Treatment of high risk follicular lymphoma

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DISCLOSURE OF AFFILIATIONS

W. Jurczak

Celgene (Research support)
Gilead (Research support)
TG Therapeutics (Research support)
Merck (Research support)
Beigene (Research support)
Pharmacyclics (Research support)
Pfizer (Research support)
Teva (Research support)
Servier (Research support)
Celgene (Research support)
Sandoz Novartis (Advisory board, research support)
Roche (Advisory board, research support)
Janssen (Advisory board, research support)
Acerta (Advisory board, research support)
AbbVie (Advisory board, research support)
Takeda (Advisory board, research support)
NovoNordisk (Advisory board, research support)
Celltrion (Advisory board, research support)

Prognosis of advanced FL

Chemotherapy Era

1970 - 2000

CVP
CHOP
Purine analogues

New regimens ↑ PFS
No effect on OS

OS: 5-7 years

Rituximab Era

1990 - 2010

R - Chemotherapy

↑ PFS
↑ OS

OS: 10-12 y.

Current standard

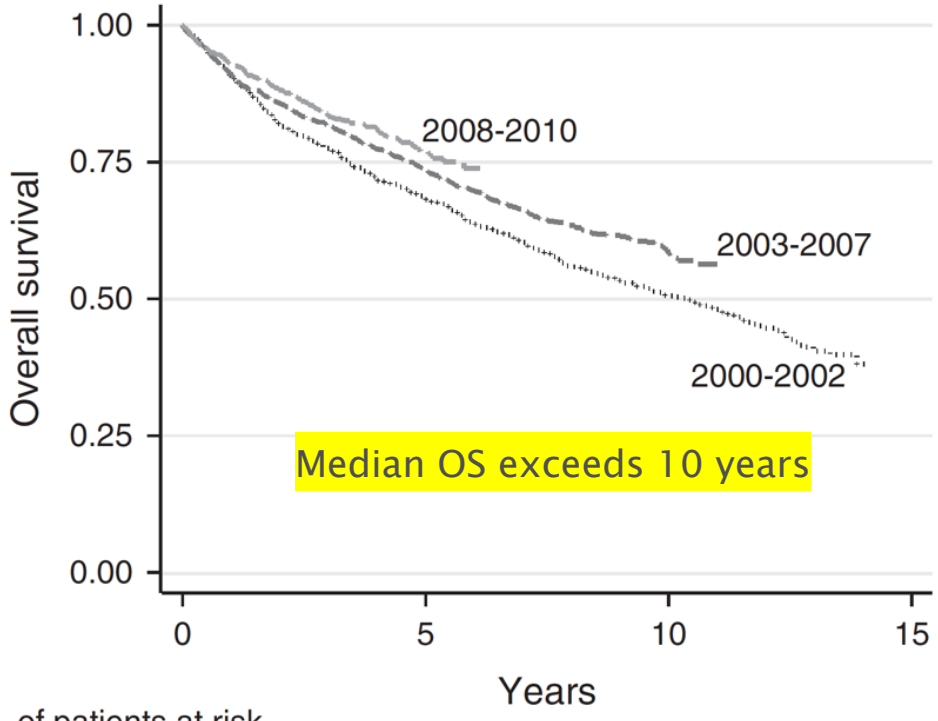
2010s

Chemo-immunotherapy
New drugs
(BCR, BCL2, IMiDs …)
New MoAb

Further ↑ PFS
Further ↑ OS

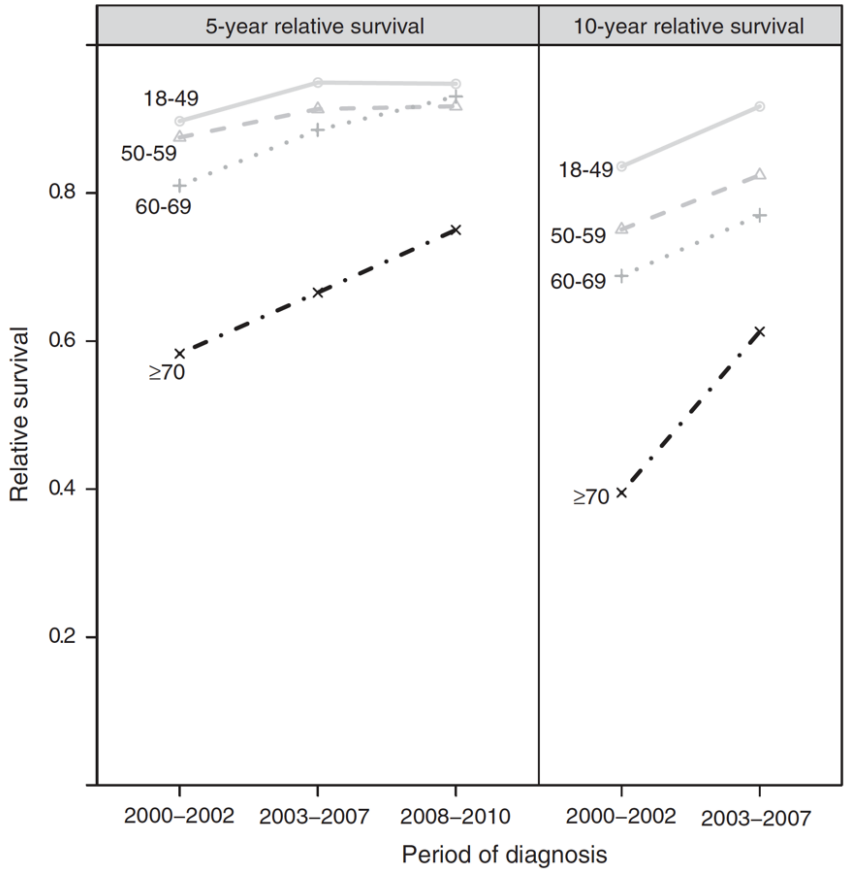
OS 15-20 y.

Follicular lymphoma in Sweden: nationwide improved survival in the rituximab era



No. of patients at risk

2000-2002	757	517	383
2003-2007	1155	845	153
2008-2010	729	195	0

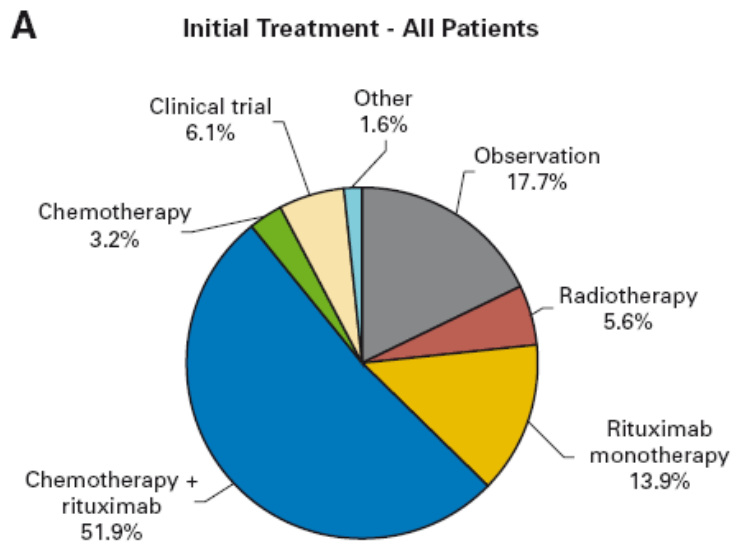


Junlen et al., Leukemia (2015)

One patient may be submitted to 5-7 lines of therapy...

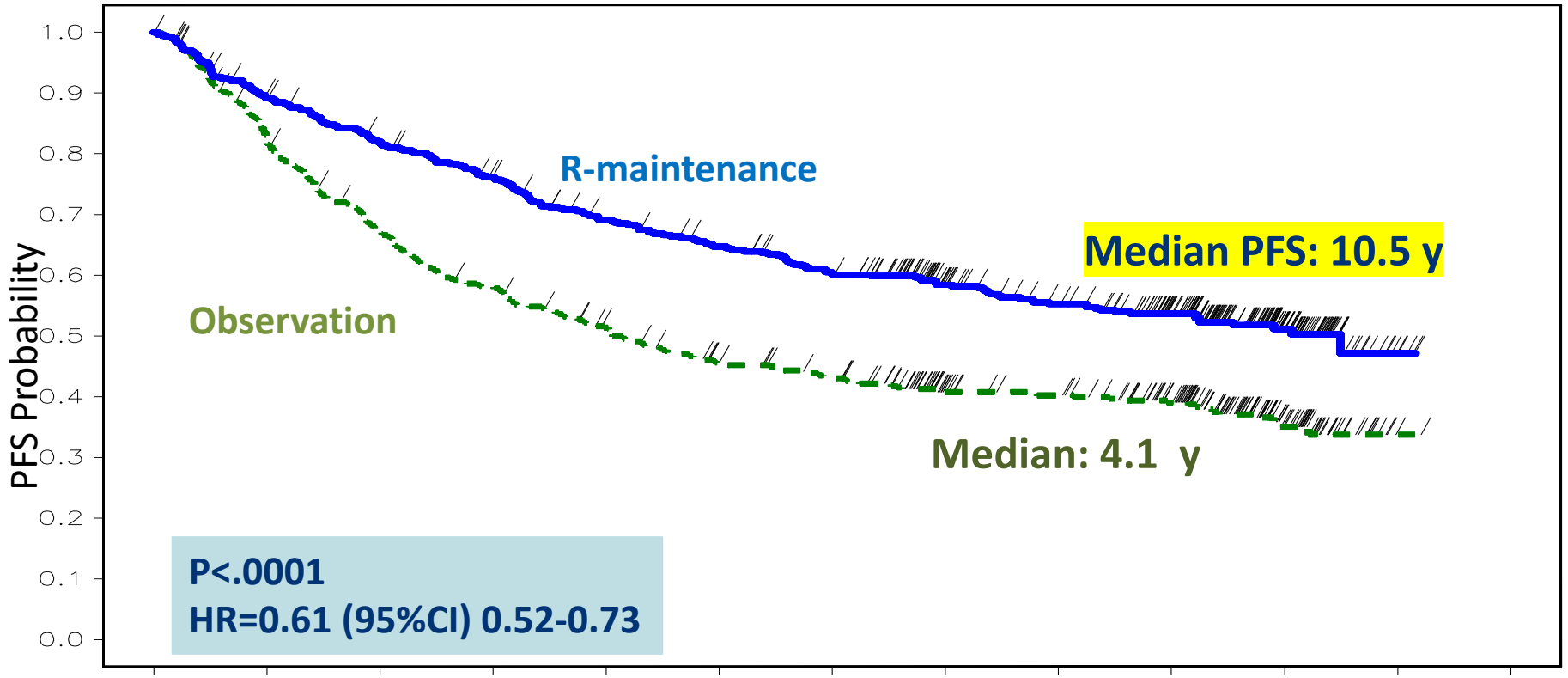
Chemotherapy without MoAb is NOT recommended

Clinical Practice in USA
FL, N= 2728, years 2004-2007



Friedberg et al., JCO 2009

PRIMA: Progression Free Survival at 10 years

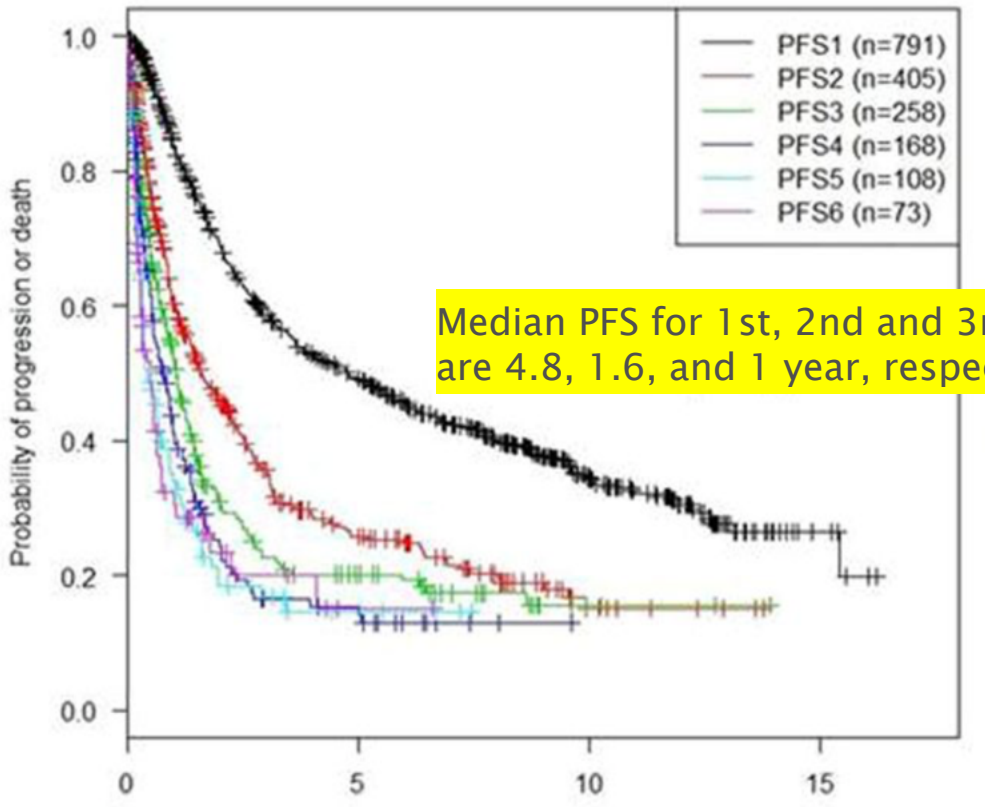


No. left												
Observation	513	415	336	290	251	217	200	155	147	122	41	1	0
Rituximab	505	445	406	372	333	309	284	231	208	170	67	4	0

Salles et al., ASH 2017

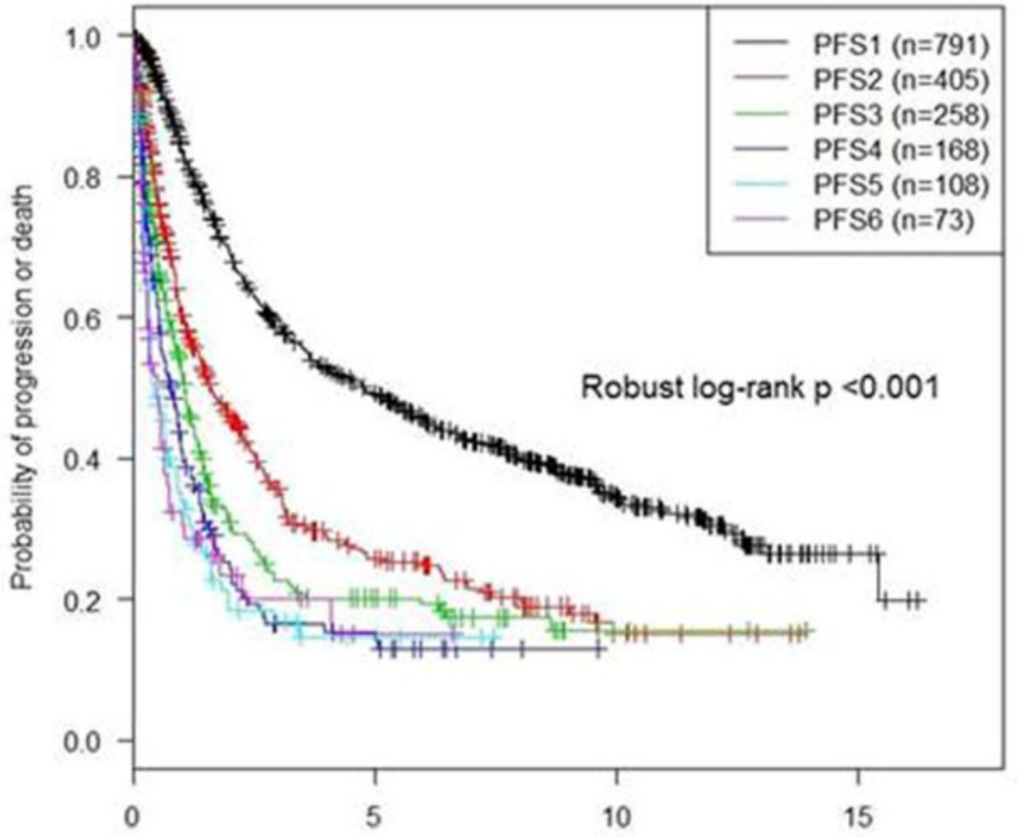
Benchmark of PFS for multiple lines of therapy in FL treated in the Rituximab Era (1998 – 2007, N=1134)

PFS by line of treatment



Median PFS for 1st, 2nd and 3rd line are 4.8, 1.6, and 1 year, respectively

OS since diagnosis



Alperovich et al., ASH (2016)

How to evaluate the novel agents ?

- **OS and PFS** - the traditional endpoint of clinical studies - require extended follow-up (median OS and PFS exceed 10 and 7 years respectively)

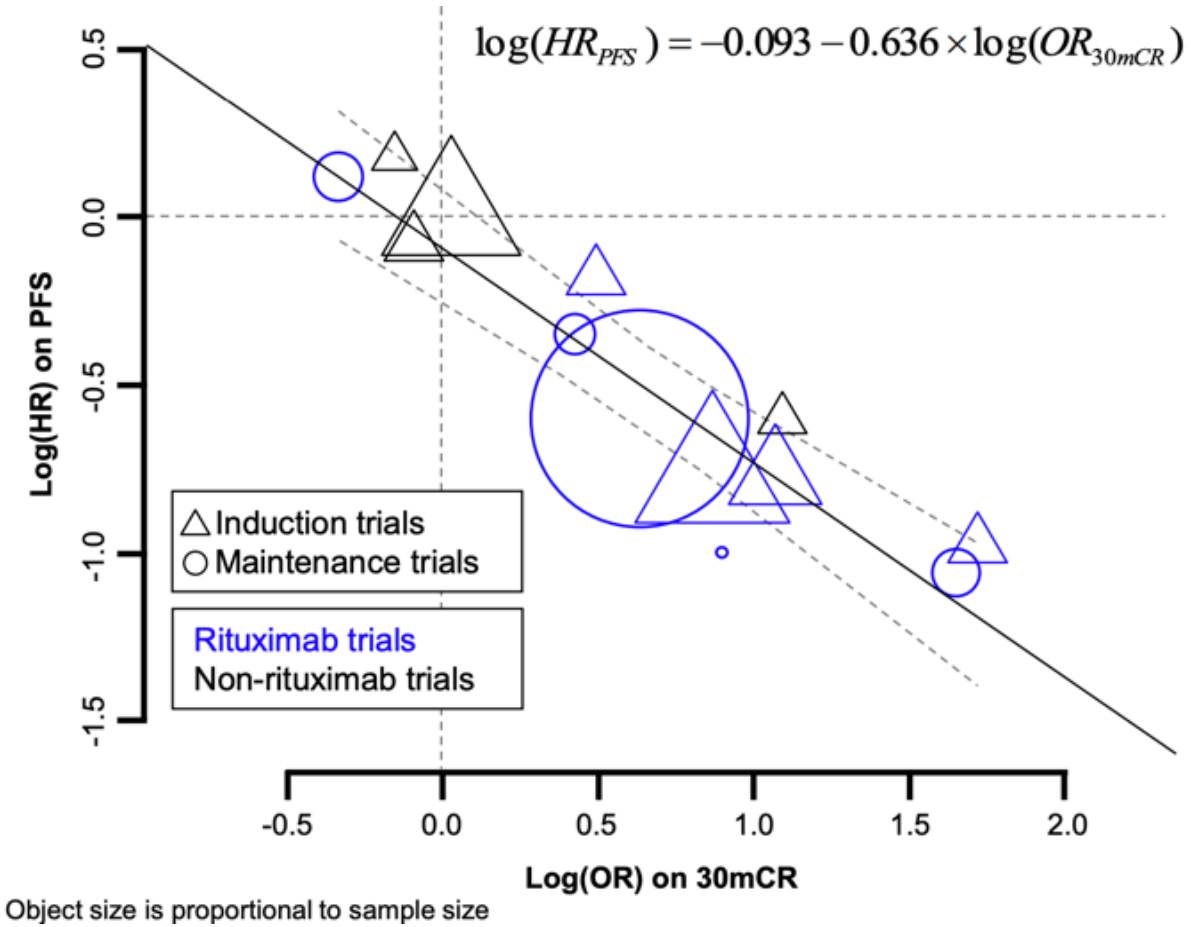
- **CCR30** (Continuous Complete Response rate at 30 months)
  - a potential surrogate of PFS

- **POD24** (Progression of Disease at 24 months)
  - a robust predictor of shortend OS

CR30 as a Surrogate End Point in First-Line Follicular Lymphoma FLASH (Follicular Lymphoma Analysis of Surrogacy Hypothesis) group

- Data from 13 randomized trials (N=3837) in FL (1980 to 2007),
- an adequately long follow-up;
- 2851 Patients on Rituximab, including 1630 on R-maintenance
- 1415 cases with high FLIPI, 1630

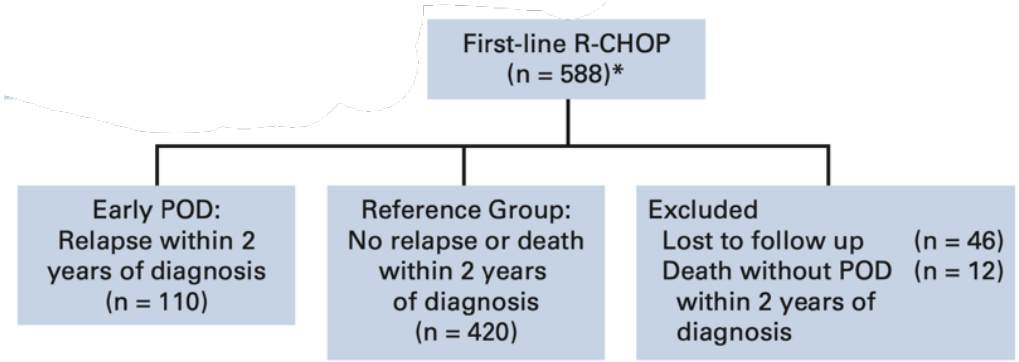
- **Assessment of the prediction of log (HRPFS) on the basis of the estimated regression model. Patient data ensuring the consistent calculation of end points**



Shi et al., JCO (2017)

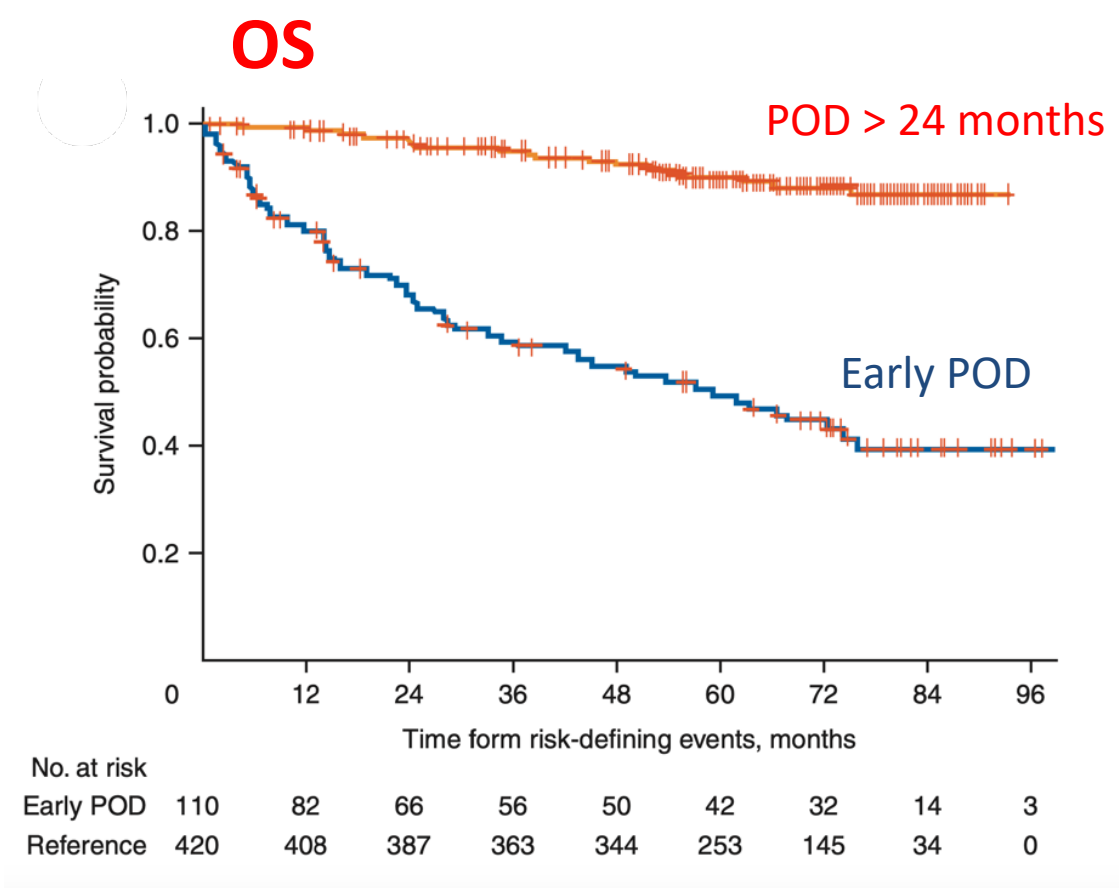
The prognostic significance of POD24 in FL: National LymphoCare Study

- NLCS register data on 2655 newly diagnosed FL patients (2004-2007)



- 110 (19%) relapsed within 2 years of diagnosis
- significantly more likely to have a high FLIPI

- **OS was markedly reduced in the POD24, with a 5-year survival rate of 50% vs 90%**

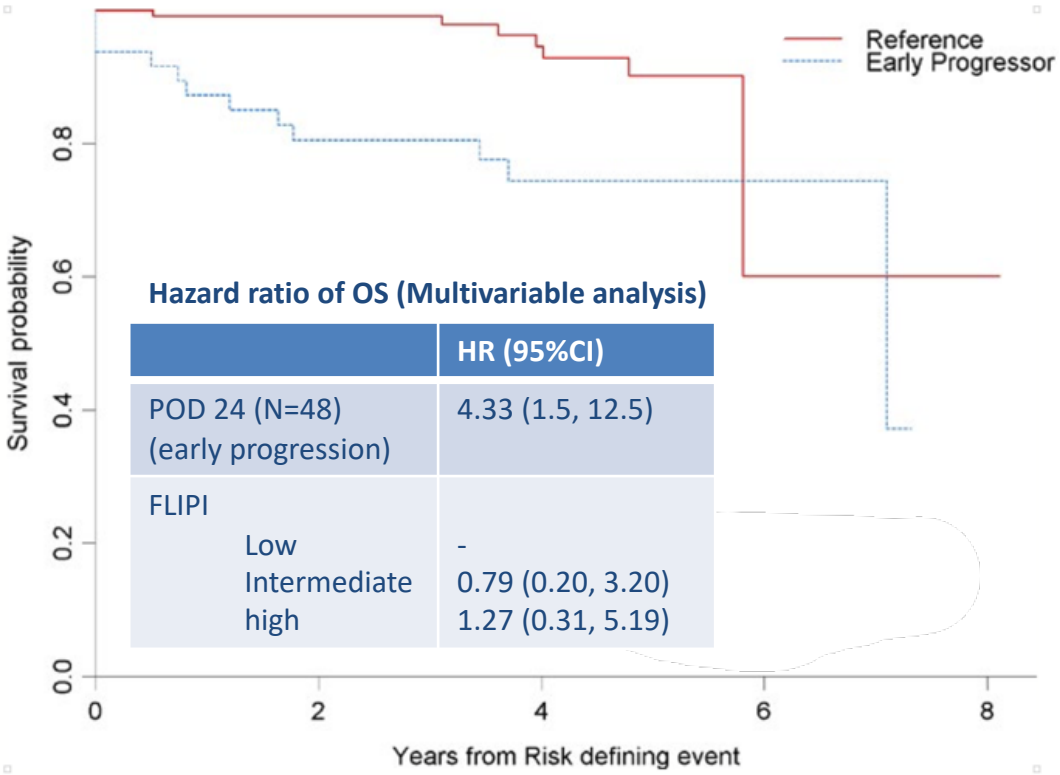


Casulo et al., JCO 2015

The prognostic significance of POD24 in FL: Results of 3 Rituximab based non-chemotherapy CALGB trials

	R-galiximab (Anti-CD80, CALGB 50402)	R-epratuzumab (Anti-CD22, CALGB 50701)	R-lenalidomide (CALGB 50803)
N	60	57	57
Age (median/ range)	57 (22-85)	54 (32-90)	52 (32-79)
FLIPI Low Intermediate High	 12 (20.7%) 25 (43.1%) 21 (36.2%)	 13 (22.8%) 26 (45.6%) 18 (31.6%)	 17 (29.8%) 38 (66.7%) 2 (3.51%)
Early Progression	25 (41.7%)	15 (26.3%)	8 (14.0%)
Median follow-up in years (range)	6.7 (0.0-10.1)	6.3 (0.3-8.1)	4.5 (0.1-5.5)

OS



Hazard ratio of OS (Multivariable analysis)

	HR (95%CI)
POD 24 (N=48) (early progression)	4.33 (1.5, 12.5)
FLIPI	
Low	-
Intermediate	0.79 (0.20, 3.20)
high	1.27 (0.31, 5.19)

Lansigan et al., Cancer Medicine 2018

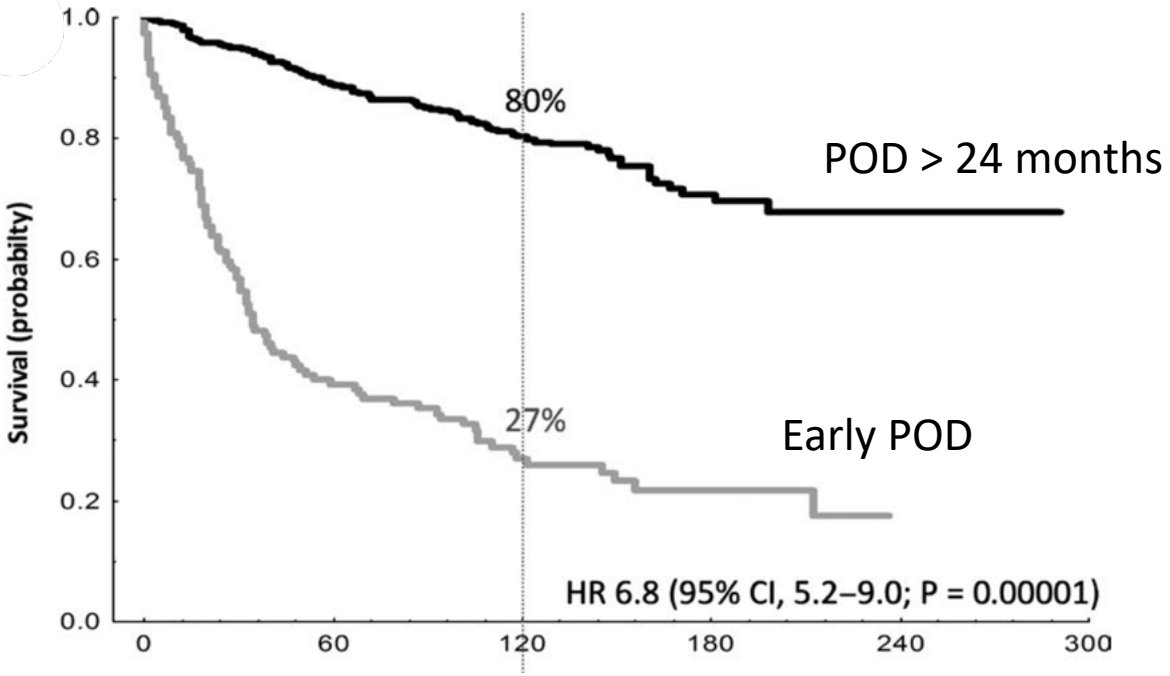
The prognostic significance of POD24 in FL: GELTAMO transplant registry data

629 patients with nontransformed FL who received ASCT (1989 – 2007) at 44 centers in Spain.

