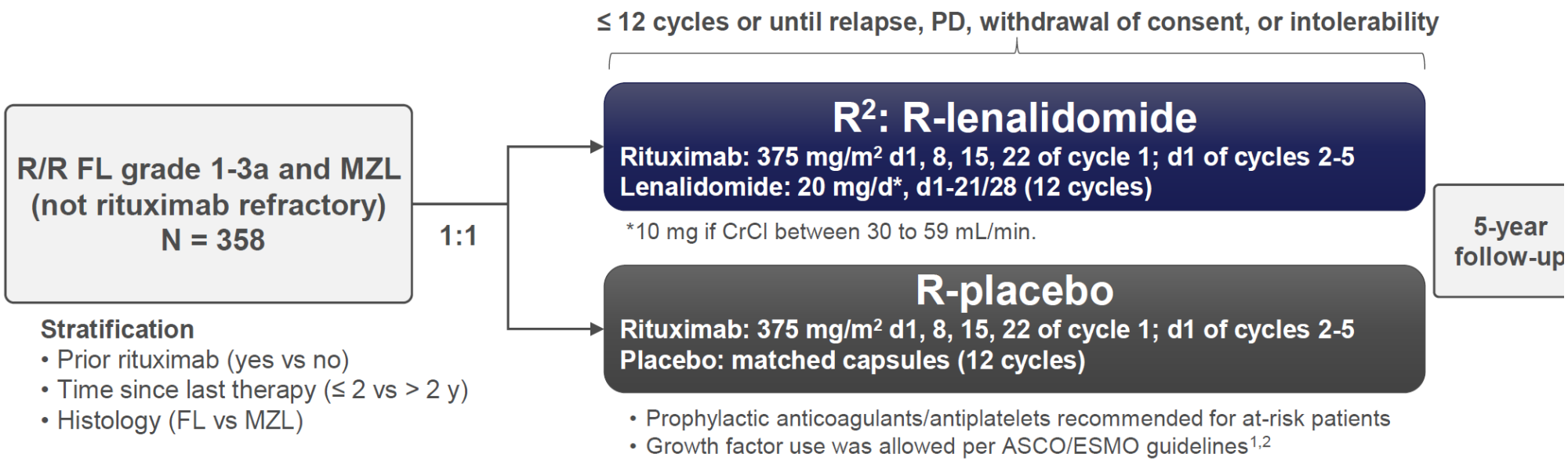
NE vs 53.9 m (40.9, NE)

HR 0.58 (0.39, 0.86), p<0.0061

*Mediana seguimiento 31 meses

Cheson et al, JCO 2018

AUGMENT PHASE III, MULTICENTER, RANDOMIZED STUDY



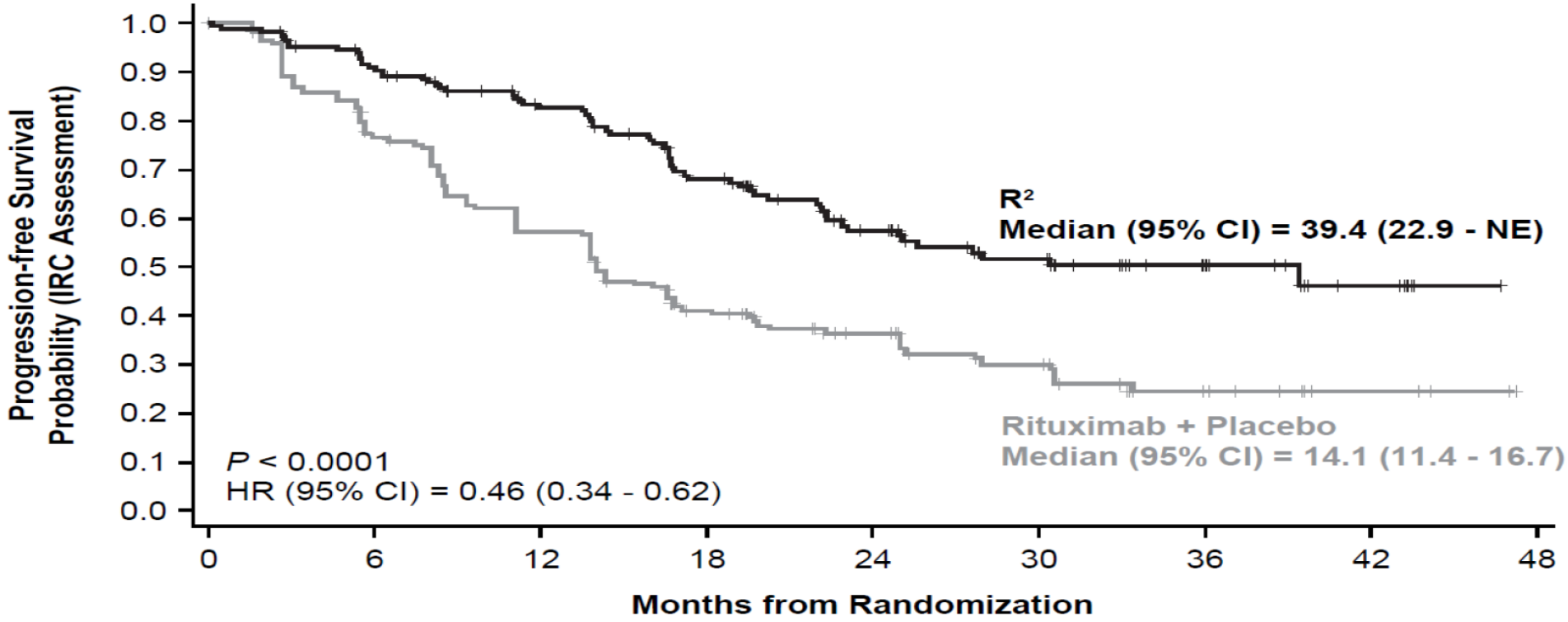
- **Primary endpoint**: PFS by IRC (2007 IWG criteria[3] without PET)
- **Secondary endpoints**: ORR, CR, DOR, OS, EFS, TTNLT

NCT01938001, EudraCT 2013-001245-14.
1. Crawford et al. *Ann Oncol.* 2010;21 Suppl 5:248-251. 2. Smith et al. *J Clin Oncol.* 2015;33:3199-3212. 3. Cheson et al. *J Clin Oncol.* 2007;25:579-586.

Leonard, ICML 2019

Rituximab vs. R^2

Figure 1. Primary Endpoint PFS per IRC Assessment



Number of Patients at Risk									
R^2	178	148	124	91	59	39	20	7	0
Rituximab + Placebo	180	132	92	58	40	26	10	4	0

Leonard JP, ASH 2018; J Clin Oncol 2019;37:1188-99

Recommendations – Treatment in 1st R/R

Patients treated with immunochemotherapy at induction, with an early relapse who respond to the salvage therapy could receive as post-induction:

- Maintenance with obinutuzumab (if used at salvage).

