

Simposio ROCHE – Jornada Chilena de Hematología y Medicina Transfusional

**Mejorando las estrategias del tratamiento
de pacientes con linfoma no hodgkin**



Bienvenidos

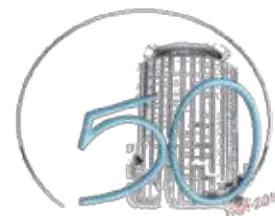
**GAZYVA (*obinutuzumab*) en
el tratamiento de 1L del
linfoma folicular.
Resultados del estudio
GALLIUM**

Dr. Miguel Angel Canales

Obinutuzumab en el tratamiento de primera línea del linfoma folicular

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Conflictos de interés

Honorarios como ponente	Celgene, Gilead, Janssen, Roche, Takeda
Consultor o asesor remunerado	Celgene, Janssen, Roche, Sanofi
Ayudas a investigación	NA
Ayudas a formación continuada	Janssen, Roche, Sanofi

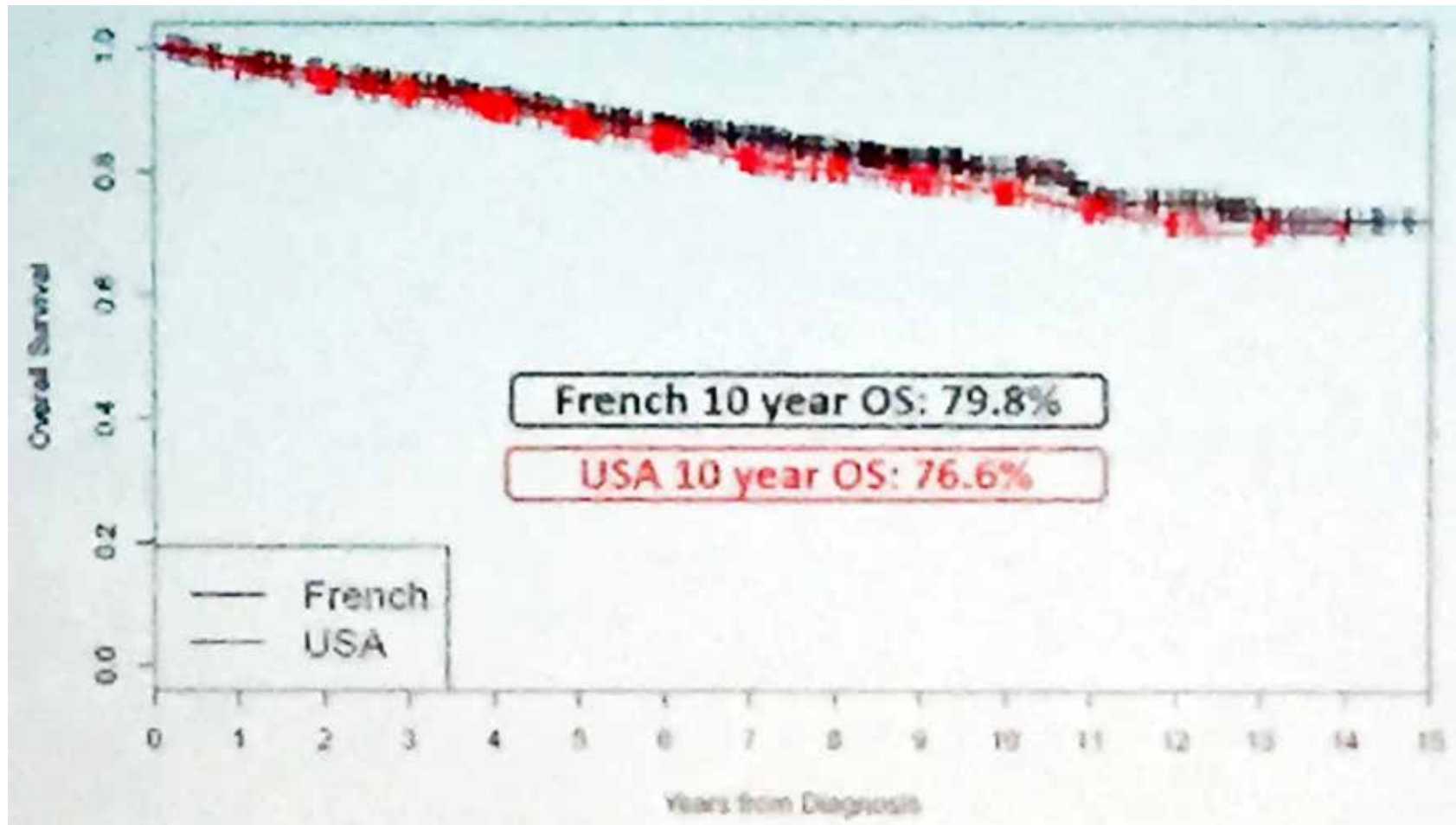
En la presentación se discutirán sobre las siguientes indicaciones *off label*:
Obinutuzumab en primera línea de tratamiento del LNH folicular

Es tiempo de cambios en los objetivos terapéuticos del linfoma folicular

1. El linfoma folicular es una enfermedad heterogénea, que no sigue un curso clínico indolente en todos los pacientes
 - Importante identificar pacientes de alto riesgo
 - Existen todavía necesidades no cubiertas en el tratamiento del linfoma folicular

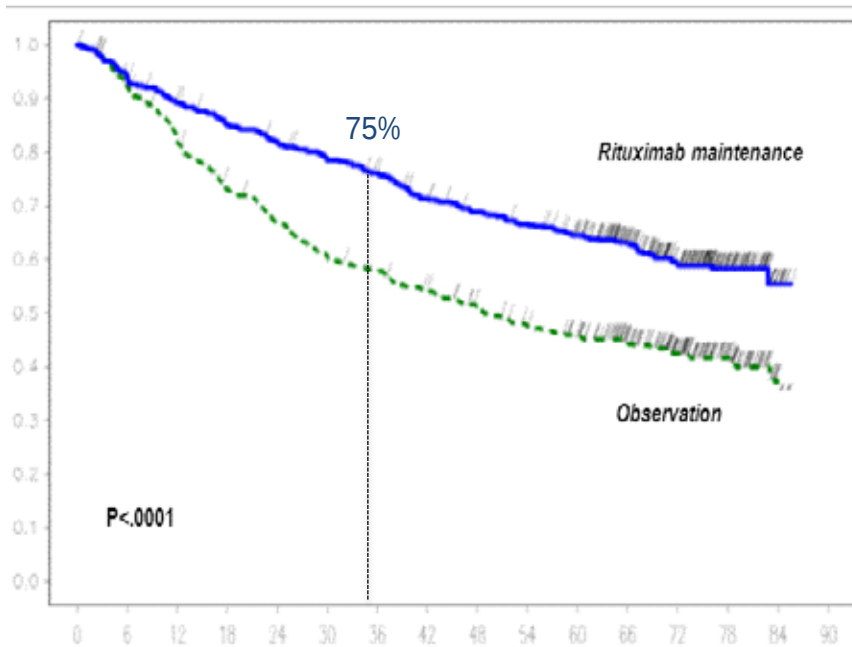
2. Es necesario incorporar nuevos fármacos que han demostrado eficacia en pacientes en recaída y refractarios, al tratamiento de primera línea
 - Obinutuzumab (ensayo GALLIUM) como ejemplo

La inmunquimioterapia ha aumentado la supervivencia del linfoma folicular

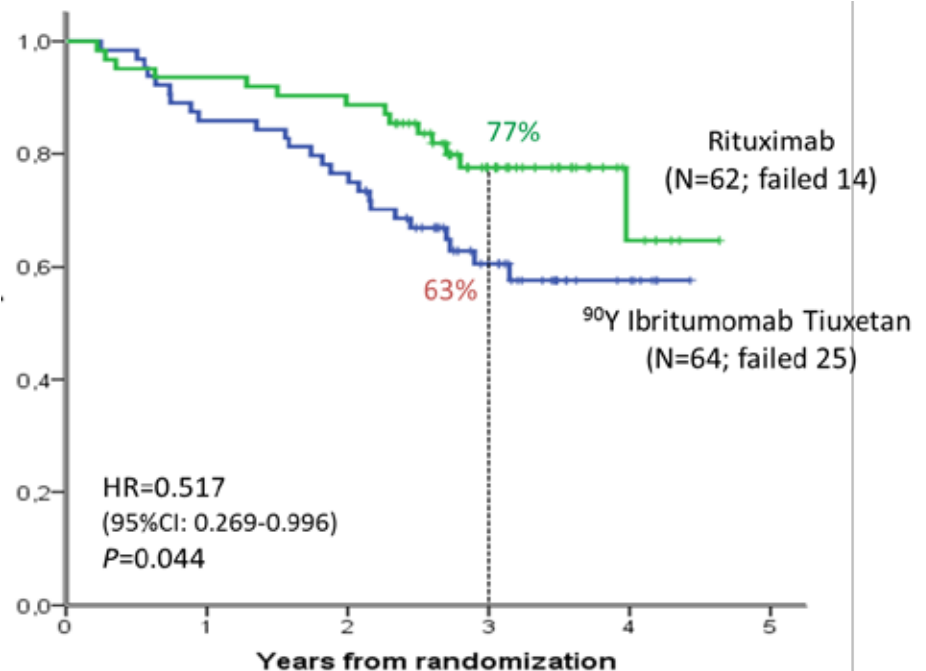


Inmunoquimioterapia con rituximab y mantenimiento como estándar

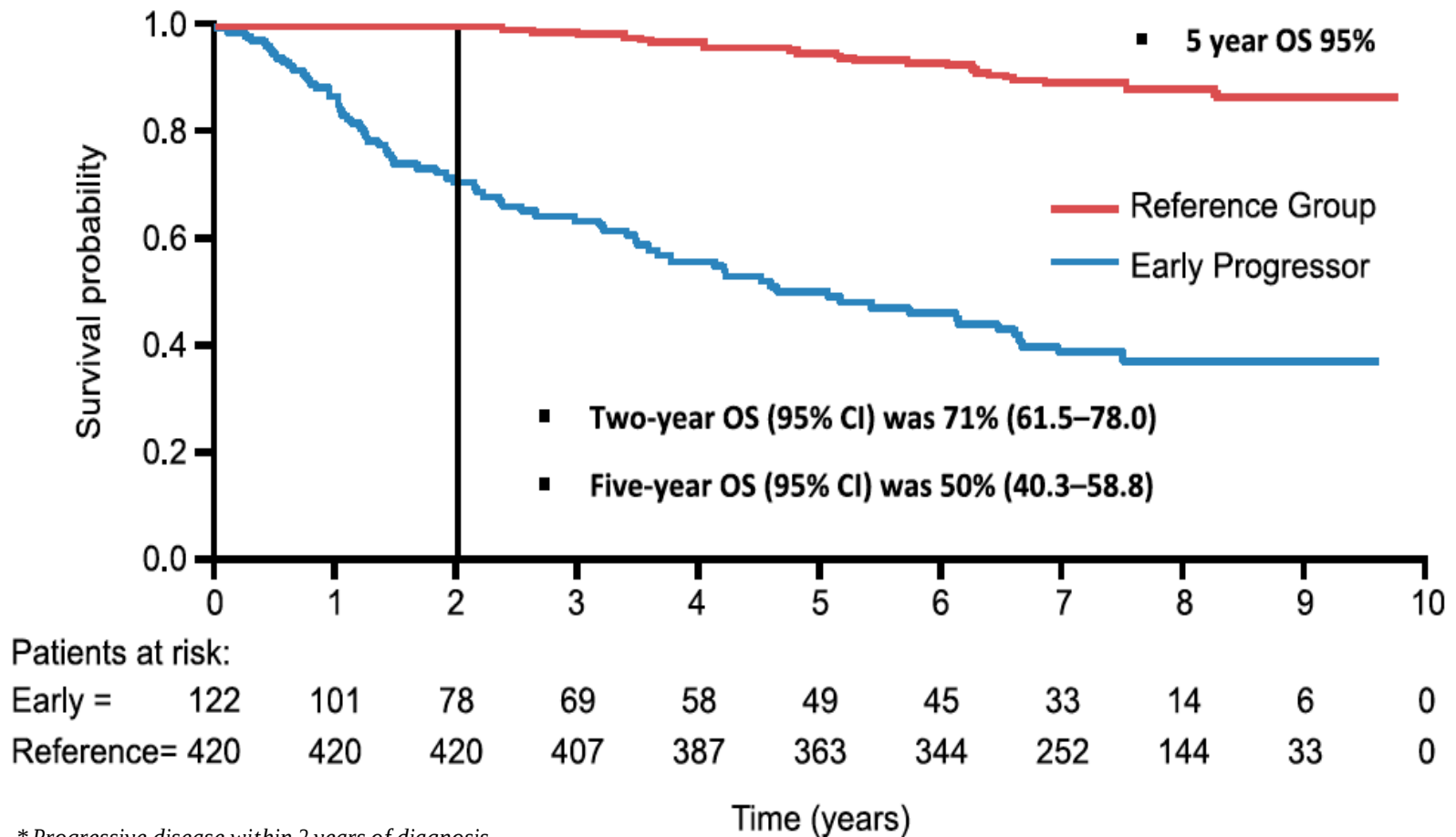
Ensayo **PRIMA**:
Rituximab es superior a observación