Disease status at ASCT

CR1	203 (32.5%)
CR2	174 (28%)
CR3	28 (4.5%)
PR1	140 (22%)
PR ≥ 2	81 (13%)

OS

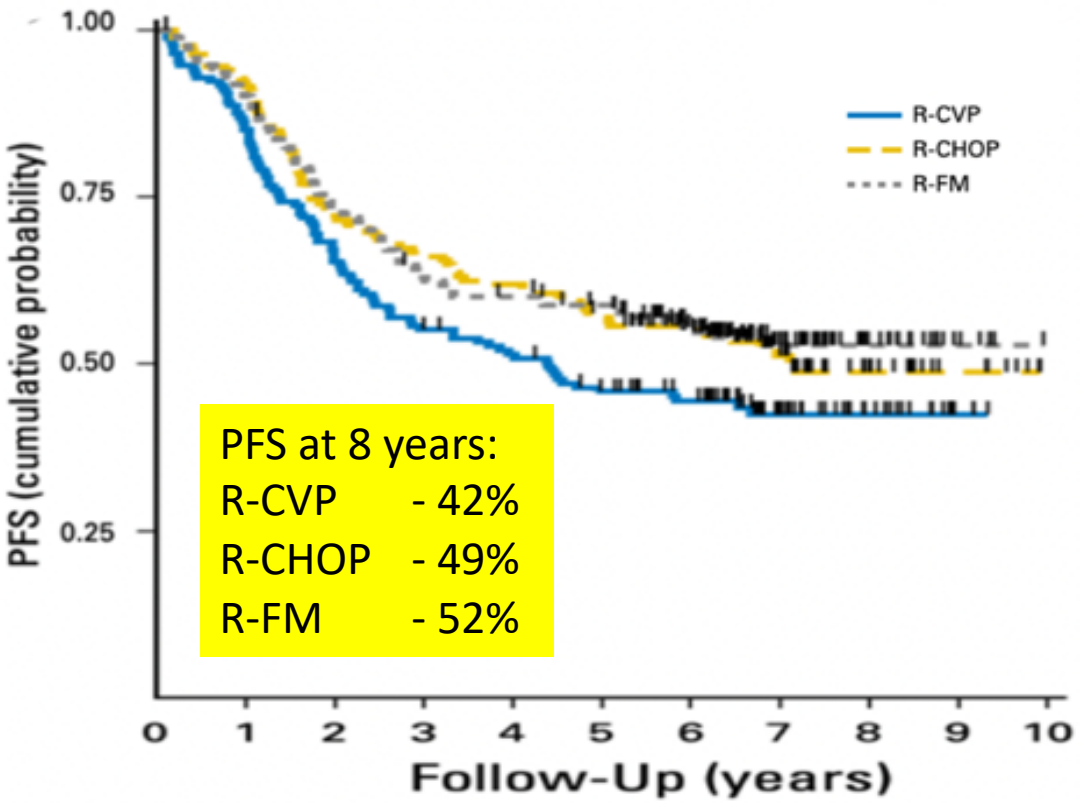


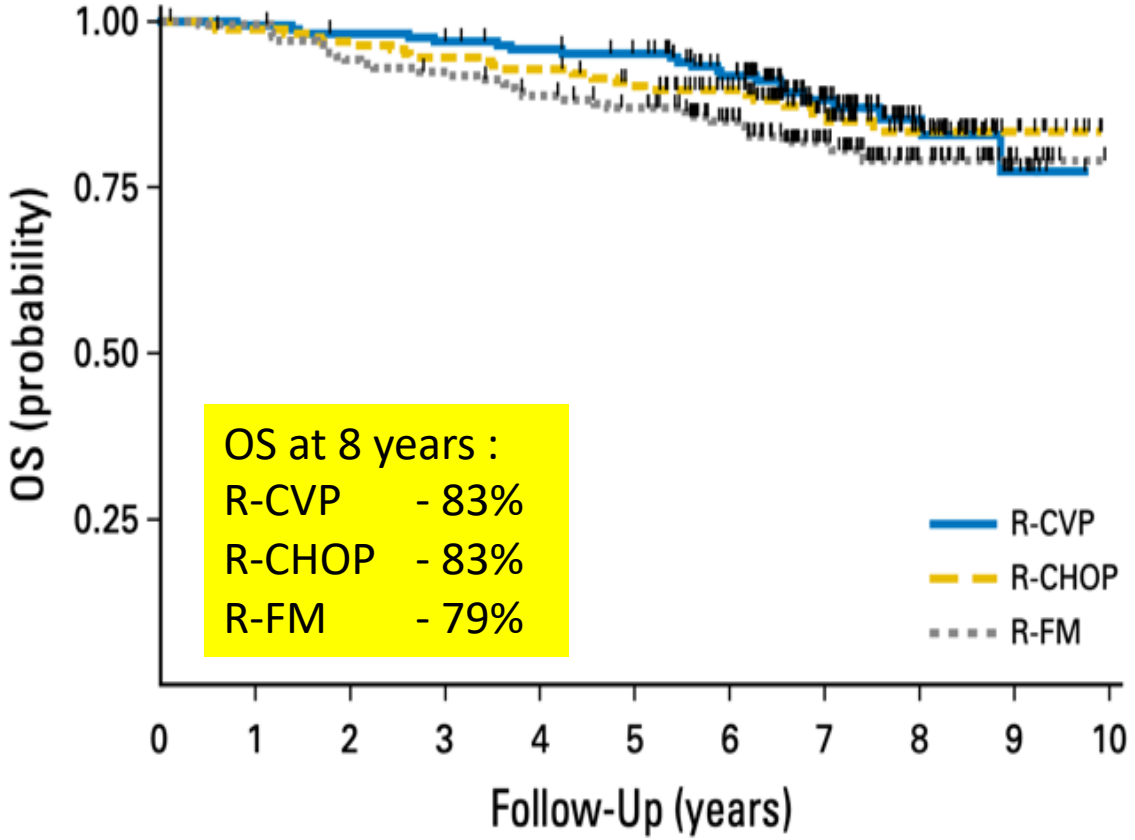
Jiménez-Ubieto et al., Cancer Medicine 2017

First line Immuno-chemotherapy in FL 3-rd phase studies

Study	Patient number	Regimen/design	ORR, % (CR, %)	PFS/TTF	OS
Marcus et al. [51]	321			TTF (mFU 30 months)	At 4 years:
		CVP	57 (10)	7 months	77%
		R-CVP	81 (41)	27 months	83%
				(*P*<0.0001)	(*P*=0.029)
Hiddeman et al. [50]	428			18 month TTF rate:	
		CHOP	90 (17)	12.6%	17 deaths
		R-CHOP	96 (20)	29.8%	6 deaths
				(*P*<0.001)	(*P*=0.016)
Federico et al. [53]	534			3-year TTF rate:	At 3-years:
		R-CVP	88 (67)	46%	95% for all patients
		R-CHOP	93 (73)	62%	
		R-FM	91 (72)	59%	
Press et al. [47]	532			5-year PFS rate	At 5 years
		R-CHOP	84 (40)	60%	92%
		CHOP-iodine-131 tositumomab	84 (45)	66%	86%
				(*P*=0.11)	(*P*=0.08)
Rummel et al. [49]	514			PFS:	Deaths:
		R-CHOP	91 (30)	31.2 months	17.8%
		BR	93 (40)	69.5 months (HR 0.58, 95% CI [0.44, 0.74]; *P*<0.0001)	16.5%
Flinn et al. [54, 55]	447			5-year PFS rate:	At 5 years
		R-CHOP/R-CVP	91 (25)	55.8%	85.0%
		BR	97 (31)	65.5% (HR 0.61, 95% CI [0.45, 0.85]; *P*=0.0025).	81.6% (HR 1.1, 95% CI [0.72, 1.84]; *P*=0.5461)
Salles et al. [57, 58]	1018 randomized		2 years after radomization	6 year PFS rate:	At 6 years
		R-CHOP/R-CVP/R-FCM	CR/CRu—52.2	42.7%	88.7%
		R-CHOP/R-CVP/R-FCM+MR	CR/CRu—71.5 (*P*=0.0001)	59.2% (HR 0.58, *P*<0.0001	87.4%
Marcus et al. [41]	1202			3-year PFS rate:	3 year estimate
		R-CHOP/R-CVP/BR+MR	86.9 (23.8)	73.3%;	92.1%
		O-CHOP/O-CVP/BO+MO	88.5 (19.5)	80.0%	94.0%
				(HR 0.66; 95% CI [0.51–0.85]; *P*=0.001)	(*P*=0.21)

FOLL05 Study comparing R-CVP vs R-CHOP vs R-FM (N= 534, no R-maintenance)

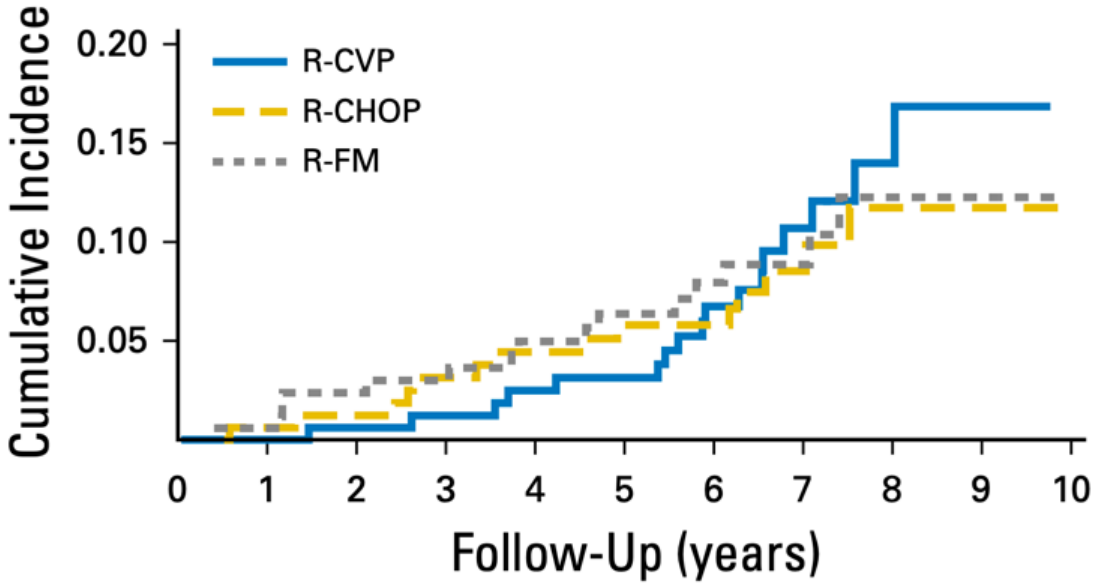




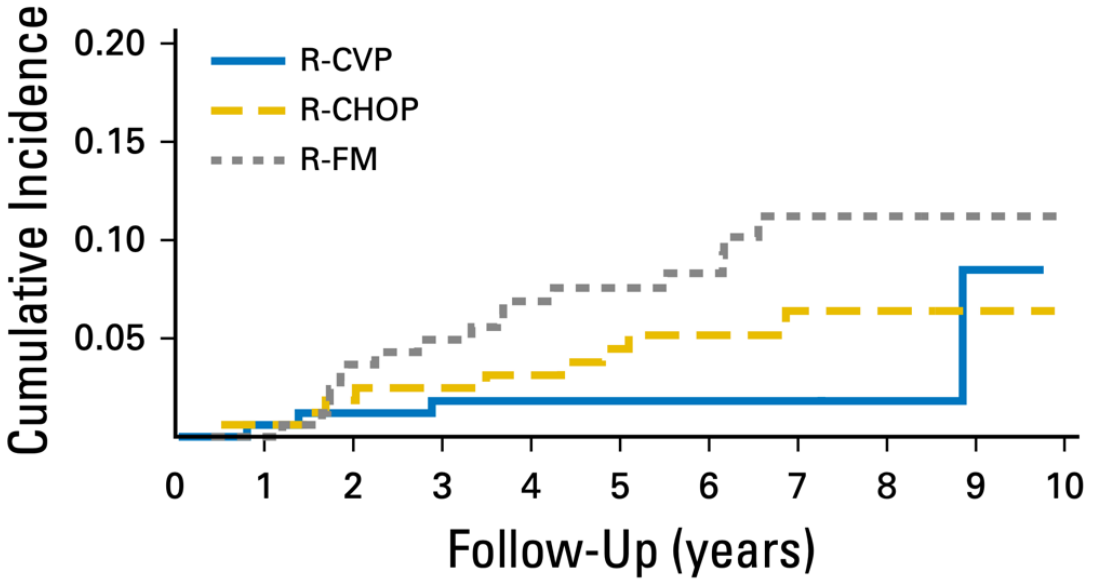
Luminari et al., JCO (2018)

FOLL05 Study comparing R-CVP vs R-CHOP vs R-FM (N= 534, no R-maintenance)

Lymphoma-related causes of death (P= 0.90)



Non-Lymphoma related causes of death (P= 0.01)



Luminari et al., JCO (2018)

The risk of SPM (second primary malignancy) in FL patients

SPM (excluding skin cancers)	R-CVP (n=165)	R-CHOP (n=166)	R-FM (n=171)
Breast cancer (female)	1	2	1
Uterine cancer	-	1	2
Prostate cancer	2	1	1
Lung cancer	-	2	1
Kaposi sarcoma/skin cancer	1	1	2
GI tract	1	1	1
Urothelial cancer	-	2	-
Prostatic cancer	-	-	1
Melanoma	1	-	1
Glioblastoma	-	1	-
AML/MDS	1	3	5
Hodgkin lymphoma	-	1	1
Multiple myeloma	-	1	-
CLL	-	1	-
SMZL	-	1	-
Total SM(%)	**7 (4.2%)**	**18 (10.8%)**	**16 (9.3%)**
Histologic transformation	**5 (3.0%)**	**4 (2.4%)**	**2 (1.1%)**

Luminari et al., JCO (2018)

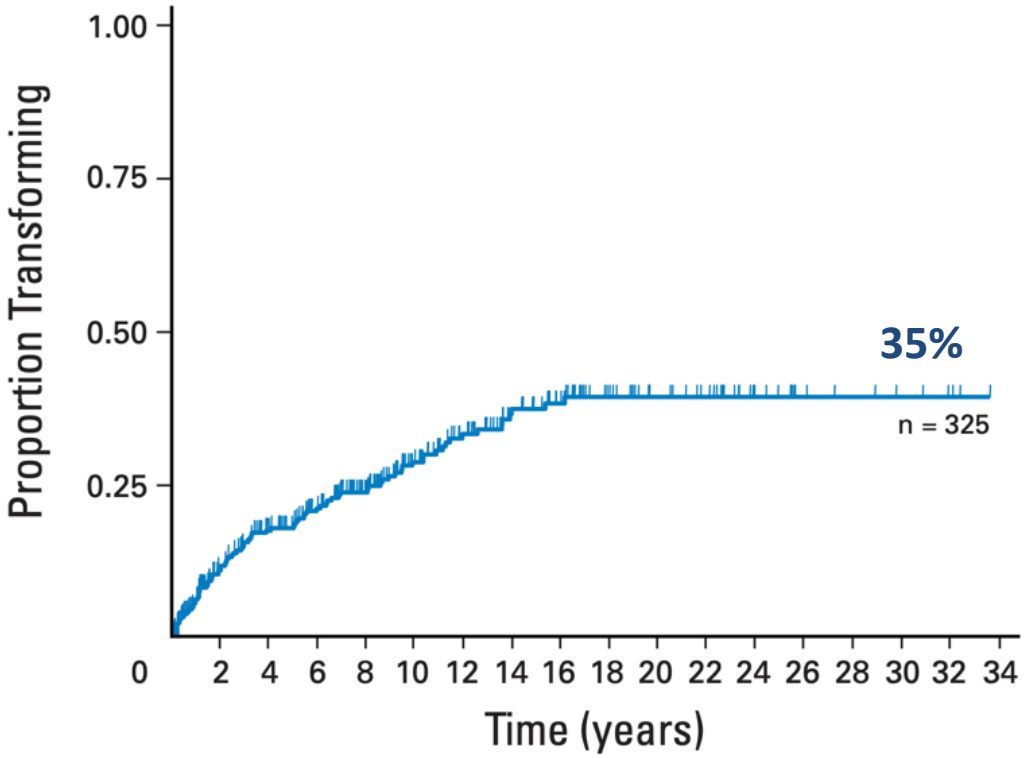
Cumulative incidence of SPM in other studies

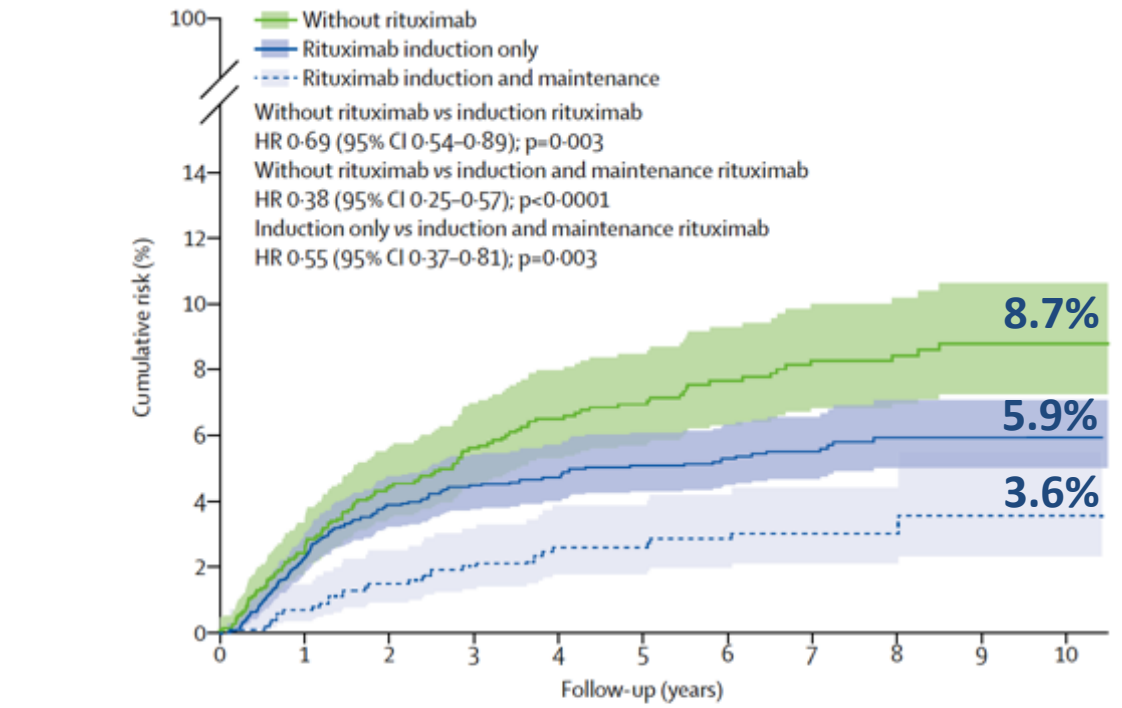
10.5% (12-years, 563 iNHL pts)
- Sacchi et al., Haematologica 2008,

27% (10-years, FND: fludarabine, mitoxantrone and dexamethason treated pts)
- Nastoupil et al., Br J Haemat 2017

8% (10 years, FCM: fludarabine, cyclo-phosphamide and mitoxantrone treated pts)
- Magnano et al. Ann Hematol 2017

Rituximab and risk of FL transformation
A retrospective pooled analysis (N=8116)



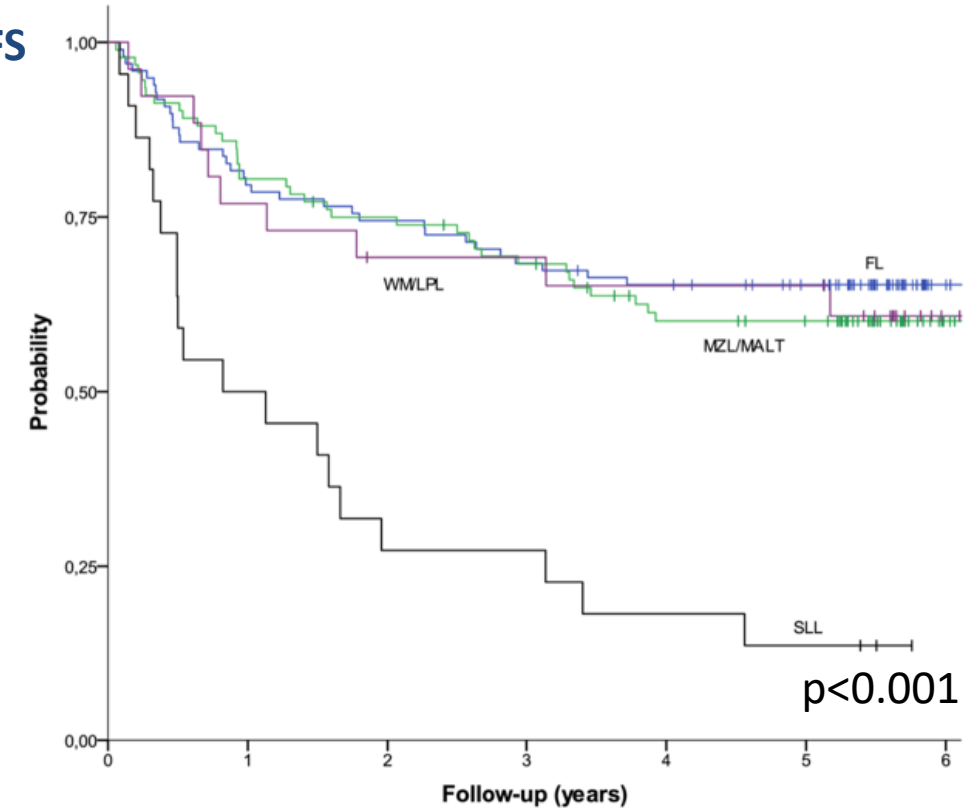


Number at risk											
Without rituximab	1616	1474	1365	1275	1177	1056	896	769	627	434	347
Rituximab induction only	2744	2549	2406	2293	2173	2018	1669	1119	723	494	348
Rituximab induction and maintenance	1022	1006	970	919	850	788	618	351	185	61	18

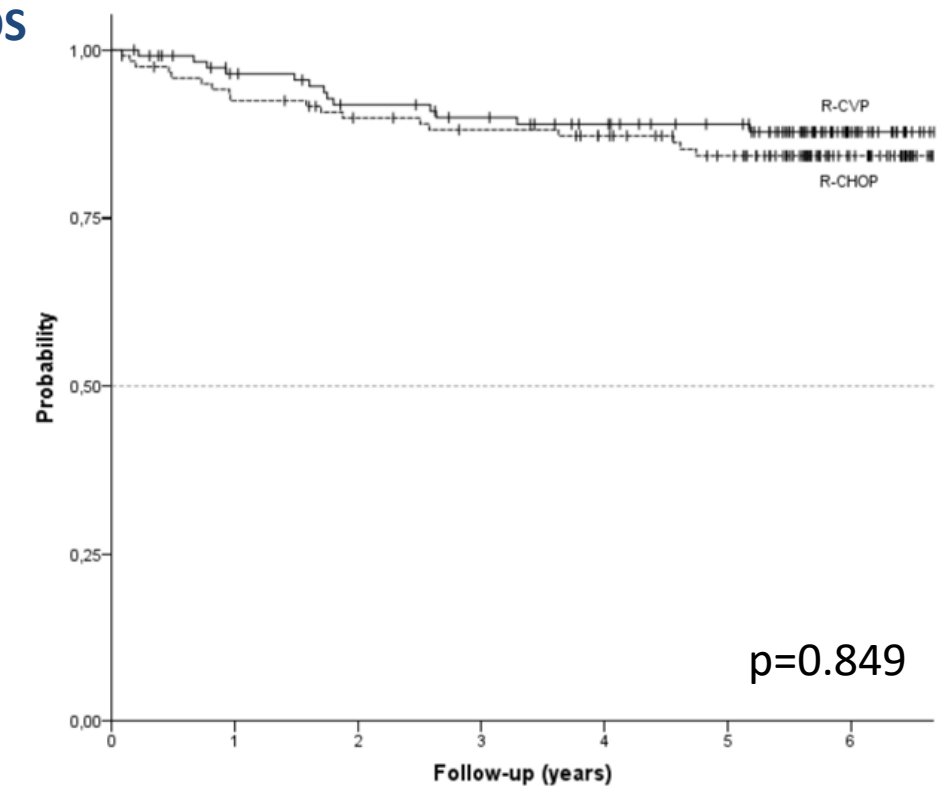
Montoto et al., JCO 2007;
Fedeerico et al., Lancet Haematol 2018

PLRG-04 (R-CVP vs R-CHOP + R-maintenance in iNHL, N=250)

EFS

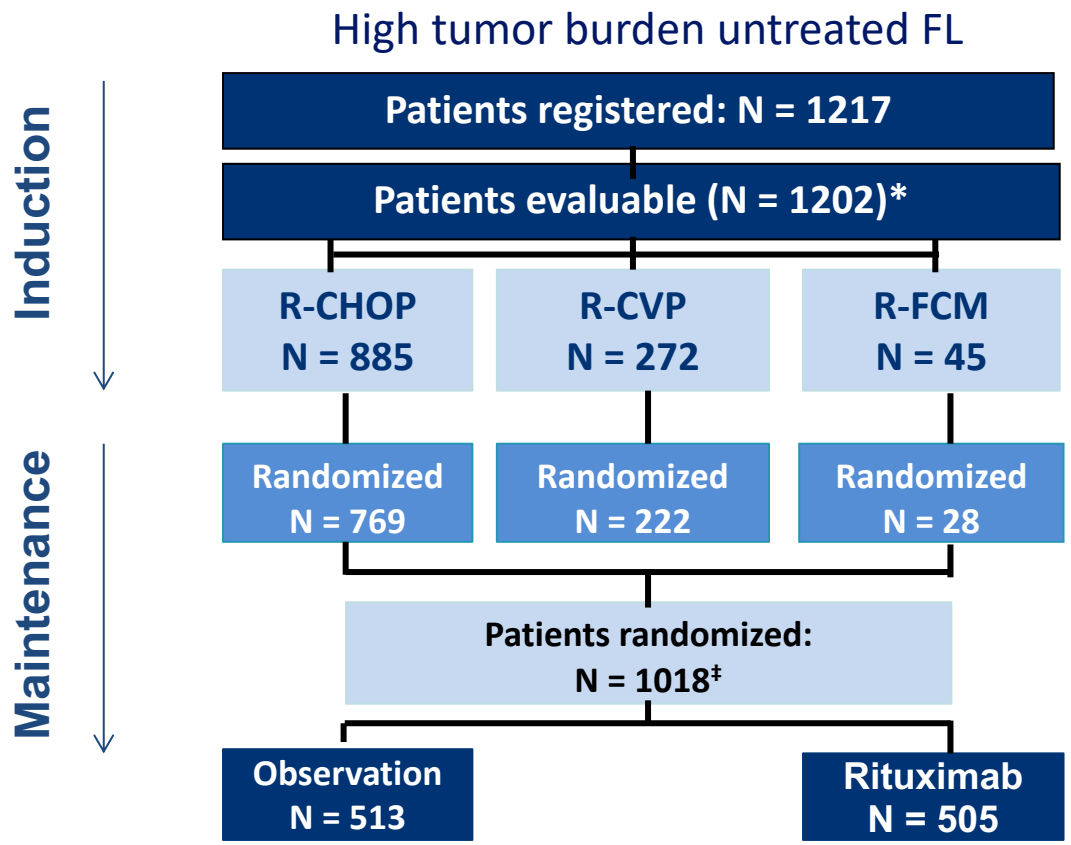


OS



Walewski et al., ICML 2019

PRIMA: Study design and Patient disposition (N=1217)



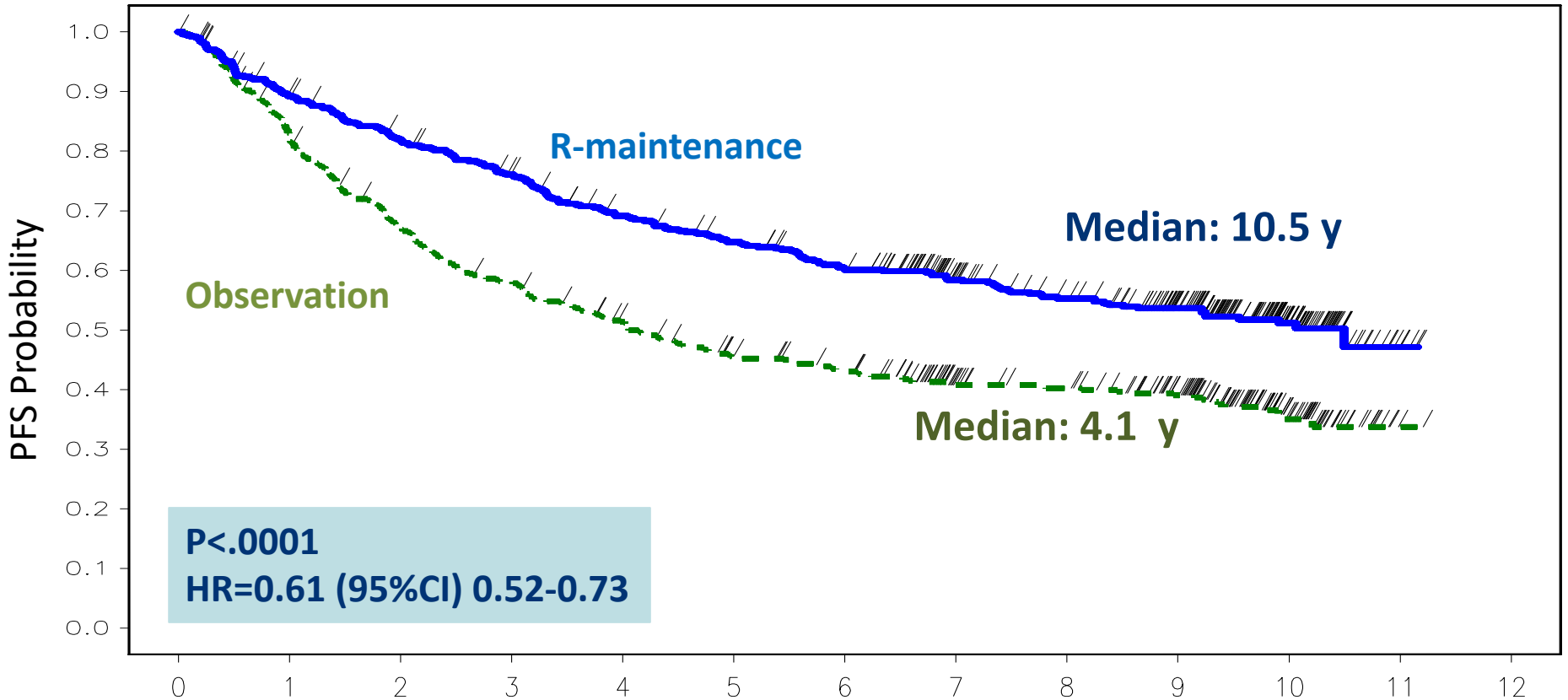
223 centres in 25 countries

- *9 pts did not receive chemo*
- *147 pts withdrew during or at the end of induction (failure to respond; toxicity)*
- *28 pts failed to be randomized on time*