GRADE system: 1B

- Maintenance with rituximab (unless refractory).

GRADE system: 2C

- Intensification with autologous SCT (if eligible by age and co-morbidities).

GRADE system: 1B

GELTAMO FL guidelines 2023

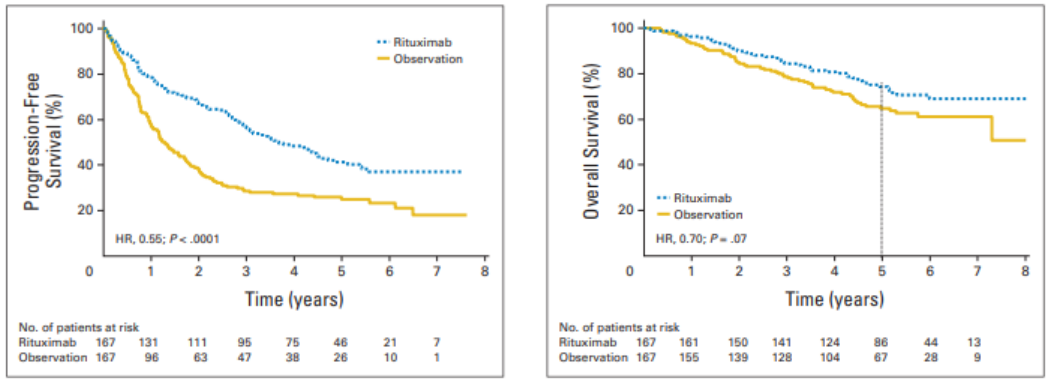
Consolidation after 2nd line therapy

Anti-CD20 maintenance

EORTC 20981 phase III trial

n=465 patients

mFU: 6 y



Van Oers *et al,* J Clin Oncol, 2010

Autologous stem cell transplant (ASCT)

ASCT in R/R FL patients (FL2000)

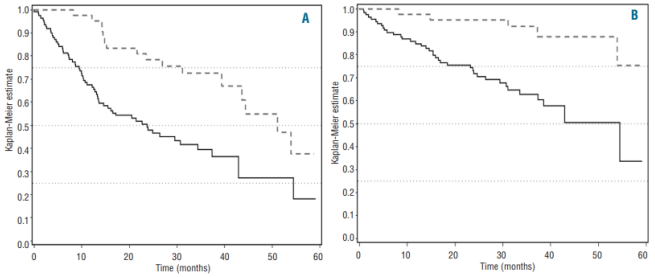
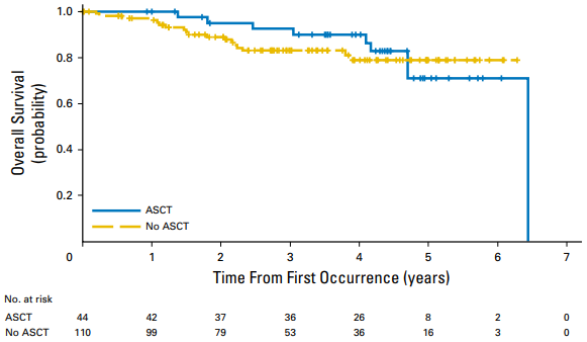


Figure 2. Outcome of patients (under the age of 70 years) according to transplantation at first progression: ----transplanted patients (n=42); —— non-transplanted patients (n=111). (A) Event-free survival (P=0.0005). (B) Overall survival (P=0.0003).

