Association of early disease progression and very poor survival in the GALLIUM study in follicular lymphoma: benefit of obinutuzumab in reducing the rate of early progression

John F. Seymour,[1] Robert Marcus,[2] Andrew Davies,[3] Eve Gallop-Evans,[4] Andrew Grigg,[5] Andrew Haynes,[6] Michael Herold,[7] Thomas Illmer,[8] Herman Nilsson-Ehle,[9] Martin Sökler,[10] Ulrich Dünzinger,[11] Tina Nielsen,[12] Aino Launonen[12] and Wolfgang Hiddemann[13]

[1]Peter MacCallum Cancer Centre, Royal Melbourne Hospital and University of Melbourne, Victoria, Australia; [2]Kings College Hospital, London, UK; [3]Cancer Research UK Centre, University of Southampton, UK; [4]Velindre Cancer Centre, Cardiff, UK; [5]Austin Hospital, Melbourne, Victoria, Australia; [6]Nottingham University Hospitals NHS Trust, UK; [7]HELIOS-Klinikum Erfurt, Germany; [8]BAG Freiberg-Richter, Jacobasch, Illmer and Wolf, Dresden, Germany; [9]Section of Hematology and Coagulation, Department of Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden; [10]Eberhard-Karls-University Tübingen, Germany; [11]Roche Pharma AG, Grenzach-Wyhlen, Germany; [12]F. Hoffmann-La Roche Ltd., Basel, Switzerland and [13]Department of Medicine III, Ludwig-Maximilians-University, Munich, Germany

 doi:10.3324/haematol.2018.209015

Received: October 14, 2018.

Accepted: December 17, 2018.

Pre-published: December 20, 2018.

Correspondence: *JOHN SEYMOUR* - john.seymour@petermac.org

Supplementary material

Methods

Patient selection criteria

Patients with follicular lymphoma (FL) were eligible for enrollment if aged ≥18 years with histologically confirmed, previously untreated, CD20-positive disease (histologic grades 1-3a) of stages III or IV (or stage II with bulky disease, i.e., largest tumor diameter ≥7 cm), with at least 1 bidimensionally measurable lesion, Eastern Cooperative Oncology Group (ECOG) performance status 0-2, adequate hematologic function, and requiring treatment according to 'Groupe d'Étude des Lymphomes Folliculaires' (GELF) criteria.[10] The time between histologic confirmation of FL and randomization could not exceed 12 months. The primary study endpoint was investigator-assessed PFS, defined as time from randomization to PD, relapse, or death from any cause.

Treatments

Patients were randomized 1:1 to induction therapy with intravenous (i.v.) infusions of G 1000 mg (days 1, 8, and 15 of cycle 1 and day 1 of subsequent cycles) or R 375 mg/m^2 (day 1 of each cycle) plus chemotherapy for 6 or 8 cycles depending on the selected chemotherapy. Randomization was stratified by chemotherapy regimen, Follicular Lymphoma International Prognostic Index (FLIPI),[2] and geographic region. 1 of 3 chemotherapy regimens (cyclophosphamide, vincristine, doxorubicin, and prednisone [CHOP]; cyclophosphamide, vincristine, and prednisone [CVP]; or bendamustine) was selected upfront by each center and standard doses were used; all patients at a given center received the same regimen.

Patients with a complete or partial response at the end of induction (EOI) received maintenance therapy with the same antibody as used during induction, i.e., G 1000 mg or R 375 mg/m^2, every 2 months for 2 years or until disease progression (PD) if earlier; no crossover was allowed.

Disease progression and transformation

Response and PD were assessed using the revised response criteria for malignant lymphoma.[3] When investigators suspected PD, a full tumor assessment was performed, including a computed tomography (CT) scan (limited to areas of prior involvement if required by local authorities). For tissue samples taken at progression or suspected transformation, information from local pathology was collected. Patients with PD were followed every 6 months for OS and new anti-lymphoma treatment until the end of the study.

Alternative imaging methods

Magnetic resonance imaging (MRI) scans with a non-contrast CT scan of the chest could be used for patients for whom CT scans with contrast were contraindicated. For patients assessed by MRI at screening, MRI was also used for all subsequent scans. Combined fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT scans could be used if performed with contrast and if the resolution was sufficient to allow accurate and consistent comparison of target lesion measurements with subsequent CT scans.