‡ 1 pt died during the randomization process

Salles et al., ASH 2017

PRIMA: Progression Free Survival at 10 years



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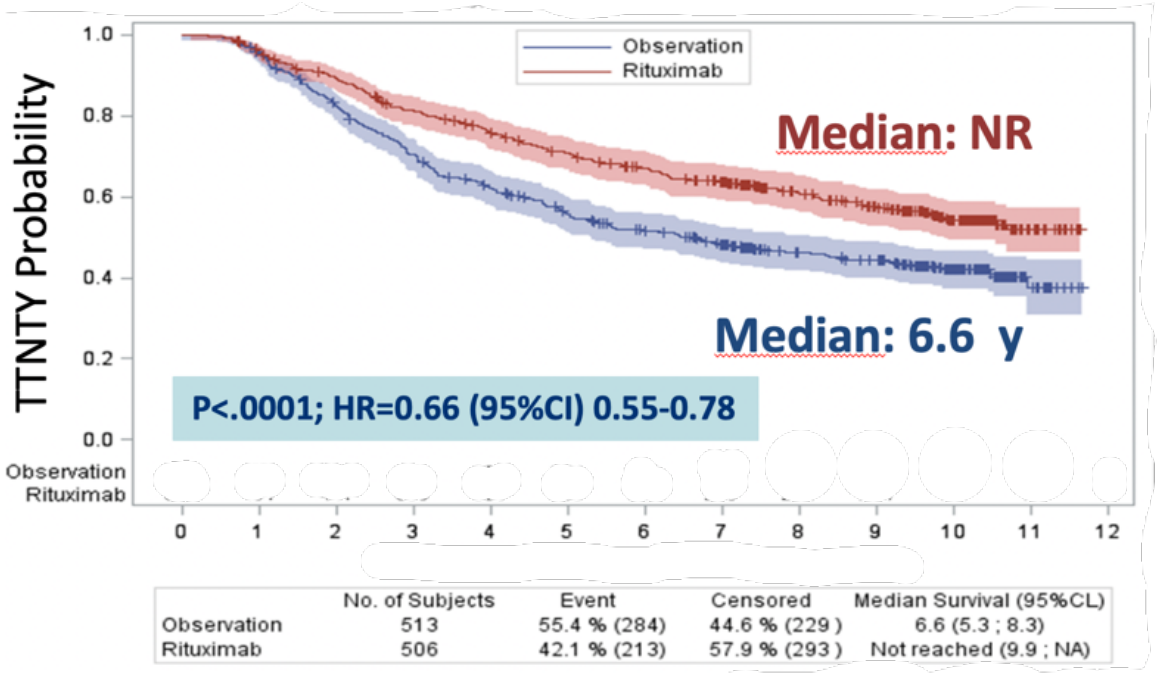
Rituximab	505	445	406	372	333	309	284	231	208	170	67	4

Salles et al., ASH 2017

PRIMA: Secondary endpoints

TTNT



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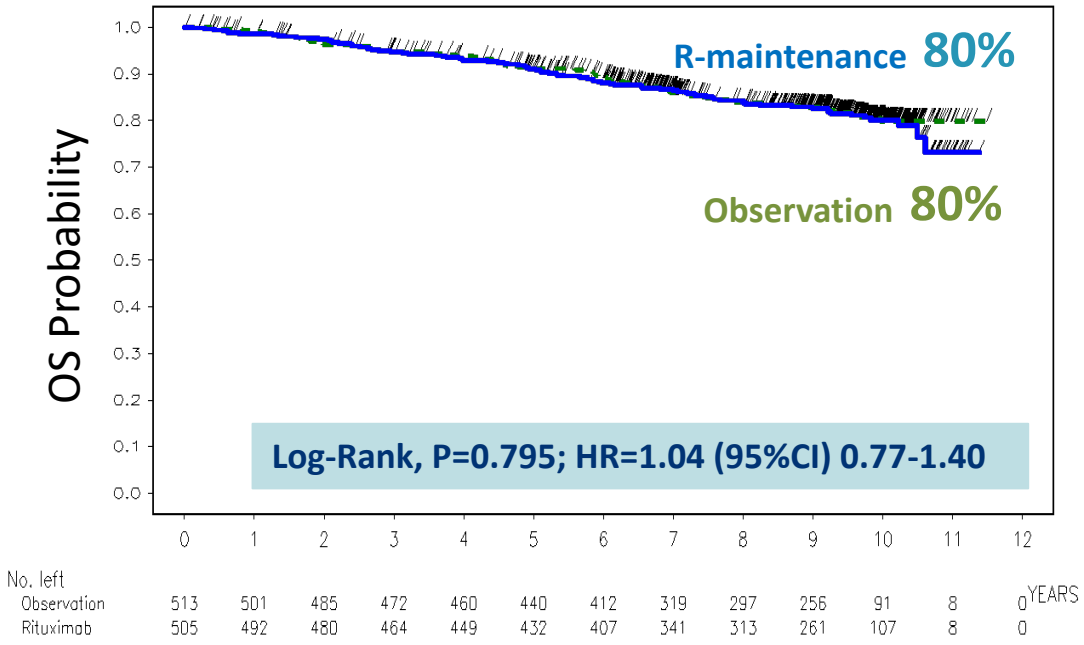


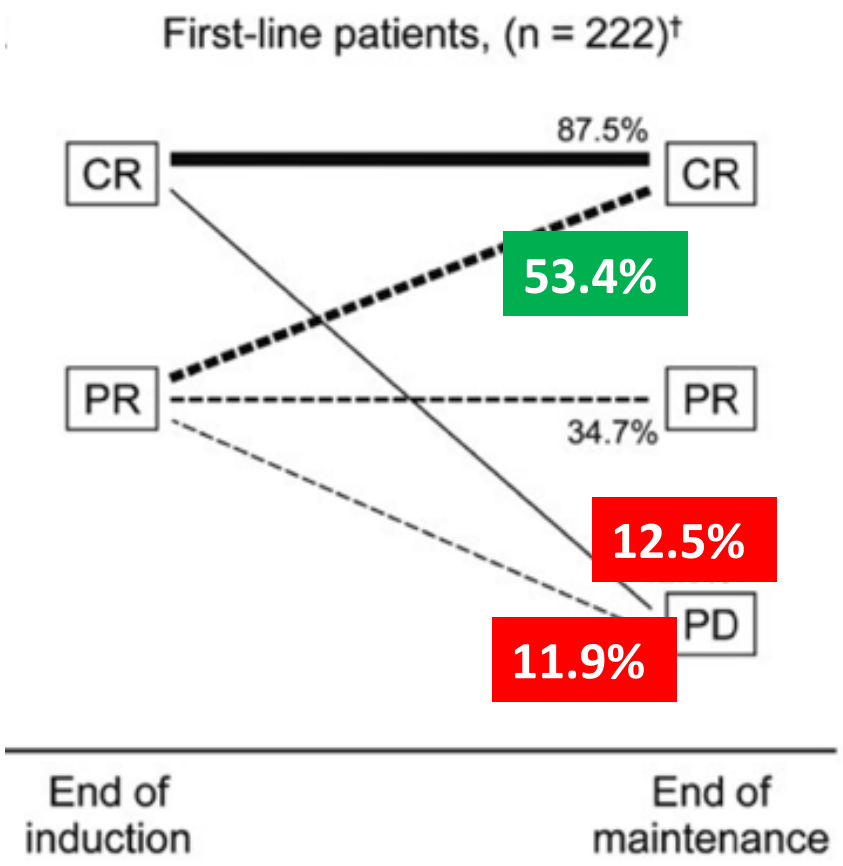
Salles et al., ASH 2017

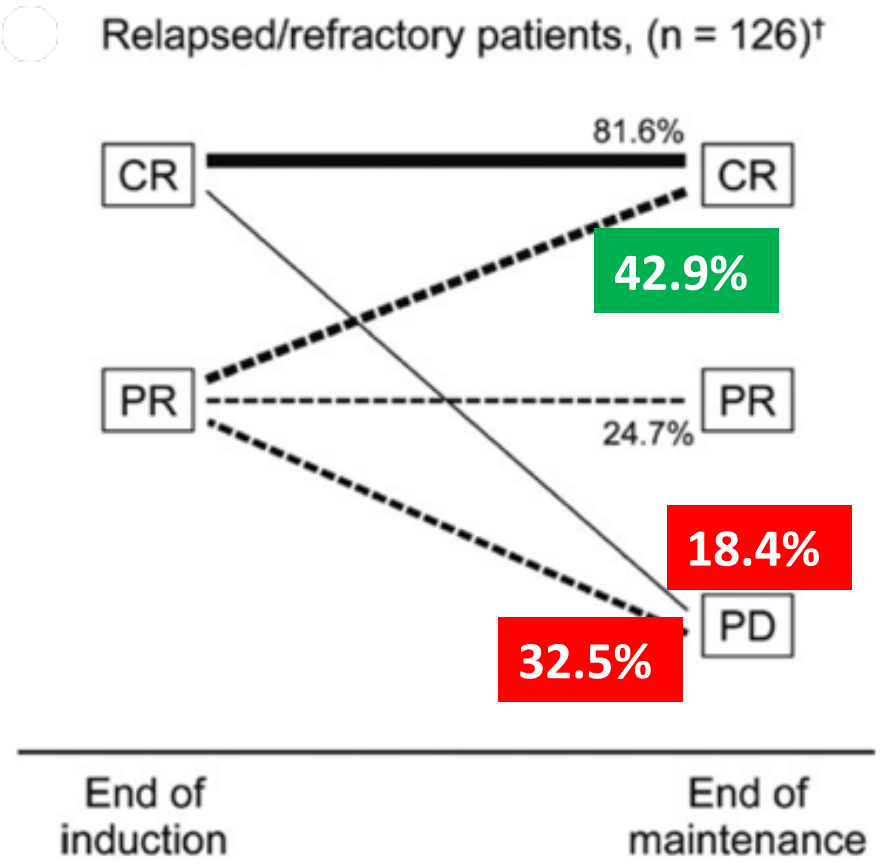
PRIMA: Adverse events

	Observation (n=508)		Rituximab maintenance (n=501)	
	Grade 3/4	Leading to treatment discontinuation	Grade 3/4	Leading to treatment discontinuation
All adverse events	84 (17%)	8 (2%)	121 (24%)	19 (4%)†
Neoplasia	17 (3%)	6 (1%)	20 (4%)	5 (1%)
Neutropenia	5 (1%)	0	18 (4%)	0
Febrile neutropenia	2 (<1%)	0	1 (<1%)	1 (<1%)
Infections	5 (1%)	0	22 (4%)	4 (1%)
CNS disorders	13 (3%)	0	10 (2%)	0
Cardiac disorders	5 (1%)	0	11 (2%)	1 (<1%)
Pregnancy	NA	2 (<1%)	NA	3 (1%)

Salles et al., Lancet 2010

PR→ CR during R- maintenance
Routine clinical practice (prospective obs. in Germany 2009-14)

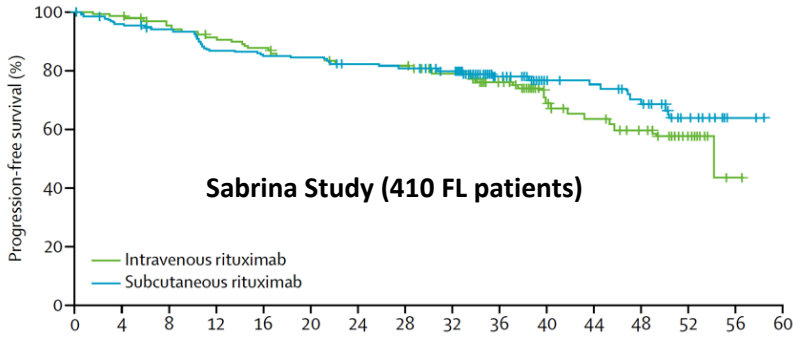




Dührsen et al., Cancer Medicine 2018

Improving R-chemotherapy results

- **s.c. Rituximab** (shortening time of therapy administration, **improving QoL**)
  - Davies et al., Lancet Haematol. 2017



- **Rituximab biosimilars** (reducing the cost of therapy, **improving treatment accessibility**)
  - Coiffier et al., Lancet Haematol 2017
  - Jurczak et al., Lancet Haematol 2017
  - Ogura et al., Lancet haematol 2018

Study	Design	Indication	Primary endpoint	N	Status
GP2013					
JP-trial	Phase I Open-label Single-arm	Indolent LTB NHL	Safety and PK of SDZ-RTX	6	Completed NCT01933516
ASSIST-RA	Phase II RCT (1:1:1) Double-blind	RA	PK equivalence between SDZ-RTX and Ref-RTX	312	Completed Published[1]
ASSIST-FL	Phase III RCT (1:1) Double-blind	Advanced FL	Therapeutic equivalence between SDZ-RTX and Ref-RTX-EU	629	Study ongoing Published[2]
ASSIST-RT	Phase III RCT (1:1) Double-Blind	RA	Safety and immunogenicity	107	Completed Published[3]

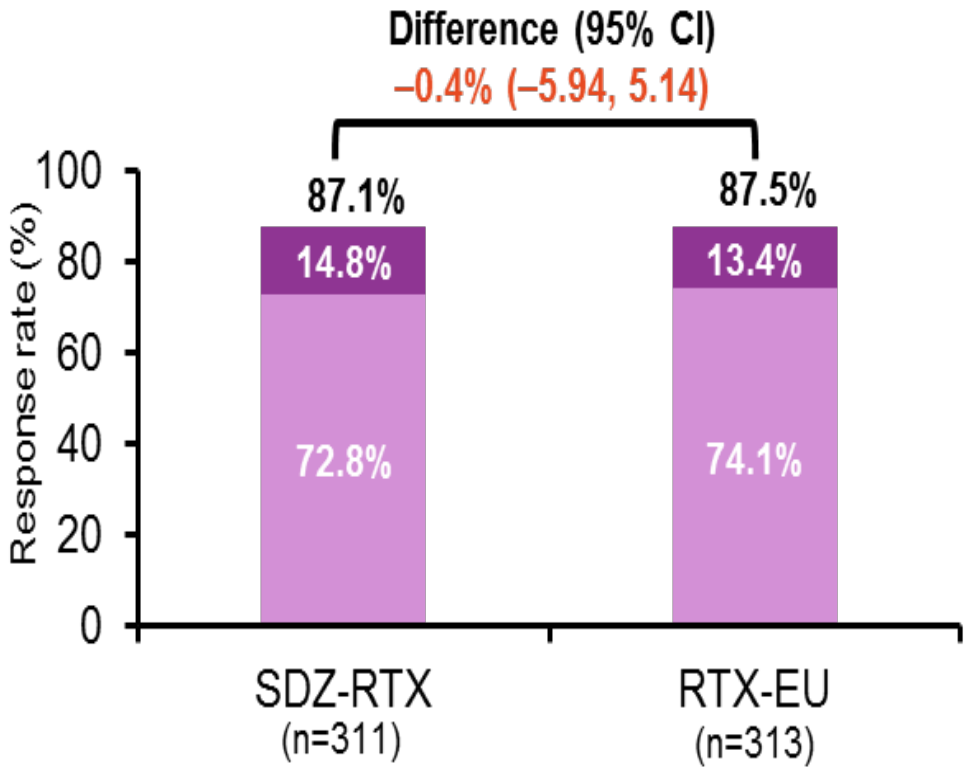
1054 patients

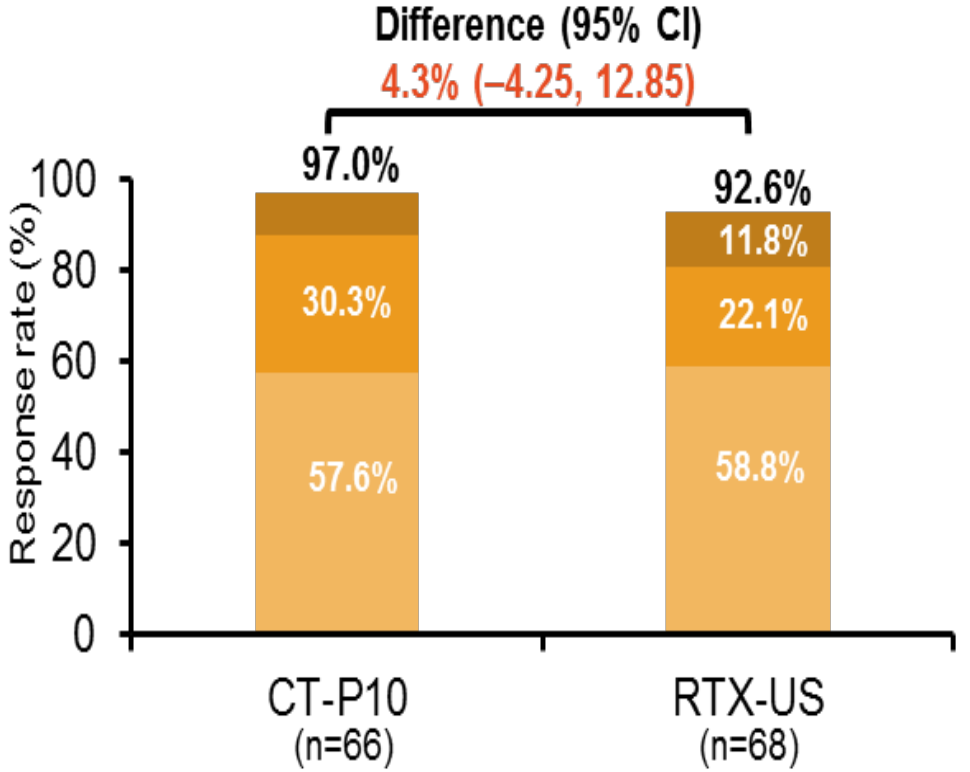
Study	Design	Indication	Primary endpoint	N	Status
CT-P10					
1.1	Phase I RCT (2:1) Double-blind	RA	PK equivalence between CT-P10 and Ref-RTX	154	Completed Published[4,5]
1.3 (1.1 follow-on study)	Phase I Open-label Single-arm	RA	Long-term efficacy and safety of CT-P10	58	Completed Published[6]
1.2	Phase I Open-label Single-arm	DLBCL	Initial evidence of CT-P10 safety	N/A	Terminated recruitment difficulties[7,8]
3.2	Phase III RCT (1:1:1) Double-blind	RA	PK and therapeutic equivalence between CT-P10 and Ref-RTX	372	Study ongoing Published[9]
3.3	Phase I/III RCT (1:1) Double-blind	Advanced FL	PK equivalence and therapeutic non-inferiority between CT-P10 and Ref-RTX-US	140	Study ongoing Published[10]
3.4	Phase III RCT (1:1) Double-Blind	LTB FL	Therapeutic equivalence between CT-P10 and Ref-RTX	258	Study ongoing Published[10]

982 patients

- **Obinutuzumab** and other glycoengineered MoAb (**prolonging PFS**)

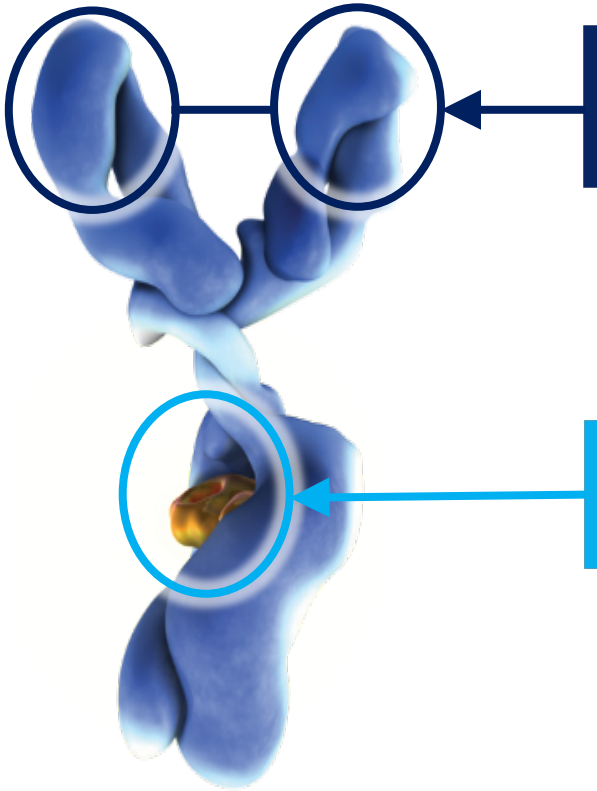
Rituximab Biosimilars in advanced stage FL





Jurczak et al, Lancet Haematol 2017; Coiffier et al, Lancet Haematol 2017

Obinutuzumab

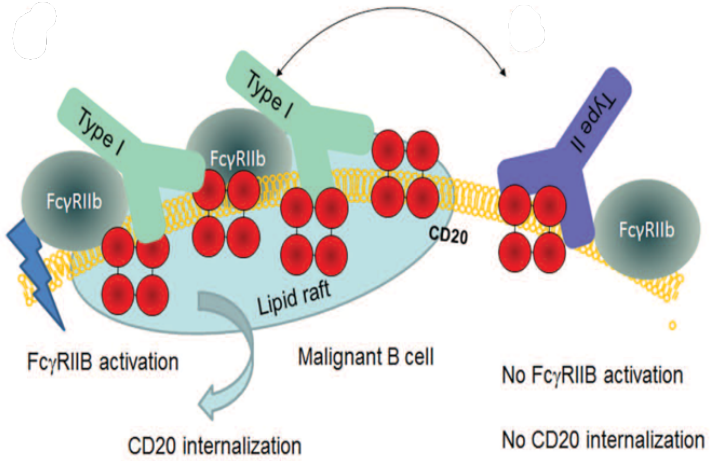


Type II anti-CD20 MoAb

Enhanced direct cellular kill and weaker complement activation compared to type I MoAbs

Glycoengineered Fc region

Enhanced affinity to FcγRIIIa/b receptor, enhanced antibody dependent cellular toxicity (ADCC) and phagocytosis (ADCP) compared to type I MoAbs

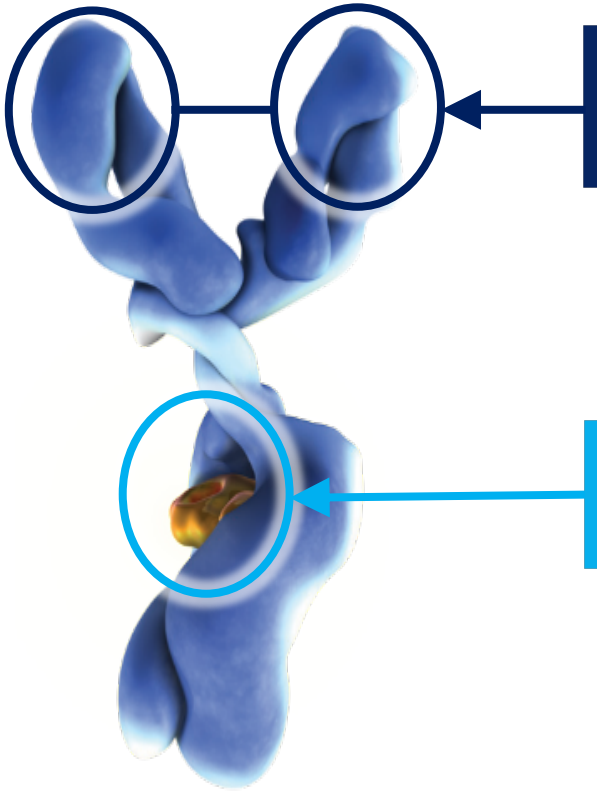


Type I-anti-CD20 mAbs binding may result in internalisation of CD20 into B Cells

Type II-anti-CD20 mAbs remainalmost exclusively on the cel surface and do not internalise

Mossner et al., 2010; Niederfellner et al., 2011; Klein C, et al. MAbs 2013; Ferrara C, et al. J Biol Chem 2006

Obinutuzumab



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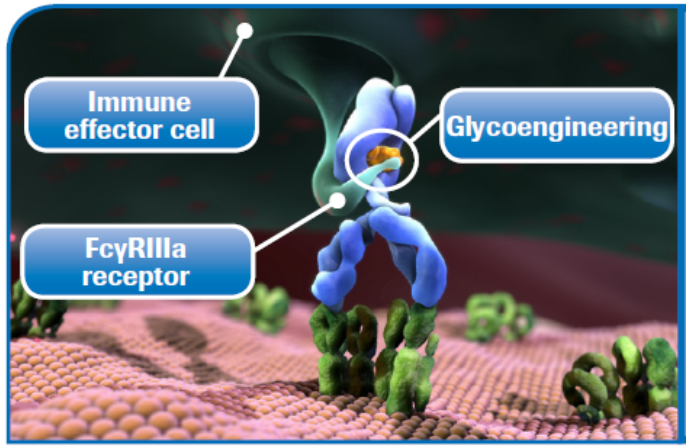
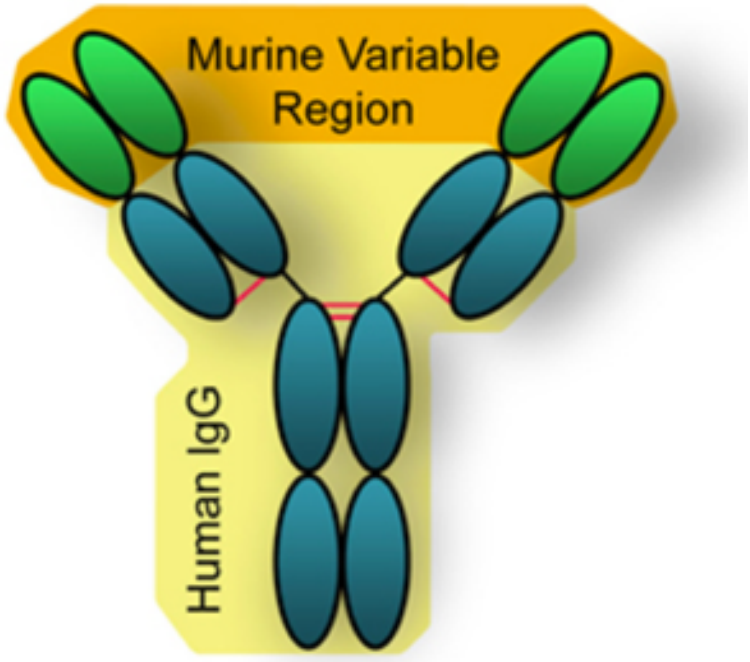


In preclinical studies, glycoengineering of the Fc region of GA101 has demonstrated up to a 100-fold increase in ADCC over nonglycoengineered MoAbs

Mossner et al., 2010; Niederfellner et al., 2011; Klein C, et al. MAbs 2013; Ferrara C, et al. J Biol Chem 2006