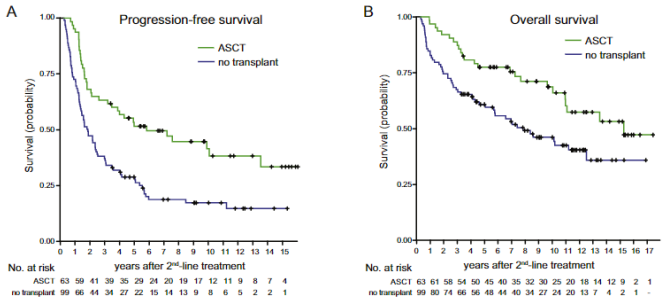
Le Gouill *et al,* Haematologica, 2011

PRIMA trial



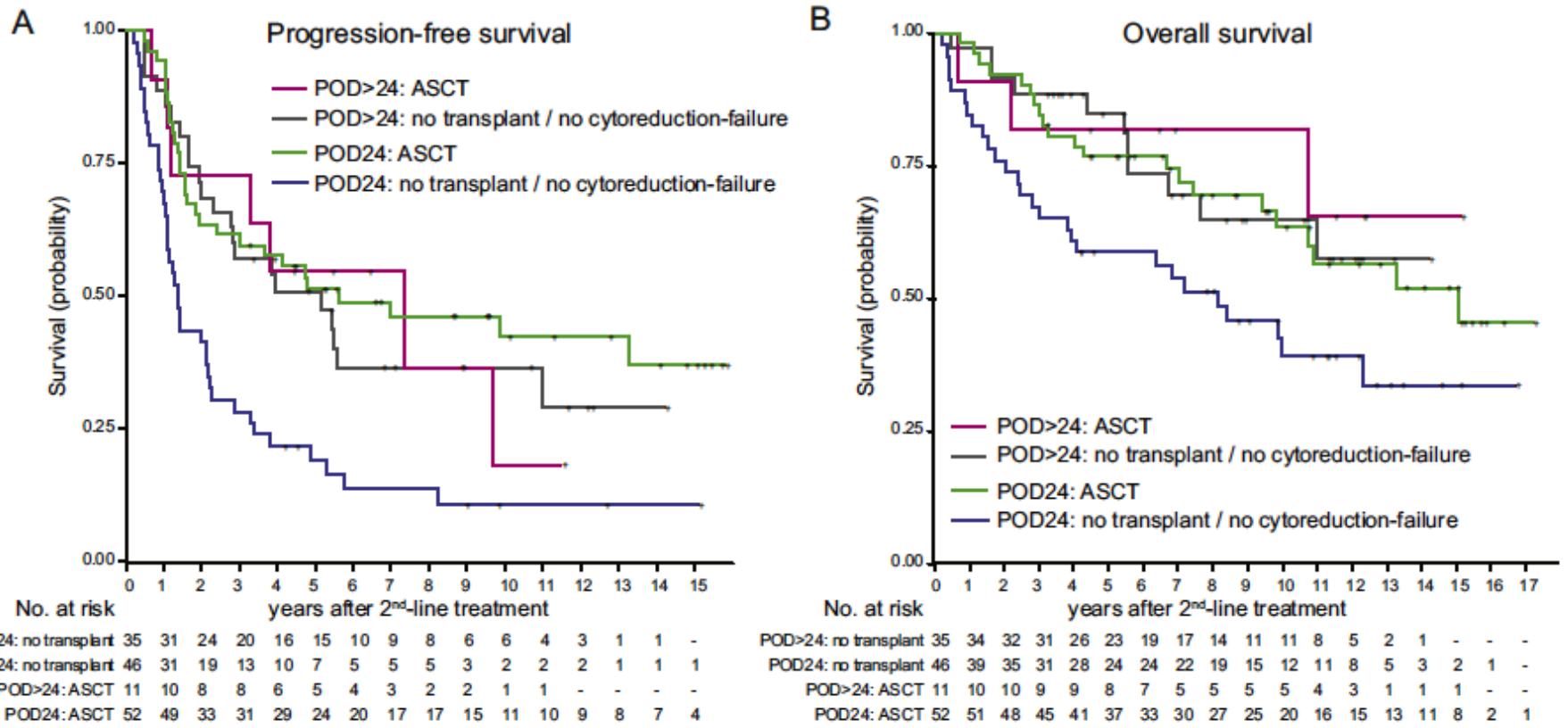
Sarkozy *et al,* J Clin Oncol, 2016

ASCT in POD24 patients



Jurinovic *et al,* BBMT, 2018

Autologous stem cell transplantation may abrogate the negative prognostic effect of early relapse after first-line chemotherapy or immunochemotherapy in patients with follicular lymphoma



Jurinovic V, Biol Blood Marrow Transplant 2018;24:1172-9

How treating POD24 follicular lymphoma patients?

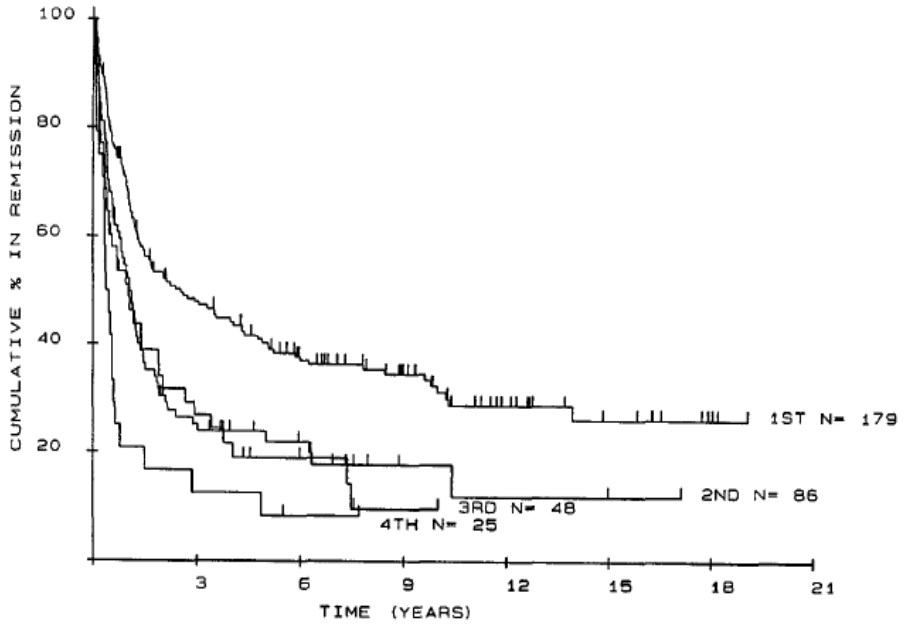
- POD24 population has been designated as a priority for novel treatment development[1]
- Role for ASCT?
- Ongoing trials with new drugs, including bi-specific and CAR-T therapies (and many other)

1) Maddocks K, J NatlCancer Inst 2017;109:djw255

Following with the patient …

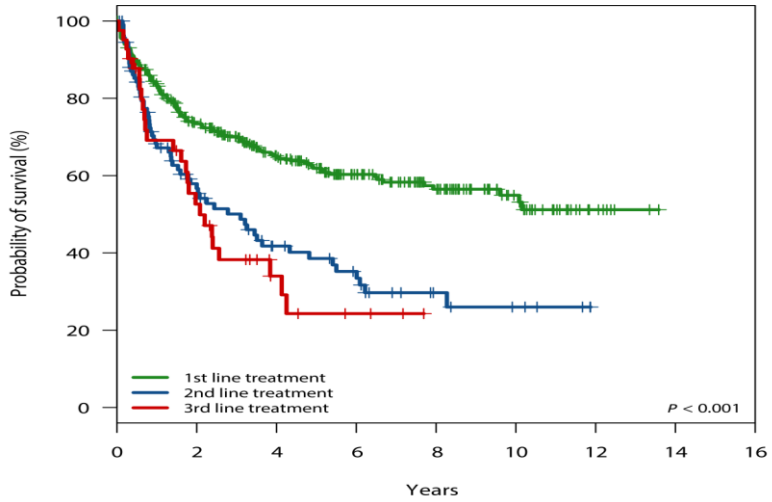
- February 2016 - a new biopsy was carried out: grade 2 FL
- R-Benda (obinutuzumab not reimbursed in Spain) → metabolic CR after 4 courses
- July 2016: autologous SCT with no major toxicity
- Patient ok for years … until March 2021 when he relapsed

Response duration progressively shortens with each relapse in FL

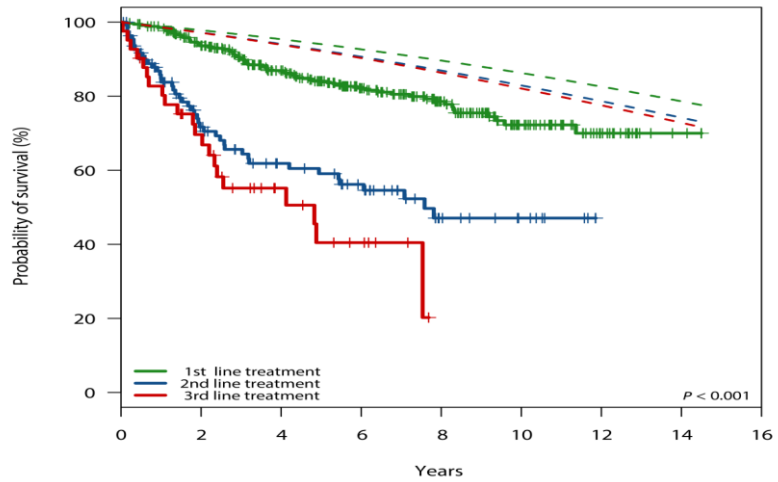


Johnson WM, J Clin Oncol *1995;13:140-7*

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*

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, …)

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]