Results

Survival and mortality by chemotherapy regimen, FLIPI risk category and treatment arm

Fewer POD24 events occurred in G-chemo *versus* R-chemo patients across all 3 chemotherapy regimen groups, with the highest rate of events observed in patients treated with CVP (cumulative incidence: bendamustine 7.4% *versus* 16.1%; CHOP 12.5% *versus* 16.9%; CVP 16.9 *versus* 26.9%, respectively;*Online Supplementary Table S5*). Average risk reduction was 56.2% (95% CI: 28.9-73.0%), 27.2% (95% CI: -24.4-57.4%) and 45.5% (-27.7-75.4%) for the bendamustine, CHOP and CVP treatment groups, respectively. Excluding those patients treated with CVP from the analysis, fewer POD24 events were observed in G-chemo patients versus R-chemo patients (cumulative incidence 9.3% *versus* 16.4%, respectively), with an average risk reduction of 45.7% (95% CI: 22.4-65.2%). 2-year post-progression survival was broadly similar between the G- and R-chemo treatment arms for patients in the bendamustine (0.54 *versus* 0.60, respectively) and CHOP (0.76 *versus* 0.74, respectively) groups. Differences were observed in the CVP group (2-year post-progression survival 0.90 *versus* 0.61 for the G- *versus* R-chemo arm, respectively), although patient numbers were small in this subgroup.

POD24 events were more common in patients with a high FLIPI scores when compared with those with intermediate and low scores (G-chemo *versus* R-chemo: high, 12,7% *versus* 22.2%; intermediate, 7.2% *versus* 14.8%; low, 10.0% *versus* 11.6%; *Online Supplementary Table S6*). Risk reduction was 46.4% (16.2-65.7%),

54.6% (95% CI: 15.8-75.5%) and 15.0% (95% CI: -83.3-61.2%) for those with high, intermediate and low FLIPI scores, respectively.

Histologic transformation

During the first 24 months, G-chemo reduced the risk of disease transformation by 43% relative to R-chemo (95% CI: −19.8-72.8%; *P*=0.1330, Gray's test for equality), a similar proportional reduction to that seen for the risk of POD24 events. The cumulative incidence of transformation, in which POD24 and death without prior progression or transformation are considered as competing events, is shown in *Online Supplementary Figure S4*. The overall cumulative incidence rates for transformation were 1.9% (G-chemo) and 3.3% (R-chemo). Lymphoma types at transformation are listed in *Online Supplementary Table S7*.

NALT

Some differences were seen in the type of NALT received after PD according to the timing of POD. POD24 patients were more likely to be treated with immunochemotherapy or anti-CD20 monotherapy, whereas noPOD24 patients were more likely to receive radiotherapy or other therapy; however, in the POD24 and noPOD24 groups, there were no major differences between treatment arms in the type of NALT received after PD, whenever this occurred (see *Online Supplementary Table S8*).

REFERENCES

1. Brice P, Bastion Y, Lepage E, et al. Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol. 1997; 15(3):1110-1117.
2. Solal-Céligny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood. 2004;104(5):1258-1265.
3. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25(5):579-586.

Supplementary Table S1. Deaths in each treatment arm and relationship to PD for 1071 patients with at least 24 months' response follow-up.[a]

	POD24 (n=155)			noPOD24 (n=916)		
n (%)	G-chemo (n=57)	R-chemo (n=98)	All (n=155)	G-chemo (n=478)	R-chemo (n=438)	All (n=916)
First 24 months after randomization						
PD	57 (100)	98 (100)	155 (100)	0	0	0
Deaths following PD	11 (19)	22 (22)	33 (21)	0	0	0
In patients with disease transformation	5	8	14	0	0	0
Deaths unrelated to PD	1 (2)	7 (7)	8 (5)	0	0	0
In patients with disease transformation	1 (2)	0	1 (1)	0	0	0
Any time during the study (overall follow-up)						
All deaths	19 (33)	37 (38)	56 (36)	10 (2)	6 (1)	16 (2)
Deaths following PD	15 (26)	25 (26)	40 (26)	1 (0)[b]	0	1 (0)
In patients with disease transformation	2 (4)	0	2 (1)	0	0	0
Deaths unrelated to PD	4 (7)	12 (12)	16 (10)	9 (2)	6 (1)	15 (2)
In patients with disease transformation	0	0	0	0	0	0

Abbreviations: G-chemo: obinutuzumab plus chemotherapy; PD: progressive disease; POD: progressive disease or death due to progressive disease; R-chemo: rituximab plus chemotherapy.

