Emerging targeted therapies for follicular lymphoma
A future without chemotherapy

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FOLLICULAR LYMPHOMA: GENERAL ASPECTS

- **Follicular lymphoma**: the paradigm of indolent lymphomas.
- Slow-growing disease, rarely with systemic symptoms.
- High response rates to first-line standard treatments (immuno-chemotherapy) but with tendency to relapse or transformation.

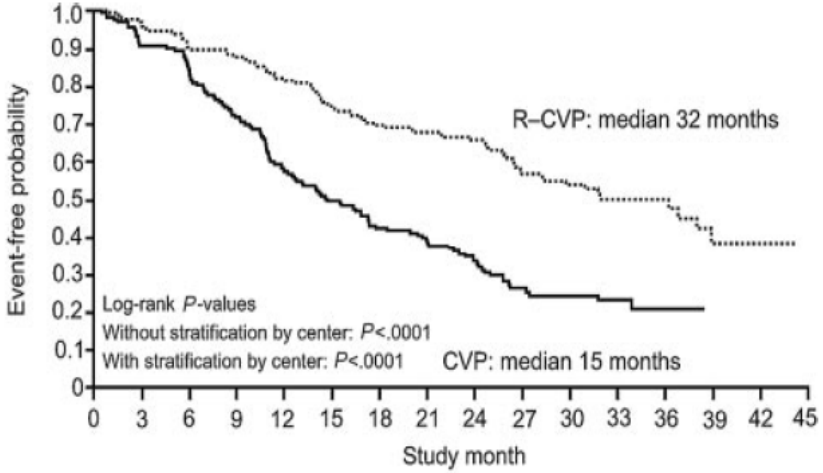
- Progression-free survival, disease-free survival and time-to-next treatment intervals (rather than overall survival) to be considered to compare different treatment policies.

- **Stage** (limited *vs* diffuse disease spreading): dictates the initial management of the patient (type of treatment and possibly timing).
- **Symptomatic disease (i.e. tumor burden)**: dictates treatment timing (watch and wait *vs* immuno-chemotherapy initiation).

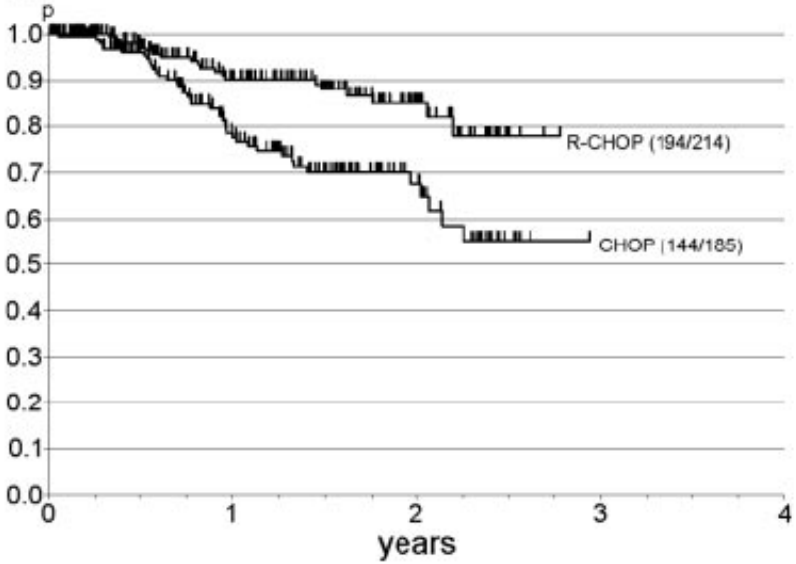
- **New drugs** needed to manage multiply relapsed disease and to bridge patients to transplantation procedure when required.

GOALS ACHIEVED WITH CHEMOIMMUNOTHERAPY

STEP 1: RITUXIMAB + CHEMOTHERAPY = CHEMOIMMUNOTHERAPY



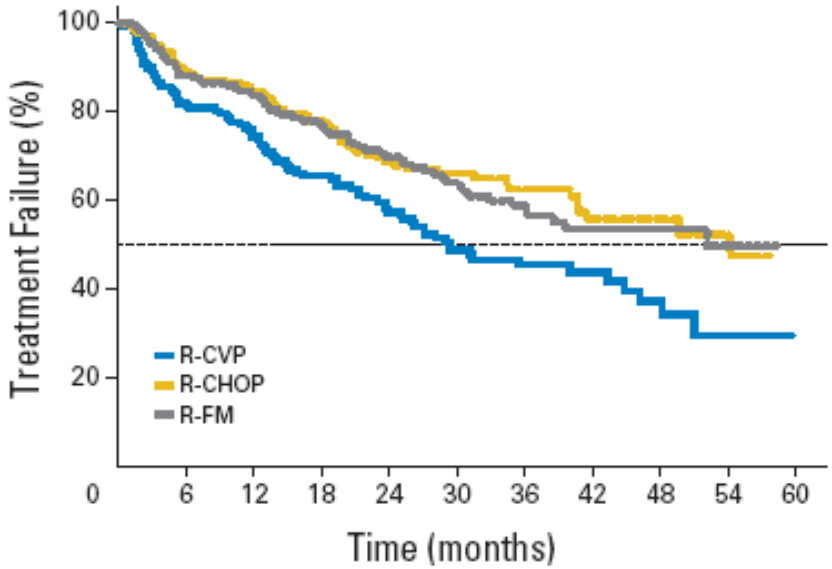
Marcus R. *Blood*, 2005; 105: 1417-1423



Hiddemann W. *Blood*, 2005; 106: 3725-3732

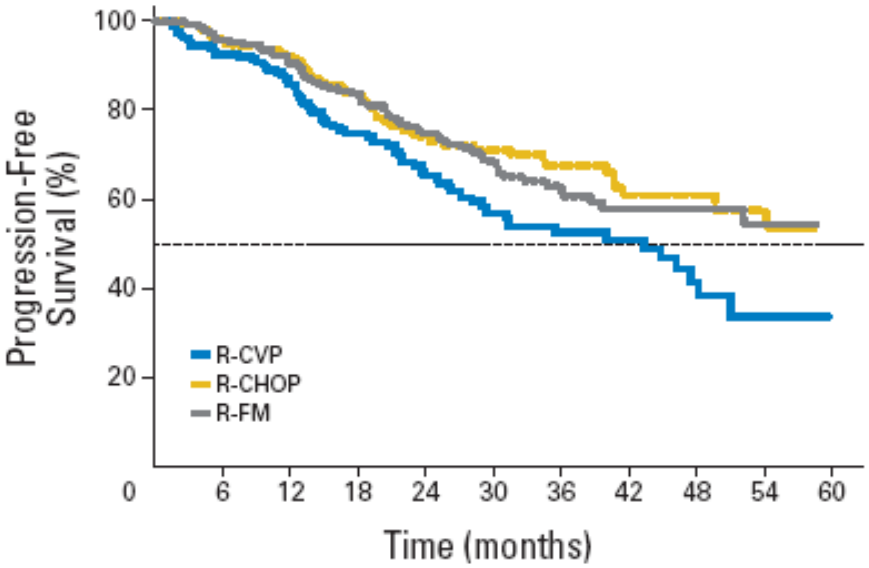
R-CVP Versus R-CHOP Versus R-FM for the Initial Treatment of Patients With Advanced-Stage Follicular Lymphoma: Results of the FOLL05 Trial Conducted by the Fondazione Italiana Linfomi

	R-CVP	R-CHOP	R-FM
CR rate	67%	73%	72%
ORR (CR + PR)	88%	93%	91%
< PR	11%	6%	8%
Relapse rate	33%	24%	22%



No. at risk

R-CVP	168	136	119	95	74	51	36	23	13	5	1
R-CHOP	165	147	137	120	83	66	47	32	19	12	5
R-FM	171	150	139	120	95	68	50	32	20	12	4



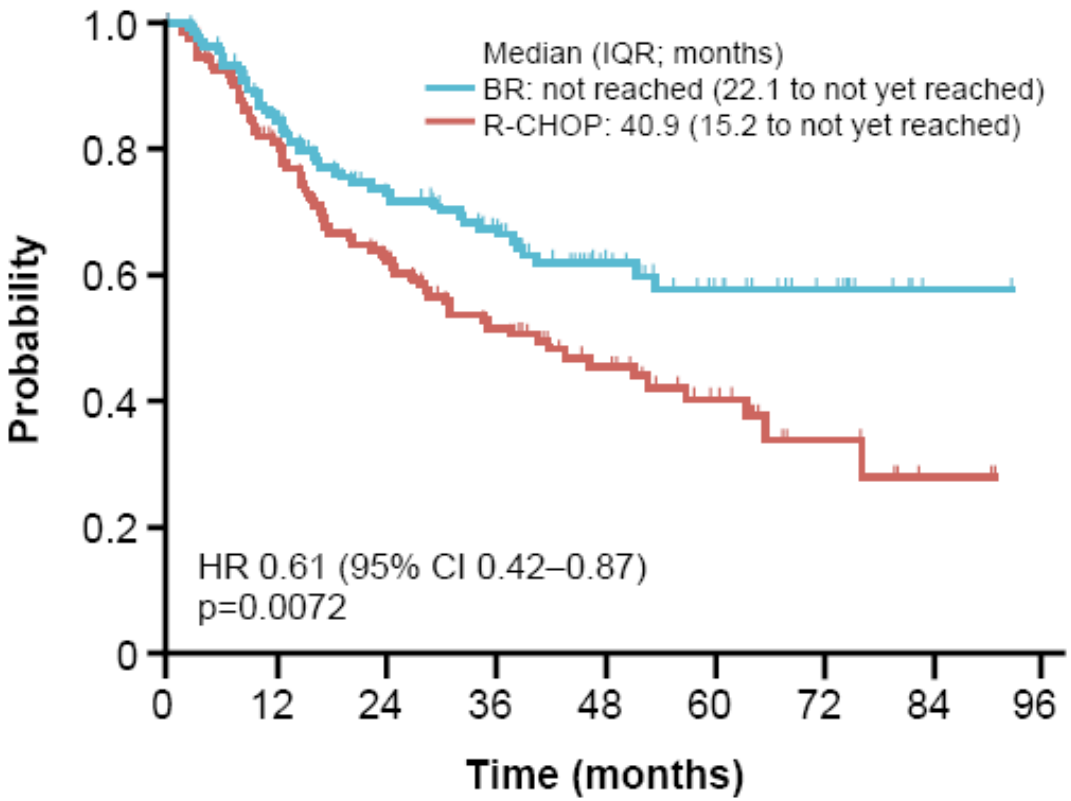
No. at risk

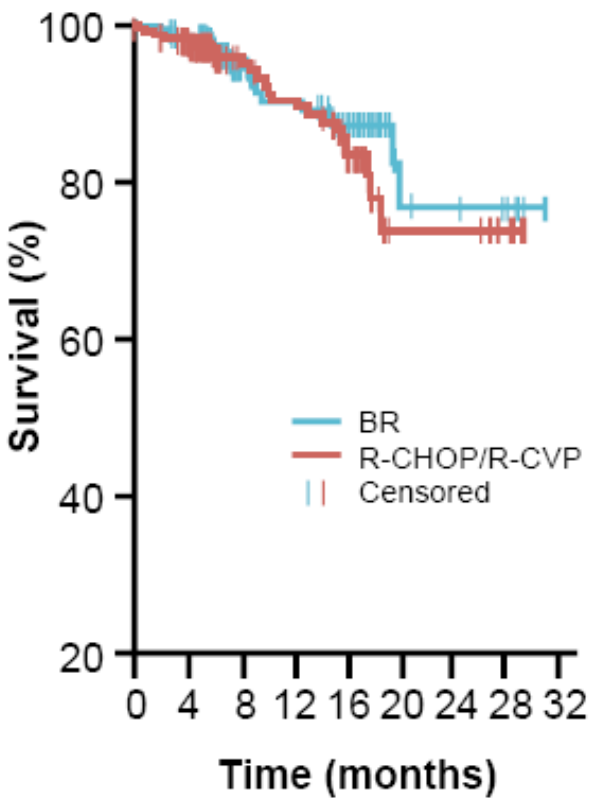
R-CVP	168	154	136	108	85	60	41	27	14	6	1
R-CHOP	165	157	147	128	89	70	51	36	22	14	6
R-FM	171	163	151	130	101	73	55	36	23	14	5