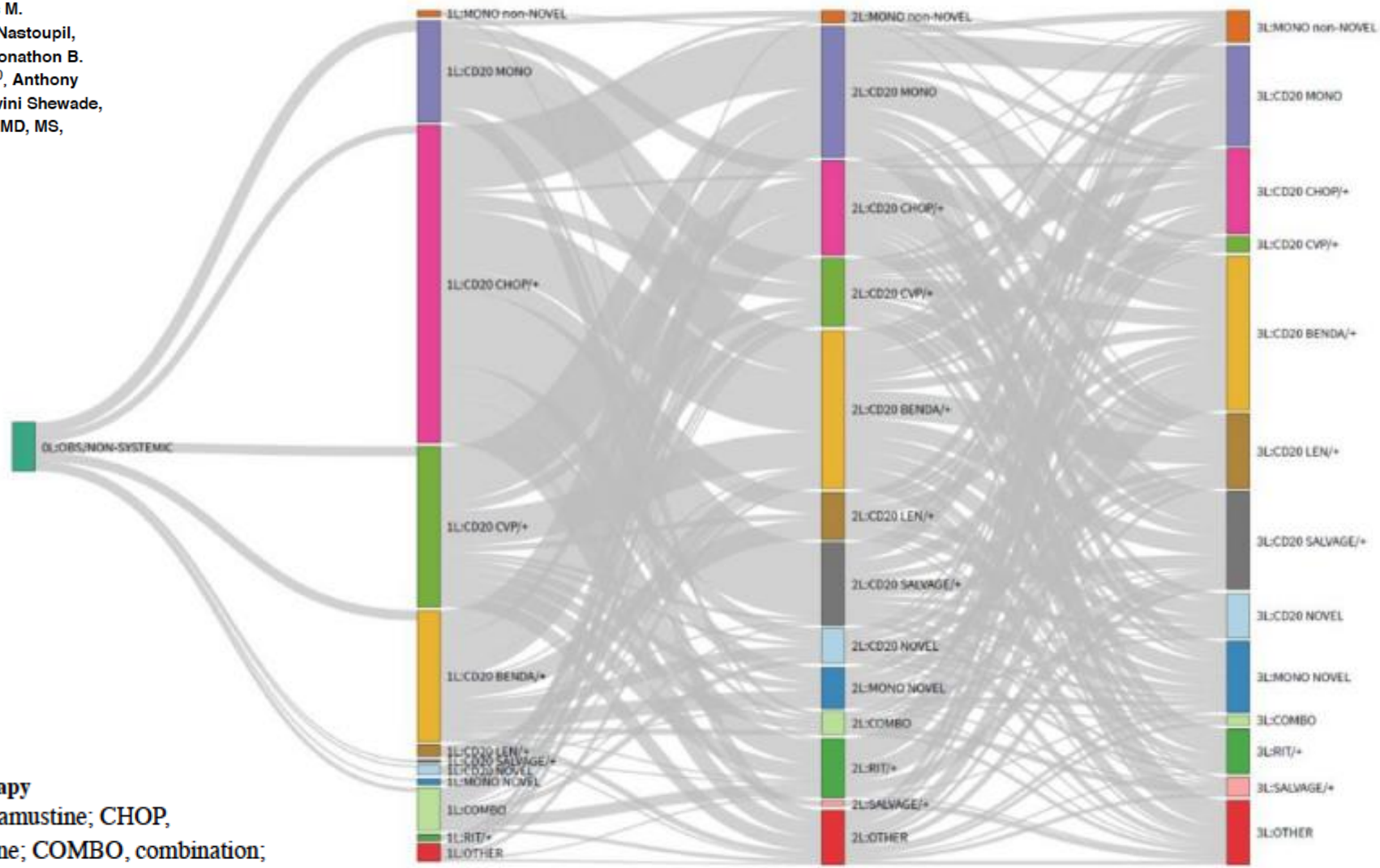


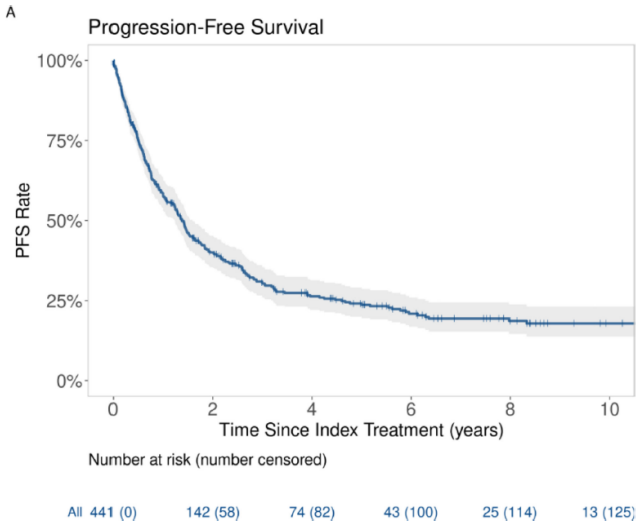
Figure 1. Sankey plot of treatment patterns across lines of therapy

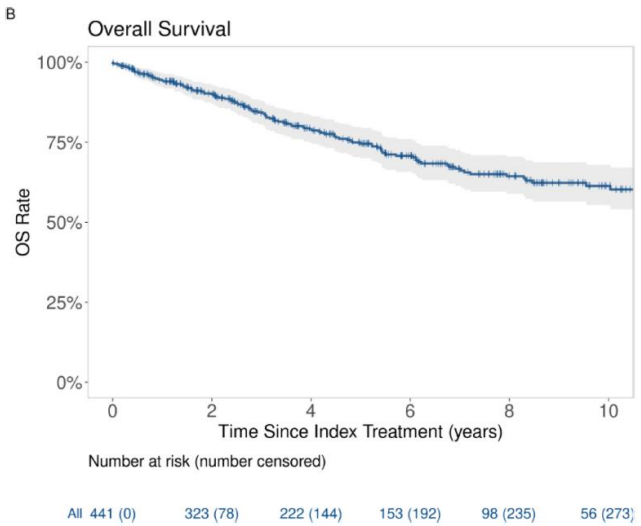
1L, first-line; 2L, second-line; 3L, third-line; BENDA, bendamustine; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; COMBO, combination; CVP, cyclophosphamide, vincristine, and prednisolone; LEN, lenalidomide; MONO, monotherapy; RIT, rituximab.

