Novità nella Terapia dei Linfomi

Pier Luigi Zinzani
Istituto di Ematologia «L. e A. Seràgnoli»
Università di Bologna

GAZYVARO (GA101 - Obinituzumab)

Approvazione Gazyvaro nel FL Rit refrat

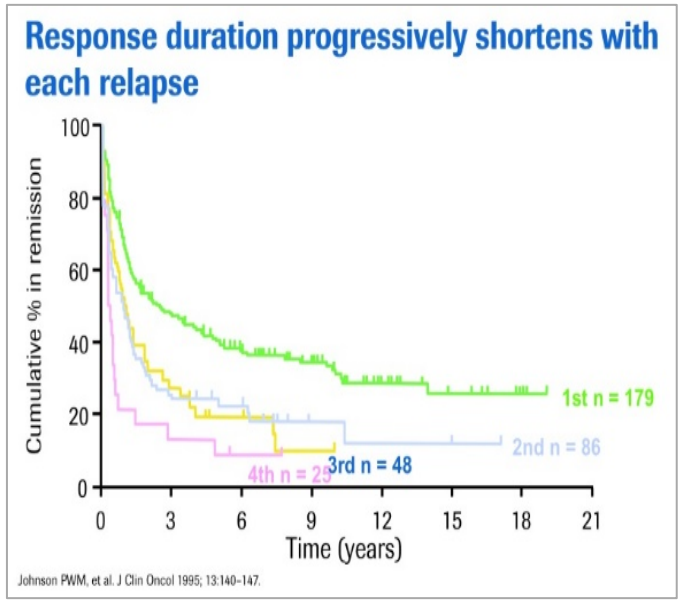
- Il 26 febbraio 2016 **FDA** approva Gazyvaro + Bendamustina seguito da Gazyvaro in Mantenim nel FL Rit refr

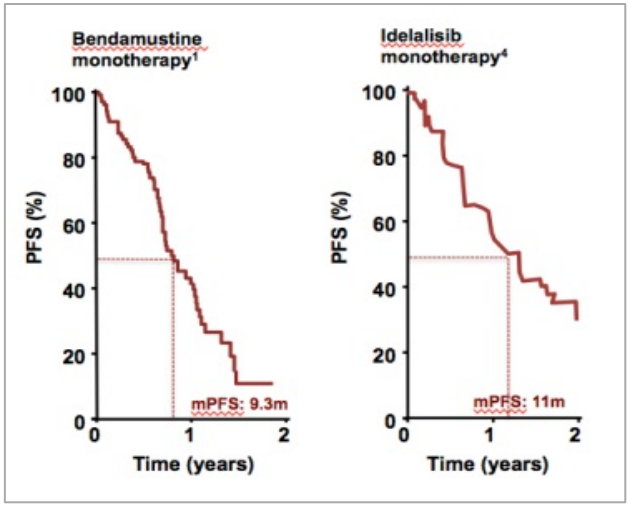
- Il 15 giugno 2016 l'**EMA** ha espresso il seguente parere:
  "Gazyvaro in associazione a bendamustina, seguito da Gazyvaro in mantenimento è indicato nel trattamento di pazienti con linfoma follicolare (LF) che non rispondono o che hanno avuto progressione di malattia durante o dopo 6 mesi dal trattamento con rituximab o un regime contenente rituximab"

Lo studio Pivotal Fase III GADOLIN è pubblicato su Lancet Oncology:
L.H. Shen et al, Lancet Oncology (http://dx.doi.org/10.1016/S1470-2045(16)30097-3)

Unmet medical needs in FL

- **1L:** 55% of patients progressed or died within 5 years*
- **2L+:** With each successive relapse, duration of remission decreases**
- Patients not benefiting from Rituximab-containing regimen: mPFS < 1 year





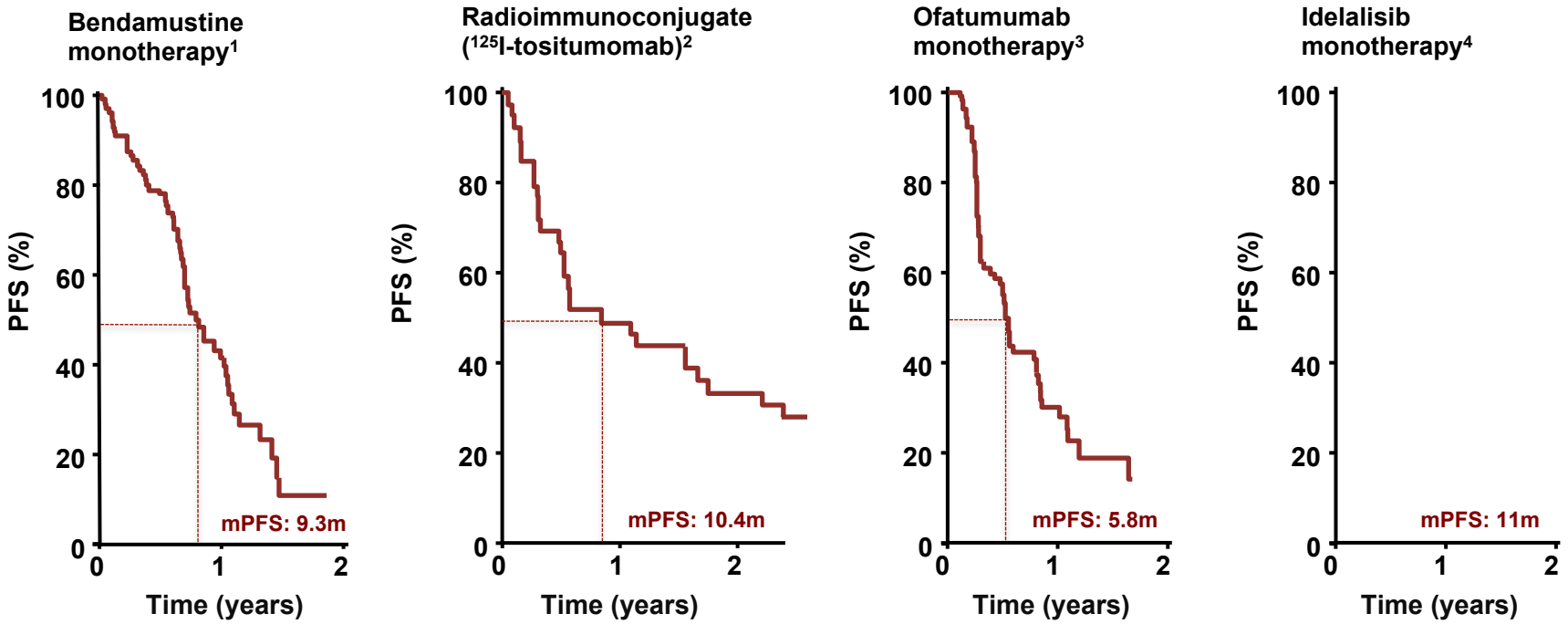
GAZYVARO

ORPHAN DESIGNATION DRUG

by EMA and FDA

FL Follicular Lymphoma
* estimates based on outcome in the PRIMA study / ** Johnson PWM et al JCO 1995

Fewer than 50% of refractory patients achieve responses > 1 year following salvage treatment



1. Kahl B, et al. Cancer 2010; 116:106–114; 2.Horning SJ, et al. J Clin Oncol 2005; 23:712–719
3. Czuczman MS, et al. Blood 2012; 119:3698–3704; 4..Gopal A et al. N Engl J Med 2014;370:1008-18.

