MODULE 3: Contemporary Management of Newly Diagnosed and R/R Follicular Lymphoma

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Disclosures

Advisory Committee	AbbVie Inc, Astellas, AstraZeneca Pharmaceuticals LP, Celgene Corporation, Dr Reddy's Laboratories Ltd, Epizyme, Genentech, Gilead Sciences Inc, Karyopharm Therapeutics, MorphoSys, Pharmacyclics LLC, an AbbVie Company, Roche Laboratories Inc, SymBio Pharmaceuticals Limited, TG Therapeutics Inc
Consulting Agreements	Astellas, Karyopharm Therapeutics, MorphoSys, Parexel International Corporation, SymBio Pharmaceuticals Limited
Contracted Research	AbbVie Inc, Adaptive Biotechnologies, Bristol-Myers Squibb Company, Celgene Corporation, Genentech, Gilead Sciences Inc, Pharmacyclics LLC, an AbbVie Company, Roche Laboratories Inc, Seattle Genetics, TG Therapeutics Inc, Trillium Therapeutics Inc

Case Presentation: Dr Kale

76-year-old man

- Presents with a small (4 cm) bowel obstruction requiring resection
  - No constitutional symptoms, no cytopenia
  - Multiple comorbidities (HTN, DM2, CAD, COPD)
- Diagnosis: Stage III, Grade 2 follicular lymphoma, with chest, abdomen and pelvic lymphadenopathy
- Rituximab weekly x 4 → monitoring
- 1.5 years later develops symptomatic progressive lymphadenopathy

Additional questions regarding the management of FL

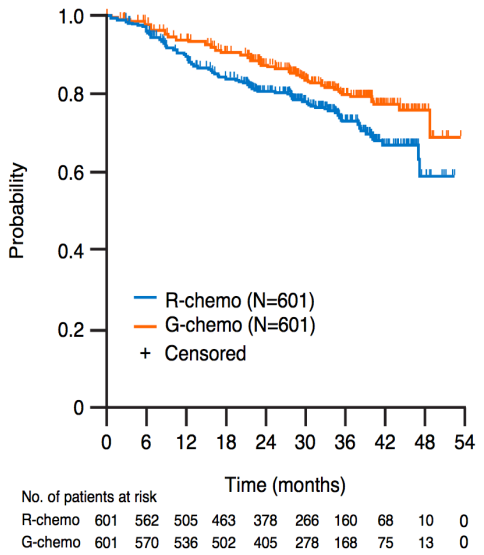
Dr Brenner

Dr Khan

Dr Lamar

GALLIUM Study: R-Chemo vs G-Chemo in Untreated FL

INV-assessed PFS (FL; primary endpoint)

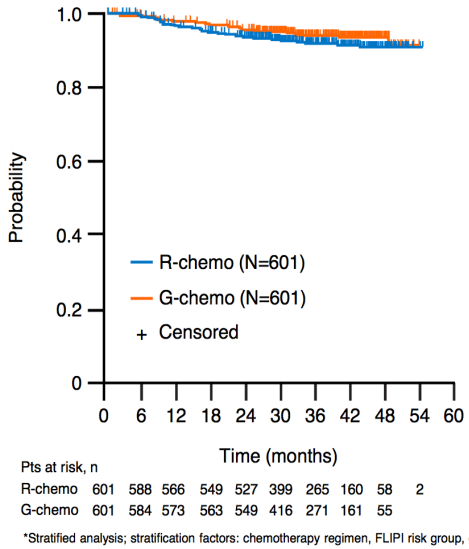


*Stratified analysis; stratification factors: chemotherapy regimen, FLIPI risk group, geographic region

	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

OS (FL)



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

	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

Marcus et al, NEJM 377:1331, 2017

GALLIUM Safety Data

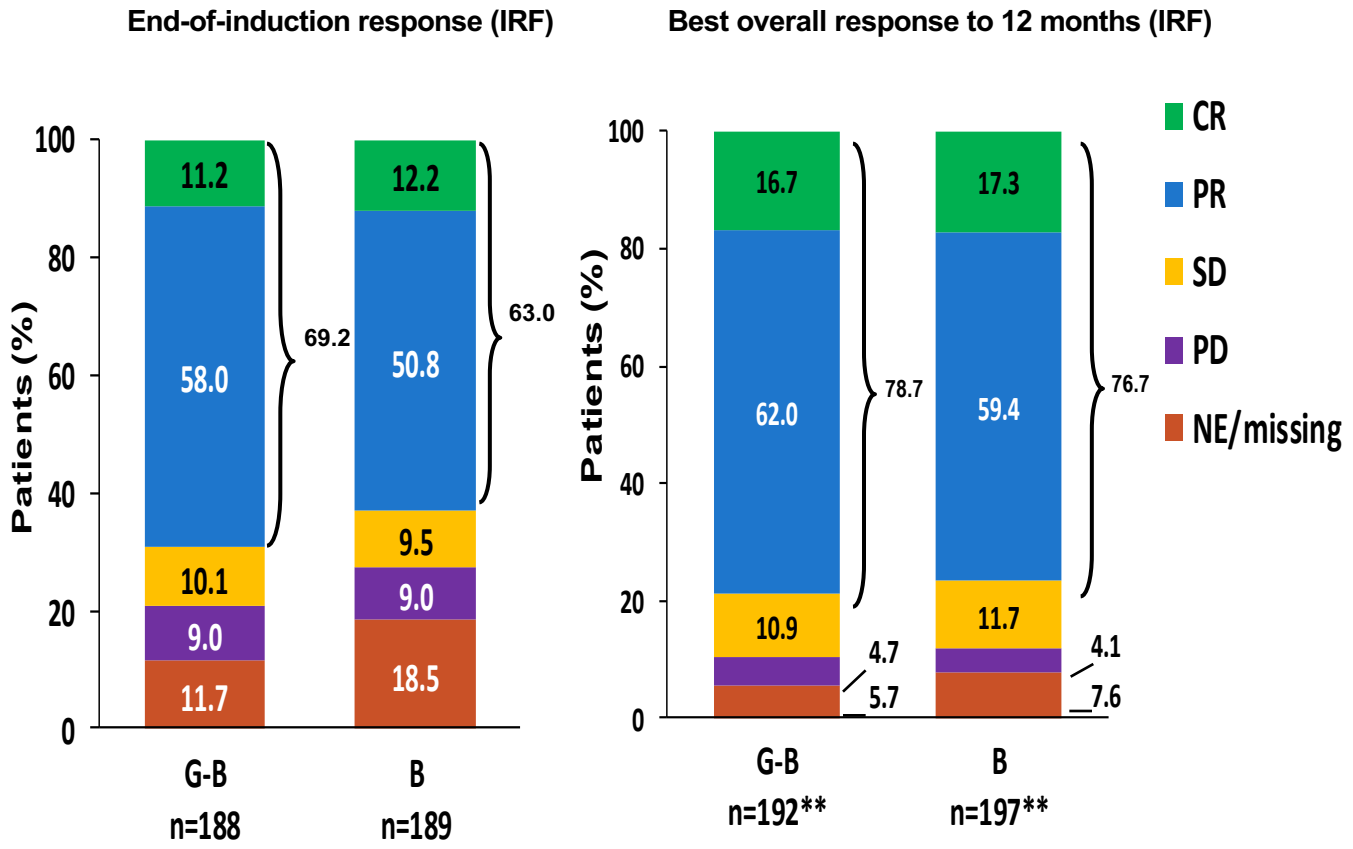
Safety summary (FL)

% (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

Marcus R et al. *N Engl J Med* 2017;377(14):1331-44.