Federico M. *J Clin Oncol*, 2013; 31: 1506-1513

Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial

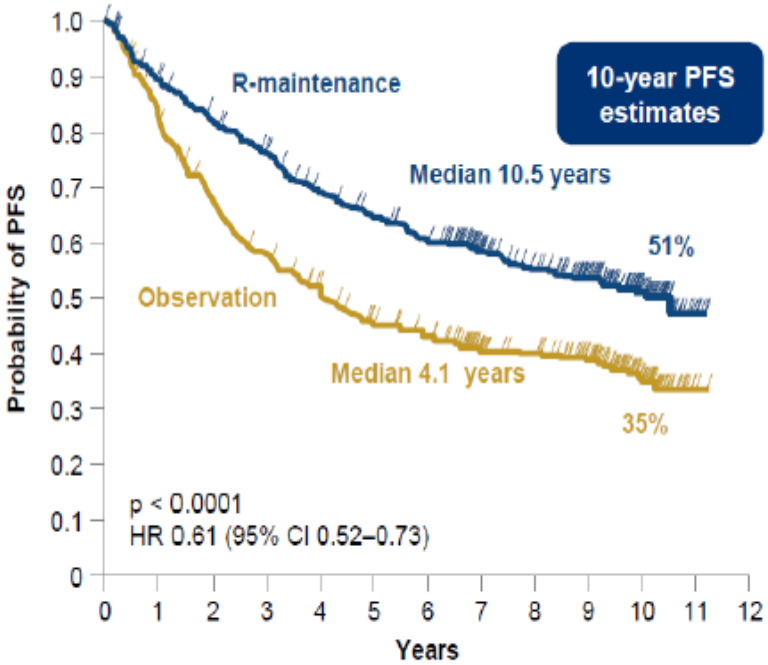
Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study



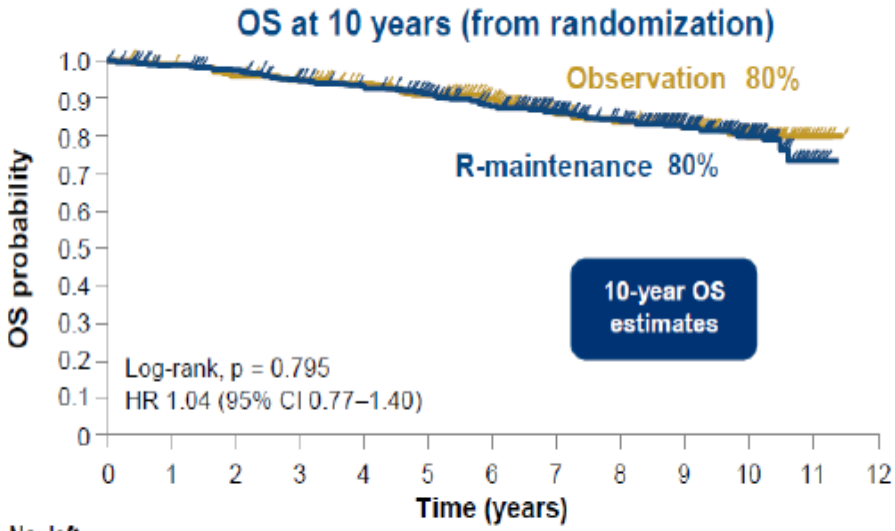


Rummel MJ. *Lancet*, 2013; 381: 1203-1210
Flinn IW. *Blood*, 2014; 123: 2944-2952

STEP 2: RITUXIMAB MAINTENANCE



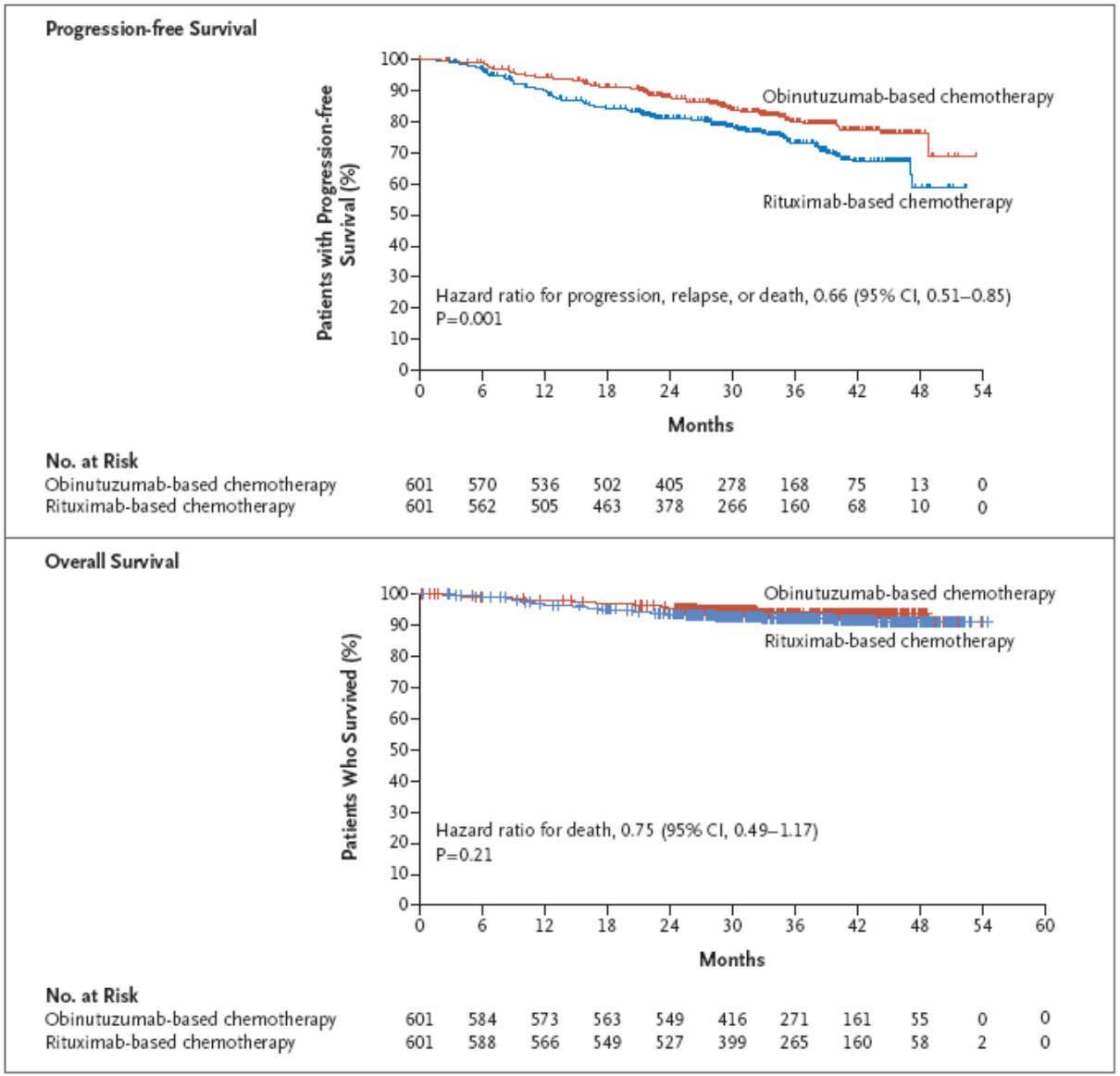
No. left												
Observation	513	415	336	290	251	217	200	155	147	122	41	1	0
Rituximab	505	445	406	372	333	309	284	231	208	170	67	4	0



No. left												
Observation	513	501	485	472	460	440	412	319	297	256	91	8	0
Rituximab	505	492	480	464	449	432	407	341	313	261	107	8	0

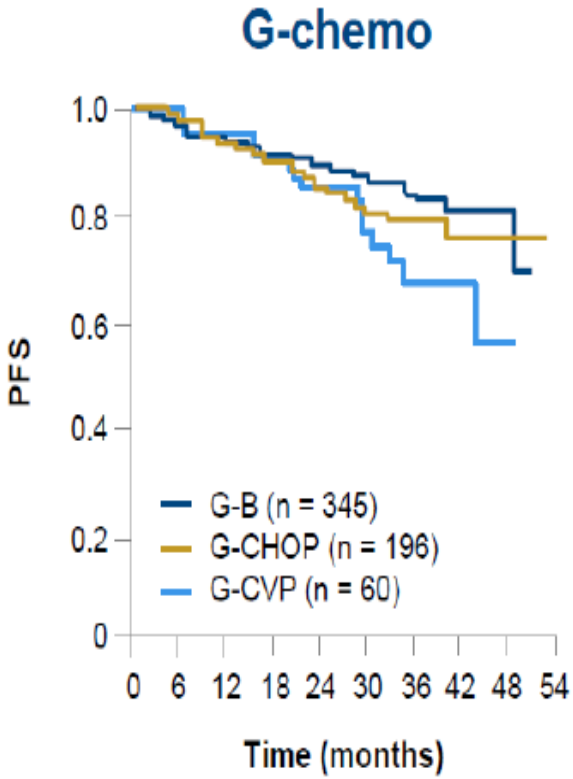
Salles G. *Lancet*, 2011; 377: 42-51 – Updated ASH 2017

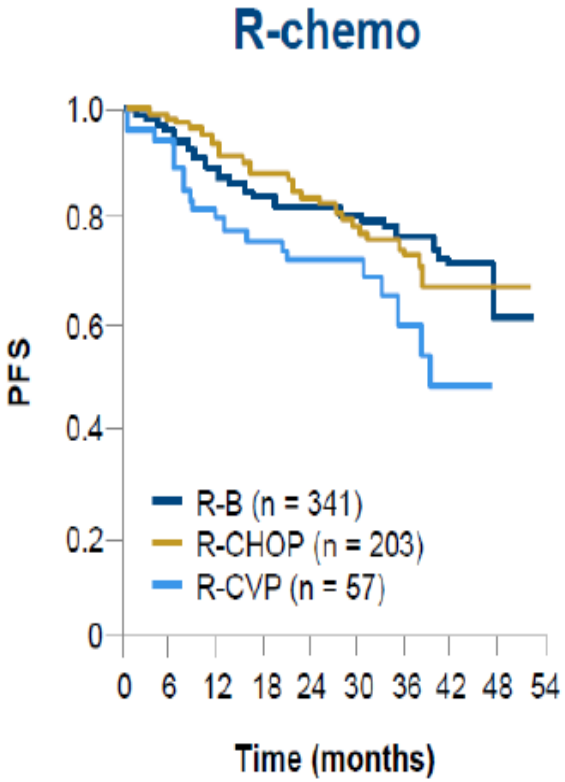
STEP 3: OBINUTUZUMAB + CHEMOTHERAPY



Marcus R. *N Engl J Med*, 2017; 377: 1331-1344

Immunochemotherapy With Obinutuzumab or Rituximab for Previously Untreated Follicular Lymphoma in the GALLIUM Study: Influence of Chemotherapy on Efficacy and Safety





	HR (95% CI)
G-B vs R-B	0.61 (0.43–0.86)
G-CHOP vs R-CHOP	0.77 (0.50–1.20)
G-CVP vs R-CVP	0.63 (0.32–1.21)