Efficacy results from the idelalisib pivotal study DELTA 2014

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PI3Kδ Inhibition by Idelalisib in Patients with Relapsed Indolent Lymphoma (A.Gopal et al)

125 pts

Gopal 2014: refractory to both rituximab and alkylating; **58% FL**

The overall response rate was **57%**

With **6%** meeting the criteria for complete response

The mPFS was **11 months**

Zydelig (Idelalisib) EU approval: Zydelig is indicated as monotherapy for the treatment of adult patients

with **FL** that is **refractory to two prior lines** of treatment

GADOLIN: Primary results from a phase III study of obinutuzumab plus bendamustine compared with bendamustine alone in patients with rituximab-refractory indolent non-Hodgkin lymphoma

L.H. Sehn[1], N. Chua[2], J. Mayer[3], G. Dueck[4], M. Trneny[5], K. Bouabdallah[6], N. Fowler[7], V. Delwail[8], O. Press[9], G. Salles[10], J. Gribben[11], A. Lennard[12], P.J. Lugtenburg[13], N. Franklin[14], E. Wassner-Fritsch[15], G. Fingerle-Rowson[15], B.D. Cheson[16]

L Sehn et al, Abstract LB691 presented at 20th EHA Congress, 11–14 June 2015, Vienna, Austria

Introduction

- Despite an increase in the number of chemotherapeutic options, advanced stage indolent NHL remains incurable
- Addition of rituximab to chemotherapy during induction followed by maintenance has significantly improved outcomes in patients with indolent NHL
- Patients with disease which is refractory to a rituximab-containing therapy have limited treatment options
  - **Bendamustine was shown to be effective in this patient population (75–77% ORR) but median progression-free survival (PFS) was short (7–9 months)[1,2]**
- The GADOLIN study was designed to evaluate whether the combination of obinutuzumab, a novel anti-CD20 monoclonal antibody, with bendamustine followed by obinutuzumab maintenance could improve outcome in patients with rituximab-refractory indolent NHL

1.Friedberg JW, et al. *J Clin Oncol* 2008;26:204–10
2. Kahl BS, et al. *Cancer* 2010;116:106–14

L Sehn et al, Abstract LB691 presented at 20th EHA Congress, 11–14 June 2015, Vienna, Austria

Clinical Potential of Obinutuzumab (GA101)

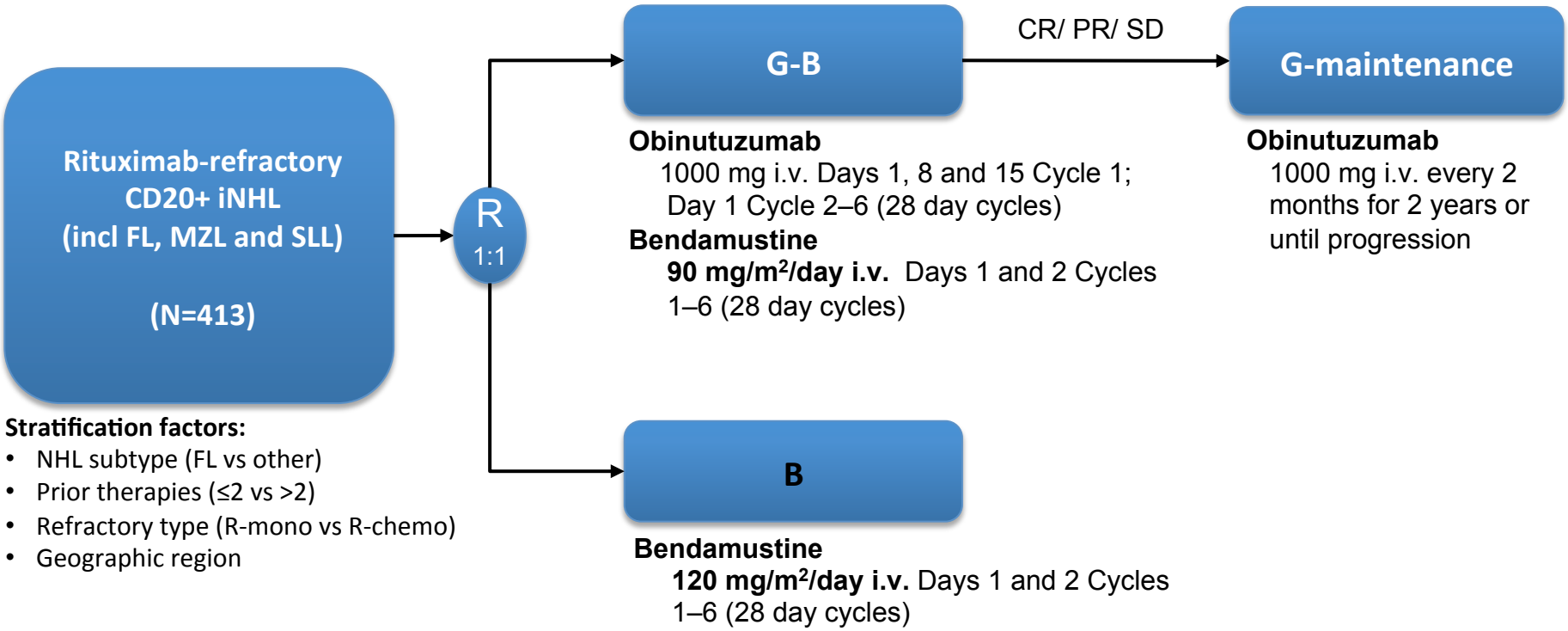
Comparison of commercially available anti-CD20 antibodies

Antibody	Obinutuzumab	Rituximab	Ofatumumab
Trade name (EU)	Gazyvaro	MabThera	Arzerra
Manufacturer	Roche	Roche	GlaxoSmithKline
Antibody type	II	I	I
IgG subclass	IgG1	IgG1	IgG1
Structure	Humanized	Chimeric	Fully human
Binding to CD20 epitope	Large loop	Large loop	Large and small loop
Binding to lipid rafts	–	++	++++
ADCC	++++	++	++
CDC	+	++	++++
Direct cell death induction	++++	+	+

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity; I Ig, immunoglobulin.

Smolej L. et al, Pharmacogenomics and Personalized Medicine 2015:8

GADOLIN: Study design (NCT01059630)



Stratification factors:

- NHL subtype (FL vs other)
- Prior therapies (≤2 vs >2)
- Refractory type (R-mono vs R-chemo)
- Geographic region

- International, randomized, open-label study
- Response monitored by CT scan post-induction, then every 3 months for 2 years, then every 6 months

iNHL, indolent non-Hodgkins lymphoma; G-B, obinutuzumab plus bendamustine; G, obinutuzumab.

L Sehn et al, Poster LB691 presented at 20th EHA Congress, 11–14 June 2015, Vienna, Austria

GADOLIN: Study endpoints

- **Primary endpoint:** PFS as assessed by an Independent Radiology Facility (IRF)
- **Secondary endpoints:**
  - PFS as assessed by investigator, OS
  - End of induction response
  - Best overall response
  - Duration of response, EFS, DFS
  - MRD
  - Safety
  - Pharmacokinetic profile
  - Pharmacoeconomics
  - Patient-reported outcomes (PROs)
- **Statistical assumptions**
  - 410 patients/260 events required for an 80% power to detect a hazard ratio of G-B vs B of 0.70 **(43% improvement in median PFS from 9.3 to 13.3 months)**, with a two-sided log-rank test α of 0.05
  - Interim efficacy analysis planned once 170 (65%) PFS events observed

Based on IDMC recommendation, the study is reported at the planned interim efficacy analysis because the primary endpoint was met

L Sehn et al, Poster LB691 presented at 20th EHA Congress, 11–14 June 2015, Vienna, Austria

GADOLIN: Patient selection and definition of rituximab-refractory

- Patients had rituximab-refractory CD20+ iNHL (including FL, MZL and SLL)
  - No exposure to bendamustine in the last 2 years
  - No exposure to mAbs (except rituximab) in the last 3 months or any exposure to obinutuzumab