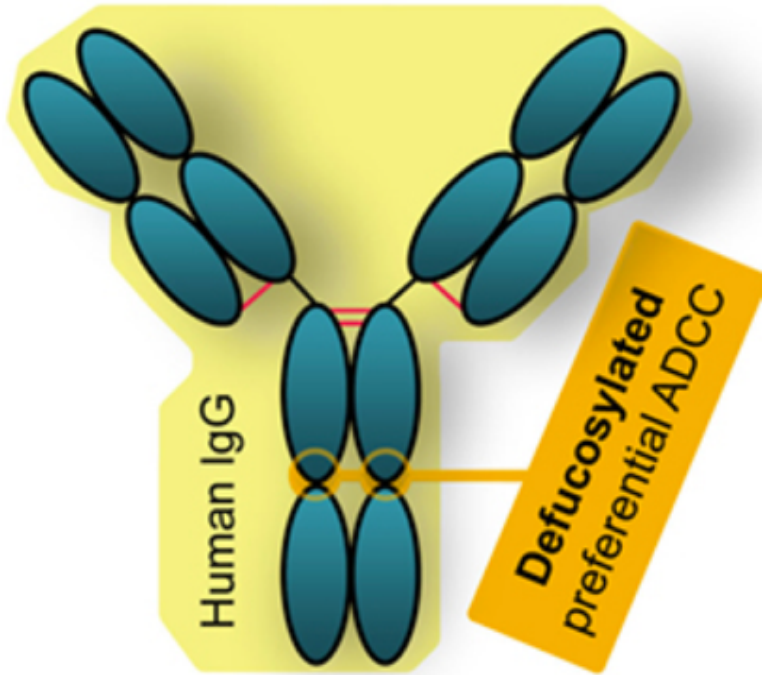
Obinutuzumab a glycoengeneered MoAb



Type I

Direct Killing	+
CDC	+++
ADCC	++
ADP	++

Rituximab



Type II

Direct Killing	+++
CDC	+
ADCC	+++
ADP	+++

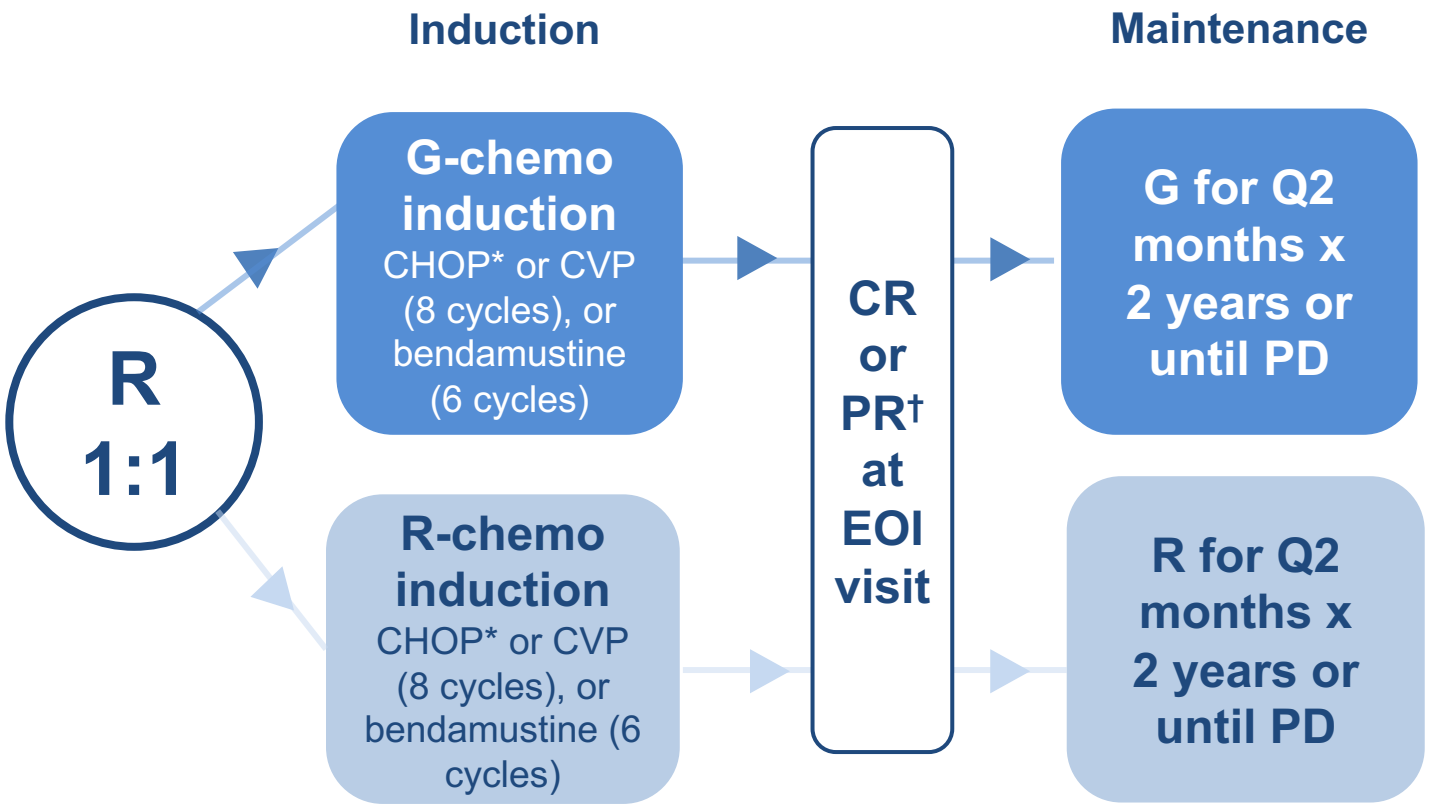
Obinutuzumab

CDC – Complement Dependent cytotoxicity

ADCC - antibody dependent cellular toxicity

ADP - antibody dependent phagocytosis

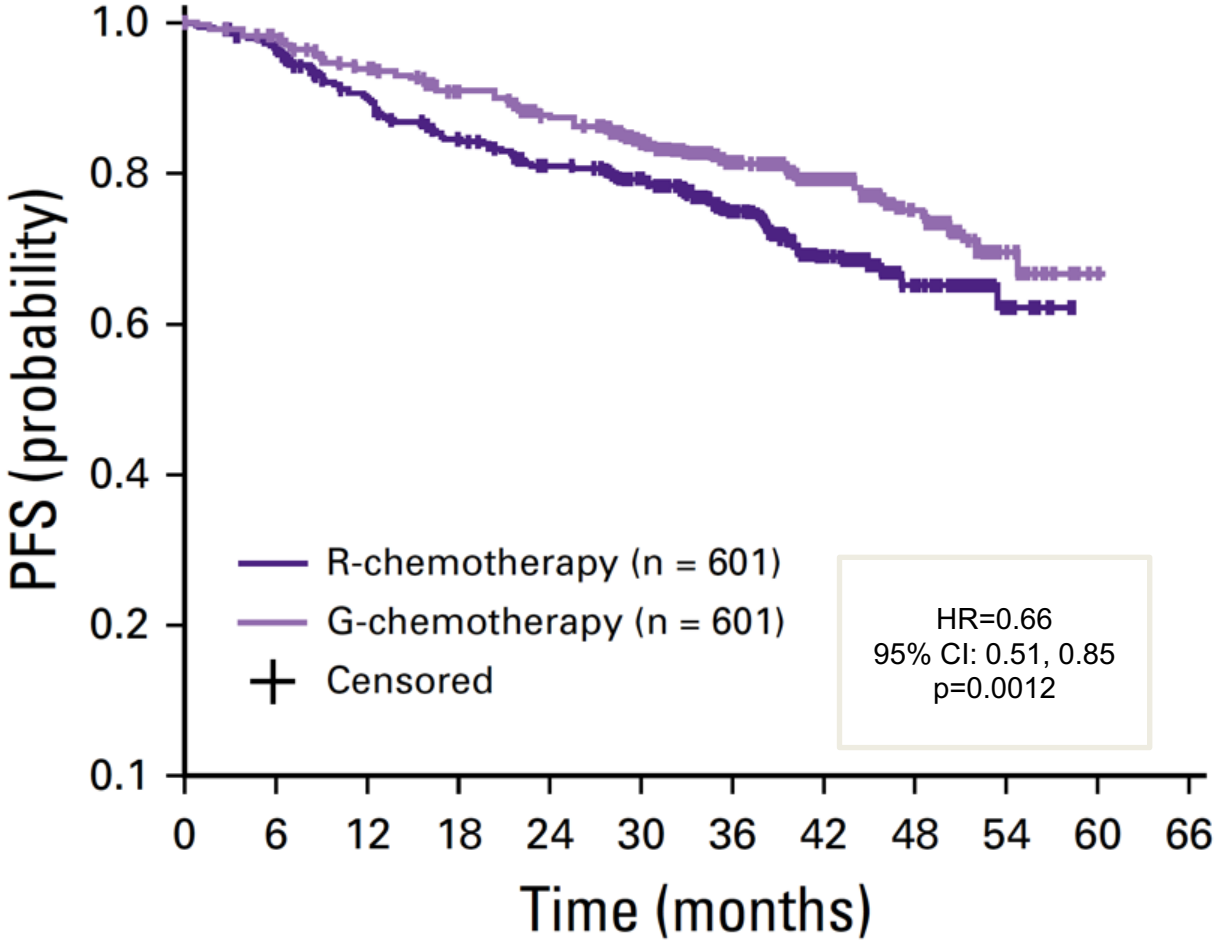
GALLIUM: Study design and baseline characteristics (N=1202)



	R-chemo (n=601)	G-chemo (n=601)
Median age, years (range)	58 (23–85)	60 (26–88)
Ann Arbor stage at dgn, n (%)		
I	8 (1.3)	10 (1.7)
II	44 (7.3)	41 (6.8)
III	209 (34.8)	208 (34.6)
IV	336 (55.9)	339 (56.4)
FLIPI risk group, n (%)		
Low (0–1)	125 (20.8)	128 (21.3)
Intermediate (2)	223 (37.1)	224 (37.3)
High (≥3)	253 (42.1)	249 (41.4)
B symptoms, n/N (%)	206/600 (34.3)	201/601 (33.4)
Bone marrow inv. n/N (%)	295/598 (49.3)	318/592 (53.7)
Extranodal inv., % (n)	396 (65.9)	392 (65.2)
Bulky disease (≥7 cm), n/ (%)	271/600 (45.2)	255/600 (42.5)

Marcus et al., NEJM 2017; Hiddemann et al., JCO 2018

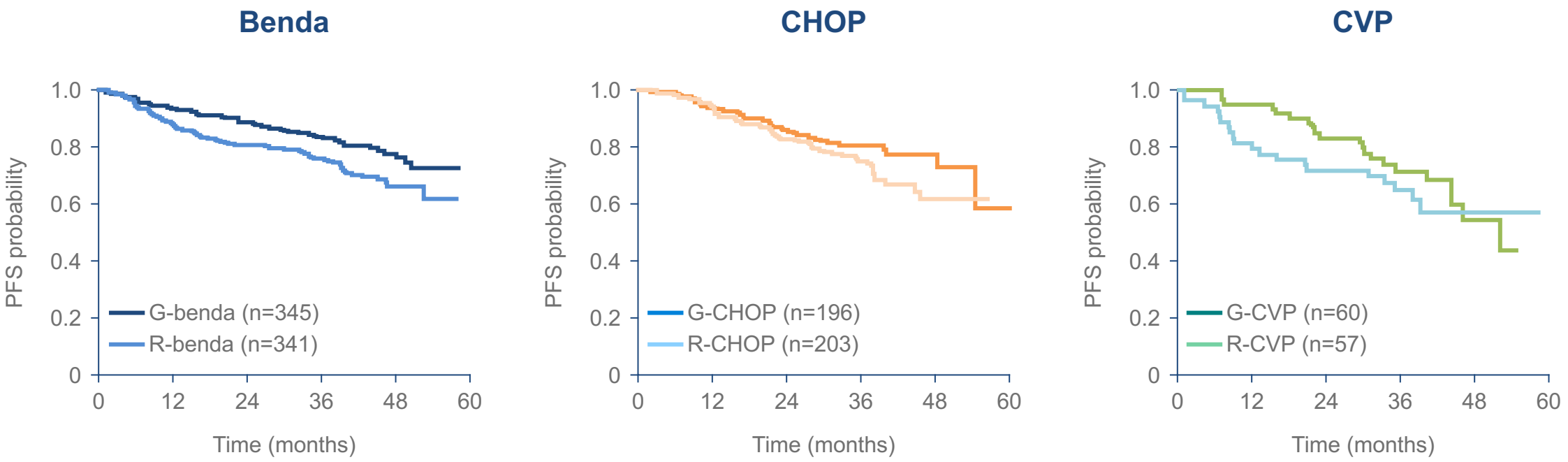
GALLIUM: PFS (primary target)



- No significant differences in neither CR nor ORR
- More Obinutuzumab treated patients achieved a deep MRD response
- Obinutuzumab **decreased number of POD24** (9% vs 16%)

Marcus et al., NEJM 2017; Hiddemann et al., JCO 2018

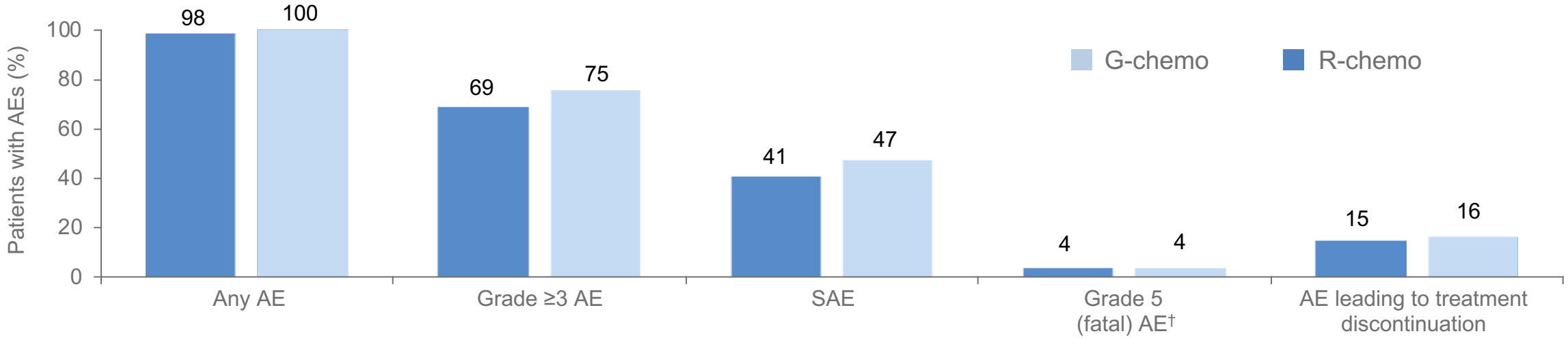
GALLIUM: PFS – subgroup analysis



- The study was not powered to demonstrate significant differences between the treatment arms in the different chemotherapy subgroups
- The frequency of **all grade 3 to 5 AEs was higher in patients treated with CHOP** than in patients treated with bendamustine and CVP, however **Bendamustine** was associated with **higher rates of grade 3-5 infections** than CHOP or CVP during the maintenance and follow-up phases
- In patients age **> 70 years**, treated with **Bendamustine**, **fatal events** that occurred before new anticancer treatment were more common

Marcus et al., NEJM 2017; Hiddemann et al., JCO 2018

GALLIUM: tolerability profile

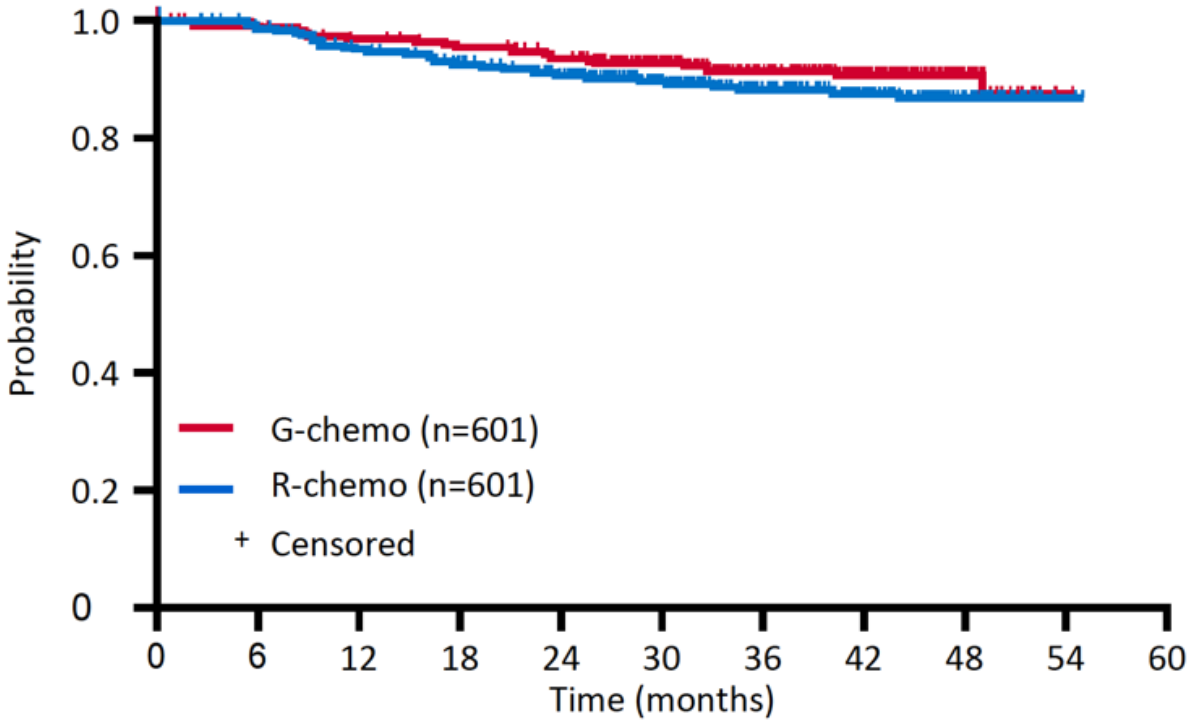


Patients reporting at least one grade ≥3 selected AESI, %	G-chemo (n=595)	R-chemo (n=597)
Neutropenia	47	40
Infections	20	16
Infusion-related reactions	7	4
Second malignancies	5	4
Cardiac events	4	3

Nature of tumours	R-chemo (n=597)	G-chemo (n=595)
Second malignancies*	21 (4%)	29 (5%)
Other solid tumours†	18 (3%)	15 (3%)
Haematological tumours‡	0	6 (1%)
Non-melanoma skin cancer	3 (1%)	8 (1%)

Marcus et al., NEJM 2017; Hiddemann et al., JCO 2018

GALLIUM: OS



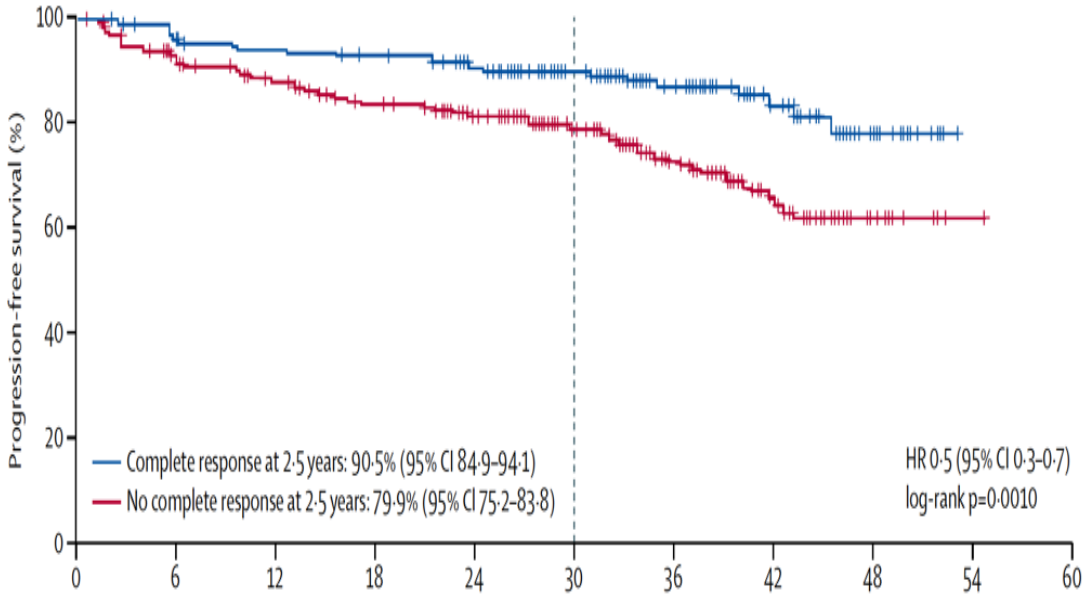
	R-chemo (n=601)	G-chemo (n=601)
Patients with event, n (%)	46 (7.7)	35 (5.8)
3-year OS, % (95% CI)	**92.1** (89.5, 94.1)	**94.0** (91.6, 95.7)
HR (95% CI), p-value*	0.75 (0.49, 1.17), p=0.21	

Median follow-up: 34.5 months

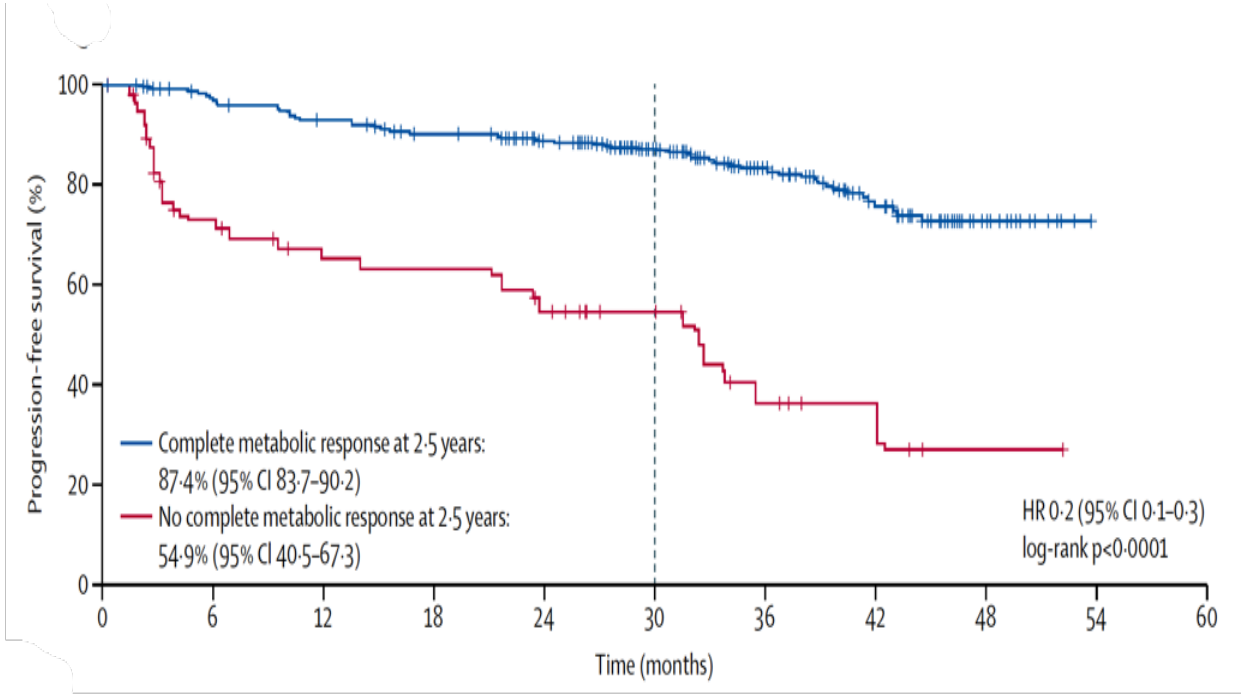
Marcus et al., NEJM 2017; Hiddemann et al., JCO 2018

GALLIUM: PET data

PFS by CR status - CT based as per IHP 2007 response criteria

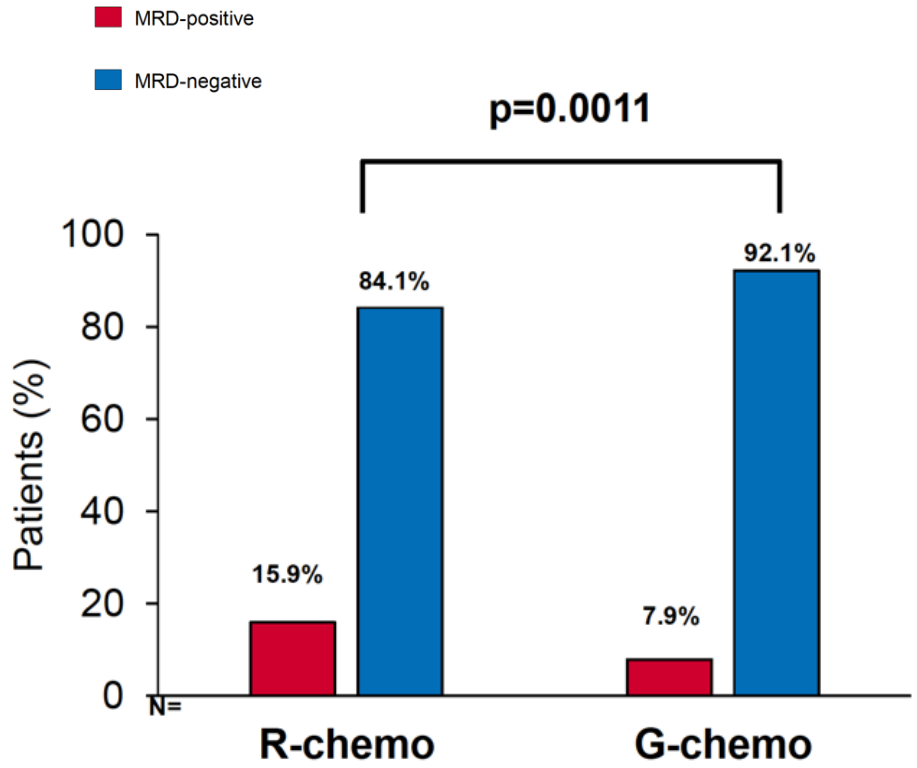


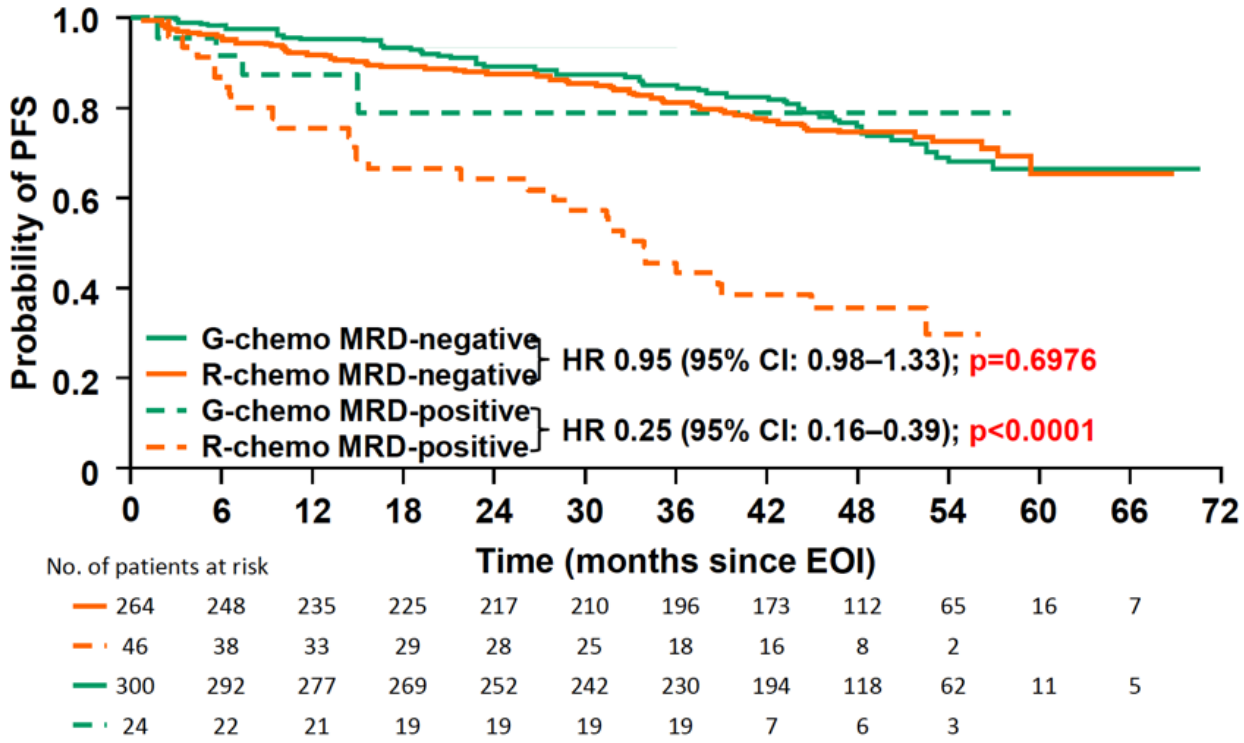
PFS by CR status - PET complete metabolic response



Trotman et al., Lancet Oncol 2018

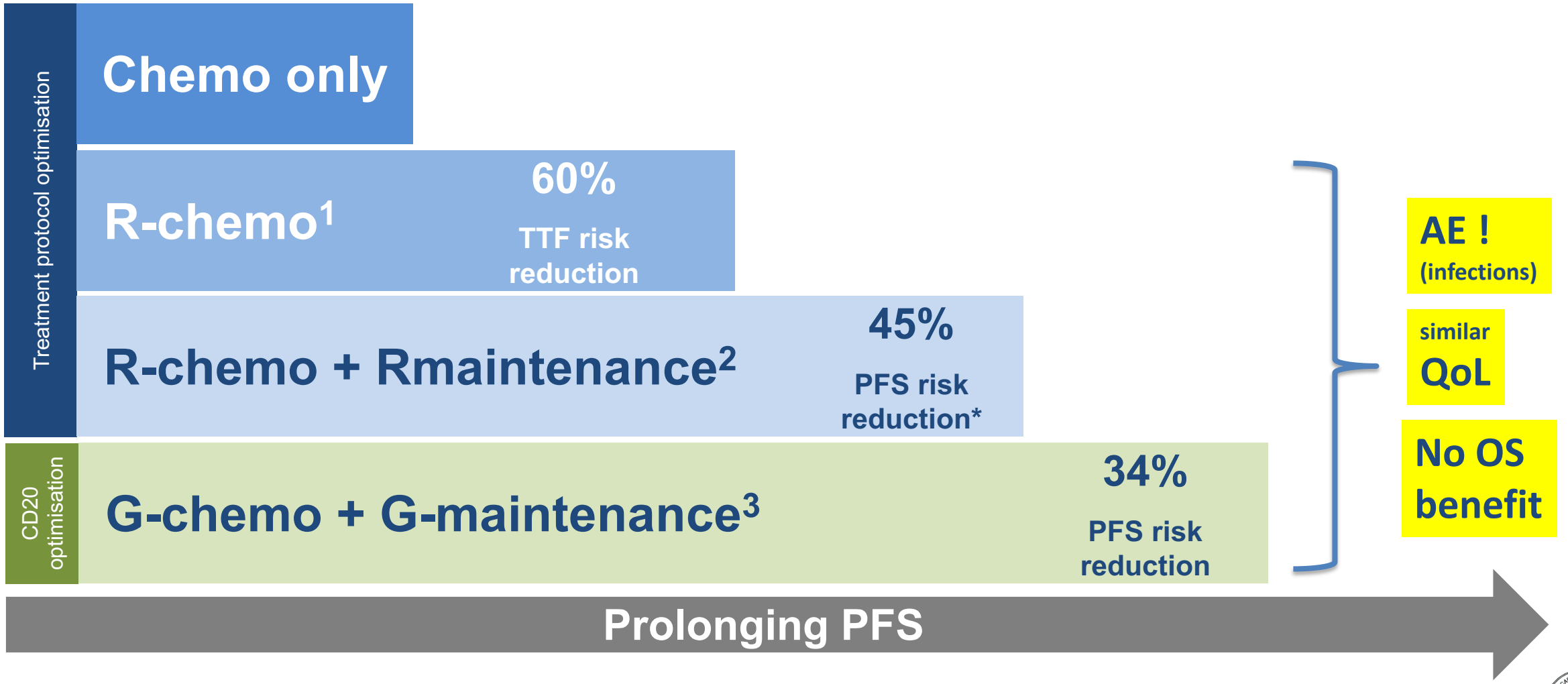
GALLIUM: PFS by MRD status at end of induction





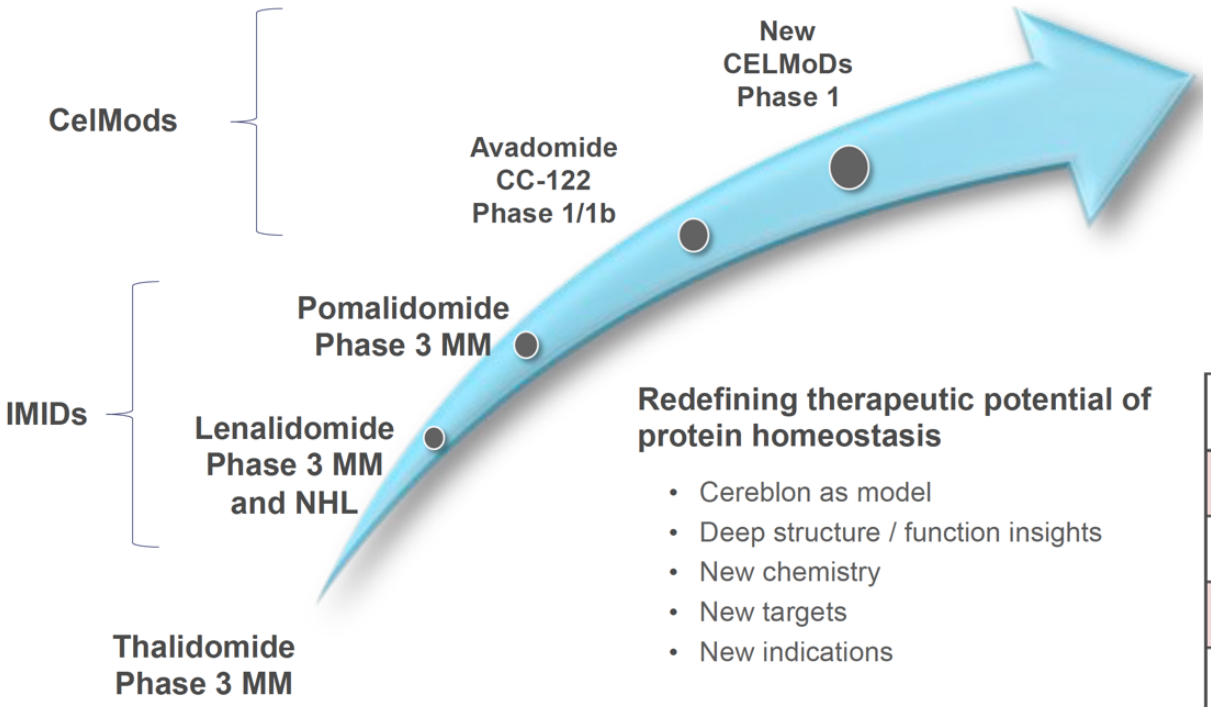
Pott et al., ASH 2018

Is prolonged PFS an improvement ?