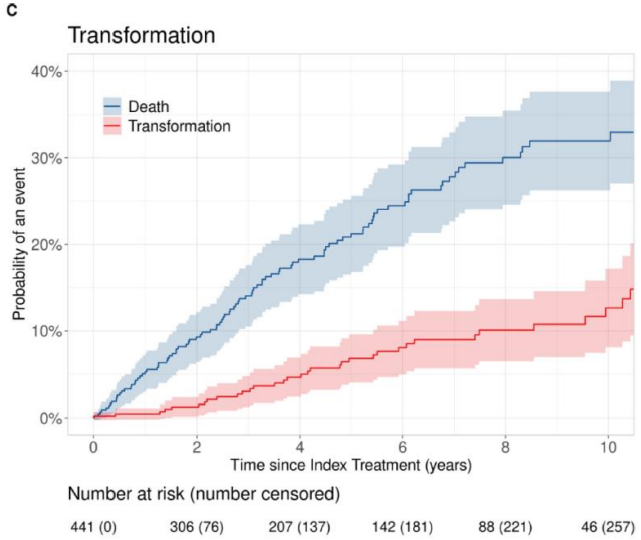
Lancet Haematol. 2022 April ; 9(4): e289–e300. doi:10.1016/S2352-3026(22)00033-3.

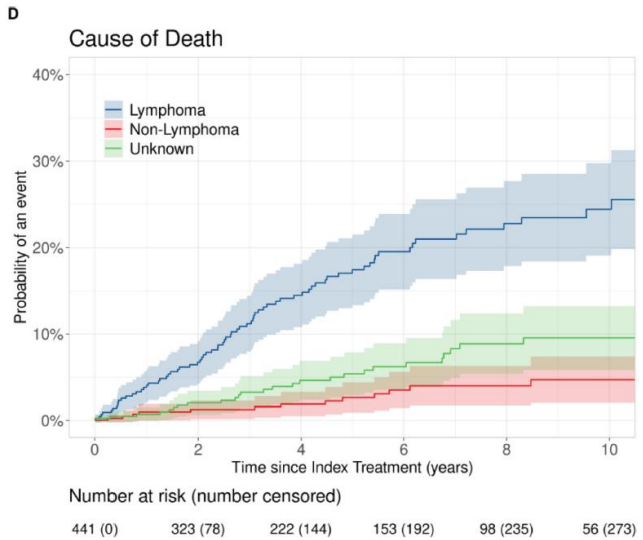
Treatment Patterns and Outcomes of Patients with Relapsed/ Refractory Follicular Lymphoma Receiving Three or More Lines of Systemic Therapy: Results from a Lymphoma Epidemiology of Outcomes Consortium Observational Study

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]







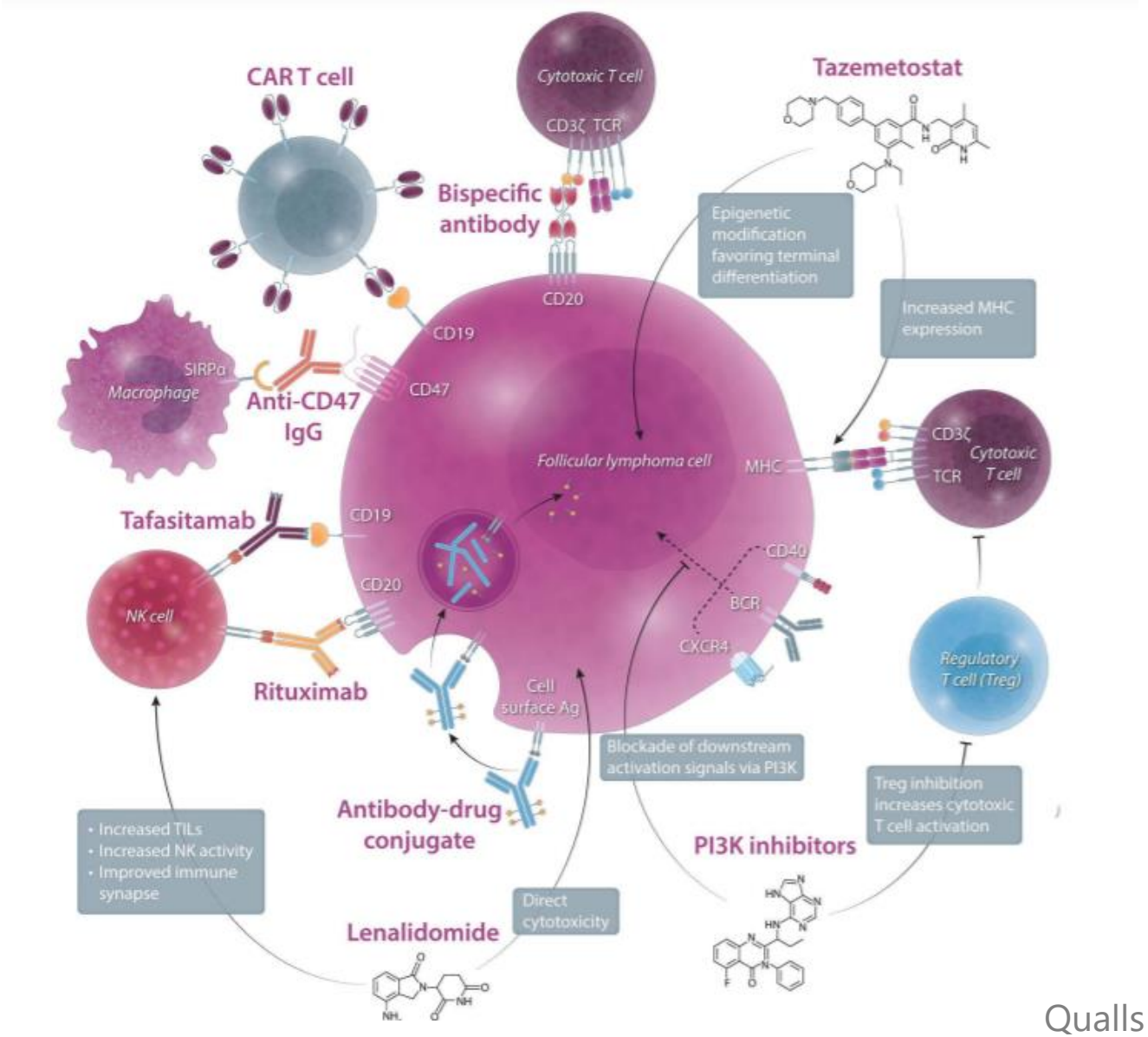


"New" drugs in R/R FL:

