Lymphomes Folliculaires

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Lymphomes Folliculaires

- Focus sur première ligne avec nécessité de traitement (les fortes masses)

- Focus sur les échecs/rechutes

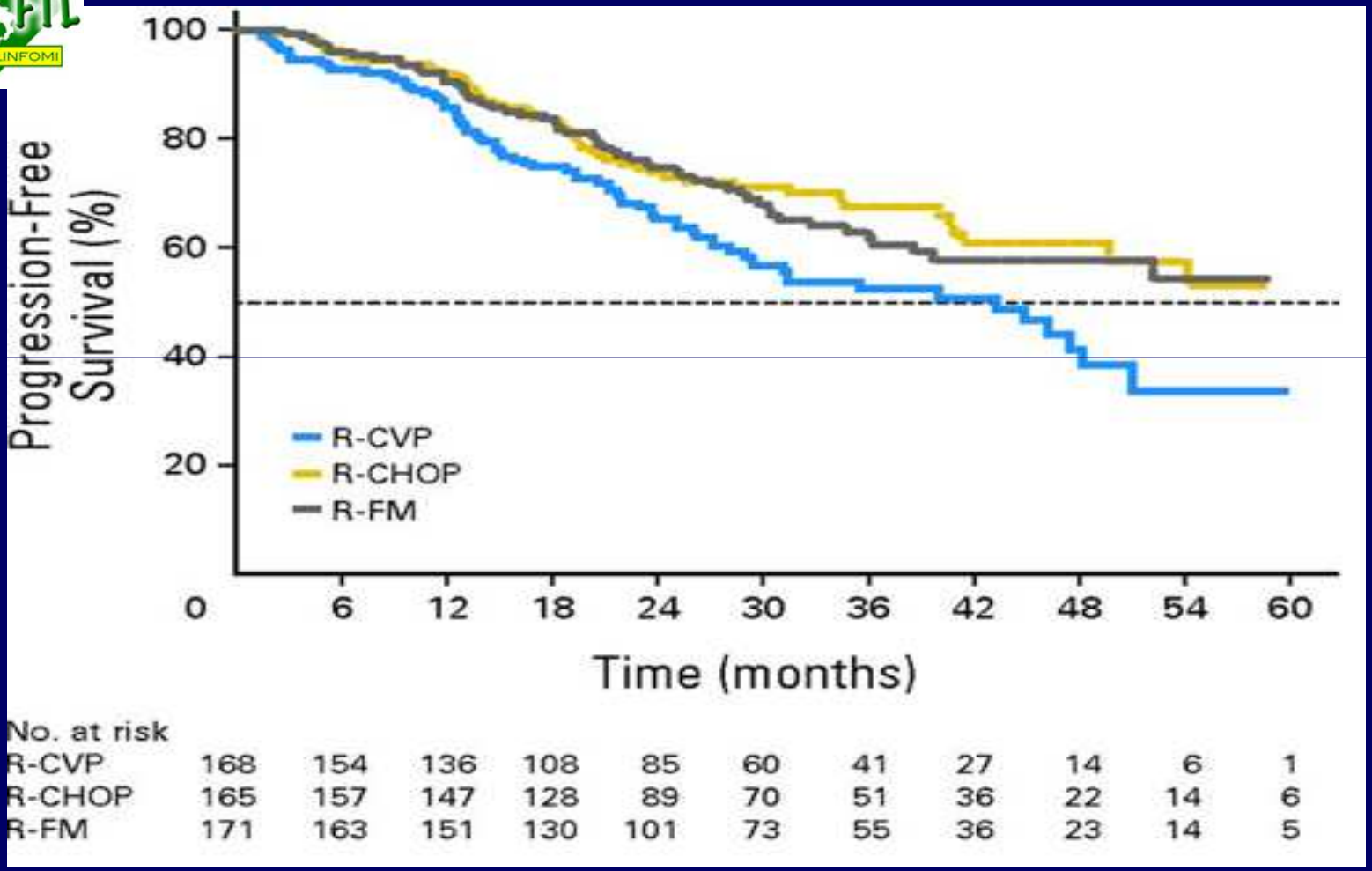
Follicular lymphoma
First line strategy

1. **Limited stage patients :**
   - Is radiation therapy the standard of care ?

2. **Low tumor burden patients**
   - Watch and wait or early intervention ?

3. **High tumor burden patients**
   - Is there an optimal chemo regimen ?
   - Consolidation or maintenance?

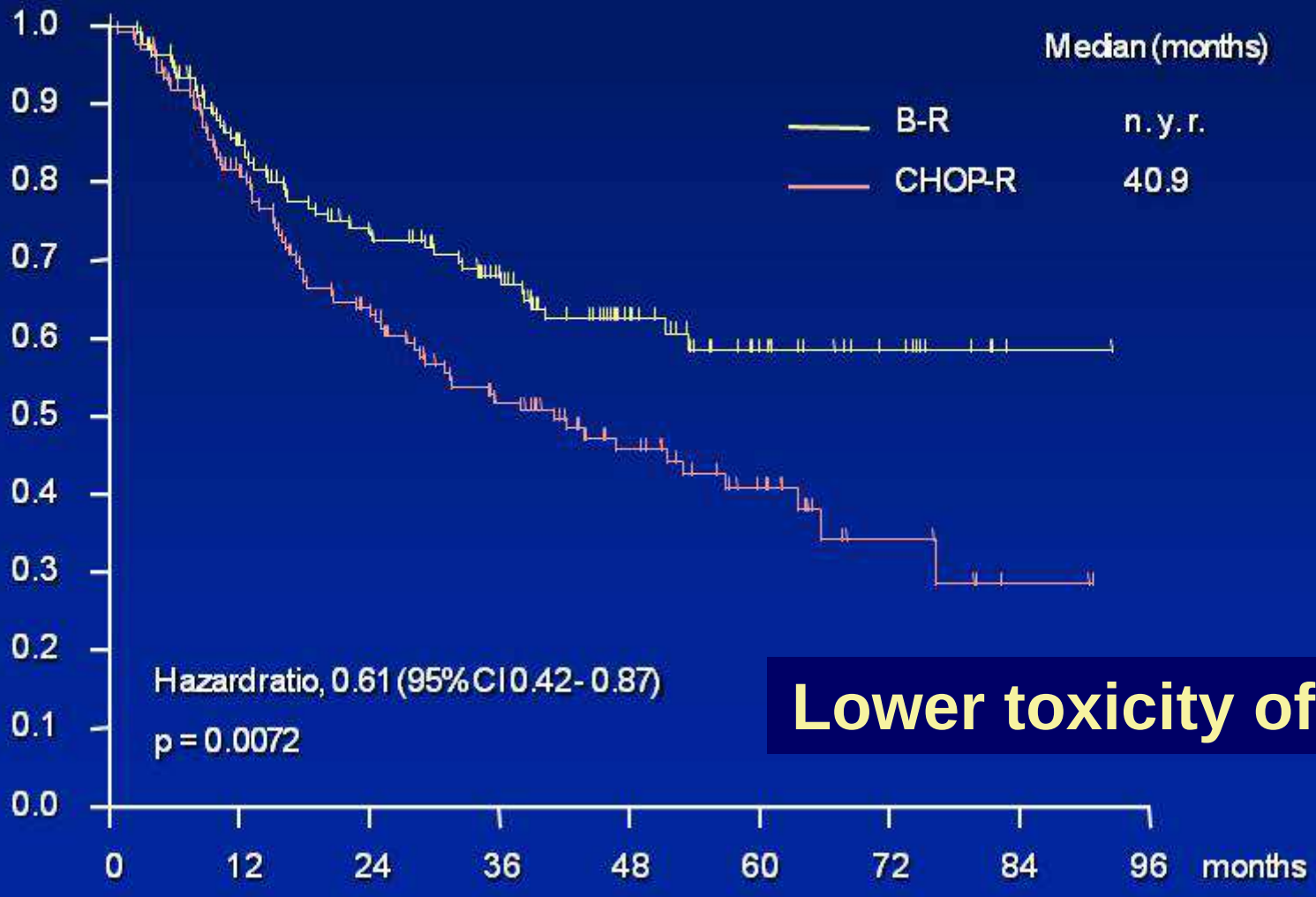
Italian FIL foll05 study: PFS by arm (N=504)



Federico M et al. J Clin Oncol. 2013 Apr 20;31(12):1506-1

R-Bendamustine versus R-CHOP

Progression free survival Follicular lymphoma (n=279 pts)

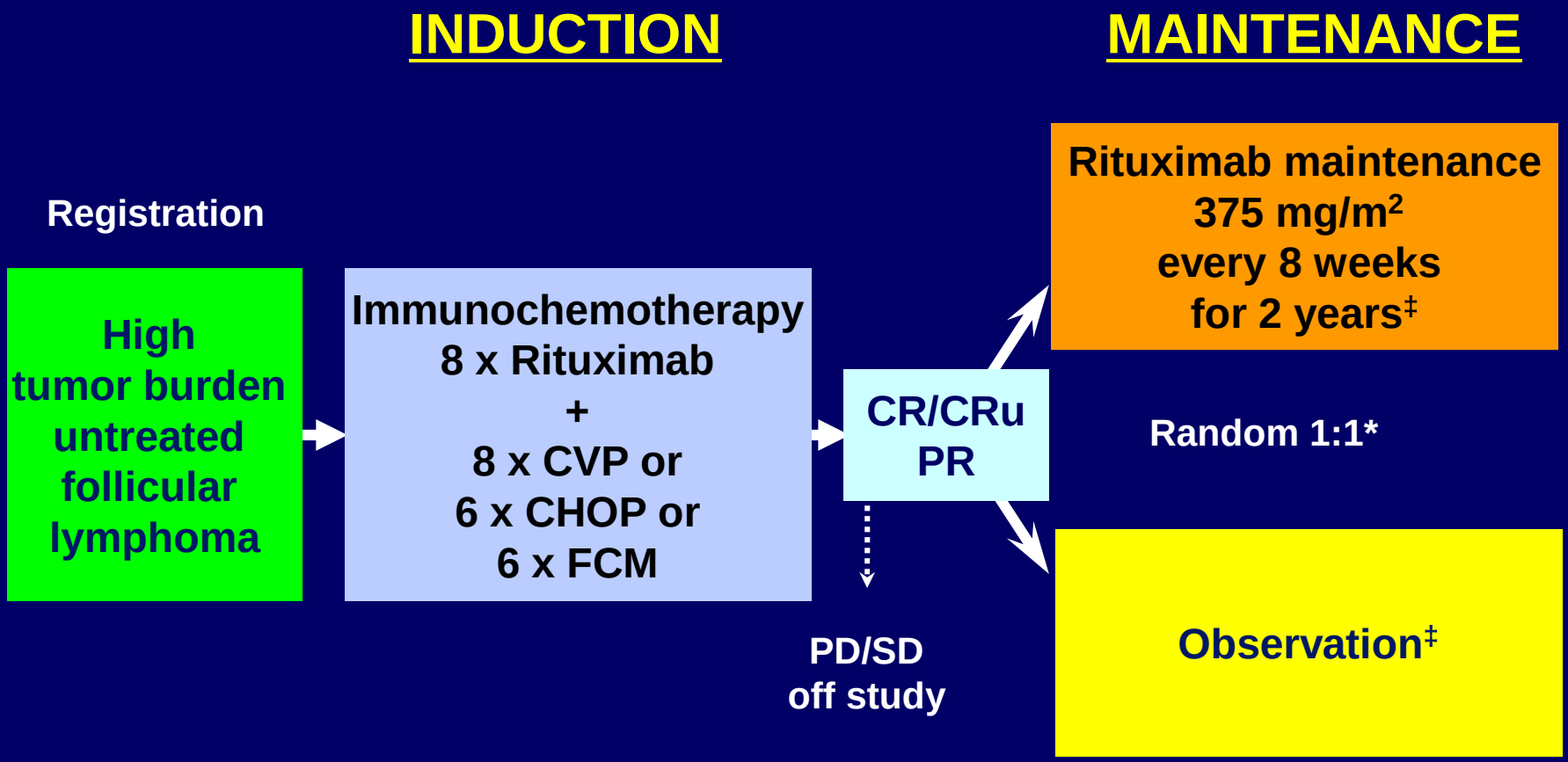


Lower toxicity of B-R

StiL Studiengruppe indolente Lymphome

Rummel et Al, Lancet 2013 MJR

PRIMA: study design

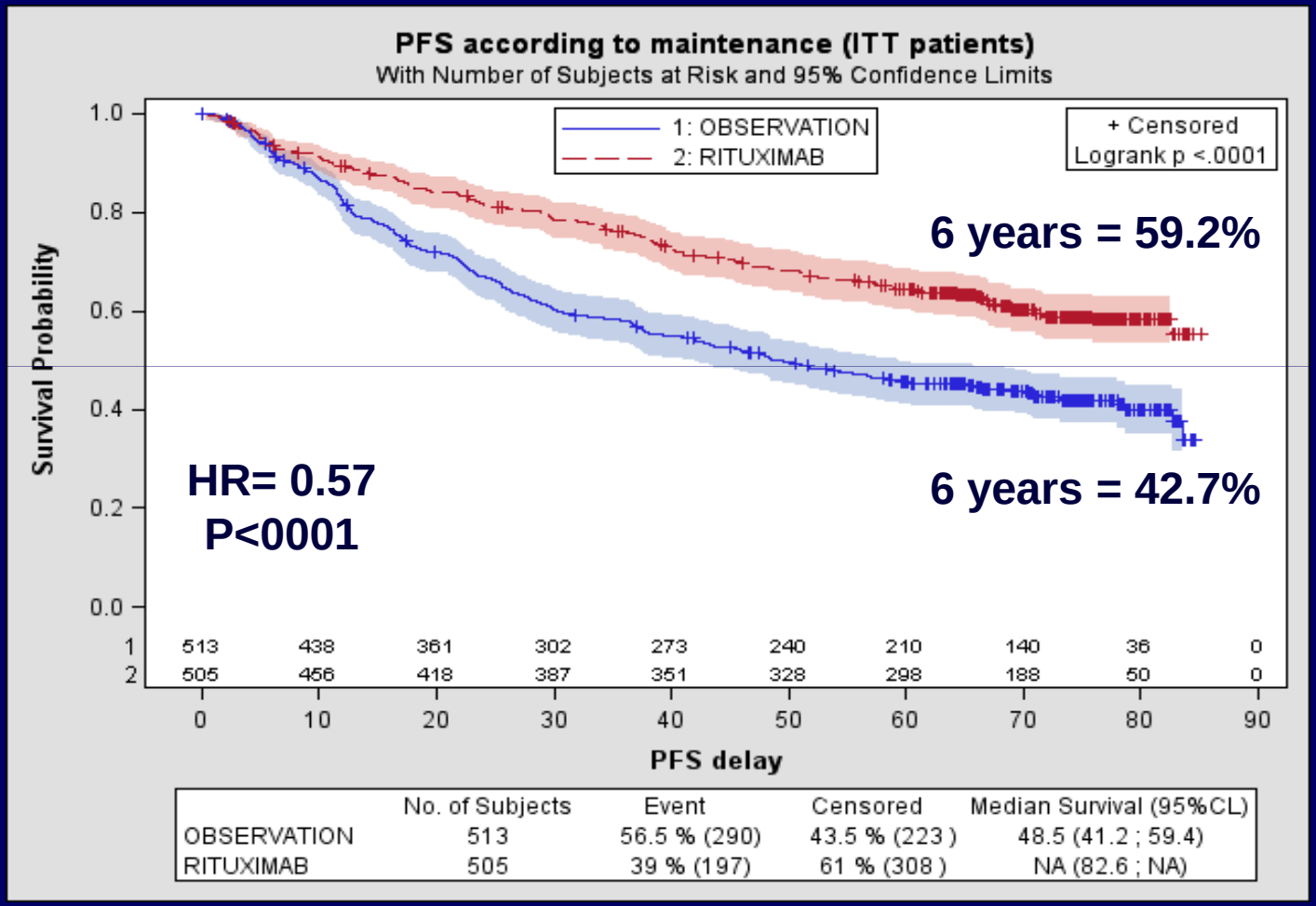


* Stratified by response after induction, regimen of chemo, and geographic region