GADOLIN in Rituximab-Refractory FL/iNHL



- 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.

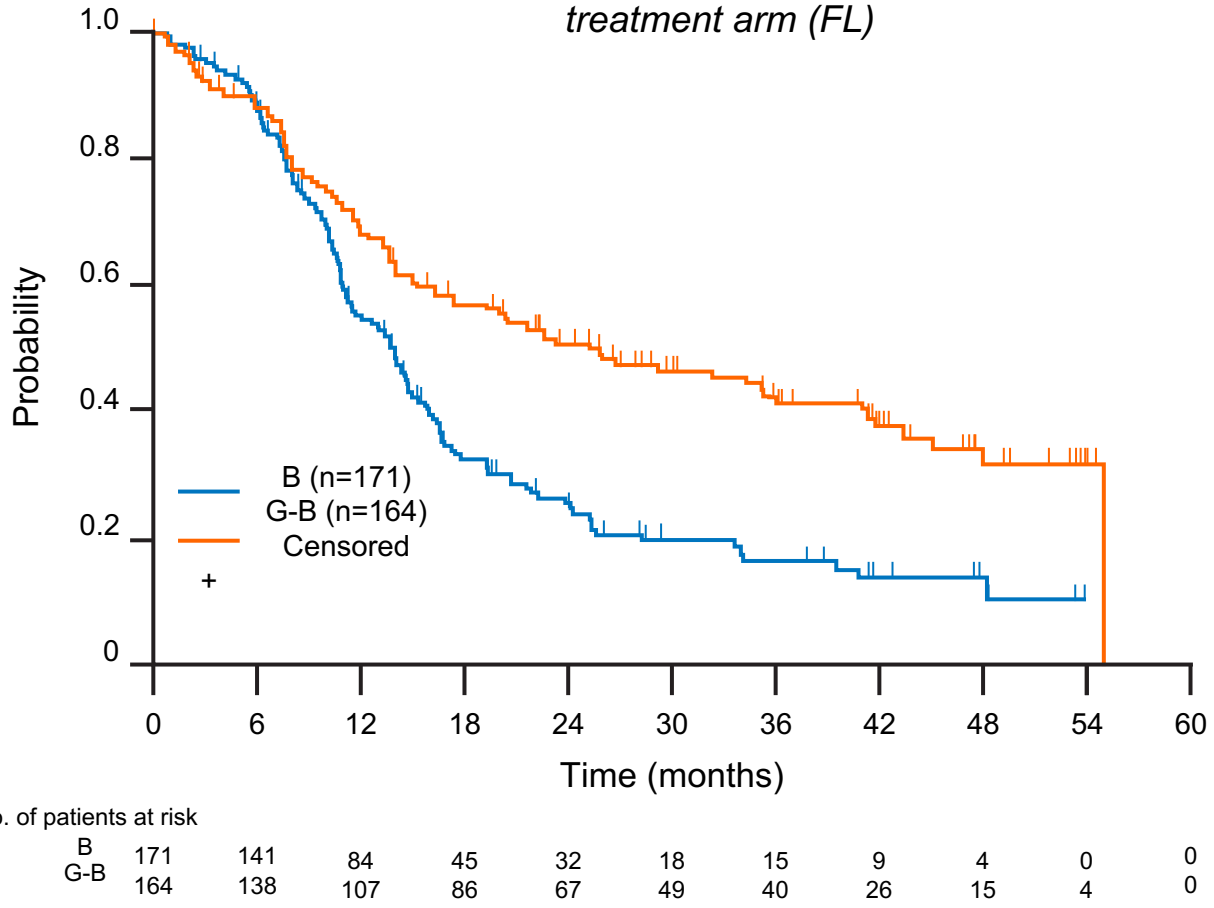
** Best overall response excludes ongoing patients who have not yet reached the first response assessment.

IRF, independent radiology facility

Sehn LH et al. *Lancet Oncol* 2016;17(8):1081-93; *Proc ASCO* 2015;Abstract LBA8502.

GADOLIN: 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	

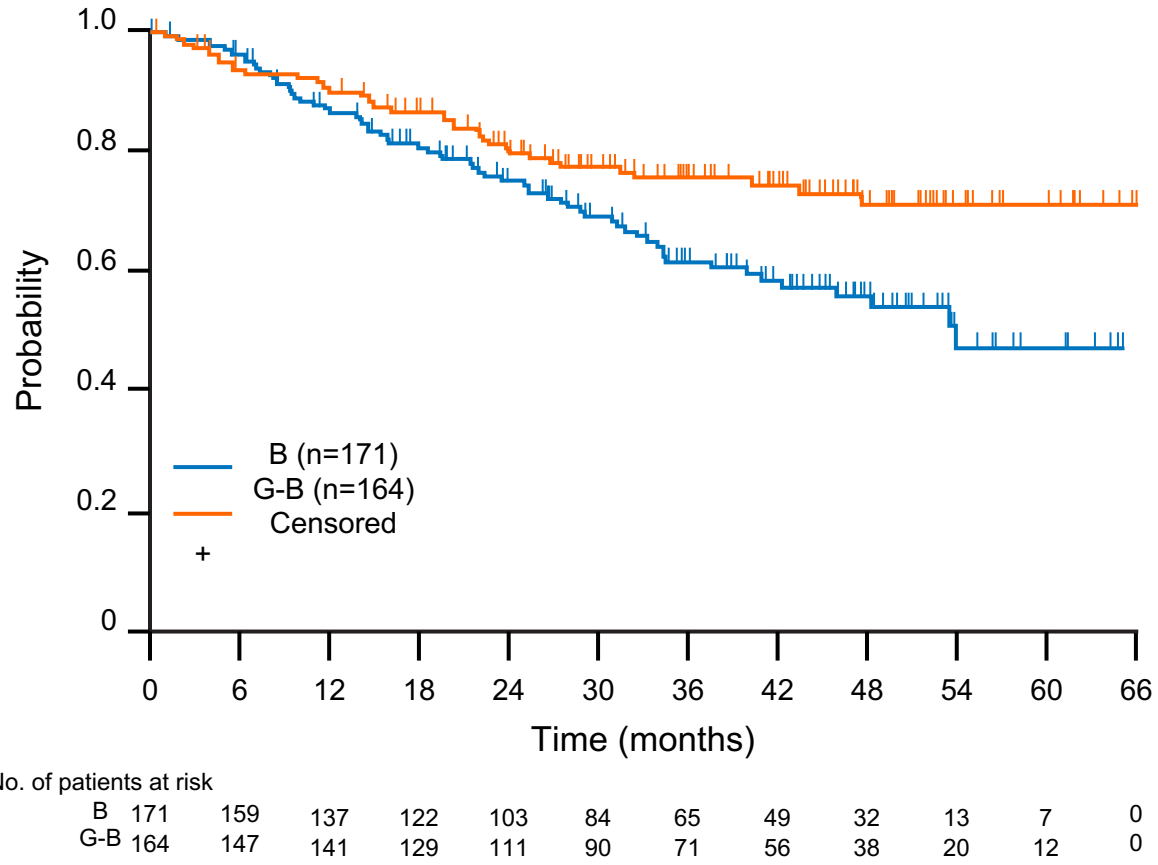
Median follow-up (FL): 31.2 months
(vs 21.1 months in primary analysis)

