6. Hematolojik Onkoloji Kongresi

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1997

Nüks/dirençli foliküler lenfomada obinutuzumab

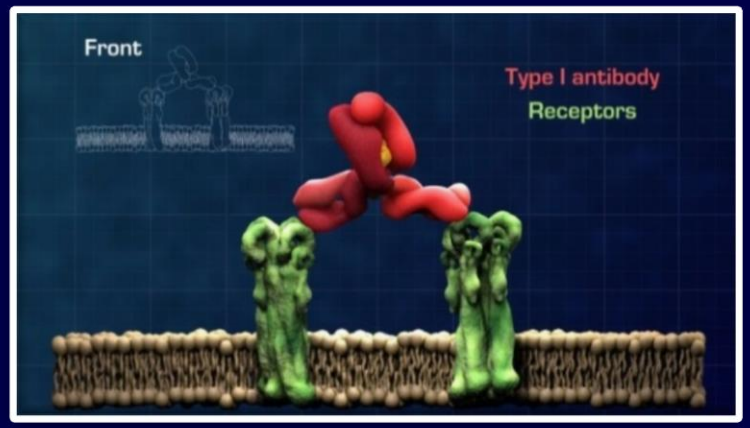
Dr. Emre TEKGÜNDÜZ
Maltepe Üniversitesi Tıp Fakültesi, İç Hastalıkları AD-Hematoloji BD
Memorial Bahçelievler Hastanesi Hematoloji ve HKHN Merkezi
20.09.2019-KKTC

Çıkar çatışması beyanı

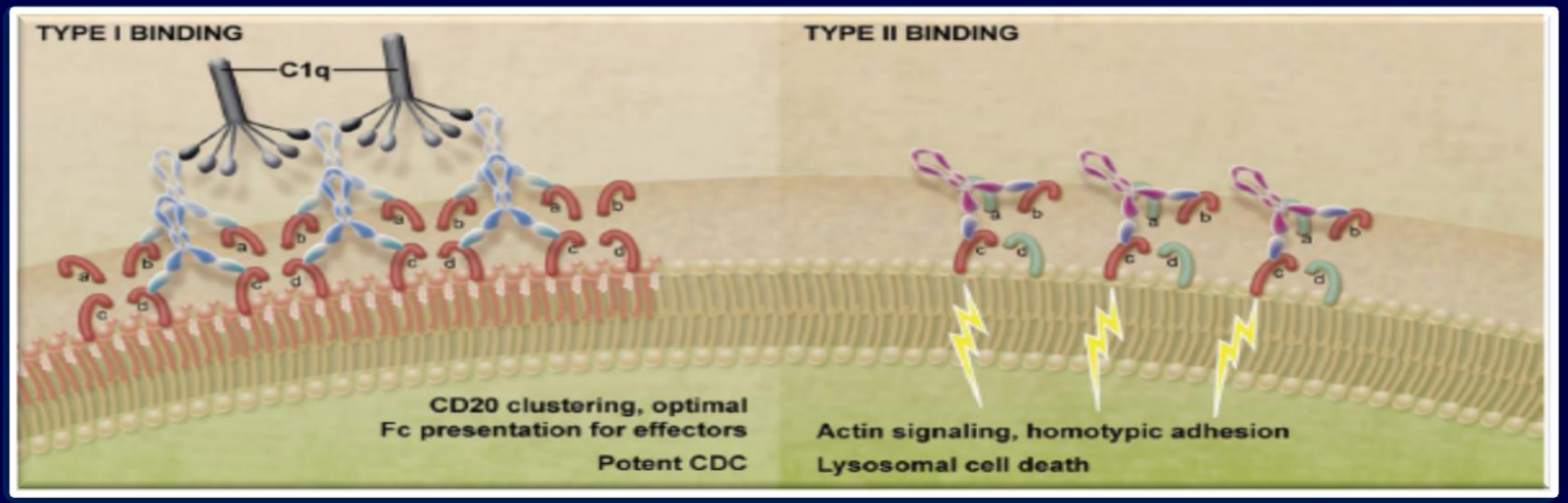
- Danışma kurulu: Amgen, Sanofi, Roche, Jazz, Celgene, Terumo
- Ücretli konuşma: Amgen, Roche, Sanofi, Jazz, BMS, Novartis, Astellas
- Bilimsel araştırma desteği: Alexion

Tip I ve Tip II Antikorlar

Tip I ve Tip II CD20 bağlanma modeli



Tip I:
inter-tetramerik bağlanma
ör: rituksimab



Tip II:
intra-tetramerik bağlanma
ör: obinutuzumab

Niederfellner G, *et al. Blood* 2011; 118:358–367. Cragg MS. *Blood* 2011; 118:219–220

Tip II Antikor : Obinutuzumab

Tip II
anti-CD20 mAb[1,2]

Artmış direkt hücre ölümü [2]

Gliko-işlenmiş
Fc bölgesi[2]

Artmış antikor bağımlı hücresel sitotoksisite(ADCC) ve fagositoz (ADCP)[2,3]
Reseptör afinitesi X10
Etki X100

1. Niederfellner G, *et al. Blood* 2011; 118:358–367
2. Mössner E, *et al. Blood* 2010; 115:4393–4402
3. Herter S, *et al. Blood* 2010; 116:Abstract 3925.

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Overall Survival Benefit in Patients With Rituximab-Refractory Indolent Non-Hodgkin Lymphoma Who Received Obinutuzumab Plus Bendamustine Induction and Obinutuzumab Maintenance in the GADOLIN Study

Bruce D. Cheson, Neil Chua, Jiri Mayer, Greg Dueck, Marek Trněný, Kamal Bouabdallah, Nathan Fowler, Vincent Delwail, Oliver Press,† Gilles Salles, John G. Gribben, Anne Lennard, Pieternella J. Lugtenburg, Günter Fingerle-Rowson, Federico Mattiello, Andrea Knapp, and Laurie H. Sehn

J Clin Oncol 2018; 36: 2259

Açık etiketli, randomize, faz-3 çalışma
14 ülke, 83 merkez

- ✓≥ 18 yaş
- ✓$CD20^+$ R dirençli iNHL
- ✓ECOG 0-2
- ✓BT: ≥ 1.5 cm. uzun çapı olan en az bir lezyon
- ✓Lenfoma için tedavi almış olmak (en fazla 4 KT içeren rejim)

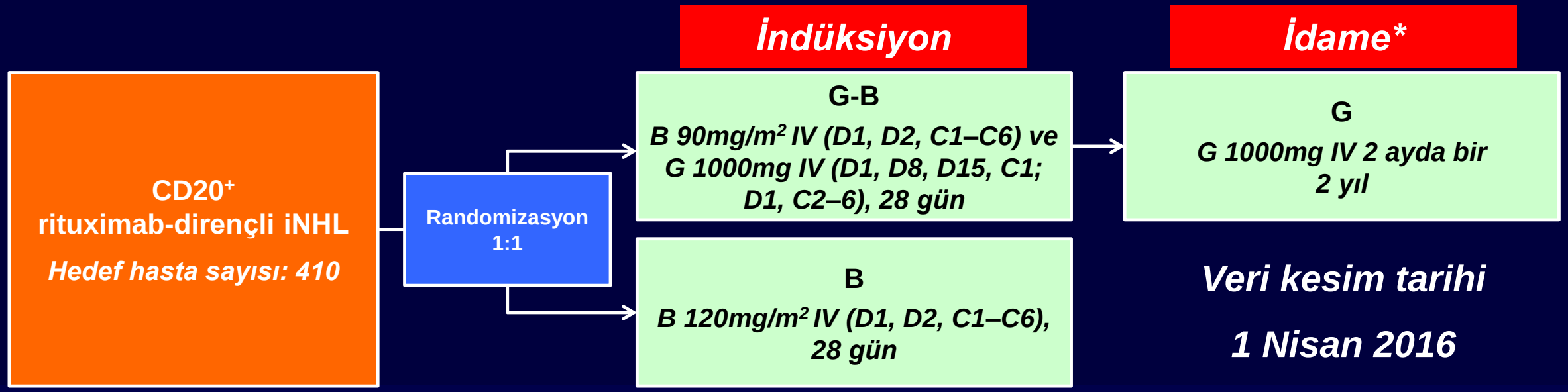
Dışlama kriterleri

- ✓Son 2 yılda B tedavisi
- ✓Daha önce G kullanımı
- ✓Ciddi kardiyopulmoner hastalık
- ✓Aktif enfeksiyon
- ✓MSS lenfoması

Direnç tanımı

- ✓R içeren monoterapi ya da kombinasyon kemoterapisine yanıtsız ya da tedavi altında progresyon
- ✓İndüksiyon/idame R son dozundan sonra ≤ 6 ay içinde progresyon

Çalışma tasarımı



End Point	ITT Population, No. (%)		Patients With FL, No. (%)	
	G-B	B Monotherapy	G-B	B Monotherapy
No. of patients	204	209	164	171
Median observation time*, months (range)	34.0 (0.4-65.9)	30.0 (0.0-65.1)	32.6 (0.4-65.9)	29.3 (0.0-65.1)
PFS assessed by investigator				
Events	115 (56.4)	146 (69.9)	93 (56.7)	125 (73.1)
Median (95% CL), months	25.8 (19.5, 41.1)	14.1 (12.6, 16.0)	25.3 (17.4, 36.0)	14.0 (11.3, 15.3)
HR (95% CL, stratified† log-rank *P* value)	0.57 (0.44, 0.73); $P < .001$		0.52 (0.39, 0.69); $P < .001$	
OS				
Events	52 (25.5)	73 (34.9)	39 (23.8)	64 (37.4)
Median (95% CL), months	NE	NE (48.2, NE)	NE	53.9 (40.9, NE)
HR (95% CL, stratified† log-rank *P* value)	0.67 (0.47, 0.96); $P = .0269$		0.58 (0.39, 0.86); $P = .0061$	
Time to start of new antilymphoma treatment				
Events	100 (49.0)	139 (66.5)	82 (50.0)	121 (70.8)
Median (95% CL), months	40.8 (28.3, NE)	19.4 (16.2, 24.3)	33.6 (25.3, NE)	18.0 (15.4, 21.3)
HR (95% CL, stratified analysis)‡	0.59 (0.45, 0.77)		0.57 (0.43, 0.75)	
End of induction response (IRC)§				
Overall response rate (complete or partial response)	136 of 204 (66.7)	134 of 208 (64.4)	111 of 164 (67.7)	111 of 170 (65.3)
Percentage difference (95% CL, stratified *P* value by Cochran-Mantel-Haenszel test†)	2.24 (−7.20, 11.69); $P = .83$		2.39 (−8.07, 12.85); $P = .70$	

Abbreviations: B, bendamustine; CL, confidence limit; FL, follicular lymphoma; G, obinutuzumab; HR, hazard ratio; IRC, independent review committee; ITT, intention-to-treat; NE, not estimated; OS, overall survival; PFS, progression-free survival.

*Time from random assignment date until last date known to be alive.

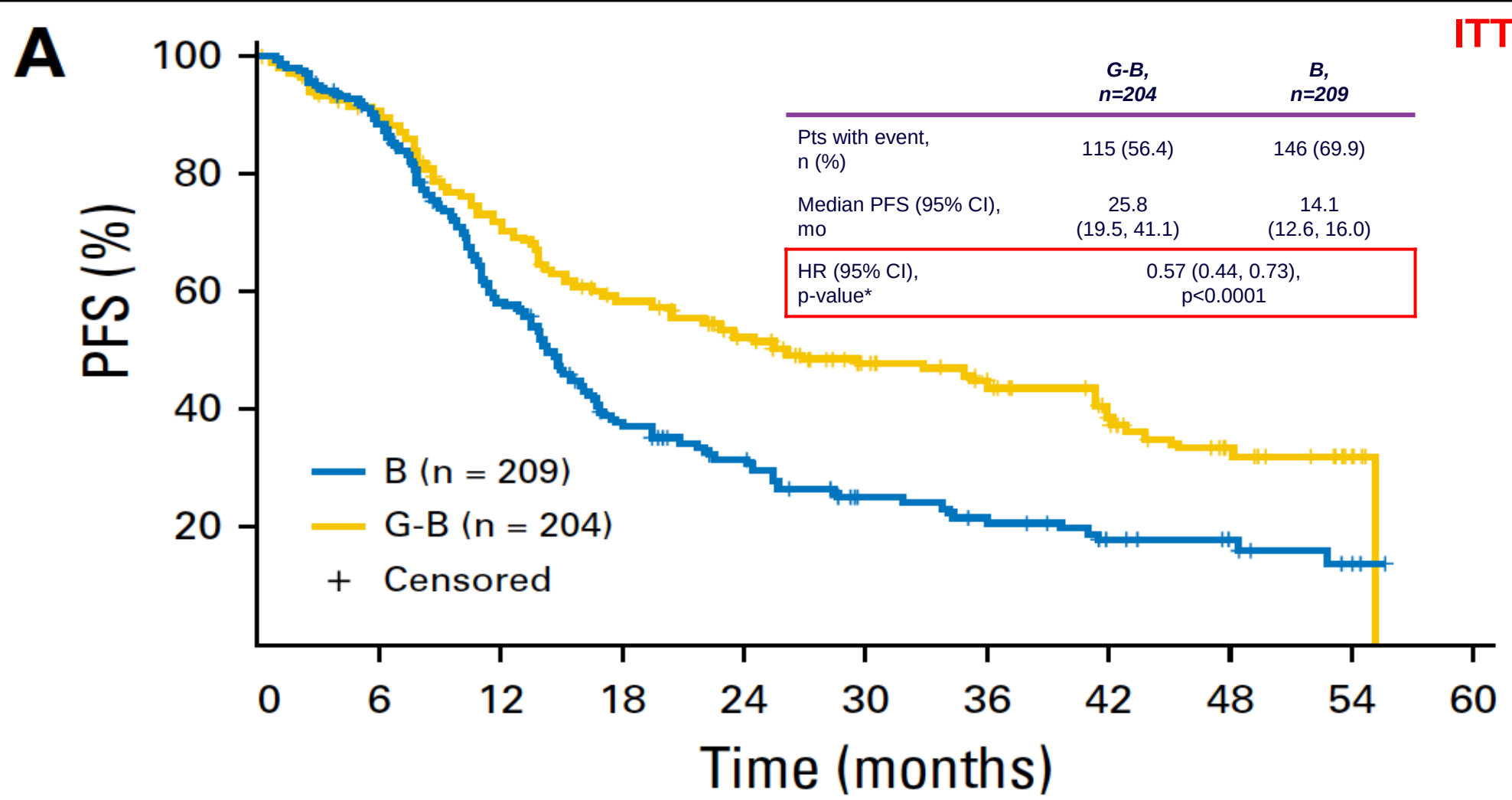
†Stratification factors were indolent non-Hodgkin lymphoma subtype (follicular *v* other; ITT population only), refractory type (rituximab monotherapy *v* rituximab plus chemotherapy), and prior therapies (two or fewer *v* more than two).