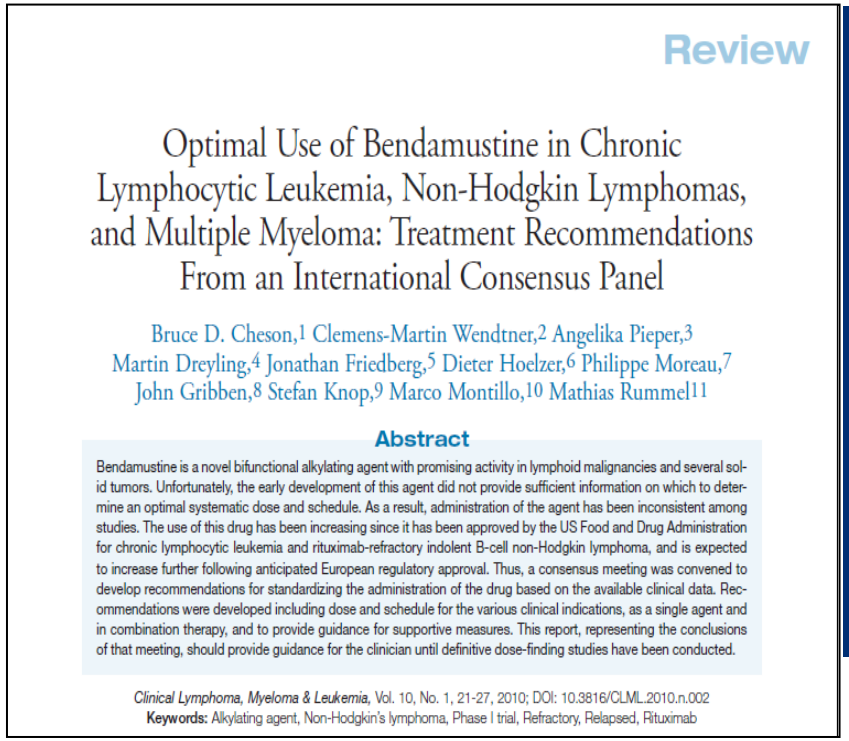
- Patients were considered **rituximab-refractory** if they:
  - Did not respond to either rituximab monotherapy or rituximab in combination with chemotherapy

    or
  - Progressed within 6 months of completion of the last dose of a rituximab-containing regimen
    - After at least 4 doses of rituximab monotherapy or 4 cycles of rituximab + chemotherapy

L Sehn et al, Poster LB691 presented at 20th EHA Congress, 11–14 June 2015, Vienna, Austria

Bendamustine dosing: an internal consensus

- Different doses of Bendamustine are actually recommended by an international consensus panel of haematologists, guided by efficacy, safety and tolerability principles



Review

Optimal Use of Bendamustine in Chronic Lymphocytic Leukemia, Non-Hodgkin Lymphomas, and Multiple Myeloma: Treatment Recommendations From an International Consensus Panel

Bruce D. Cheson,[1] Clemens-Martin Wendtner,[2] Angelika Pieper,[3] Martin Dreyling,[4] Jonathan Friedberg,[5] Dieter Hoelzer,[6] Philippe Moreau,[7] John Gribben,[8] Stefan Knop,[9] Marco Montillo,[10] Mathias Rummel[11]

Abstract

Bendamustine is a novel bifunctional alkylating agent with promising activity in lymphoid malignancies and several solid tumors. Unfortunately, the early development of this agent did not provide sufficient information on which to determine an optimal systematic dose and schedule. As a result, administration of the agent has been inconsistent among studies. The use of this drug has been increasing since it has been approved by the US Food and Drug Administration for chronic lymphocytic leukemia and rituximab-refractory indolent B-cell non-Hodgkin lymphoma, and is expected to increase further following anticipated European regulatory approval. Thus, a consensus meeting was convened to develop recommendations for standardizing the administration of the drug based on the available clinical data. Recommendations were developed including dose and schedule for the various clinical indications, as a single agent and in combination therapy, and to provide guidance for supportive measures. This report, representing the conclusions of that meeting, should provide guidance for the clinician until definitive dose-finding studies have been conducted.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 10, No. 1, 21-27, 2010; DOI: 10.3816/CLML.2010.n.002
Keywords: Alkylating agent, Non-Hodgkin's lymphoma, Phase I trial, Refractory, Relapsed, Rituximab

- **In combination with an antiCD20**
  - B is administered at a lower dose of 90 mg/m2 every 4 weeks
- **In monotherapy**
  - Bendamustine is administered at the 120 mg/m2 dose every 4 weeks

Cheson BD, et al. Clin Lymphoma Myeloma Leuk 2010;10:452-7

GADOLIN: Patient characteristics

Characteristic	G-B (n=194)	B (n=202)
Median age, years (range)	63 (34–87)	63 (21–87)
Male, n (%)	110 (57)	118 (58)
FLIPI at initial diagnosis, n/patients with data (%)		
Low (0–1)	42/155 (27)	34/165 (21)
Intermediate (2)	47/155 (30)	58/165 (35)
High (≥3)	60/155 (39)	67/165 (41)
Unknown	6/155 (4)	6/165 (4)
β2 microglobulin at diagnosis, n/patients with data (%)		
<3.5 mg/L	145/185 (78)	136/183 (74)
≥3.5 mg/L	40/185 (22)	47/183 (26)
Bone marrow involvement at enrollment, n/ patients with data (%)	60/187 (32)	69/188 (37)
Extranodal involvement at enrollment, n/patients with data (%)	107/194 (55)	98/201 (49)
Bulky disease (>6 cm) at enrollment, n/patients with data (%)	66/194 (34)	70/199 (35)

L Sehn et al, Poster LB691 presented at 20th EHA Congress, 11–14 June 2015, Vienna, Austria

GADOLIN: Baseline characteristics

Sono pz in 3L

Pz Double Refractory

100% dei pz refrattari a R

Characteristic	G-B (n=194)	B (n=202)
Mean time from diagnosis to randomization, years (range)	4.2 (0.3–32)	4.2 (0.3–30)
Median prior lines of therapy, n (range)	2 (1–10)	2 (1–7)
Median time since last dose of last prior regimen, months (maximum)	4.0 (128.4)	3.7 (64.0)
Number of patients refractory to last treatment, n (%)	178 (92)	187 (93)
Patients double refractory to rituximab and alkylators, n (%)*	147 (76)	164 (81)
Rituximab refractory type, n (%) R-chemo** R-mono	 156 (80) 38 (20	 157 (78) 45 (22)

*Double refractory to rituximab and an alkylating agent from the same or different regimens
**Including pazients who relapsed during or withing 6 months of R-maintenance following R-chemo