Estudio **ZAR**:
Rituximab es superior a RIT

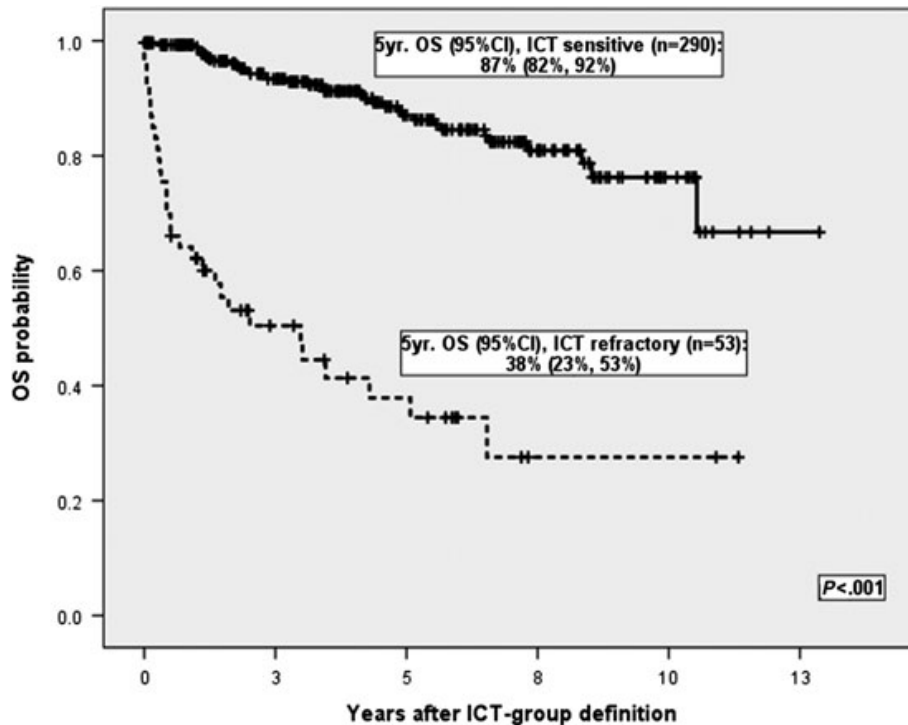


Pacientes con linfoma folicular con peor pronóstico (progresión precoz)*

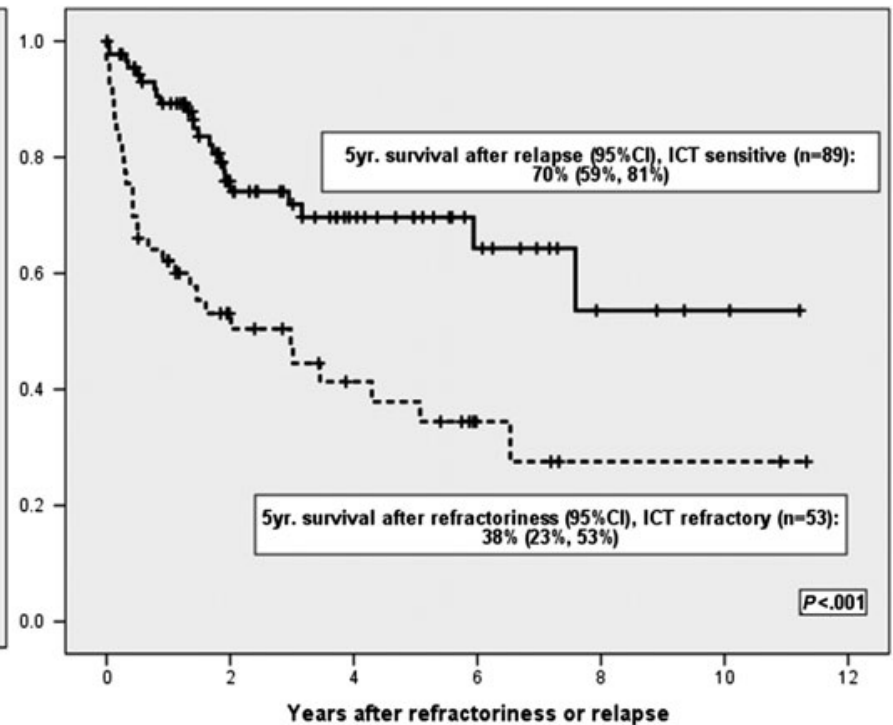


* Progressive disease within 2 years of diagnosis

Pacientes con linfoma folicular con peor pronóstico (quimiorrefractarios)*



*Death because of lymphoma progression:
40% vs 87% ($P < 0.001$)*

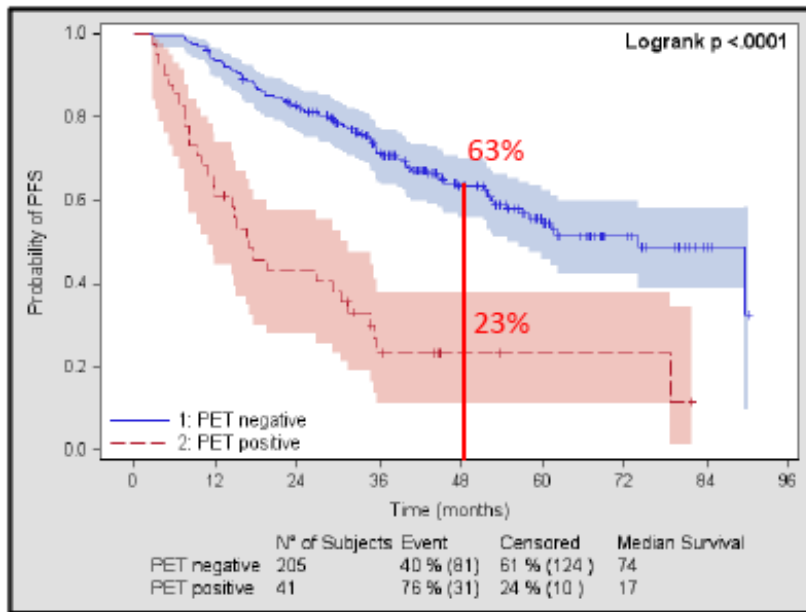


*Refractoriness to second-line therapy:
23% vs 48% ($P = 0.01$)*

* ICT-refractory patients, defined as those with less than partial response or progression or relapse within 6 months of first-line response assessment

Valor pronóstico de la PET (al final del tratamiento) en el linfoma folicular

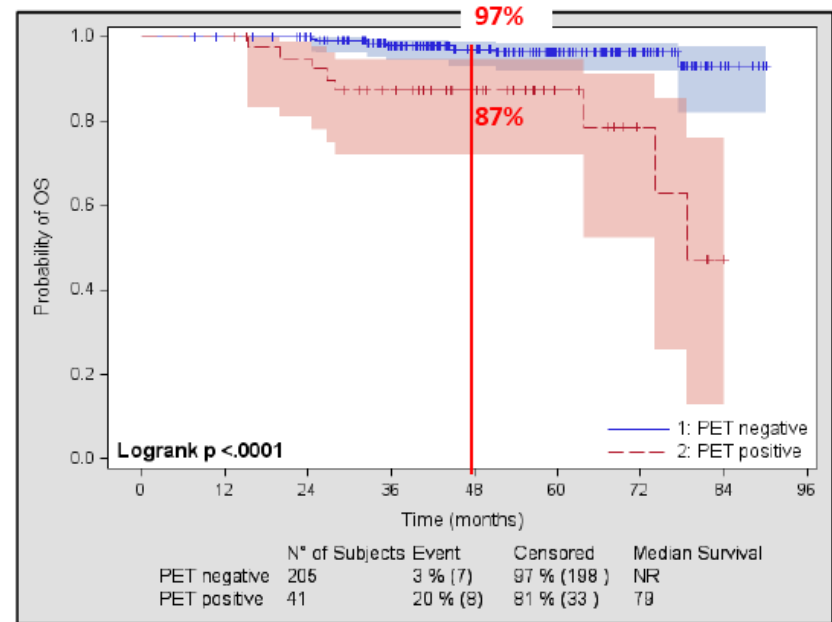
PFS & OS According to PET Scan Score (Cutoff ≥ 4)



HR 3.9 (95% CI 2.5-5.9, p<.0001)

Median PFS:

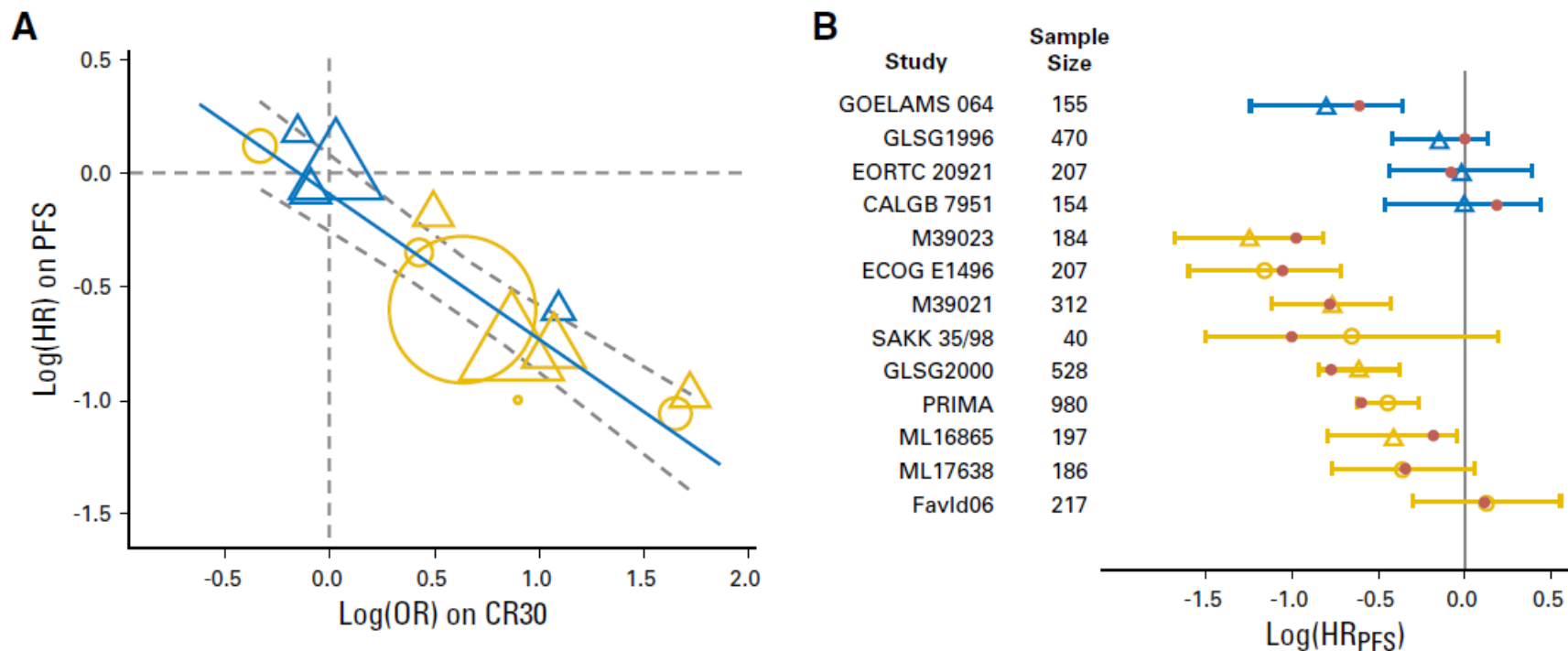
17 (10.8-31.4) vs. 74 mo (54.7-NR)