Hiddemann W. *J Clin Oncol*, 2018; 36: 2395-2404

TOWARDS CHEMO-FREE APPROACHES

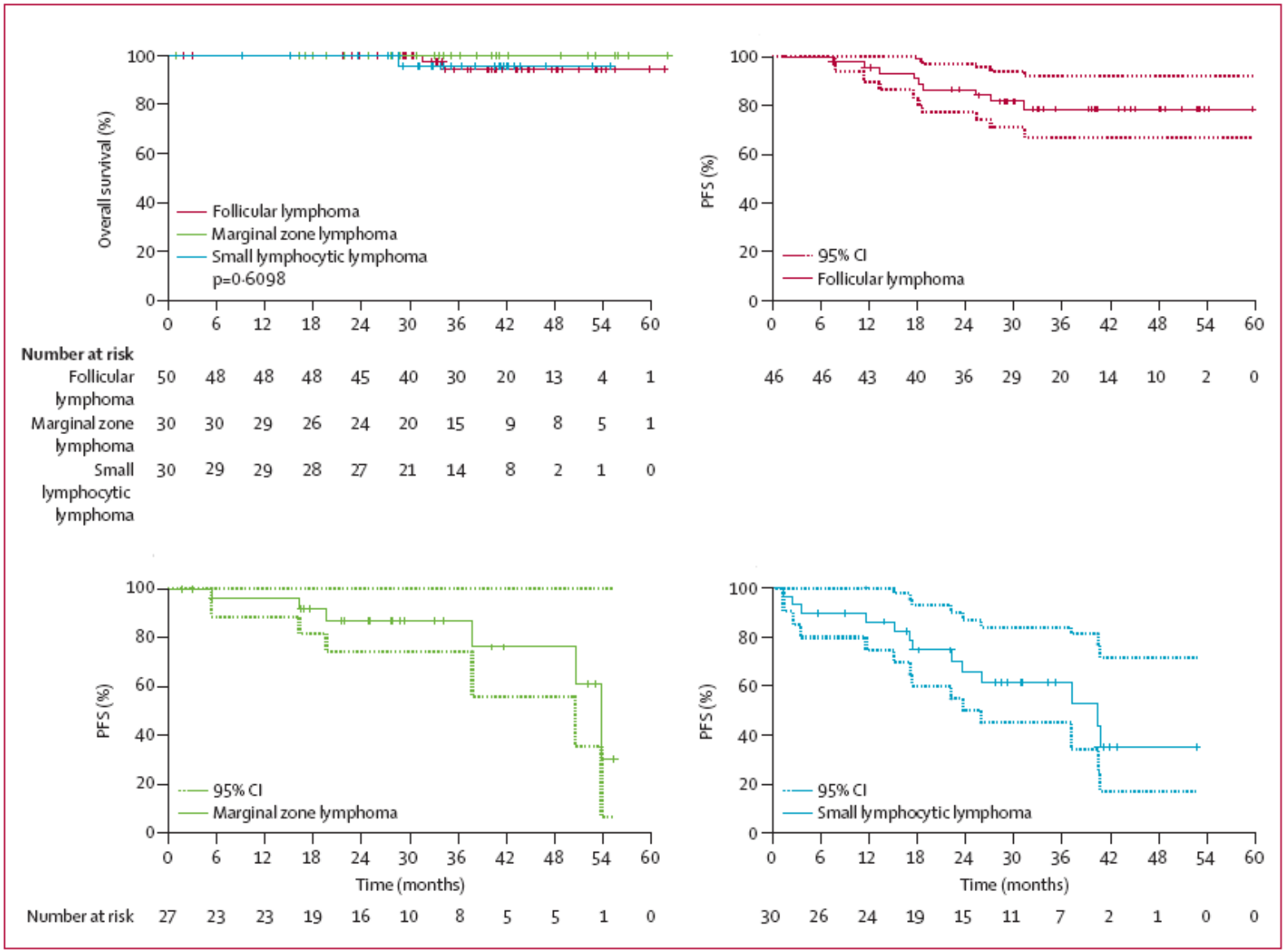
THE R^2 CONCEPT: RITUXIMAB + LENALIDOMIDE

	Follicular lymphoma (n=50)	Marginal zone lymphoma (n=30)	Small lymphocytic lymphoma (n=30)
Age (years; median, range)	56 (35–84)	59 (36–77)	59 (34–76)
Sex, female	22 (44%)	18 (60%)	12 (40%)
Stage			
III	23 (46%)	9 (30%)	0
IV	27 (54%)	21 (70%)	30 (100%)
High tumour burden (as per GELF)	27 (54%)	13 (43%)	14 (47%)
FLIPI score			
0–1	11 (22%)	..	..
2	25 (50%)	..	..
3–5	14 (28%)	..	..

Data are number (%), unless otherwise indicated. GELF=Groupe d'Etudes des Lymphomes Folliculaires. FLIPI=Follicular Lymphoma International Prognostic Index.

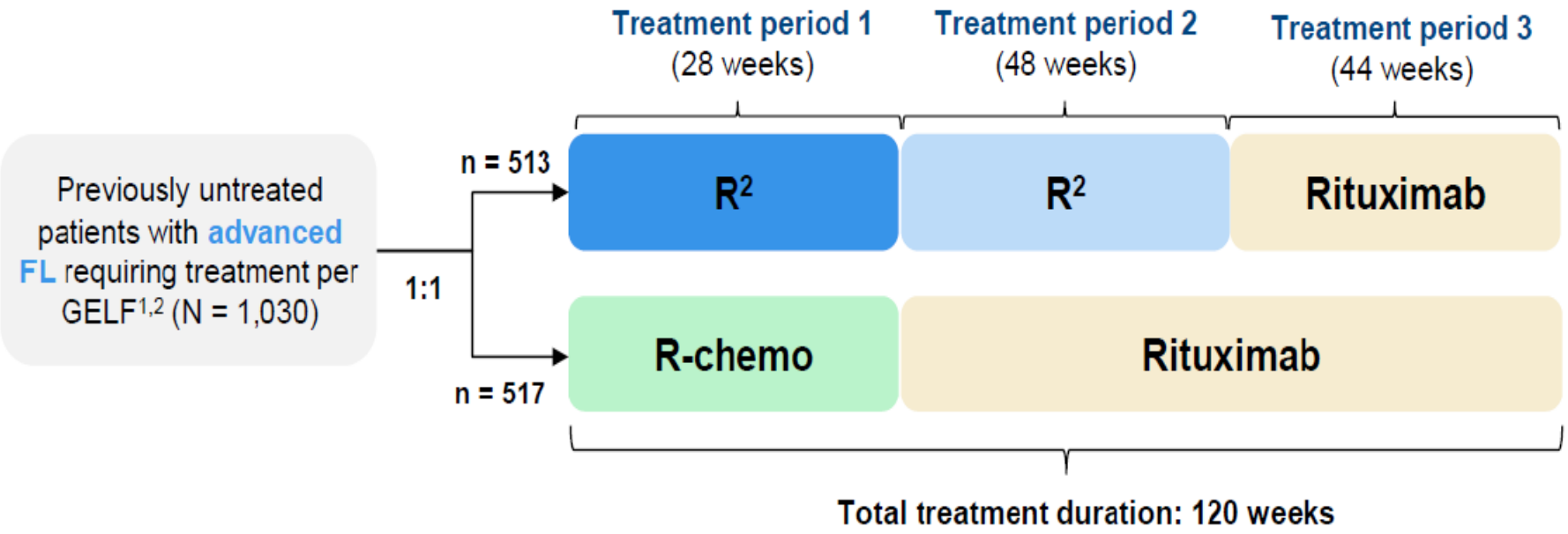
Fowler NH. *Lancet Oncol*, 2014; 15: 1311-1318

Safety and activity of lenalidomide and rituximab in untreated indolent lymphoma: an open-label, phase 2 trial



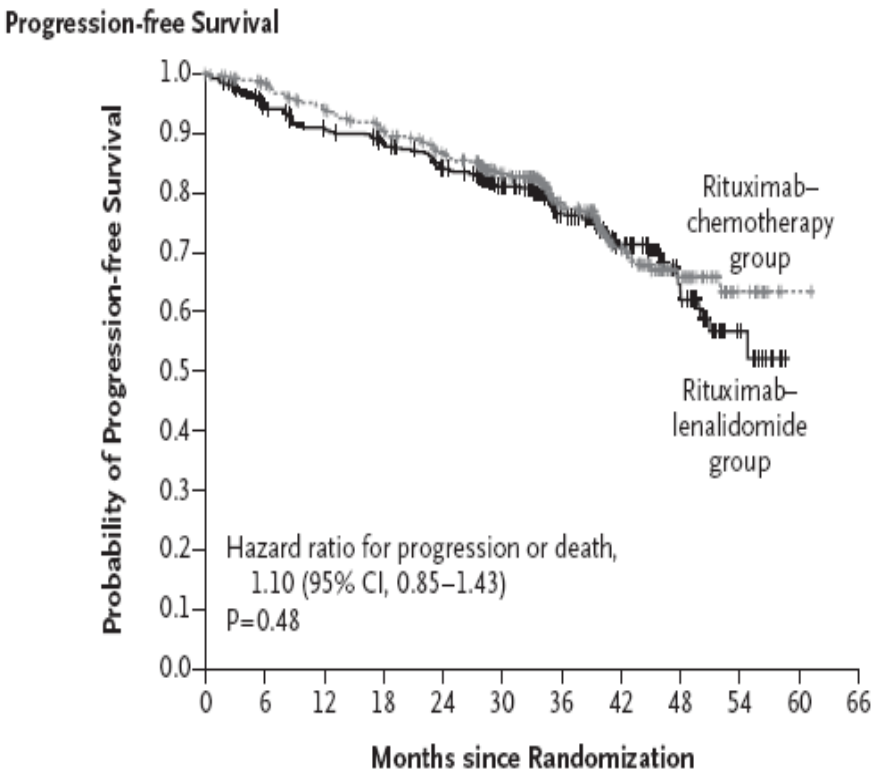
Fowler NH. *Lancet Oncol*, 2014; 15: 1311-1318

Rituximab plus Lenalidomide in Advanced Untreated Follicular Lymphoma

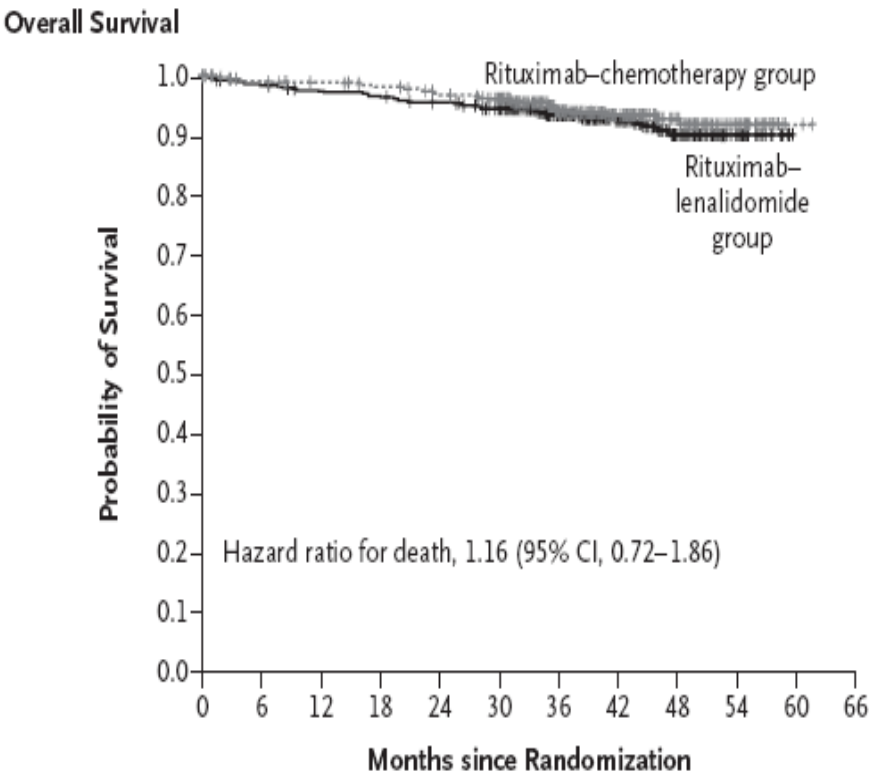


Morschhauser F. *N Engl J Med*, 2018; 379: 934-947

Rituximab plus Lenalidomide in Advanced Untreated Follicular Lymphoma



No. at Risk												
Rituximab–lenalidomide group	513	435	409	393	364	282	174	107	49	13	0	
Rituximab–chemotherapy group	517	474	446	417	387	287	175	109	51	14	1	0



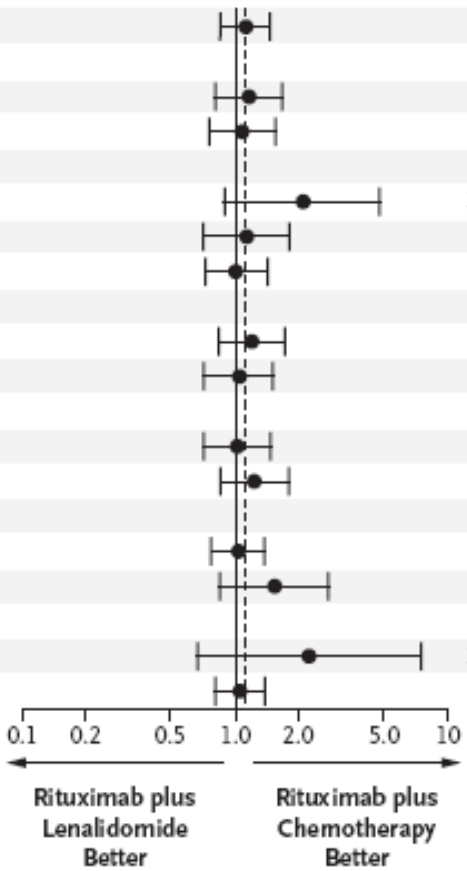
No. at Risk												
Rituximab–lenalidomide group	513	499	491	486	479	459	312	194	105	24	0	
Rituximab–chemotherapy group	517	496	487	481	470	453	298	193	115	32	2	0