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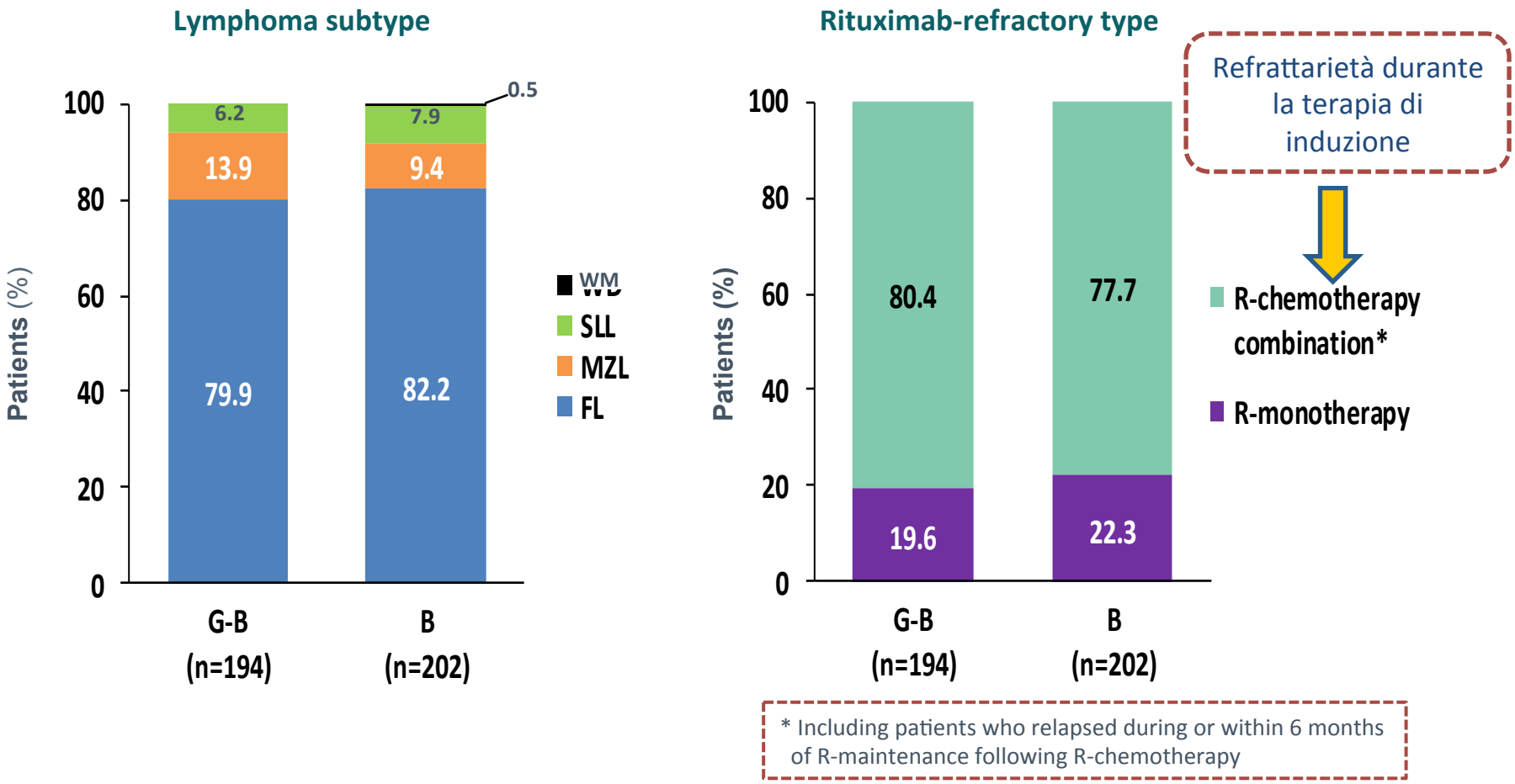
GADOLIN: Baseline disease characteristics



FL, follicular lymphoma; MZL, marginal zone lymphoma including extranodal, nodal and splenic; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

Adapted from
L Sehn et al, Poster LB691 presented at 20th EHA Congress, 11–14 June 2015, Vienna, Austria

GADOLIN: Study drug exposure

Maintenance therapy	G 1000 mg q2 months (n=143)
All 12 maintenance doses received, n (%)	36 (25)
Patients still receiving maintenance, n (%)	46 (32)
Median duration of exposure, months (range)	10.8 (0.5–23.7)

Induction therapy	G-B		B
	G 1000 mg x 8 (n=194)	B 90 mg/m^2 x 12 (n=193)	**120 mg/m^2 x 12 (n=198)**
All scheduled doses received, n (%)	145 (75)		
Mean no. of doses received (SD)	7.2 (1.74)		
Patients with ≥1 dose reduction*	NA		
Median cumulative dose, mg/m^2 (range)**	NA		
Patients with ≥90% dose intensity***, n (%)	175 (90)		

Meno pazienti nel braccio benda hanno completato i 6 cicli pianificati. Nel braccio benda:
- Drop out per AE > PD

* B dose reduction of ≥25% (B-arm) or ≥33% (G-B arm)
** Based on calculated BSA at baseline
*** Percentage of planned dose based on dose at C1D1 for cycles received.

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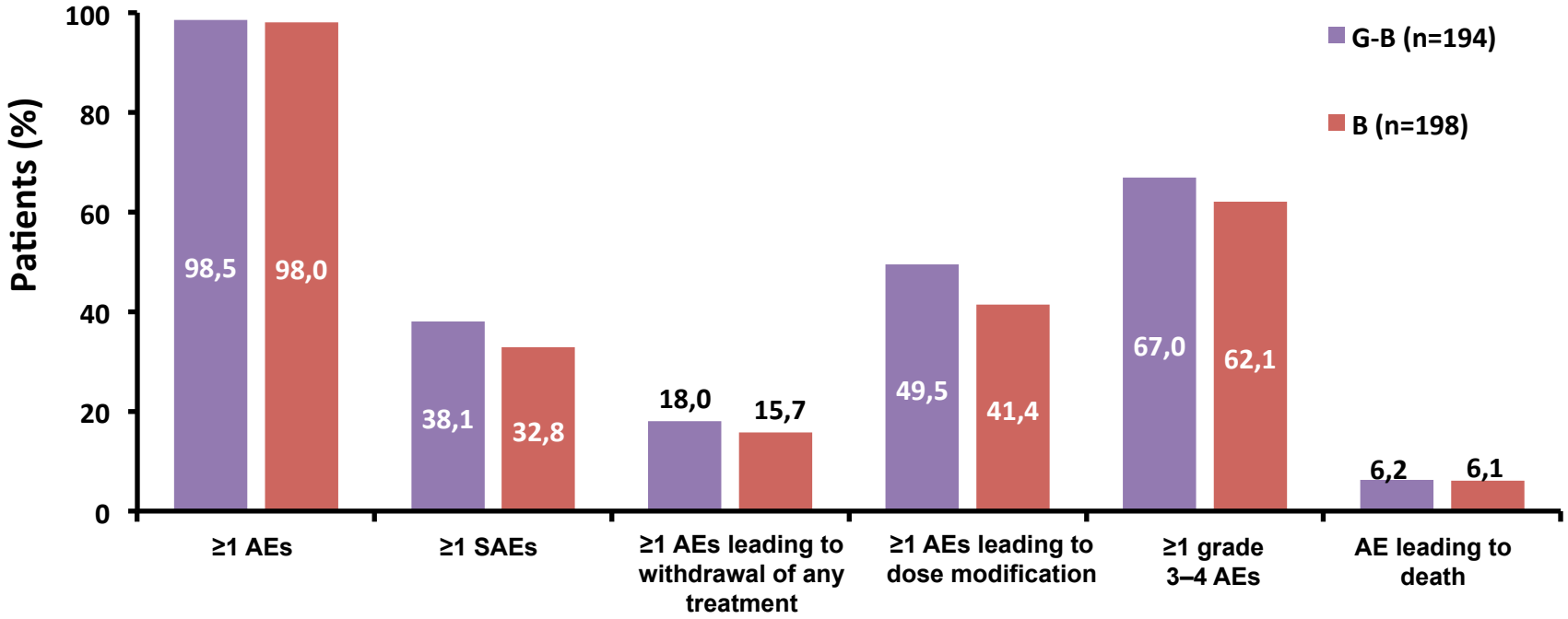
GADOLIN: Overview of AEs

- AE, adverse event; SAE, serious adverse event



Adapted from
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GADOLIN: Adverse Events Grade 3–4

Hematological AEs

AE, n (%)*	G-B (n=194)	B (n=198)
Neutropenia	**64 (33.0)**	**52 (26.3)**
Thrombocytop.	**21 (10.8)**	**32 (16.2)**
Anemia	15 (7.7)	20 (10.1)
Febrile neutropenia	9 (4.6)	7 (3.5)
Leukopenia	2 (1.0)	3 (1.5)

* Multiple occurrences of same AE in an individual were only counted once

IRR, infusion related reaction

Non-hematological AEs**

AE, n (%)*	G-B (n=194)	B (n=198)
IRR***	**21 (10.8)**	**11 (5.6)**
Vomiting	4 (2.1)	2 (1.0)
Decreased appetite	3 (1.5)	2 (1.0)
Fatigue	3 (1.5)	5 (2.5)
Nausea	2 (1.0)	6 (3.0)
Diarrhea	2 (1.0)	5 (2.5)
Pyrexia	2 (1.0)	0
Headache	1 (0.5)	2 (1.0)