1. Hiddemann et al., 2005; 2. Salles et al., 2011; 3. Marcus et al., 2017

Cereblon binding agents

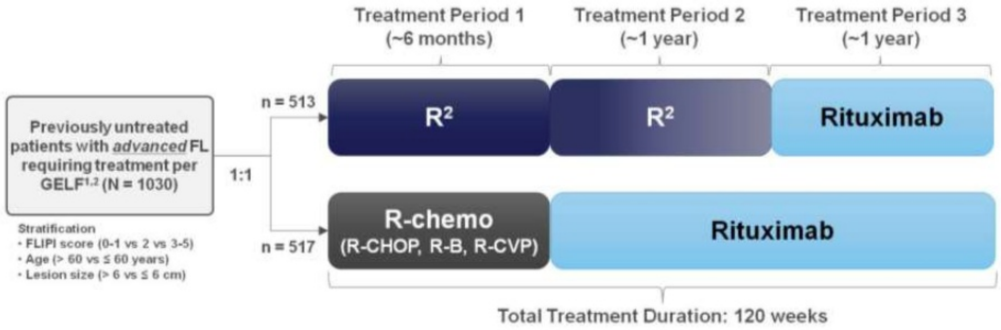


Redefining therapeutic potential of protein homeostasis

- Cereblon as model
- Deep structure / function insights
- New chemistry
- New targets
- New indications

	G1-2	G3-4	G1-2	G3-4	G1-2	G3-4	G1-2	G3-4	G1-2	G3-4
Study	**Neutropenia**		**Thrombocytopenia**		**Diarrhea**		**Rash**		**Tumor flare**	
Relevance[1]	75%	32%	53%	2%	37%	2%	29%	4%	6%	1%
Augment[2]	58%	50%	15%	2%	31%	3%	11%	1%	11%	1%
Magnify[3]	NA	28%	NA	4%	NA	NA	NA	NA	NA	NA
CC122-ST-01[4]	29%	27%	NA	NA	15%	0%	12%	0%	NA	NA
CC122-NHL-01[5]	62%	58%	38%	13%	24%	2%	NA	NA	4%	4%

REVELANCE: Study design and baseline characteristics (N=1030)



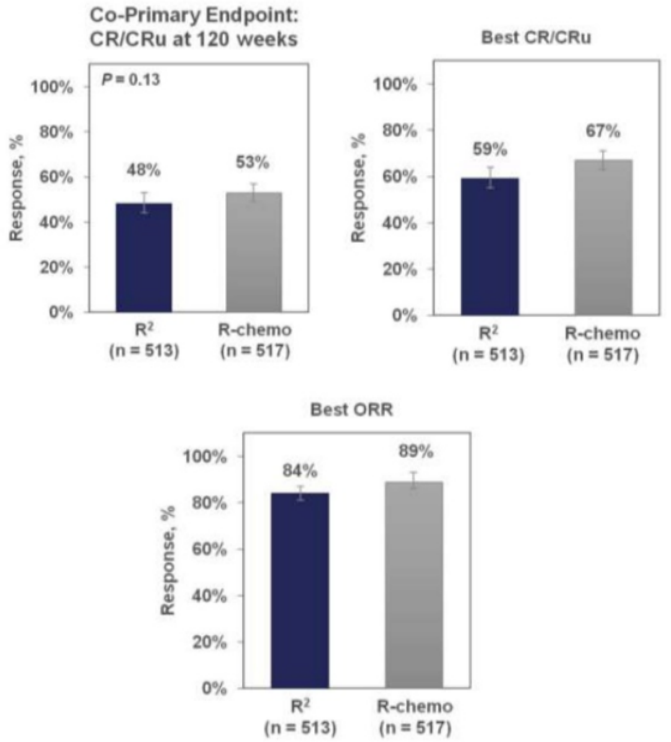
Treatment Period	R² Arm	R-Chemo Arm
1 (~6 months)	• Lenalidomide: 20 mg/d, d2-22/28 • Rituximab: 375 mg/m²	Investigator/patient choice prior to randomization • R-CHOP (72%) • R-B (23%) • R-CVP (5%)
2 (~1 year)	• Lenalidomide: 20 or 10 mg/d per response at 6, 9, or 12 cycles • Rituximab: 375 mg/m²	• Rituximab: 375 mg/m²
3 (~1 year)	• Rituximab: 375 mg/m²	• Rituximab: 375 mg/m²

Characteristics		R² (n=513) n (%)	R-Chemo (n=517) n (%)
Median age, years (range) **Age >70 years**		59 (30-89) 80 (16)	59 (23-83) 78 (15)
Male		251 (49)	251 (49)
ECOG PS	0 1 2 Not evaluated	341 (66) 157 (31) 13 (3) 2 (<1)	345 (67) 157 (30) 14 (3) 1 (<1)
Ann Arbor stage	I/II III/IV	30 (6) 483 (94)	40 (8) 477 (92)
Bulky disease (>7 cm)		218 (42)	199 (38)
FL grade[a]	1 or 2 3a	437 (85) 65 (13)	443 (86) 63 (12)
FLIPI score	Low risk (0-1) Intermediate risk (2) High risk (3-5)	77 (15) 183 (36) 253 (49)	76 (15) 191 (37) 250 (48)
Lactate dehydrogenase (>ULN)		156 (30)	137 (26)

Morschhauser et al., NEJM 2018

REVELANCE: Efficacy - Response Rates

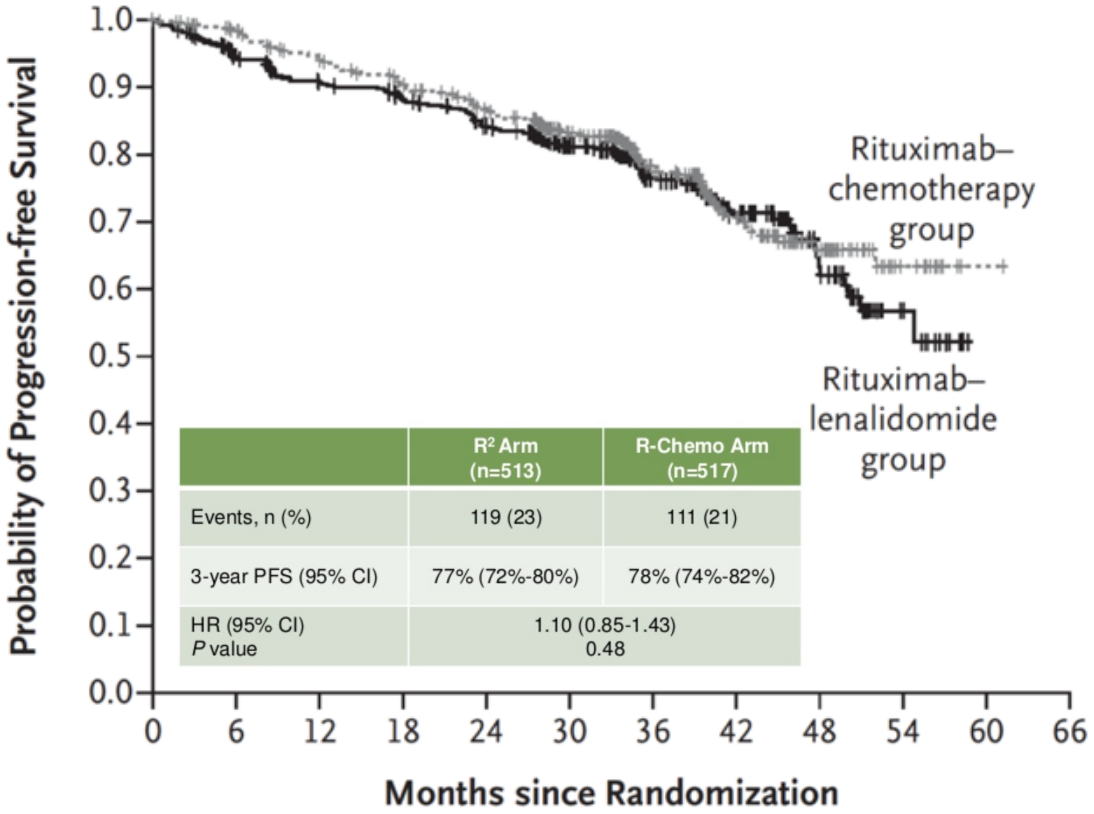
Variable	Rituximab–Lenalidomide Group (N=513)	Rituximab–Chemotherapy Group (N=517)
Response status at 120 weeks, as assessed by independent review committee		
Overall response — no. (% [95% CI])	312 (61 [56–65])	336 (65 [61–69])
Confirmed or unconfirmed complete response — no. (% [95% CI])	247 (48 [44–53])	274 (53 [49–57])
Complete response, confirmed — no. (%)	142 (28)	169 (33)
Complete response, unconfirmed — no. (%)	105 (20)	105 (20)
Partial response — no. (%)	65 (13)	62 (12)
Stable disease — no. (%)	2 (<1)	0
Progressive disease or death — no. (%)*	87 (17)	79 (15)
Not evaluated or data missing — no. (%)†	112 (22)	102 (20)



Morschhauser et al., NEJM 2018

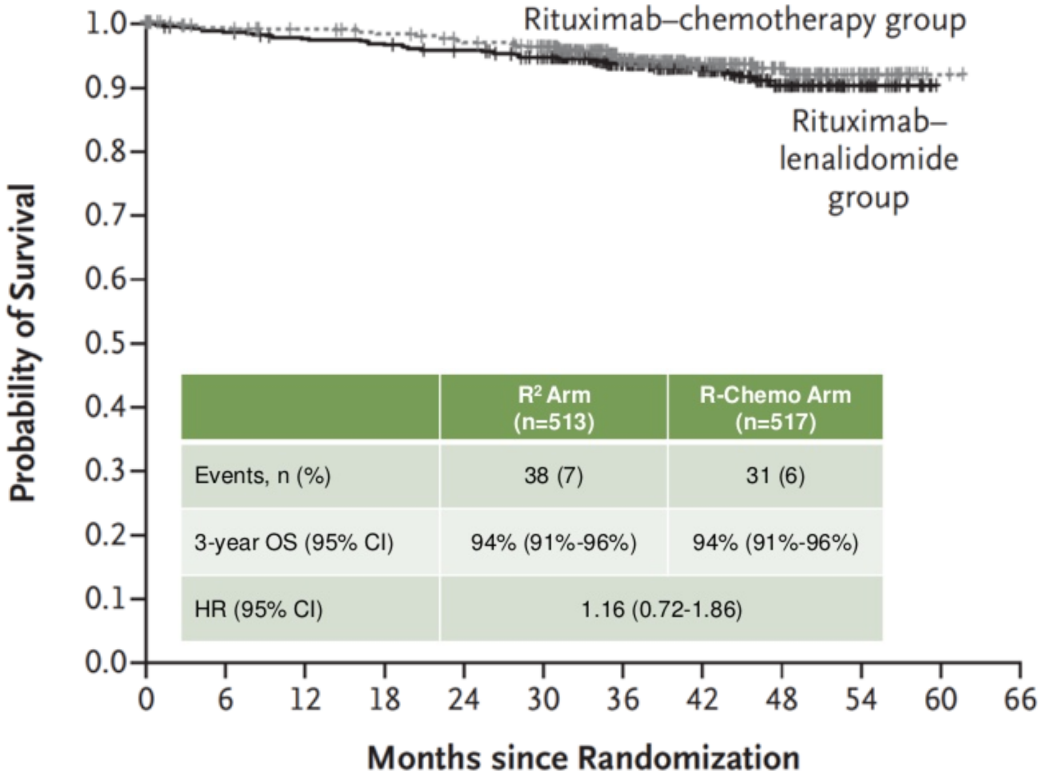
REVELANCE: Efficacy - PFS and OS

PFS



	R² Arm (n=513)	R-Chemo Arm (n=517)
Events, n (%)	119 (23)	111 (21)
3-year PFS (95% CI)	77% (72%-80%)	78% (74%-82%)
HR (95% CI) *P* value	1.10 (0.85-1.43) 0.48	

OS



	R² Arm (n=513)	R-Chemo Arm (n=517)
Events, n (%)	38 (7)	31 (6)
3-year OS (95% CI)	94% (91%-96%)	94% (91%-96%)
HR (95% CI)	1.16 (0.72-1.86)	

Morschhauser et al., NEJM 2018

REVELANCE: AE

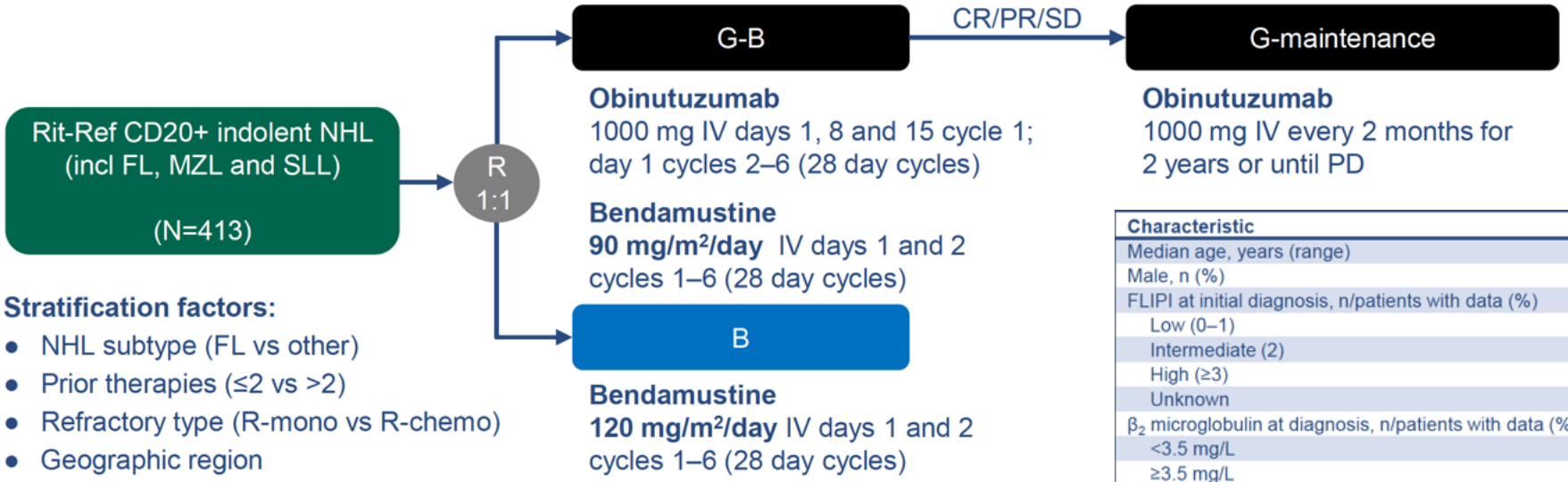
	R² (n=507)	R-Chemo (n=507)
More frequent AE	• cutaneous reactions, • tumor flare, • diarrhea	• neutropenia (grade 3/4), GCSF usage, • febrile neutropenia, • nausea &vomiting, • neuropathy, • alopecia,
Similar rate of discontinuation	31% (PD – 13%, toxicity – 8%)	29% (PD – 14%, toxicity – 3%)
Similar rate of SPM	7% (5% invasive SPM)	10% (5% invasive SPM)
Deaths related to treatment	1 case	1 case

Patients, n (%)	R² (n=507)	R-Chemo (n=503)
Grade 3/4 neutropenia[a]	160 (32)	252 (50)
Grade 4 neutropenia	41 (8)	154 (31)
Nadir ANC <100/μL	5 (1)	32 (6)
Median time to onset of first grade 3/4 lab	3.7 months	0.6 months
Grade 3/4 infections associated with grade 3/4 neutropenia	10 (2)	20 (4)
Febrile neutropenia[a]	11 (2)	34 (7)
Febrile neutropenia requiring hospitalization	8 (2)	26 (5)
Infections requiring hospitalization	46 (9)	60 (12)
Received growth factors	117 (23)	340 (68)

Morschhauser et al., NEJM 2018

R/R FL

GADOLIN study – R/R iNHL (N=413)

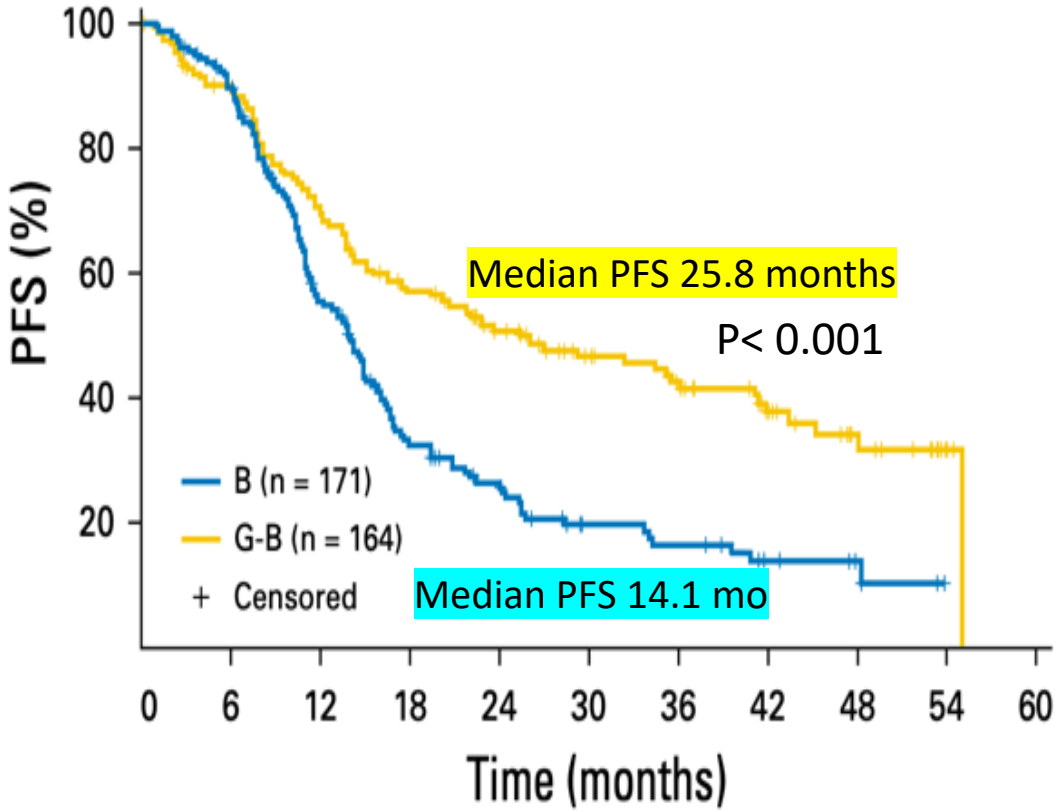


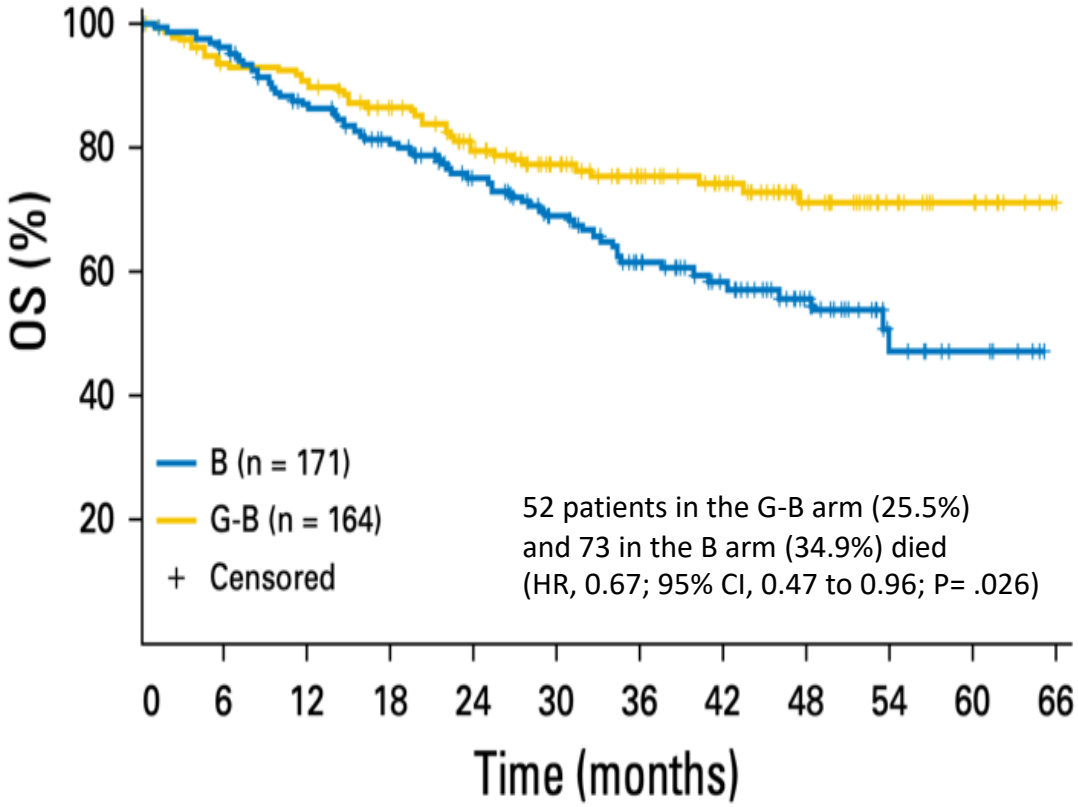
Characteristic	G-B (n=194)	B (n=202)
Median age, years (range)	63 (34–87)	63 (21–87)
Male, n (%)	110 (57)	118 (58)
FLIPI at initial diagnosis, n/patients with data (%)		
Low (0–1)	42/155 (27)	34/165 (21)
Intermediate (2)	47/155 (30)	58/165 (35)
High (≥3)	60/155 (39)	67165 (41)
Unknown	6/155 (4)	6/165 (4)
β_2 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 enrolment, n/patients with data (%)	60/187 (32)	69/188 (37)
Extranodal involvement at enrolment, n/patients with data (%)	107/194 (55)	98/201 (49)
Bulky disease (≥6 cm) at enrolment, n/patients with data (%)	66/194 (34)	70/199 (35)
Mean time from diagnosis to randomisation, years (range)	4.2 (0.3–32)	4.2 (0.3–30)
Median prior lines of therapy, (range)	2 (1–10)	2 (1–7)
Median time since last dose of 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)
Lymphoma subtype, n (%)		
Follicular lymphoma	155 (80)	166 (82)
Marginal zone lymphoma (including nodal, extranodal and splenic)	27 (14)	19 (9)
Small lymphocytic lymphoma	12 (6)	16 (8)
Waldenström macroglobulinaemia	0	1 (1)
Rituximab-refractory type, n (%)		
R-chemo**	156 (80)	157 (78)
R-mono	38 (20)	45 (22)

Median prior lines of therapy : 2 (1-10)
Double refractory Patients : 81%

Cheson et al., JCO 2018

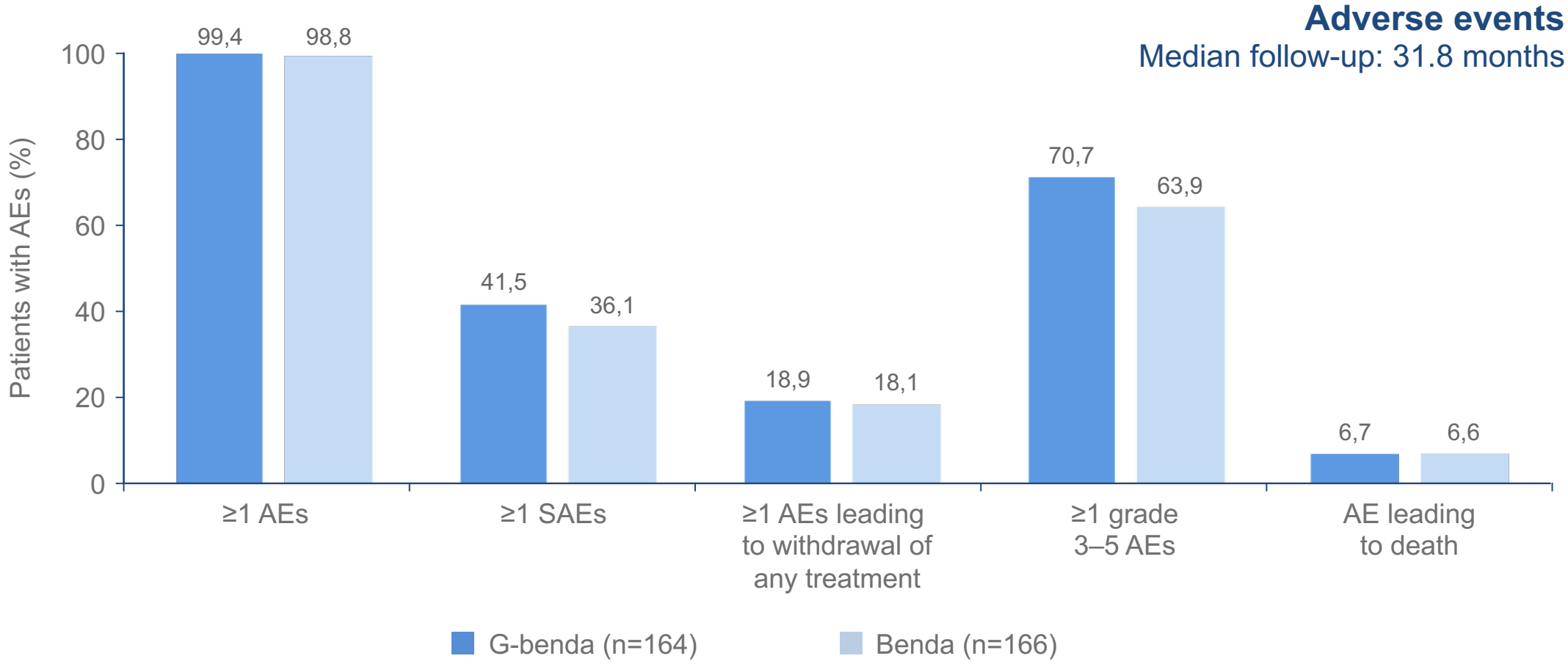
GADOLIN study – R/R iNHL (N=413)
Median follow-up of 31.5 months





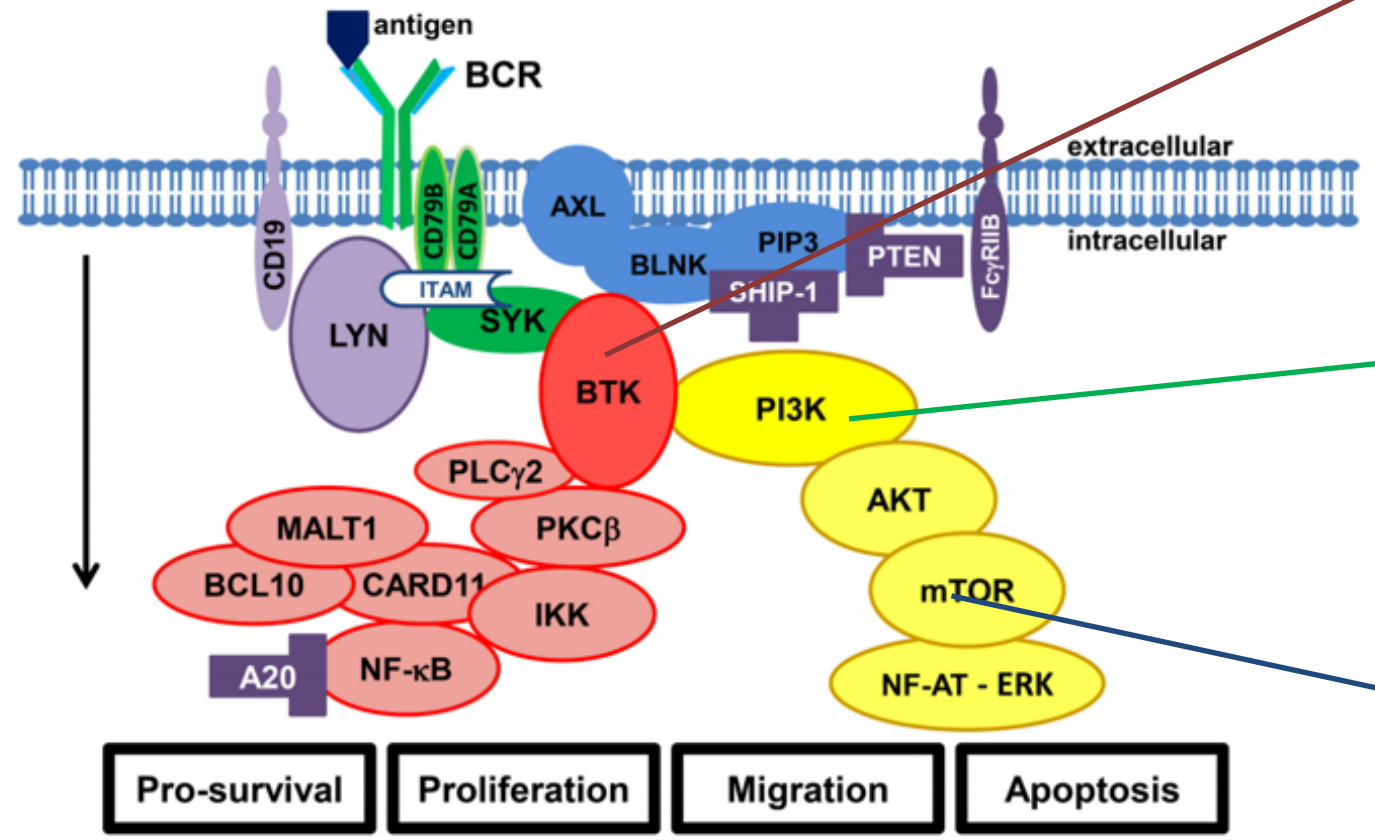
Cheson et al., JCO 2018

GADOLIN study – R/R iNHL (N=413) - tolerability profiles



Cheson et al., JCO 2018

BCR pathway inhibitors

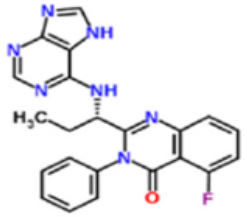


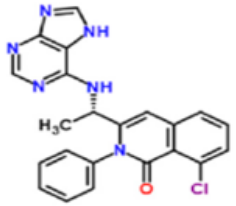
BTK Inhibitors
- Ibrutynib
- Acalabrutynib
- BGB 3111
- M7583