‡Exploratory analyses only; no *P* values calculated.

§Patients who had an end-of-induction response assessment or withdrew prematurely.

J Clin Oncol 2018; 36: 2259

ITT



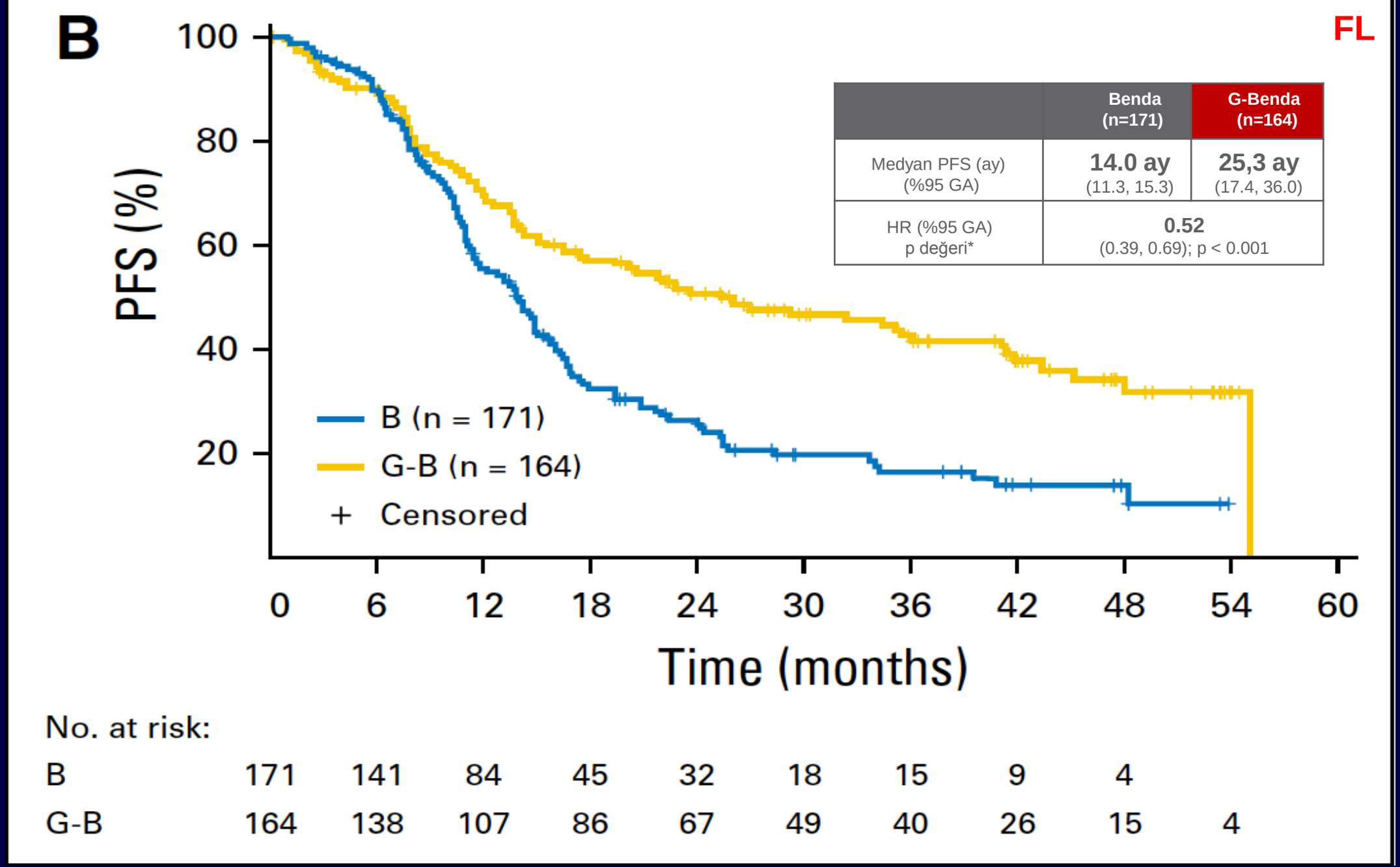
	G-B, n=204	B, n=209
Pts with event, n (%)	115 (56.4)	146 (69.9)
Median PFS (95% CI), mo	25.8 (19.5, 41.1)	14.1 (12.6, 16.0)
HR (95% CI), p-value*	0.57 (0.44, 0.73), p<0.0001	

No. at risk:

B	209	170	106	63	47	29	23	16	10	2
G-B	204	175	135	109	88	64	50	33	21	5

J Clin Oncol 2018; 36: 2259

FL

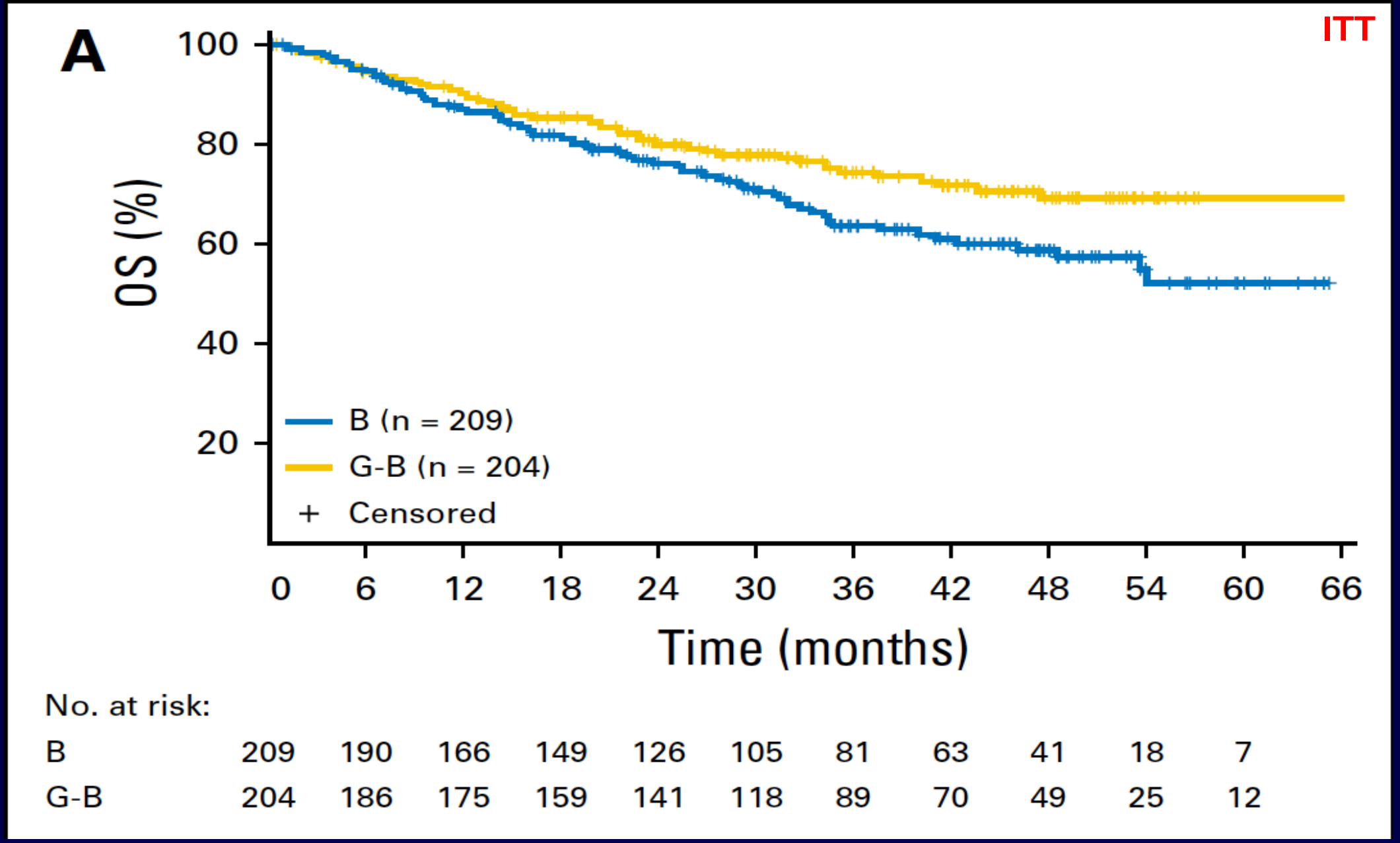


	Benda (n=171)	G-Benda (n=164)
Medyan PFS (ay) (%95 GA)	**14.0 ay** (11.3, 15.3)	**25,3 ay** (17.4, 36.0)
HR (%95 GA) p değeri*	**0.52** (0.39, 0.69); p < 0.001	

No. at risk:

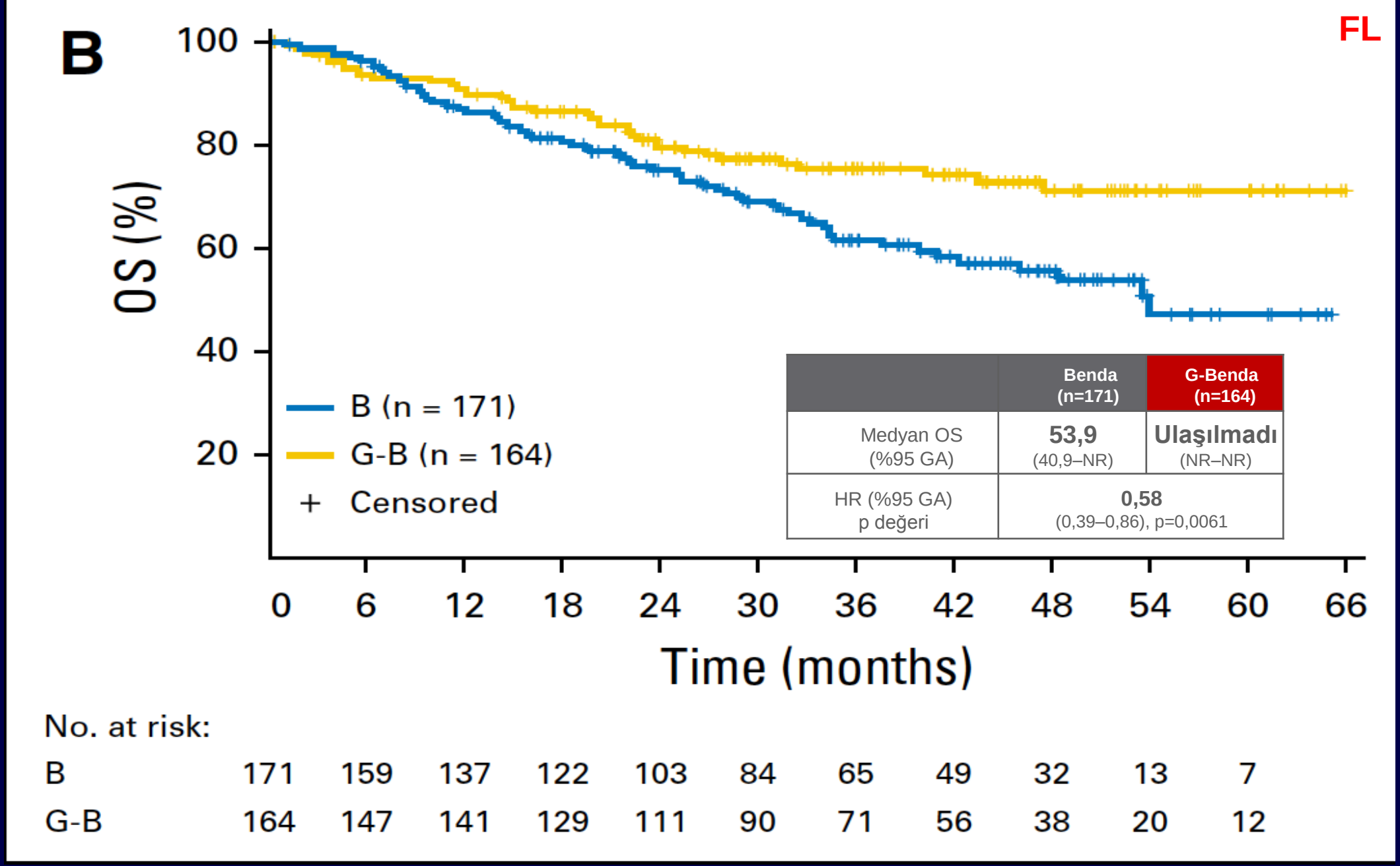
B	171	141	84	45	32	18	15	9	4	
G-B	164	138	107	86	67	49	40	26	15	4