‡ Frequency of clinical, biological and CT-scan assessments identical in both arms

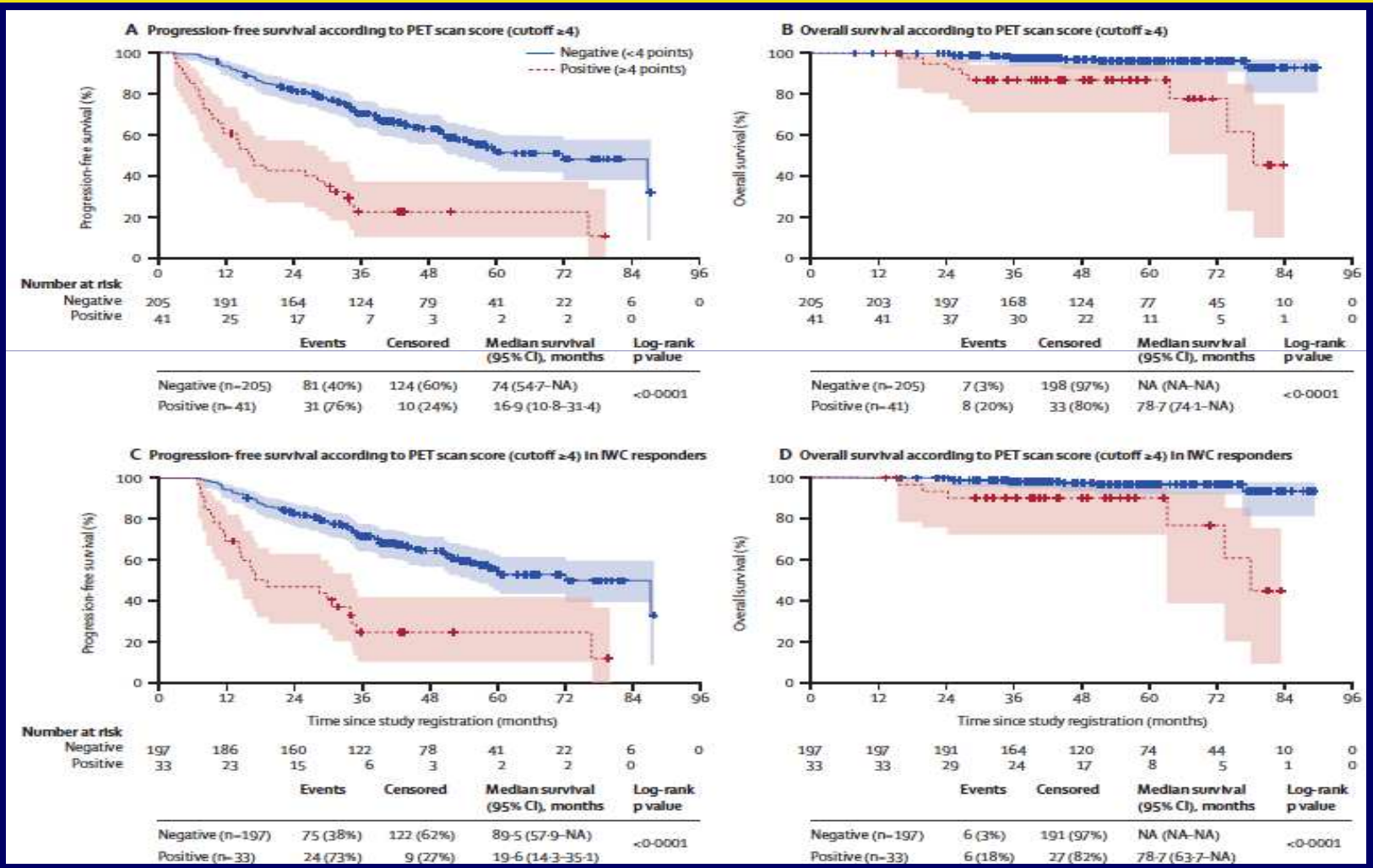
Five additional years of follow-up

PRIMA 6 years follow-up
Progression free survival from randomization



Median follow-up since randomization : 73 months

Prognostic Value of PET-CT After Frontline Therapy in FL



Trotman et al. *Lancet Haem*. 2014. epub.

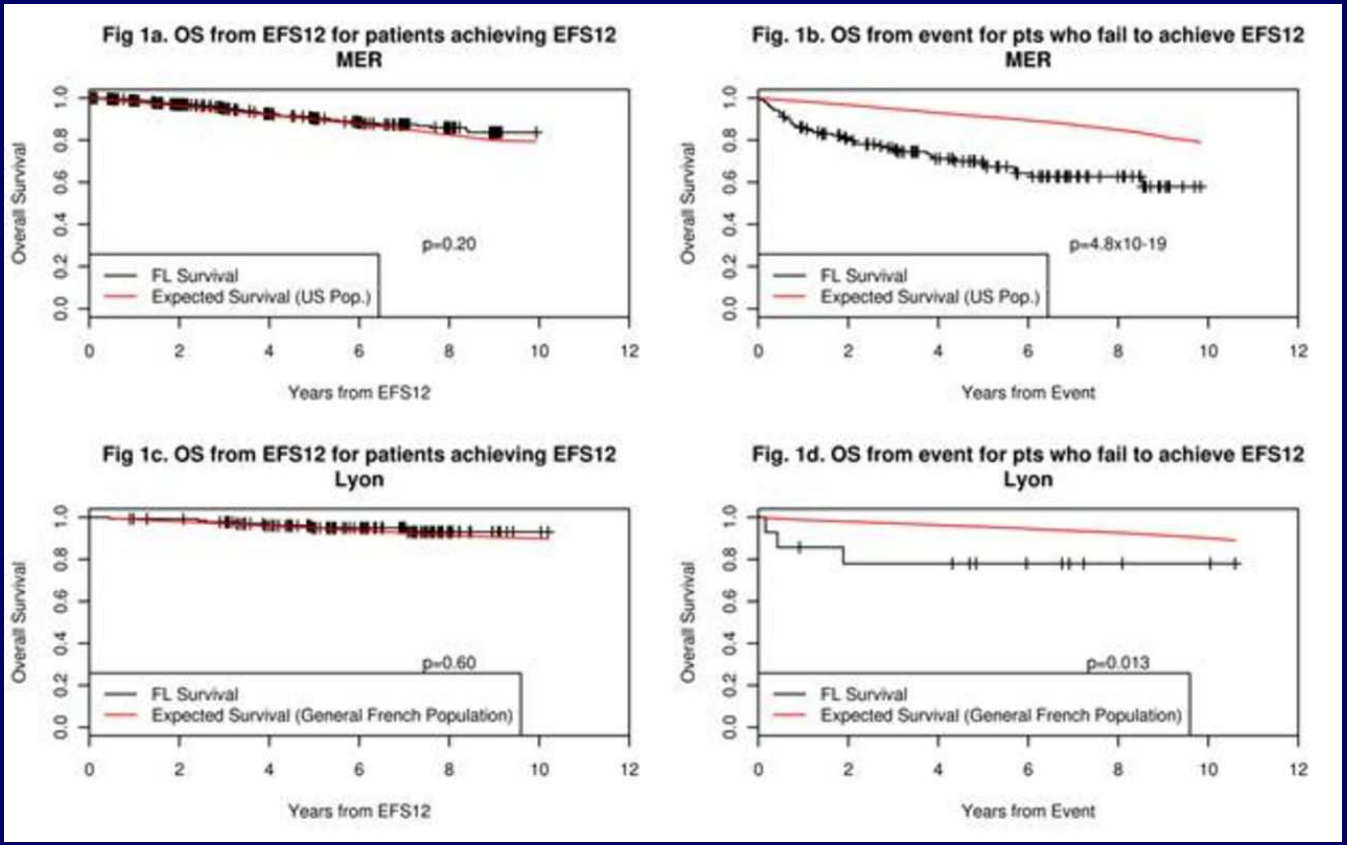
Future strategies for the treatment of patients with FL

1. **Monoclonal antibodies**
   - New anti-CD20
     - GALLIUM
     - Benda + Obinutuzmab in rituximab refractory pts (GADOLIN)
   - Antibody drug conjugates
2. **Kinase inhibitors :**

   - idelalisib (and Co) ; ibrutinib (and Co)
3. **Improving Rituximab efficacy with other agents:**
   - Immune checkpoints blockers ?
   - Imids ® : waiting for Relevance results
4. **New agents: Venetoclax, Tamezetostat, etc…**

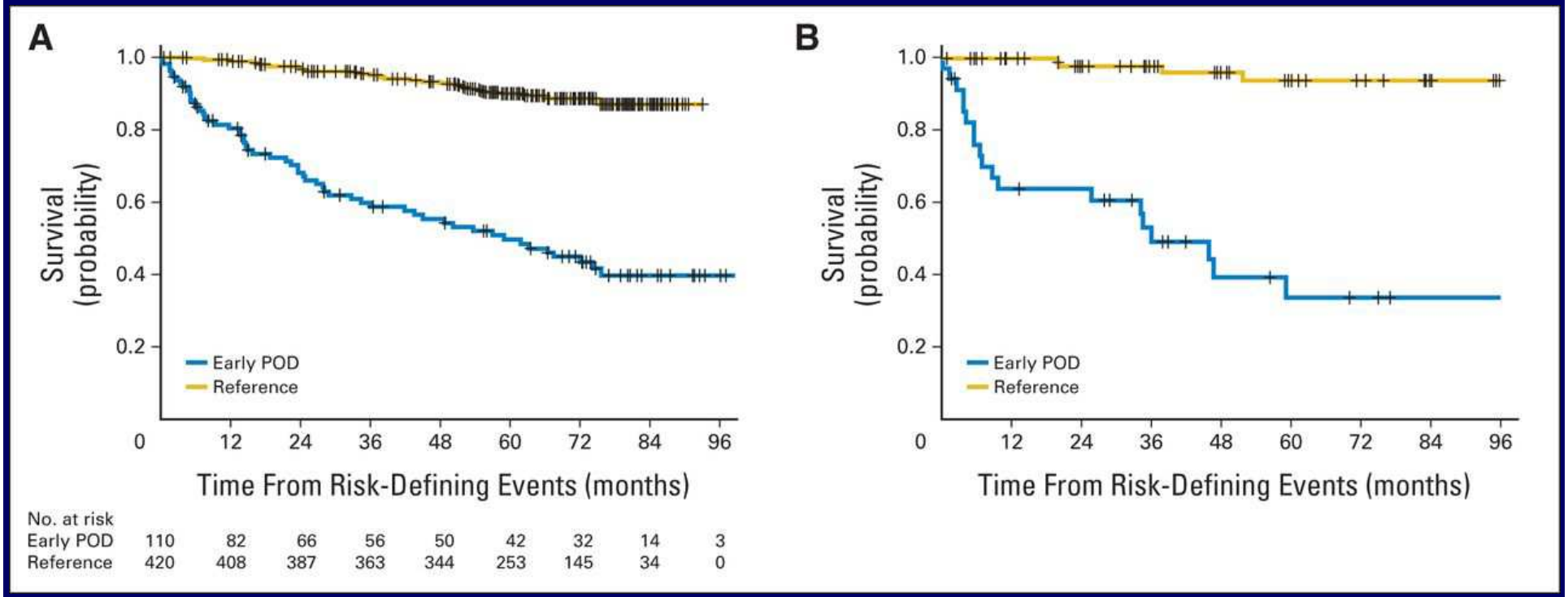
What are our goals for FL patients management ?

Event-Free Survival at 12 Months (EFS12) from Diagnosis Is a Robust Endpoint for Disease-Related Survival in Patients with FL in the Immunochemotherapy Era



Maurer MJ, Bachy E, et al. Am J Hematol 2016

Overall survival from a risk-defining event after diagnosis in patients who received rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy in the National LymphoCare Study group.



Carla Casulo et al. JCO 2015;33:2516-2522

JOURNAL OF CLINICAL ONCOLOGY ASCO

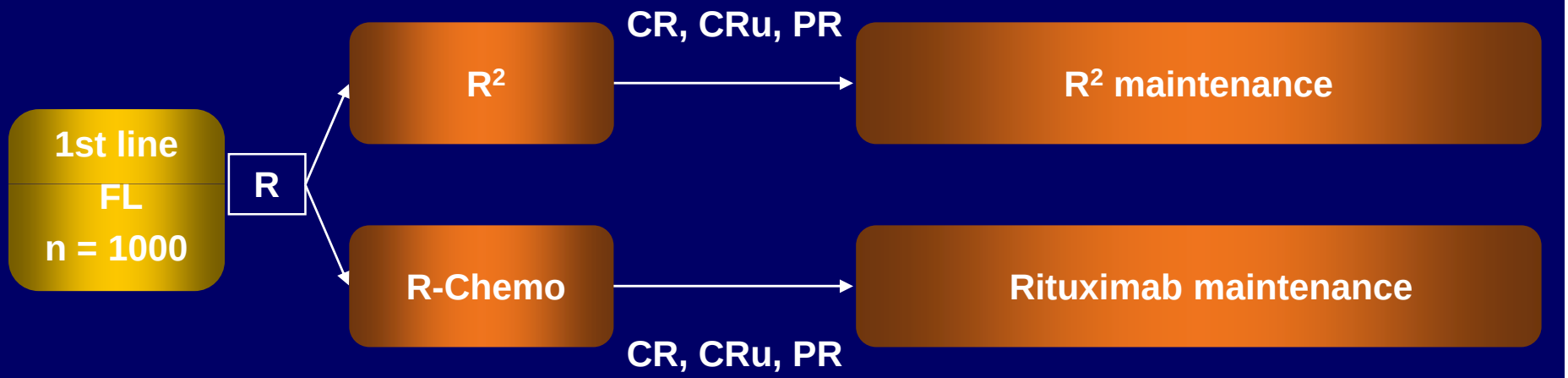
Les nouvelles approches en première ligne