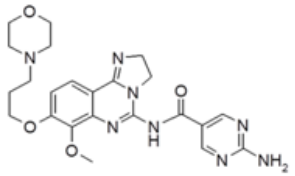
IP3K Inhibitors:
- Idelalisib,
- Duvalisib,
- Copanlisib,
- Umbralisib

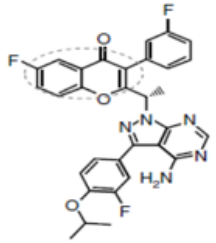
mTOR inhibitors:
- Temsirolimus

IP3K inhibitors









Isoform	Idelalisib (IC_{50}-nM)[1]	Duvelisib (IC_{50}-nM)[2]	Copanlisib (IC_{50}-nM)[3]	TGR-1202 (IC_{50}-nM)[4]
P110a	20,000	1410	0.4–1	10,000
P110b	1,900	26.2	10–18	800
P110g	3,000	19.6	93	400
P110d	8	0.36	3–10	24

Idelalisib in double refractory iNHL (N=125)

Single-Arm Study (N=125)

Enrolled April 2011 to October 2012

Idelalisib 150 mg BID

Therapy maintained until progression

Long Term follow-up

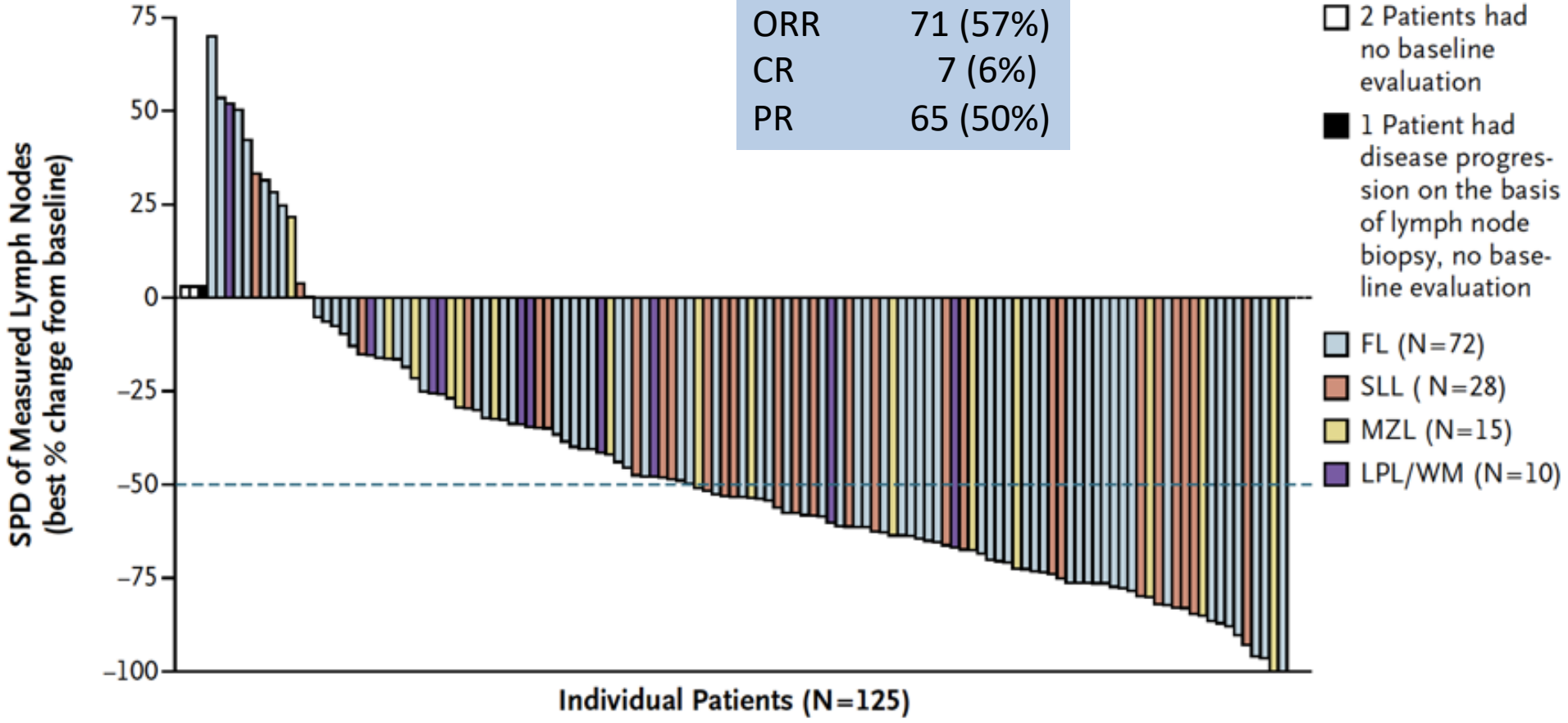
Median prior lines of therapy : 4 (2-12)
Double refractory Patients : 100 %

Characteristic	N=125
No of prior regimens Median, [Range]	4 [2 – 12]
Prior Therapy	
Rituximab	125 (100%)
Alkylating Agent	125 (100%)
Bendamustine	81 (65%)
Anthracycline	80 (64%)
Purine Analog	42 (33%)
Stem Cell Transplantation	14 (11%)
Disease type, n (%)	
FL	72 (58%)
SLL	28 (22%)
LPL/WM	10 (8%)
MZL	15 (12%)
LDH (>ULN), n (%)	38 (30%)
Bulky Disease (≥ 5 cm)	59 (47%)
Bulky Disease (≥ 7 cm)	33 (26%)

Gopal et al, NEJM 2014

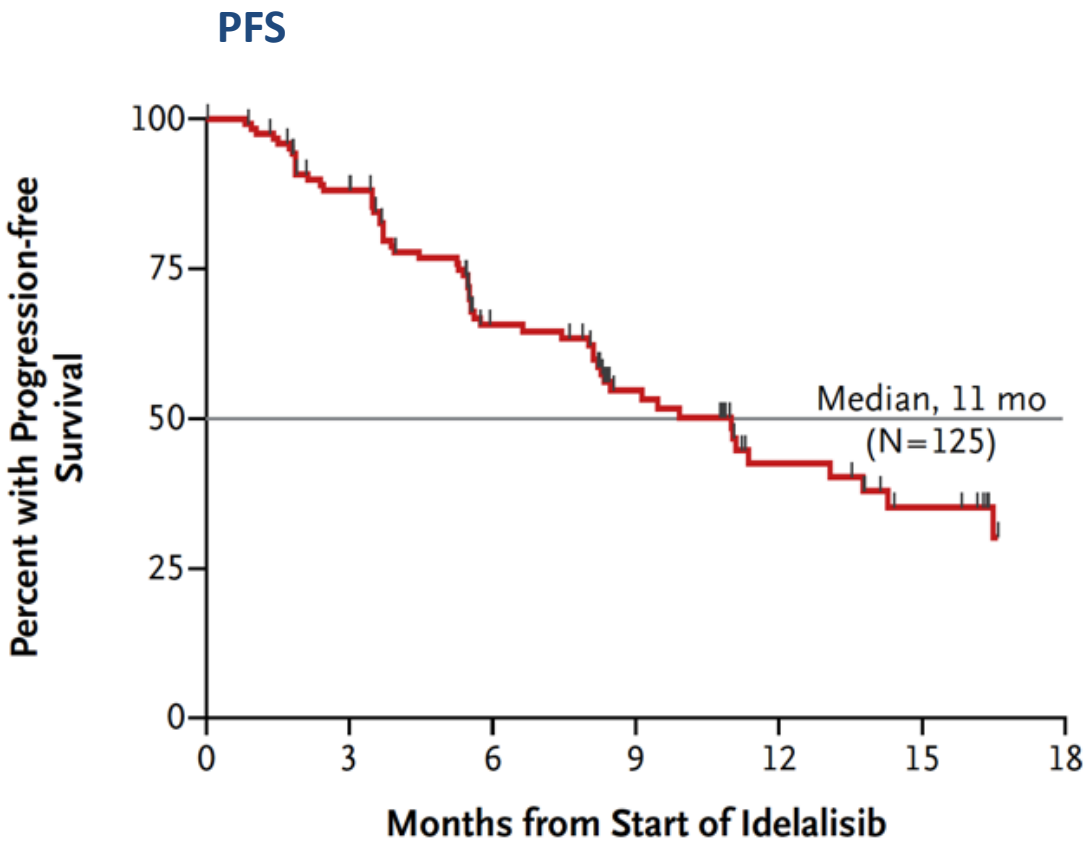
Idelalisib in double refractory iNHL (N=125)

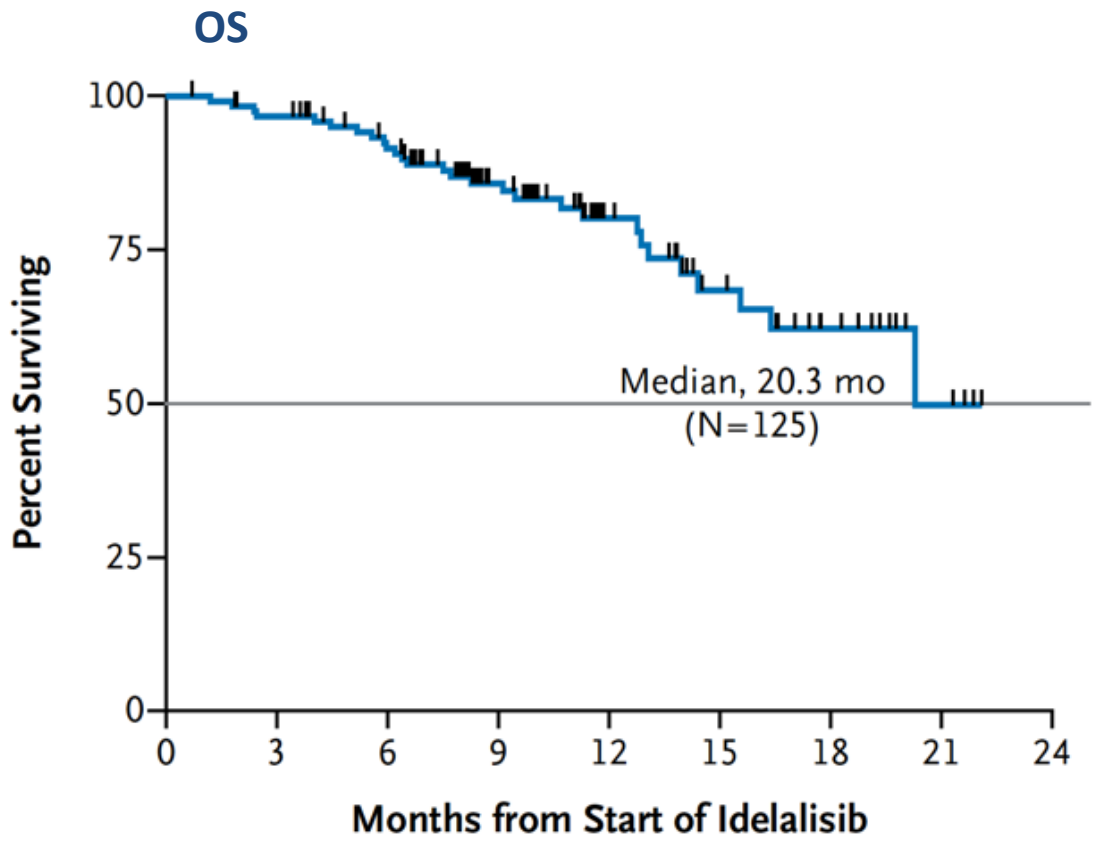
ORR	71 (57%)
CR	7 (6%)
PR	65 (50%)



Gopal et al, NEJM 2014

Idelalisib in double refractory iNHL (N=125)





Gopal et al, NEJM 2014

Idelalisib in double refractory iNHL (N=125)

AE	Any Grade N, %	Grade ≥ 3 N, %
Diarrhea	54 (43%)	16 (13%)
Fatigue	37 (30%)	2 (2%)
Nausea	37 (30%)	2 (2%)
Cough	36 (29%)	None
Pyrexia	35 (28%)	2 (2%)
Dyspnea	22 (18%)	4 (3%)
Decreased appetite	22 (18%)	1 (1%)
Abdominal pain	20 (16%)	3 (2%)
Vomiting	19 (15%)	3 (2%)
URI	18 (14%)	None
Decreased weight	17 (13%)	None
Rash	16 (13%)	2 (2%)
Asthenia	14 (11%)	3 (2%)
Night Sweats	14 (11%)	None
Pneumonia	14 (11%)	9 (7%)

On Study	Any Grade	Grade ≥ 3
Neutrophils decreased	70 (56%)	34 (27%)
Hemoglobin decreased	35 (28%)	2 (2%)
Platelets decreased	32 (26%)	8 (6%)

	Grade 1-2	Grade 3	Grade 4	Any Grade
ALT or AST elevated	44 (35%)	13 (10%)	3 (2%)	60 (48%)

- Grade 1-2 resolved with continued idelalisib treatment
- Grade ≥ 3 reversible with drug interruption

Gopal et al, NEJM 2014

Idelalisib in double refractory iNHL (N=125)

AE	Any Grade N, %	Grade ≥ 3 N, %
Diarrhea	**54 (43%)**	**16 (13%)**
Fatigue	37 (30%)	2 (2%)
Nausea	37 (30%)	2 (2%)
Cough	**36 (29%)**	**None**
Pyrexia	**35 (28%)**	**2 (2%)**
Dyspnea	22 (18%)	4 (3%)
Decreased appetite	22 (18%)	1 (1%)
Abdominal pain	20 (16%)	3 (2%)
Vomiting	19 (15%)	3 (2%)
URI	18 (14%)	None
Decreased weight	17 (13%)	None
Rash	16 (13%)	2 (2%)
Asthenia	14 (11%)	3 (2%)
Night Sweats	14 (11%)	None
Pneumonia	**14 (11%)**	**9 (7%)**

Gopal et al, NEJM 2014

Safety of Idelalisib in B-Cell Malignancies: Integrated Analysis of Eight Clinical Trials

	Idelalisib Monotherapy n=354		Idelalisib Combination Therapy n=406	
AE, n (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Pyrexia	96 (27)	7 (2)	169 (42)	47 (12)
Diarrhea/colitis	131 (37)	38 (11)	161 (40)	68 (17)
Fatigue	112 (32)	6 (2)	130 (32)	13 (3)
Nausea	91 (26)	5 (1)	125 (31)	30 (7)
Cough	80 (22)	3 (1)	118 (29)	21 (5)
Rash	60 (17)	7 (2)	99 (24)	30 (7)
Chills	49 (14)	0	86 (21)	23 (6)
Pneumonia	47 (13)	40 (11)	74 (18)	56 (14)
Constipation	39 (11)	0	68 (17)	1 (<1)
Dyspnea	43 (12)	7 (2)	68 (17)	10 (3)
Abdominal pain	40 (11)	4 (1)	67 (17)	5 (1)
Vomiting	53 (15)	5 (1)	60 (15)	18 (4)
Decreased appetite	46 (13)	8 (2)	62 (15)	2 (<1)

Coutre et al., EHA 2016

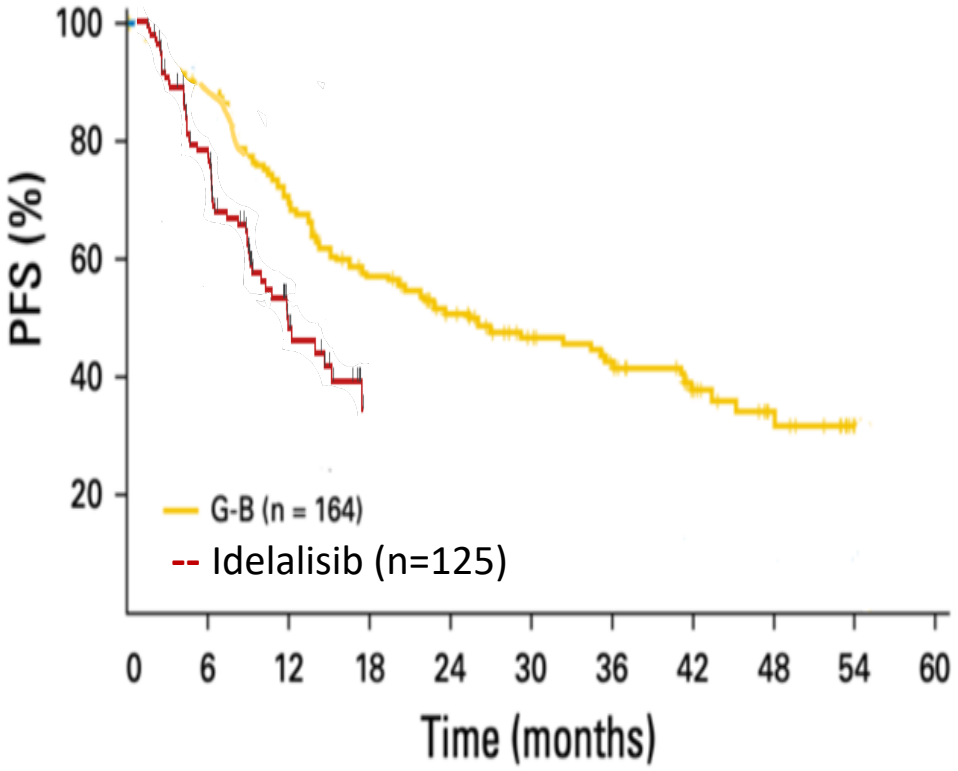
Safety of Idelalisib in B-Cell Malignancies: Integrated Analysis of Eight Clinical Trials

			+ Idela	Control
*Idela +/- BR	untreated	CLL	N=664 7.4% death	N=402 3.5% death
*Idela +/- R	Prev treated	NHL		
*Idela +/- BR	Prev treated	NHL		
Idela +/- R	2-3 prior therapies	CLL	N=491 23.2% death	N=406 31.5% death
Idela +/- Ofa	2-3 prior therapies	CLL		
Idela +/- BR	2-3 prior therapies	CLL		

*Idela + R untreated NHL, *Idela + R untreated del17p CLL,
*Idela +obinu v Chlor + obinu untreated CLL, *ISTs for untreated

Coutre et al., EHA 2016

Comparison of incomparable studies



Characteristics	Obinutuzumab + Bendamustine [17]	Idelalisib[18]
AE (G3-5)	65.5%	54%
Neutropenia	**34.8%**	27%
Thrombocytopenia	**10.8%**	6%
Anaemia	**7.4%**	2%
Transaminase elevations		**13%**
Diarrhoea		**13%**
Skin rash		**2%**
Infections	10.1%	9%
Thromboses		
AE which led to treatment discontinuation	20.1%	20%
SAE	**43.5%**	26%
Fatal AE	**7.8%**	3.2%

Cheson et al., JCO 2018; Gopal et al, NEJM 2014

Copanlisib in R/R iNHL (N=142)

Single-Arm Study (N=142)

Enrolled Nov 2013 to Feb 2016

Copanlisib 60 mg iv on days 1,8 and 15 of 28- day cycle

Therapy maintained until progression

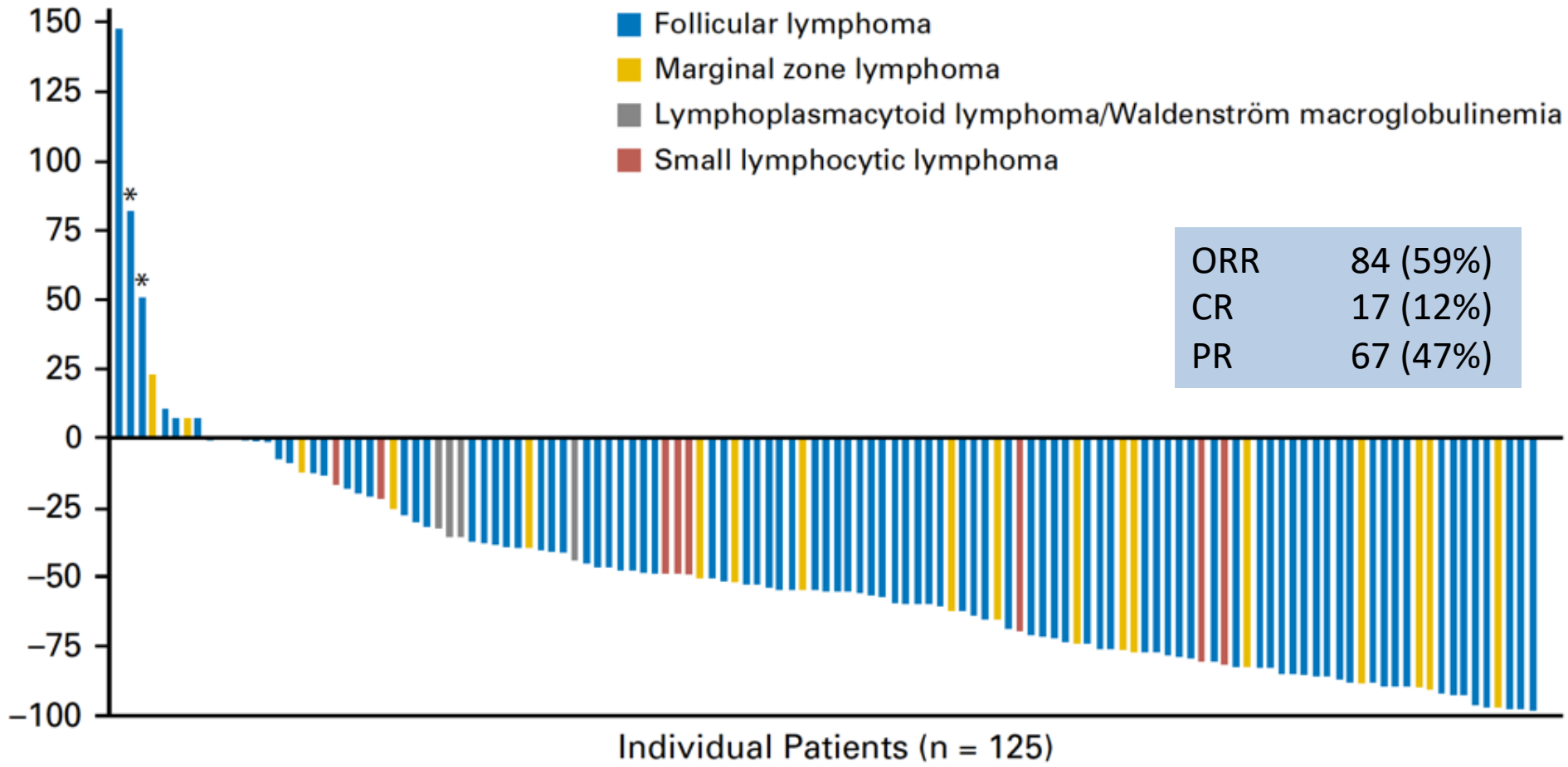
Long Term follow-up

Median prior lines of therapy : 3 (2-9)
Double refractory Patients : 100 %

Characteristic	N=125
No of prior regimens Median, [Range]	4 [2 – 12]
Prior Therapy	
Rituximab	142 (100%)
Alkylating Agent	142 (100%)
Refractory to the last therapy	
Rituximab	80 (56%)
Alkylating Agent	60 (42%)
Rituximab+Alkylating Agent	62 (43%)
Disease type, n (%)	
FL	104 (73%)
SLL	8 (6%)
LPL/WM	6 (4%)
MZL	23 (16%)

Dreyling et al., JCO 2017

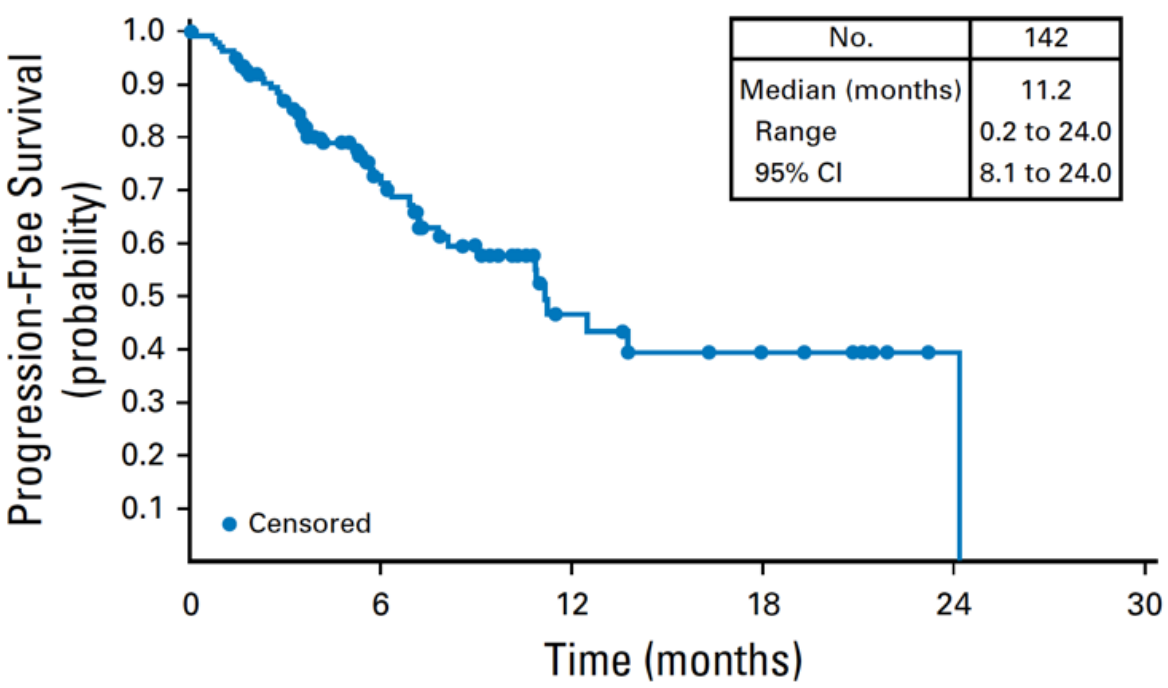
Copanlisib in R/R iNHL (N=142)

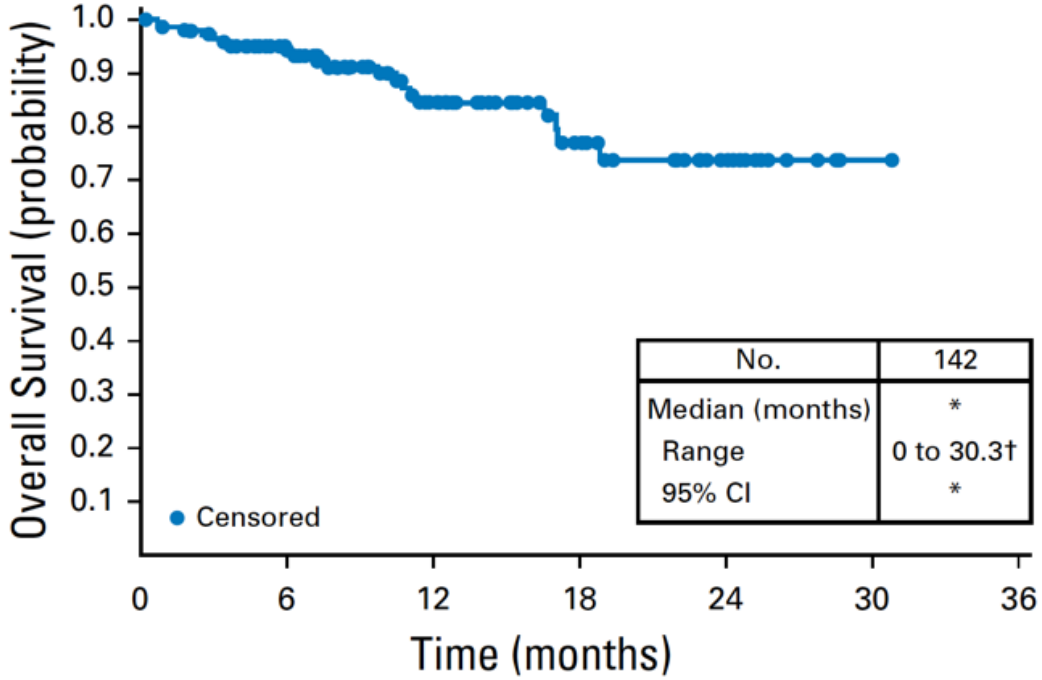


ORR	84 (59%)
CR	17 (12%)
PR	67 (47%)

Dreyling et al., JCO 2017

Copanlisib in R/R iNHL (N=142)





Dreyling et al., JCO 2017

Copanlisib in R/R iNHL (N=142)

Adverse Event	Grade, No. (%)			
	All	3	4	5
Any treatment-emergent adverse event	140 (99)	75 (53)	38 (27)	6 (4)
Nonhematologic toxicities				
Hyperglycemia	71 (50)	48 (34)	10 (7)	0
Diarrhea	48 (34)	7 (5)	0	0
Fatigue	43 (30)	3 (2)	0	0
Hypertension	43 (30)	34 (24)	0	0
Fever	36 (25)	6 (4)	0	0
Nausea	33 (23)	1 (1)	0	0
Lung infection	30 (21)	18 (13)	3 (2)	2 (1)
Oral mucositis	28 (20)	4 (3)	0	0
Upper respiratory infection	26 (18)	4 (3)	0	0
Cough	23 (16)	0	0	0
Maculopapular rash	18 (13)	1 (1)	0	0
Constipation	17 (12)	0	0	0
Bronchial infection	16 (11)	2 (1)	0	0
Flu-like symptoms	16 (11)	1 (1)	0	0
Anorexia	15 (11)	0	0	0
Skin infection	15 (11)	1 (1)	0	0