J Clin Oncol 2018; 36: 2259



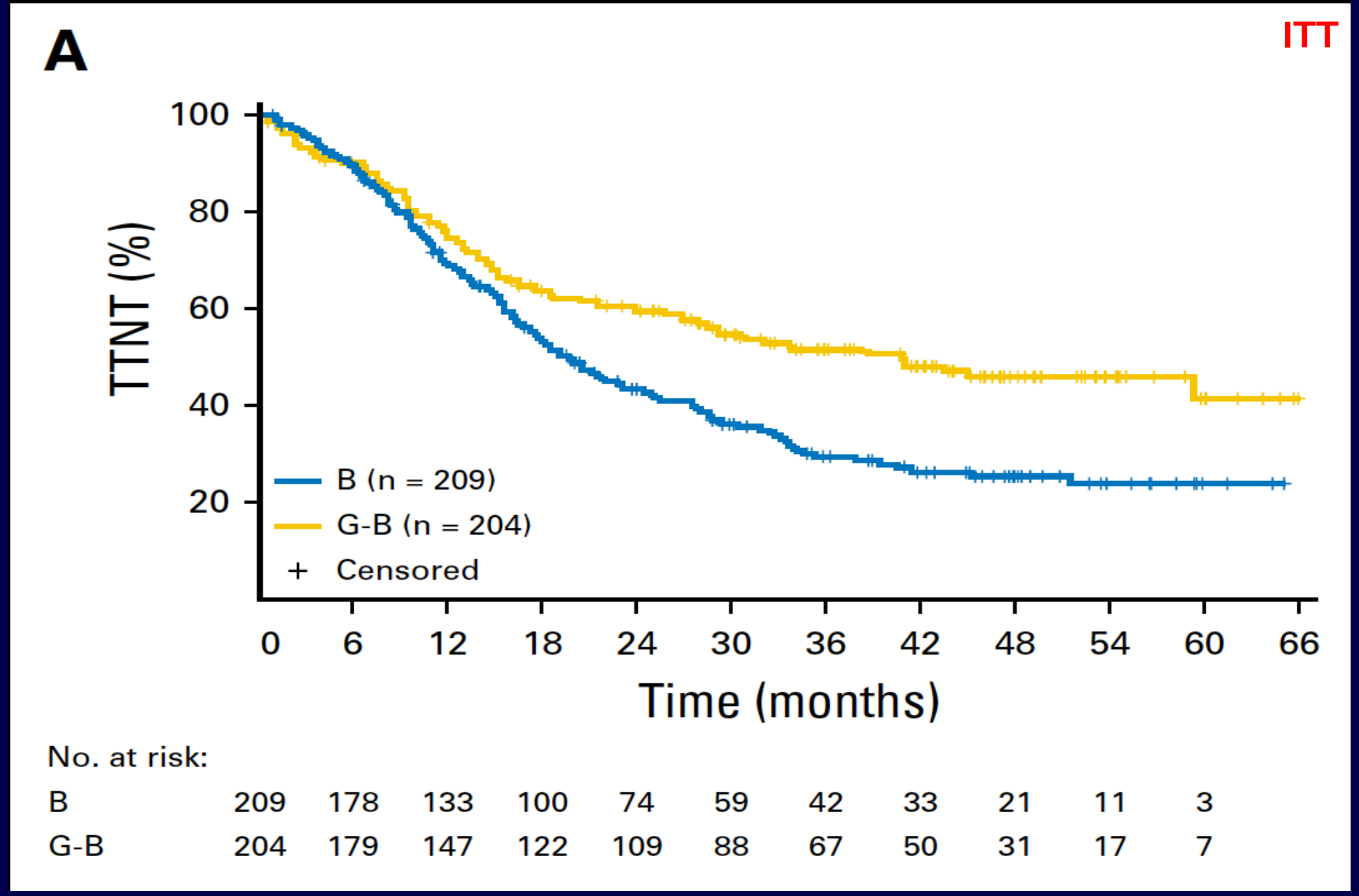
J Clin Oncol 2018; 36: 2259

FL



	Benda (n=171)	G-Benda (n=164)
Medyan OS (%95 GA)	**53,9** (40,9–NR)	**Ulaşılmadı** (NR–NR)
HR (%95 GA) p değeri	**0,58** (0,39–0,86), p=0,0061	

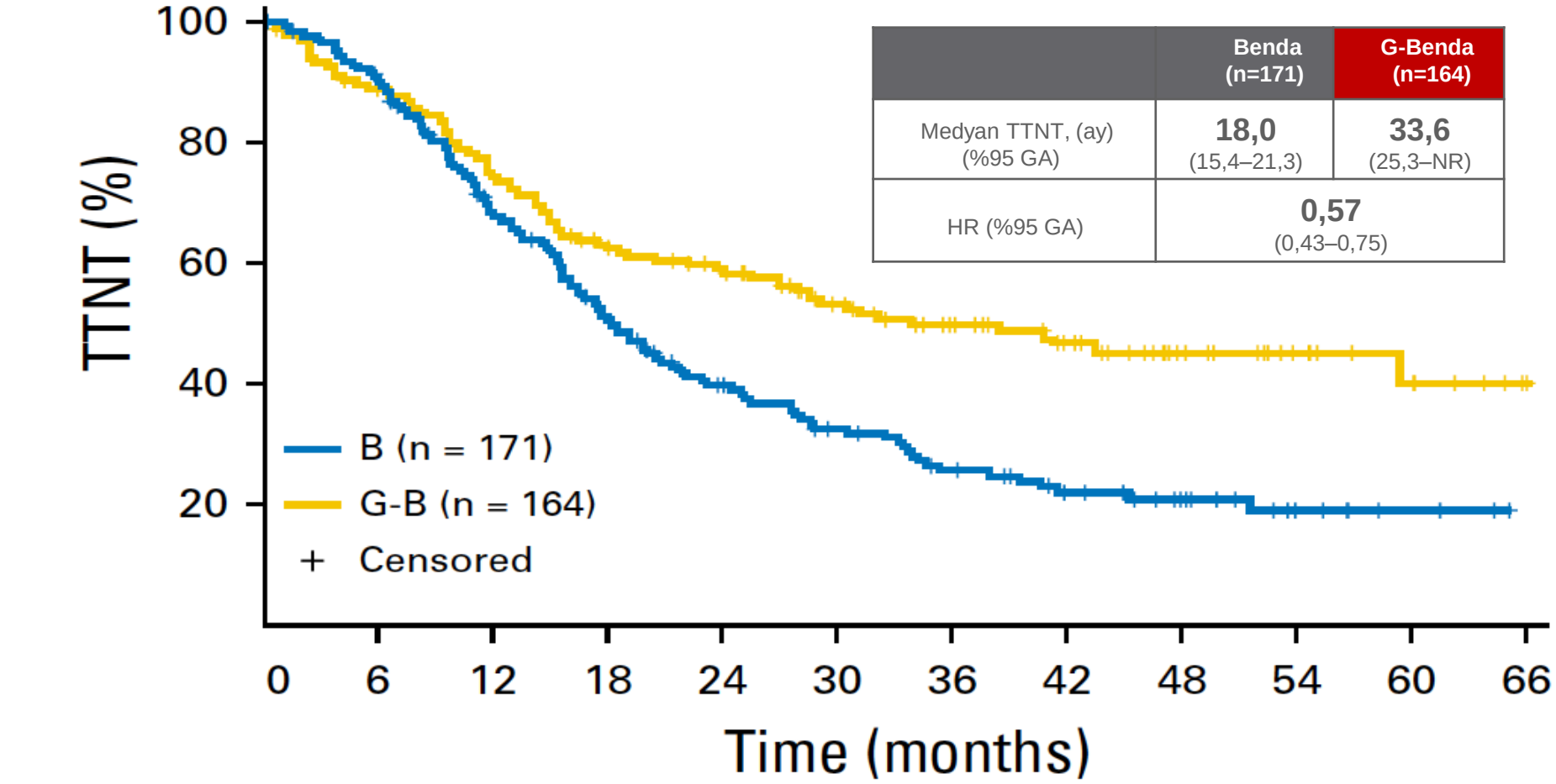
J Clin Oncol 2018; 36: 2259



J Clin Oncol 2018; 36: 2259

FL

B



	Benda (n=171)	G-Benda (n=164)
Medyan TTNT, (ay) (%95 GA)	**18,0** (15,4–21,3)	**33,6** (25,3–NR)
HR (%95 GA)	**0,57** (0,43–0,75)	

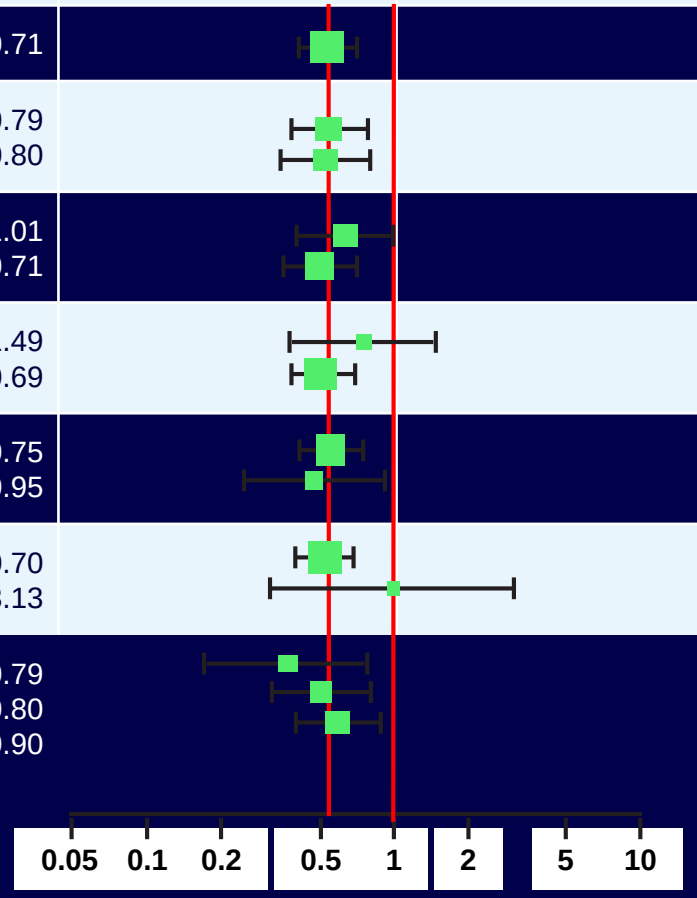
No. at risk:

B	171	147	107	78	55	43	31	22	15	7	3
G-B	164	141	117	95	84	66	51	37	22	13	7

J Clin Oncol 2018; 36: 2259

FL: PFS

			G-B			B					
Baseline factors		Total, N	n	Events	1-year KM rate	n	Events	1-year KM rate	HR*	95% Wald CI	Favors G-B / Favors B
All patients		335	164	93	68.766	171	125	55.386	0.54	0.41, 0.71	
Sex	Male Female	189 146	91 73	53 40	70.455 66.828	98 73	69 56	57.145 53.183	0.55 0.53	0.38, 0.79 0.35, 0.80	
Bulky disease at baseline (≥6cm)	Yes No	113 220	53 111	32 61	68.116 69.061	60 109	43 82	55.336 55.503	0.63 0.50	0.40, 1.01 0.36, 0.71	
B symptoms (≥1) at baseline	Yes No	49 283	21 142	14 79	66.667 68.841	28 141	20 104	55.632 55.739	0.75 0.51	0.38, 1.49 0.38, 0.69	
Double-refractory status	Yes No	266 69	129 35	77 16	66.922 75.758	137 34	105 20	51.455 74.121	0.56 0.48	0.41, 0.75 0.25, 0.95	
ECOG PS at baseline	0–1 2	318 15	156 8	87 6	70.404 37.500	162 7	118 6	55.928 51.429	0.53 1.00	0.40, 0.70 0.32, 3.13	
Refractory to	R monotherapy R-chemo induction R-maintenance after (immuno-) chemotherapy induction	67 122 142	25 57 79	10 35 47	77.579 71.125 65.050	42 65 63	68.147 51.790 52.205	70.427 55.923 53.503	0.37 0.51 0.60	0.17, 0.79 0.33, 0.80 0.40, 0.90	