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

Cheson et al, JCO 36:2259,2018

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

Cheson et al, JCO 36:2259,2018

AUGMENT: Randomized double blind phase III trial

Relapsed/refractory FL and MZL (N = 358)

1:1

≤ 12 cycles or until PD, relapse, or intolerability

R-lenalidomide (R^2)
Rituximab: 375 mg/m^2 d1, 8, 15, 22 of cycle 1; d1 of cycles 2-5
Lenalidomide: 20 mg/d*, d1-21/28 (12 cycles)

*10 mg if CrCl between 30 to 59 mL/min.

R-placebo
Rituximab: 375 mg/m^2 d1, 8, 15, 22 of cycle 1; d1 of cycles 2-5
Placebo: matched capsules (12 cycles)

5-year follow-up for OS, SPMs, subsequent treatment, and histological transformations

- Prophylactic anticoagulation / antiplatelet Rx recommended for at risk patients
- Growth factor use was allowed per ASCO/ESMO guidelines[1,2]

Stratification

- Prior rituximab (yes vs no)
- Time since last therapy (≤ 2 vs > 2 y)
- Histology (FL vs MZL)

Key eligibility criteria

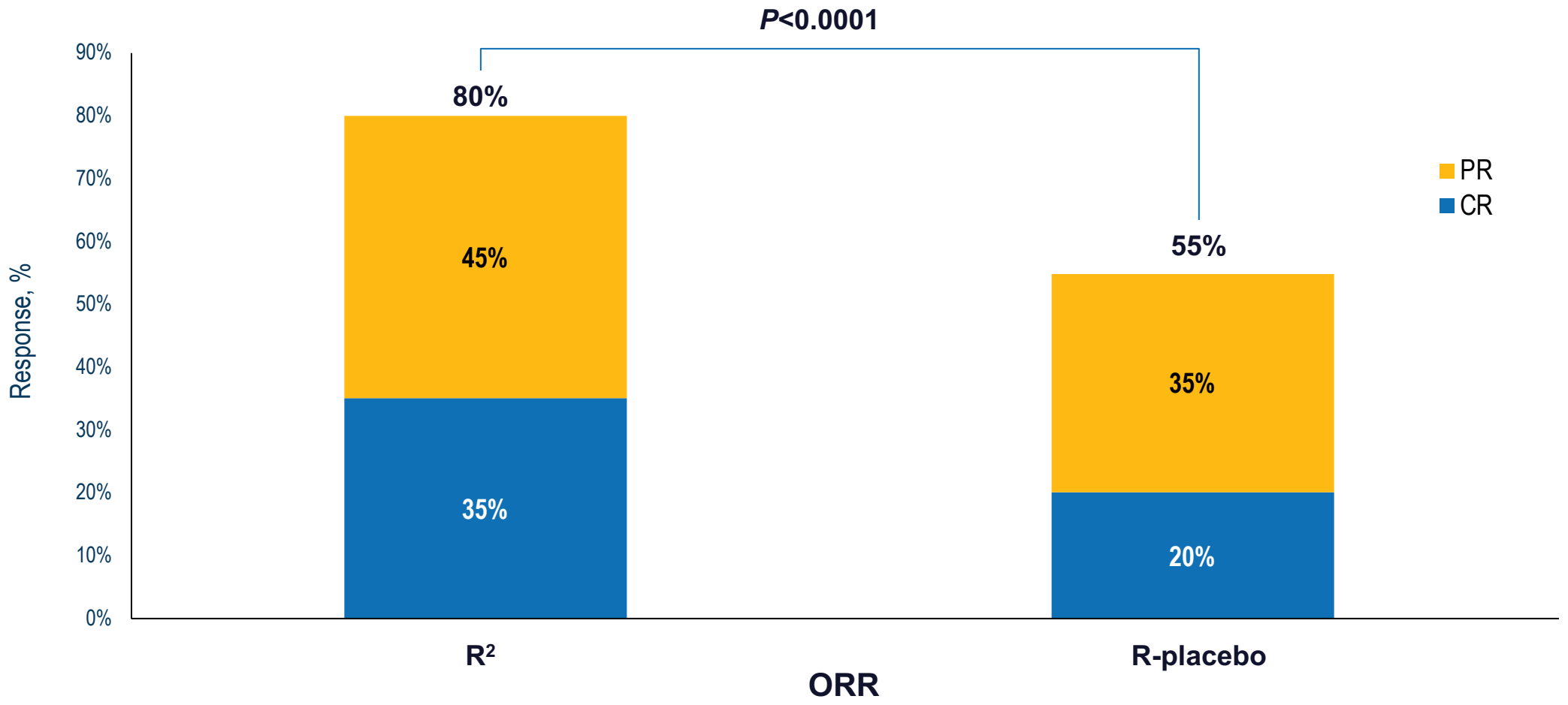
- MZL or FL (grades 1-3a) in need of treatment
- ≥ 1 prior chemotherapy, immunotherapy or chemoimmunotherapy
- Not rituximab refractory

Primary endpoint: PFS by IRC
(2007 IWG criteria w/o PET)

NCT01938001
1. Crawford et al. *Ann Oncol.* 2010;21 Suppl 5:248-251. 2. Smith et al. *J Clin Oncol.* 2015;33:3199-3212.