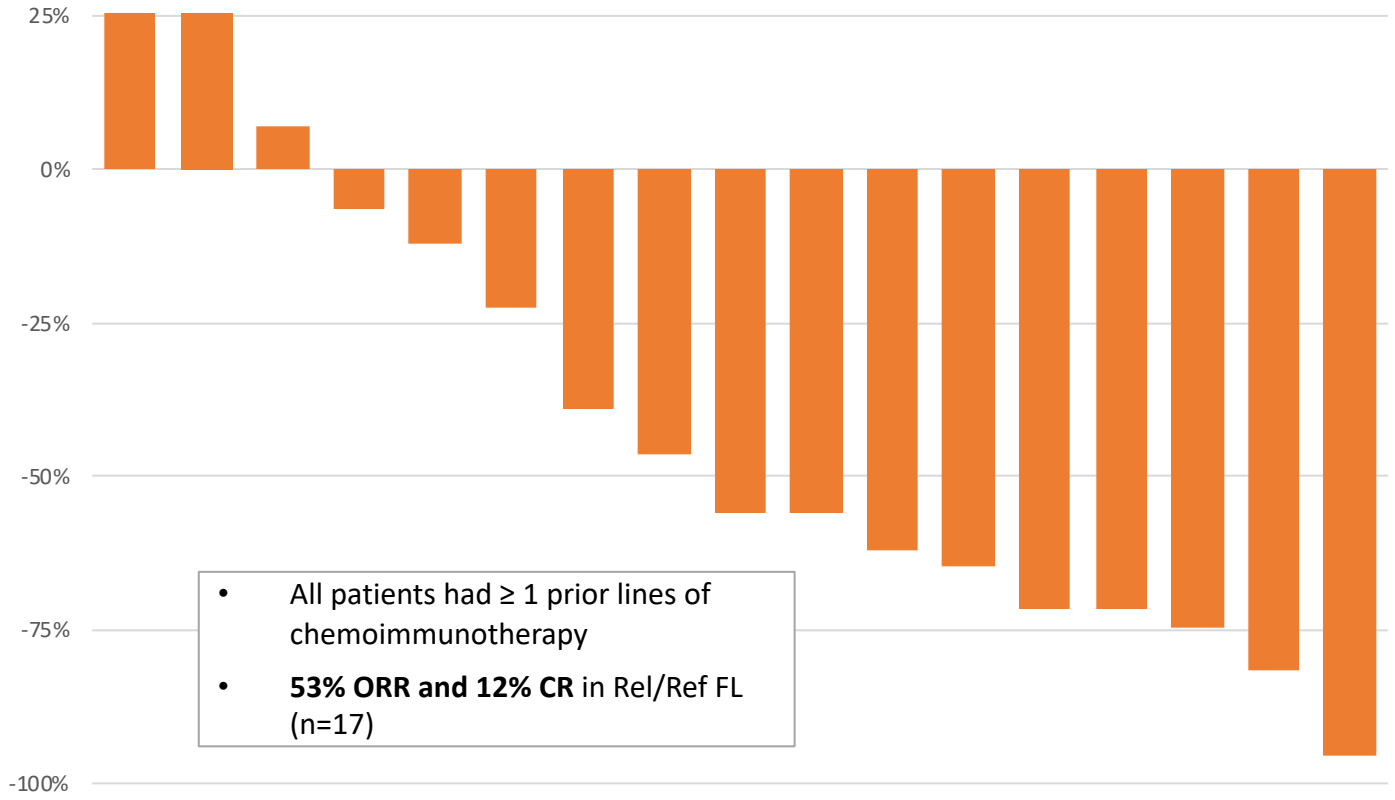
Adverse Event	Grade, No. (%)			
	All	3	4	5
Hematologic toxicities				
Decreased neutrophil count	42 (30)	11 (8)	23 (16)	0
Decreased platelet count	29 (20)	9 (6)	1 (1)	0
Anemia	22 (15)	6 (4)	0	0
Adverse events of special interest				
Pneumonitis (noninfectious)	11 (8)	2 (1)	0	0
Colitis	1 (1)	0	1 (1)	0
Laboratory toxicities				
Elevated AST*	39 (28)	1 (1)	1 (1)	0
Elevated ALT*	32 (23)	1 (1)	1 (1)	0

Dreyling et al., JCO 2017

TGR-1202 (Umbralisib) is a next generation PI3Kδ inhibitor

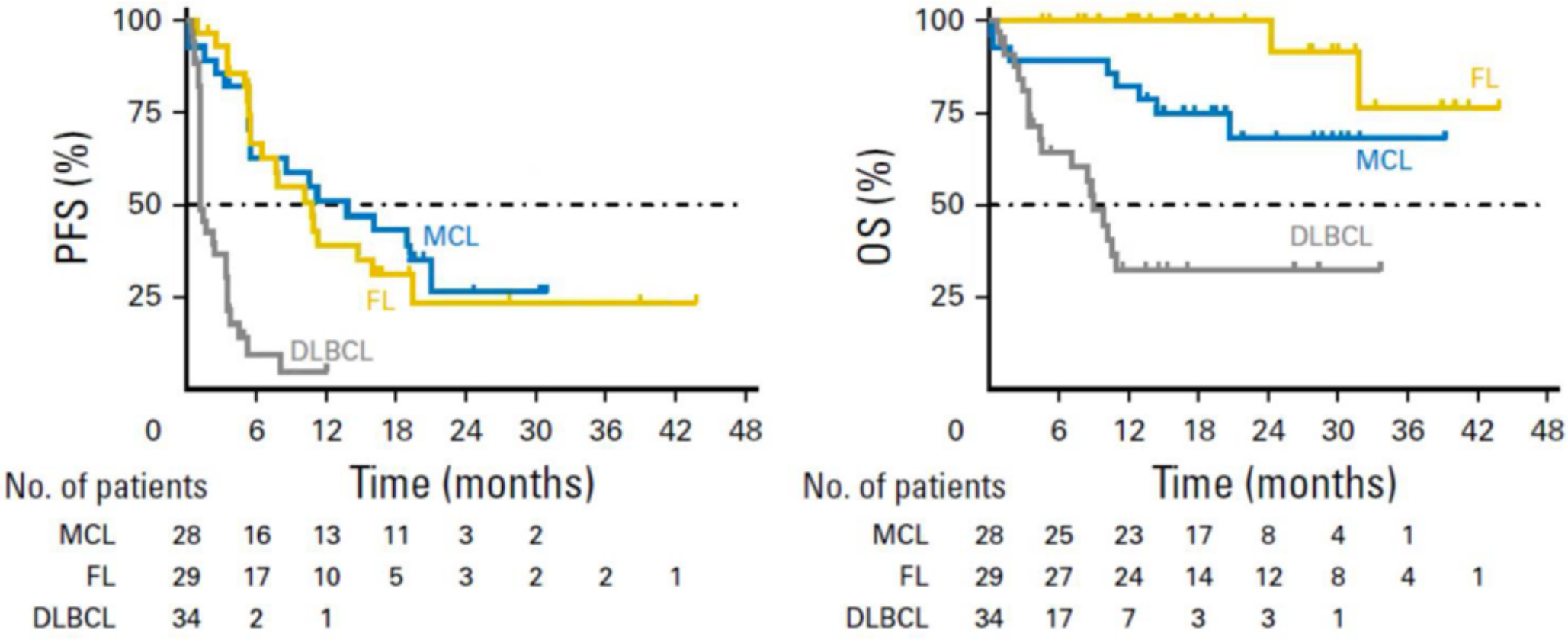
- **a unique structure and activity profile** distinct from other PI3Kδ inhibitors in development including:
- A **prolonged half-life** and accumulation that enables once-daily dosing
- A **differentiated safety profile** from other PI3Kδ inhibitors, notably with respect to hepatic toxicity and colitis to date
- **Doublets and Triplets** being evaluated

Umbralisib Monotherapy R/R FL



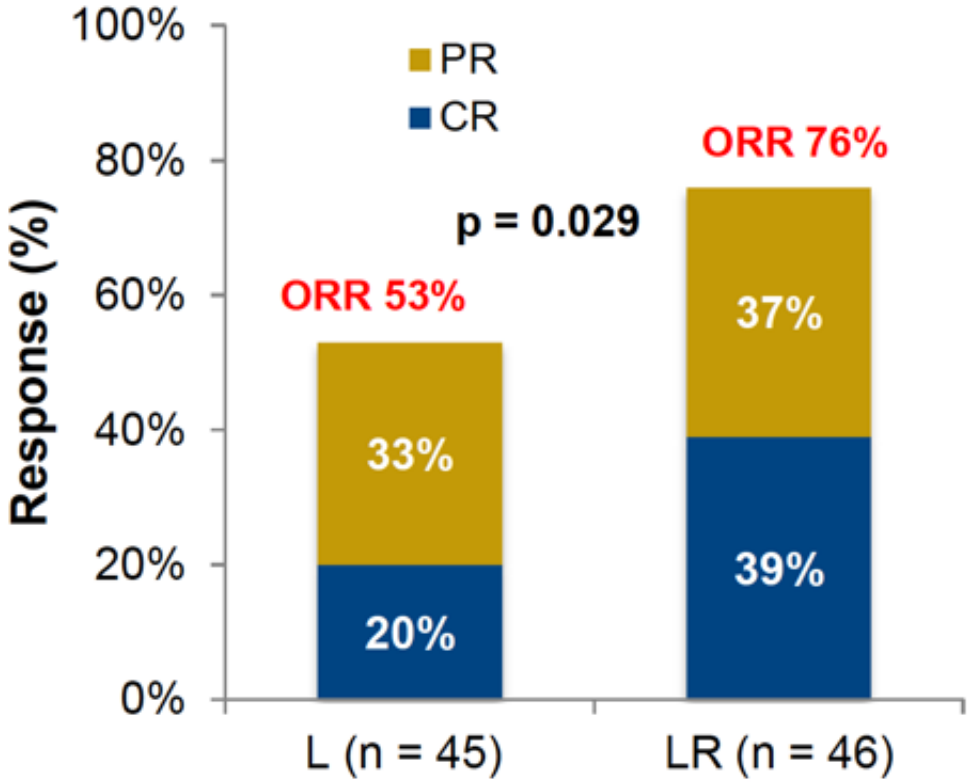
Burris HA, et al. *Lancet Oncol.* 2018

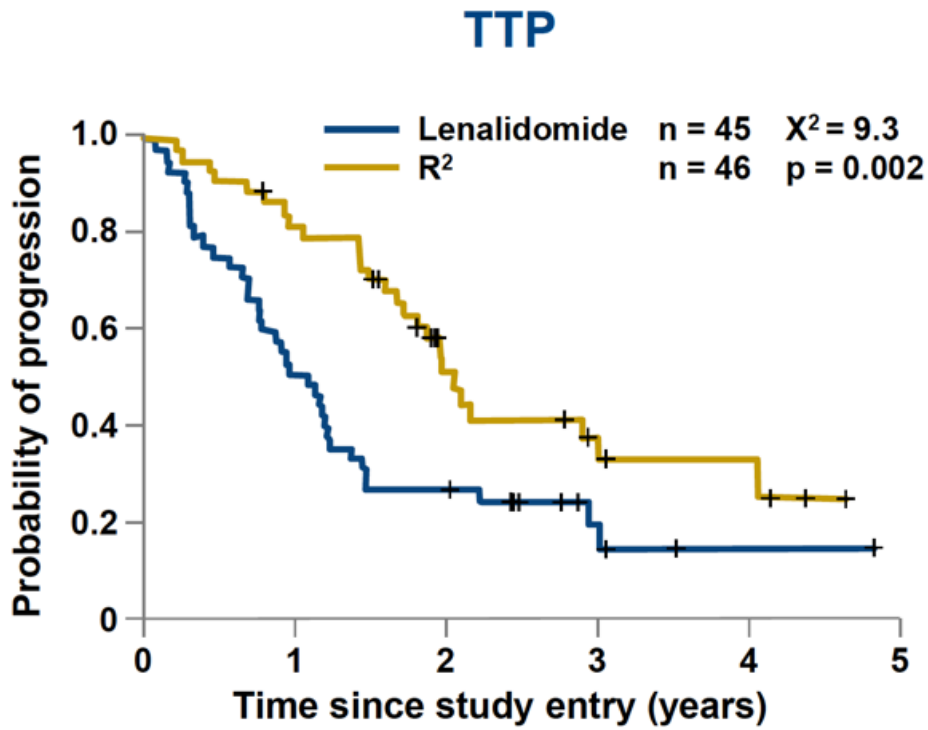
Venetoclax in NHL phase I/II study



Fawler et al., ASH 2016

ALLIANCE: R^2 vs Lenalidomide in R/R FL (phase II)





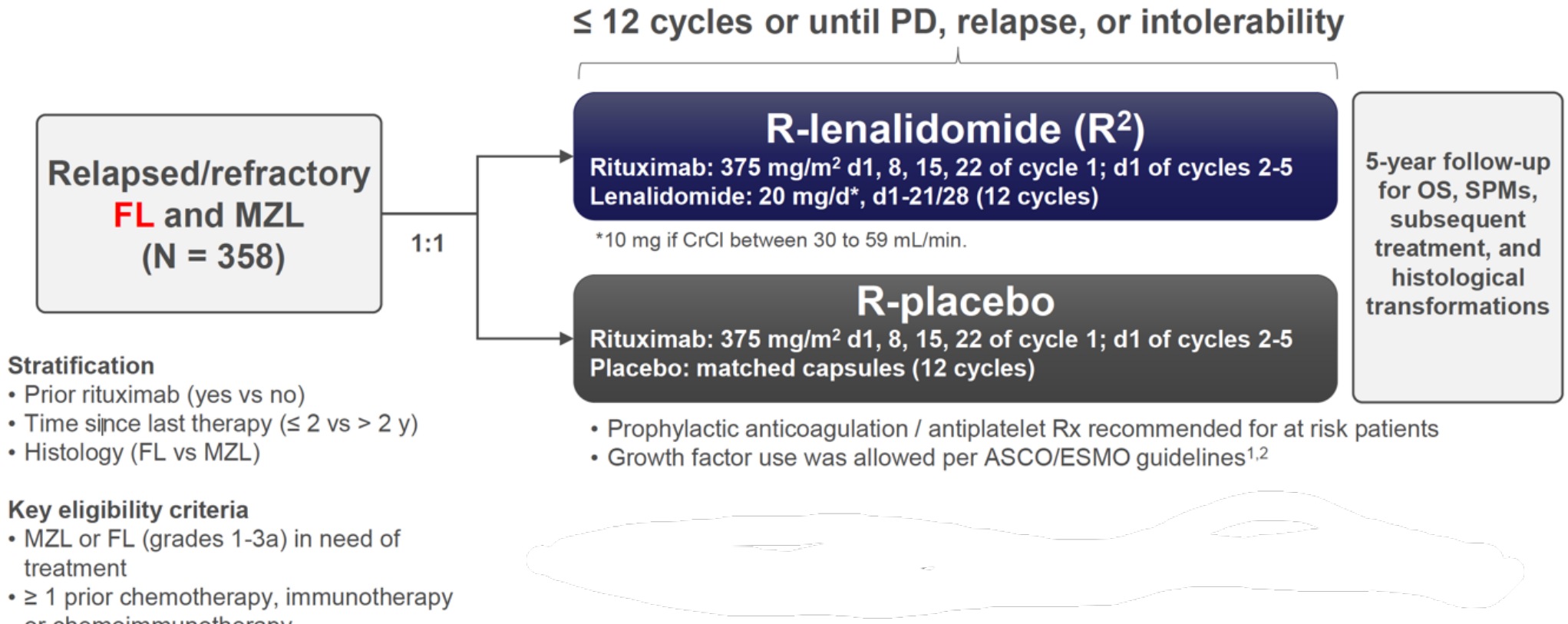
Leonard et al., JCO 2015

ALLIANCE: R^2 vs Lenalidomide in R/R FL (phase II)

Grade 3–4 AEs in > 1 patient, %		Lenalidomide (n = 45)		R^2 (n = 44)	
		Gr. 3	Gr. 4	Gr. 3	Gr. 4
Haematologic	Neutropenia	16	0	16	4
	Thrombocytopenia	0	0	4	0
	Lymphopenia	1	0	3	0
Fatigue		9	0	11	2
Thrombosis		9	7	2	2
Rash		2	2	4	0
Infection (with neutropenia)		4	0	2	0
AST		4	0	0	0

Leonard et al., JCO 2015

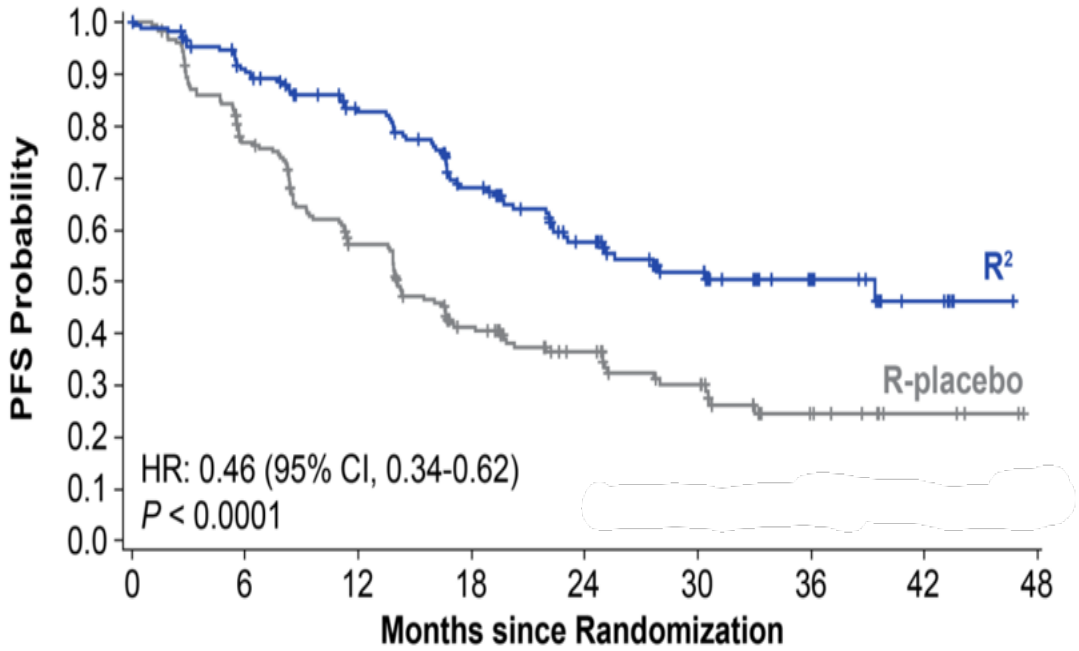
AUGMENT: R^2 vs Rituximab+Placebo in R/R iNHL (phase III)



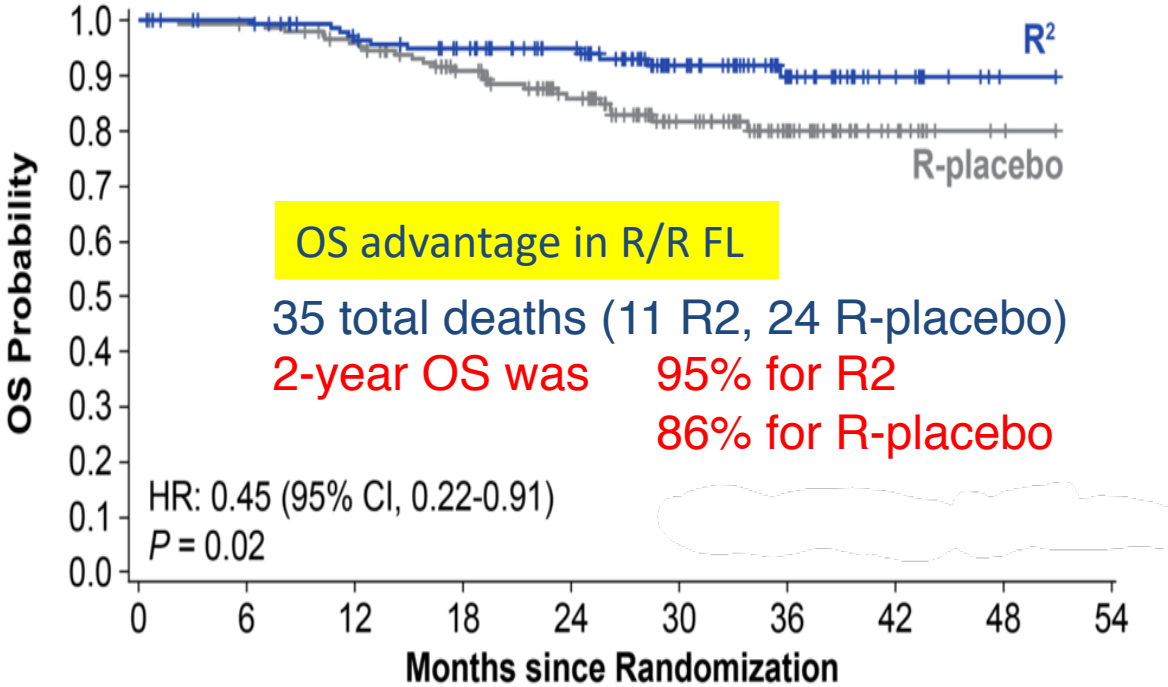
Leonard et al., ASH 2018

AUGMENT: R^2 vs Rituximab+Placebo in R/R iNHL (phase III)

A ”positive study”
- Significant difference in PFS (primary target)



Median observation of 28 months



OS advantage in R/R FL

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

2-year OS was 95% for R2

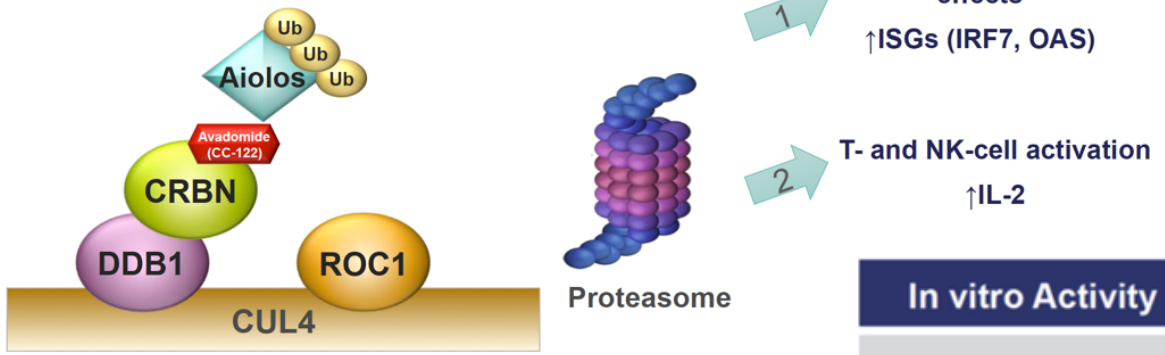
86% for R-placebo

Median observation of 28 months

Leonard et al., ASH 2018

CC-122 in R/R B cell NHL

Aiolos: transcriptional repressor of ISGs in lymphoma cells and IL-2 in T cells



CRBN, cereblon; CUL4, cullin 4; DDB1, DNA damage-binding protein 1; IRF, interferon regulatory factor; ISG, interferon-stimulated gene; IL, interleukin; NK, natural killer; OAS, oligoadenylate synthetase; ROC1, regulator of cullins 1; Ub, ubiquitin.

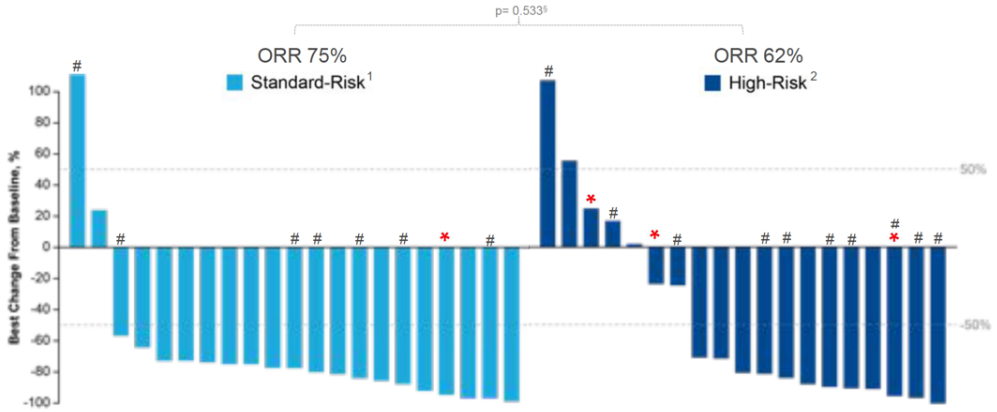
In vitro Activity		Thalidomide	Lenalidomide	CC-122
Cell autonomous tumoricidal activity	ABC DLBCL[1]		++	++
	GCB DLBCL[1]		+	++
	FL		+	++
Immunomodulation[3]		-	+	++
Anti-angiogenic[3]		++	+	++
Aiolos degradation[1]		-	+	++++
CK1α degradation[2]		-	+	-

Michot et al., TAC 2018

CC-122-NHL-001

The combination of CC122, an investigational pleiotropic pathway modulator, and the second generation antiCD20 antibody obinutuzumab

	Follicular Lymphoma/ Marginal Zone Lymphoma (n = 30)	Diffuse Large B-cell Lymphoma (n = 19)	All Patients (n = 49)
ORR	23 (77%)	9 (47%)	32 (65%)
CR	12 (40%)	2 (11%)	14 (29%)
PR	11 (37%)	7 (37%)	18 (37%)
SD	2 (7%)	3 (16%)	5 (10%)
PFS, median	16.6 months[a]	4.7 months	13.8 months
DOR, median	19.4 months[a]	10.2 months	10.2 months



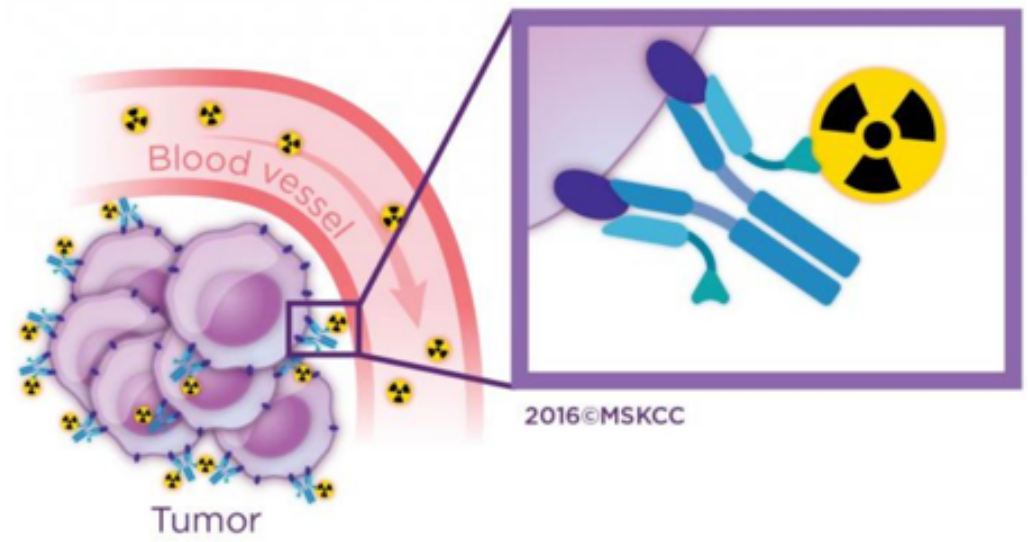
Michot et al., TAC 2018

^{90}Yttrium-ibritumomab-tiuxetan in R/R FL

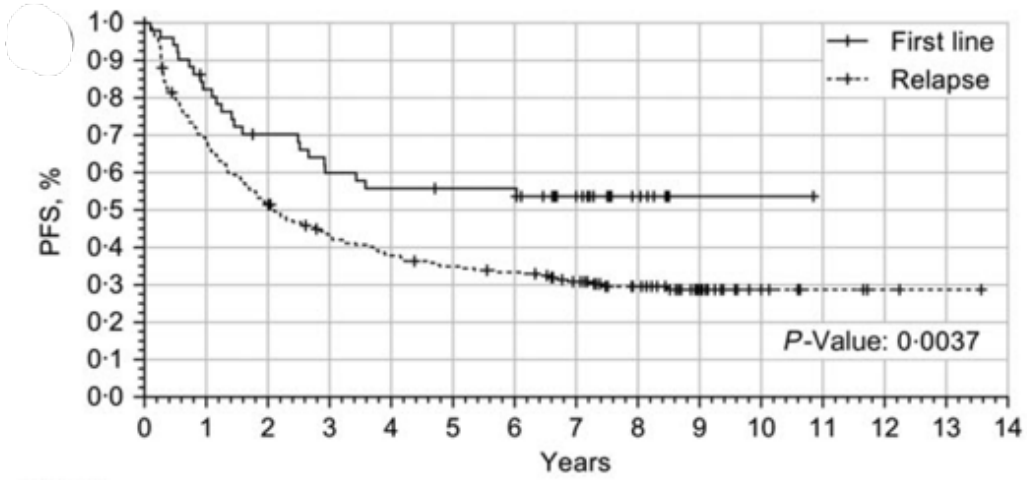
- **^{131}I tositumomab** is no longer commercially available (Beta and Gamma emitting isotopoe, **anti-CD20** MoAb, **half-life of 8.01 days** and a decay energy of 0.971 MeV)

- **^{90}Yttrium-ibritumomab-tiuxetan** is hardly avaliable(Beta-emitting isotope, **anti-CD20** MoAb, **half-life of 2.66 days** and a decay energy of 2.28 MeV)

- **^{177}Lu-satetraxetan-lilotomab** is being investigated (Beta-emitting isotope, **anti-D37** MoAb (**half-life of 6.64 days** and a decay energy of 6.183 MeV)

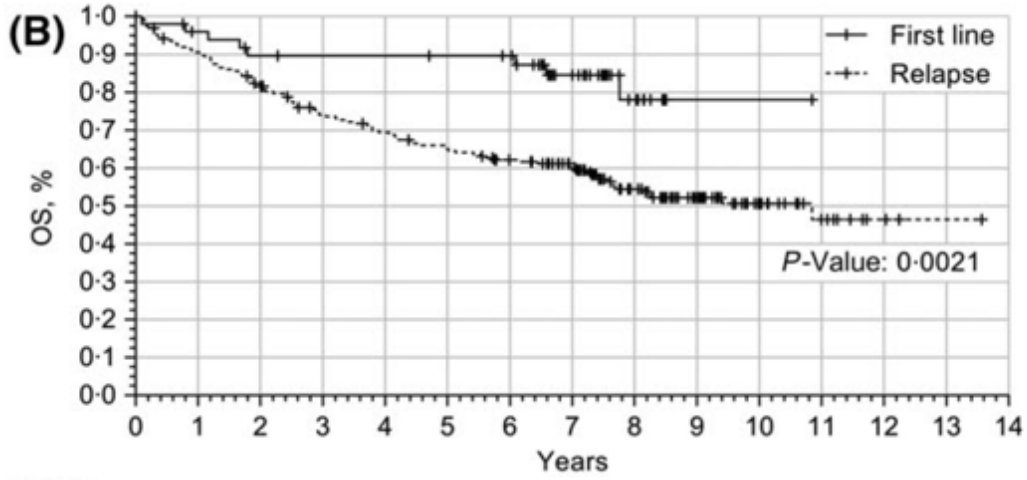


Radioimmunotheray in FL – registry data



At risk:														
First line	52	41	34	29	27	26	26	19	8	1	1			
Relapse	229	153	114	91	79	72	68	55	41	24	9	5	2	1