* Multiple occurrences of same AE in an individual were only counted once
** Adverse events with≥15% incidence across all grades
*** AEs occurring during or within 24 hours after an infusion and considered to be related to any study drug

Le IRR erano gestibili, senza la necessità di emendamento del protocollo oppure di split di dosaggio nel primo ciclo (sebbene contemplato)

Nel Mantenimento con G, non sono stati registrati eventi avversi IRR di grado 3-4
- Nessun IRR è stato fatale, grave, o ha portato alla sospensione del trattamento
- IRR <5% nel Mantenimento

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GADOLIN: Serious Adverse Events

Hematological SAEs

SAE, n (%)*	G-B (n=194)	B (n=198)
Febrile neutropenia	**8 (4.1)**	6 (3.0)
Neutropenia	**6 (3.1)**	1 (0.5)
Thrombocytop.	4 (2.1)	0
Anemia	3 (1.5)	3 (1.5)
Leukopenia	0	1 (0.5)

* Multiple occurrences of same SAE in an individual were only counted once

IRR, infusion related reaction

Non-hematological SAEs**

SAE, n (%)*	G-B (n=194)	B (n=198)
IRR***	**8 (4.1)**	3 (1.5)
Sepsis	6 (3.1)	7 (3.5)
Pneumonia	5 (2.6)	**10 (5.1)**
Pyrexia	5 (2.6)	3 (1.5)

* Multiple occurrences of same SAE in an individual were only counted once
** SAEs with ≥2.5% incidence
*** SAEs occurring during or within 24 hours after an infusion and considered to be related to any study drug

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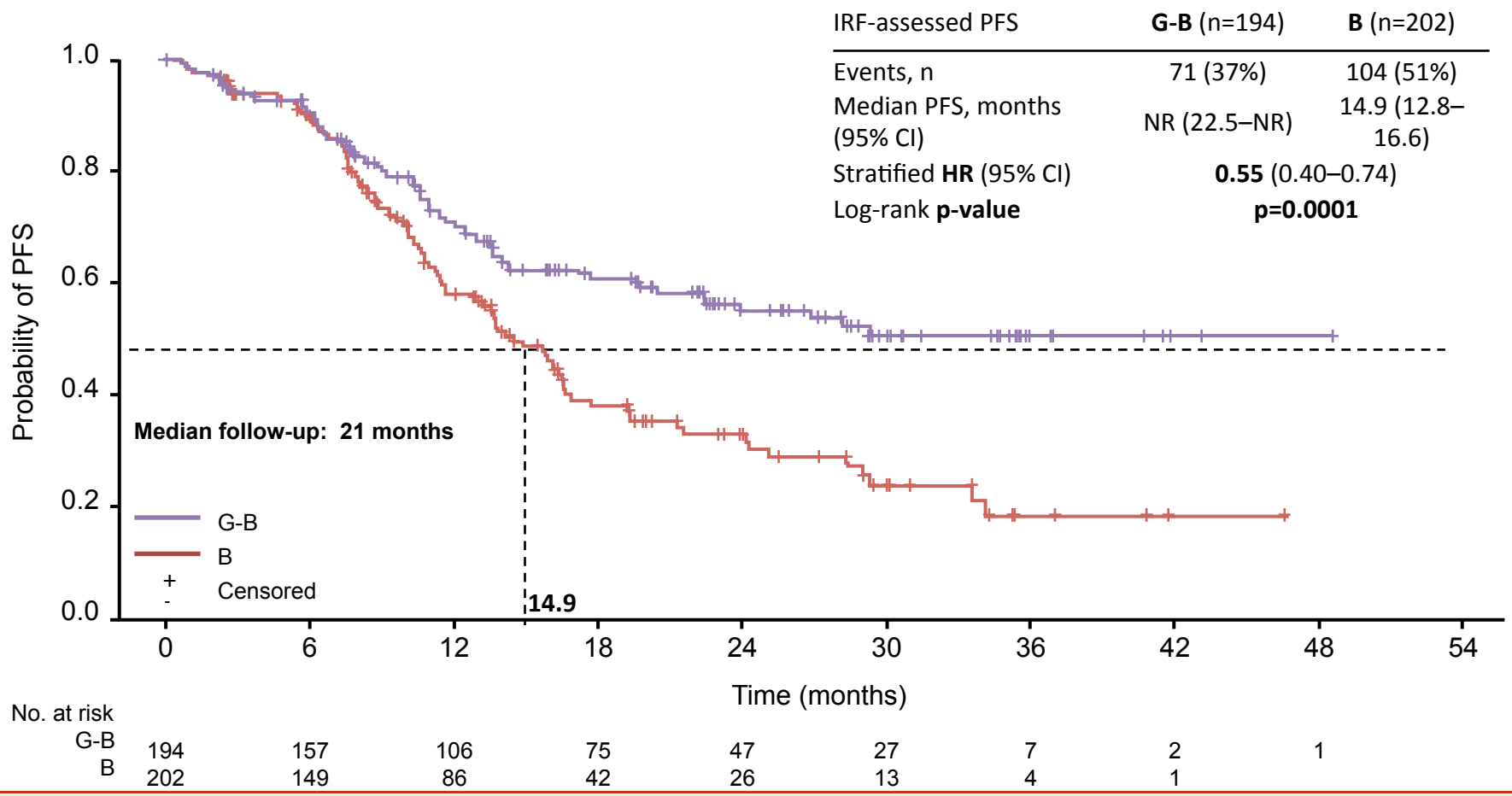
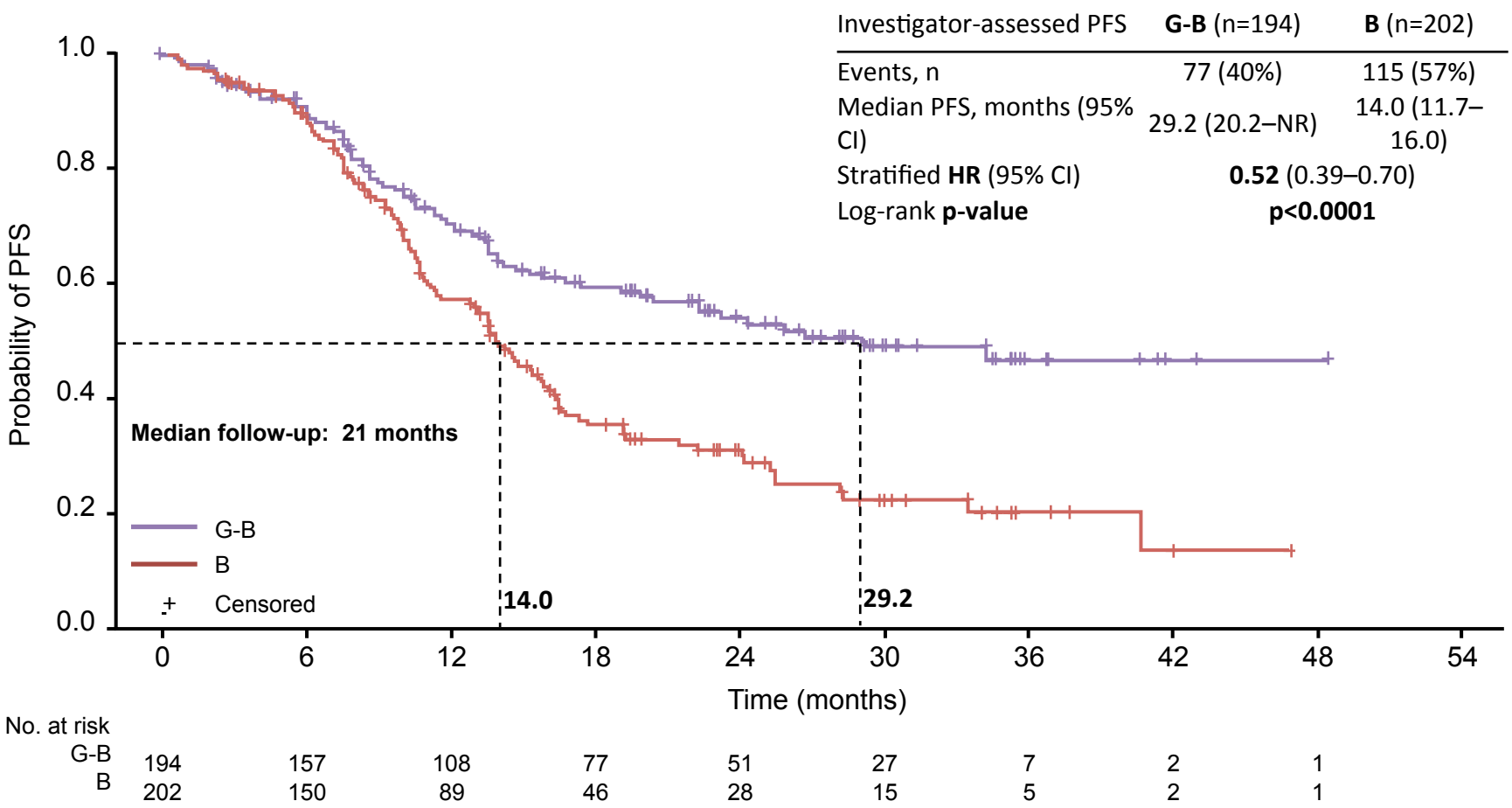
GADOLIN primary outcome: IRF-assessed PFS