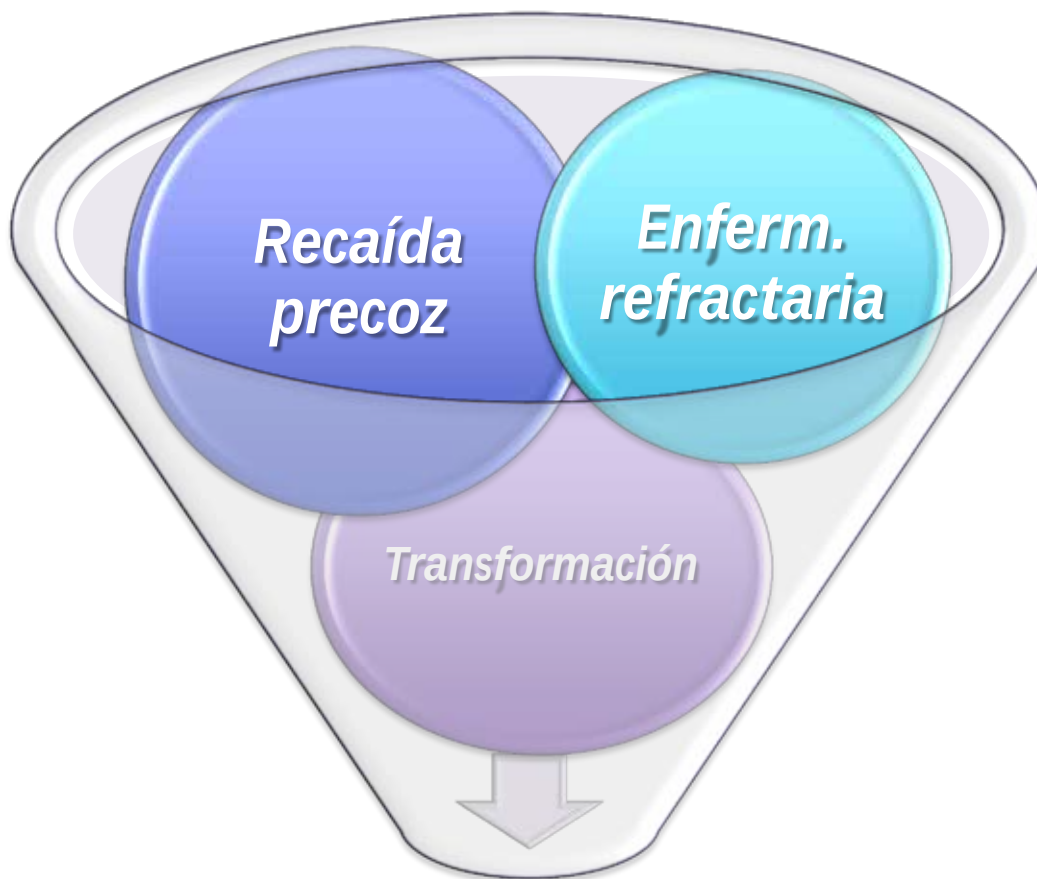
HR 6.7, 95% CI 2.4-18.5, p=0.0002

Median OS: 79 months vs. NR

CR30 como marcador de SLP en linfoma folicular



No todos los pacientes con linfoma folicular siguen un curso indolente



Necesidad no cubierta

Ninguno de los índices pronósticos identifica a este subgrupo de pacientes

Índice	Factores de riesgo	Categorías	Valor pronóstico
FLIPI ⁽¹⁾	Edad>60 años Estadio III-IV Hb<12 g/dL LDH elevada <4 areas ganglionares	0-1: Bajo riesgo 2: Intermedio 3-5: Alto riesgo	–Supervivencia global y tiempo hasta fallo tratamiento –Riesgo de transformación –Supervivencia 5 años desde primera progresión
FLIPI2 ⁽²⁾	Edad>60 años MO infiltrada Hb<12 g/dL b2M elevada >6cm diámetro ganglionar	0: Bajo riesgo 1-2: Intermedio 3-5: Alto riesgo	–Supervivencia libre de progresión y global 3 y 5 años
m7-FLIPI ⁽³⁾	FLIPI >2 ECOG PS >1 Mutaciones en EZH2, ARID1A, MEF2B, EP300, FOXO1, CREBBP, CARD11	<0,8: Bajo riesgo ≥0,8: Alto riesgo	–Supervivencia global y libre de fallo de tratamiento

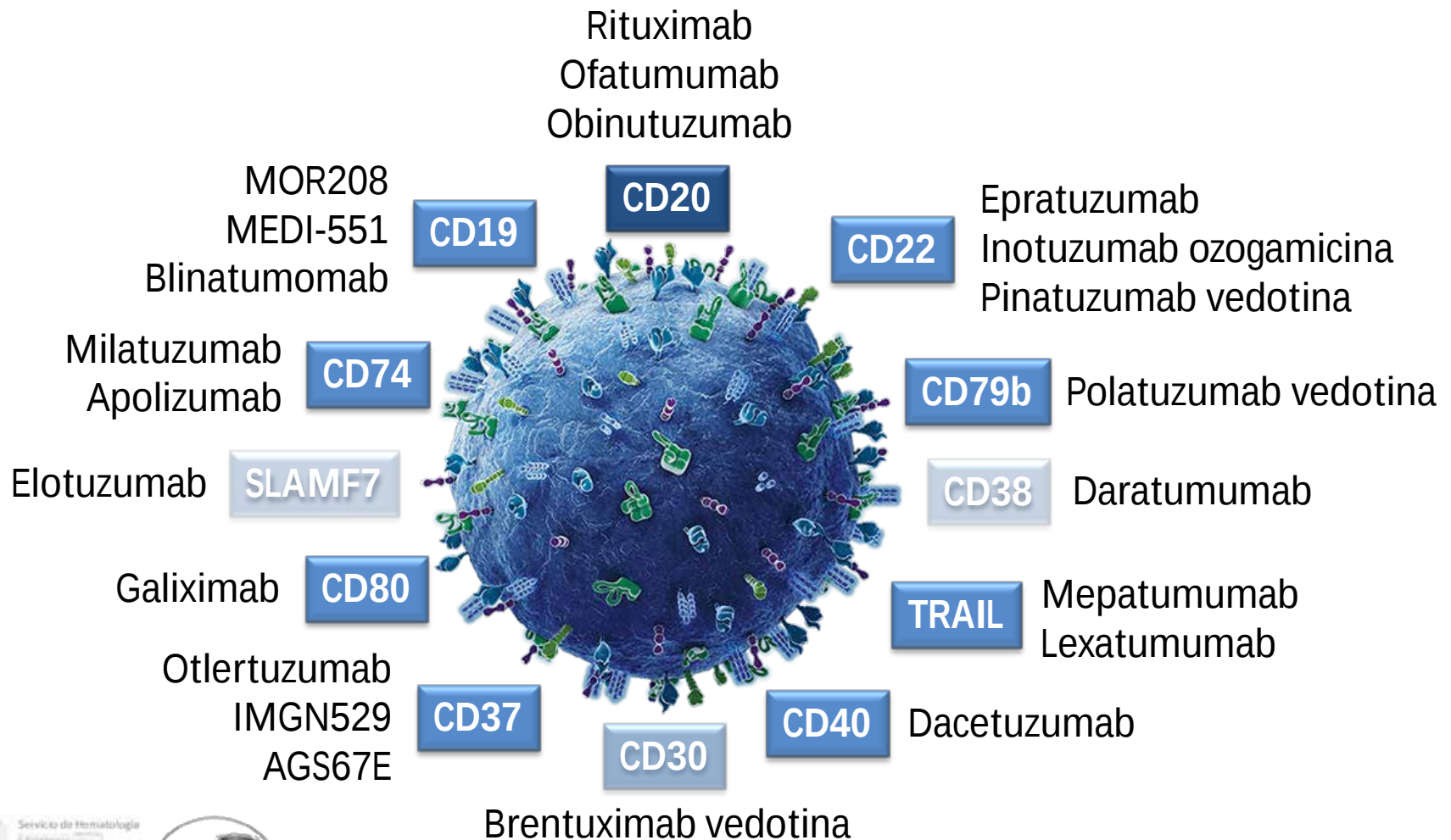
1. Solal-Celigny P, et al. Blood 2004;104:1258–65
2. Federico M, et al. J Clin Oncol 2009;27:4555–62
3. Pastore A, et al. Lancet Oncol 2015;16:1111–22

¿Cómo mejorar los resultados en pacientes con linfoma folicular?

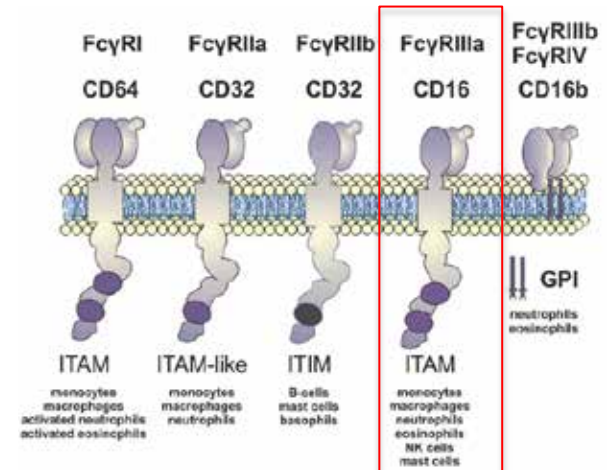
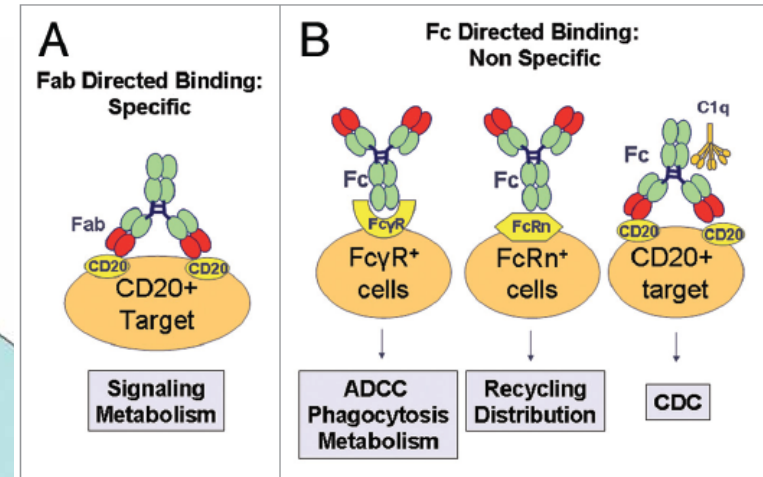
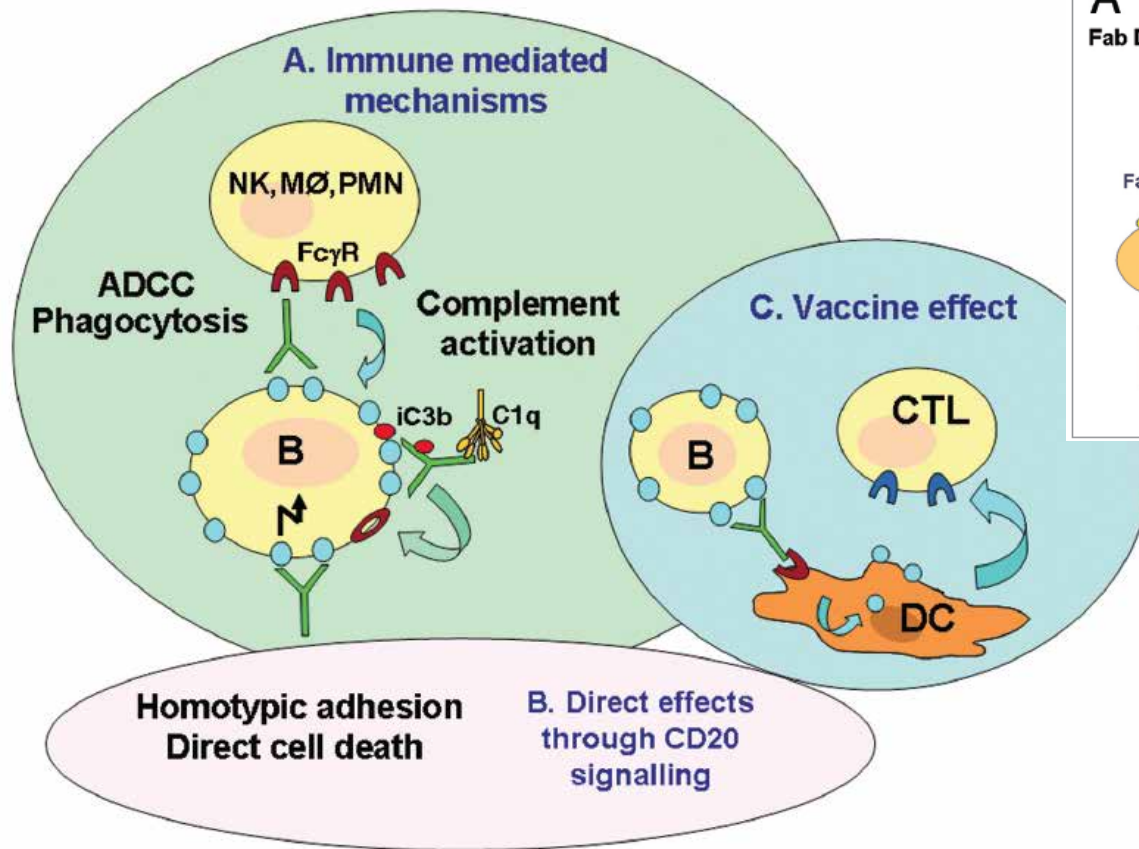
- ✓ La progresión precoz, la ausencia de RC por PET-TC y de RC a los 30 meses (CR30, estudio FLASH) define una población de pacientes con linfoma folicular de alto riesgo
- ✓ El reto es poder identificar marcadores clínicos, genéticos y moleculares (m7-FLIPI, TMTV, Nanostring, ...) y así diseñar ensayos clínicos adaptados al riesgo
- ✓ Existen en la actualidad nuevos fármacos y combinaciones que han demostrado eficacia en pacientes refractarios
- ✓ Sin embargo, parece más apropiado incorporar los agentes y esquemas más eficaces en la terapia de inducción inicial con el objetivo de alcanzar respuestas prolongadas

¿Cómo podemos mejorar los resultados?