- l’étude RELEVANCE
- l’étude GALLIUM

RELEVANCE : phase 3 study design

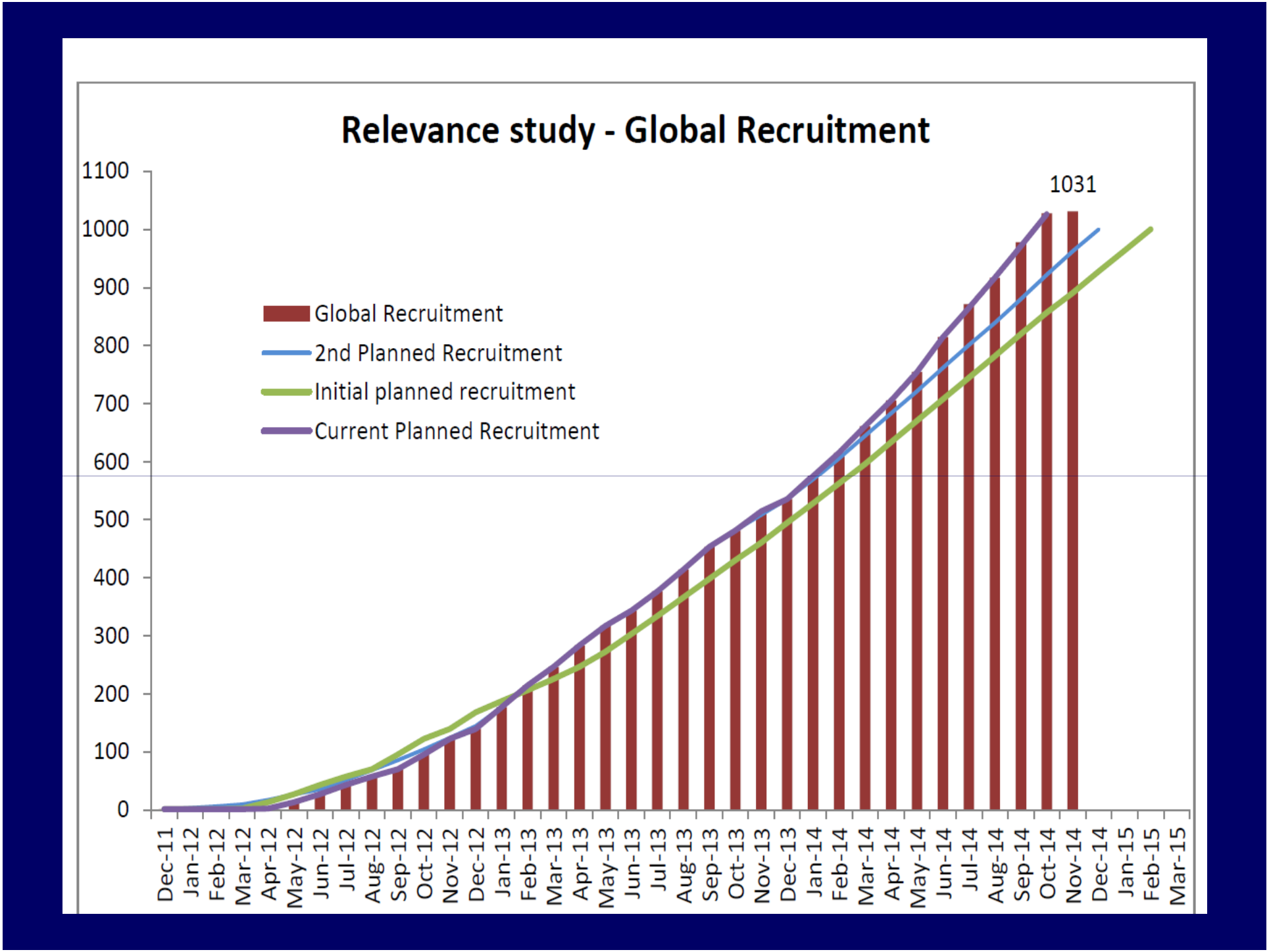
(Rituximab and LEnalidomide Versus ANy ChEmotherapy, FL-001)

International, multi-centre, randomised study
(Frank Morchhauser, Nathan Fowler)



- **R-Chemo**
  - **investigator choice of R-CHOP, R-CVP, R-B**
- **Lenalidomide**
  - **20 mg x 6 cycles, if CR then 10 mg**

- **Co-primary endpoints**
  - **CR/CRu rate at 2.5 years**
  - **PFS**


Relevance study - Global Recruitment
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Global Recruitment
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Initial planned recruitment
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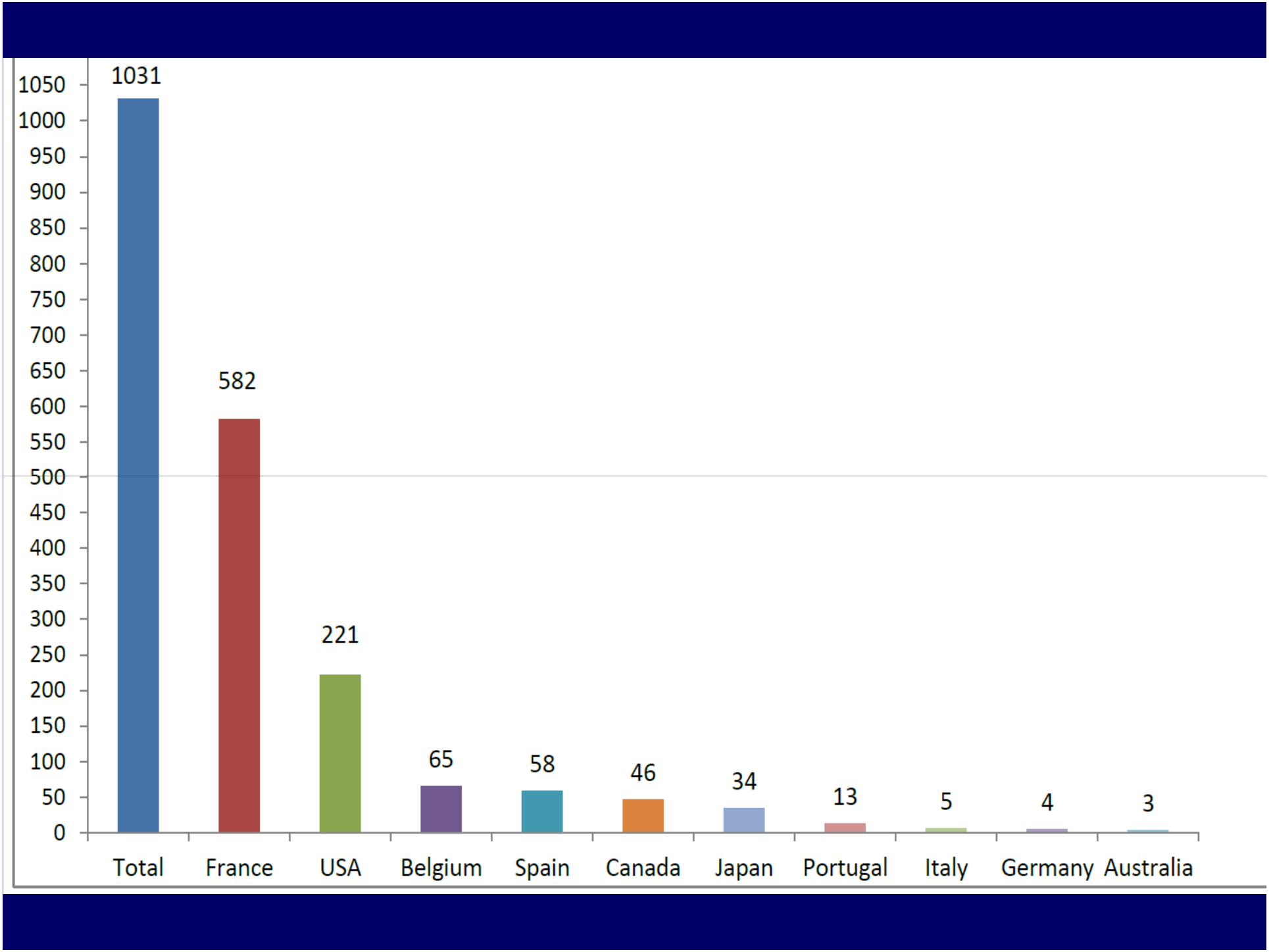
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582
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3
Total
France
USA
Belgium
Spain
Canada
Japan
Portugal
Italy
Germany
Australia

Les nouvelles approches en première ligne

- l'étude RELEVANCE
- l'étude GALLIUM

Obinutuzumab-based induction and maintenance prolongs progression-free survival (PFS) in patients with previously untreated follicular lymphoma: primary results of the randomized Phase III GALLIUM study

Robert Marcus,[1] Andrew Davies,[2] Kiyoshi Ando,[3] Wolfram Klapper,[4] Stephen Opat,[5] Carolyn Owen,[6] Elizabeth Phillips,[7] Randeep Sangha,[8] Rudolf Schlag,[9] John F Seymour,[10] William Townsend,[7] Marek Trněný,[11]Michael Wenger,[12] Günter Fingerle-Rowson,[13] Kaspar Rufibach,[13] Tom Moore,[13] Michael Herold,[14] Wolfgang Hiddemann[15]

[1]Kings College Hospital, London, United Kingdom; [2]Cancer Research UK Centre, University of Southampton, Southampton, United Kingdom; [3]Tokai University School of Medicine, Isehara, Kanagawa, Japan; [4]University of Kiel, Kiel, Germany; [5]Monash Health and Monash University, Melbourne, Australia; [6]Foothills Medical Centre and Tom Baker Cancer Centre, Calgary, AB, Canada; [7]Cancer Research UK and UCL Cancer Trials Centre, London, United Kingdom; [8]Cross Cancer Institute, Edmonton, AB, Canada; [9]Gemeinschaftspraxis Dr. Rudolf Schlag/Dr. Björn Schöttker, Würzburg, Germany; [10]Peter MacCallum Cancer Centre, Melbourne, Australia; [11]Charles University, Prague, Czech Republic; [12]Genentech Inc, South San Francisco, CA, USA; [13]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [14]HELIOS-Klinikum, Erfurt, Germany; [15]Ludwig-Maximilians-University, Munich, Germany

GLSG NCRI National Cancer Research Institute OSHO

Background

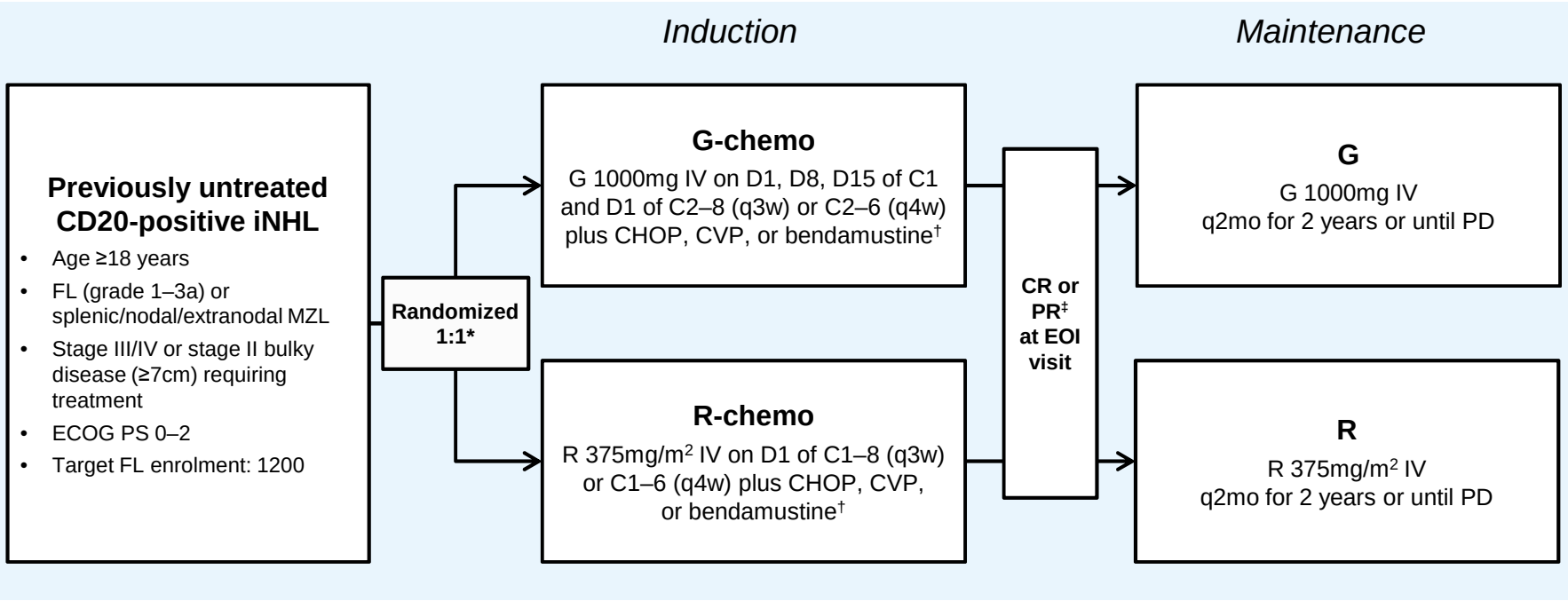
- Significant benefit with rituximab (R)-based induction + maintenance in pts with previously untreated advanced-stage symptomatic FL
  - Median PFS now >6 yrs[1]
- Obinutuzumab (GA101; G)
  - Glycoengineered type II anti-CD20 mAb
  - Greater direct cell death induction and ADCC/ADCP activity than R[2,3]
  - Active with chemo in pts with NHL who had previously received R[4–6]
  - Prolonged PFS when combined with bendamustine in R-refractory iNHL[6]
- GALLIUM (NCT01332968) compares the efficacy and safety of G-based and R-based regimens in pts with previously untreated iNHL

ADCC, antibody-dependent cell-mediated cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; FL, follicular lymphoma; mAb, monoclonal antibody; iNHL, indolent non-Hodgkin lymphoma

1. Salles G, et al. Blood 2013; 2. Herter S, et al. Mol Cancer Ther 2013
3. Mössner E, et al. Blood 2010; 4. Radford J, et al. Blood 2013
5. Zelenetz et al. 2013; 6. Sehn et al. 2016

Study design

International, open-label, randomized Phase III study



Primary endpoint

- PFS (INV-assessed in FL)

Secondary and other endpoints

- PFS (IRC-assessed)§
- OS, EFS, DFS, DoR, TTNT
- CR/ORR at EOI (+/− FDG-PET)
- Safety

*FL and MZL pts were randomized separately; stratification factors: chemotherapy, FLIPI (FL) or IPI (MZL) risk group, geographic region; †CHOP q3w × 6 cycles, CVP q3w × 8 cycles, bendamustine q4w × 6 cycles; choice by site (FL) or by pt (MZL); ‡Pts with SD at EOI were followed for PD for up to 2 years; §Confirmatory endpoint