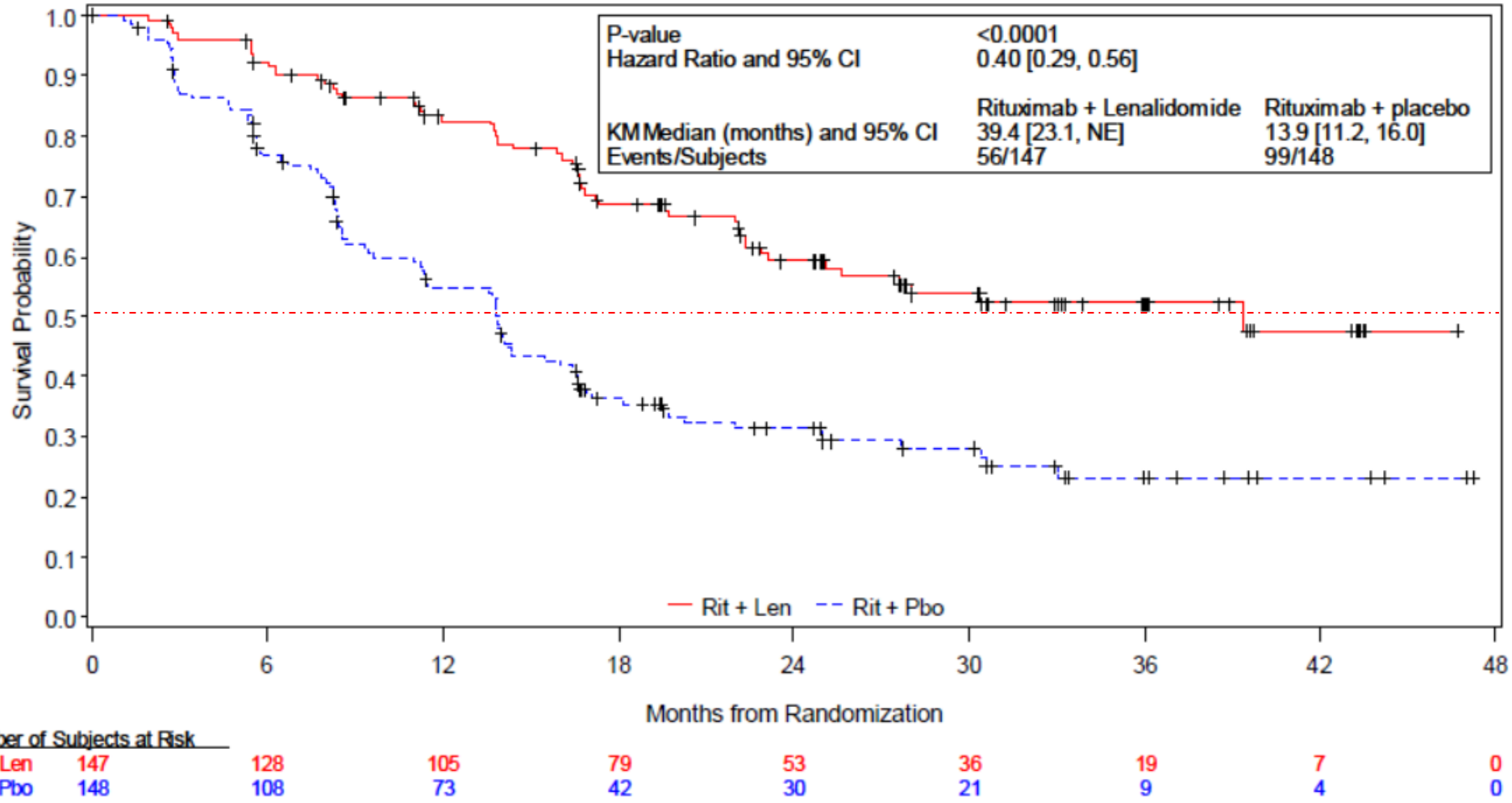
Leonard et al, JCO 37:1188, 2019

Best Response by IRC (FL)



Leonard et al, JCO 37:1188, 2019

AUGMENT: PFS (FL sub-population)