[a]NOTE. At the clinical cut-off date, 95 patients had died; 23 of these patients (G-chemo, n=14; R-chemo, n=9) are not shown above as they had insufficient response follow-up.

[b]Received no study treatment; no response assessments done, but reason for death was progression of disease.

Supplementary Table 2. Baseline disease and patient characteristics in patients with a POD event within 6 months of randomization.

Characteristic[a]	POD event within first 6 months (n=22)
Age, years	59.8 (39-80)
Aged ≥65 years	6 (27.3)
Male	14 (63.6)
Ann Arbor stage at diagnosis	
I or II[b]	2/22 (9.1)
III	6/22 (27.3)
IV	14/22 (63.6)
Bone marrow involvement	9/22 (40.9)
Time from diagnosis to randomization, months	1.12 (0.0-26.0) (n=21)
FLIPI	
Low (0-1)	3 (13.6)
Intermediate (2)	6 (27.3)
High (≥3)	13 (59.1)
FLIPI-2	
Low (0)	1 (5.0)
Intermediate (1-2)	9 (45.0)

High (≥3)	10 (50)
Bulky disease	12/22 (54.5)
Randomized antibody treatment	
Obinutuzumab	5 (22.7)
Rituximab	17 (77.3)

Abbreviations: FL: follicular lymphoma; FLIPI: Follicular Lymphoma International Prognostic Index.
[a]Data are n (%), n/N (%), or median (range).
[b]Eighteen patients were randomized to study treatment after being assessed as stage II or above by the investigators, meeting study eligibility criteria, but were reassessed as stage I after medical review. Staging data were missing for seven patients (POD24, n=1; noPOD24, n=6).

Supplementary Table 3. Non-PD-related causes of death in the POD24 and noPOD24 groups throughout the whole study period.

POD within 24 months of randomization		POD >24 months after randomization	
G-chemo (n=57)	R-chemo (n=98)	G-chemo (n=477)	R-chemo (n=437)
Lower respiratory tract infection	Pneumonia	Non-small cell lung cancer	Chronic obstructive pulmonary disease
Lung infection	Malignant melanoma	Non-small cell lung cancer stage IV	Cerebral hematoma
Septic shock with multiple organ failure, influenza, and aspergillus pneumonic, hepatic GvHD	Hypercalcemia	Pulmonary neoplasia[a]	Thrombosis of celiac artery with ischemic stomach following removal of mass in adrenal gland
Multiple system organ failure	Ischemic stroke	Acute myeloid leukemia	Colon cancer
	Gastric cancer	Gastric hemorrhage	Myocardial infarction
	Heart attack	Ill-defined disorder	Lung adenocarcinoma
	Cerebrovascular accident	Respiratory tract infection	
	Septic shock	Pneumonia aspiration	
	Pneumonitis	Acute lung injury	
	Myocardial infarction		
	Unknown		
	Possible heart attack		

Abbreviations: G-chemo: obinutuzumab plus chemotherapy; GvHD: graft versus host disease; PD: disease progression; POD: progressive disease or death due to progressive disease; R-chemo: rituximab plus chemotherapy.
[a]Death not related to treatment

Supplementary Table 4. Crude death rates by POD24 status and treatment arm.

	G-chemo		R-chemo	
	Deaths	**Crude death rates per 100 patient–years (95% CI)**	**Deaths**	**Crude death rates per 100 patient–years (95% CI)**
Overall mortality	43	2.1 (1.6, 2.8)	52	2.6 (2.0, 3.4)
Mortality following POD24 event	19/57	17.4 (11.1-27.3)	37/98	20.6 (14.9-28.5)
Mortality following late POD event[a]	1/40[b]	2.4 (0.3-17.3)	0/48	0 (0, 0)
NoPOD24 mortality[c]	24/601[b]	1.2 (0.8-1.8)	15/601	0.8 (0.5-1.4)

Abbreviations: CI: confidence interval; G-chemo: obinutuzumab plus chemotherapy; POD: progressive disease or death due to progressive disease; R-chemo: rituximab plus chemotherapy.

[a]POD events occurring later than 24 months after randomization.