- Il tempo di Induzione + Mantenimento è di 2.5 anni (30 mesi)
- Considerato il F-U med. di 21 mesi, il dato di PFS è maturo riguardo l'impatto dell'Induzione mentre è immaturo riguardo l'impatto del Mantenimento (solo il 25% dei pz ha completato il Mantenimento e la sua durata mediana di esposizione è di soli 10.8 mesi rispetto ai 24 mesi previsti di Mantenimento)
- La PFS di G-B supera di gran lunga l'assunzione statistica (miglioramento 43% , con PFS da 9 a 13 mesi) e anche la PFS di Benda supera quella storica (7-9 mesi)

GADOLIN: Investigator-assessed PFS



HR, hazard ratio; CI, confidence interval; NR, not reached.

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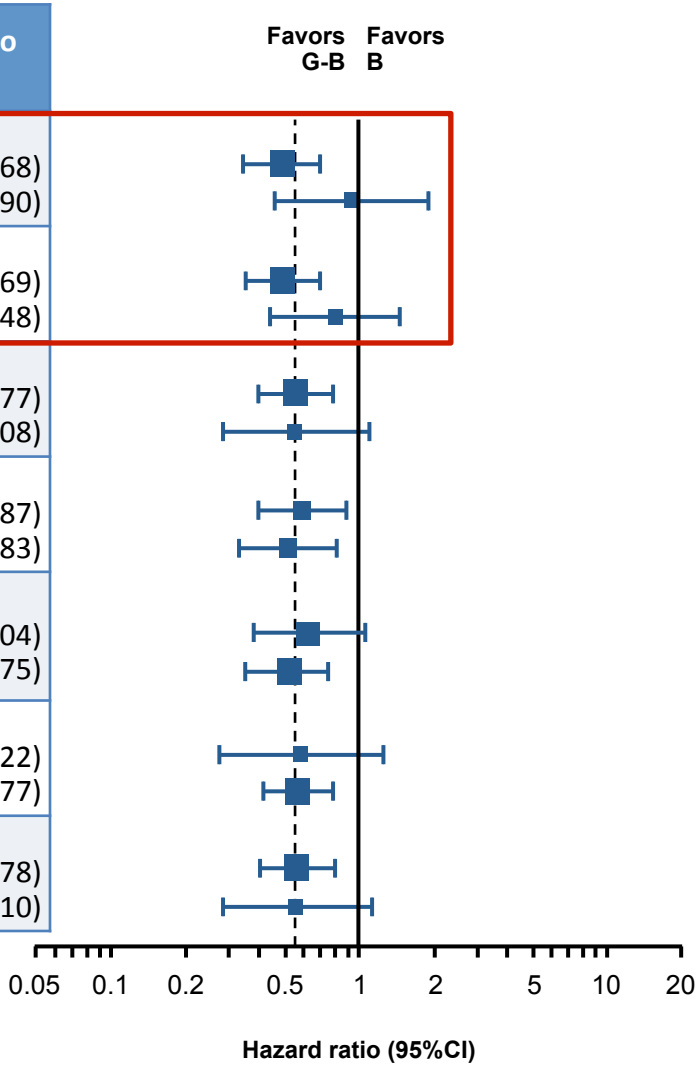
GADOLIN: PFS by sub-group

Subgroup	Total	G-B (n=194)		B (n=202)		Hazard ratio (95%CI)
	n	n	Events	n	Events	
Follicular lymphoma						
Yes (Vantaggio)	321	155	54	166	90	0.49 (0.35–0.68)
No	75	39	17	36	14	0.94 (0.46–1.90)
No. of prior therapies						
≤2 (Vantaggio sino 3L)	312	154	51	158	83	0.49 (0.34–0.69)
>2	84	40	20	44	21	0.80 (0.43–1.48)
Refractory type						
Rituximab + Chemother	313	156	57	157	82	0.55 (0.39–0.77)
Rituximab monotherapy	83	38	14	45	22	0.55 (0.28–1.08)
Sex						
Male	228	110	41	118	57	0.58 (0.39–0.87)
Female	168	84	30	84	47	0.52 (0.33–0.83)
Bulky disease at baseline						
Yes (>6 cm)	136	66	27	70	37	0.63 (0.38–1.04)
No (≤6 cm)	257	128	44	129	67	0.51 (0.35–0.75)
B symptoms at baseline						
Yes	58	30	12	28	16	0.57 (0.27–1.22)
No	335	163	59	172	87	0.55 (0.40–0.77)
Double refractory status						
Yes	311	147	55	164	87	0.56 (0.40–0.78)
No	85	47	16	38	17	0.55 (0.28–1.10)