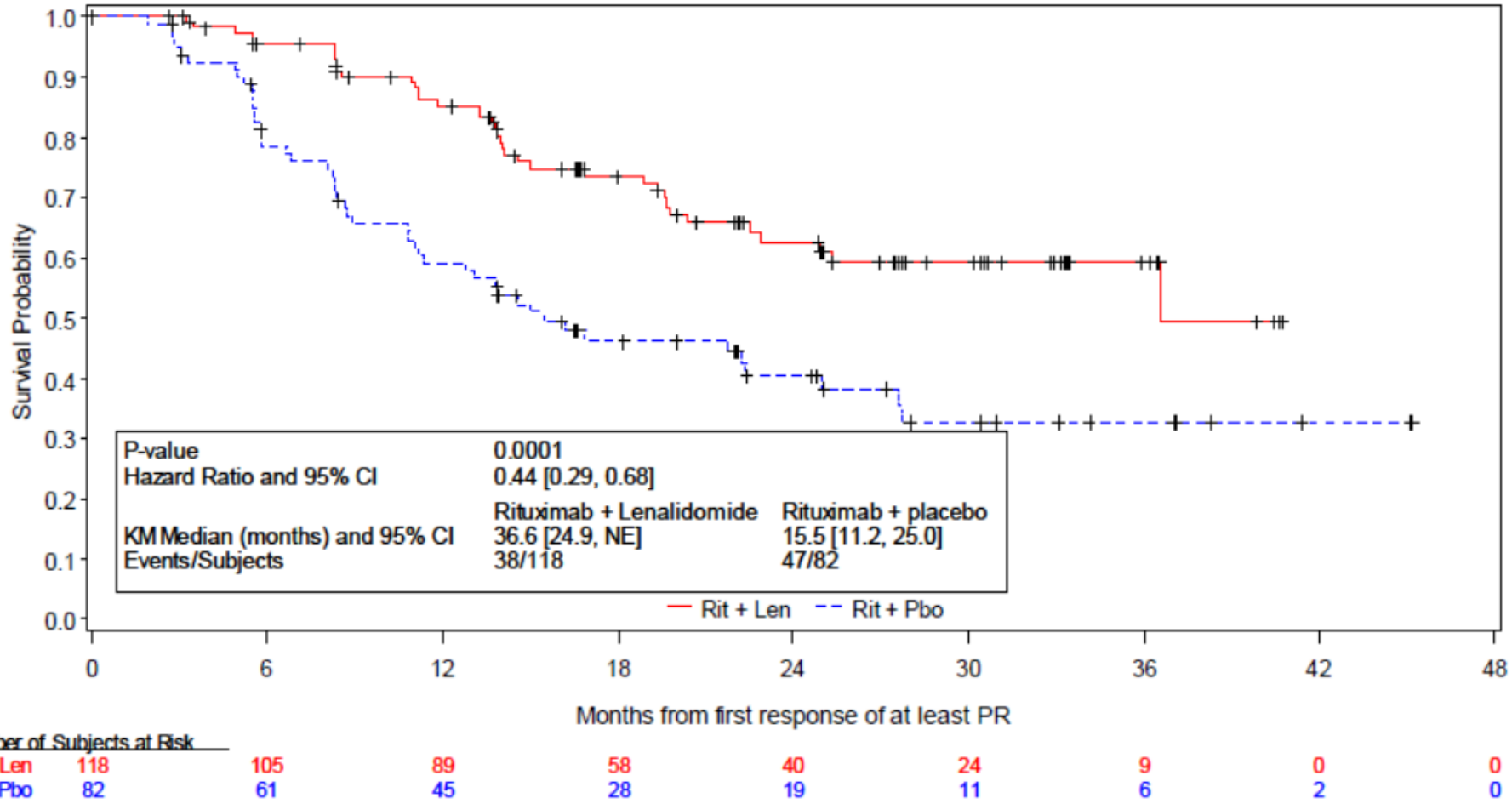


Kaplan-Meier Curves of Progression-free Survival by IRC Assessment in FL Patients between R^2 Arm versus Control Arm

Data cutoff June 22, 2018.

Leonard et al, JCO 37:1188, 2019

AUGMENT: Duration of Response (FL)



Kaplan-Meier Curve of Duration of Response by IRC Assessment per IWGRC 2007 in Subjects with FL

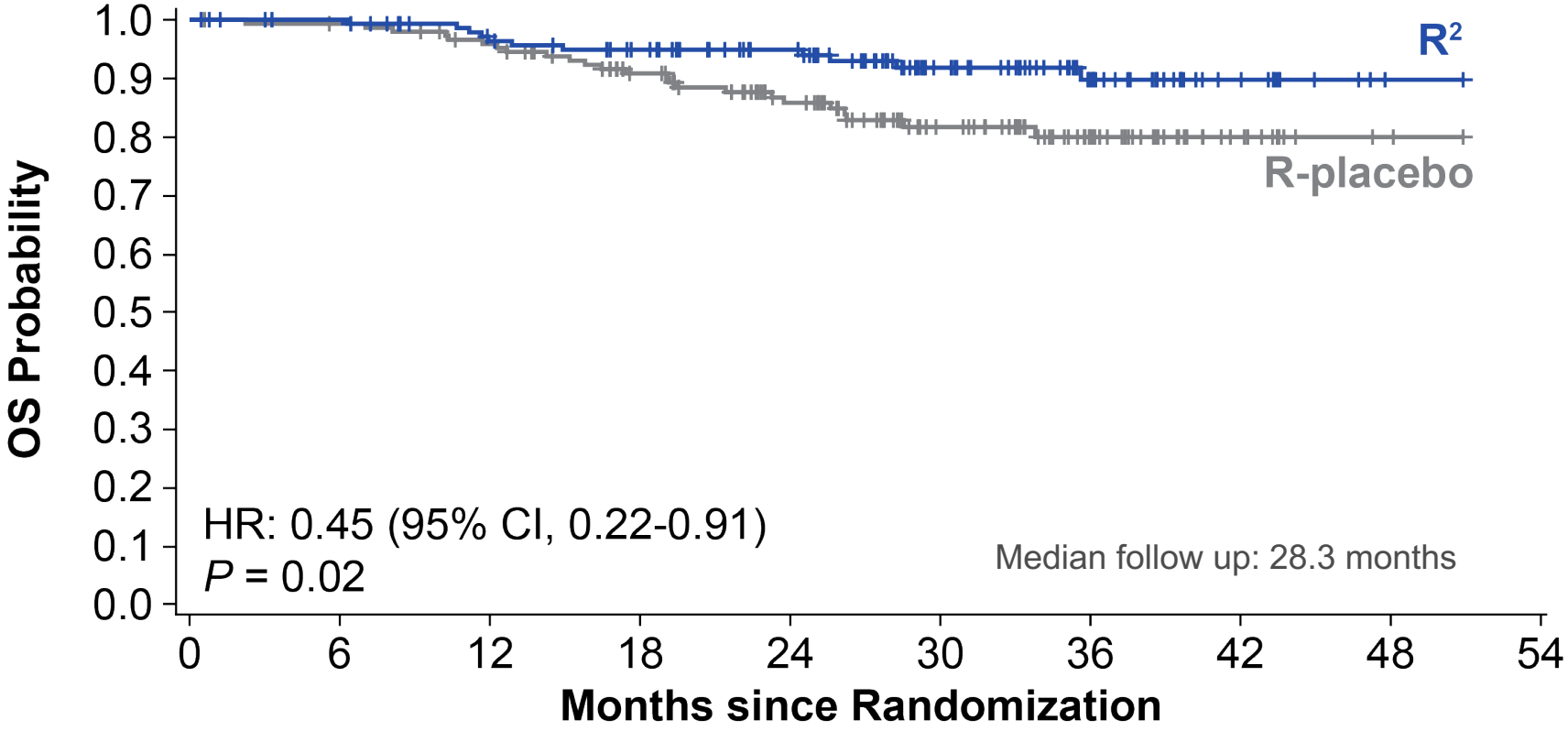
Leonard et al, JCO 37:1188, 2019

Leonard et al, JCO 37:1188, 2019

Leonard et al, JCO 37:1188, 2019

OVERALL SURVIVAL IN PATIENTS WITH FL

(PRESPECIFIED SUBGROUP ANALYSIS)



No. at Risk										
R²	147	142	130	121	105	70	39	13	1	0
R-placebo	148	145	137	117	94	64	35	12	2	0