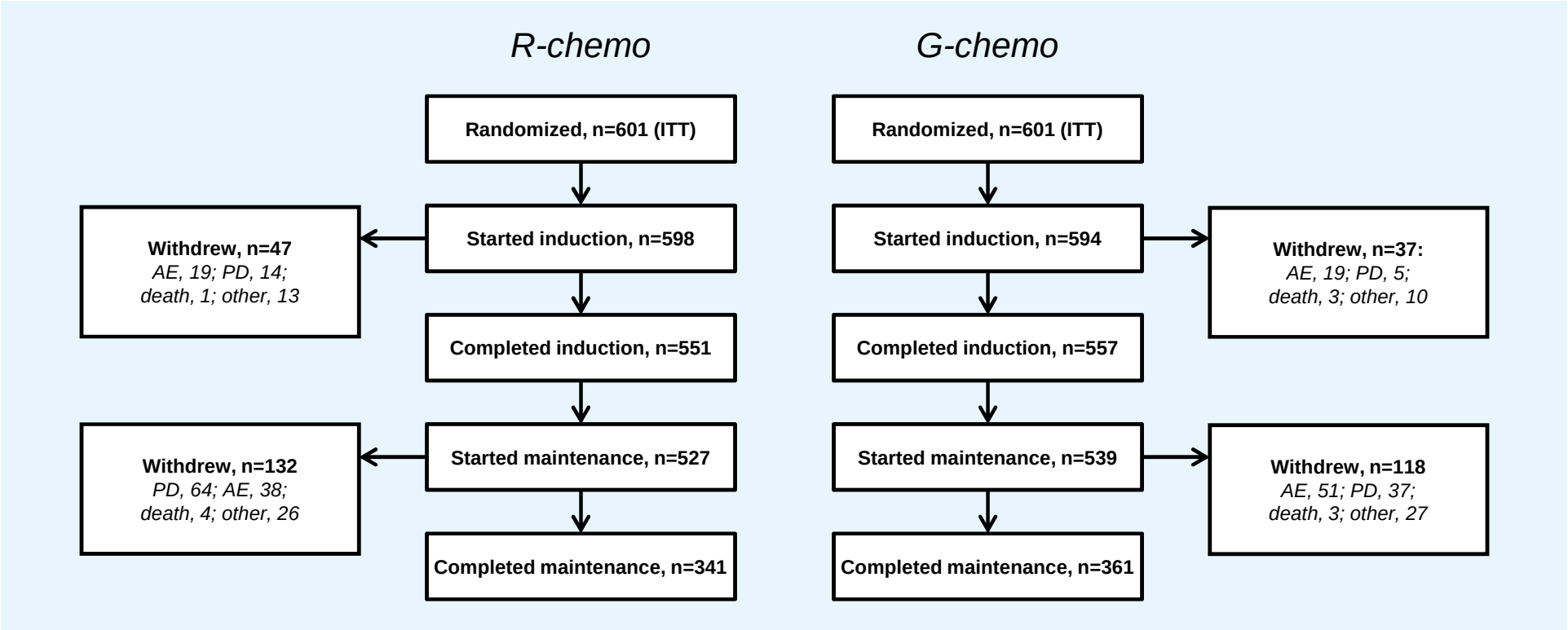
Statistical considerations

- Projected improvement in 3-yr PFS rate from 70.7% to 77.4% or in median PFS from 6.0 to 8.1 years
  - 80% power to detect HR of 0.74 in FL pts (two-sided stratified log-rank test; α=0.05; 370 PFS events needed)
- Study unblinded (per IDMC recommendation) after pre-planned interim efficacy analysis
  - Data cut-off date: January 31 2016 (245 of the 370 PFS events)
  - Significance level: α=0.012
- IDMC found that PFS in FL pts was superior for G-chemo
  - Subject of current analysis

IDMC, Independent Data Monitoring Committee

Patient disposition (FL)

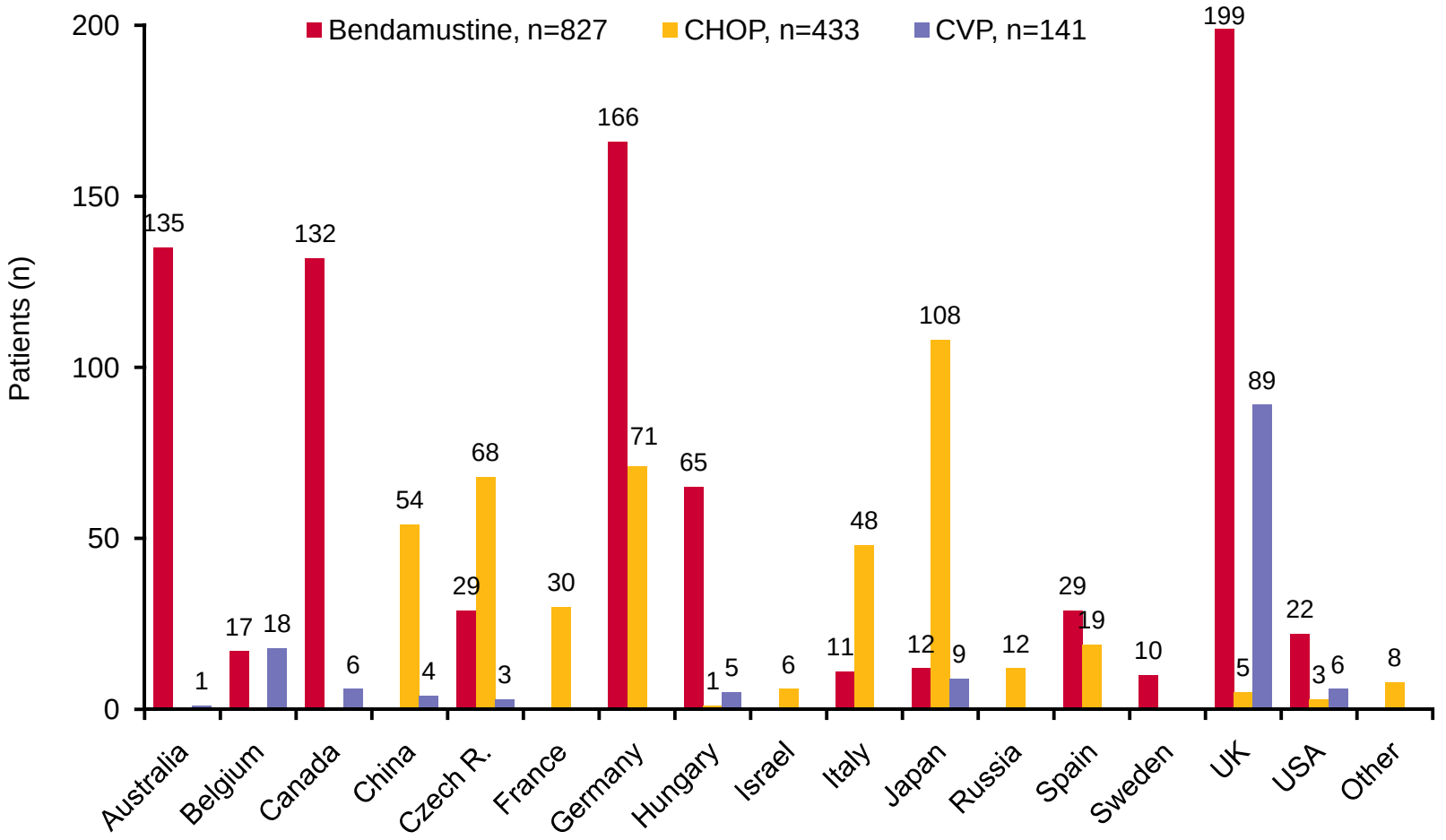
1202 FL pts enrolled and randomized to treatment



- *Median follow-up = 34.5 mo; maintenance ongoing in 114 pts (R-chemo, 54; G-chemo, 60)*
- *ITT population* = 1202 pts; safety population† = 1192 pts*

*All randomized FL pts (R-chemo, 601; G-chemo, 601); †All randomized pts who received any amount of study drug (R-chemo, 597; G-chemo, 595)

Patients by country and chemotherapy regimen



Baseline patient and disease characteristics (FL)

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)		
I	1.3% (8)*	1.7% (10)†
II	7.4% (44)*	6.9% (41)†
III	35.0% (209)*	34.8% (208)†
IV	56.3% (336)*	56.7% (339)†
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 (≥7cm), % (n)	45.2% (271)‡	42.5% (255)‡
Median (range) time from diagnosis to randomization, months	1.4 (0–168.1)	1.5 (0.1–121.6)¶

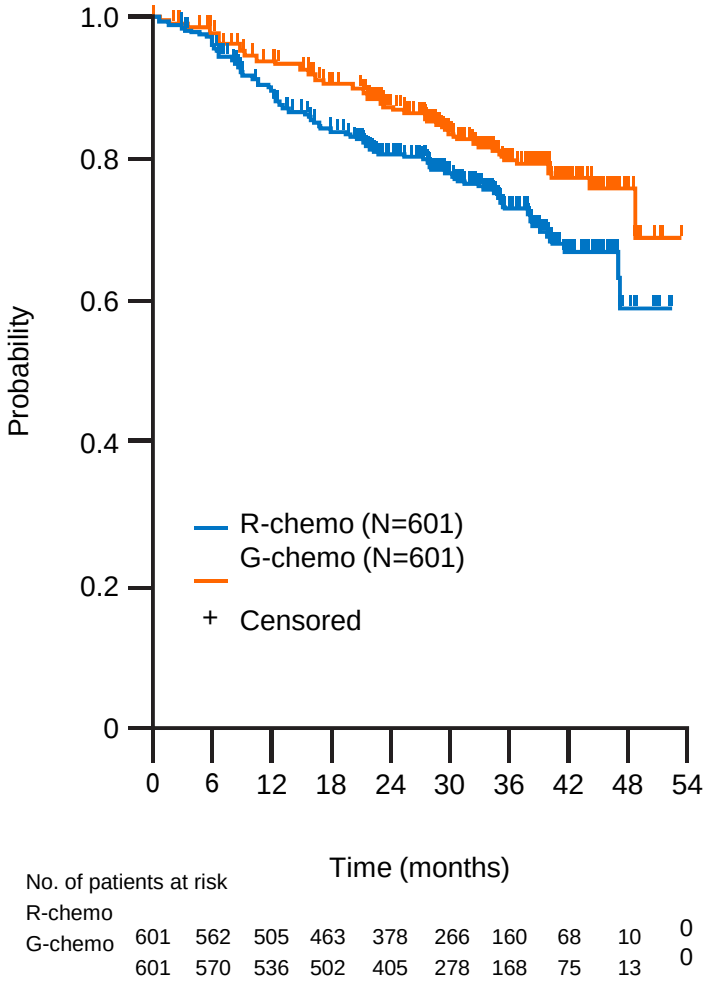
*n=597; †n=598; ‡n=600; §n=592; ¶n=598, value not determined in three pts

Response rates at end of induction (FL)*

	CT (by investigator)	
% (n); 95% CI	*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)

*INV-assessed using the Revised Response Criteria for Malignant Lymphoma (Cheson BD, et al. J Clin Oncol 2007)
INV, investigator

INV-assessed PFS (FL; primary endpoint)

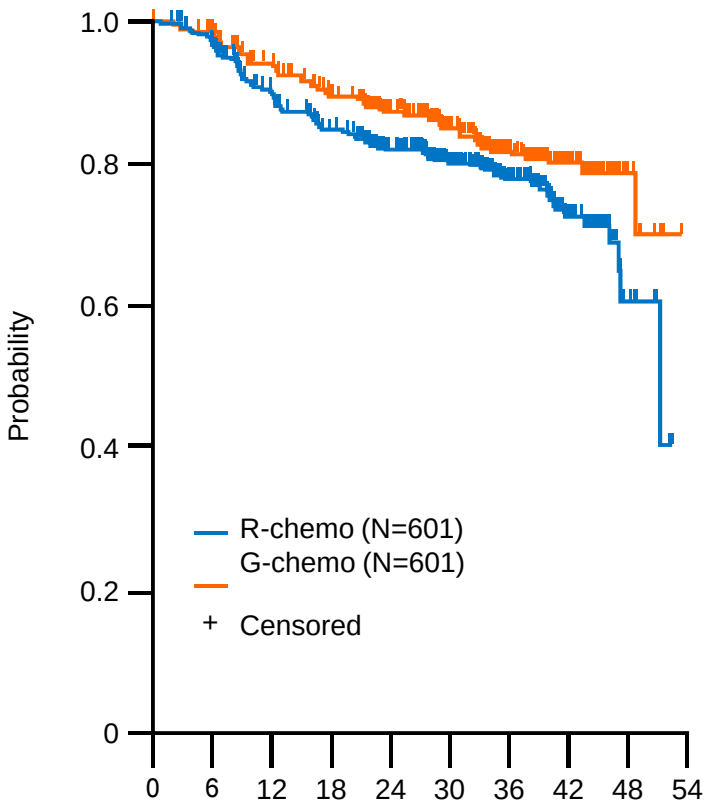


	R-chemo, n=601	*G-chemo, n=601*
Pts with event, n (%)	144 (24.0)	101 (16.8)
3-yr PFS, % (95% CI)	73.3 (68.8, 77.2)	80.0 (75.9, 83.6)
HR (95% CI), p-value*	0.66 (0.51, 0.85), p=0.0012	

Median follow-up: 34.5 months

*Stratified analysis; stratification factors: chemotherapy regimen, FLIPI risk group, geographic region

IRC-assessed PFS (FL)



No. of patients at risk

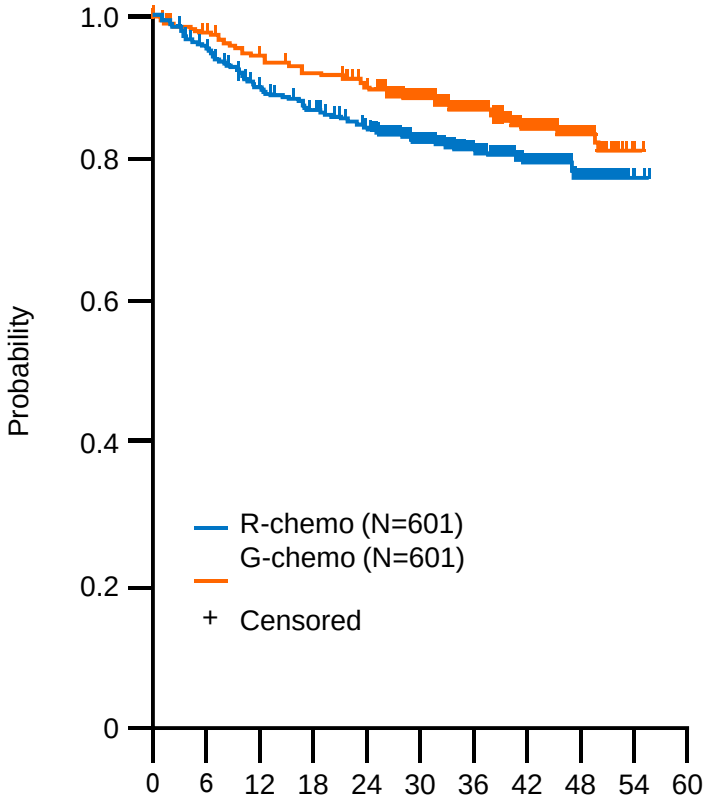
R-chemo	601	563	500	460	372	263	160	66	10	0
G-chemo	601	569	528	491	385	270	162	73	10	0

	R-chemo, n=601	*G-chemo, n=601*
Pts with event, n (%)	125 (20.8)	93 (15.5)
3-yr PFS, % (95% CI)	77.9 (73.8, 81.4)	81.9 (77.9, 85.2)
HR (95% CI), p-value*	0.71 (0.54, 0.93), p=0.0138	

Median follow-up: 34.5 months

*Stratified analysis; stratification factors: chemotherapy regimen, FLIPI risk group, geographic region