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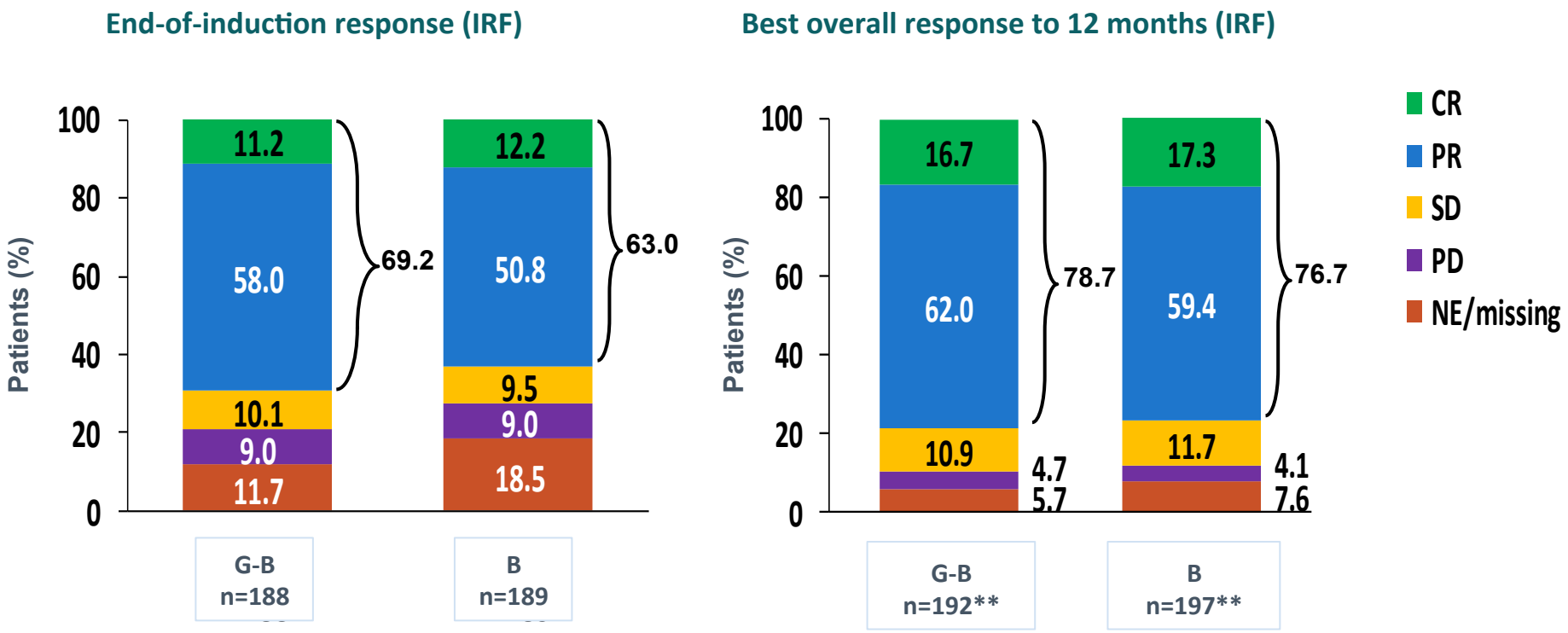
GADOLIN: Response to therapy



- 19 patients still in induction (G-B, n=6; B, n=13)*

* Patients ongoing in induction therapy are excluded from analysis. Patients with end of induction response assessment performed >60 days after last induction dose shown as missing.

** Best overall response excludes ongoing patients who have not yet reached the first response assessment.

IRF, independent radiology facility

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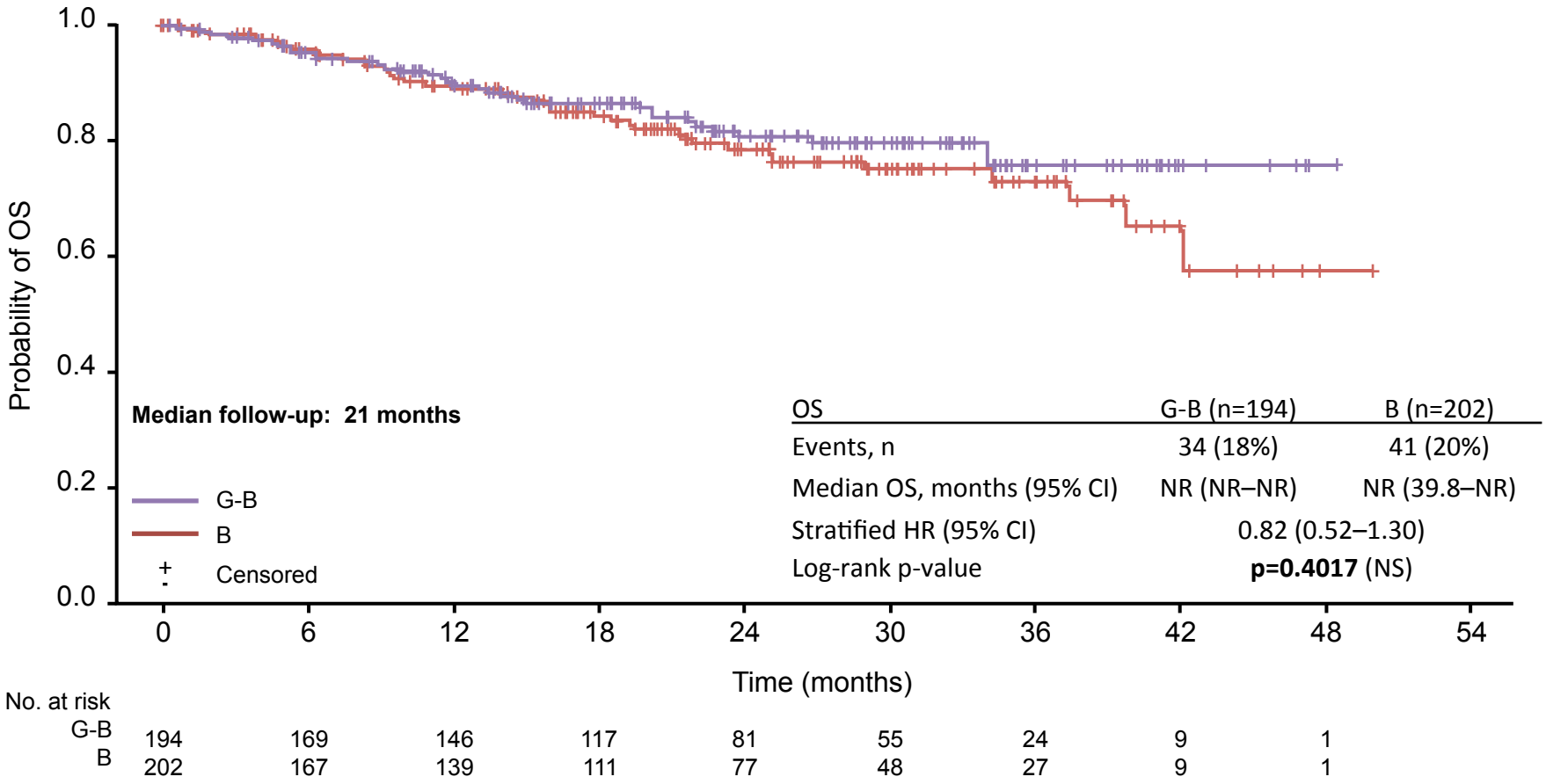
GADOLIN: Overall survival



OS	G-B (n=194)	B (n=202)
Events, n	34 (18%)	41 (20%)
Median OS, months (95% CI)	NR (NR–NR)	NR (39.8–NR)
Stratified HR (95% CI)	0.82 (0.52–1.30)	
Log-rank p-value	**p=0.4017** (NS)	

- 34 (18%) patients died in the G-B arm vs 41 (20%) in the control arm
  - In the G-B arm, 22 (65%) deaths were due to disease progression vs 29 (71%) deaths in the B arm

HR, hazard ratio; NR, not reached; NS, not significant

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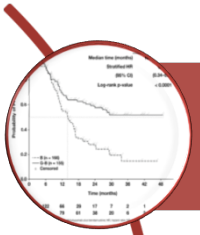
Summary

- Obinutuzumab plus bendamustine followed by obinutuzumab maintenance resulted in a statistically significant and clinically meaningful **PFS benefit** compared with bendamustine monotherapy
  - IRF-assessed median PFS: not reached in G-B arm vs 14.9 months in B arm (HR=0.55)
  - Consistent findings across the majority of subgroups tested
- No difference in response rates between treatment arms
  - **Bendamustine dose was higher in the B monotherapy arm** (120 mg/m2 vs 90 mg/m2)
- No new safety signals were observed
- **Obinutuzumab plus bendamustine followed by obinutuzumab maintenance represents** an **effective treatment option for patients** with relapsed/refractory iNHL who are **refractory to rituximab**

L Sehn et al, Poster LB691 presented at 20th EHA Congress, 11–14 June 2015, Vienna, Austria