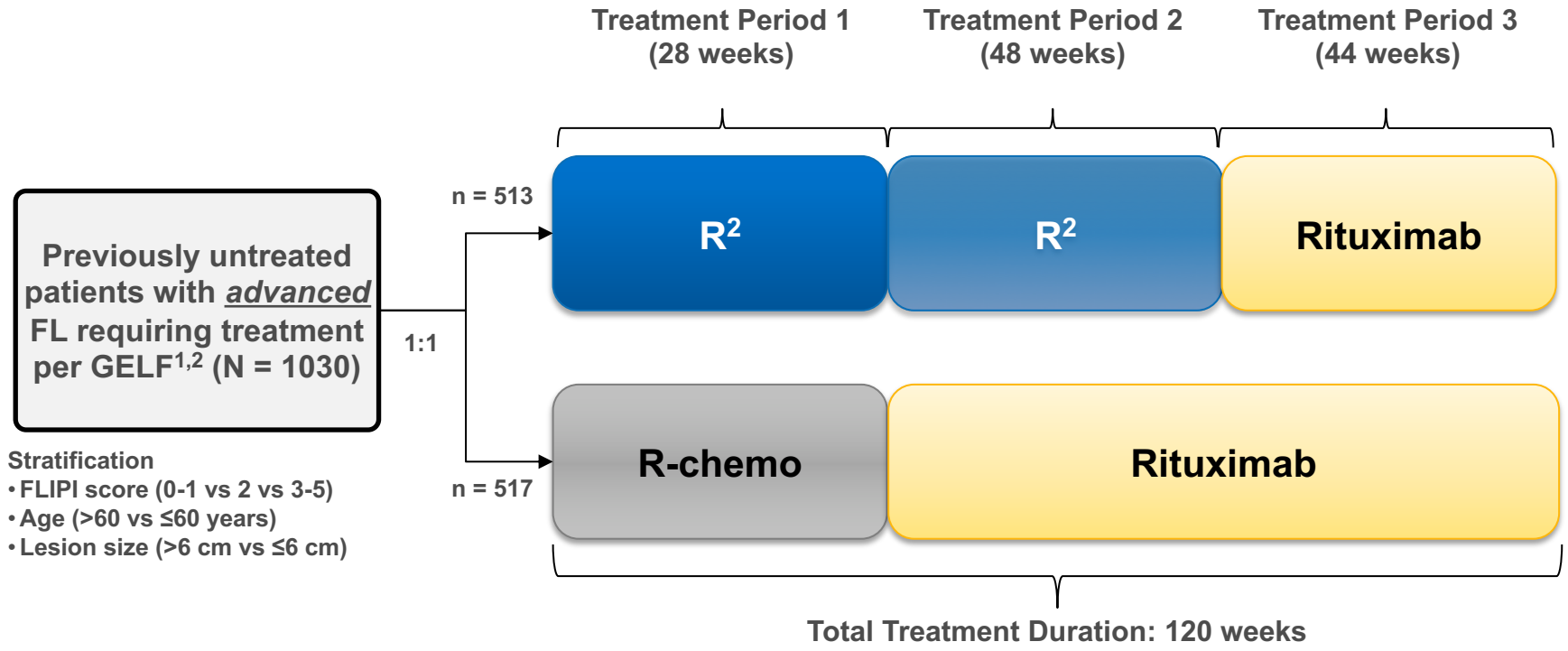
35 total deaths (11 R², 24 R-placebo)

2-year OS was 95% (95% CI, 90%-98%) for R² and 86% (95% CI, 79%-91%) for R-placebo

Data cutoff June 22, 2018.

Leonard et al, JCO 37:1188, 2019

RELEVANCE: Study Design



Co-primary endpoints per 1999 IWG criteria*

- CR/CRu at 120 weeks
- PFS (first interim analysis at ~50% of targeted events)

Dosing schedule

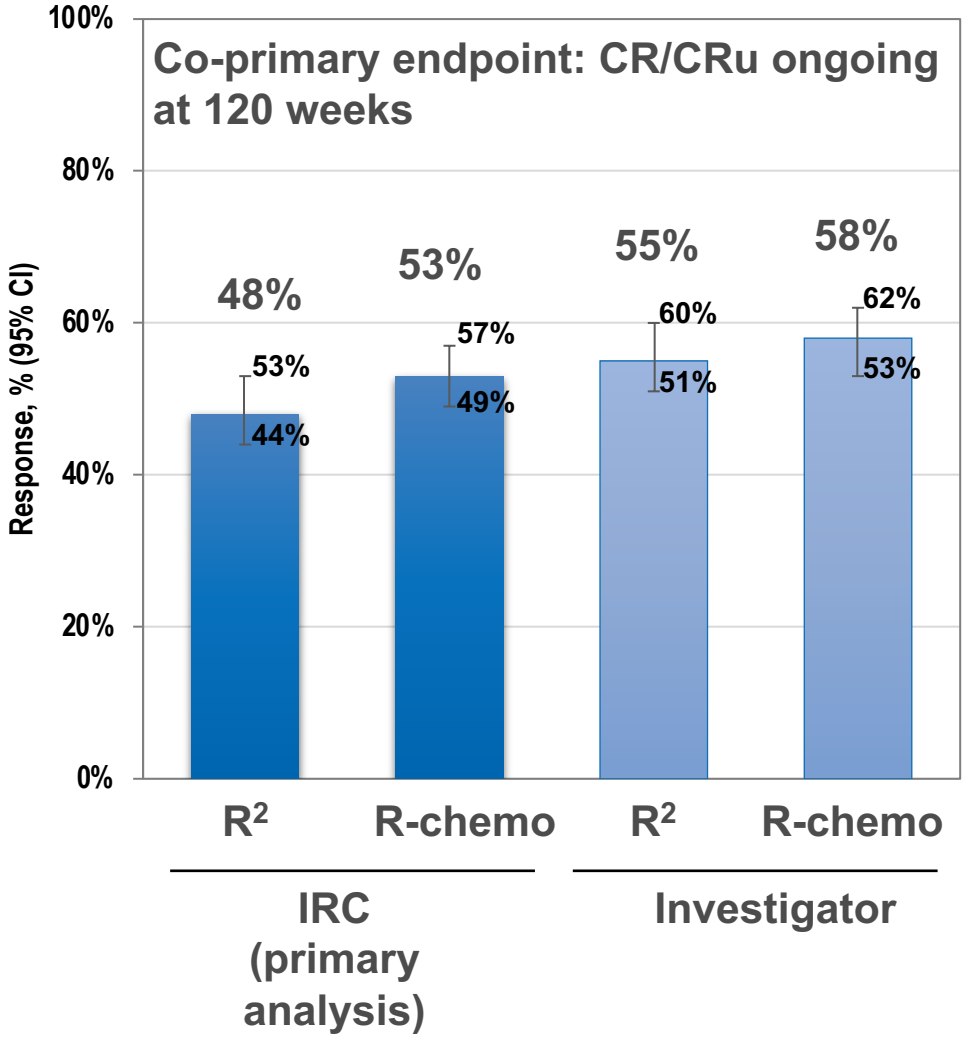
- **R²:** Lenalidomide 20 mg/d, d2-22/28 until CR/CRu at 6, 9, or 12 cycles, then 10 mg/d (total 18 cycles) and rituximab 375 mg/m²/wk c1 and d1 c2-6; continued in responders q8wk for 12 cycles
- **R-chemo:** 3 options (R-CHOP, R-B, R-CVP) plus 2 years rituximab maintenance
  - Included 72% R-CHOP, 23% R-B, and 5% R-CVP

NCT01476787; NCT01650701; EUDRA 2011-002792-42. *Per central (IRC) review by 1999 IWG with CT.