- High response rates

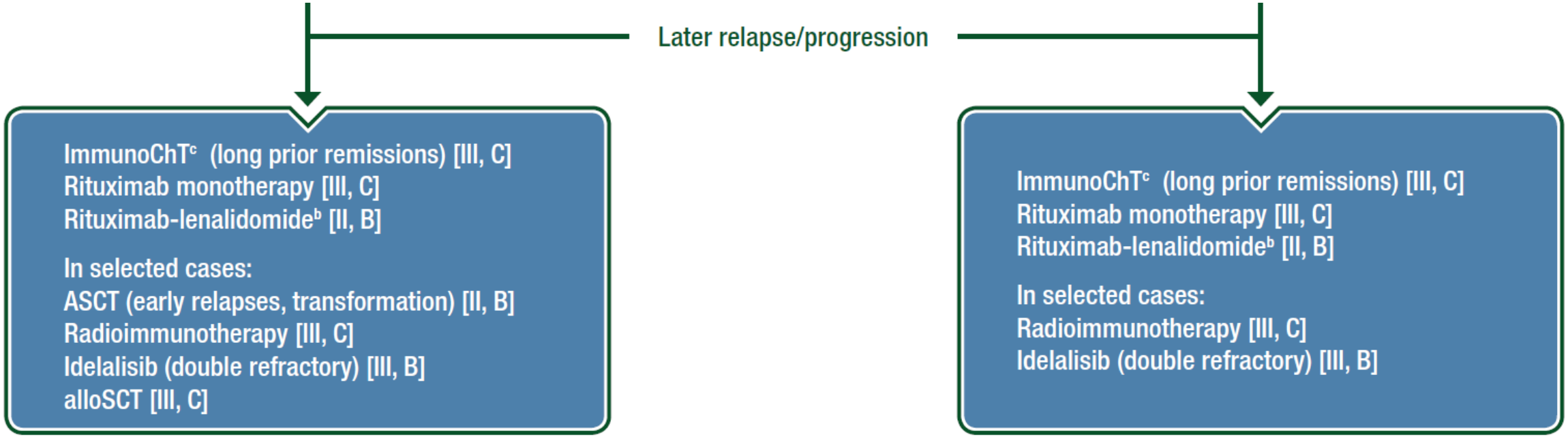
- but … of short duration!

Emerging therapies



Qualls & Salles, Haematologica, 2022

Follicular lymphoma
ESMO guidelines



Dreyling M, Ann Oncol 2021;32:298-308

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 $\geq 3^{rd}$ line; axicel in $\geq 4^{th}$ line)	1B*
▪ Palliative care	1C

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

PI3k inhibition in R/R FL

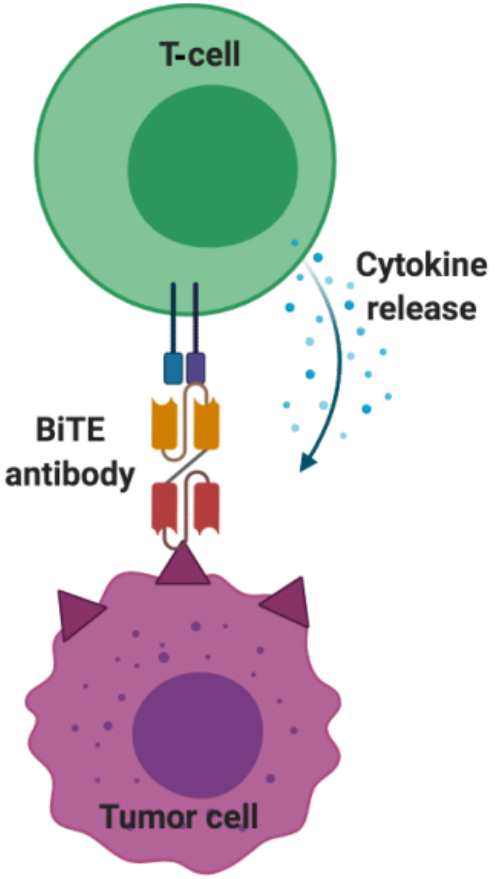
	Copanlisib (n=104)	Duvelisib (n=83)	Idelalisib (n=72)
Inclusion criteria	R/R iNHL after at least 2 lines	iNHL refractory to rituximab and chemo or RIT	iNHL refractory to rituximab and alkylators
Treatment regimen	60 mg d 1, 8 and 15 every 28d, iv	Duvelisib 25 mg/12h po	Idelalisib 150 mg/12h po
Median previous lines	3	3	4
ORR	59% (14% CR)	42% (1% CR)	56% (14% CR)
PFS	11 months	9.5 months	11 months
OS	NR	NR	NR
Grade ≥ 3 AE in at least 10% of patients	hyperglycemia (41%) hypertension (24%) neutropenia (24%) pneumonia (16%)	neutropenia (25%) diarrhea (15%) anemia (15%) thrombocytopenia (12%)	neutropenia (27%) diarrhea (13%) ALT elevation (13%)

Dreyling M et al J. Clin. Oncol. 2017;35:3898–905
Flinn IW et al. J. Clin. Oncol. 2019. https://doi.org/10.1200/ JCO.18.00915
Salles GA, et al. Haematologica 2016;102(4):e156-e159

Bispecific T-cell engagers: CD20 x CD3

EMA: positive opinion, recommending the granting of a conditional marketing authorization

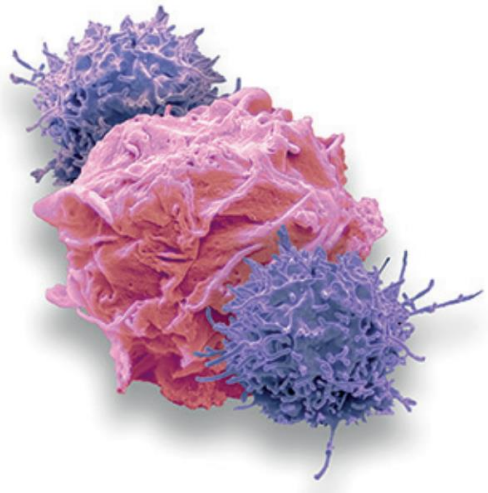
	N	Median # of prior lines	Previous POD24	ORR (%)	CRR (%)	mPFS	DoR	AEs
Mosunetuzumab[1]	90	3	52%	79%	58%	18 mo	NR	CRS, ICANS and cytopenias
Glofitamab[2]	72	3	55%	Glofi: 81% Glofi-O: 100%	Glofi: 70% Glofi-O: 74%	12 mo	-	



[1]Budde *et al*, ASH, 2021
[2]Morschhauser *et al*, ASH, 2021

Anti-CD19 CAR-T cells

	Axi-cel (Yescarta)	Tisa-cel (Kymriah)
Trial	Phase 2, **ZUMA-5**[1]	Phase 2, **ELARA**[2]
Histology	G1-3A FL or MZL	G1-3A FL
Setting	≥2 previous lines (including anti-CD20 and alkylator)	≥2 previous lines or post-ASCT relapse
Population	N=153 (127 FL)	N=97 (infused)
Technical aspects	Flu/Cy cond. x3d, 2M/kg (single dose)	Flu/Cy x3d or benda x2d cond., 10-600 M (single dose)
ORR/CRR	94%/79% (50% PR → CR) median time to CR: 1 month	86%/69% (87% of CR lasting 9+ mo)
PFS	65% at 1.5 y	67% at 1 y
OS	87% at 1.5 y	~95% at 1 y
CRS G3+	6%	0
ICANS G3+	15%	1%
Agencies	EMA: ≥3 previous lines FDA: ≥2 previous lines	EMA: ≥2 previous lines FDA: priority review (≥2)