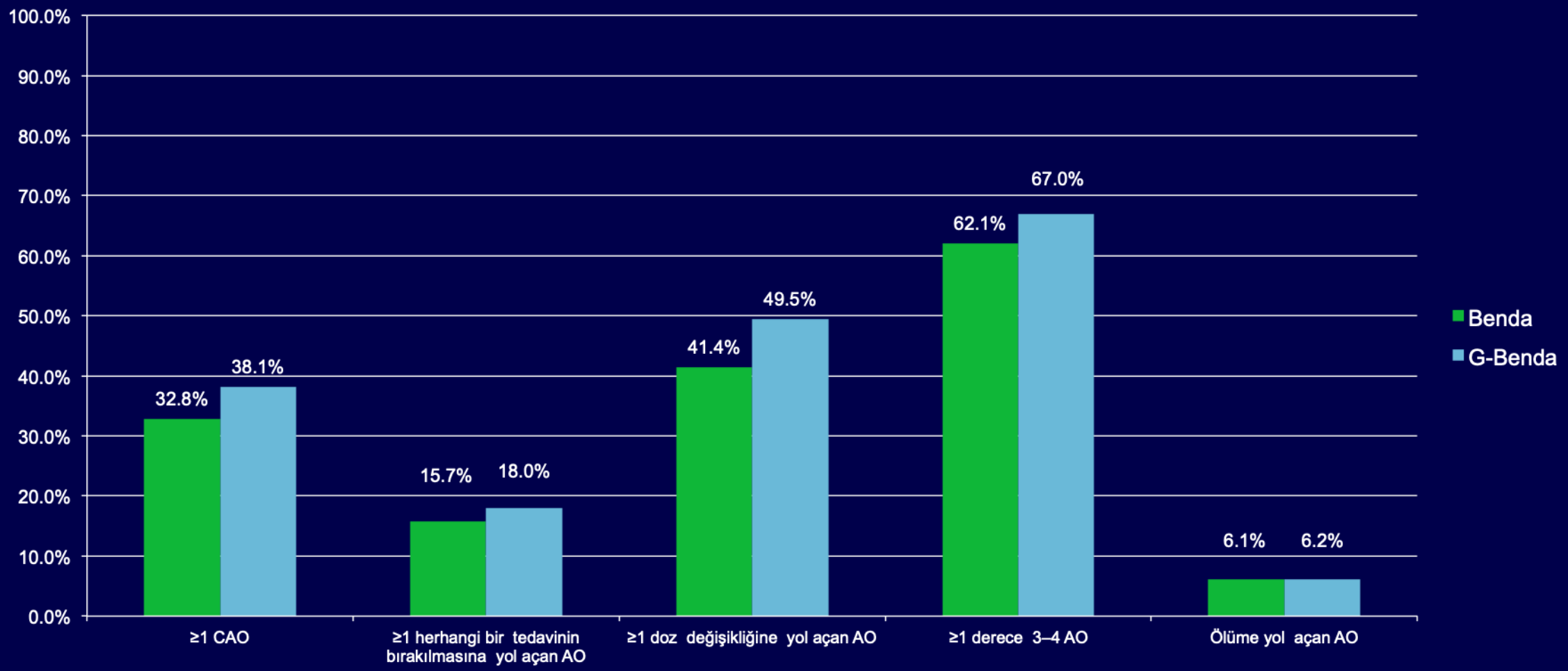
Yan etkiler

Table 3. AEs by Treatment Phase (Safety Population)

AE	Overall Study*, No. (%)		Induction, No. (%)		Maintenance, No. (%)	Post-Treatment Follow-Up†, No. (%)		
							After Induction	
	G-B	B Mono	G-B	B Mono	G	After Maintenance	After G-B	After B Mono
No. of patients	204	203	204	205	158	146	42	191
No. of events	3,187	2,565	2,219	2,242	777	177	14	334
Patients with at least one								
AE	202 (99.0)	200 (98.5)	199 (97.5)	201 (98.0)	126 (79.7)	63 (43.2)	5 (11.9)	104 (54.5)
Grade 3-5 AE	148 (72.5)	133 (65.5)	113 (55.4)	108 (52.7)	53 (33.5)	38 (26.0)	5 (11.9)	50 (26.2)
Grade 5 AE (fatal)	16 (7.8)‡	13 (6.4)‡	3 (1.5)‡	5 (2.4)‡	1 (0.6)‡	9 (6.2)	3 (7.1)	8 (4.2)
SAE	89 (43.6)	75 (36.9)	58 (28.4)	45 (22.0)	26 (16.5)	25 (17.1)	5 (11.9)	36 (18.8)
AE that led to withdrawal of any treatment	41 (20.1)	35 (17.2)	29 (14.2)	35 (17.1)	13 (8.2)	0	0	0
AE that led to any study drug modification	102 (50.0)	86 (42.4)	86 (42.2)	87 (42.4)	32 (20.3)	0	0	0

J Clin Oncol 2018; 36: 2259

Benzer Güvenlilik Profili (iNHL)

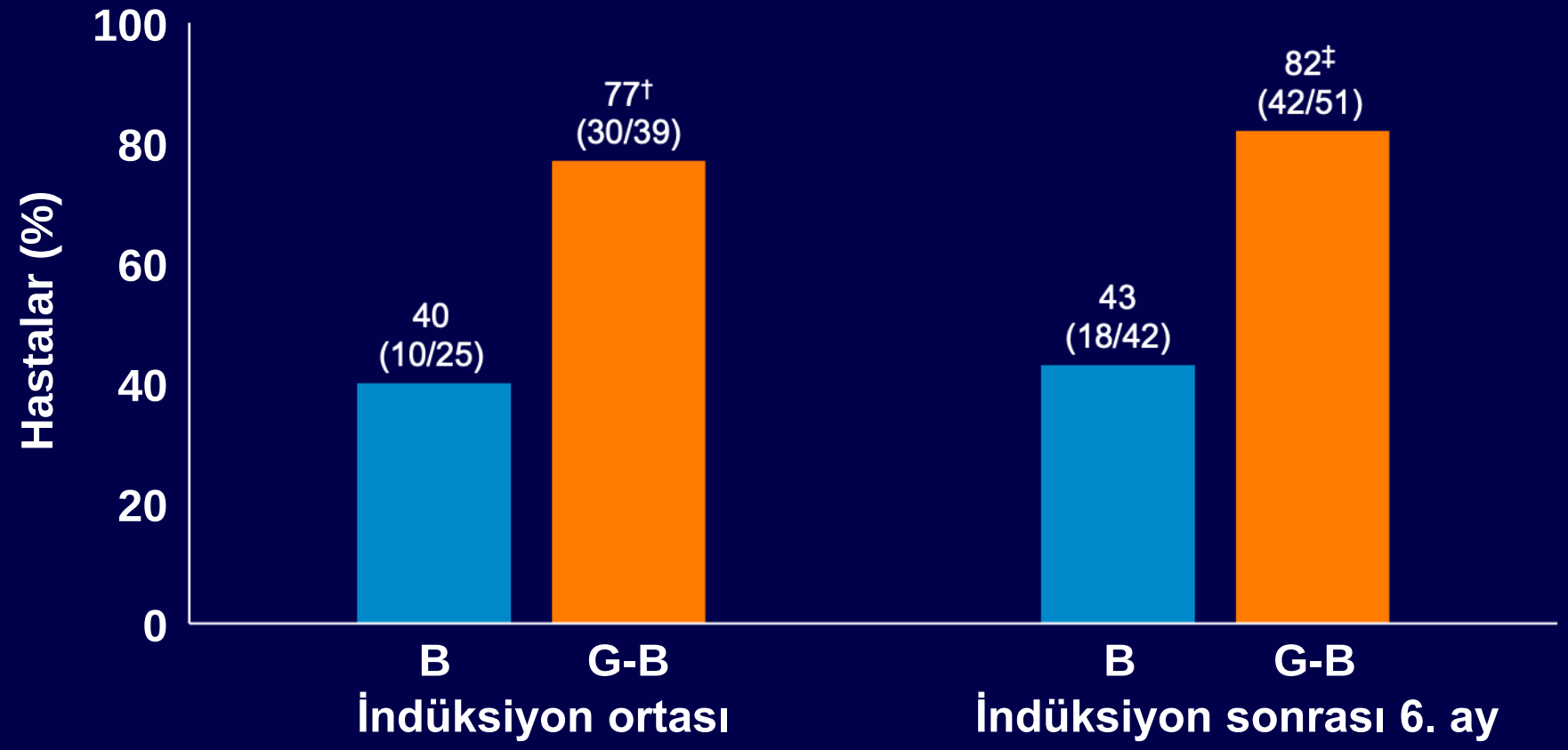


AO, advers olay; Benda, bendamustin; iNHL, indolent Hodgkin dışı lenfoma

Sehn L, et al. Lancet Oncol 2016;17:1081-93; Sehn L, et al. ASCO May/June 2015. Oral presentation
Sehn L, et al. EHA June 2015. Poster presentation; Cheson B, et al. ICML June 2015. Oral presentation

FL: MRD-negatif yanıt

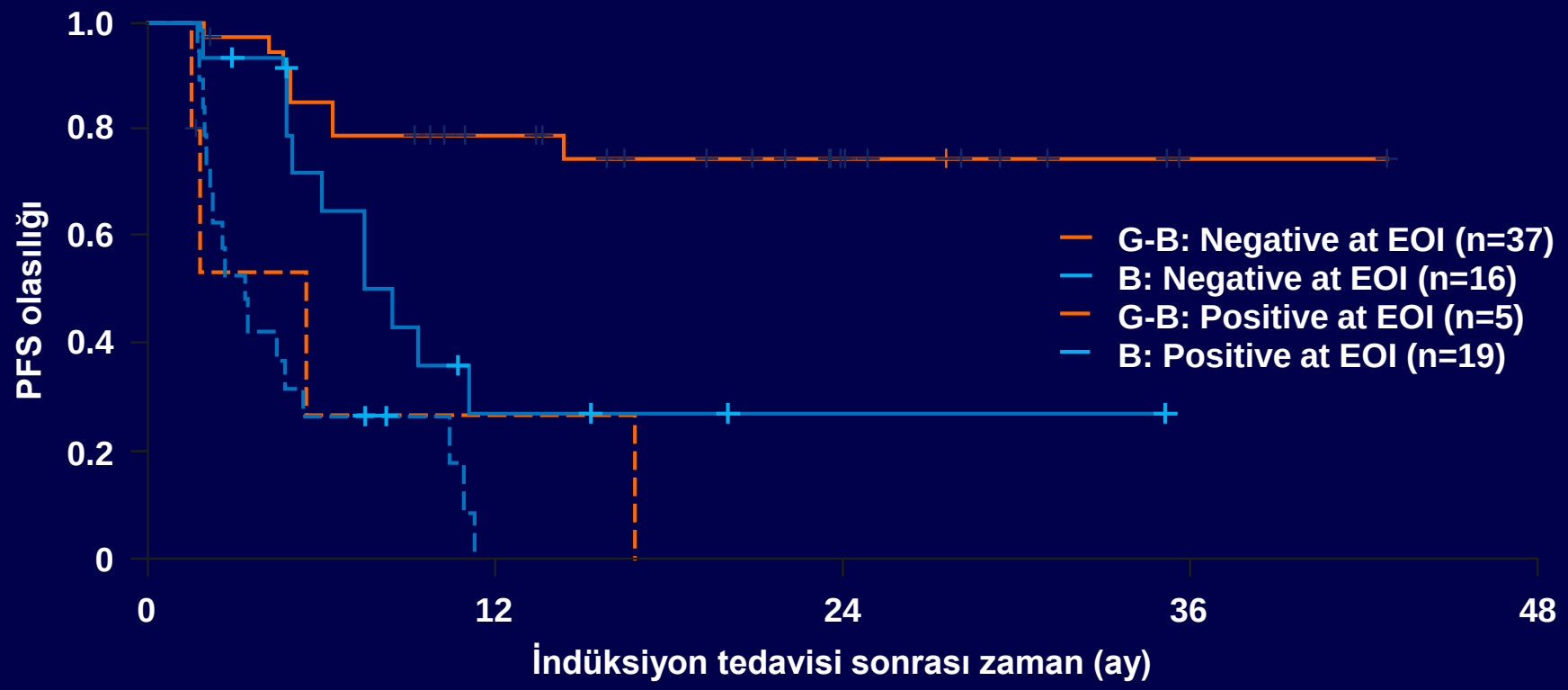
Periferik kanda indüksiyon ortası (5. siklus 1. gün) ve indüksiyon bitiminden 6 ay sonra MRD analizi *[1]



*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

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

FL: MRD-PFS İlişkisi



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

GADOLIN Çalışma Özeti

G+Benda ile Benda'ya kıyasla

- ✓ **Daha Uzun Genel Sağkalım**
- ✓ **Daha Uzun Progresyonsuz Sağkalım (+11,3 ay)**
- ✓ **Daha Uzun Bir Sonraki Tedaviye Kadar Geçen Süre (+15,6 ay)**

GAZYVA Foliküler Lenfoma Endikasyonu

- **Rituksimab ile birlikte kemoterapi uygulanmış foliküler lenfoma olgularında yanıtsızlık veya nüks gelişmesi durumunda bendamustin ile kombine kullanımda endikedir (yalnızca indüksiyonda)**