1. Salles et al. *Lancet.* 2011;377:42-51. 2. Brice et al. *J Clin Oncol.* 1997;15:1110-1117.

Morschhauser et al, NEJM 379:934, 2018

RELEVANCE: response (ITT)

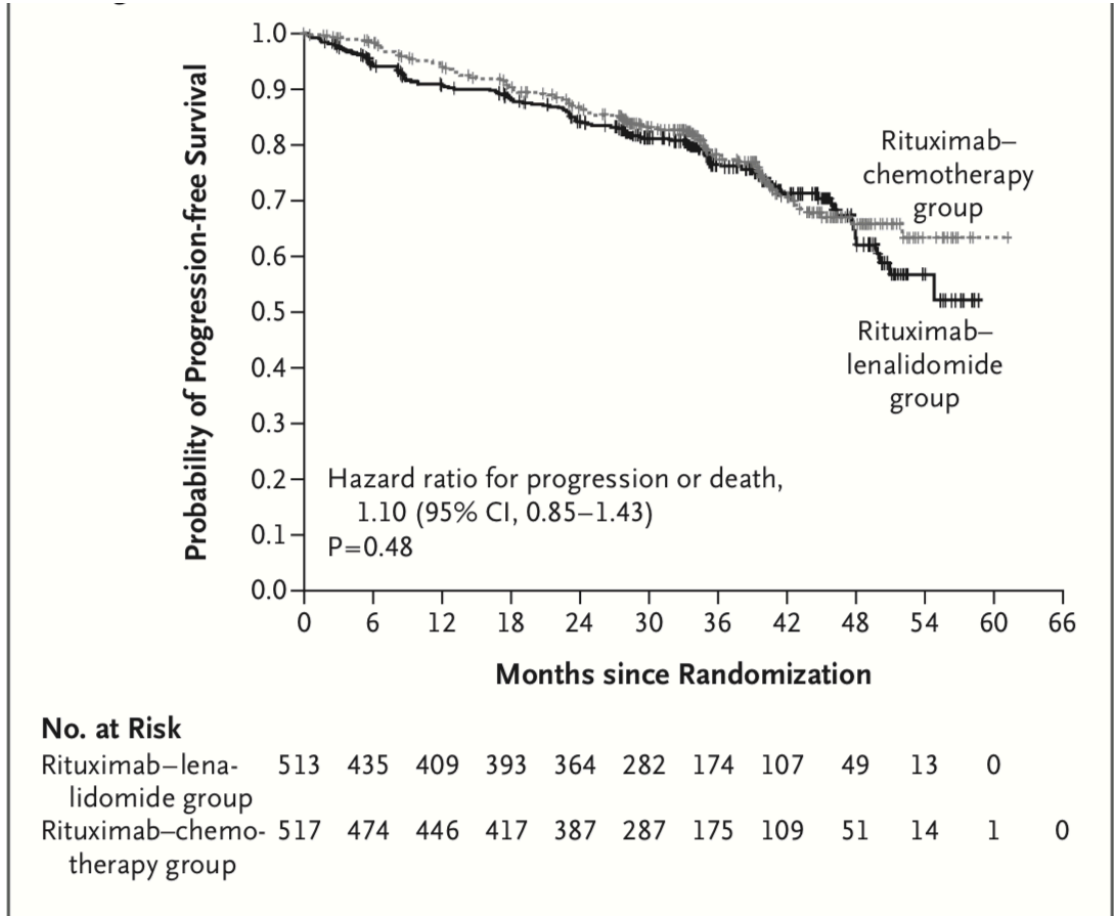


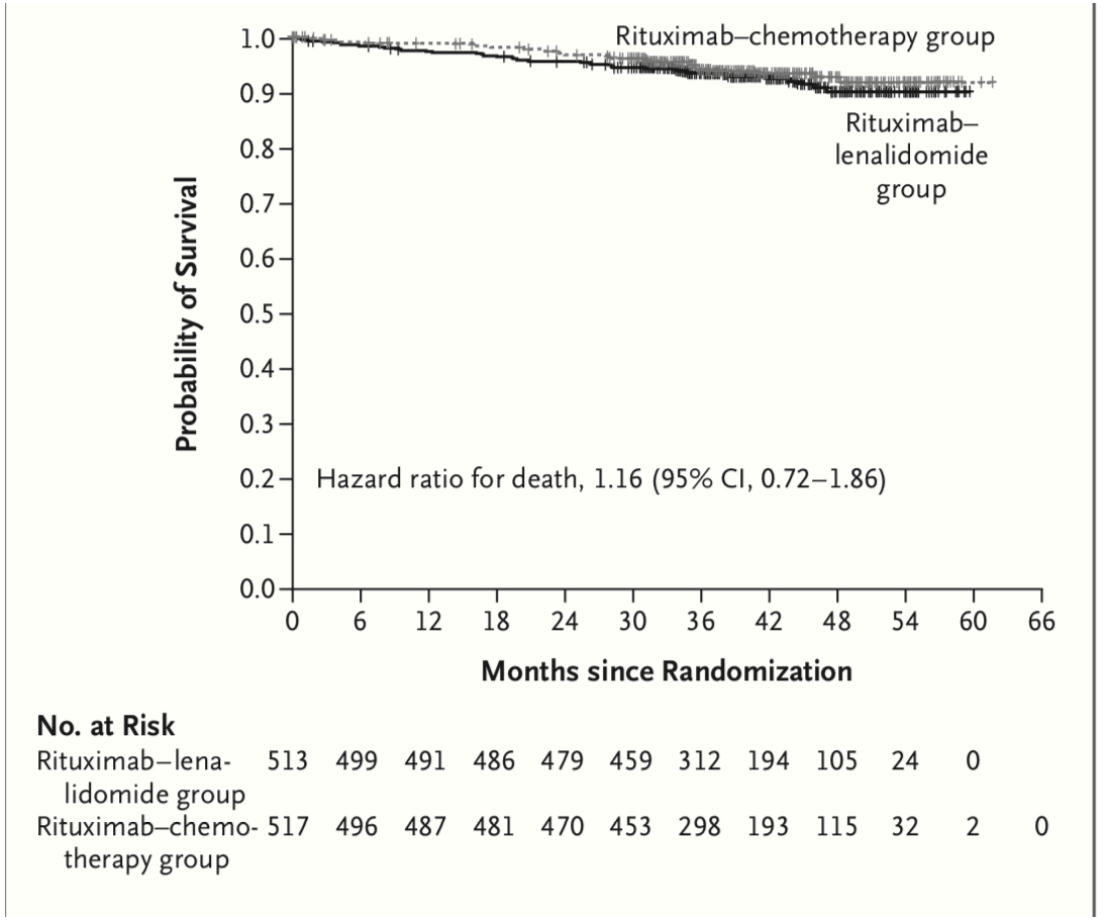
- Best overall response (CR+CRu+PR)
  - 84% R^2 vs 89% R-chemo (IRC)
  - 86% R^2 vs 92% R-chemo (investigator)
- SPD reduction of ≥ 50% at 12 weeks was 81% for R^2 and 90% for R-chemo
- ORR ongoing at 120 weeks
  - 61% R^2 vs 65% R-chemo (IRC)
  - 65% R^2 vs 68% R-chemo (investigator)
- Probability of maintaining response (CR/CRu/PR) for ≥ 3 years for R^2 vs R-chemo, respectively
  - 77% vs 74% (IRC)
  - 82% vs 77% (investigator)

Data cut-off 31May2017. SPD, sum of the products of the diameters.