[1]Jacobson *et al*, Lancet Oncol, 2022
[2]Fowler *et al*, Nat Med, 2021

New therapies in R/R FL (Cellular therapy and bi-specific antibodies)

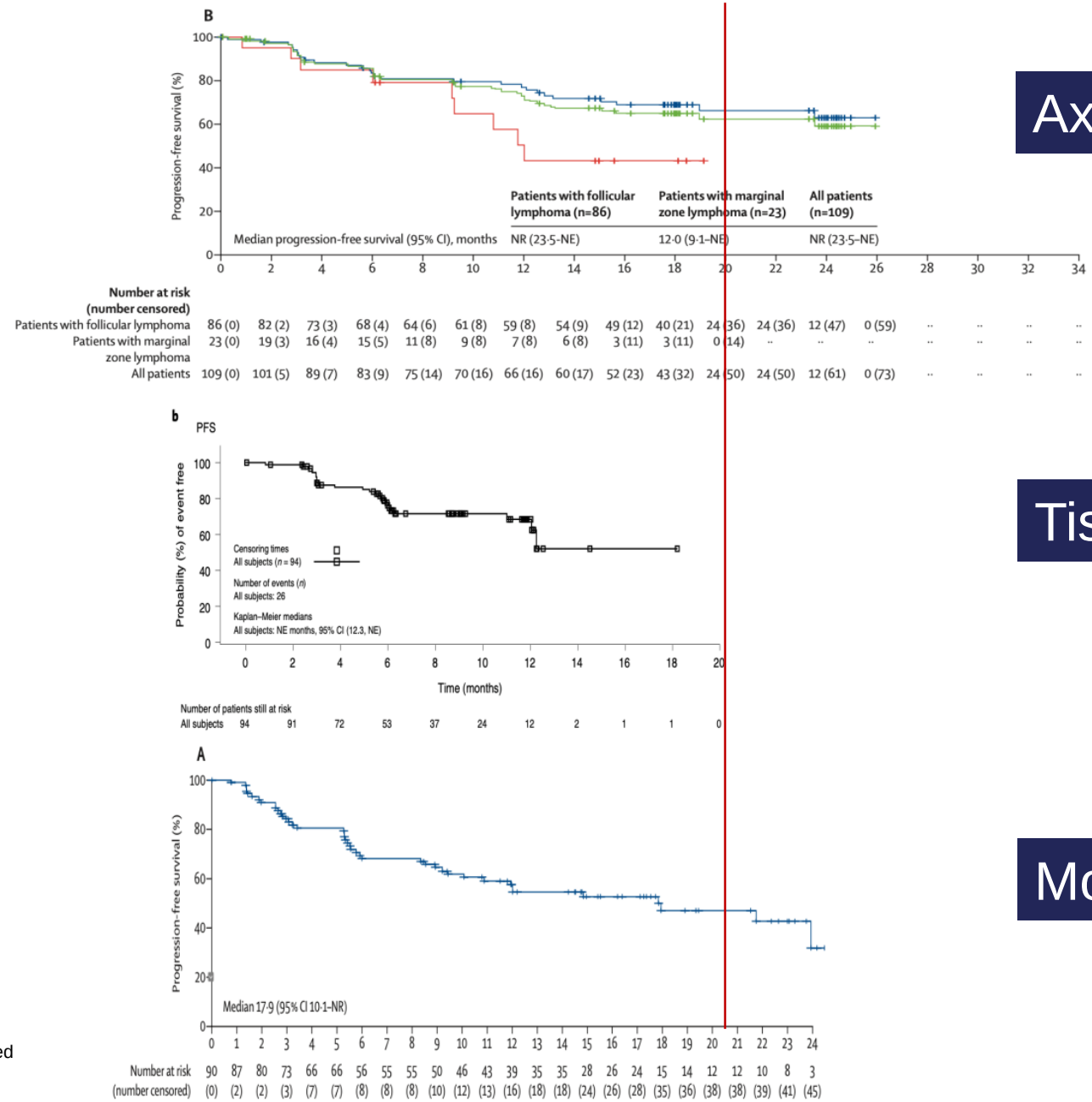
Efficacy results

	ZUMA-5[1] (Axicel)	ELARA[2] (Tisacel)	Mosunetuzumab[3] (CD20xCD3)
ORR (%)	94	86	80
CR (%)	79	69	60
Time to CR (mo.)	1	1	3
Median follow-up (mo.)	23	17	18
CR duration (at 1 yr; in %)	74	≈75	71
PFS			
Median (mo.)	NR	NR	18
12-mo. (%)	≈74 (65% at 18 mo.)	67	58
TTNT			
Median (mo.)	NR	NR	NR
12-mo. (%)	?	87	68
OS			
Median (mo.)	NR	NR	NR
12-mo. (%)	≈95 (87% at 18 mo.)	95	93

mo.: months; NR: not reached

1) Jaconson CA, Lancet 2022;23:91-103; 2) Fowler NH, Nat Med 2022;28:325-32; 3) Budde LE, Lancet 2022;23:1055-65

PFS



Axicel

Tisacel

Mosunetuzumab

1) Jaconson CA, Lancet 2022;23:91-103; 2) Fowler NH, Nat Med 2022;28:325-32; 3) Budde LE, Lancet 2022;23:1055-65

Recommendations – Treatment in 2nd or later relapse

- Allogeneic stem-cell transplantation restricted to young poor-risk patients, relapsed after ASCT and/or CAR-T therapy, with adequate age and performance status.

GRADE system: 1B

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Following with the patient …

- March 2021: relapse
  - 69 years; stage IV
  - Biopsy ruled out transformation
- Rituximab / lenalidomide → PR
- Severe COVID, but recovered from it
- May 2022: progression; clinical trial with a bi-specific
- After PR, new progression
- Currently in preparation to an academic anti-CD19 CAR-T (ari-001); no bridging necessary.