TTNT (FL)



No. of patients at risk

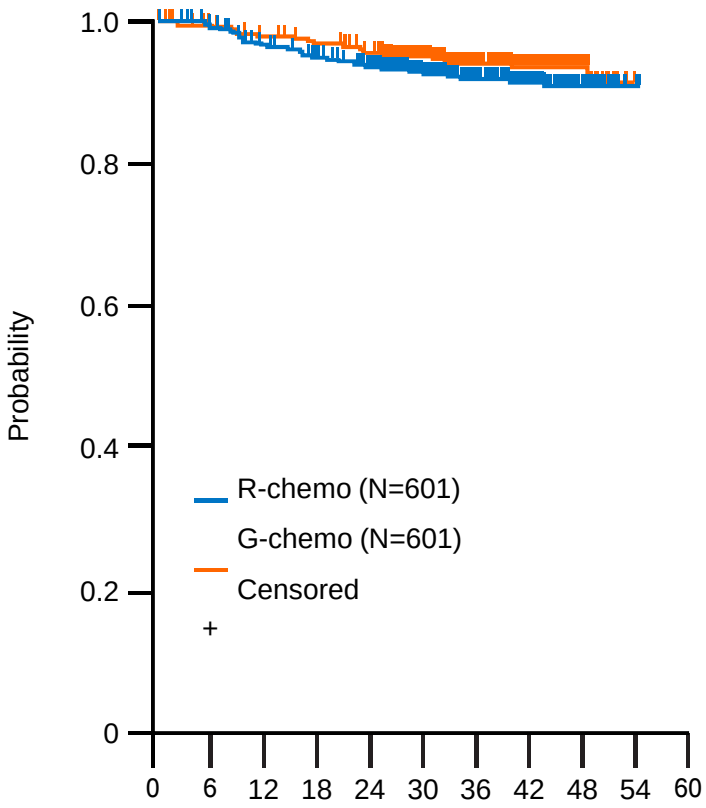
R-chemo	601	565	525	503	475	352	231	131	47	2	0
G-chemo	601	574	551	539	519	385	249	145	51	0	0

	R-chemo, n=601	*G-chemo, n=601*
Pts with event, n (%)	111 (18.5)	80 (13.3)
3-yr TTNT, % (95% CI)	81.2 (77.6, 84.2)	87.1 (84.0, 89.6)
HR (95% CI), p-value*	0.68 (0.51, 0.91), p=0.0094	

Median follow-up: 34.5 months

*Stratified analysis; stratification factors: chemotherapy regimen, FLIPI risk group, geographic region

OS (FL)



	R-chemo, n=601	*G-chemo, n=601*
Pts with event, n (%)	46 (7.7)	35 (5.8)
3-yr OS, % (95% CI)	92.1 (89.5, 94.1)	94.0 (91.6, 95.7)
HR (95% CI), p-value*	0.75 (0.49, 1.17), p=0.21	

Median follow-up: 34.5 months

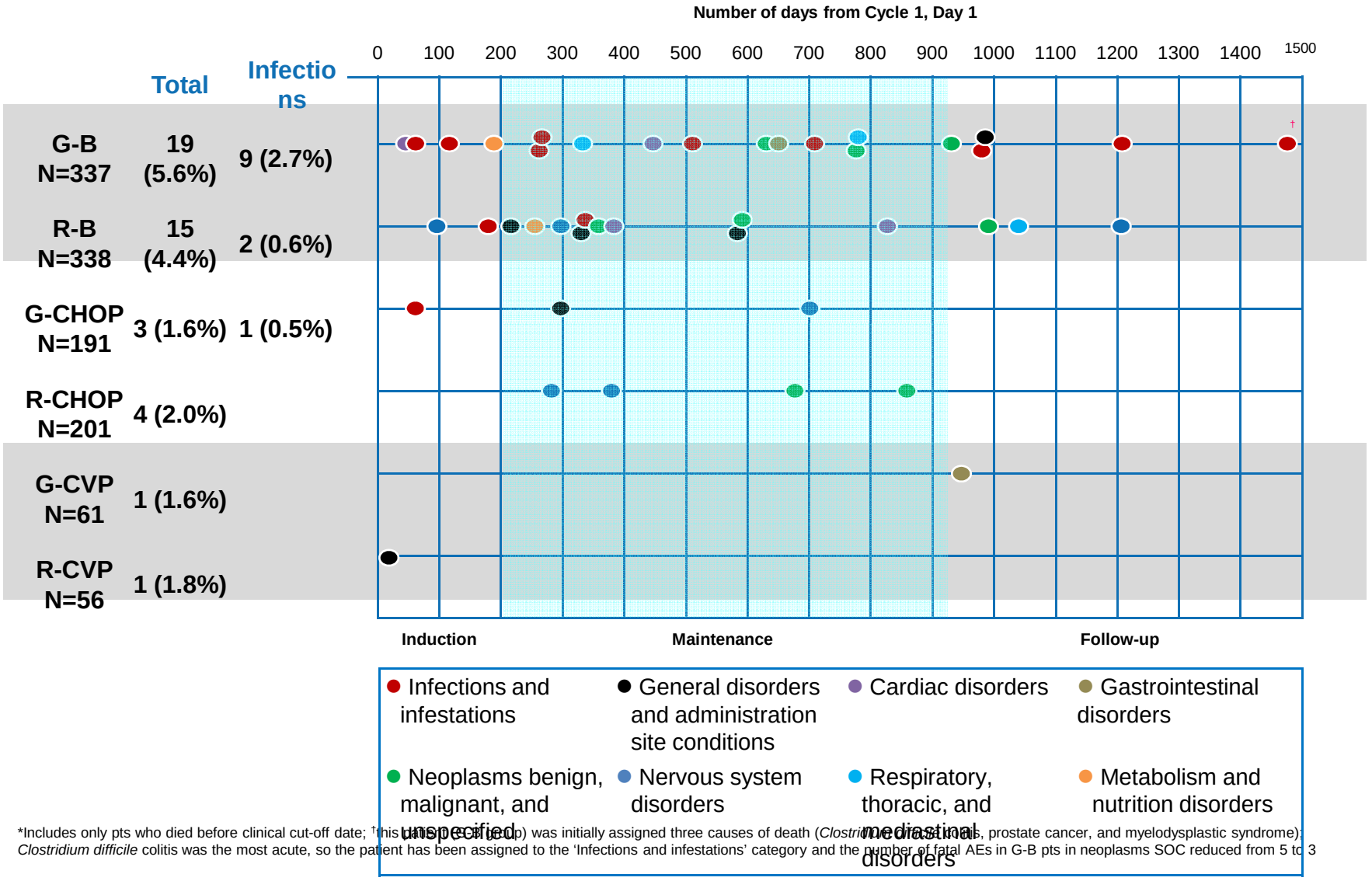
*Stratified analysis; stratification factors: chemotherapy regimen, FLIPI risk group, geographic region

Safety summary (FL)

% (n)	*R-chemo (n=597)*	*G-chemo (n=595)*
Any AE	98.3% (587)	99.5% (592)
Grade ≥3 AEs (≥5% in either arm)	67.8% (405)	74.6% (444)
Neutropenia	37.9% (226)	43.9% (261)
Leucopenia	8.4% (50)	8.6% (51)
Febrile neutropenia	4.9% (29)	6.9% (41)
IRRs*	3.7% (22)	6.7% (40)
Thrombocytopenia	2.7% (16)	6.1% (36)
Grade ≥3 AEs of special interest by category (selected)		
Infections†	15.6% (93)	20.0% (119)
IRRs‡	6.7% (40)	12.4% (74)
Second neoplasms§	2.7% (16)	4.7% (28)
SAEs	39.9% (238)	46.1% (274)
AEs causing treatment discontinuation	14.2% (85)	16.3% (97)
Grade 5 (fatal) AEs	3.4% (20)	4.0% (24)**
Median (range) change from baseline in IgG levels at end of induction, g/l¶	-1.46 (-16.4–9.1)††	-1.50 (-22.3–6.5)‡‡

*As MedDRA preferred term; †All events in MedDRA System Organ Class 'Infections and Infestations'; ‡Any AE occurring during or within 24h of infusion of G or R and considered drug-related; §Standardized MedDRA query for malignant or unspecified tumors starting 6 mo after treatment start; ¶Ig levels were measured during screening, at EOI and end of maintenance and during follow-up; **Includes patient who died after clinical cut-off date from AE starting before cut-off date; ††n=472; ‡‡n=462

Grade 5 (fatal) AEs by treatment (FL)*

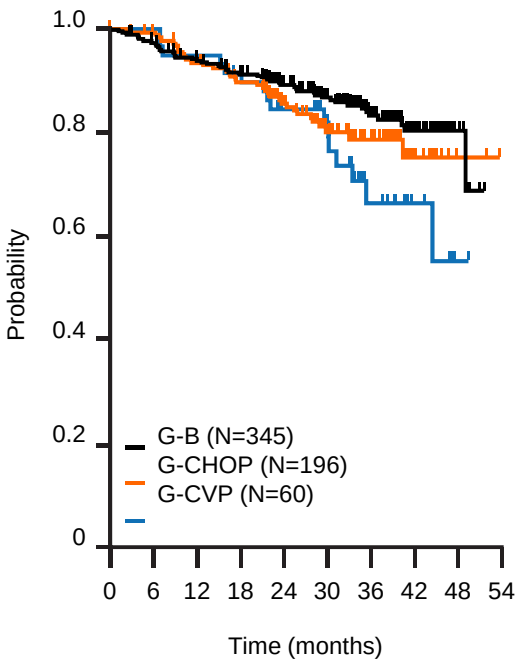


*Includes only pts who died before clinical cut-off date; †this patient (G-B group) was initially assigned three causes of death (*Clostridium difficile* colitis, prostate cancer, and myelodysplastic syndrome); *Clostridium difficile* colitis was the most acute, so the patient has been assigned to the 'Infections and infestations' category and the number of fatal AEs in G-B pts in neoplasms SOC reduced from 5 to 3

INV-assessed PFS by chemo regimen (FL)

Post-hoc analysis: study not powered to detect differences between chemotherapy regimens in either treatment arm

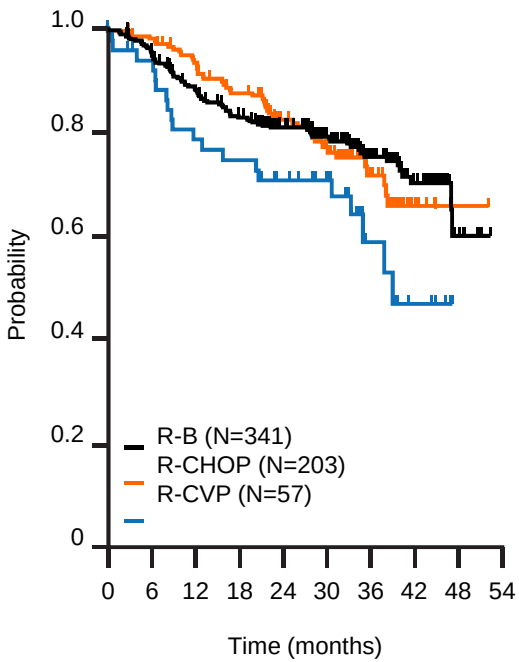
G-chemo arm



No. of patients at risk

G-B	345	322	304	285	239	180	113	56	9
G-CHOP	196	188	176	165	124	70	41	12	3
G-CVP	60	60	56	52	42	28	14	7	1

R-chemo arm



No. of patients at risk

R-B	341	319	283	260	217	164	108	49	9
R-CHOP	203	194	181	164	128	77	42	14	1
R-CVP	57	49	41	39	33	25	10	5	

	HR* (95% CI)
G-B vs R-B	0.61 (0.43, 0.86)
G-CHOP vs R-CHOP	0.77 (0.50,1.20)
G-CVP vs R-CVP	0.63 (0.32, 1.21)

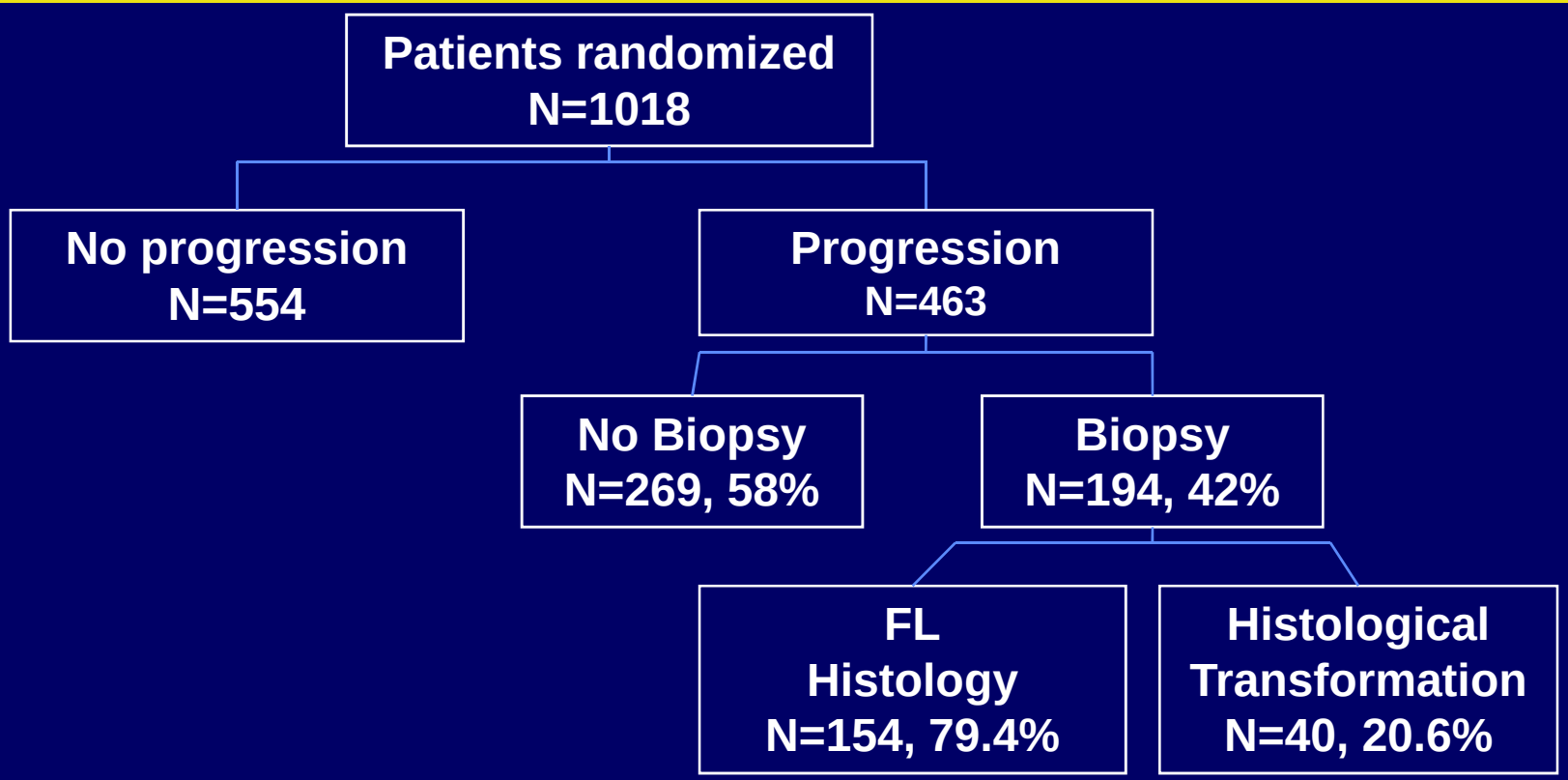
*Unstratified analysis

Conclusions

- G-chemo + maintenance superior to R-chemo + maintenance in untreated advanced FL patients at interim efficacy analysis
  - Clinically meaningful improvement in PFS: 34% reduction in risk; HR=0.66
  - PFS result supported by other time-to-event endpoints
- Non-fatal AEs were higher in the G arm
  - IRRs, cytopenias, and infection
- Fatal AEs more common in patients on bendamustine in both arms
- G-based therapy significantly improves outcome compared with R-based therapy and should now be considered as a first-line treatment for FL

Quid des patients en rechute ou réfractaires (au rituximab)?