- **İlk nükste kullanılabilir.**

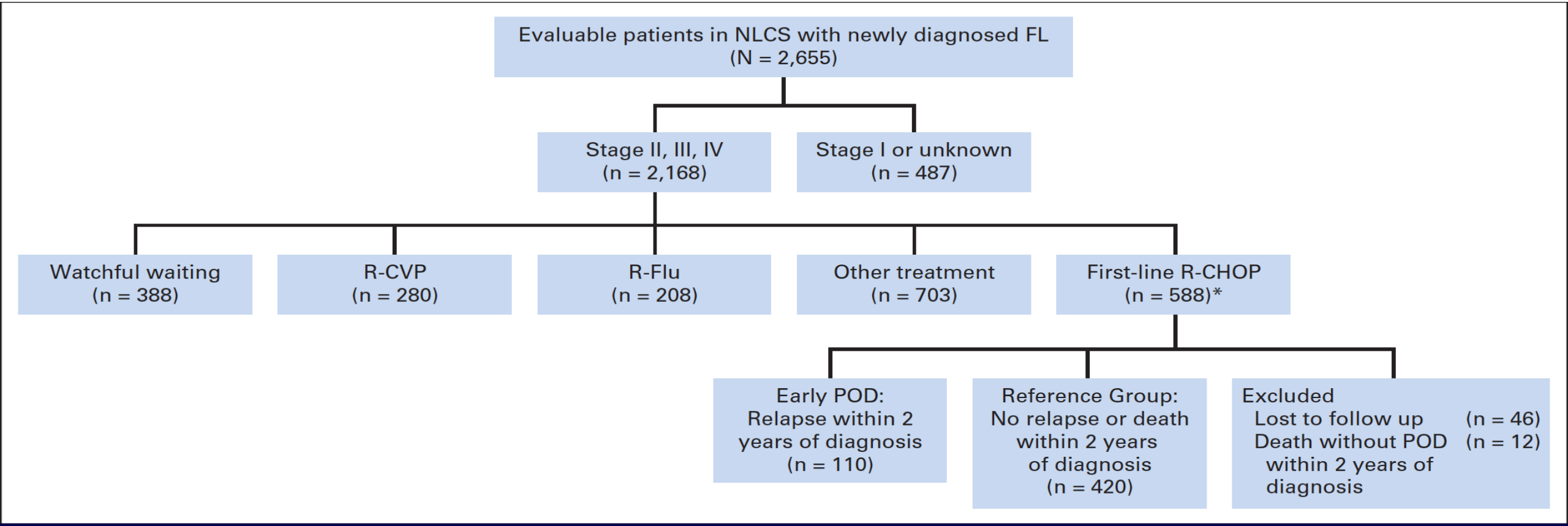
GAZYVA Premedikasyon

Premedikasyon	1. SİKLUS: 1 ve 2. günler	SONRAKİ İNFÜZYONLAR		
	Tüm hastalar	Herhangi bir IRR semptomu görülmeyen hastalar	Önceki infüzyonla Grade 1-2 (hafif-orta şiddette) IRR görülen hastalar	Önceki infüzyonla Grade 3 (şiddetli) IRR görülen ya da yeni tedavi öncesi lenfosit sayısı bir >25x10/l olan hastalar
İNFÜZYONDAN 60 DAKİKA ÖNCESİNE KADAR **İntravenöz kortikosteroid** (100 mg prednizon/prednizolon ya da 20 mg deksametazon ya da 80 mg metilprednizolon)	●			●
İNFÜZYONDAN 30 DAKİKA ÖNCESİNE KADAR **Antihistaminik ilaç** (50 mg difenhidramin)	●		●	●
İNFÜZYONDAN 30 DAKİKA ÖNCESİNE KADAR **Analjezik/Antipiretik** (1000 mg asetaminofen/parasetamol)	●	●	●	●

JOURNAL OF CLINICAL ONCOLOGY

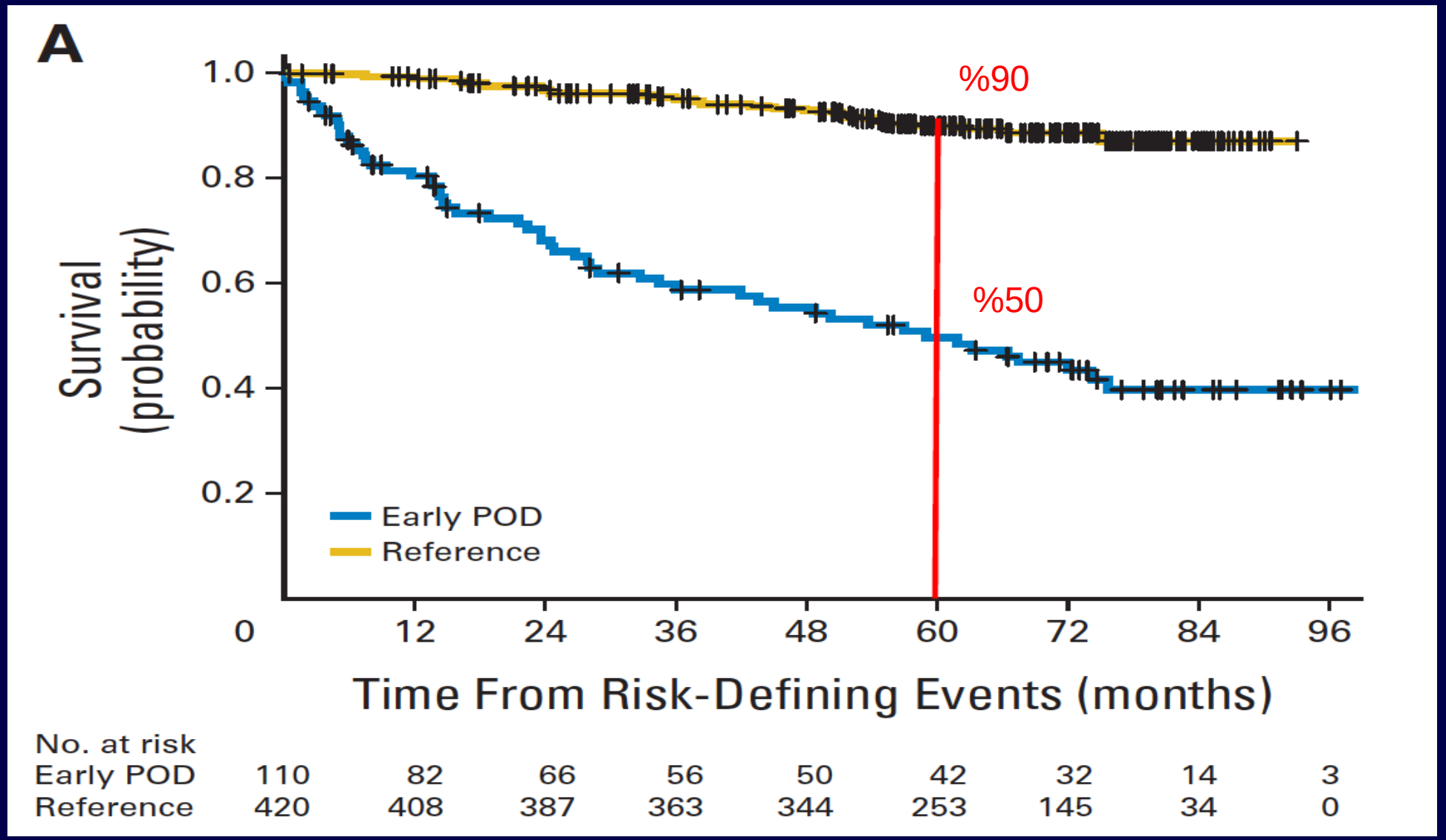
ORIGINAL REPORT

Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study



Casulo C. J Clin Oncol 2015; 33: 2516-22

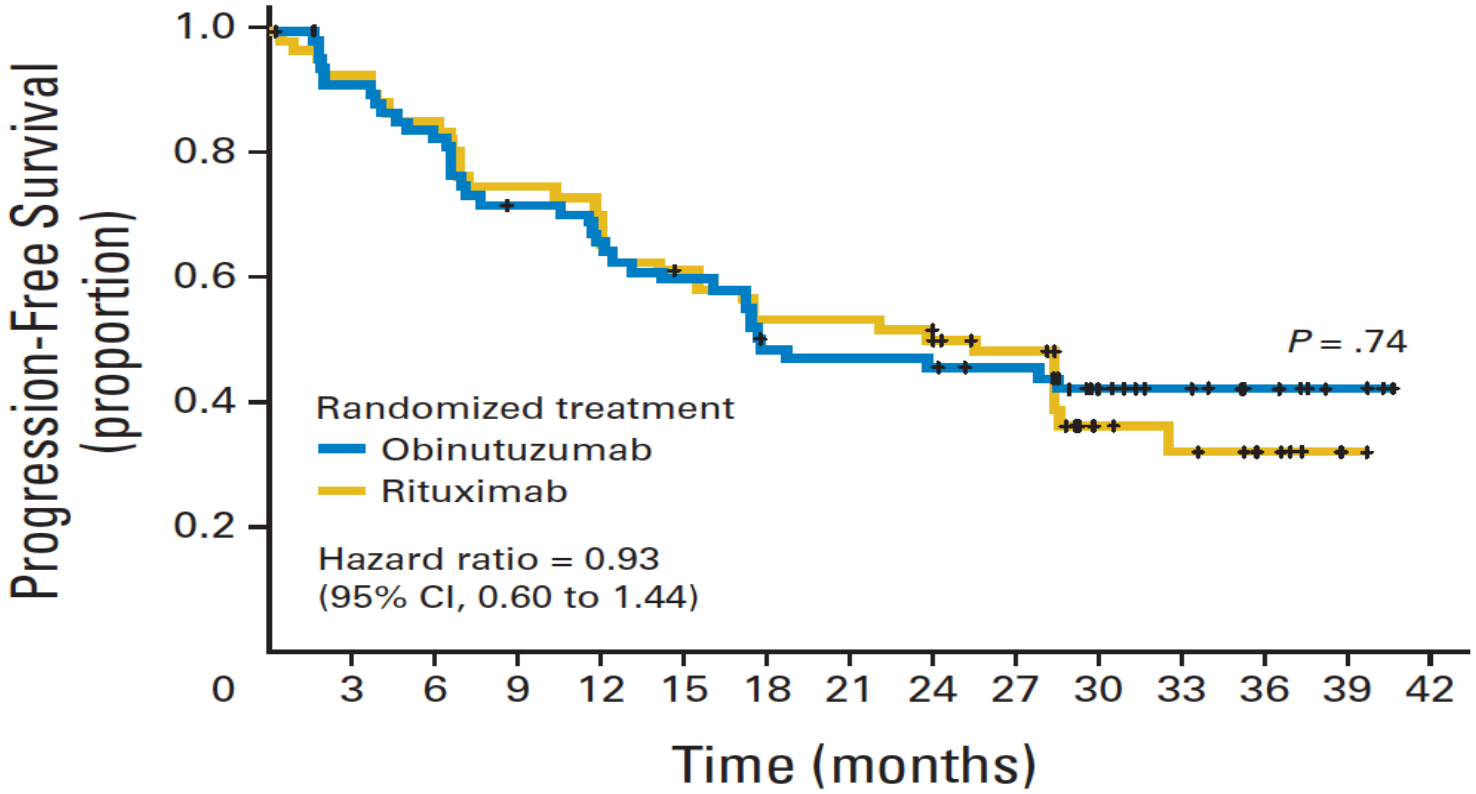
İlk 24 ayda progresyon kötü prognoz ile ilişkili



Casulo C. J Clin Oncol 2015; 33: 2516-22

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized Phase II Trial Comparing Obinutuzumab (GA101) With Rituximab in Patients With Relapsed CD20+ Indolent B-Cell Non-Hodgkin Lymphoma: Final Analysis of the GAUSS Study