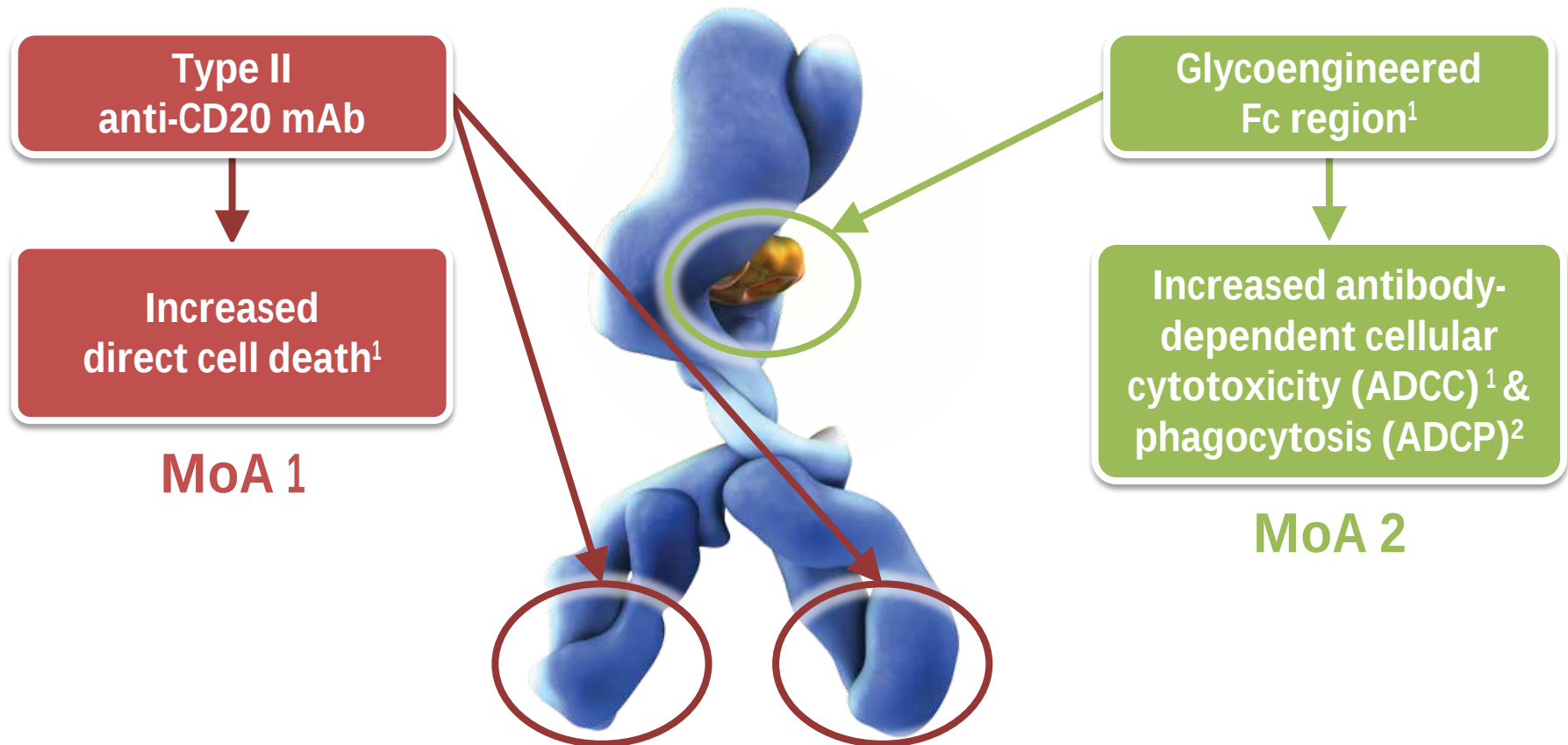
El '*surface-ome*' como diana terapéutica



¿Por qué son tan eficaces los anticuerpos monoclonales?



Obinutuzumab es un 'nuevo' anti-CD20



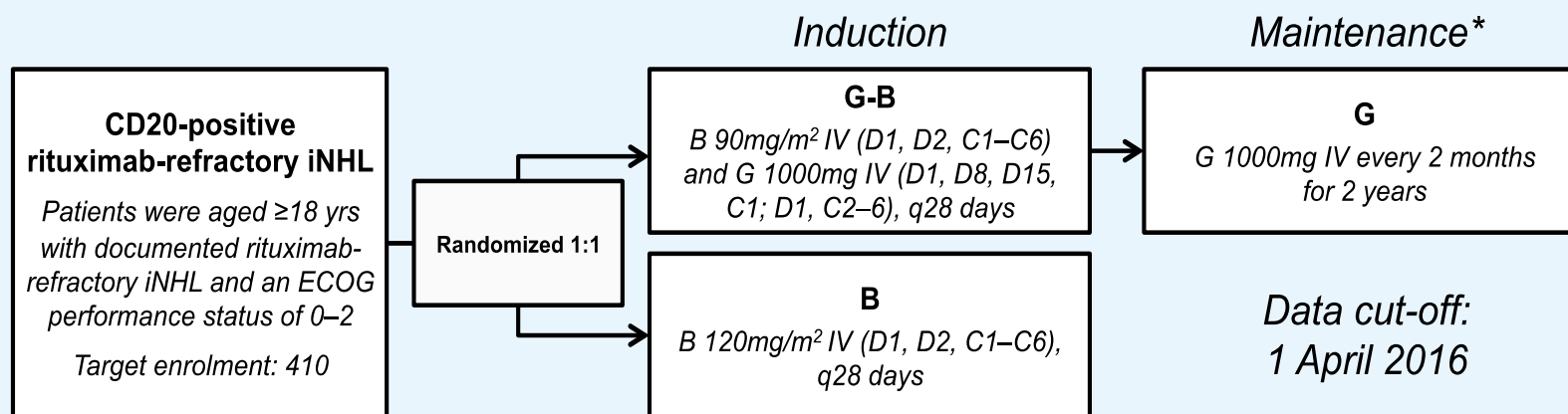
Justificación para el empleo de Obinutuzumab en primera línea

- ✓ Estudio fase II **GAUSS** demuestra mejores tasas de respuestas en comparación directa con rituximab¹
- ✓ Estudio fase Ib **GAUDI** demuestra tasas de respuesta >90% en combinación con CHOP o FC en recaída² y en combinación con CHOP o bendamustina en primera línea con SLP 3a del 87%³
- ✓ Estudio fase III **GADOLIN** demuestra ventajas en SLP y SG en combinación con bendamustina^{4,5}

1. Sehn LH, et al. J Clin Oncol 2015;33:3467–74
2. Radford J, et al. Blood. 2013;122:1137–43
3. Grigg A, et al. Haematologica 2017;102:7655–72
4. Sehn LH, et al. Lancet Oncol. 2016;17:1081–93
5. Cheson BD, et al. ASH 2016 (oral presentation)

Obinutuzumab en linfomas indolentes refractarios a rituximab (GADOLIN)

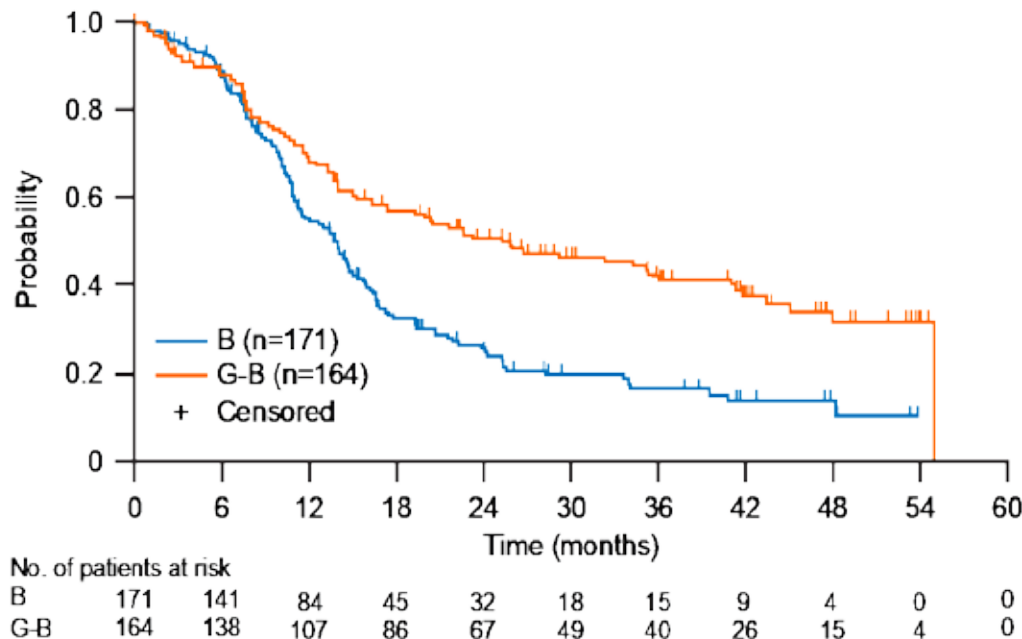
Open-label, multicenter, randomized, Phase III study in rituximab-refractory iNHL patients



- **Rituximab-refractory definition:** Failure to respond to, or progression during any prior rituximab-containing regimen (monotherapy or combined with chemotherapy), or progression within 6 months of the last rituximab dose, in the induction or maintenance settings
- **Endpoints considered in current analysis:** PFS (INV), OS, TTNT, safety

Reducción del riesgo de progresión con Obinutuzumab en LF refractario

Kaplan-Meier plot of INV-assessed PFS by treatment arm (FL)

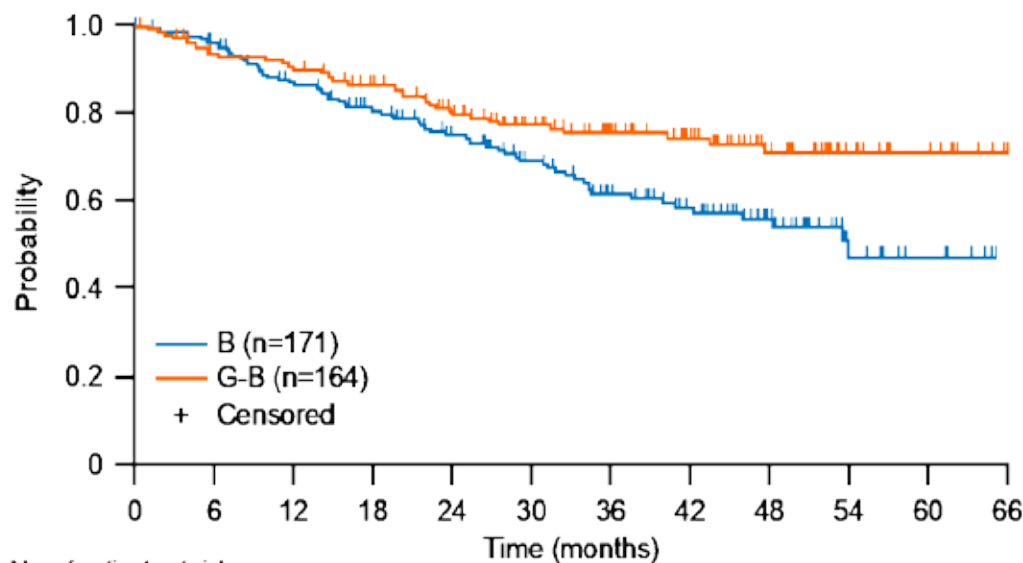


	G-B, n=164	B, n=171
Pts with event, n (%)	93 (56.7)	125 (73.1)
Median PFS (95% CI), mo	25.3 (17.4, 36.0)	14.0 (11.3, 15.3)
HR (95% CI), p-value*	0.52 (0.39, 0.69), p<0.0001	