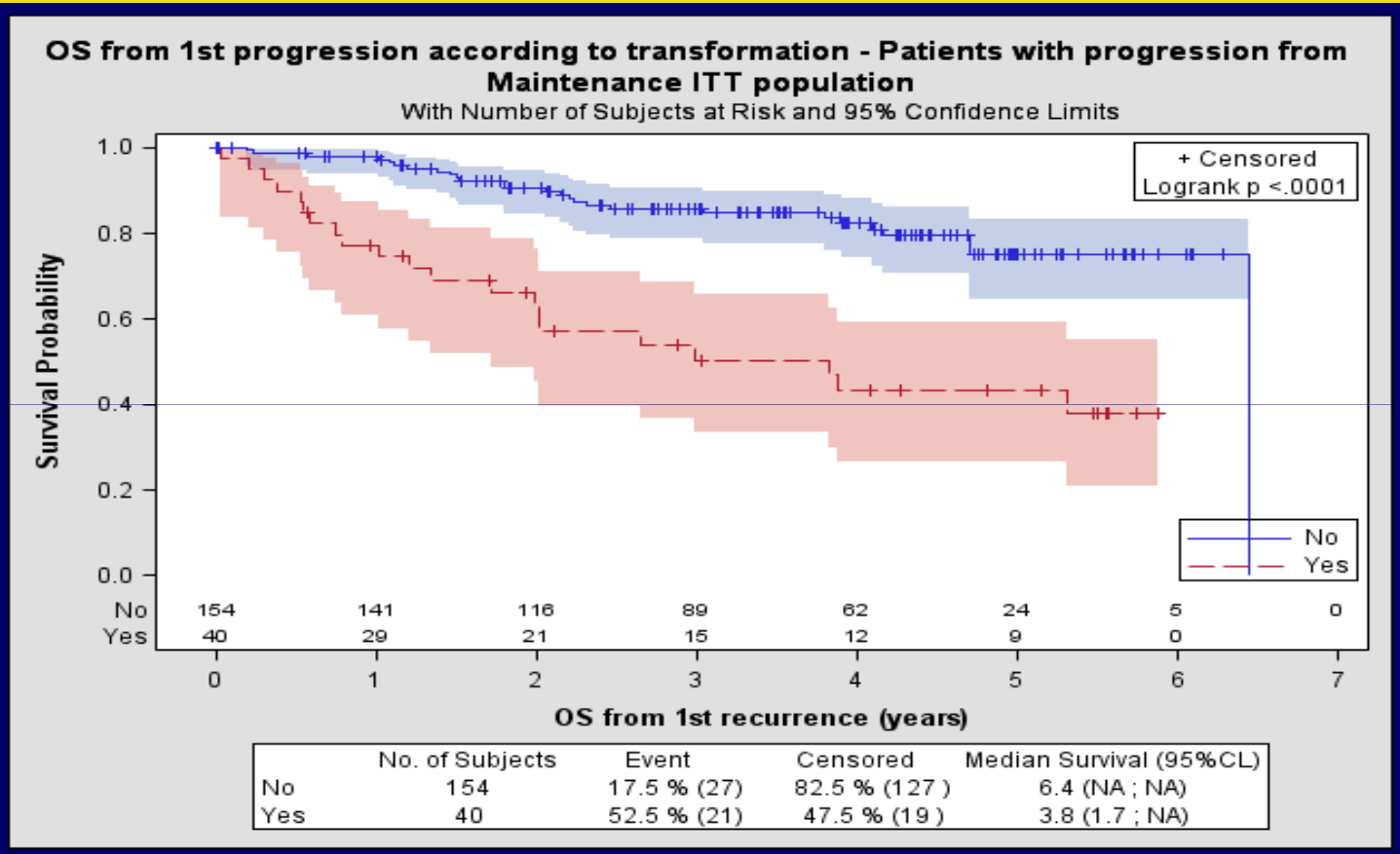
Histological transformation at first progression in PRIMA patients



- Progression with HT appears to occur early (10 vs. 23 months)
- More than 1/3rd (37%) of the biopsies performed during the first year of follow-up showed transformed disease (58% of all HT)

Sarkozy et al, JCO 2016

Histological Transformation an event with poor prognosis

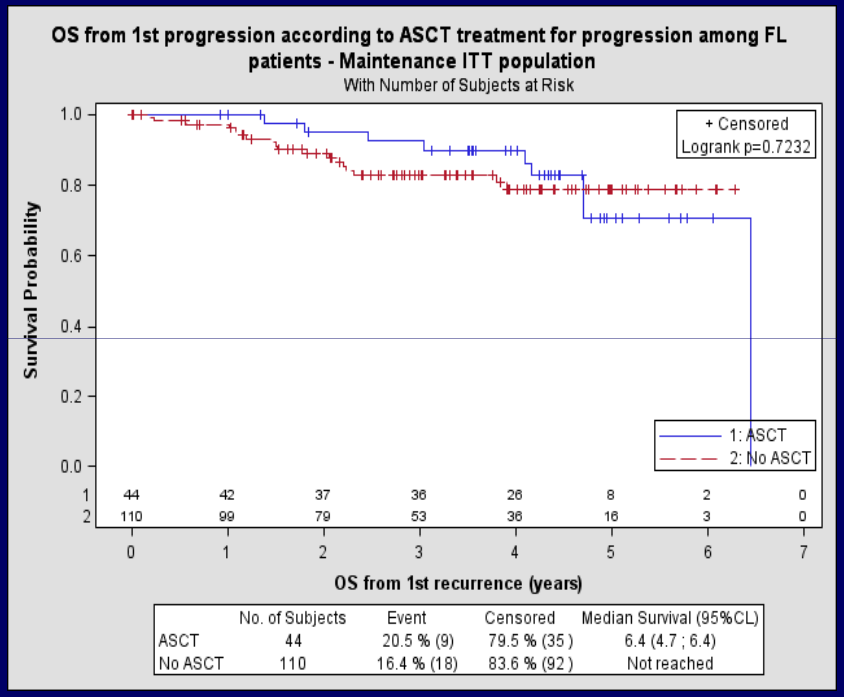


	No. of Subjects	Event	Censored	Median Survival (95%CL)
No	154	17.5 % (27)	82.5 % (127)	6.4 (NA ; NA)
Yes	40	52.5 % (21)	47.5 % (19)	3.8 (1.7 ; NA)

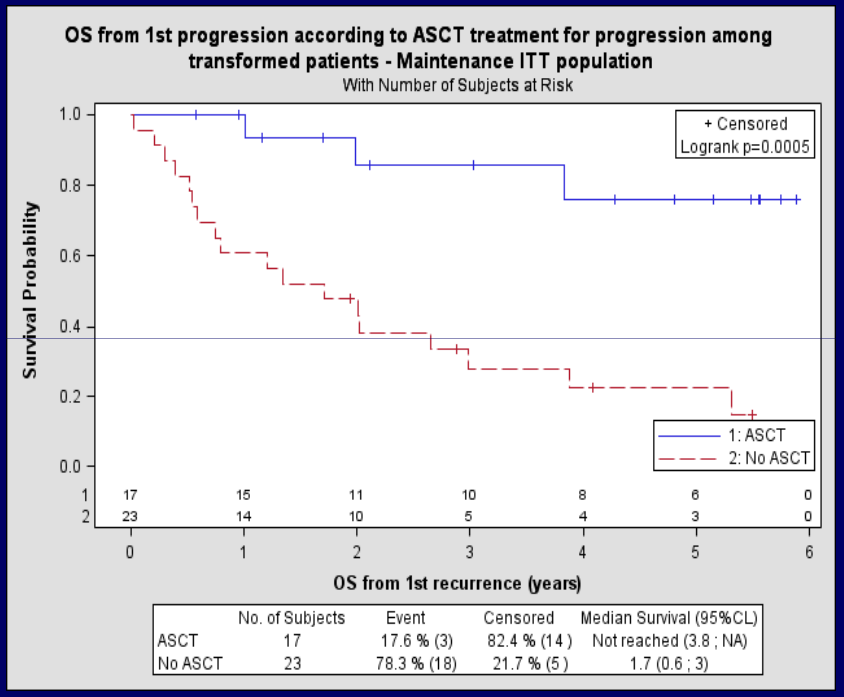
HT patients have a poorer Overall Survival of 3.8 y compared to 6.4 y for patients with FL histology at recurrence

Autologous transplant in patients with and without HT at time of their first progression

Follicular lymphoma histology



Transformed histology

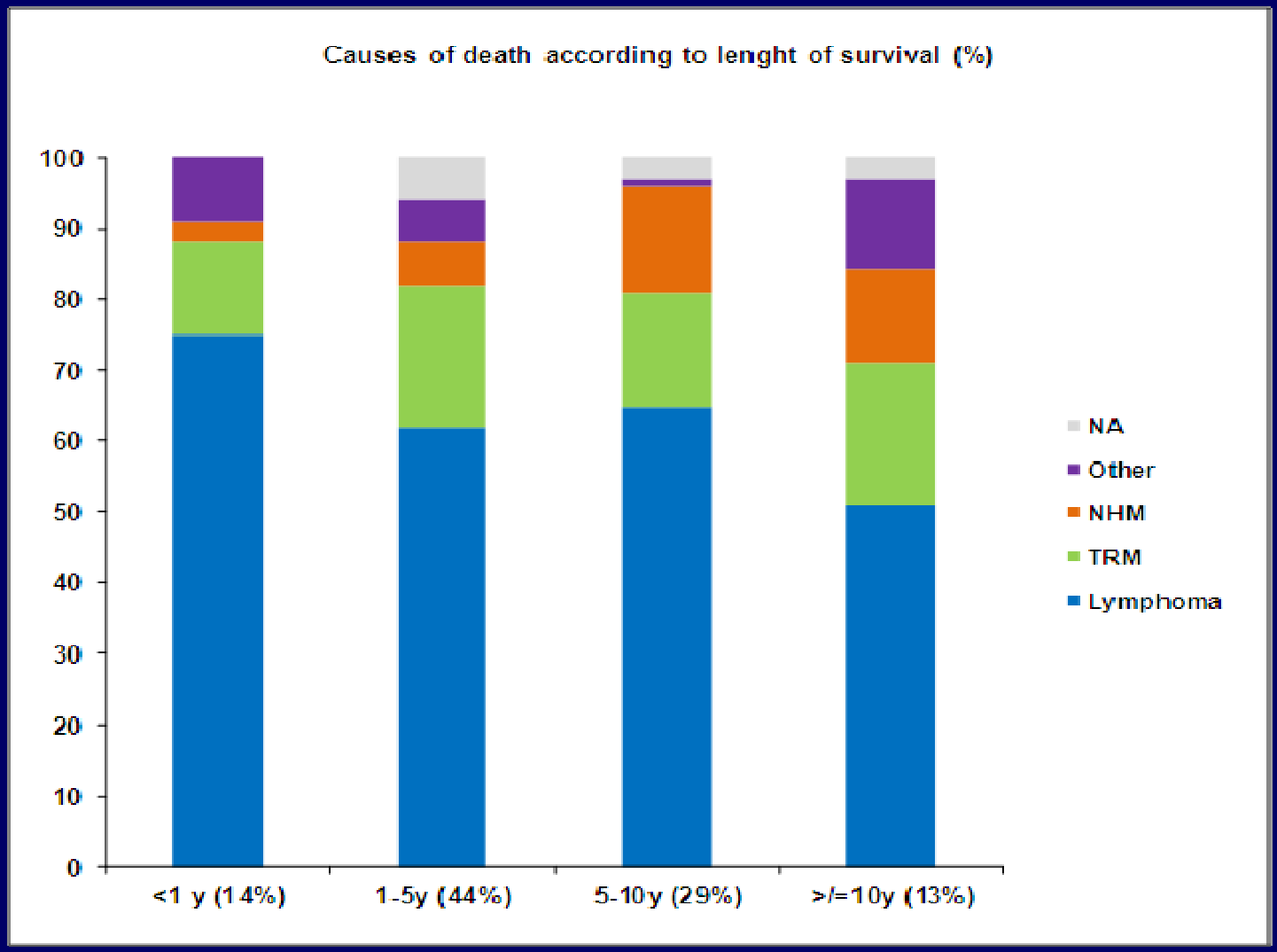


Patients with an HT might benefit from ASCT

Lysa
THE LYMPHOMA STUDY ASSOCIATION

Sarkozy et al, JCO 2016

Cause of death in patients with FL



Lyon data, unpublished results

Obinutuzumab plus bendamustine followed by obinutuzumab maintenance prolongs overall survival compared with bendamustine alone in patients with rituximab-refractory indolent non-Hodgkin lymphoma: updated results of the GADOLIN study