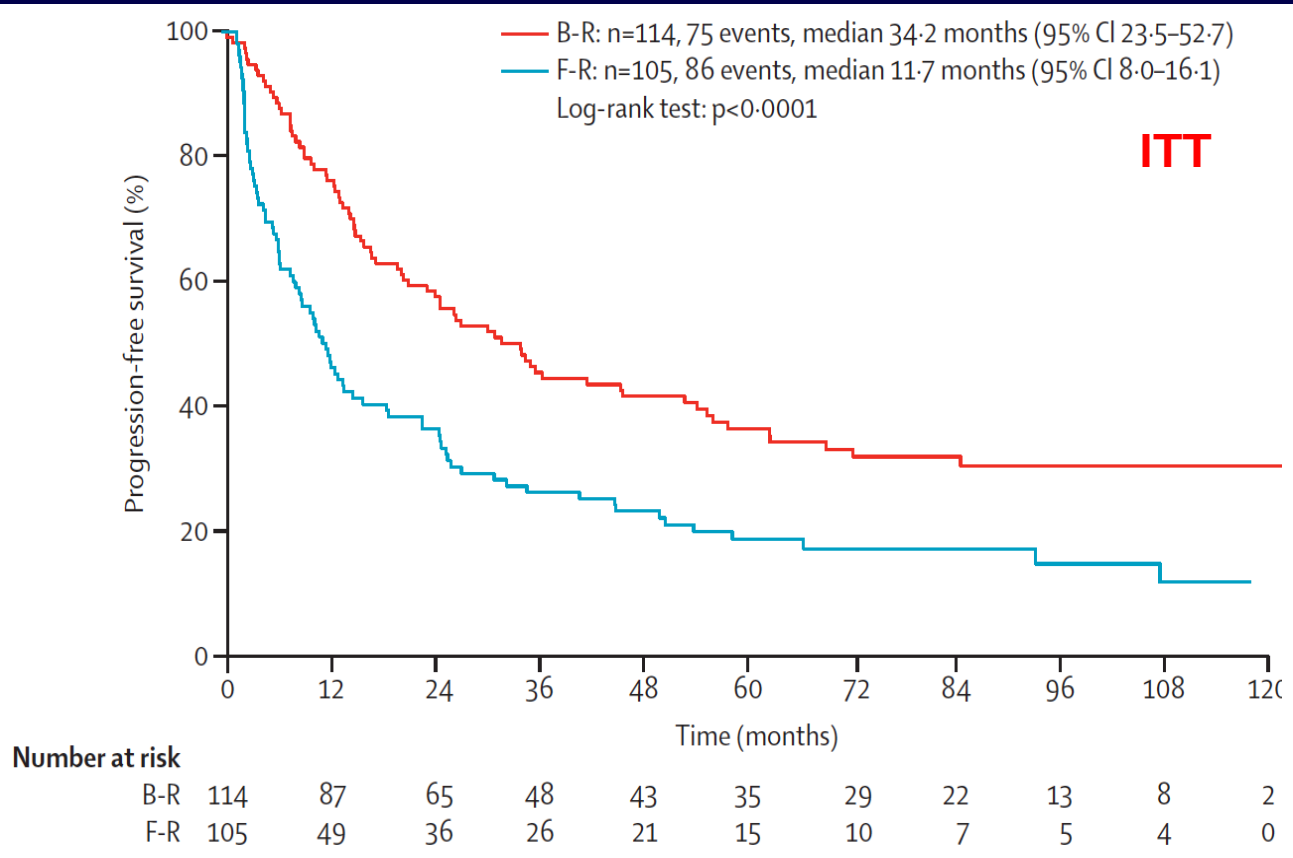


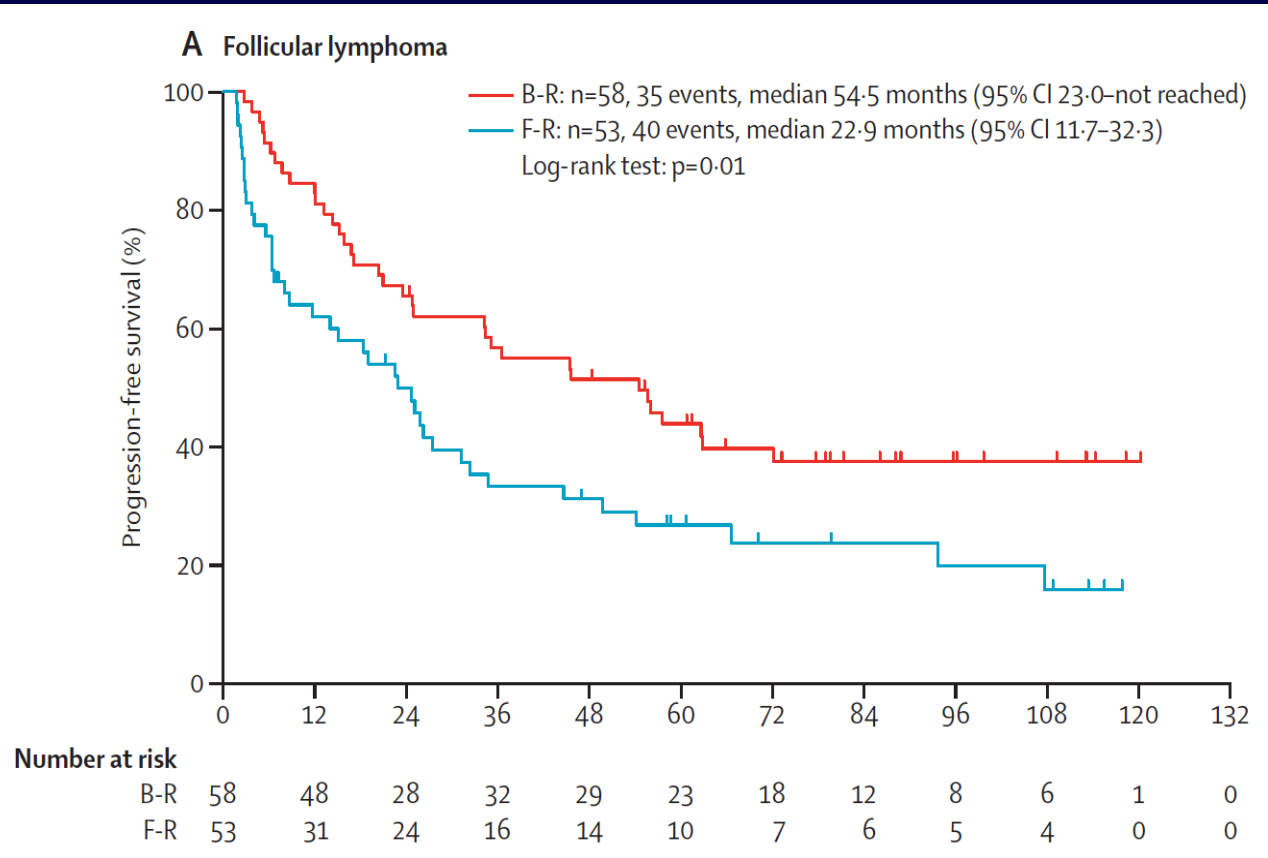
No. at risk															
Obinutuzumab	74	62	56	47	42	39	31	30	28	27	19	15	7	3	0
Rituximab	75	63	56	50	41	39	34	34	29	27	10	8	5	1	0

İlk basamakta R içeren bir rejime yanıtlı FL hastalarında nüks anında R, G kadar etkili

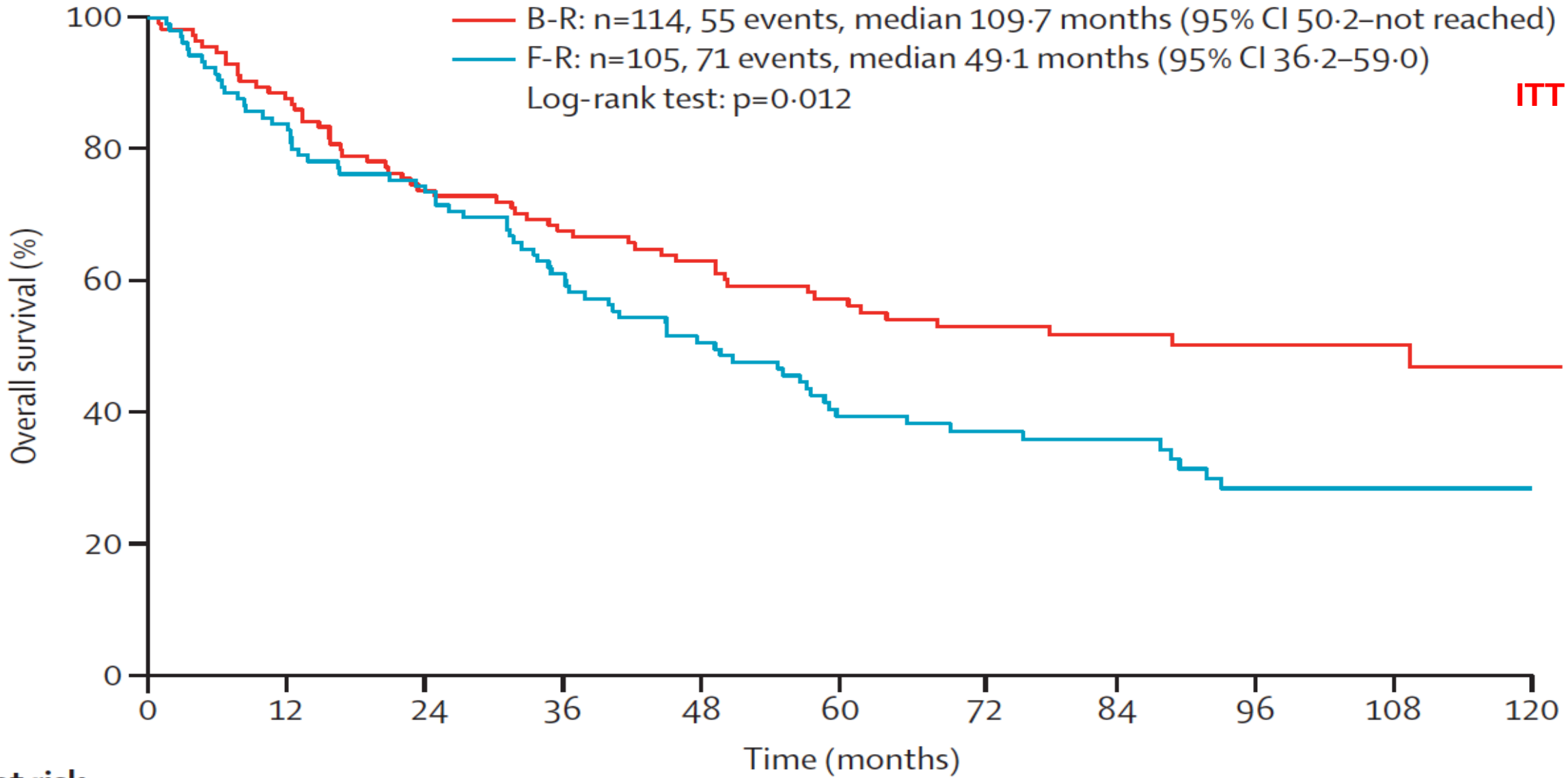
Sehn LH. J Clin Oncol 2015; 33: 3467-74

Bendamustine plus rituximab versus fludarabine plus rituximab for patients with relapsed indolent and mantle-cell lymphomas: a multicentre, randomised, open-label, non-inferiority phase 3 trial