Morschhauser F. *N Engl J Med*, 2018; 379: 934-947

Rituximab plus Lenalidomide in Advanced Untreated Follicular Lymphoma

Progression-free Survival

Subgroup	Rituximab–Lenalidomide Group	Rituximab–Chemotherapy Group	Hazard Ratio (95% CI)
	no. of events/total no.		
Overall	119/513	115/517	1.10 (0.85 to 1.43)
Age			
≤60 yr	58/281	55/282	1.15 (0.79 to 1.66)
>60 yr	61/232	56/235	1.06 (0.74 to 1.53)
FLIPI score			
0 or 1	14/77	9/76	2.06 (0.88 to 4.80)
2	37/183	35/191	1.12 (0.70 to 1.78)
3–5	68/253	67/250	1.00 (0.72 to 1.41)
Longest diameter of the longest node			
≤6 cm	62/253	58/271	1.19 (0.83 to 1.71)
>6 cm	57/260	53/246	1.04 (0.71 to 1.51)
Sex			
Male	61/251	59/251	1.02 (0.71 to 1.46)
Female	58/262	52/266	1.23 (0.85 to 1.79)
Country			
Other than North America	93/384	92/379	1.03 (0.77 to 1.38)
North America	26/129	19/138	1.53 (0.84 to 2.76)
Disease stage			
I or II	6/30	5/40	2.23 (0.66 to 7.55)
III or IV	113/483	106/477	1.06 (0.82 to 1.39)



Morschhauser F. *N Engl J Med*, 2018; 379: 934-947

CHEMO-FREE OPTIONS IN RELAPSED DISEASE

CHEMO-FREE OPTIONS IN RELAPSED DISEASE

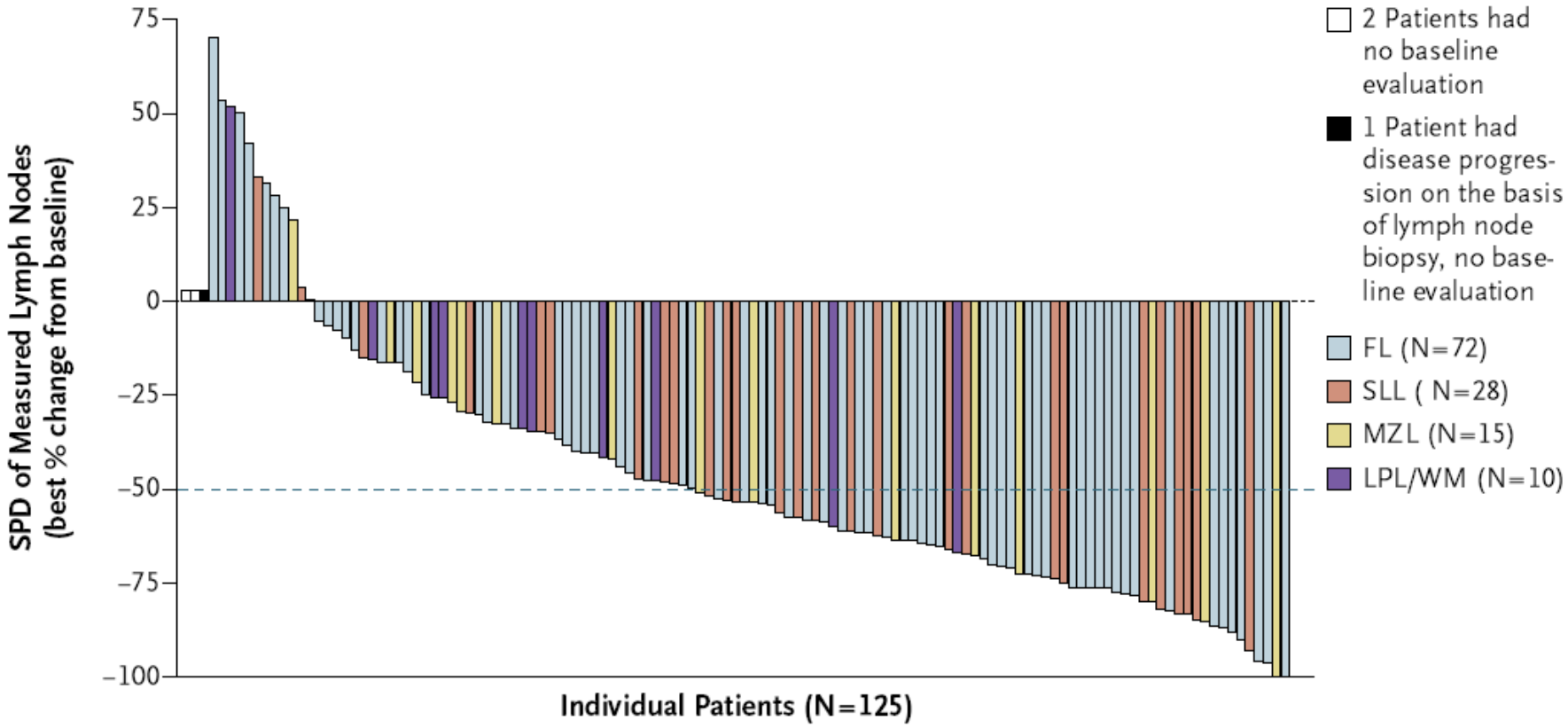
Conventional strategies

- Rituximab ± Maintenance
- Chemoimmunotherapy
  - ± Maintenance
- Obinutuzumab + bendamustine
- Radioimmunotherapy
- External beam radiation
- Autologous transplant
- Allogeneic transplant

Newer strategies

- PI3K inhibitors
  - Idelalisib
  - Duvelisib
  - Copanlisib
- Immunomodulatory drugs
  - Lenalidomide + Rituximab
- Clinical trials
  - new immunomodulatory drugs
  - anti-PD1 antibodies
  - anti-«eat me» antibodies
  - bispecific antibodies

1 - IDELALISIB



Gopal AK. *N Engl J Med*, 2014; 370: 1008-1018

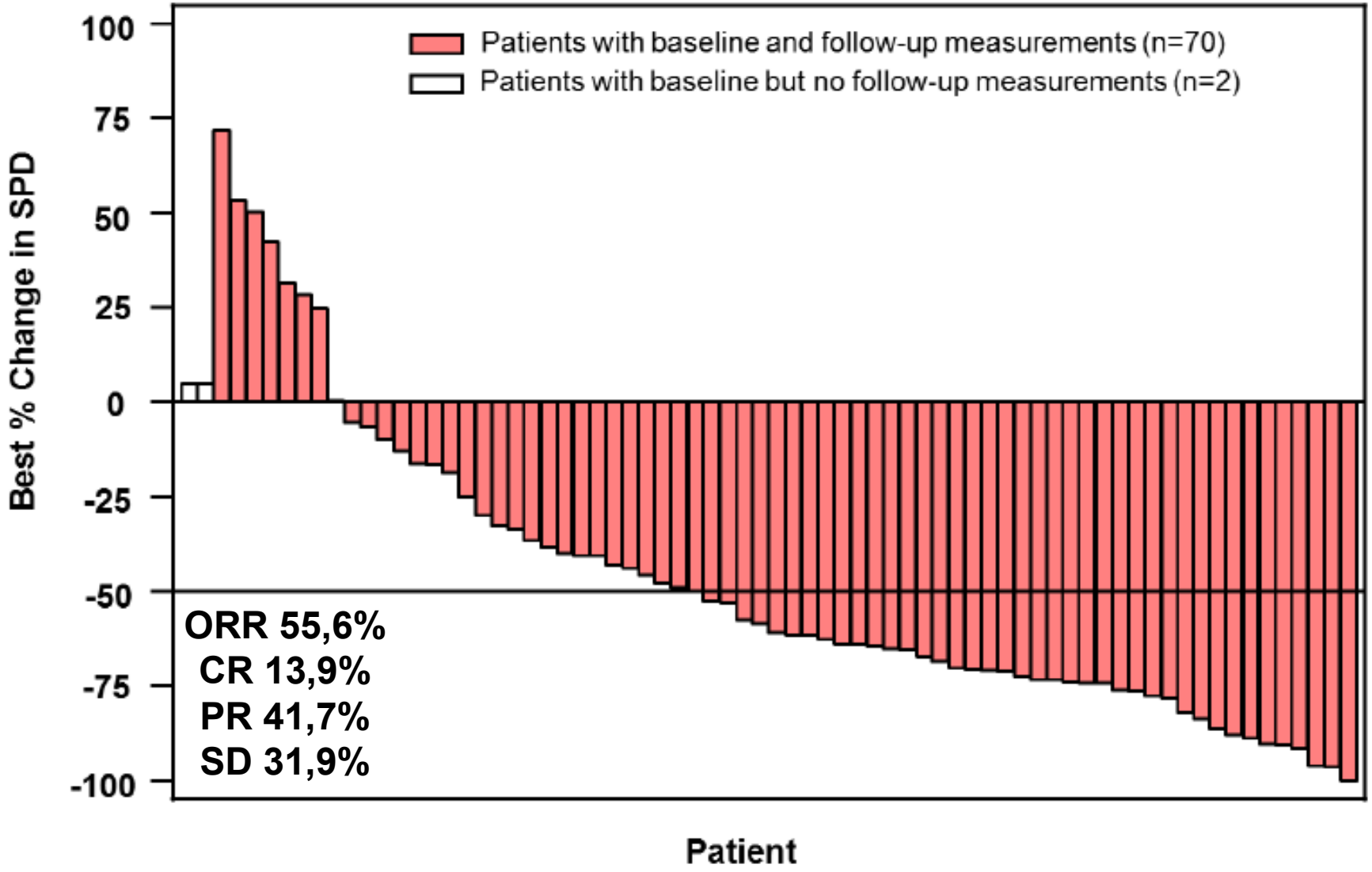
Efficacy and safety of idelalisib in patients with relapsed, rituximab- and alkylating agent-refractory follicular lymphoma: a subgroup analysis of a phase 2 study

Characteristic (N = 72)	Patients
Median (range) age, y	62 (33–84)
Men, n. (%)	39 (54.2)
White, n. (%)	64 (88.9)
FL grade, n. (%)	
1	21 (29.2)
2	39 (54.2)
3a	12 (16.7)
Disease burden, n. (%)	
Stage III or IV	60 (83.3)
Elevated LDH†	21 (29.2)
Bulky disease‡	16 (22.2)
FLIPI risk score at baseline, n. (%)	
Low	15 (20.8)
Intermediate	18 (25.0)
High	39 (54.2)
ECOG, n. (%)	
0	31 (43.1)
1	35 (48.6)
2	6 (8.3)
Baseline cytopenia, n. (%)§	
Neutropenia	8 (11.1)
Anemia	8 (11.1)
Thrombocytopenia	5 (6.9)

Characteristic (N = 72)	Patients
Median (range) lines of prior therapy, n.	4 (2–12)
Prior therapy, n. (%)	
Rituximab	72 (100)
Alkylating agents	72 (100)
Bendamustine	50 (69.4)
Anthracycline	51 (70.8)
Purine analog	17 (23.6)
Autologous stem-cell transplantation	12 (16.7)
Prior therapy to which disease was refractory, n. (%)‖	
Rituximab	72 (100)
Bendamustine and rituximab	33 (45.8)
Bendamustine	32 (44.4)
R-CHOP	27 (37.5)
R-CVP	16 (22.2)
Disease refractory to ≥2 regimens	57 (79.2)
Disease refractory to most recent regimen	62 (86.1)
Treatment disposition at time of data cutoff, n. (%)	
Ongoing	7 (9.7)
Discontinued	
PD	38 (52.8)
AE	15 (20.8)
Investigator request¶	4 (5.6)
Death	5 (6.9)
Withdrew consent	3 (4.2)
Received antibiotic prophylaxis	10 (13.9)

Salles G. *Haematologica*, 2017; 102: e156-e159

Efficacy and safety of idelalisib in patients with relapsed, rituximab- and alkylating agent-refractory follicular lymphoma: a subgroup analysis of a phase 2 study