Clinical Value EFFICACY in FL



52% risk reduction of progression

G-B
29.2
B 13.7

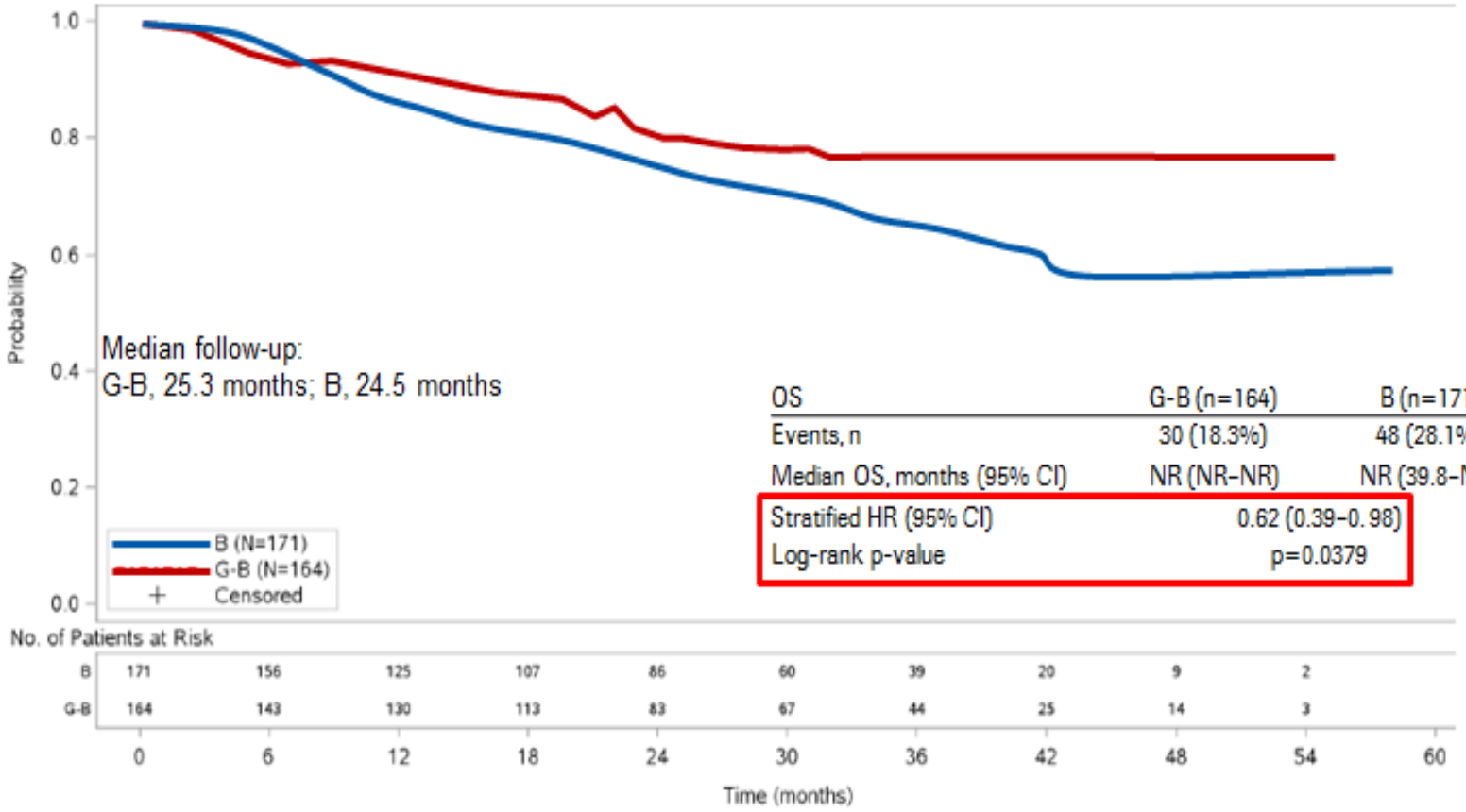
More than doubling mPFS

BREAKING NEWS

Overall Survival in FL

GADOLIN: Overall Survival (FL)

Based on follow-up analysis (standard 90-day safety update for FDA)



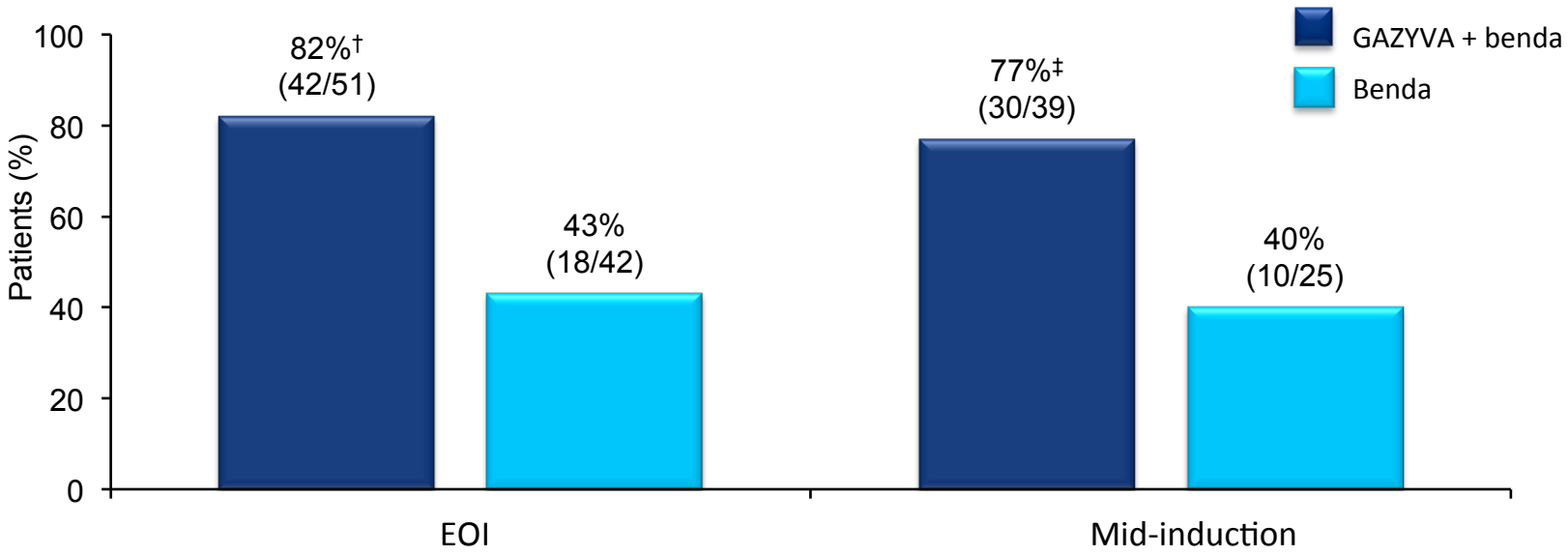
OS	G-B (n=164)	B (n=171)
Events, n	30 (18.3%)	48 (28.1%)
Median OS, months (95% CI)	NR (NR–NR)	NR (39.8–NR)
Stratified HR (95% CI)	0.62 (0.39–0.98)	
Log-rank p-value	p=0.0379	

Data cut-off date (CCOD): 1st May 2015 – unplanned analysis

FL

GADOLIN: A greater proportion of patients in the GAZYVARO + benda arm achieved MRD*-negative status

Patients achieving MRD-negative status at EOI and at mid-induction by treatment arm



GAZYVA significantly contributes to depth of response to benda, compared with benda alone, during induction

These MRD data may help to inform the apparent disconnect between response at EOI and the near doubling of PFS seen with GAZYVA + benda vs benda in the primary analysis

*MRD was analysed by t(14;18) and/or Ig variable domain allele-specific RQ-PCR in patients with a clonal marker detectable at diagnosis in PB or BM by consensus PCR and defined as negative if RQ-PCR and subsequent nested PCR produced a negative result

†$p<0.0001$ vs benda arm

‡$p=0.0029$ vs benda arm

Benda, bendamustine; BM, bone marrow; EOI, end-of-induction; PB, peripheral blood; MRD, minimal residual disease; RQ-PCR, real-time quantitative-polymerase chain reaction