Rummel M. Lancet Oncol 2015; 17: 57-66

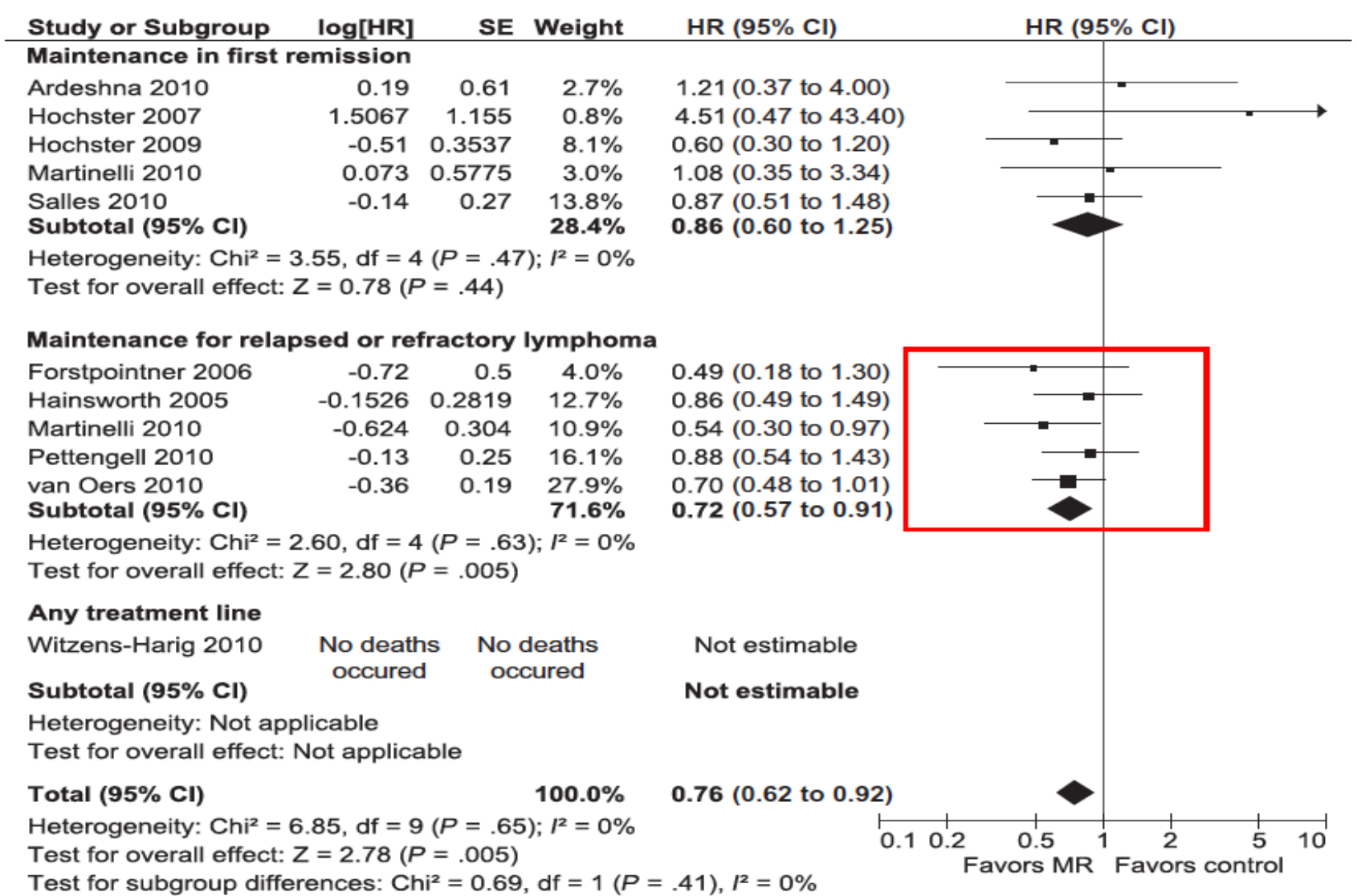


Number at risk

B-R	114	100	84	75	67	57	48	40	26	16	3
F-R	105	87	78	64	50	37	30	25	18	10	1

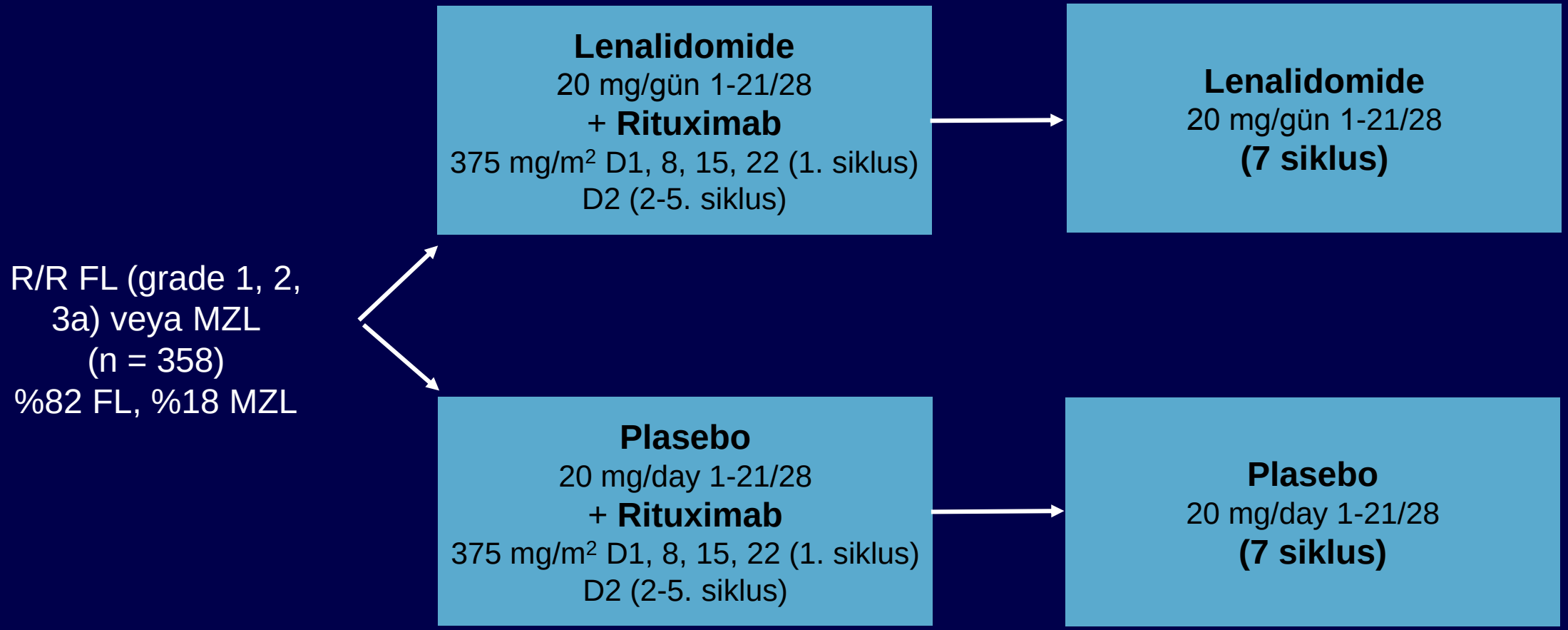
Rummel M. Lancet Oncol 2015; 17: 57-66

Rituximab Maintenance for the Treatment of Patients With Follicular Lymphoma: An Updated Systematic Review and Meta-analysis of Randomized Trials