Salles G. *Haematologica*, 2017; 102: e156-e159

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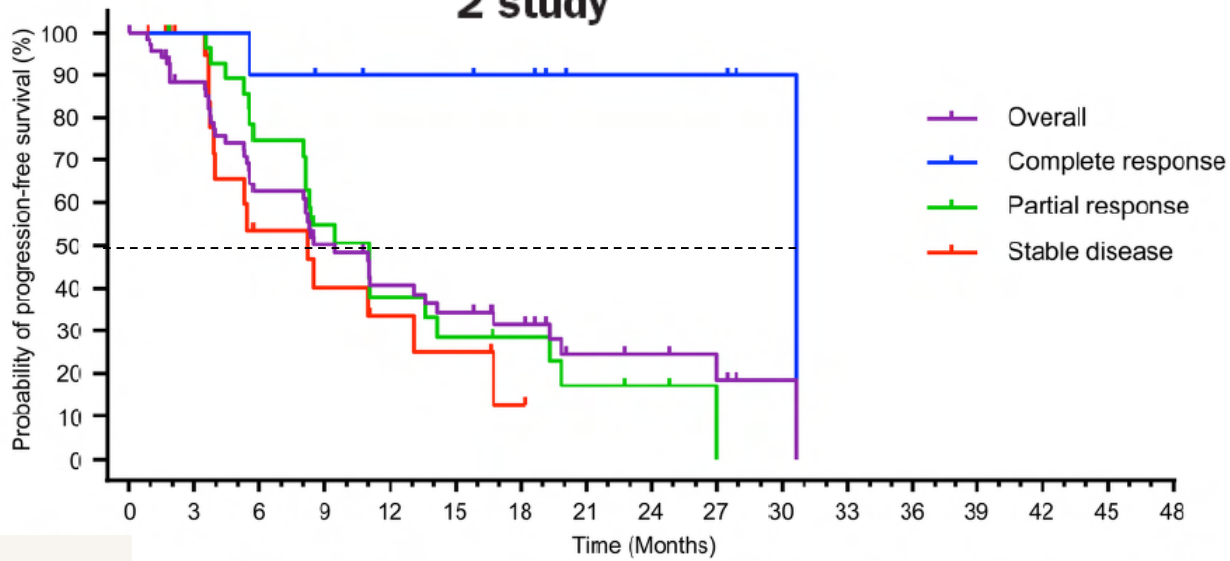
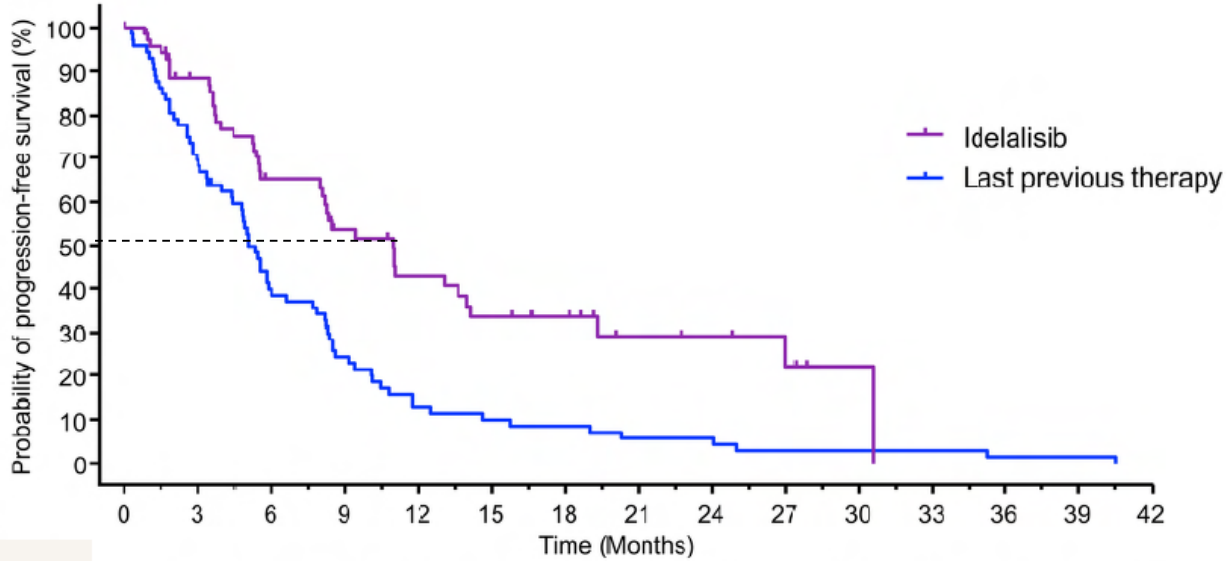




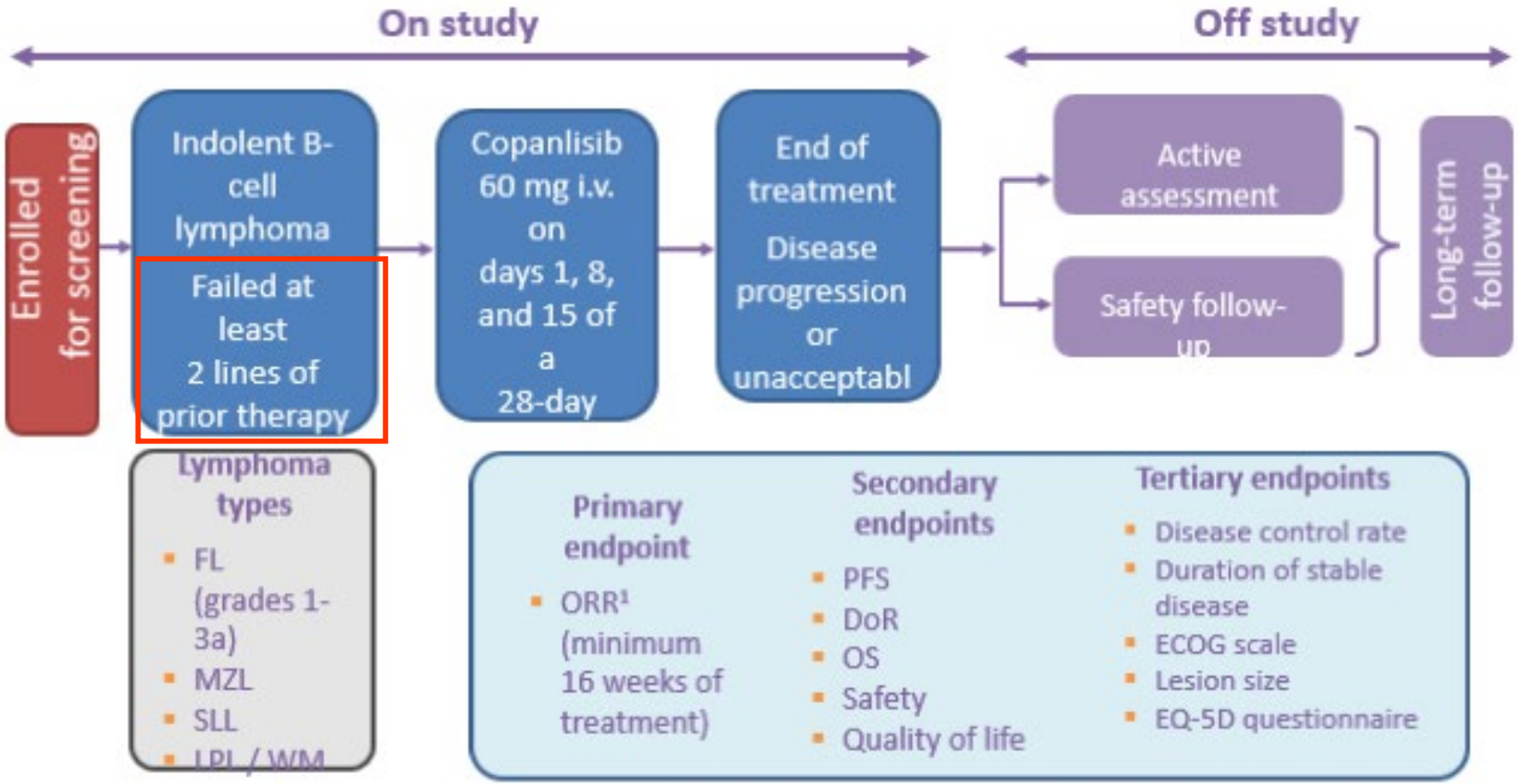
Salles G. *Haematologica*, 2017; 102: e156-e159

2 - PI3K-INHIBITORS IN R/R FOLLICULAR LYMPHOMA

Response rates

Isoform	Drug	DLBCL	FL	MCL	SLL/CLL	T-Cell	HL
PI3K-δ	Idelalisib	-	57%	40%	72%	-	12%
	TGR-1202	30%	38%	33%	59%	-	13%
PI3K-ϒδ	Duvelisib	-	41%	-	68%	42%	33%
PI3K-αδ	Copanlisib	25%	40%	63%	67%	21%	-
	Buparlisib	12%	25%	23%	-	-	-
PI3K-δ/ϒ	RP6530	-	-	-	-	62%	29%

Phosphatidylinositol 3-Kinase Inhibition by Copanlisib in Relapsed or Refractory Indolent Lymphoma



[1]Patients who discontinued treatment for any reason other than progressive disease entered active assessment follow-up
DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; LPL / WM, lymphoplasmacytoid lymphoma / Waldenström macroglobulinemia;
MZL, marginal zone lymphoma; ORR objective response rate; OS, overall survival; PFS, progression-free survival

Dreyling M. *J Clin Oncol*, 2017; 35: 3898-3905

Phosphatidylinositol 3-Kinase Inhibition by Copanlisib in Relapsed or Refractory Indolent Lymphoma

Best Response	Tumor, No. (%)				
	FL (n = 104)	MZL (n = 23)	SLL (n = 8)	LPL/WM (n = 6)	Total (N = 142)*
Complete response	15 (14)	2 (9)	0	0	17 (12)
Partial response	46 (44)	14 (61)	6 (75)	1 (17)	67 (47)
Stable disease	35 (34)†	4 (17)	1 (13)	3 (50)	43 (30)†
Progressive disease	2 (2)	0	1 (13)	0	3 (2)
Not evaluable	0	1 (4)	0	0	1 (< 1)
Not available‡	6 (6)	2 (9)	0	2 (33)	11 (8)
Objective response rate	61 (59)	16 (70)	6 (75)	1 (17)	84 (59)
95% CI§	49 to 68	47 to 87	35 to 97	0.4 to 64	51 to 67
Disease control rate‖	91 (88)	20 (87)	7 (88)	4 (67)	122 (86)‖
95% CI§	80 to 93	66 to 97	47 to 100	22 to 96	79 to 91

Abbreviations: FL, follicular lymphoma; LPL/WM, lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma.

*One patient with diffuse large B-cell lymphoma was included because the initial investigator assessment was indolent non-Hodgkin lymphoma, which was later confirmed by the investigator and central pathology review to be diffuse large B-cell lymphoma.

†Includes one patient with unconfirmed early stable disease (stable disease was assessed < 7 weeks after start of treatment).