	Median PFS	8 year PFS
First line	NR	53·6%
Relapse	2·11 years	29·6%

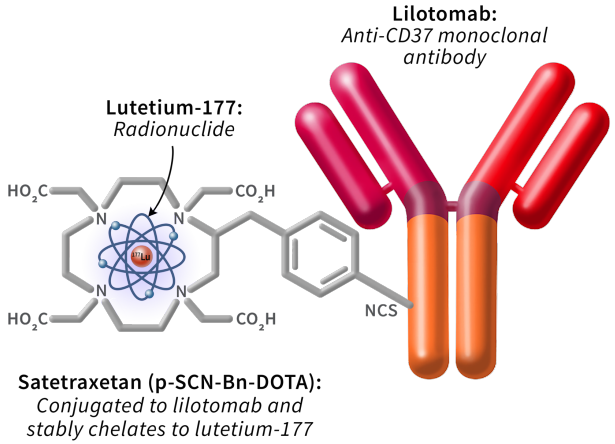


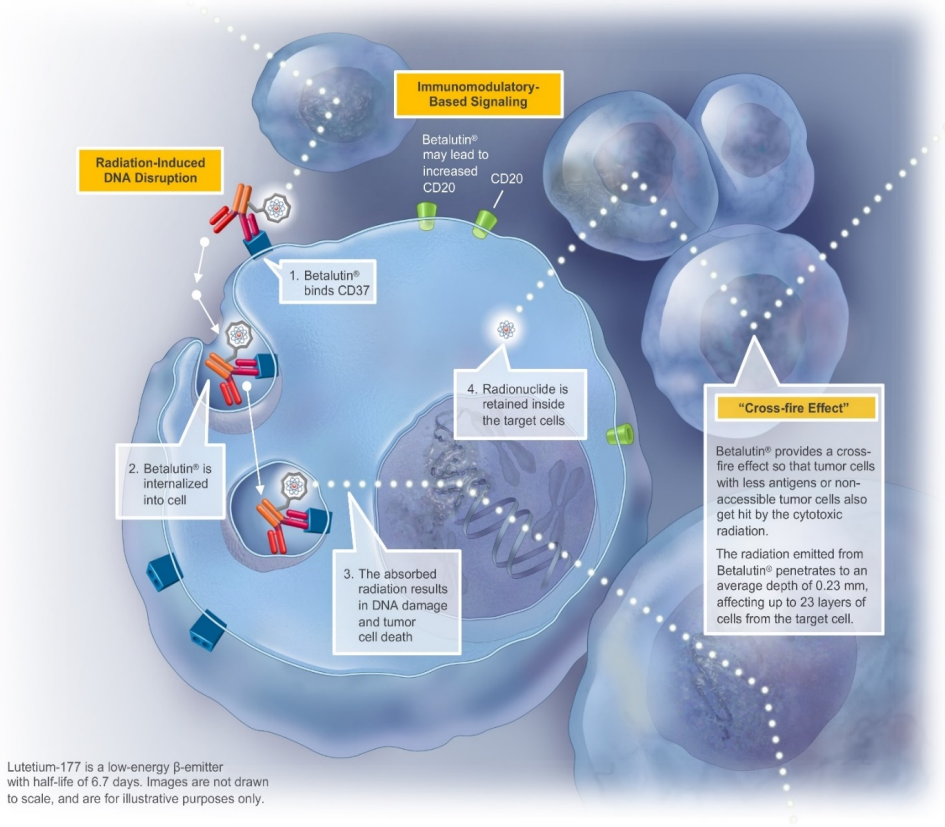
At risk:														
First line	52	46	42	41	41	40	39	27	11	1	1			
Relapse	229	201	179	157	146	136	125	109	77	48	23	10	3	1

	Median OS	8 year OS
First line	NR	78·1%
Relapse	10·8 years	54·5%

Hohloch et al., Br.J.Haematol 2019

^{177}Lu-satetraxetan-lilotomab: a CD37-targeting radioimmunotherapy



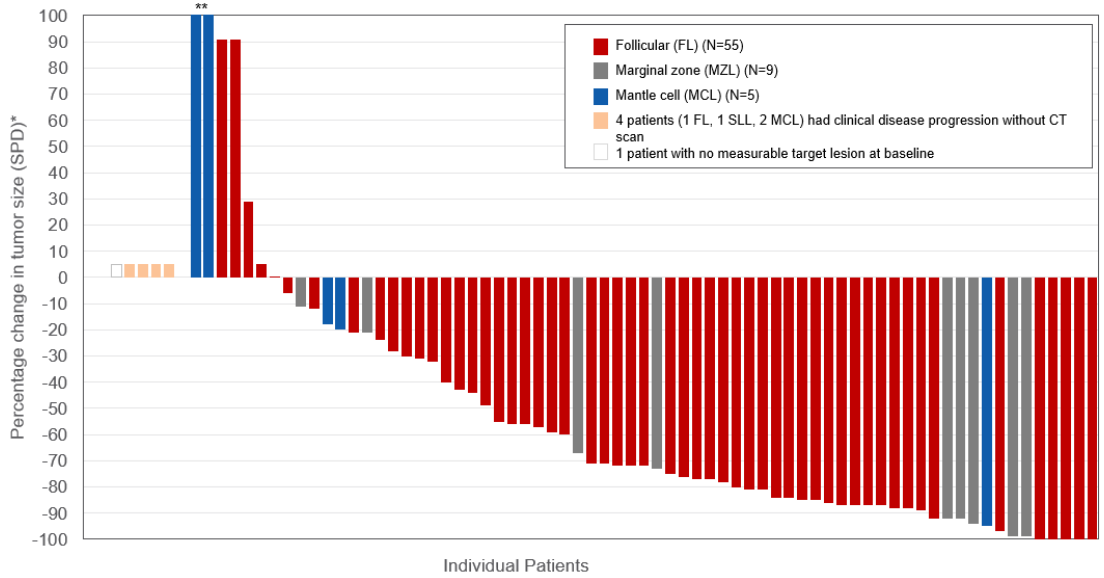


- CD37 is a tetraspanin membrane protein involved in cellular differentiation and proliferation, highly expressed in B-NHL[1] (from B cell to late plasmablast)
- Lutetium-177 is a low energy β-emitter with a half-life matching the circulation time of the anti-CD37 IgG (6.7 days)
- ^{177}Lu-satetraxetan-lilotomab (Betalutin®) is a next generation beta-emitting anti-CD37 radioimmunoconjugate in a ready-to-use formulation for single-dose administration.

1. Flinn et al., *Blood* 2011; 2. Palomba et al., *Blood* 2013

^{177}Lu-satetraxetan-lilotomab monotherapy in R/R iNHL(N=74)

Subtype	ORR n (%)	CR n (%)	PR n (%)	SD n (%)	PD n (%)
All patients	61%	28%	32%	19%	20%
FL (n=57)	37 (65%)	16 (28%)	21 (37%)	10 (18%)	10 (18%)
MZL (n=9)	7 (78%)	4 (44%)	3 (33%)	2 (22%)	--
MCL (n=7)	1 (14%)	1 (14%)	--	2 (28%)	4 (57%)
SLL (n=1)	--	--	--	--	1



- Median age: 69; median no. prior therapies: 3
- Highly active in 3L FL (n=37): ORR 70%, CR 32% mDoR: 9 months; 20.7 months with CR (on-going)
- Main grade 3/4 toxicities: Reversible neutropenia (G3/4: 35/19%) and thrombocytopenia (25/20%). 2 patients received platelets for bleeding, both G3; low incidence of infections, no febrile neutropenia
- Global Phase 2b RCT “PARADIGME” (3L CD20-refractory FL; n=130) now enrolling

Kolstad A, et al. from ASH 2018. Abstract 2879

GLGL
Study Group

FL POD24 patients subjected to ASCT

	Characteristics		POD24 ASCT (n=52)	POD24 No transplant (n=61)
1st-line treatment	**Age** *[median in years (range)]*		*47 (21; 60)*	*51 (19; 60)*
	Male gender *[No. (%)]*		*38 (73%)*	*31 (51%)*
	Clinical risk factors *[No. (%)]*	High-risk FLIPI	*20 (39%)*	*28 (46%)*
		Nodal sites > 4	*41 (79%)*	*48 (79%)*
		LDH elevated	*14 (27%)*	*24 (39%)*
		Hb < 120g/l	*12 (23%)*	*19 (31%)*
		ECOG > 1	*5 (10%)*	*13 (21%)*
	Treatment *[No. (%)]*	CHOP	*37 (71%)*	*44 (72%)*
		MCP	*5 (10%)*	*12 (20%)*
		R-CHOP	*10 (19%)*	*5 (8%)*

ASCT *vs* no transplant

5-year 2nd-line PFS 51% *vs* 19%
(HR 0.38, 95%-CI) [0.24;0.62], $p<0.0001$)

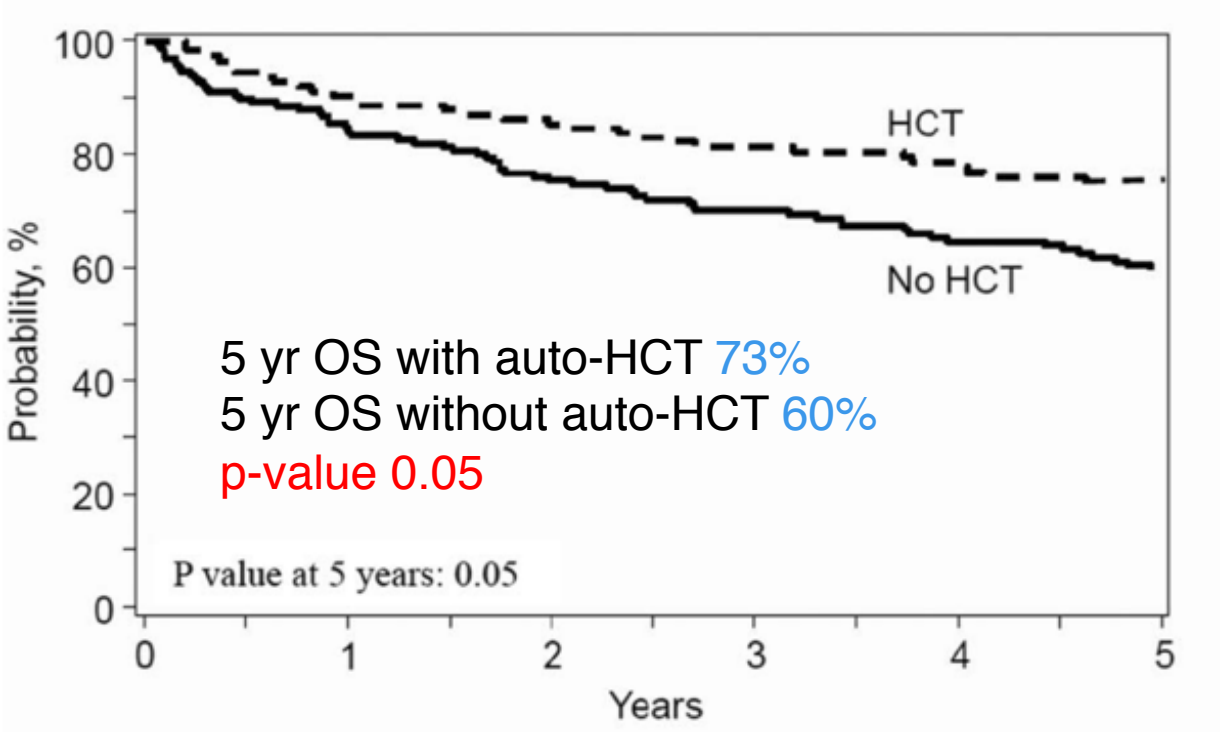
5-year 2nd-line OS of 77% *vs* 59%
(HR 0.54, 95%-CI [0.30;0.95], $p=0.031$)

A significant survival benefit for Patients subjected to ASCT

Jurinovic et al., Biol of Bone Marrow Transpl 2018

FL POD24 patients subjected to ASCT (N=349)

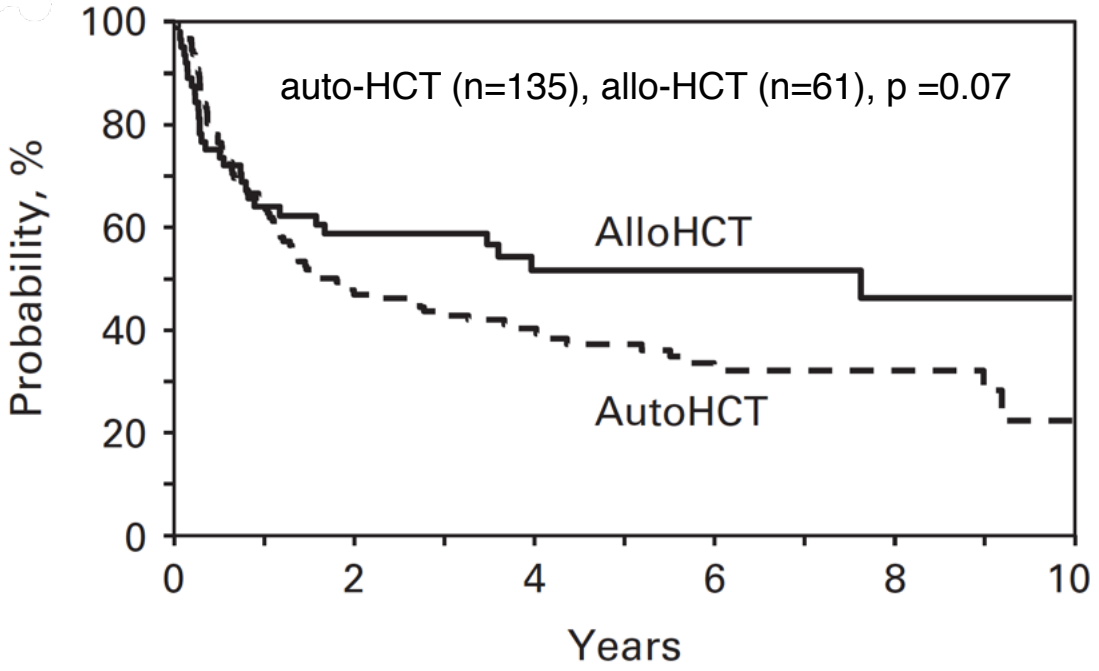
- Retrospective analysis CIBMTR, Center for International Blood and Marrow Transplant Research; NLCS, National LymphoCare Study
- 349 pts with POD24 after rituximab-based I-st line therapy
- Matched, half received auto-SCT, half did not



Casulo C, et al. Biol Blood Marrow Transplant. 2018

RIC allo vs ASCT in FLGIIIa – CIBMTR registry data

PFS



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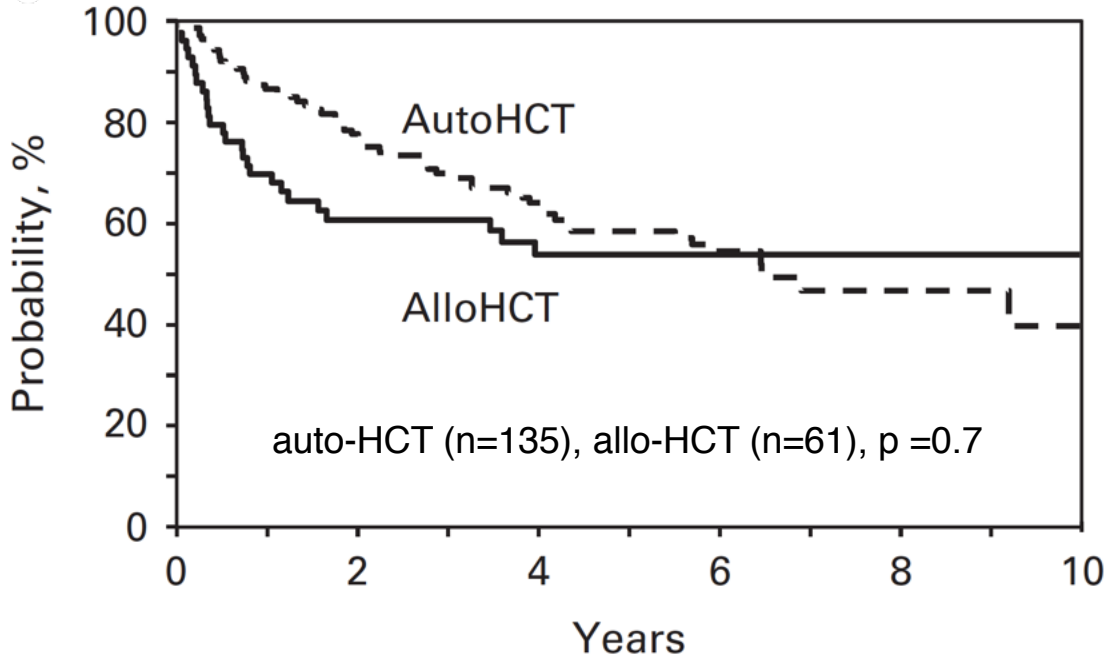
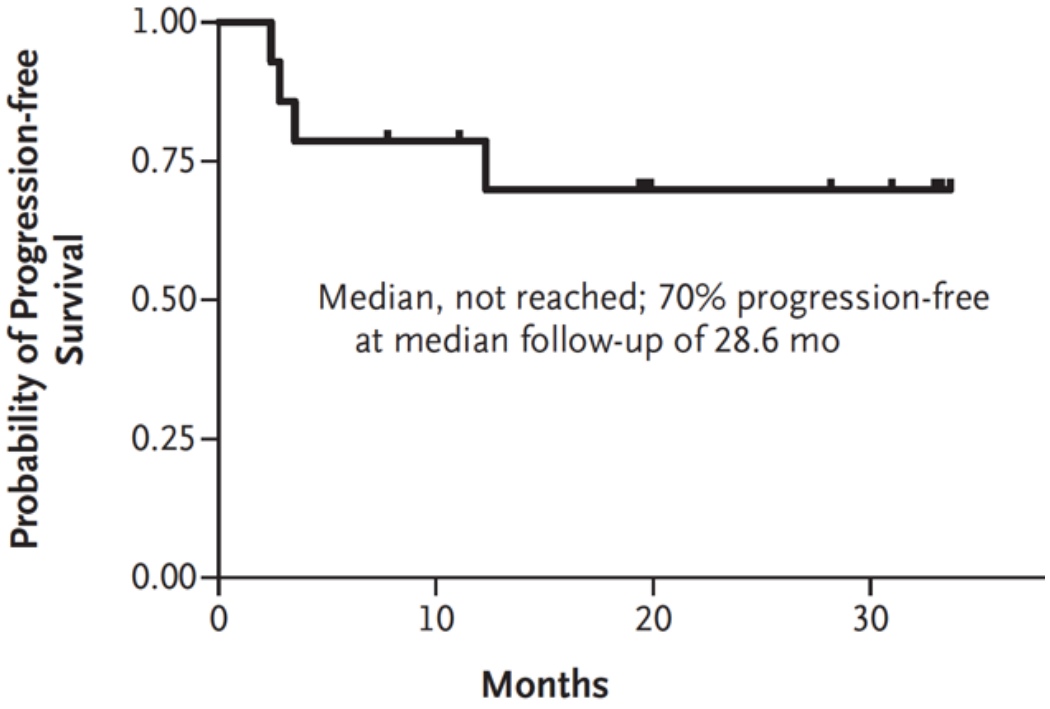


Klyuchnikov et al., Bone Marrow Transplant 2015

CART in R/R FL patients (N=14)

PFS



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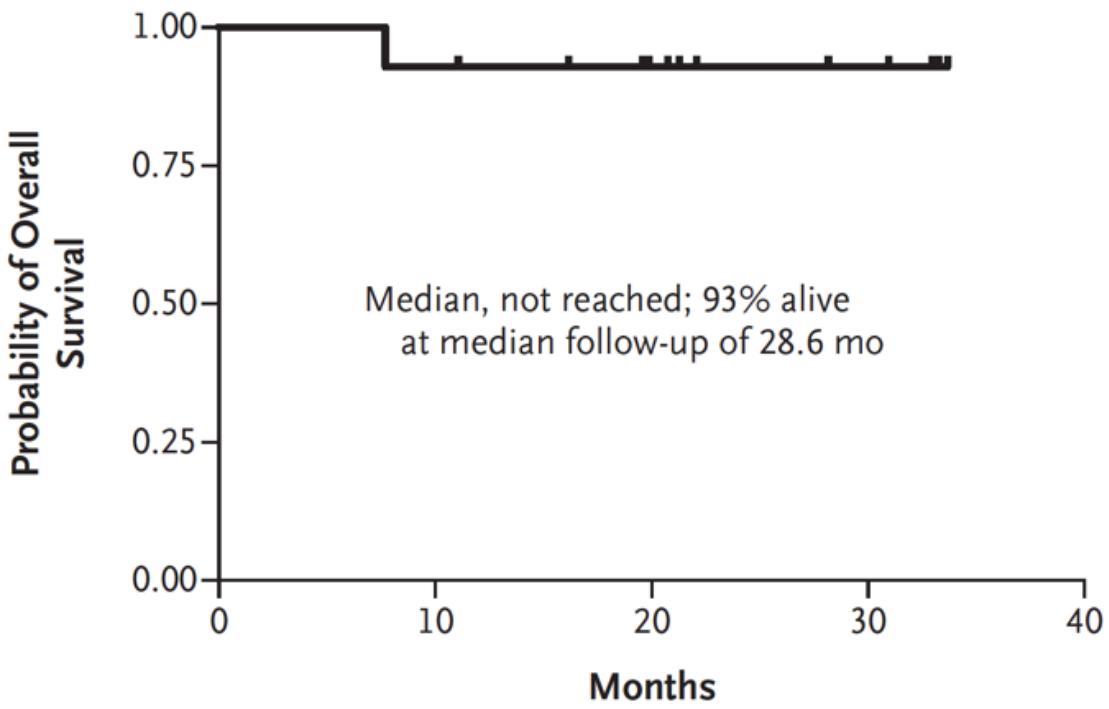
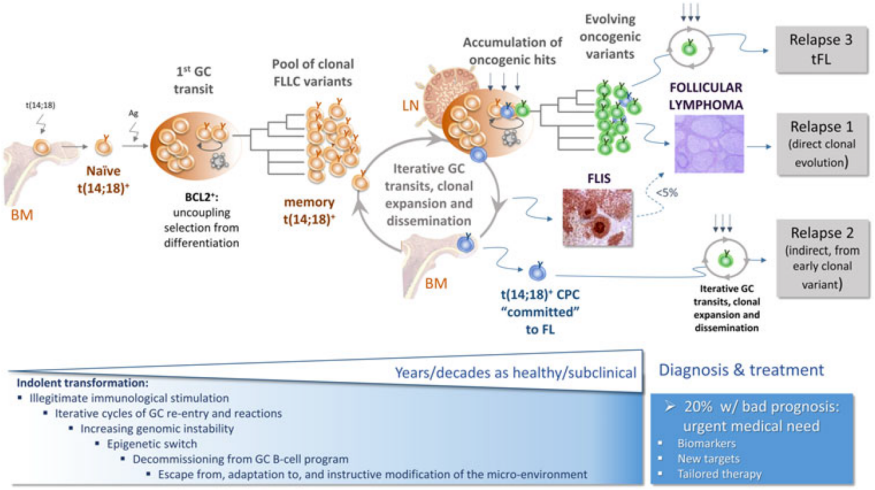


Schuster et al., NEJM 2017

Recurrent genetic alterations in FL

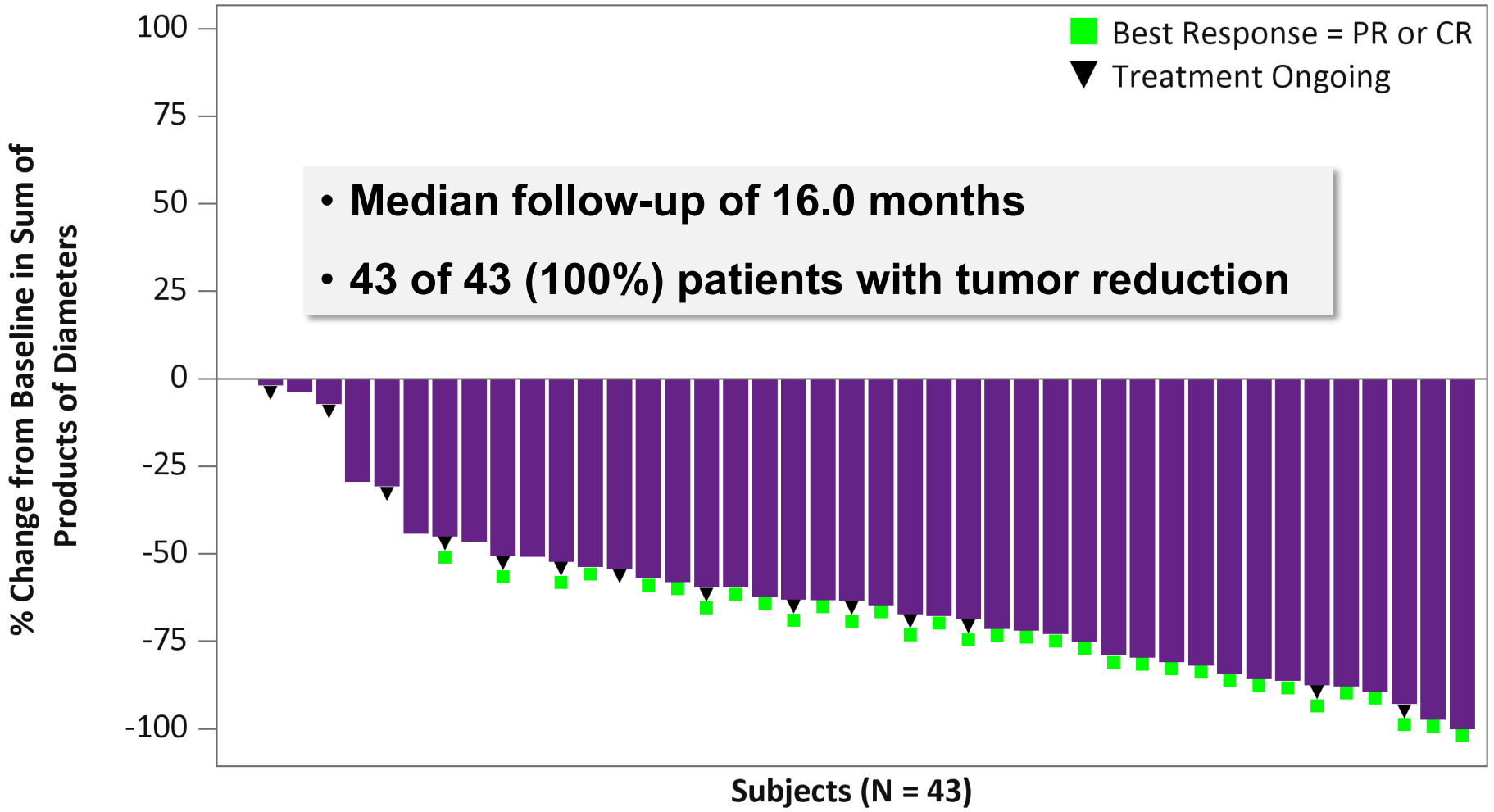
Genetic Alteration	Frequency, %	Function
Gene regulatory element mutations	100	Transcriptional control
t(14;18)(q32, q21.3)	85-90	Antiapoptosis
KMT2D mutations	80-90	Histone modification
Mutations of *IGH* epitopes that promote N-glycosylation	85-95	BCR signaling
CREBBP mutations	40-65	Histone modification and immune escape
BCL2 mutations*	40-65	Antiapoptosis?
Deletion 6q including *EPH7A* deletion/methylation, *TNFAIP3* mutation/deletion and *PRDM1* deletions[15,16]	60-70	Tumor suppressor
TNFRSF14 mutations/deletions, LOH	50	Direct proliferative signal? Immune escape?
EZH2 mutations	20-30	Histone modification
Core histone genes, eg, *HIST1H1E*	20-30	Histone modification
RRAGC mutations	~17	mTORC1 signaling
MEF2B mutations	10-15	Transcription factor
STAT6 mutations	10-15	JAK-STAT signaling
EP300 mutations	~10	Histone acetylation
ARID1A mutations	~10	Chromatin remodelling
OCT2 mutations	5-10	Transcription factor
CARD11 mutations	5-10	BCR signaling
FOXO1 mutations	5-10	BCR signaling
GNA13 mutations	5-10	Focal adhesion/mobility
B2M mutations	5-10	Immune escape
SGK1 mutations	5-10	Protein kinase



Accumulation of oncogenic alterations occurring through the increased genomic instability

Gascoyne et al., Hematological Oncology. 2017

Phase II multicenter study - Tazemetostat an EZH2 inhibitor, R/R FL



Morschhauser et al., EHA 2019

Jagiellonian University Lymphoma Team participated in registration trials of:

BTK Inhibitors

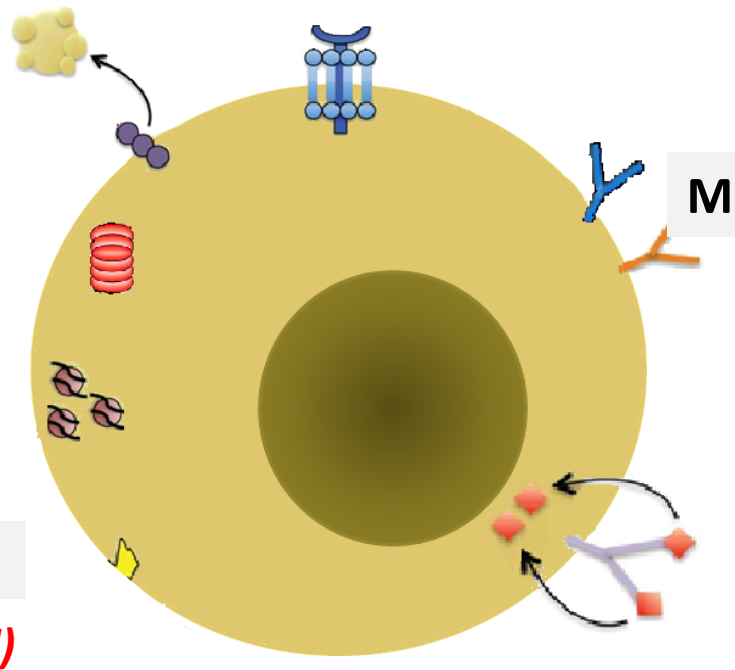
(Ibrutinib, Acalabrutynib)

IP3K Inhibitors

(Idelalisib)

bcl-2 Inhibitors

(Venetoclax)



MoAb

HIDAC inhibitors

Belinostat

Rituximab Biosimilars

(Truxima, Rixathon)

Obinutuzumab

(Gazyvaro)

IMIDS

(Lenalidomid)

Brentuximab Vedotin *(Adcetris)*

Take home messages:

- **Majority of FL patients diagnosed in 2018 will die with the disease and not of the disease** – in assessing the new regimens, their increased clinical efficacy has to be balanced against their adverse effects and quality of life.

- **The choice of the first line therapy in high risk FL patients remains an unmet medical need**, which was not yet addressed in the randomized clinical studies.

- Introducing / developing new monoclonal antibodies and more recently "small molecules" targeting intracellular pathways, may be regarded **milestones in FL** therapy, prolonging OS.

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