[b]1 patient died after a late POD event; this patient was randomized to G-chemo but received no study treatment (new anti-lymphoma treatment was started 1 week after randomization). There was no disease follow-up but after 3 years the patient had died, reportedly following disease progression (exact time of POD event unknown). This patient is also included in the numerator for patients with no prior POD24 event.

[c]All patients started in the noPOD24 group at randomization and moved to the POD24 group at the time of the POD24 event.

Supplementary Table 5. POD24 and post-progression mortality rates, stratified by chemotherapy regimen.

Chemotherapy regimen	Number of POD24 patients, n/N (%)		24-month cumulative incidence, % (95% CI)		Relative POD24 risk reduction, % (95% CI)	2-year PPS		Crude PPS death rates	
	G-chemo	R-chemo	G-chemo	R-chemo		G-chemo	R-chemo	G-chemo	R-chemo
Bendamustine	24/345 (7.0)	52/341 (15.2)	7.4 (4.9-10.6)	16.1 (12.3-20.3)	56.2 (28.9-73.0)	0.54	0.60	23.56 (12.7-43.8)	25.32 (17-37.8)
CHOP	23/195 (11.8)	32/203 (15.8)	12.5 (8.2-17.7)	16.9 (11.9-22.6)	27.2 (-24.4-57.4)	0.76	0.74	14.79 (7-31)	15.78 (7.9-31.6)
CVP	10/61 (16.4)	14/57 (24.6)	16.9 (8.6-27.5)	26.9 (15.6-39.4)	45.5 (-22.7-75.4)	0.90	0.61	10.29 (2.6-41.2)	14.78 (6.2-35.5)
Excluding CVP	47/540 (8.7)	84/544 (15.4)	9.26 (6.9-12.0)	16.4 (13.3-19.7)	46.6 (22.4-62.0)	0.65	0.65	18.9 (11.8-30.5)	22.0 (15.6-31.3)

Abbreviations: CHOP: cyclophosphamide, vincristine, doxorubicin, prednisone; CVP: cyclophosphamide, vincristine, prednisone; CI: confidence interval; POD: progressive disease or death; PPS: post-progression survival.

Supplementary Table 6. POD24 and post-progression mortality rates, stratified by FLIPI score category.

FLIPI score category	Number of POD24 patients (n/N, %)		24-month CIF rate, % (95% CI)		POD24 risk reduction, % (95% CI)	2-year PPS		Crude PPS death rates	
	G-chemo	R-chemo	G-chemo	R-chemo		G-chemo	R-chemo	G-chemo	R-chemo
High	30/249 (12.0)	54/253 (21.3)	12.7 (8.8-17.3)	22.2 (17.2-27.6)	46.4 (16.2-65.7)	0.60	0.56	26.07 (15.3-44)	27.65 (18.8-40.6)
Intermediate	15/225 (6.7)	31/223 (13.9)	7.2 (4.2-11.2)	14.8 (10.4-20.0)	54.6 (15.8-75.5)	0.86	0.73	6.62 (1.7-26.5)	13.99 (7-28)
Low	12/127 (44.4)	13/125 (10.4)	10.0 (5.5-16.2)	11.6 (6.5-18.3)	15.0 (-83.3-61.2)	0.73	0.77	11.86 (3.8-36.8)	10.67 (3.4-33.1)

Abbreviations: CI: confidence interval; FLIPI: Follicular Lymphoma International Prognostic Index; G-chemo: obinutuzumab plus chemotherapy; POD: progressive disease or death; PPS: post-progression survival, R-chemo: rituximab plus chemotherapy.

Supplementary Table 7. New lymphoma histology in patients with disease transformation at time of PD

	POD within 24 months of randomization		POD >24 months after randomization	
	G-chemo (n=57)	R-chemo (n=98)	G-chemo (n=40)	R-chemo (n=48)
Any transformation, n	11	19	2	3
Diffuse large B-cell lymphoma	9	14	0	1
Other high-grade lymphoma	2	2	0	0
Follicular lymphoma grade 3b	0	3	2	2

Abbreviations: G-chemo: obinutuzumab plus chemotherapy; PD: progressive disease; POD: progressive disease or death due to progressive disease; R-chemo: rituximab plus chemotherapy.