*Median follow-up (FL): 31.2 months
(vs 21.1 months in primary analysis)*

Beneficio en supervivencia global en pacientes con linfoma folicular

Kaplan-Meier plot of OS by treatment arm (FL)



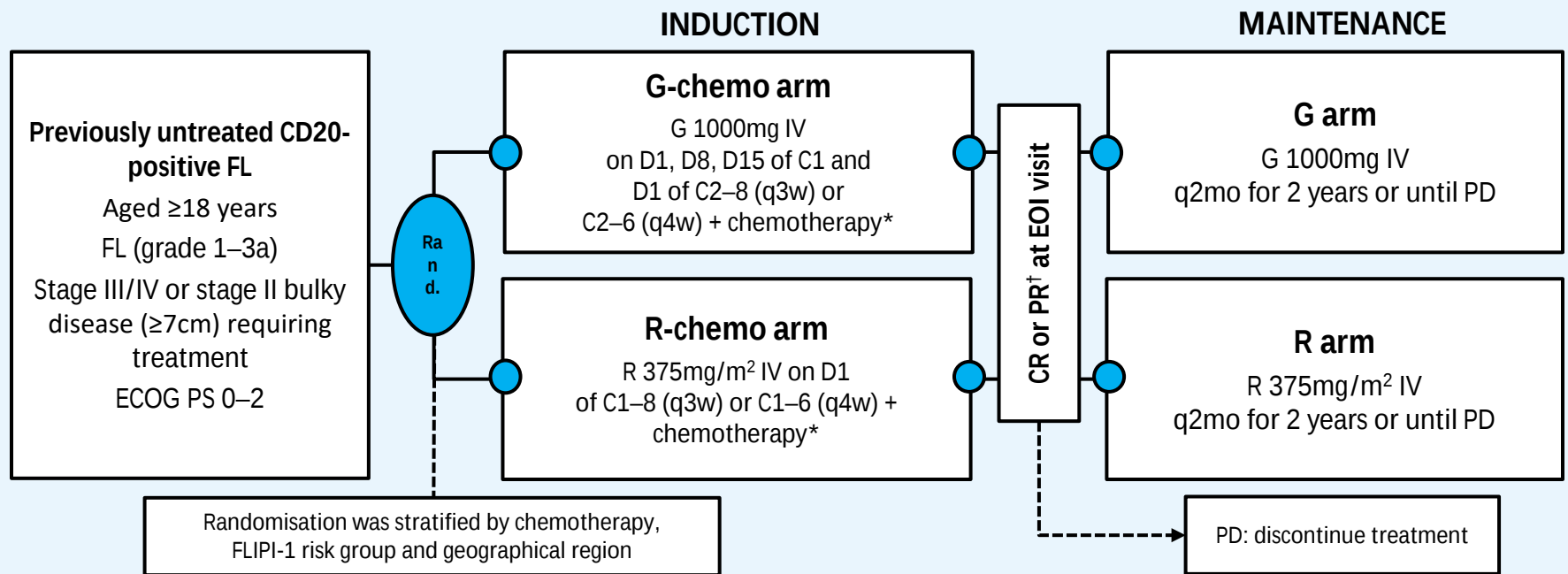
No. of patients at risk												
B	171	159	137	122	103	84	65	49	32	13	7	0
G-B	164	147	141	129	111	90	71	56	38	20	12	0

	G-B, n=164	B, n=171
Pts with event, n (%)	39 (23.8)	64 (37.4)
Median OS (95% CI), mo	NR (NR, NR)	53.9 (40.9, NR)
HR (95% CI), p-value*	0.58 (0.39, 0.86), p=0.0061	

Median follow-up (FL): 31.2 months
(vs 21.1 months in primary analysis)

Estudio GALLIUM en pacientes con linfoma foliular en primera línea

International, open-label, randomised Phase III study in 1L pts (NCT01332968)



Primary endpoint

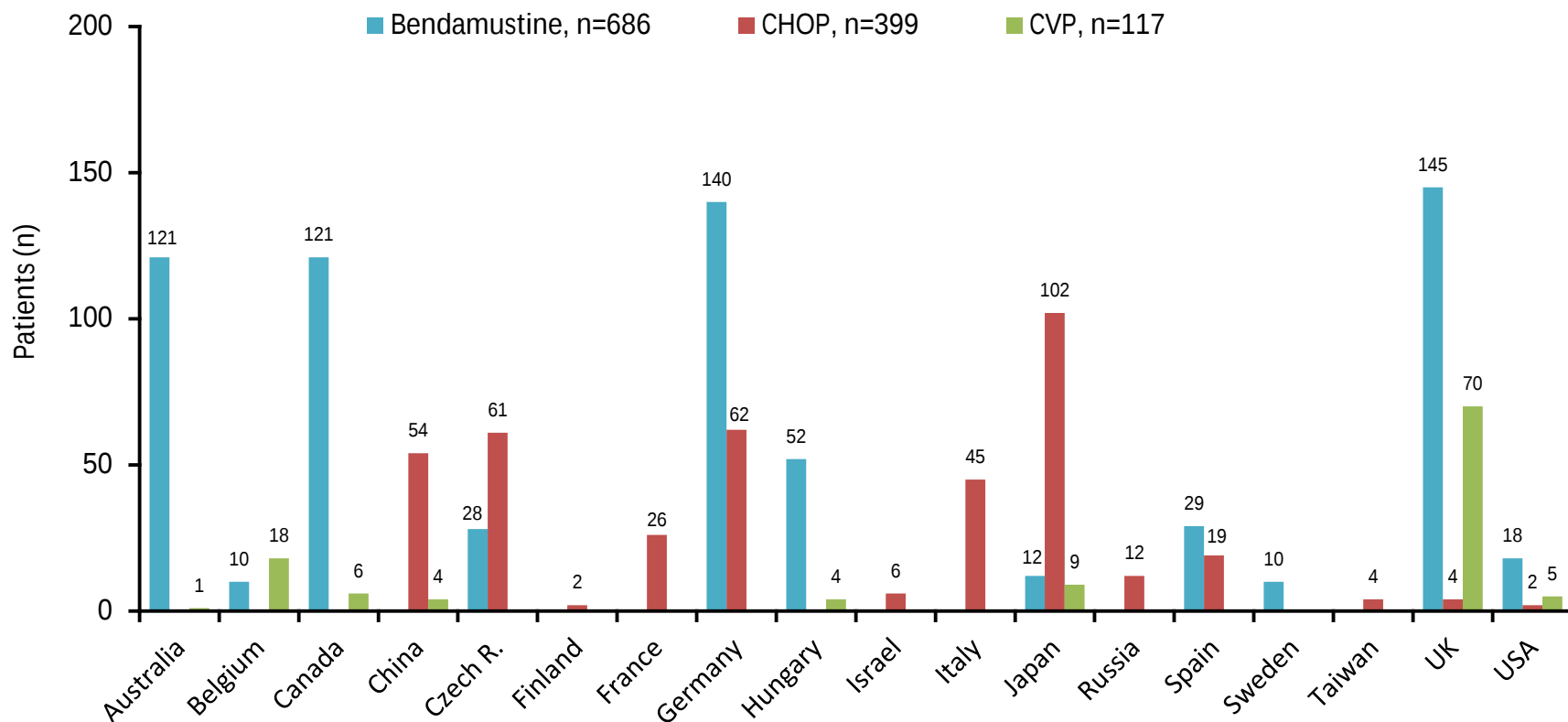
- PFS (INV-assessed)

Secondary endpoints

- PFS (IRC-assessed)
- OS, EFS, DFS, DoR, TTNALT
- ORR/CR at EOI (+/– FDG-PET)
- Safety
- PROs

*CHOP q3w × 6 cycles, CVP q3w × 8 cycles, bendamustine q4w × 6 cycles; chemo regimen chosen by site prior to initiation and received by all FL pts at site; †patients with SD at EOI entered observation for up to 2 years or until PD if earlier

Distribución de pacientes por país y esquema de quimioterapia



Chemo regimen chosen by site prior to initiation and received by all FL pts at site

Características basales

(población por intención de tratamiento)

Characteristic	R-chemo, n=601	G-chemo, n=601
Median age, years (range)	58 (23–85)	60 (26–88)
Male, % (n)	46.6% (280)	47.1% (283)
Ann Arbor stage at diagnosis, % (n)		
III	34.8% (208)*	34.9% (209) [†]
IV	56.4% (337)*	56.5% (338) [†]
FLIPI risk group, % (n)		
Low (0–1)	20.8% (125)	21.3% (128)
Intermediate (2)	37.1% (223)	37.3% (224)
High (≥ 3)	42.1% (253)	41.4% (249)
B symptoms, % (n)	34.3% (206) [‡]	33.4% (201)
Bone marrow involvement, % (n)	49.3% (295) [†]	53.7% (318) [§]
Extranodal involvement, % (n)	65.9% (396)	65.2% (392)
Bulky disease (≥ 7 cm), % (n)	45.2% (271) [‡]	42.5% (255) [‡]
Median (range) time from diagnosis to randomization, mo	1.4 (0–168.1) [¶]	1.5 (0.1–121.6) [¶]

ITT population; *n=597; [†]n=598; [‡]n=600; [§]n=592; [¶]n=598

Características basales por esquema de quimioterapia

n (%)	Benda, n=686	CHOP, n=399	CVP, n=117
Median age, years (range)	59 (23–88)	58 (31–85)	59 (32–85)
Age ³ 80 years	23 (3.4)	3 (0.8)	4 (3.4)
Male	332 (48.4)	177 (44.4)	54 (46.2)
Charlson Comorbidity Index score ³ 1 [†]	163 (23.8)	69 (17.3)	22 (18.8)
ECOG PS 2	24 (3.5)	8 (2.0)	6 (5.1)
FLIPI high risk (≥ 3)	274 (39.9)	187 (46.9)	41 (35.0)
Bulky disease (≥ 7 cm)	274 (39.9)	206 (51.6)	46 (39.3)

ITT population; [†]scored retrospectively based on conditions reported on medical history page of CRF

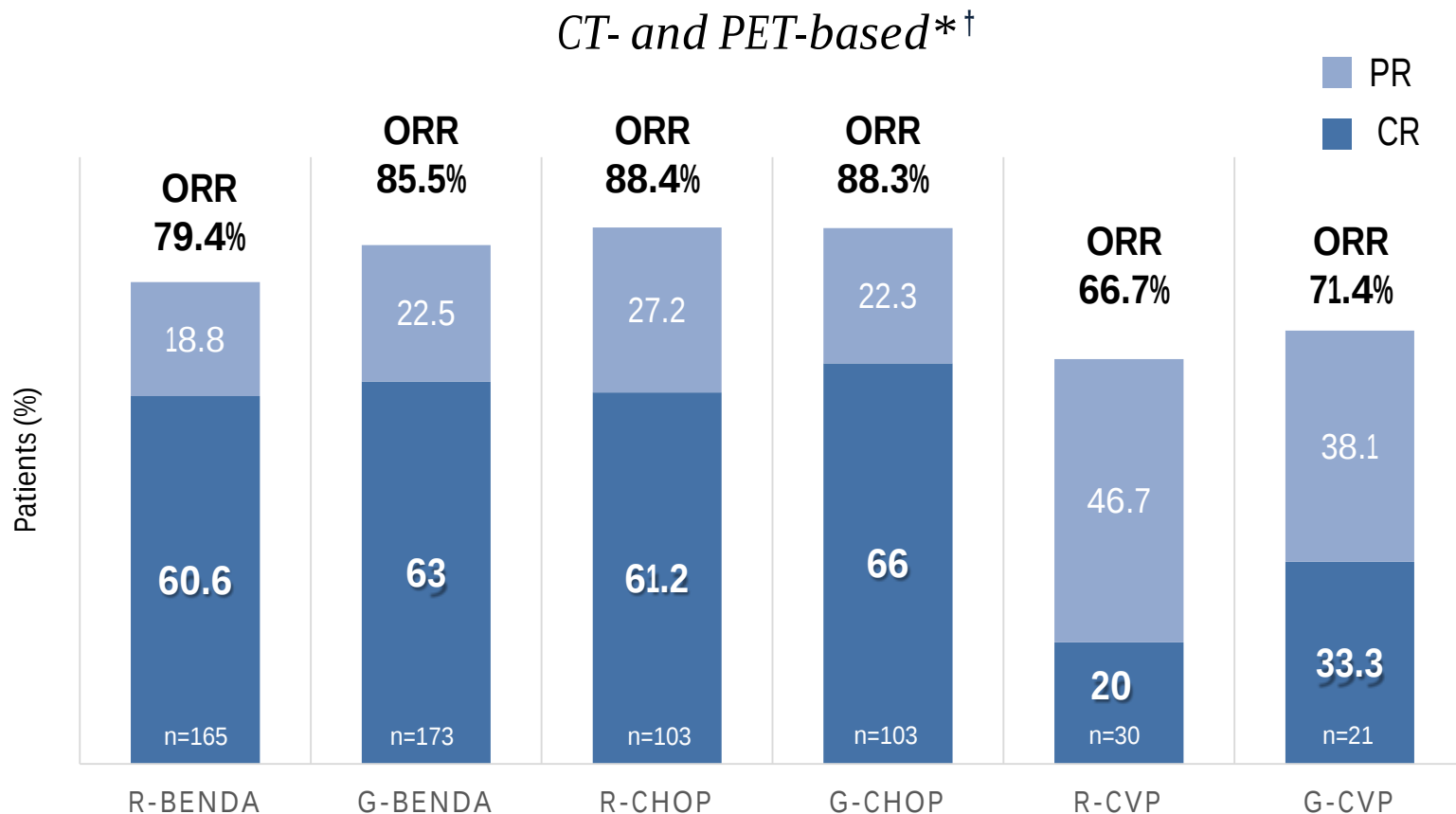
Proporción de respuestas al final del tratamiento de inducción (INV)