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Background

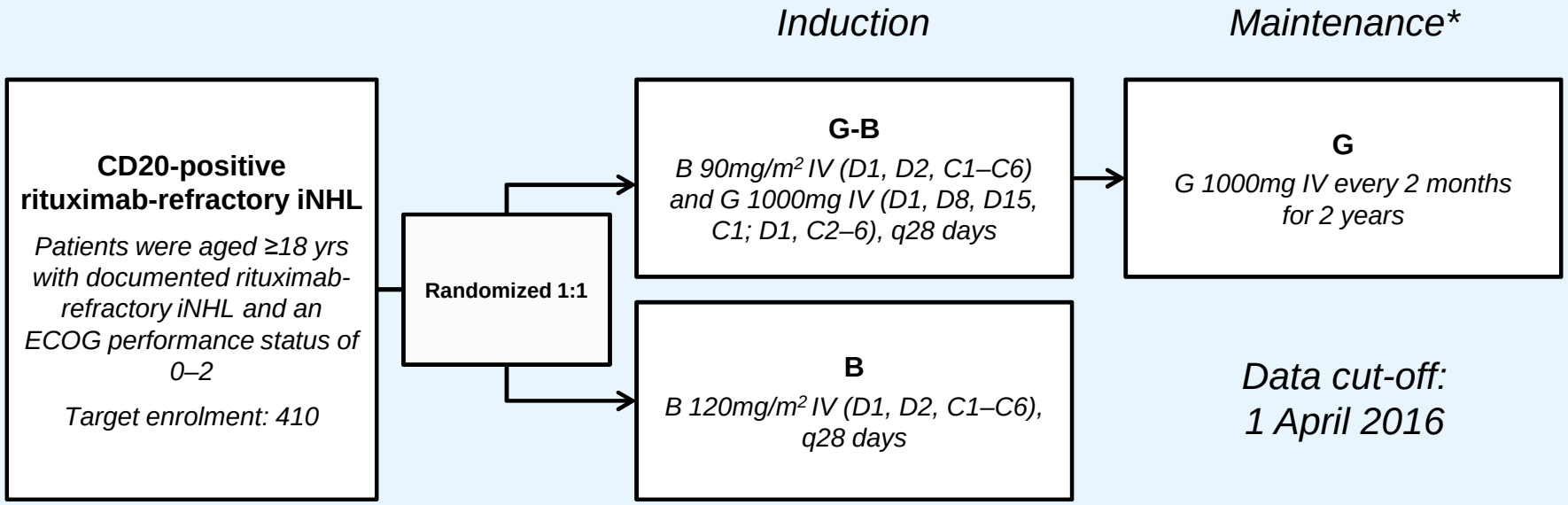
- Treatment options for pts with relapsed or refractory iNHL are limited
- GADOLIN (NCT01059630) is comparing the efficacy and safety of obinutuzumab (GA101; G) plus bendamustine (B) induction followed by G maintenance (G-B arm), with B induction (B arm) in rituximab-refractory iNHL pts
- In the primary analysis (data cut-off: 1 September 2014; 396 iNHL pts), median IRC-assessed PFS was not reached in the G-B arm (194 pts) and was 14.9 months in the B arm (202 pts), a 45% reduction in risk of progression or death (HR 0.55; 95% CI 0.40, 0.74; p=0.0001)[1]
  - EOI response rates were similar, but MRD negativity was significantly more common in the G-B arm[2]
  - Safety profiles were comparable
  - OS data were immature
- Seventeen additional pts were enrolled after the data cut-off for the primary analysis
- We report updated time-to-event and safety results from a planned analysis of all GADOLIN pts (n=413) using a data cut-off of 1 April 2016

EOI, end of induction; MRD, minimal residual disease

1. Sehn LH, et al. Lancet Oncol 2016;17:1081–93; 2. Pott C, et al. Blood 2015;126:3978

Study design

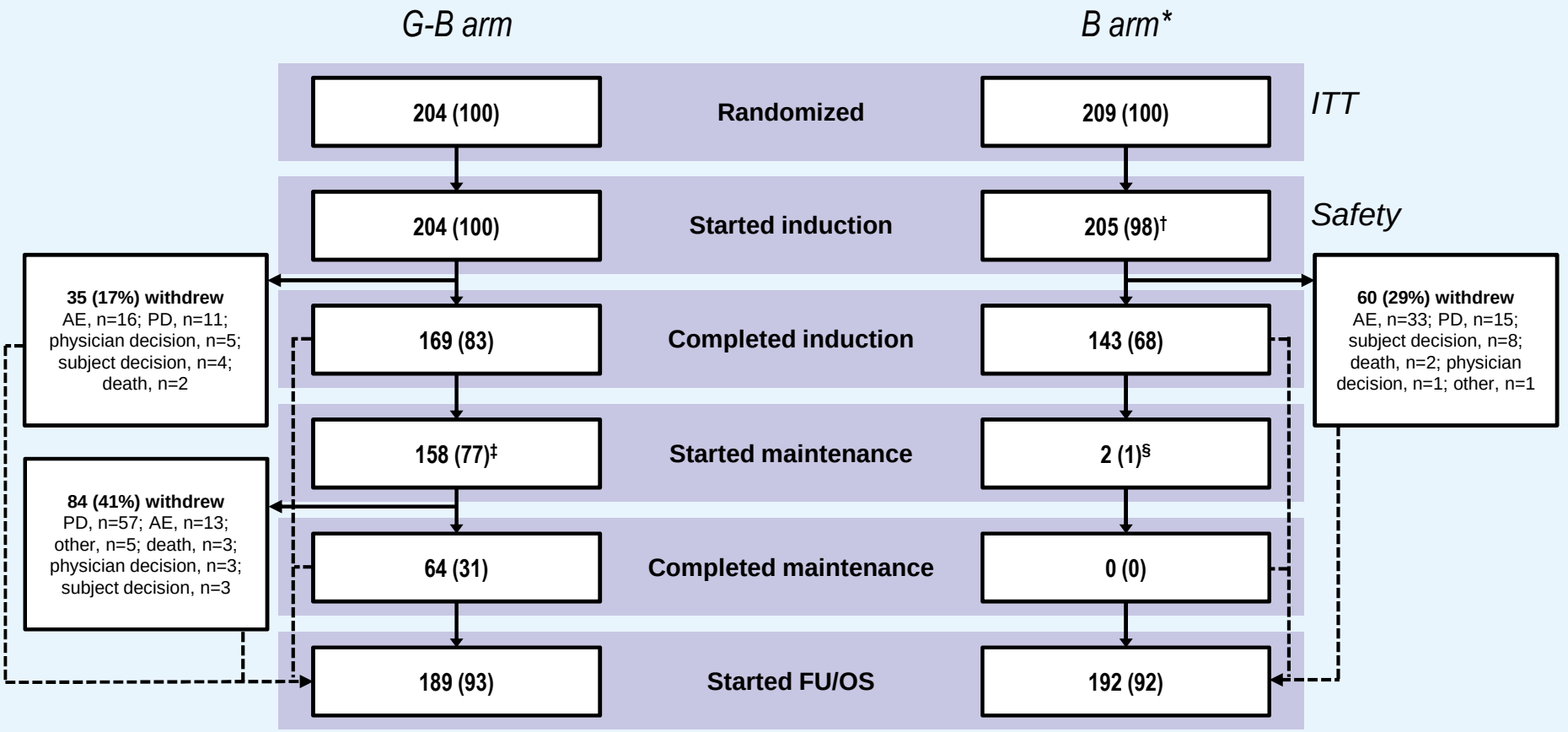
Open-label, multicenter, randomized, Phase III study in rituximab-refractory iNHL patients



- **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

*Patients in the G-B arm without evidence of progression following induction received G maintenance

Patient disposition in the iNHL population



*2 patients crossed over from the B arm to G maintenance at the end of induction; †2 ongoing; ‡10 ongoing; §2 ongoing (crossover patients)

Baseline patient and disease characteristics in the iNHL population

Characteristic, % (n)	*G-B, n=204*	*B, n=209*
Mean age, years (range)	62.0 (34–87)	61.9 (21–87)
Mean time from diagnosis to randomization, years (range)	4.2 (0.3–32.1)	4.2 (0.3–29.9)
Male	56.9 (116)	58.4 (122)
ECOG performance status at baseline		
0–1	95.6 (195)	95.1 (196)*
2	4.4 (9)	4.9 (10)*
Bone marrow involvement at baseline	32.5 (64/197)	35.9 (70/195)
Extranodal involvement	55.4 (113)	49.5 (103)†
Bulky disease at baseline (≥6cm)	34.3 (70)	35.9 (74)*
FLIPI at diagnosis (FL pts only)		
Low (0–1)	25.6 (42)‡	20.6 (35)§
Intermediate (2)	31.1 (51)‡	35.3 (60)§
High (≥3)	39.0 (64)‡	40.6 (69)§
Unknown	4.3 (7)‡	3.5 (6)§

- *80.4% (164 patients) in the G-B arm and 81.8% (171 patients) in the B arm had a FL diagnosis; characteristics were similar to the iNHL population*

*n=206; †n=208; ‡n=164; §n=170; FLIPI, Follicular Lymphoma International Prognostic Index

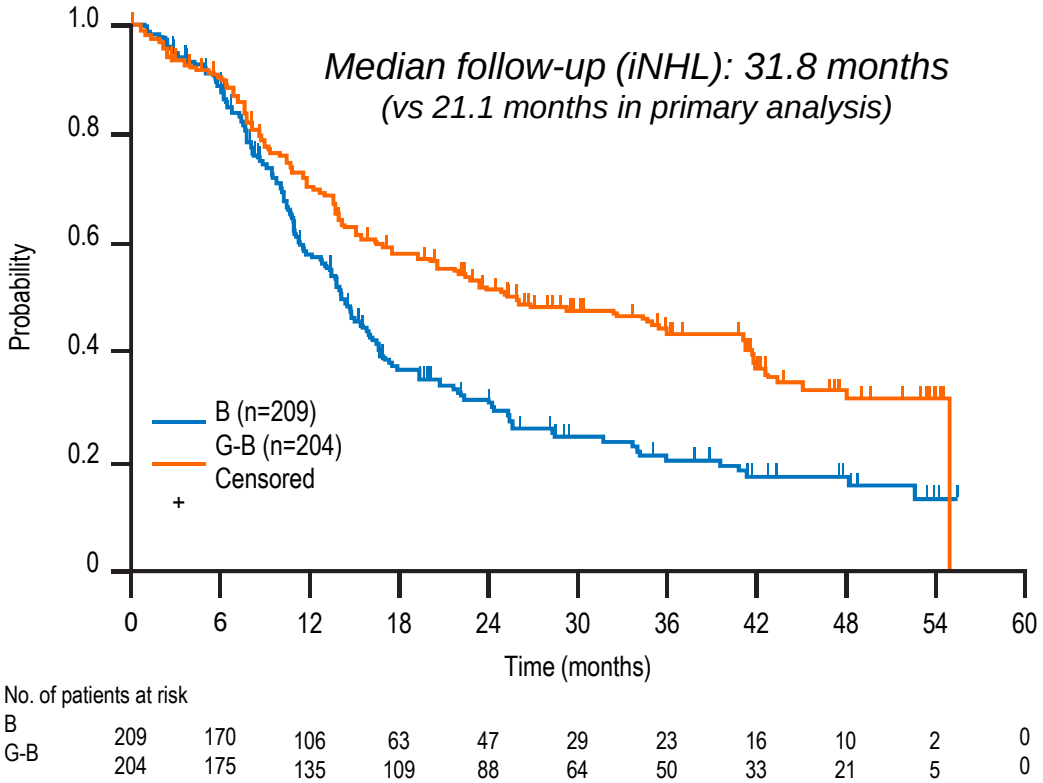
Treatment history in the iNHL population

Characteristic, % (n)	*G-B, n=204*	*B, n=209*
Median prior regimens, n (range)	2 (1–7)	2 (1–10)
Median time since completion of last regimen, months (range)	3.9 (0.1–128.4)	3.9 (0.5–64.0)
Patients refractory to last regimen	92.2 (188)	92.3 (193)
Patients rituximab-refractory to		
0 regimen	1.5 (3)	0.0 (0)
1 regimen	80.9 (165)	77.5 (162)
2 regimens	16.2 (33)	17.7 (37)
3 regimens	1.0 (2)	4.3 (9)
4 regimens	0.5 (1)	0.5 (1)
Patients double refractory to rituximab and an alkylating agent overall	77.5 (158)	81.3 (170)

- *Treatment history was similar in the FL population*

INV-assessed PFS in the iNHL population

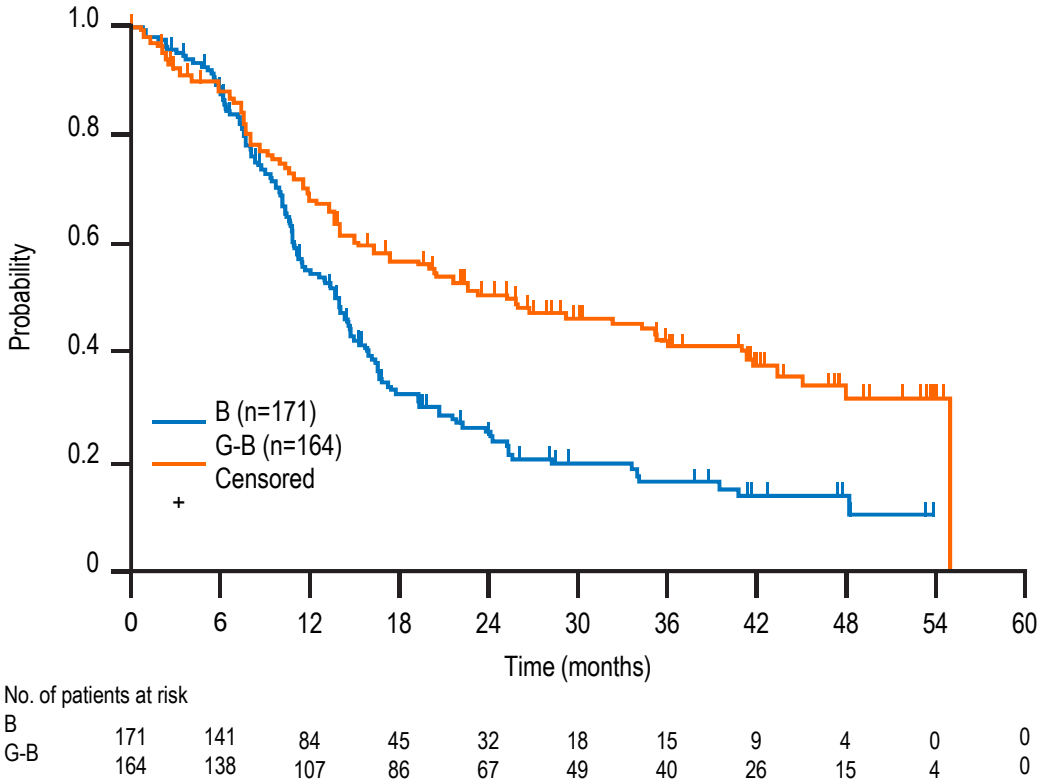
Kaplan-Meier plot of INV-assessed PFS by treatment arm (iNHL)



	G-B, n=204	B, n=209
Pts with event, n (%)	115 (56.4)	146 (69.9)
Median PFS (95% CI), mo	25.8 (19.5, 41.1)	14.1 (12.6, 16.0)
HR (95% CI) -value*	0.57 (0.44, 0.73), p<0.0001	