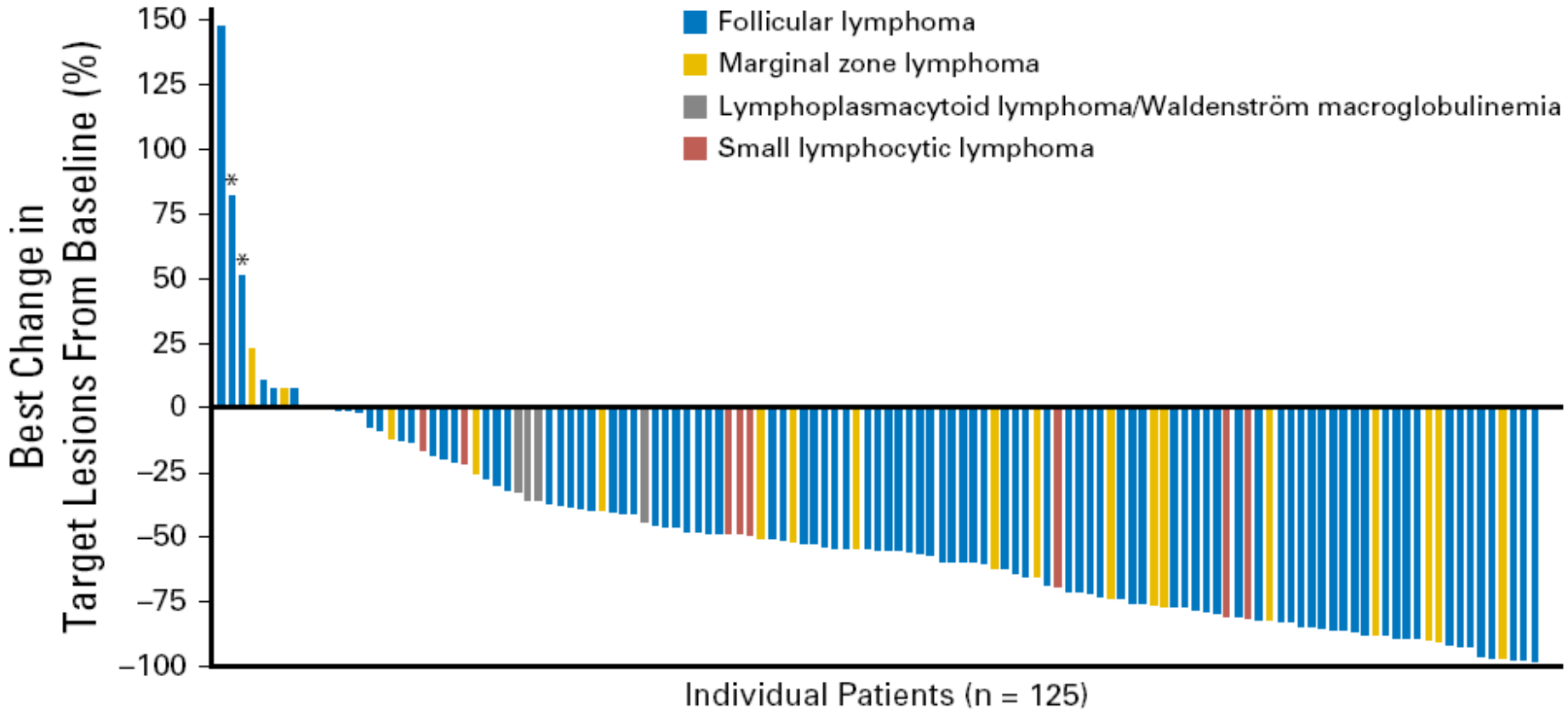
‡Of the full analysis set of 142 patients, data for 11 (8%) were not available for the analysis of the primary efficacy variable (objective response rate).

§95% CIs by exact binomial calculation.

‖One patient with unconfirmed stable disease and four with stable disease or partial response recorded > 35 days from the last treatment were excluded from the calculation.

Dreyling M. *J Clin Oncol*, 2017; 35: 3898-3905

Phosphatidylinositol 3-Kinase Inhibition by Copanlisib in Relapsed or Refractory Indolent Lymphoma



Dreyling M. *J Clin Oncol*, 2017; 35: 3898-3905

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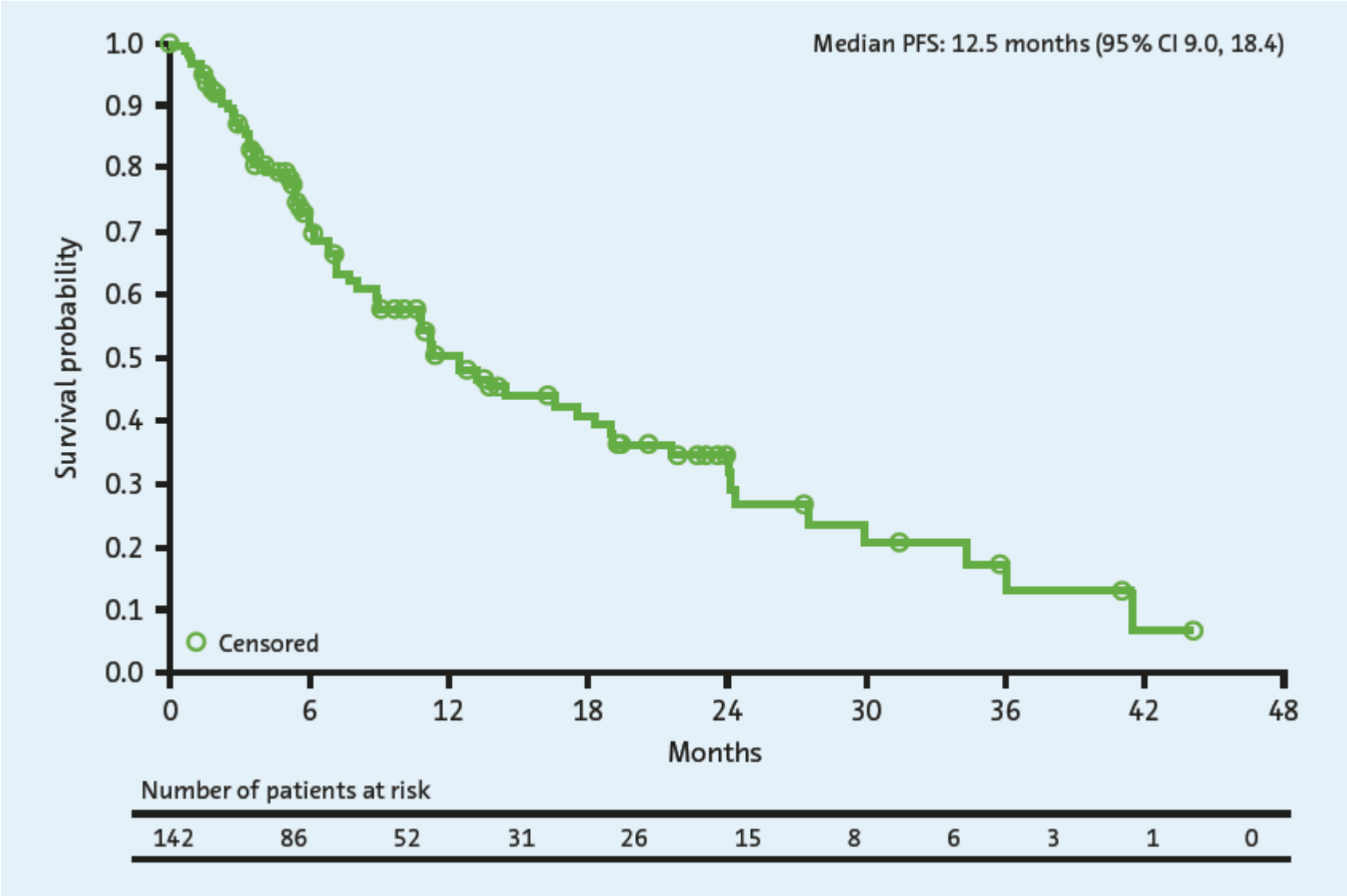


Dreyling M. *Blood (ASH annual meeting abstracts)*, 2018; 132: 1595a

Outcomes for patients with high-risk relapsed or refractory indolent B-cell lymphoma treated with copanlisib in the CHRONOS-1 study

	POD <24 (*n*=93)	POD ≥24 (*n*=47)	Total (*N*=140)[a]
Male, *n* (%)	47 (50.5)	24 (51.1)	71 (50.7)
Median age, years (range)	61 (25-82)	66 (33-81)	63 (25-82)
Ann Arbor Stage III or IV at study entry, *n* (%)	80 (86.0)	34 (72.3)	114 (81.4)
Median time from first-line treatment to first POD, months (range)	11.0 (0-24)	35.3 (24-127)	17.3 (0-127)
Median prior anti-cancer therapy lines (range)	3.0 (1-7)	3.0 (1-9)	3.0 (1-9)
Median time since last systemic anti-cancer therapy until progression, months (range)	7.0 (0-100)	15.7 (0-108)	10.0 (0-108)
Refractory to last regimen, *n* (%)	61 (65.6)	23 (48.9)	84 (60.0)
Refractory to any line of prior treatment, *n* (%)	81 (87.1)	31 (66.0)	112 (80.0)

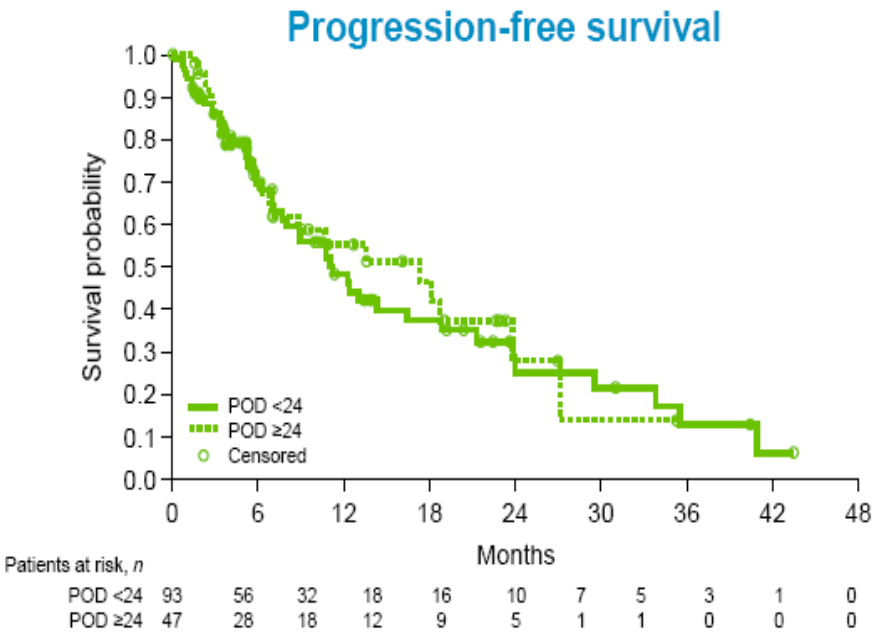
Santoro A. *Blood (ASH annual meeting abstracts)*, 2018; 132: 395a

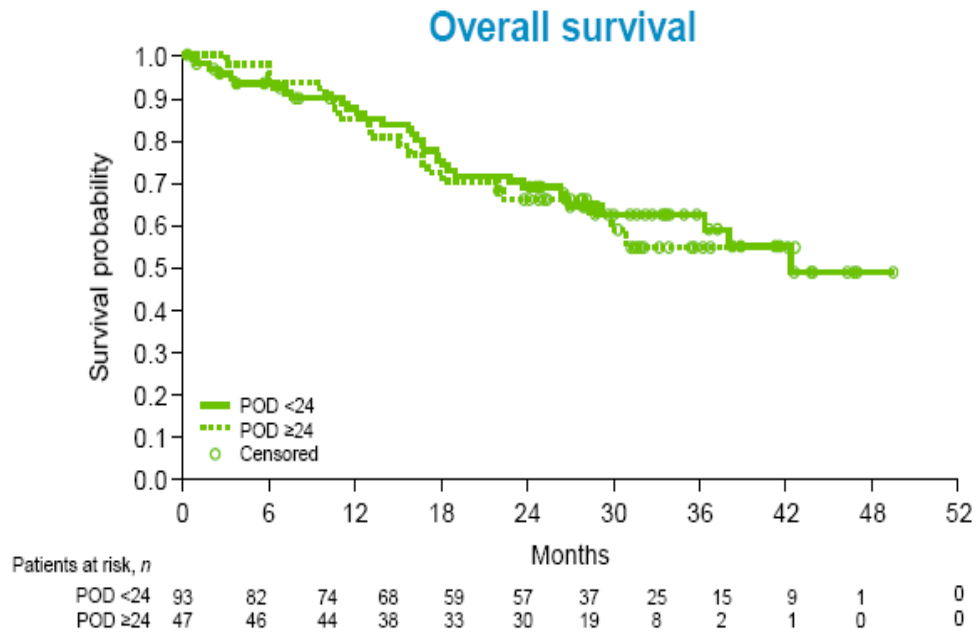
Outcomes for patients with high-risk relapsed or refractory indolent B-cell lymphoma treated with copanlisib in the CHRONOS-1 study