<i>Number of patients</i> % (n); 95% CI	<i>CT (by investigator)*</i>	
	R-chemo, n=601	G-chemo, n=601
ORR	86.9% (522); 83.9, 89.5	88.5% (532); 85.7, 91.0
CR	23.8% (143); 20.4, 27.4	19.5% (117); 16.4, 22.9
PR	63.1% (379)	69.1% (415)
SD	1.3% (8)	0.5% (3)
PD	4.0% (24)	2.3% (14)
Not evaluable / missing	3.5% (21) / 4.3% (26)	4.0% (24) / 4.7% (28)

**Revised Response Criteria for Malignant Lymphoma (Cheson BD, et al. J Clin Oncol 2007)*

Marcus RE, et al. ASH 2016 (abstract #6)

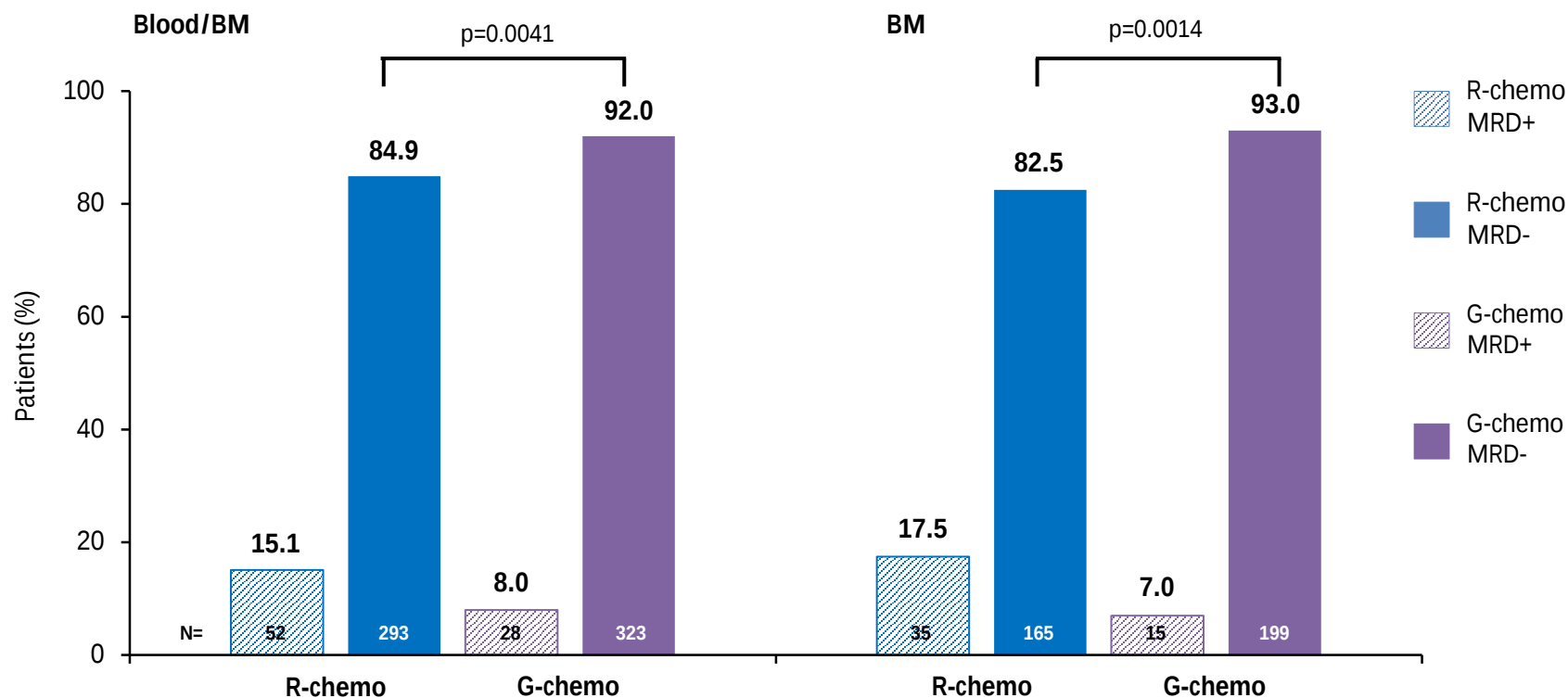
Proporción de respuestas al final del tratamiento de inducción (INV)



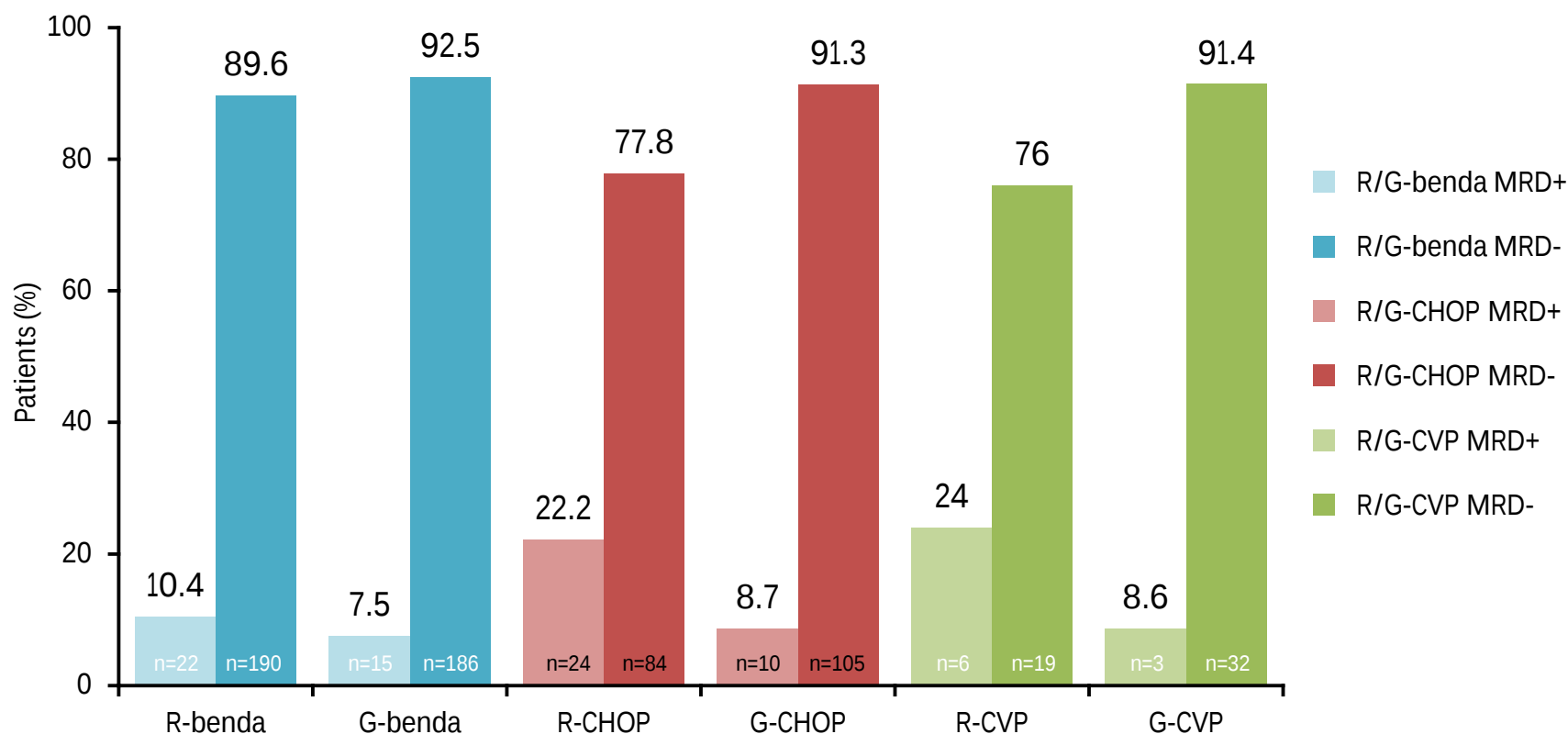
*PET ITT population i.e. all randomised FL pts who had PET-avid lesions representing lymphoma at baseline

†Assessed according to Revised Response Criteria for Malignant Lymphoma (Cheson BD, et al. J Clin Oncol 2007)

EMR al final del tratamiento de inducción

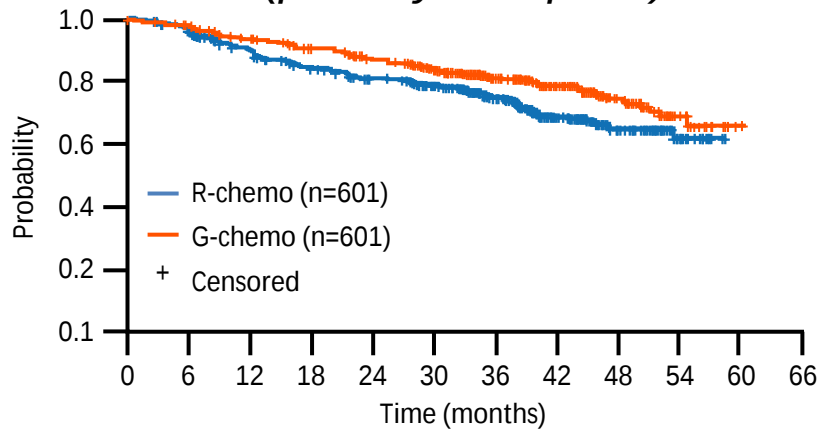


EMR al final del tratamiento de inducción



Beneficio sobre la SLP de Obinutuzumab sobre Rituximab

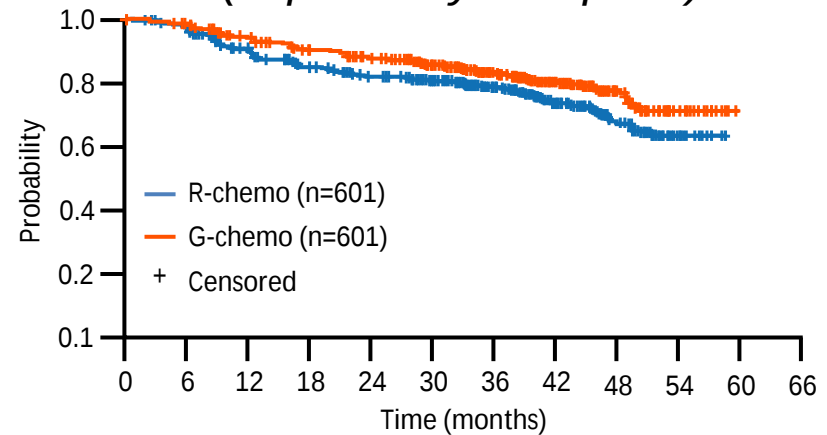
*INV-assessed PFS **
(primary end-point)



No. of patients at risk

G-chemo	601	561	505	464	438	396	267	149	77	18	
R-chemo	601	569	535	505	478	420	291	176	85	25	1

*IRC-assessed PFS **
(exploratory end-point)



No. of patients at risk

G-chemo	601	563	502	463	438	394	271	151	73	16
R-chemo	601	571	532	497	476	414	287	179	79	22