Supplementary Table 8. NALT started after PD, by time of POD and treatment arm.[a]

	POD within 24 months of randomization				POD >24 Months After Randomization			
	G-chemo (n = 57)		R-chemo (n = 98)		G-chemo (n=40)		R-chemo (n=48)	
n (%)	Patients starting NALT (n=37)	Lines of treatment (n=51)	Patients starting NALT (n=63)	Lines of treatment (n=94)	Patients starting NALT (n=11)	Lines of treatment (n=12)	Patients starting NALT (n=13)	Lines of treatment (n=13)
Immunochemotherapy	20 (54)	27 (53)	37 (59)	50 (53)	5 (45)	6 (50)	5 (38)	5 (38)
HDT + autologous SCT	9 (24)	9 (18)	12 (19)	12 (13)	2 (18)	2 (17%)	0	0
Allogeneic SCT	0	0	1 (2)	1 (1)	0	0	0	0
Radiotherapy	6 (16)	6 (12)	5 (8)	5 (5)	3 (27)	3 (25)	2 (15)	2 (15)
Multimodality therapy	2 (5)	2 (4)	9 (14)	9 (10)	0	0	1 (8)	1 (8)
Radioimmunotherapy	2 (5)	2 (4)	0	0	0	0	0	0
Anti-CD20 monotherapy	4 (11)	4 (8)	2 (3)	2 (2)	0	0	1 (8)	1 (8)
Other therapy	2 (5)	2 (4)	13 (21)	15 (16)	2 (18)	2 (17)	4 (31)	4 (31)

Abbreviations: G-chemo: obinutuzumab plus chemotherapy; HDT: high-dose therapy; NALT: new anti-lymphoma treatment; POD: progressive disease or death after progressive disease; R-chemo: rituximab plus chemotherapy; SCT: stem cell transplantation.
[a]All new lines of therapy after progression are included; some patients received more than 1 line of therapy.

Supplementary Table 9. Crude death rates by POD24 status.

	n	Deaths	Crude death rates per 100 patient–years (95% CI)	Median follow-up from time of PD, months	Patient–years at risk
Mortality following POD24 event	155	56	19.4 (14.9-25.2)	22.6	289[a]
NoPOD24 mortality[b]	1,202	39	1.0 (0.8-1.4)	39.8	3772[c]

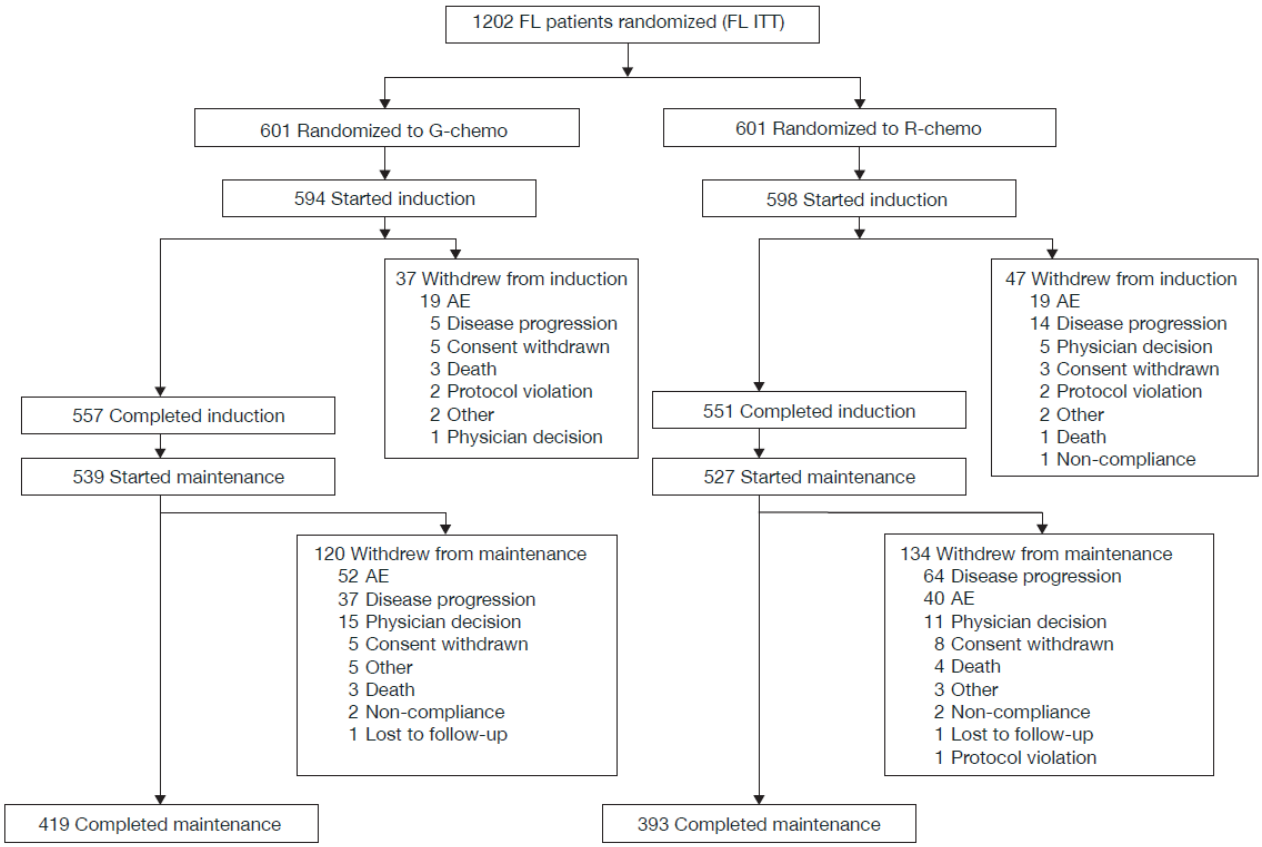
Abbreviations: CI: confidence interval; PD: progressive disease; POD: progressive disease or death due to progressive disease.
[a]Calculated as time between a POD24 event and the earlier of death or the end of follow-up.
[b]All patients started in the noPOD24 group at randomization, and moved to POD24 group at the time of the POD24 event.
[c]Calculated as time between randomization and the earliest of POD24 event, death, or the end of follow-up.