	All histologies (*N*=140)		Follicular lymphoma (*n*=102)		Total (*N*=140)
	POD <24 (*n*=93)	POD ≥24 (*n*=47)	POD <24 (*n*=68)	POD ≥24 (*n*=34)	
Best response, *n* (%)					
Complete response	16 (17.2)	8 (17.0)	15 (22.1)	6 (17.6)	24 (17.1)
Partial response	38 (40.9)	24 (51.1)	26 (38.2)	14 (41.2)	62 (44.3)
Stable disease	26 (28.0)	12 (25.5)	21 (30.9)	11 (32.4)	38 (27.1)
Unconfirmed early stable disease	1 (1.1)	0	1 (1.5)	0	1 (0.7)
Progressive disease	1 (1.1)	2 (4.3)	0	2 (5.9)	3 (2.1)
NE / NA	11 (11.8)	1 (2.1)	5 (7.4)	1 (2.9)	12 (8.6)
ORR, *n* (%)	54 (58.1)	32 (68.1)	41 (60.3)	20 (58.8)	86 (61.4)
95% CI	47.4, 68.2	52.9, 80.9	47.7, 72.0	40.7, 75.4	52.8, 69.5

Santoro A. *Blood (ASH annual meeting abstracts)*, 2018; 132: 395a

Outcomes for patients with high-risk relapsed or refractory indolent B-cell lymphoma treated with copanlisib in the CHRONOS-1 study





- Median PFS was 11.3 months (range 0-44.2 months) in the POD <24 group and 17.6 months (range 0-35.8 months) in the POD ≥24 group
- Median OS was 42.6 months (range 0.2-49.8 months) in the POD <24 group and had not yet been reached in the POD ≥24 group (range 3.0-43.0 months)

Santoro A. *Blood (ASH annual meeting abstracts)*, 2018; 132: 395a

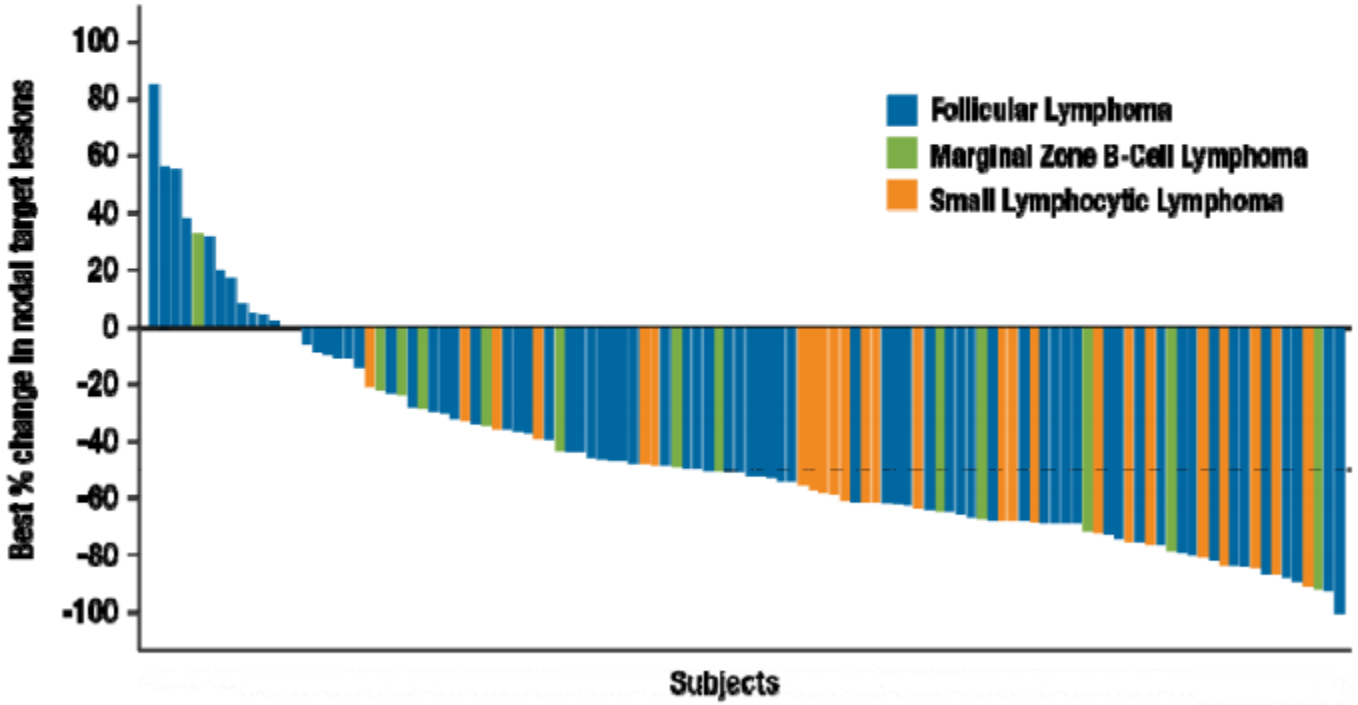
DYNAMO: A Phase 2 Study of Duvelisib in Patients With Refractory Indolent Non-Hodgkin Lymphoma

Phase 2, Single arm, n=129

Accrual Complete; Analysis as of April 2016 (last pt enrolled + 6 mo.)

Duvelisib 25 mg BID Continuously

Treatment until progression or unacceptable toxicity



- **83% of pts had reduction in target lymph nodes (per IRC)**

Flinn IW. *Blood (ASH annual meeting abstracts)*, 2016; 128: 1218a

DYNAMO: A Phase 2 Study of Duvelisib in Patients With Refractory Indolent Non-Hodgkin Lymphoma

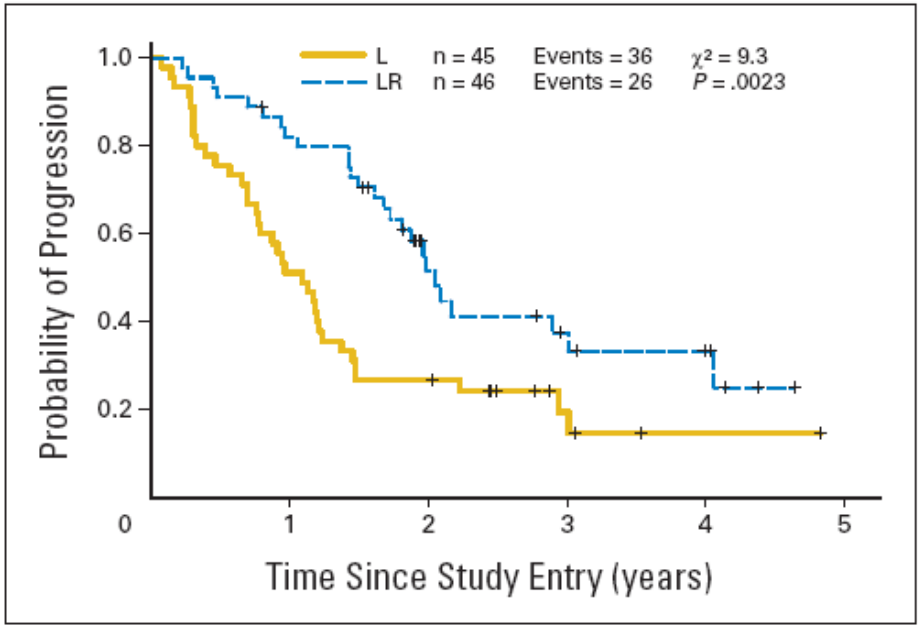
	OVERALL N = 129	FL N = 83	SLL N = 28	MZL N = 18
ORR per IRC, %	*46*	*41*	*68*	*33*
P-value	*p=0.0001**	--	--	--
95% CI	*(37-55)*	--	--	--
Complete Response	0	0	0	0
Partial Response	46	41	68	33
ORR per Investigator, %	*58*	*53*	*79*	*50*
Complete Response	2	1	4	0
Partial Response	57	52	75	50

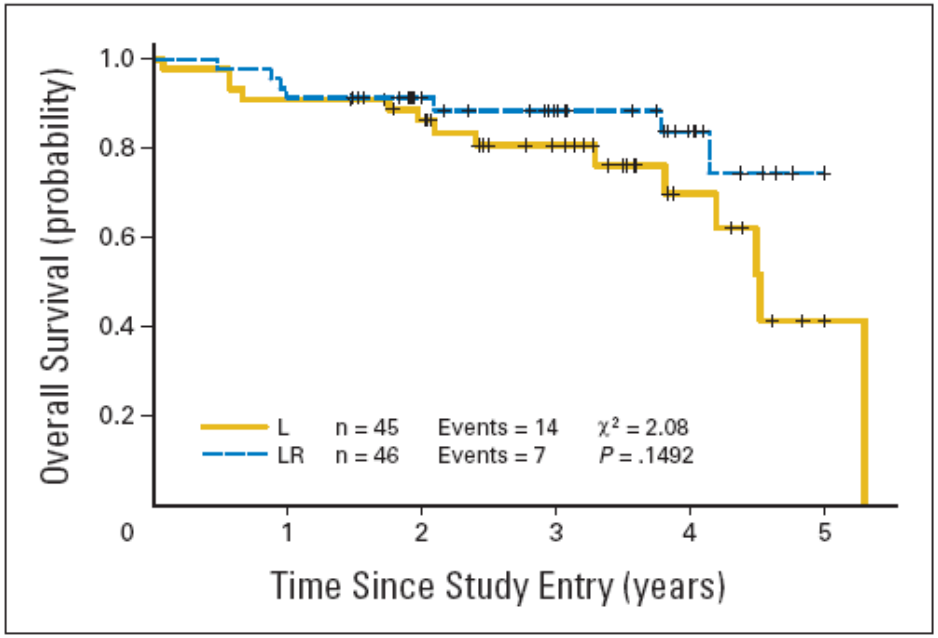
* The study met the primary endpoint (p=0.0001 against null hypothesis that ORR was ≤ 30% per IRC)

Flinn IW. *Blood (ASH annual meeting abstracts)*, 2016; 128: 1218a

3 - R² IN RELAPSED AND REFRACTORY FOLLICULAR LYMPHOMA

Randomized Trial of Lenalidomide Alone Versus Lenalidomide Plus Rituximab in Patients With Recurrent Follicular Lymphoma: CALGB 50401 (Alliance)





Leonard JP. *J Clin Oncol*, 2015; 33: 3635-3640

AUGMENT: A Phase III Randomized Study of Lenalidomide Plus Rituximab (R^2) vs Rituximab/Placebo in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

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)

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

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

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)

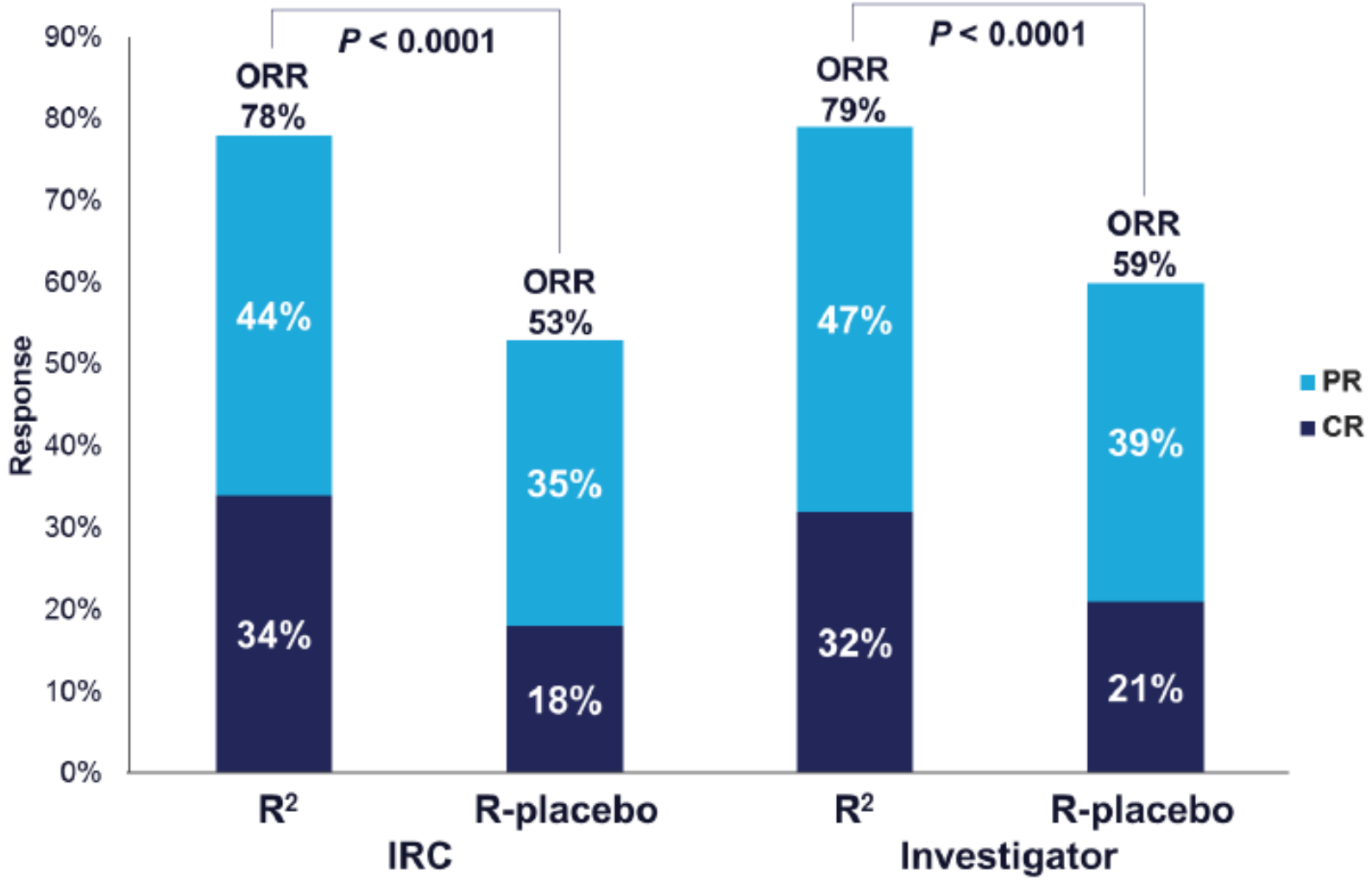
Leonard JP. *Blood (ASH annual meeting abstracts)*, 2018; 132: 445a