R-chemo, n=601 G-chemo, n=601

3-yr PFS, % (95% CI)	75.0 (71.0, 78.5)	81.5 (77.9, 84.6)
HR (95% CI), p-value [†]	0.68 (0.54, 0.87), p=0.0016	

R-chemo, n=601 G-chemo, n=601

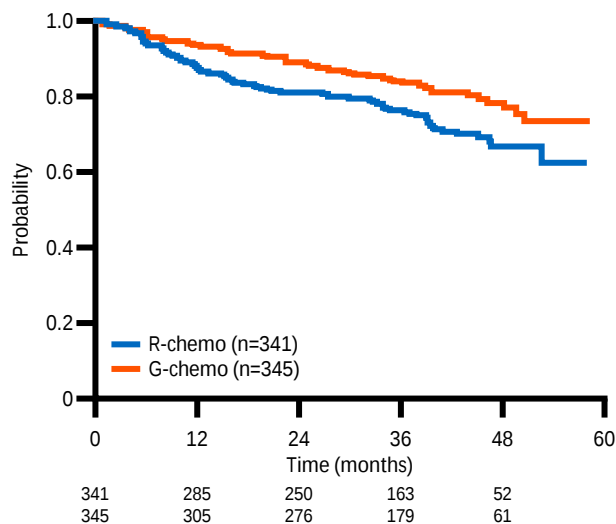
3-yr PFS, % (95% CI)	78.9 (75.2, 82.1)	83.4 (79.9, 86.3)
HR (95% CI), p-value [†]	0.72 (0.56, 0.93), p=0.0118	

* Median f/u 41.1 months

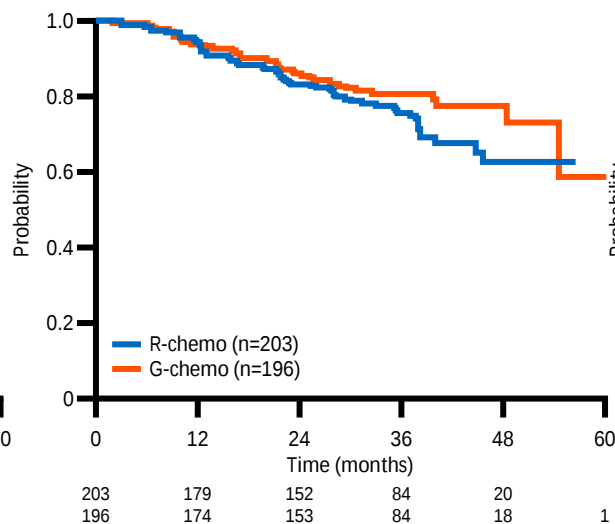
ITT population; [†]stratified analysis; stratification factors = FLIPI, chemotherapy regimen

La reducción del riesgo se mantiene con todos los esquemas de quimioterapia

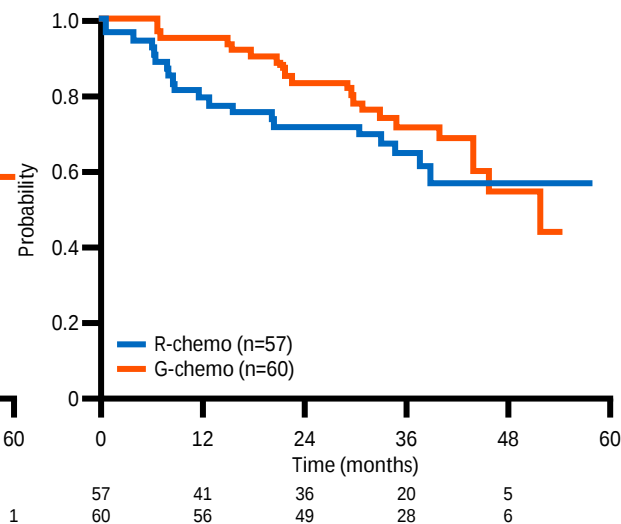
Bendamustine



CHOP



CVP



HR (95% CI)[†] 0.63 (0.46, 0.88)

3-yr PFS 84.1% G-B vs 76.4% R-B

HR (95% CI)[†] 0.72 (0.48, 1.10)

3-yr PFS 80.6% G-CHOP vs 75.6% R-CHOP

HR (95% CI)[†] 0.79 (0.42, 1.47)

3-yr PFS 71.3% G-CVP vs 64.2% R-CVP

By chemo analysis not powered to demonstrate statistically significant differences between treatment arms

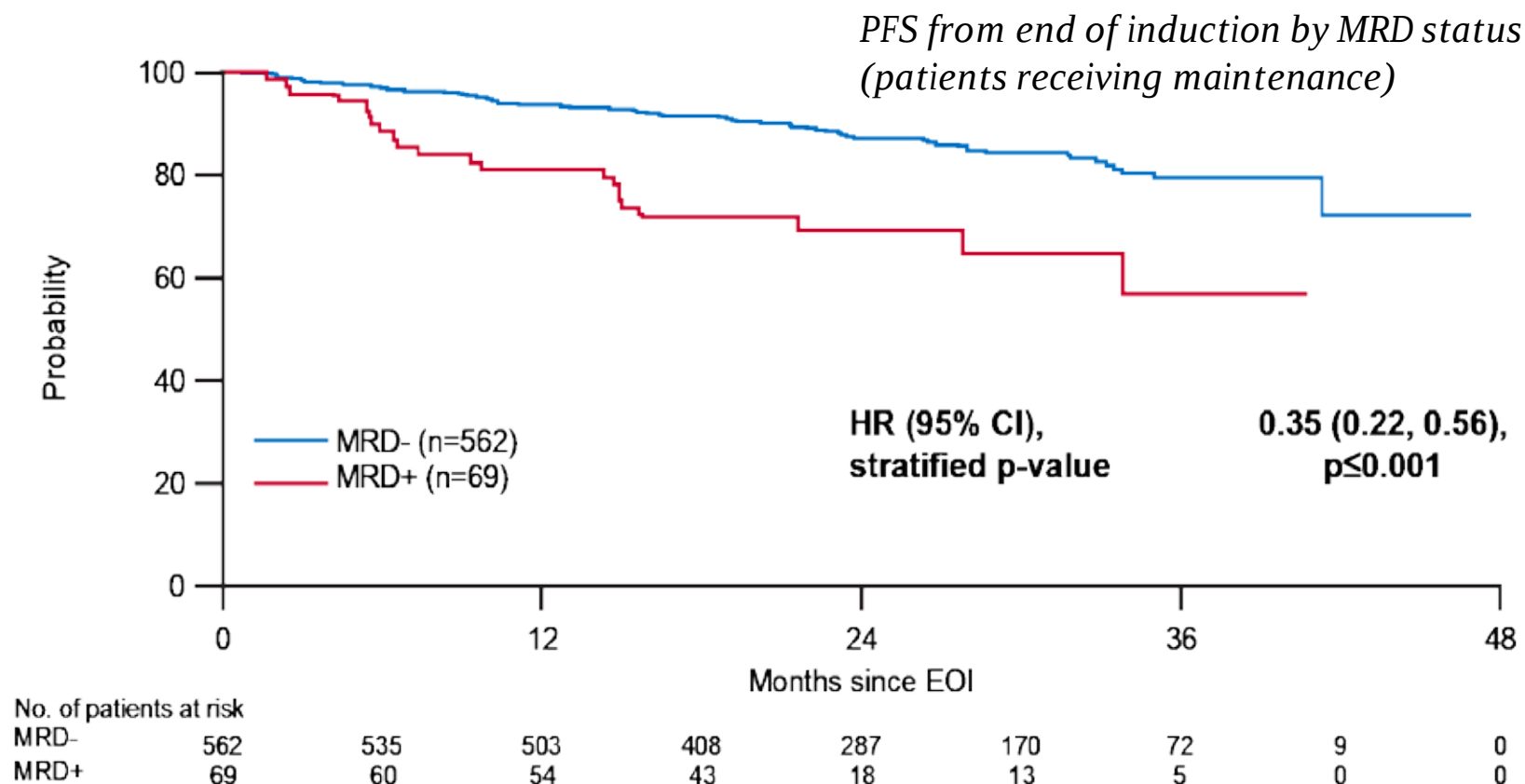
ITT population; [†]analysis stratified by IPI (as well as chemotherapy regimen)

For several cancers, it can be stated with confidence (probably greater than 95%) that patients who remain relapse free for a given time after treatment are cured.



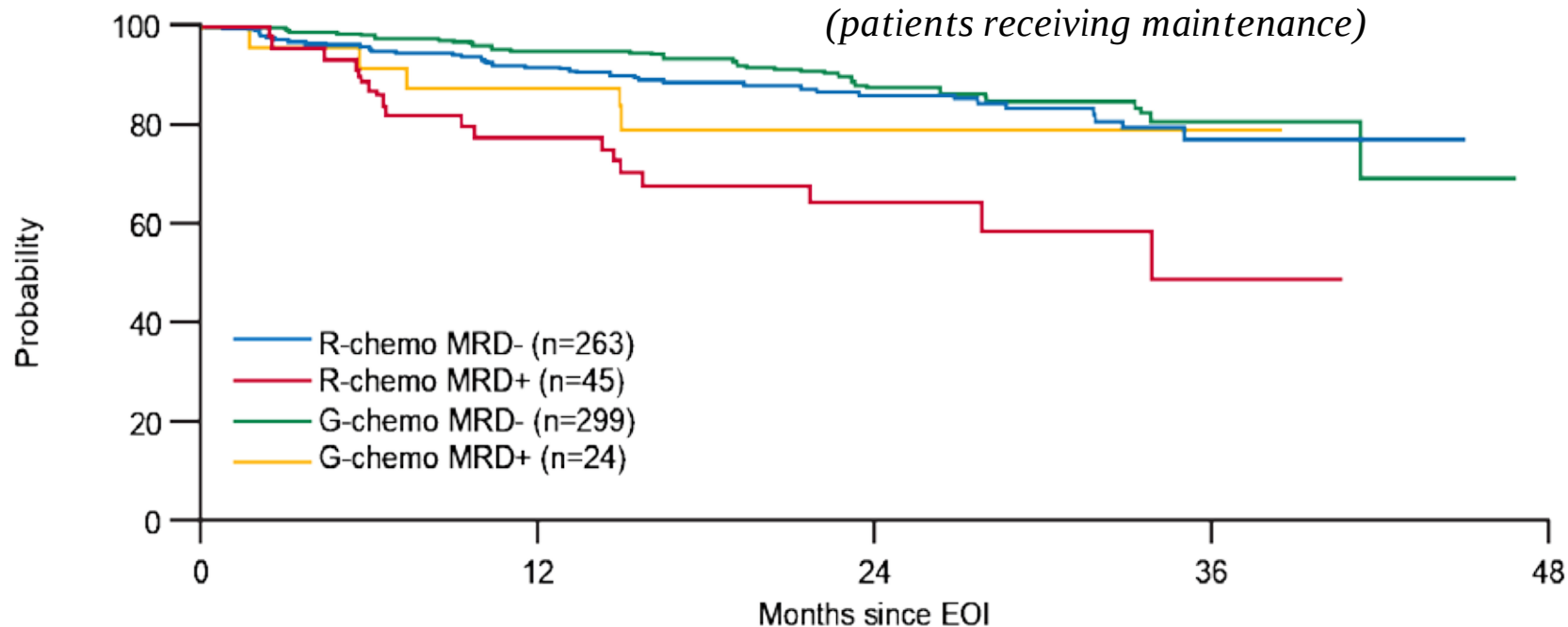
Emil Frei, III

Influencia de la EMR sobre SLP



Influencia de la EMR sobre SLP

*PFS from end of induction by MRD status
(patients receiving maintenance)*

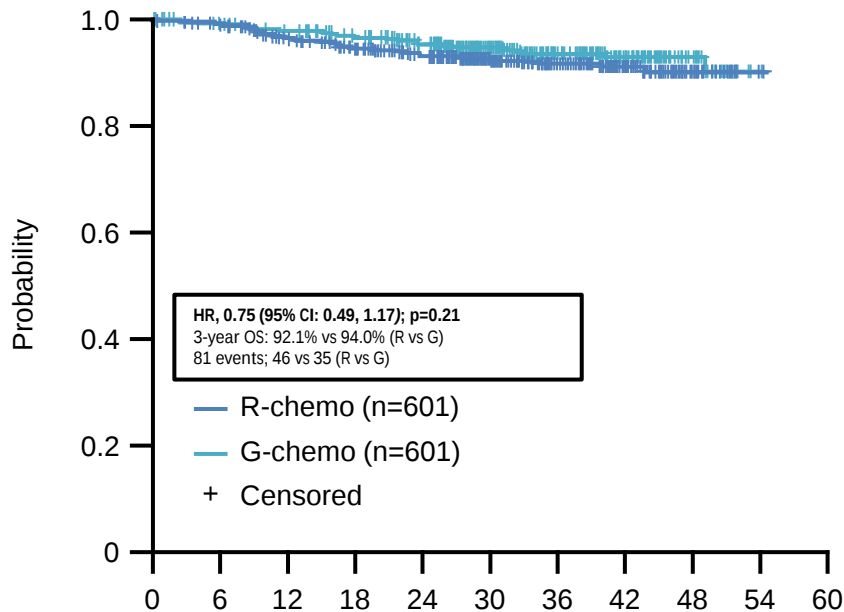


No. of patients at risk

R-chemo MRD-	263	244	230	185	134	77	31	4	0
R-chemo MRD+	45	38	33	27	12	10	4	0	0
G-chemo MRD-	299	291	273	223	153	93	41	5	0
G-chemo MRD+	24	22	21	16	6	3	1	0	0