Supplementary Table 10. Crude death rates after progression in POD24 group by treatment arm, stratified by time of progression.

	G-chemo (n=57)			R-chemo (n=98)		
Time of progression, months	**n**	**Deaths**	**Deaths per 100 patient–years (95% CI)**	**n**	**Deaths**	**Deaths per 100 patient–years (95% CI)**
0 to 6	5	4	85.3 (32.0-227.4)	17	14	79.90 (47.2-134.9)
> 6 to 12	22	11	25.0 (13.8-45.0)	36	16	23.70 (14.5-38.7)
> 12 to 18	16	3	8.39 (2.7-26.0)	30	6	9.03 (4.1-20.1)
> 18 to 24	14	1	4.05 (0.6-28.7)	15	1	3.59 (0.5-25.5)

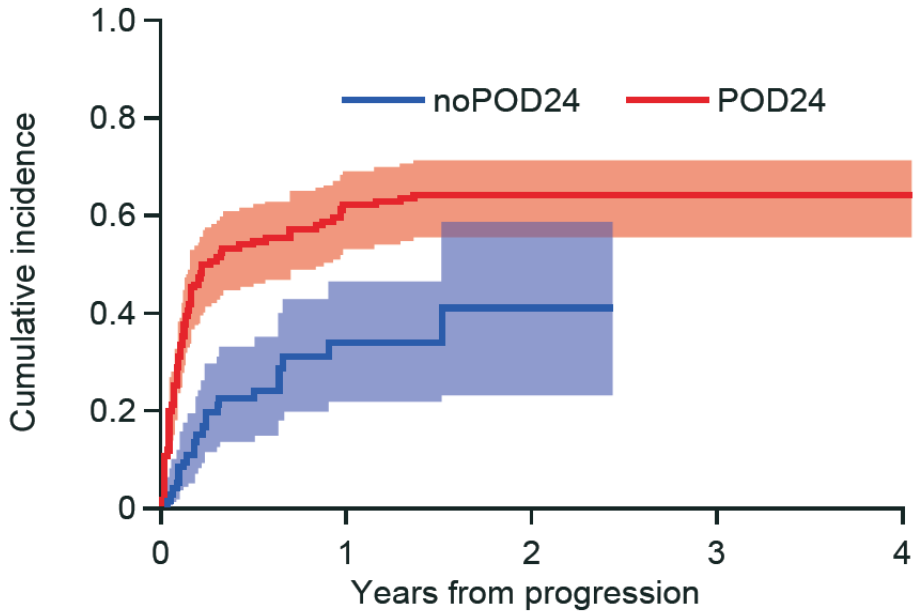
Abbreviations: CI: confidence interval; G-chemo: obinutuzumab plus chemotherapy; POD: progressive disease or death due to progressive disease; R-chemo: rituximab plus chemotherapy.