Morschhauser et al, NEJM 379:934, 2018

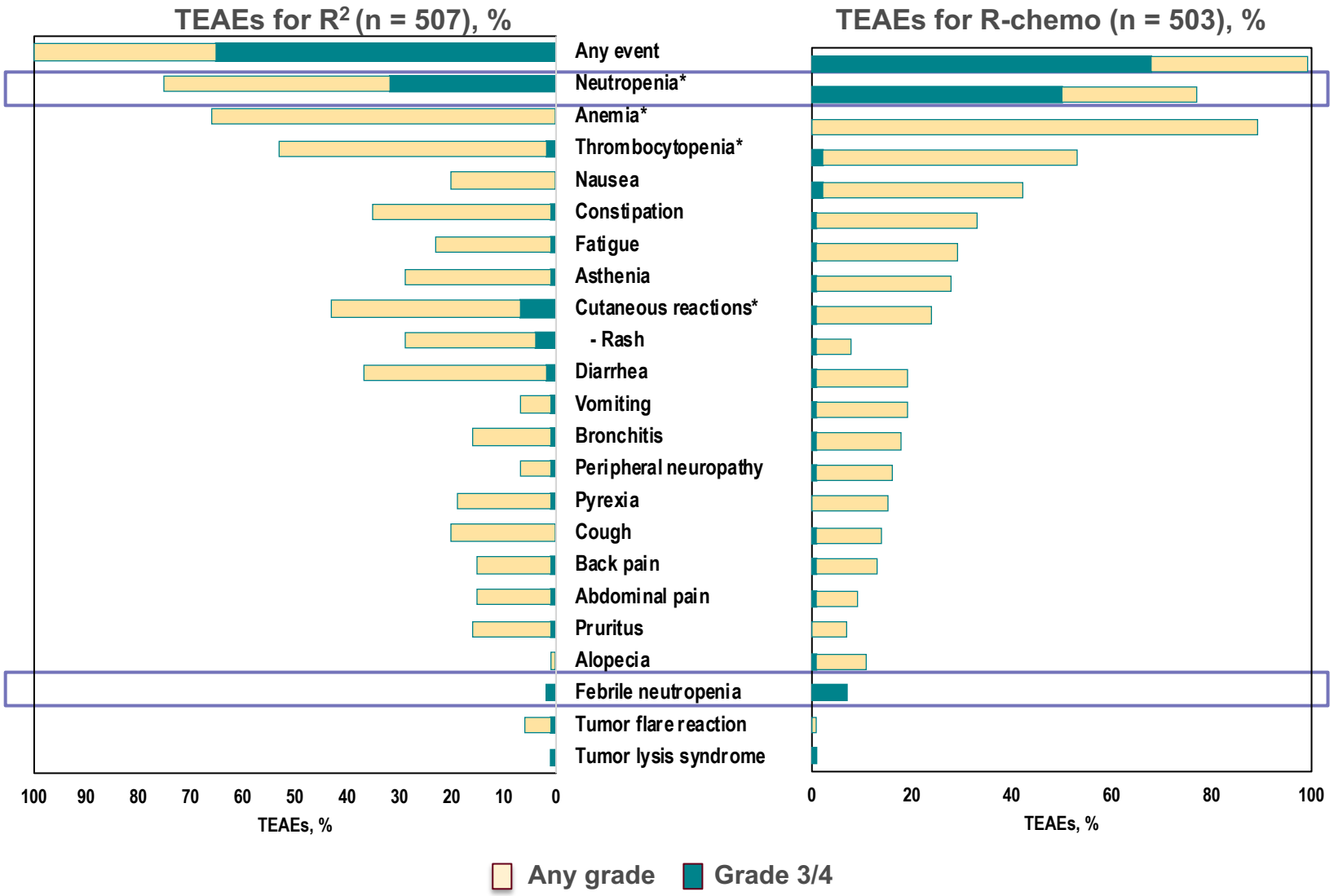
RELEVANCE – PFS and OS





Morschhauser et al, NEJM 379:934, 2018

RELEVANCE: Treatment-Emergent Adverse Events



Data cut-off 31May2017. Includes any-grade TEAEs (≥15%) and select AEs of interest as assessed per NCI CTCAE v4.03.
*Hematologic AEs were based on laboratory tests; all anemia events were grade 1. *Cutaneous reactions included preferred terms from skin and subcutaneous tissue disorders (including rash), gastrointestinal disorders, general disorders and administration site conditions, infections and infestations, and reproductive system and breast disorders.

Fowler NH et al. *Proc ASCO* 2018;Abstract 7500.

FL Response Rates for Approved and Emerging Single-Agent PI3K Inhibitors*

	Copanlisib[1–3]	Idelalisib[4,5]	Duvelisib[6–8]	Umbralisib (TGR1202)[10–13]
Current indication(s)	3rd-line FL	3rd-line FL; 3rd-line SLL; 2nd-line CLL	R/R CLL or SLL after at least 2 prior tx; 3rd-line FL	N/A
Future indication(s)	2nd-line NHL	2nd-line CLL	2nd-line PTCL	CLL; ≥2nd-line NHL
MoA	PI3Ki (α,δ)	PI3Ki (δ)	PI3Ki (δ,γ)	PI3Ki (δ), cMyc
Administration	IV	Oral	Oral	Oral
Dosing schedule	60 mg Day 1, 8, 15 (28-day cycle)	150 mg, twice daily	25 mg, twice daily	Once daily
Study population	≥3rd line[b] (FL, n=104)	≥3rd line[b] (FL, n=72)	≥3rd line[b] (FL, n=83)	≥2nd line (FL, n=12)
ORR (FL)	59%	54%	41%	53%
PFS (FL)	11.2 months	11 months	8.3 months	16
CR (FL)	14%	8%	1.2%	12

*. Cheson et al Clin Leuk Lymph Myeloma, 19:135-141, 2019

Agent	Target
Obinutuzumab/Ublituximab	CD20
Polatuzumab vedotin	CD79b
Bispecifics	CD3/CD19;20
Tafasitamab (MOR208)	CD19
Ibrutinib, Acalabrutinib, Zanubrutinib	Btk
Idelalisib, Copanlisib, Umbralisib, Duvelisib	PI3-K
Venetoclax	BCL-2
Tazemetostat	EZH2
Selinexor	Nuclear transport
Lenalidomide	Multiple
Nivolumab/Pembrolizumab	PD-1
Atezolizumab	PDL-1
Hu5F9-G4; TTI-622	CD47