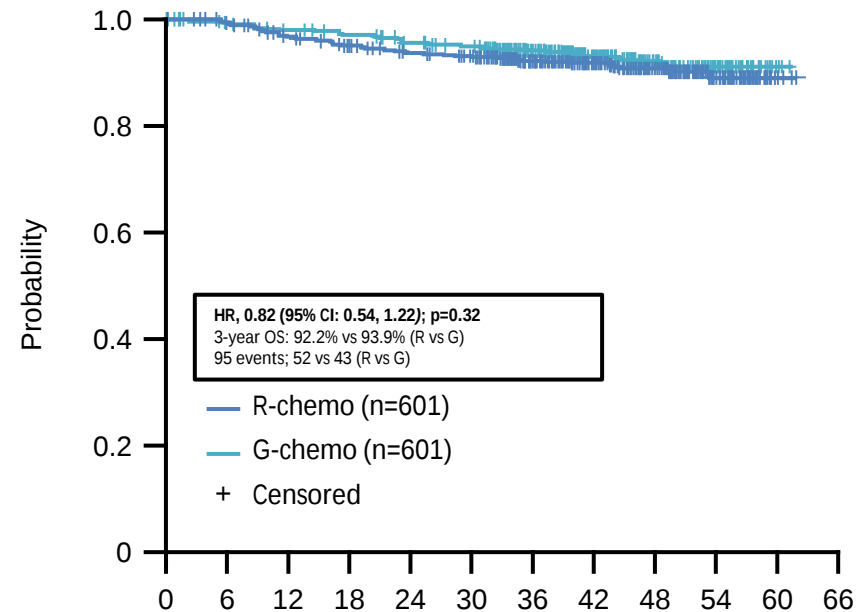
Ausencia de diferencias en supervivencia global

Primary analysis
(31 January 2016 cut-off)



No. of patients at risk	Time (months)									
R-chemo	601	586	554	524	484	356	226	126	44	2
G-chemo	601	582	566	546	520	379	240	137	48	

Updated analysis
(10 September 2016 cut-off)



No. of patients at risk		Time (months)										
		601	588	566	549	533	522	424	286	178	69	4
R-chemo		601	588	566	549	533	522	424	286	178	69	4
G-chemo		601	584	573	563	551	541	438	286	179	72	3

More all-cause deaths in the R-chemo arm (52; 8.7%) than the G-chemo arm (43; 7.2%)

Análisis de toxicidad

Efectos adversos

<i>n (%) of pts reporting ³ 1 event *</i>	<i>R-chemo, n=597</i>	<i>G-chemo, n=595</i>
Any AE	585 (98.0)	593 (99.7)
Grade 3–5 AEs	409 (68.5)	449 (75.5)
SAE	246 (41.2)	281 (47.2)
Grade 5 (fatal) AE	21 (3.5)	24 (4.0)
AE leading to treatment discontinuation	88 (14.7)	98 (16.5)

* Safety population, i.e. all randomised FL pts who received at least one dose of study drug

All-cause deaths in each arm: R-chemo, 52 (8.7%); G-chemo, 42 (7.1%)

Efectos adversos de particular interés, grados 3–5 (frecuencia >2%)

<i>n (%) of pts reporting ³ 1 event *</i>	<i>R-chemo, n=597</i>	<i>G-chemo, n=595</i>
Neutropenia	236 (39.5)	278 (46.7)
Infections [†]	98 (16.4)	121 (20.3)
Infusion-related reactions [‡]	40 (6.7)	74 (12.4)
Thrombocytopenia	16 (2.7)	36 (6.1)
Second malignancies (SMQ) [§]	21 (3.5)	29 (4.9)
Cardiac events	17 (2.8)	23 (3.9)

* AEs occurring in >2% of patients in safety population, in either treatment arm

† System Organ Class 'Infections and Infestations'

‡ Related to study treatment and occurring during or in the 24 hours after infusion

§ Standardised MedDRA query, i.e. malignant or unspecified tumours occurring >6 mo after study drug intake

Efectos adversos por esquema de quimioterapia

<i>n (%) of pts reporting ≥ 1 event *</i>	<i>R-benda, n=338</i>	<i>G-benda, n=338</i>	<i>R-CHOP, n=203</i>	<i>G-CHOP, n=193</i>	<i>R-CVP, n=56</i>	<i>G-CVP, n=61</i>
Any AE	331 (97.9)	338 (100)	201 (99.0)	191 (99.0)	56 (100)	61 (100)
Grade 3–5 AE	228 (67.5)	233 (68.9)	151 (74.4)	171 (88.6)	30 (53.6)	42 (68.9)
SAE	160 (47.3)	176 (52.1)	67 (33.0)	76 (39.4)	19 (33.9)	26 (42.6)
Grade 5 (fatal) AE [†]	16 (4.7)	20 (5.9)	4 (2.0)	3 (1.6)	1 (1.8)	1 (1.6)
AE leading to treatment discontinuation	48 (14.2)	52 (15.4)	31 (15.3)	32 (16.6)	9 (16.1)	11 (18.0)

* Safety population, i.e. all randomised FL pts who received at least one dose of study drug

[†] Includes 6 pts with fatal AEs that occurred after start of new anti-cancer therapy (G-benda, 4; R-benda, 2)

Grade 3–5 AEs most frequent with CHOP (leukopenia, neutropenia, febrile neutropenia, IRRs);
SAEs and fatal AEs most frequent with bendamustine

Efectos adversos grados 3–5 por esquema de quimioterapia

<i>n (%) of pts reporting ≥ 1 event *</i>	<i>R-benda, n=338</i>	<i>G-benda, n=338</i>	<i>R-CHOP, n=203</i>	<i>G-CHOP, n=193</i>	<i>R-CVP, n=56</i>	<i>G-CVP, n=61</i>
Cardiac events	12 (3.6)	13 (3.8)	5 (2.5)	6 (3.1)	0 (0.0)	4 (6.6)
Neutropenia	107 (31.7)	107 (31.7)	115 (56.7)	142 (73.6)	14 (25.0)	29 (47.5)
Febrile neutropenia	13 (3.8)	18 (5.3)	14 (6.9)	22 (11.4)	2 (3.6)	2 (3.3)
Second malignancies [†]	12 (3.6)	21 (6.2)	7 (3.4)	7 (3.6)	2 (3.6)	1 (1.6)
Other solid tumours	9 (2.7)	11 (3.3)	7 (3.4)	4 (2.1)	2 (3.6)	0
Hematological tumours [‡]	0	3 (0.9)	0	3 (1.6)	0	0
Non-melanoma skin cancer	3 (0.9)	7 (2.1)	0	0	0	1 (1.6)
Infections	66 (19.5)	89 (26.3)	25 (12.3)	23 (11.9)	7 (12.5)	8 (13.1)
Opportunistic infections [§]	6 (1.8)	10 (3.0)	2 (1.0)	5 (2.6)	0	0

* Safety population

[†] Standardised MedDRA query = malignant or unspecified tumours occurring >6 months after first study drug intake;

[‡] Hodgkin disease (n=3), AML (n=2), and ALL (n=1)

[§] Including fungal infections, cytomegalovirus, herpes zoster and *Pneumocystis jirovecii* pneumonia

Efectos adversos grado 5 (exitus)

SOC *†	R-benda, n=338	G-benda, n=338	R-CHOP, n=203	G-CHOP, n=193	R-CVP, n=56	G-CVP, n=61
Infections and infestations	1 (0.3)	4 (1.2)	0	1 (0.5)	0	0
Cardiac disorders	2 (0.6)	2 (0.6)	0	0	0	0
Gastrointestinal disorders	0	1 (0.3)	0	0	0	1 (1.6)
General and administration site conditions	2 (0.6)	1 (0.3)	0	1 (0.5)	1 (1.8)	0
Metabolism and nutrition disorders	1 (0.3)	1 (0.3)	0	0	0	0
Neoplasms benign, malignant and unspecified	3 (0.9)	4 (1.1)	2 (1.0)	1 (0.5)	0	0
Nervous system disorders	4 (1.2)	0	2 (1.0)	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (0.3)	3 (0.9)	0	0	0	0
Total (all SOCs)	14 (4.1%)	16 (4.7%)	4 (2.0%)	3 (1.6%)	1 (1.8%)	1(1.6%)

* Safety population; † Fatal AEs in 5 G-benda and 1 R-benda pts that occurred after new systemic anti-cancer treatment had started were not included (PD, 4 pts; new malignancies, 2 pts)

Many pts with fatal AEs had adverse risk factors, e.g. aged ≥ 80 years (benda, 6; CVP, 1), ECOG PS grade 2 (benda, 4; CVP, 1), and Charlson CI ≥ 1 (benda, 11; CHOP, 1; CVP, 1)

Hiddemann W, Barbui AM, Canales M, et al. 14-ICML 2017 (abstract #107)



Neutropenia grados 3–4 por esquema de quimioterapia y fase de tratamiento

<i>n (%) of pts reporting 3 1 event</i>	<i>R-benda, n=338</i>	<i>G-benda, n=338</i>	<i>R-CHOP, n=203</i>	<i>G-CHOP, n=193</i>	<i>R-CVP, n=56</i>	<i>G-CVP, n=61</i>
All study periods	102 (30.2)	100 (29.6)	111 (54.7)	137 (71.0)	13 (23.2)	28 (45.9)
Induction	87 (25.7)	73 (21.6)	103 (50.7)	124 (64.2)	13 (23.2)	24 (39.3)
Maintenance	29 (9.7)	49 (16.1)	26 (14.0)	37 (20.8)	2 (5.0)	5 (8.8)
Observation/ Follow-up†	1 (0.3)	6 (1.9)	1 (0.5)	4 (2.2)	0	1 (1.7)

Grade 3 and 4 neutropenia AEs reported as preferred term in safety population

† Includes patients not receiving maintenance therapy after induction

Infecciones grados 3–5 por esquema de quimioterapia y fase de tratamiento

<i>n (%) of pts reporting ≥ 1 event</i>	<i>R-benda, n=338</i>	<i>G-benda, n=338</i>	<i>R-CHOP, n=203</i>	<i>G-CHOP, n=193</i>	<i>R-CVP, n=56</i>	<i>G-CVP, n=61</i>
All study periods	66 (19.5)	89 (26.3)	25 (12.3)	23 (11.9)	7 (12.5)	8 (13.1)
Induction	26 (7.7)	27 (8.0)	13 (6.4)	14 (7.3)	4 (7.1)	3 (4.9)
Maintenance	39 (13.0)	51 (16.7)	11 (5.9)	7 (3.9)	1 (2.5)	5 (8.8)
Observation	12 (3.8)	28 (8.8)	6 (3.1)	3 (1.6)	3 (5.7)	1 (1.7)
<i>N (%) of pts receiving G-CSF prophylaxis</i>	48 (14.2)	54 (16.0)	108 (53.2)	112 (58.0)	13 (23.2)	10 (16.4)

Ensayo GALLIUM

Conclusiones

Análisis global

- ✓ Los datos actualizados confirman los obtenidos en el análisis inicial, con beneficio clínicamente significativo en SLP con Obinutuzumab
 - Efectos adversos grados 3–5 y SAEs más frecuentes con Obinutuzumab
 - Citopenias, infecciones y reacciones infusionales

Análisis por quimioterapia

- ✓ La reducción de riesgo de progresión se reduce con Obinutuzumab en combinación con todos los esquemas de quimioterapia
 - La comparación entre regímenes de quimioterapia no es aleatorizada y el estudio no está diseñado para demostrar diferencias entre Rituximab y Obinutuzumab dentro de cada esquema de tratamiento
- ✓ Precaución con la combinación con Bendamustina, tanto con Rituximab como con Obinutuzumab (evidencia de depleción prolongada de cel. T)

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Preguntas

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