Supplementary Figure 1. Patient disposition in all follicular lymphoma patients in GALLIUM.



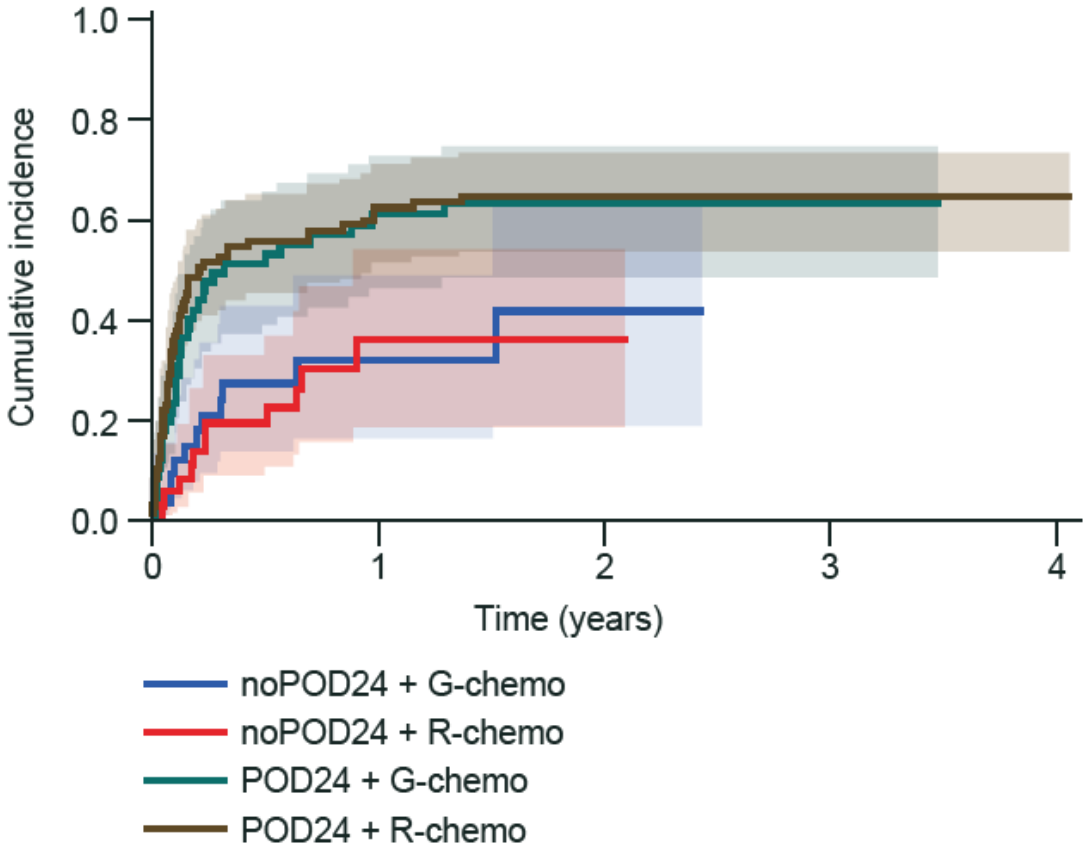
Abbreviations: AE: adverse event; FL: follicular lymphoma; G-chemo: obinutuzumab plus chemotherapy; ITT: intent-to-treat; R-chemo: rituximab plus chemotherapy.

Supplementary Figure 2. Cumulative incidence of transformation in first 24 months after randomization by treatment arm.



Abbreviations: G-chemo: obinutuzumab plus chemotherapy; R-chemo: rituximab plus chemotherapy.

Supplementary Figure 3. Cumulative incidence plot showing time from disease progression (PD) to start of new anti-lymphoma therapy by treatment arm in patients with POD24 events and patients whose disease progressed after 24 Months. Shading shows 95% confidence intervals.



Abbreviations: PD: progressive disease; POD: progressive disease or death due to progressive disease; G-chemo: obinutuzumab plus chemotherapy; POD: progressive disease or death due to progressive disease; R-chemo: rituximab plus chemotherapy.