INV-assessed PFS in the FL population

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



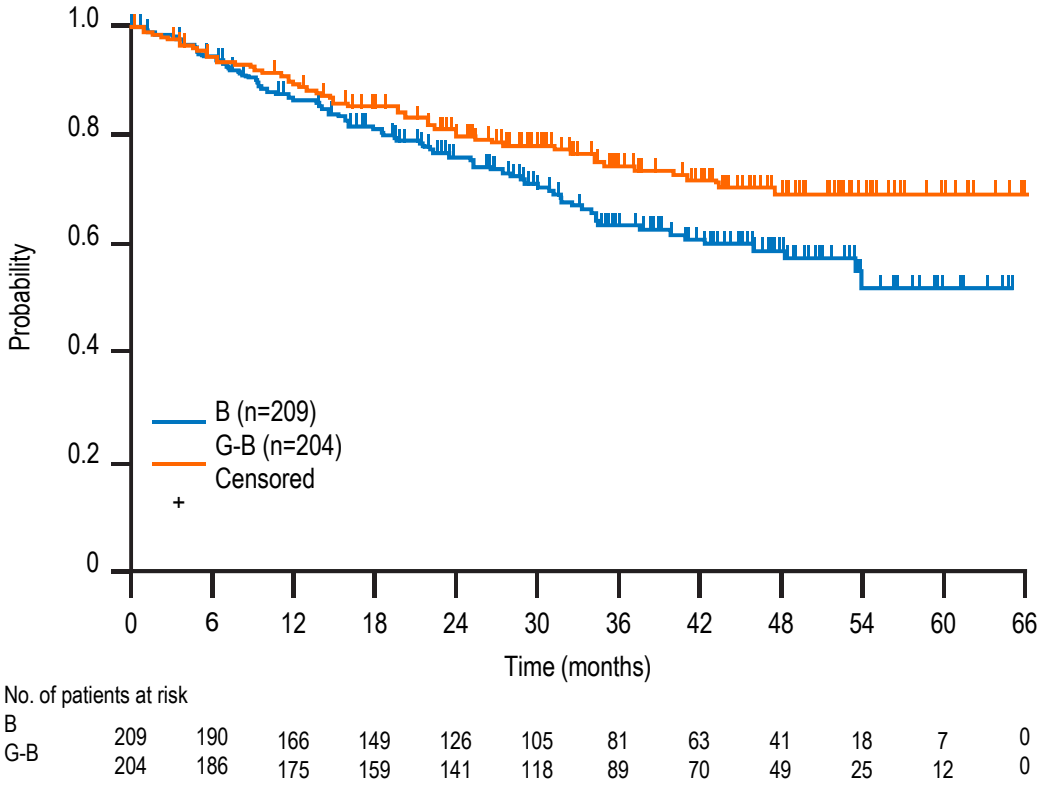
	G-B, n=164	B, n=171
Pts with event, n (%)	93 (56.7)	125 (73.1)
Median PFS (95% CI), mo	25.3 (17.4, 36.0)	14.0 (11.3, 15.3)
HR (95% CI), p-value*	0.52 (0.39, 0.69), p<0.0001	

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

*Stratified analysis; stratification factors: prior therapies, refractory type, geographical region

OS in the iNHL population

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



	G-B, n=204	B, n=209
Pts with event, n (%)	52 (25.5)	73 (34.9)
Median OS (95% CI), mo	NR (NR, NR)	NR (48.2, NR)
HR (95% CI), p-value*	0.67 (0.47, 0.96), p=0.0269	

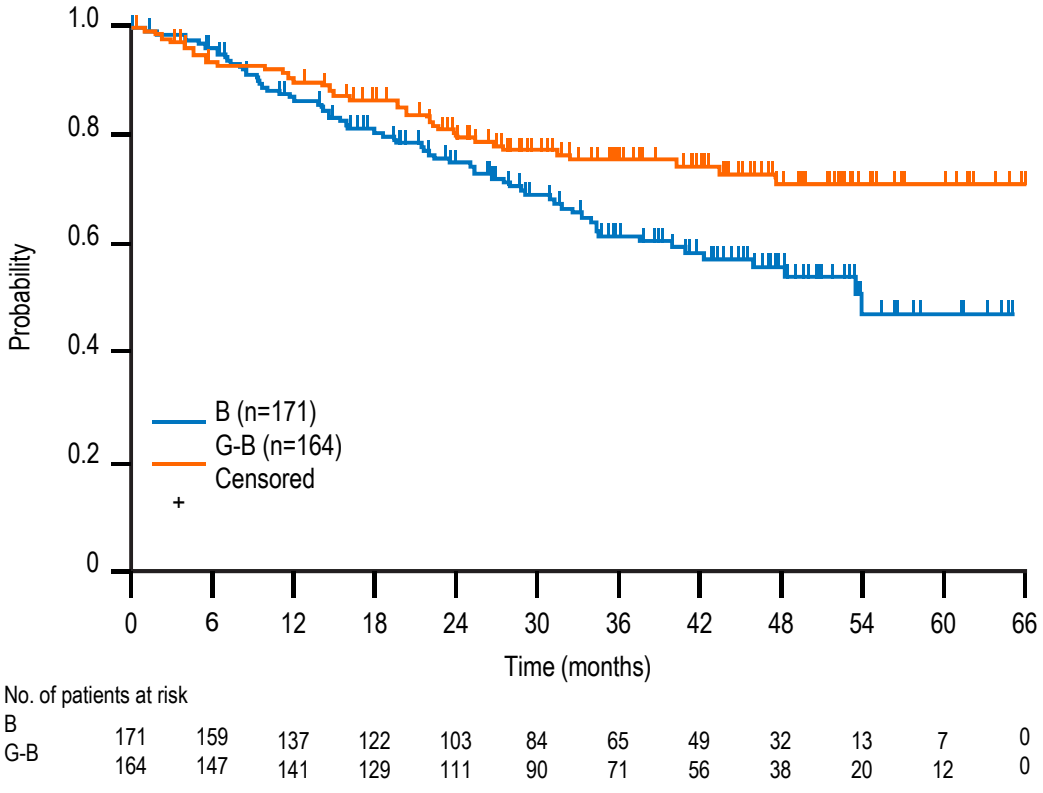
Median follow-up (iNHL): 31.8 months
(vs 21.1 months in primary analysis)

NR, not reached

*Stratified analysis; stratification factors: iNHL subtype, prior therapies, refractory type, geographical region

OS in the FL population

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



	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)

NR, not reached
*Stratified analysis; stratification factors: prior therapies, refractory type, geographical region

Adverse events in the iNHL population

% (n)	*G-B, n=204*	*B, n=203**
Any AE	99.0 (202)	98.5 (200)
Grade 3–5 AE	72.5 (148)	65.5 (133)
Grade 5 (fatal) AE	7.8 (16)	6.4 (13)
SAE	43.6 (89)	36.9 (75)
AE leading to withdrawal from any study treatment	20.1 (41)	17.2 (35)
AE leading to dose modification†	50.0 (102)	42.4 (86)

- Grade 5 (fatal) AEs listed by System Organ Class
  - G-B: infections and infestations, 6; neoplasms benign, malignant and unspecified, 5; blood and lymphatic system disorders, 1; cardiac disorders, 1; immune system disorders, 1; injury, poisoning and procedural complications, 1; renal and urinary disorders, 1
  - B: infections and infestations, 7; neoplasms benign, malignant and unspecified, 3; nervous system disorders, 2; metabolism and nutrition disorders, 1

*2 patients who crossed over from the B arm to the G-B arm during maintenance are excluded; †decrease or delay

Grade 3–5 adverse events in the iNHL population

Grade 3–5 AEs of interest by treatment arm and treatment phase

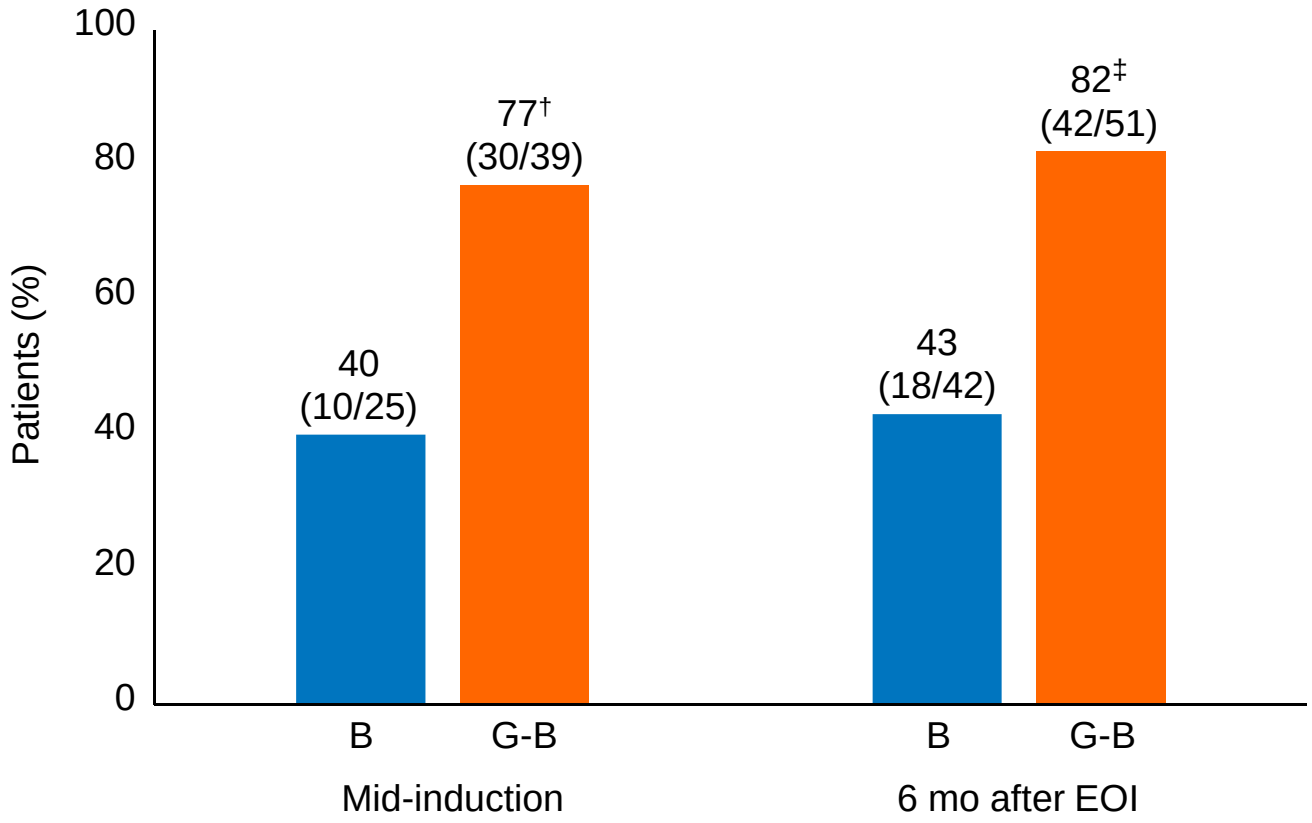
	Induction		Maintenance	Overall	
% (n)	G-B, n=204	B, n=205†	G-B, n=158*	G-B, n=204	B, n=203*
Neutropenia‡	27.5 (56)	26.8 (55)	10.8 (17)	34.8 (71)	27.1 (55)
Thrombocytopenia‡	10.3 (21)	15.6 (32)	1.3 (2)	10.8 (22)	15.8 (32)
Infections and infestations§	7.8 (16)	12.2 (25)	10.1 (16)	22.5 (46)	19.2 (39)
Infusion-related reactions‡	8.8 (18)	3.4 (7)	0.6 (1)	9.3 (19)	3.4 (7)
Neoplasms§¶	1.0 (2)	1.0 (2)	2.5 (4)	5.9 (12)	5.4 (11)
Cardiac disorders§**	2.5 (5)	1.0 (2)	1.9 (3)	4.4 (9)	1.5 (3)

Conclusions

- Updated analysis of GADOLIN
  - Confirms that G-B induction plus G maintenance significantly reduces risk of disease progression or death relative to B alone in rituximab-refractory FL patients (48% risk reduction)
  - Demonstrates a significant improvement in OS in the G-B arm (42% risk reduction in FL patients)
  - Confirms the comparable safety profile observed in the primary analysis
- Collectively, these data establish G-B induction plus G maintenance as a new standard of care for rituximab-refractory FL patients

MRD-negative response in the FL population[1]

FL patients (%) achieving MRD-negative status in PB at mid-induction (Cycle 5 Day 1) and 6 months after EOI by treatment arm[*1]*

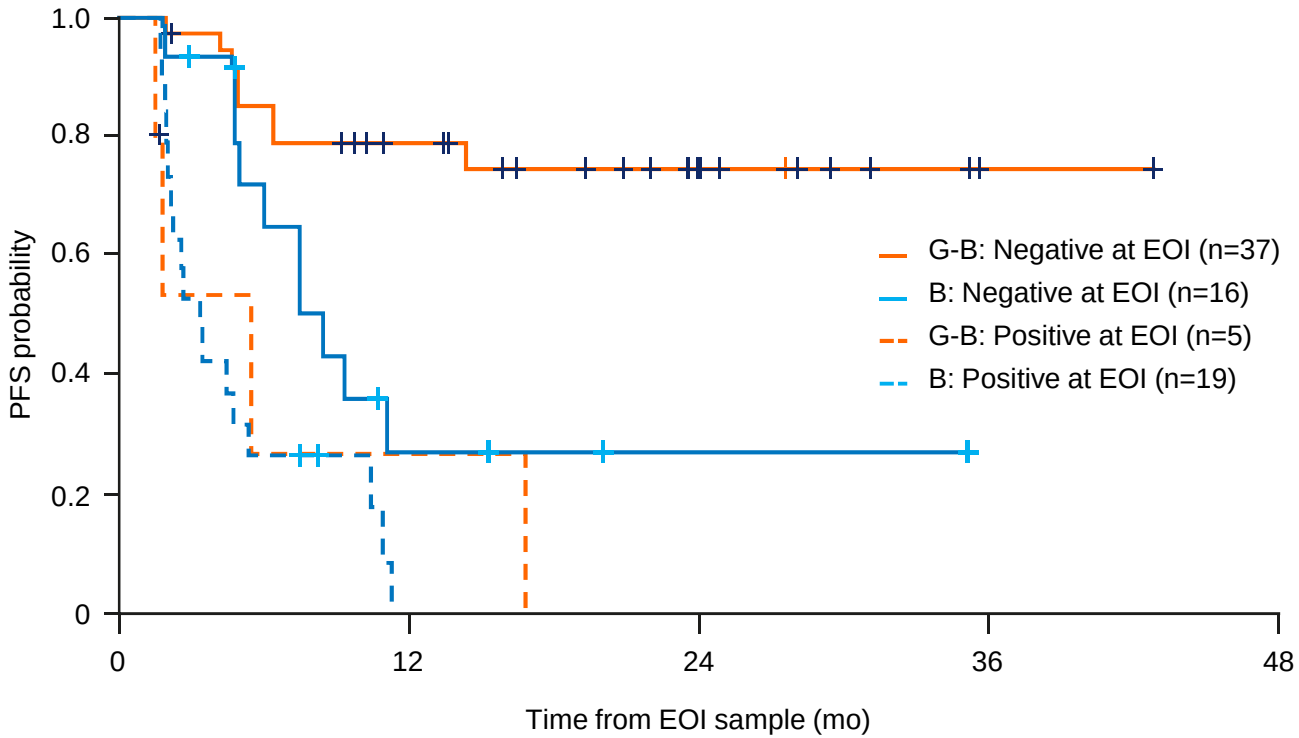


*MRD was analyzed by t(14;18) and/or Ig variable domain allele-specific RQ-PCR in patients with a clonal marker detectable at screening in PB or BM by consensus PCR and defined as negative if RQ-PCR and subsequent nested PCR produced a negative result; †p<0.0029 vs B arm; ‡p=0.0001 vs B arm

1. Pott C, et al. Blood 2015;126:3978

MRD status at EOI and association with PFS in the FL population[1]

Kaplan-Meier plot of PFS by MRD status at EOI and by treatment arm in the FL population



1. Pott C, et al. Blood 2015;126:3978

The increase in patients survival implies new challenges

Important endpoints for future/ongoing studies evaluating therapeutic strategies in FL :

- **Quality of response**
- **Surrogate for PFS ?**
- **Quality of life**
- **Ability to deliver second line treatments**
- **Long term toxicities**

… and Overall Survival