General guidelines in R/R FL (Hospital Clínic style)

- New biopsy at each relapse (when possible)
- “Low tumor burden” (asymptomatic): consider observation
- Decision making based on:
  - Previous treatments
  - Response to these therapies
  - Response duration
- In general:
  - Autologous SCT: only in 2nd line
  - Allo-SCT rarely (better option, CART)
- Remember that all these patients may be candidate to clinical trials
- Do not discard palliative care in some patients

Thank you

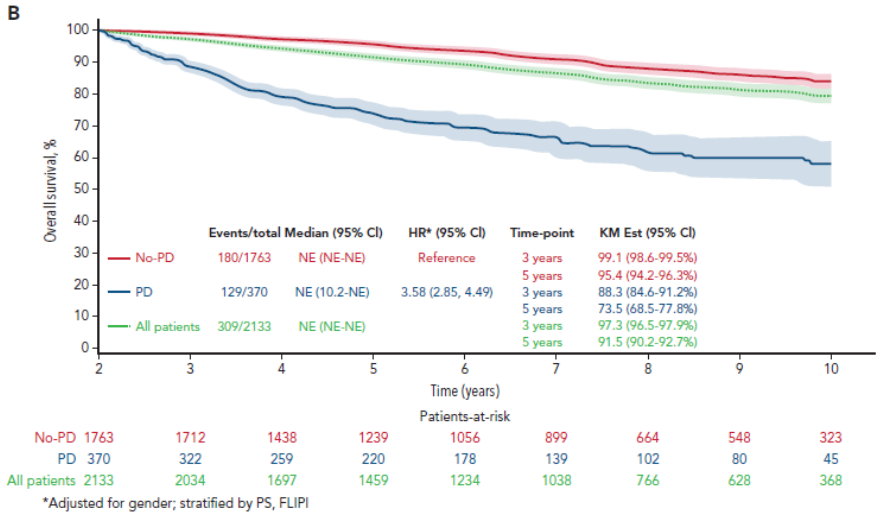
1906

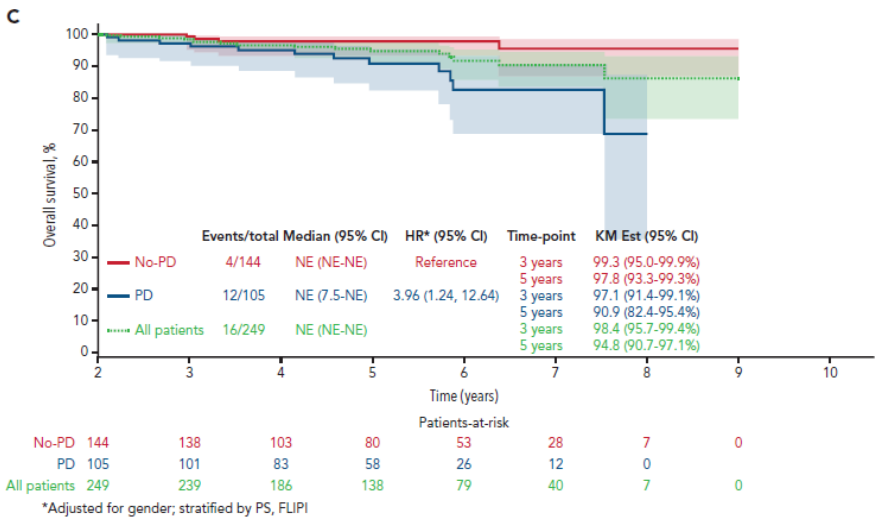
Lymphoma Research Group – IDIBAPS

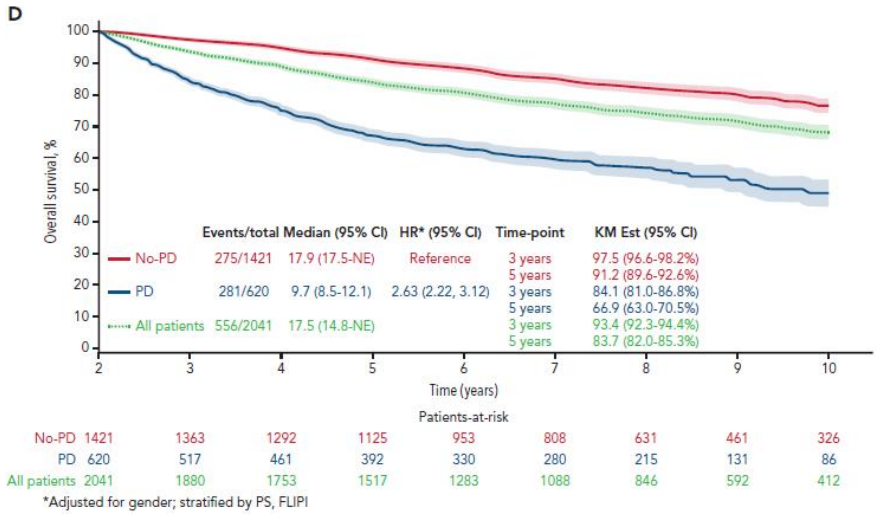
Lymphoma group – Hospital Clínic

GELTAMO

POD24 in follicular lymphoma







Patients treated with:

B – Immunochemotherapy
C – Rituximab alone
D – Chemotherapy alone

Casulo C, Blood 2022;139:1684-93

Recommendations – Relapsed/Refractory

- At relapse/progression a new biopsy is recommended, in order to rule out histological transformation.

GRADE system: 1A

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Autologous stem-cell transplant in FL

Review Article

Indications for hematopoietic stem cell transplantation in patients with follicular lymphoma: a consensus project of the EBMT-Lymphoma Working Party

Silvia Montoto,[1] Paolo Corradini,[2] Martin Dreyling,[3] Michele Ghielmini,[4] Eva Kimby,[5] Armando López-Guillermo,[6] Stephen Mackinnon,[7] Robert E. Marcus,[8] Gilles Salles,[9] Harry C Schouten,[10] Anna Sureda,[11] and Peter Dreger[12]

Table 3. Final consensus in favor.

Consensus n.	Statement n.	Agreed statement
1	1	HDT-ASCR is *not* an appropriate treatment option to consolidate first remission in patients with FL responding to immuno-chemotherapy, outside the setting of clinical trials.
2	5	In patients in first relapse with chemo-sensitive disease HDT-ASCR is an appropriate treatment option to consolidate remission.
	9	Remission consolidation with HDT-ASCR is an appropriate treatment option in 1st relapse in patients with a short response duration (<3 years) after immuno-chemotherapy.
	10	Remission consolidation with HDT-ASCR is an appropriate treatment option in 1st relapse in patients with high-risk FLIPI at relapse.
	11*	Remission consolidation with HDT-ASCR is an appropriate treatment option in 1st relapse in patients previously treated with rituximab.*
3	12	Remission consolidation with HDT-ASCR is an appropriate treatment option in patients in second or subsequent relapses with chemo-sensitive disease.
4	13	Allogeneic transplantation should be considered in patients with relapse after HDT-ASCR.
	18	*Reduced-intensity/* non-myeloablative conditioning regimens are generally more appropriate in patients receiving an allogeneic transplant.
5	19	In FL, the available biological and genetic risk factors are not sufficient to guide treatment decisions. Treatment decisions including the indication for HDT-ASCR and allogeneic transplantation are mainly guided by the clinical course.

*Partial consensus only

AUTO

ALO

1st relapse of high risk (early relapse)

≥2nd relapse

alloSCT in relapse after auto-SCT

Montoto et al, Haematologica 2013