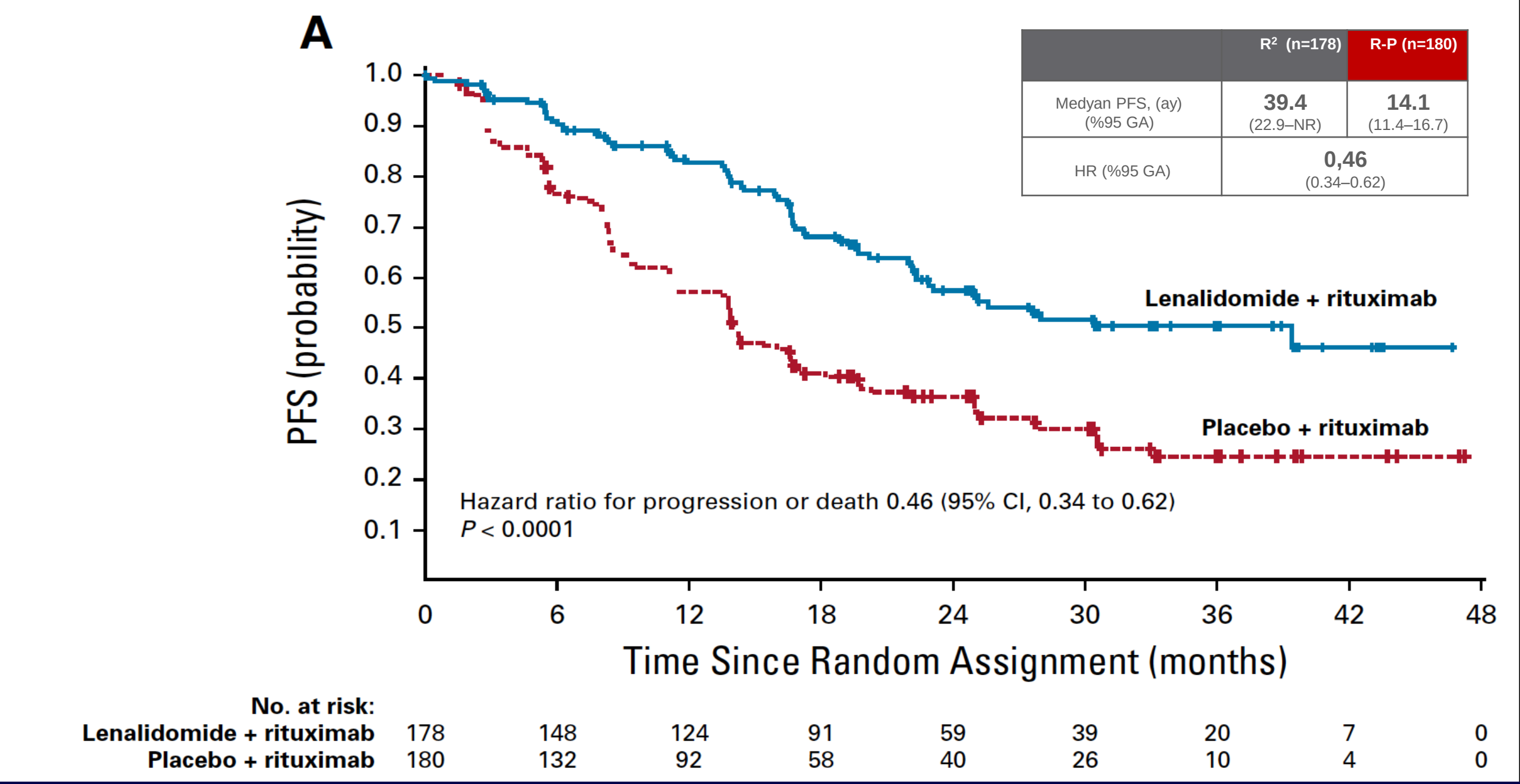


Vidal L. J Natl Cancer Inst 2011; 103: 1799-806

AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma

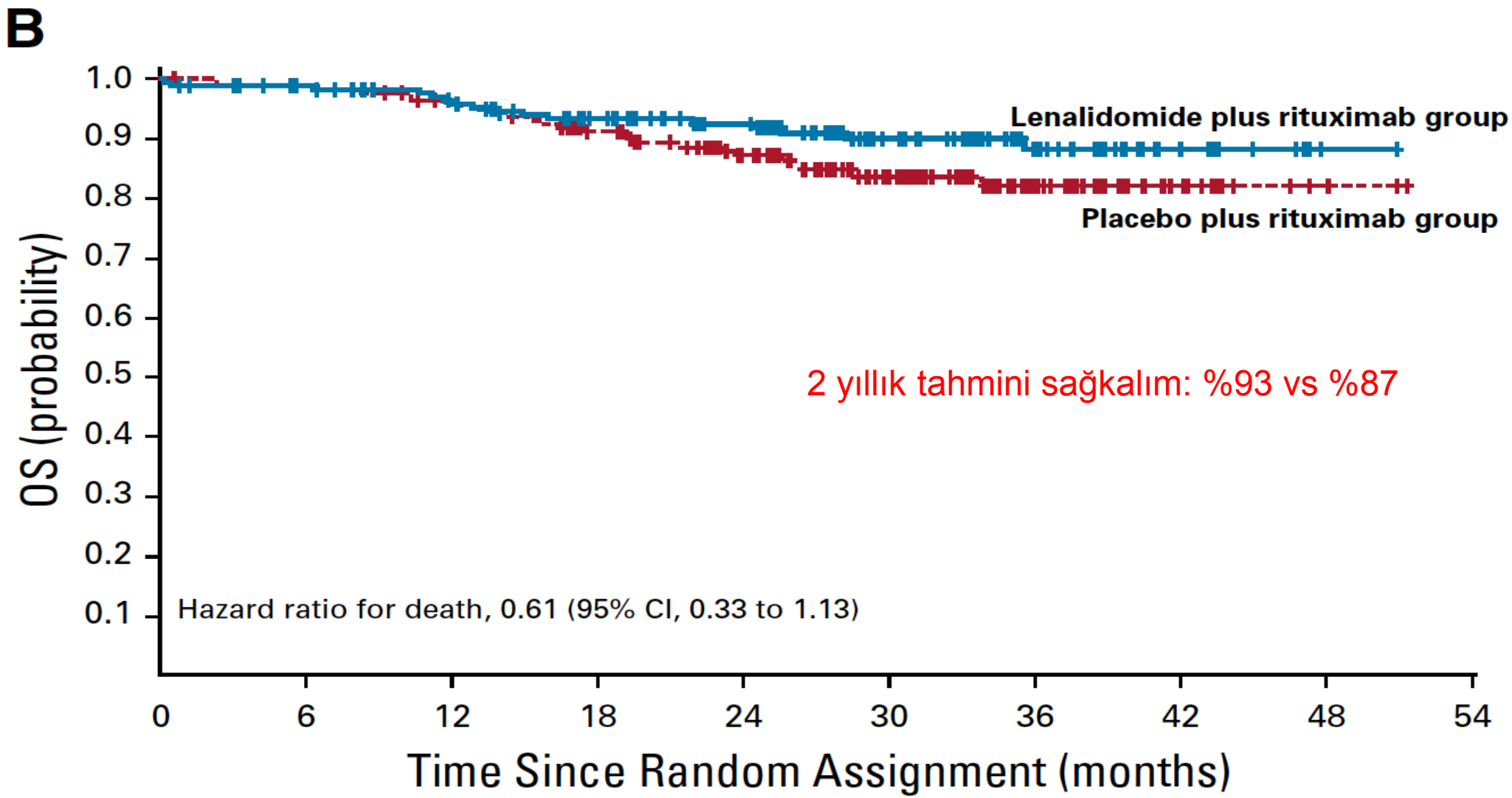


Leonard JP. J Clin Oncol 2019; 37: 1188-99



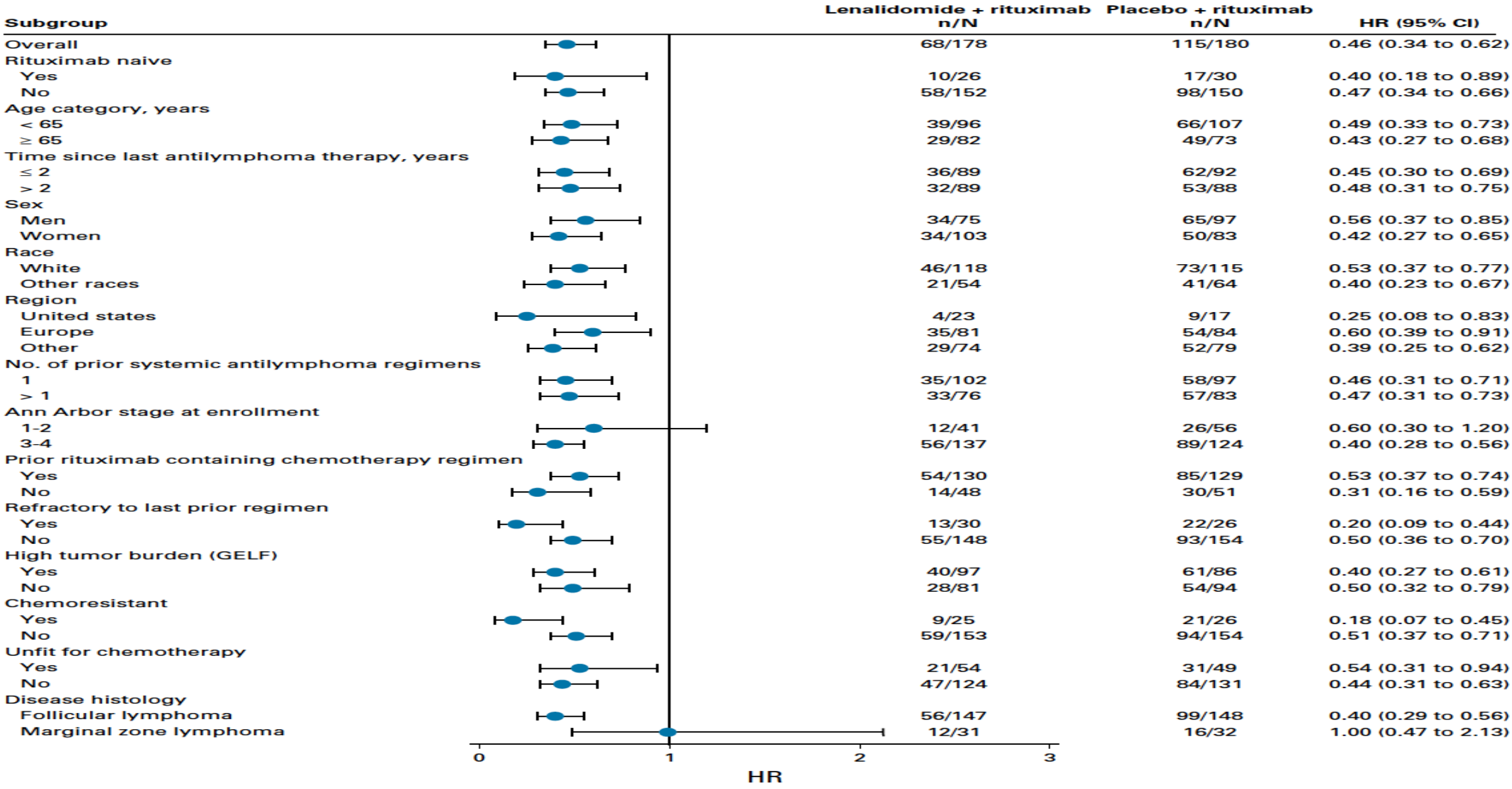
	R^2 (n=178)	R-P (n=180)
Medyan PFS, (ay) (%95 GA)	**39.4** (22.9–NR)	**14.1** (11.4–16.7)
HR (%95 GA)	**0,46** (0.34–0.62)	

Leonard JP. J Clin Oncol 2019; 37: 1188-99



No. at risk:										
Lenalidomide + rituximab	178	167	155	143	122	80	44	15	1	0
Placebo + rituximab	180	176	167	145	116	79	40	14	3	0

Leonard JP. J Clin Oncol 2019; 37: 1188-99



Leonard JP. J Clin Oncol 2019; 37: 1188-99

En az 2 sıra tedavi almış R/R FL: FDA onaylı oral PI3K inhibitörleri -1

Idelalisib

- ✓faz-2
- ✓125 erişkin iNHL (%58 FL)
- ✓Öncesinde medyan 4 dize tedavi
- ✓ORR: %57 (%6 CR)
- ✓Medyan PFS: 11 ay
- ✓Medyan OS: 20 ay

Gopal AK. N Engl J Med 2014; 370: 1008

En az 2 sıra tedavi almış R/R FL: FDA onaylı oral PI3K inhibitörleri -2

Copanlisib

- ✓faz-2
- ✓142 erişkin iNHL (104 FL)
- ✓Öncesinde medyan 3 dize tedavi
- ✓ORR: %59 (%12 CR)
- ✓Medyan PFS: 23 ay
- ✓1 yıllık OS: %80

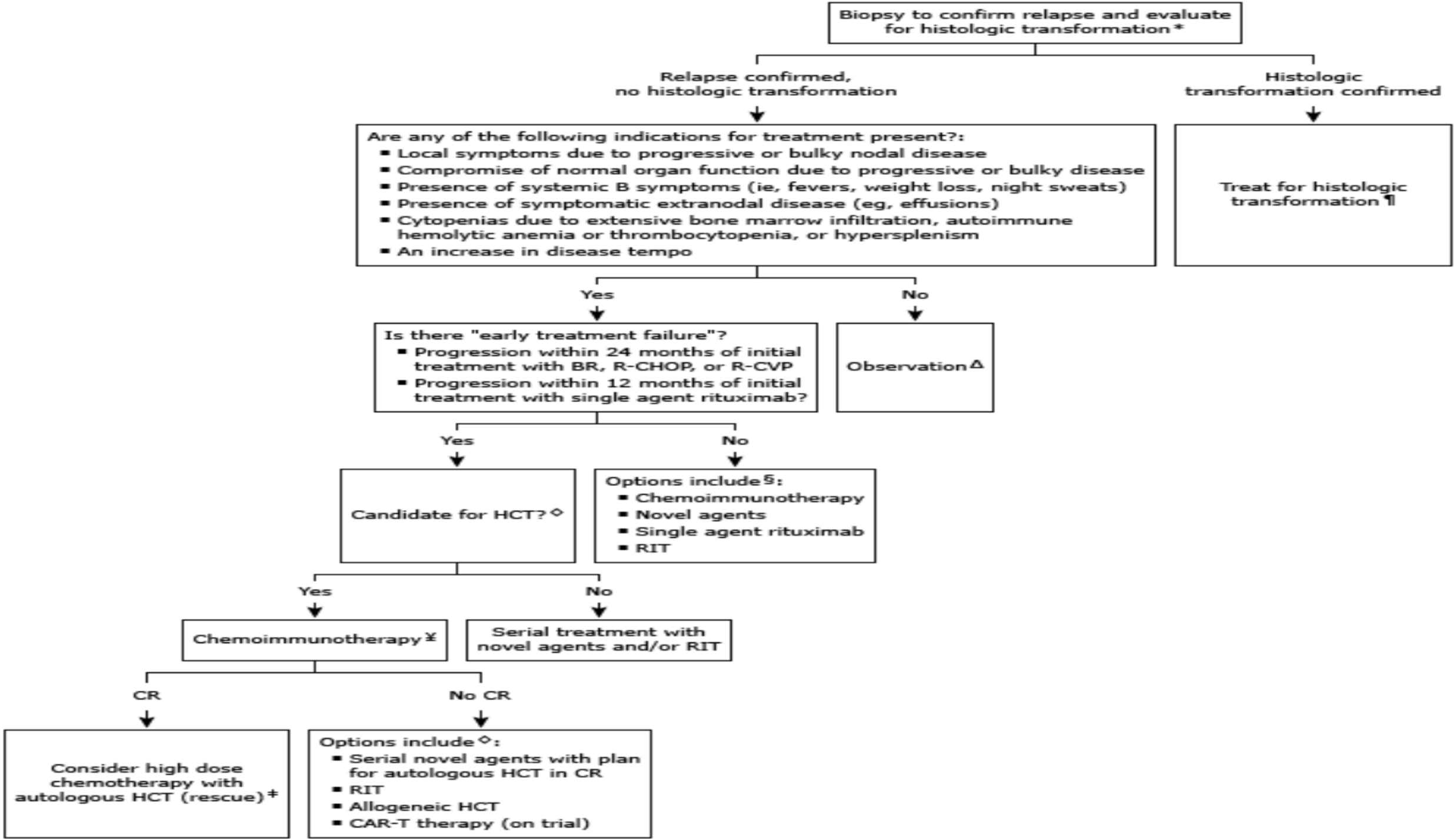
Dreyling M. J Clin Oncol 2017; 35: 3898

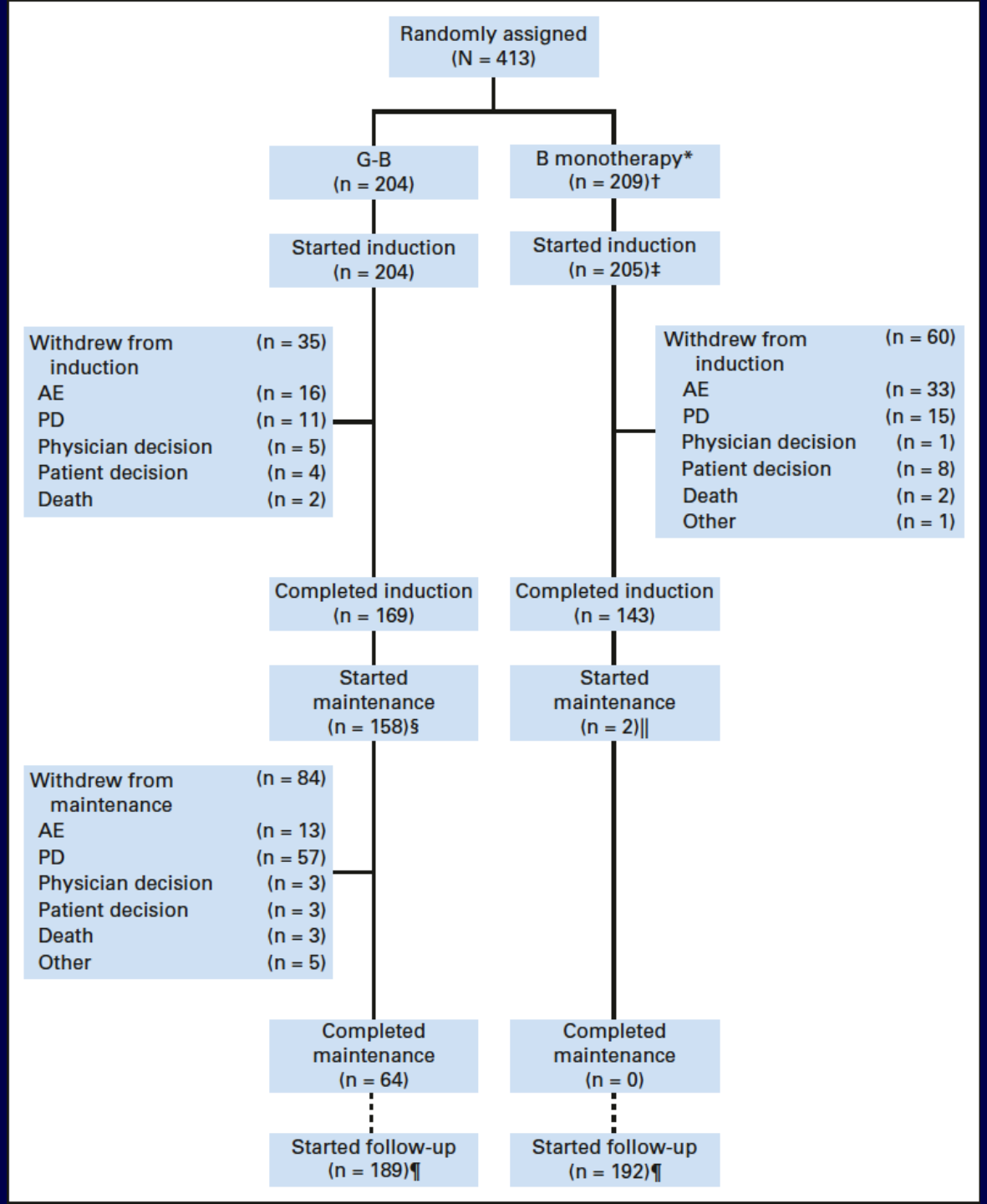
En az 2 sıra tedavi almış R/R FL: FDA onaylı oral PI3K inhibitörleri -3

Duvelisib

- ✓faz-2
- ✓83 FL
- ✓R+KT veya RIT dirençli
- ✓ORR: %42 (%1.2 CR)
- ✓Medyan PFS: 9.5 ay
- ✓Medyan OS: 28.9 ay

Flinn IW. J Clin Oncol 2019; 37: 912


Biopsy to confirm relapse and evaluate for histologic transformation*
Relapse confirmed, no histologic transformation
Histologic transformation confirmed
Are any of the following indications for treatment present?:
Local symptoms due to progressive or bulky nodal disease
Compromise of normal organ function due to progressive or bulky disease
Presence of systemic B symptoms (ie, fevers, weight loss, night sweats)
Presence of symptomatic extranodal disease (eg, effusions)
Cytopenias due to extensive bone marrow infiltration, autoimmune hemolytic anemia or thrombocytopenia, or hypersplenism
An increase in disease tempo
Treat for histologic transformation¶
Yes
No
Is there "early treatment failure"?
Progression within 24 months of initial treatment with BR, R-CHOP, or R-CVP
Progression within 12 months of initial treatment with single agent rituximab?
Observation△
Yes
No
Candidate for HCT?◇
Options include§:
Chemoimmunotherapy
Novel agents
Single agent rituximab
RIT
Yes
No
Chemoimmunotherapy¥
Serial treatment with novel agents and/or RIT
CR
No CR
Consider high dose chemotherapy with autologous HCT (rescue)‡
Options include◇:
Serial novel agents with plan for autologous HCT in CR
RIT
Allogeneic HCT
CAR-T therapy (on trial)



J Clin Oncol 2018; 36: 2259