AUGMENT: A Phase III Randomized Study of Lenalidomide Plus Rituximab (R^2) vs Rituximab/Placebo in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

Characteristic, n (%)		R^2 (n = 178)	R-placebo (n = 180)
Median age, y (range)		64 (26-86)	62 (35-88)
Age ≥ 60 y		108 (61)	106 (59)
Age ≥ 65 y		82 (46)	73 (41)
ECOG PS 1-2*		62 (35)	52 (29)
Positive BM involvement, n involved/performed (%)		33/106 (31)	31/111 (28)
Ann Arbor stage III or IV at study entry		137 (77)	124 (69)
Bulky disease† (≥ 7 cm or ≥ 3 cm x 3)		45 (25)	49 (27)
High tumor burden per GELF criteria[1,2]		97 (54)	86 (48)
Histology	FL	147 (83)	148 (82)
	MZL	31 (17)	32 (18)
LDH > ULN		43 (24)	39 (22)
B-symptoms		16 (9)	12 (7)
FLIPI score‡	0 or 1	52 (29)	67 (37)
	2	55 (31)	58 (32)
	3 to 5	69 (39)	54 (30)

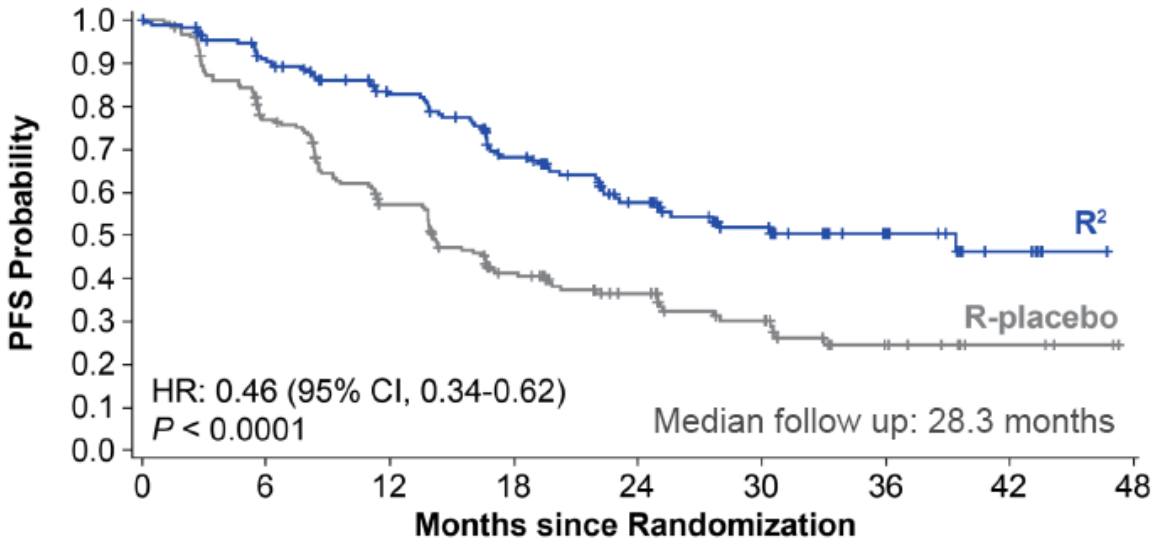
Leonard JP. *Blood (ASH annual meeting abstracts)*, 2018; 132: 445a

AUGMENT: A Phase III Randomized Study of Lenalidomide Plus Rituximab (R^2) vs Rituximab/Placebo in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma



Leonard JP. *Blood (ASH annual meeting abstracts)*, 2018; 132: 445a

AUGMENT: A Phase III Randomized Study of Lenalidomide Plus Rituximab (R^2) vs Rituximab/Placebo in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

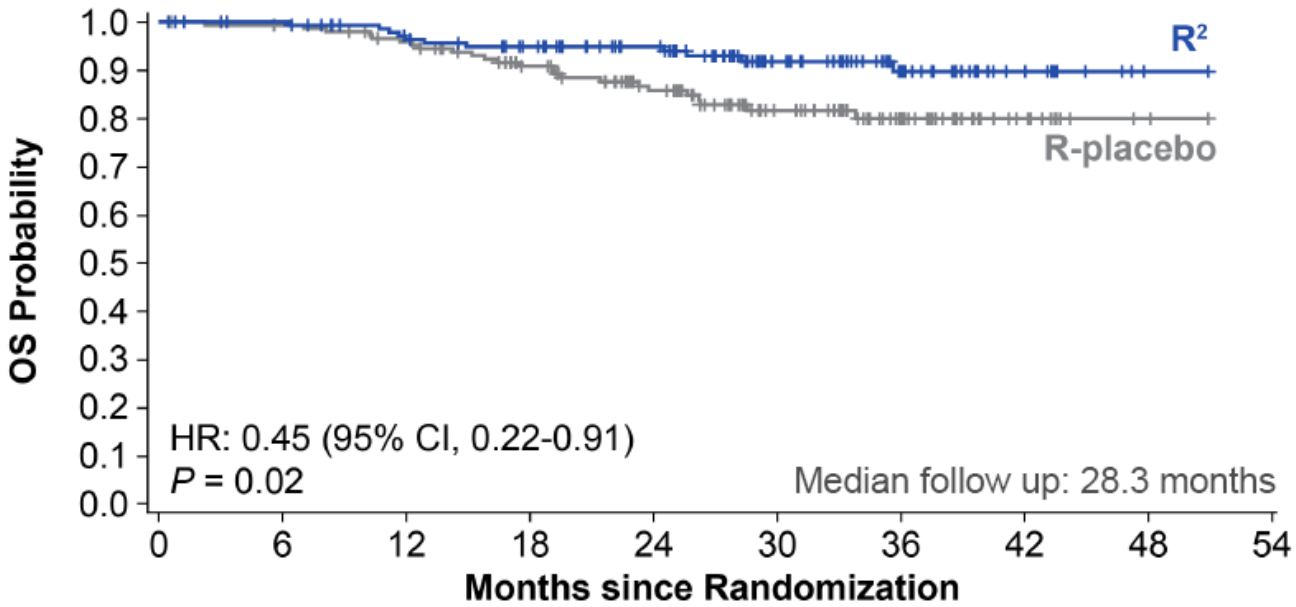


No. at Risk									
R^2	178	148	124	91	59	39	20	7	0
R-placebo	180	132	92	58	40	26	10	4	0

Median PFS	R^2 (n = 178)	R-placebo (n = 180)	HR (95% CI)	*P* Value
By IRC, mo (95% CI)	39.4 (22.9-NE)	14.1 (11.4-16.7)	0.46 (0.34-0.62)	< 0.0001
By investigator, mo (95% CI)	25.3 (21.2-NE)	14.3 (12.4-17.7)	0.51 (0.38-0.69)	< 0.0001

Leonard JP. *Blood (ASH annual meeting abstracts)*, 2018; 132: 445a

AUGMENT: A Phase III Randomized Study of Lenalidomide Plus Rituximab (R^2) vs Rituximab/Placebo in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

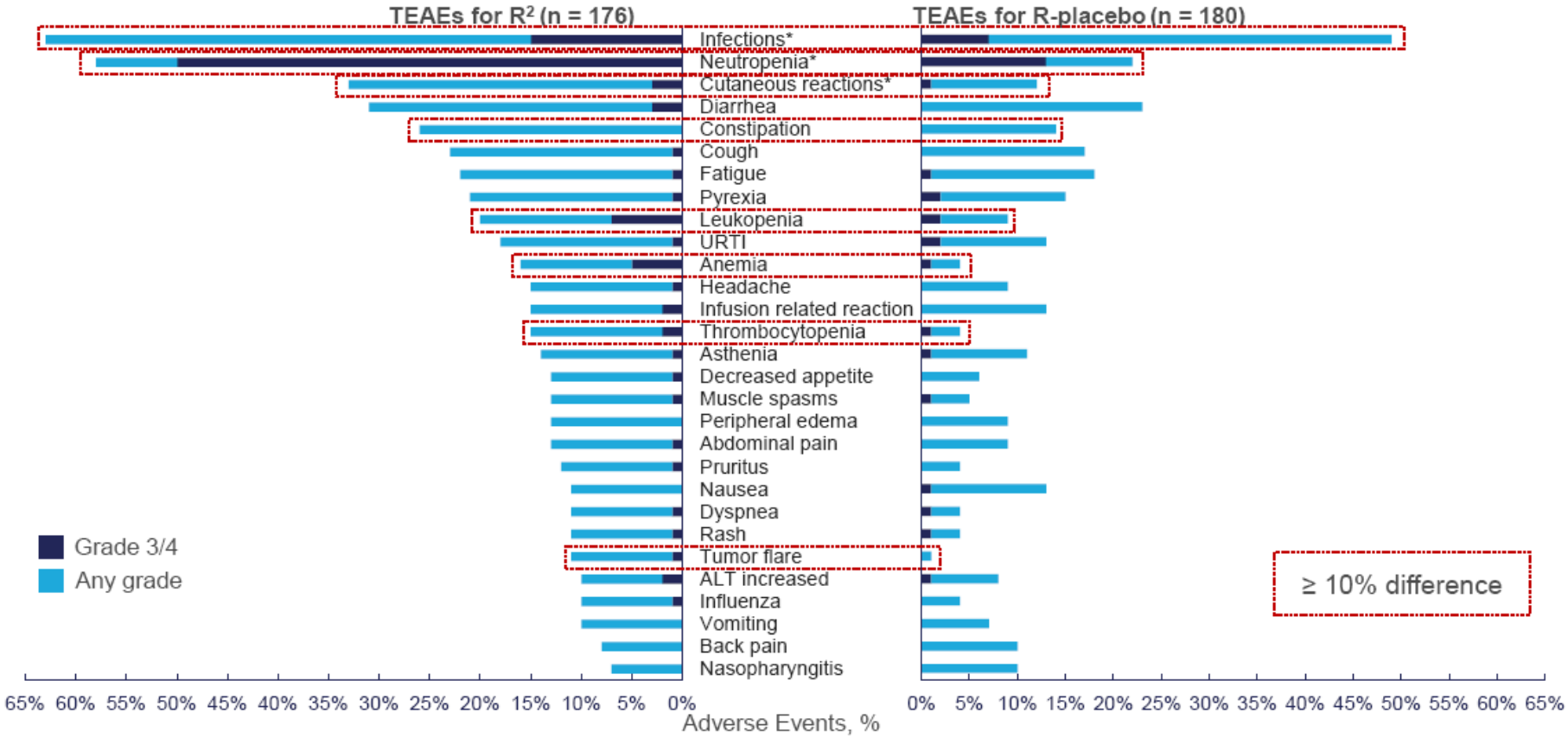


No. at Risk										
R^2	147	142	130	121	105	70	39	13	1	0
R-placebo	148	145	137	117	94	64	35	12	2	0

- 35 total deaths (11 R^2, 24 R-placebo)
- 2-year OS was 95% (95% CI, 90%-98%) for R^2 and 86% (95% CI, 79%-91%) for R-placebo

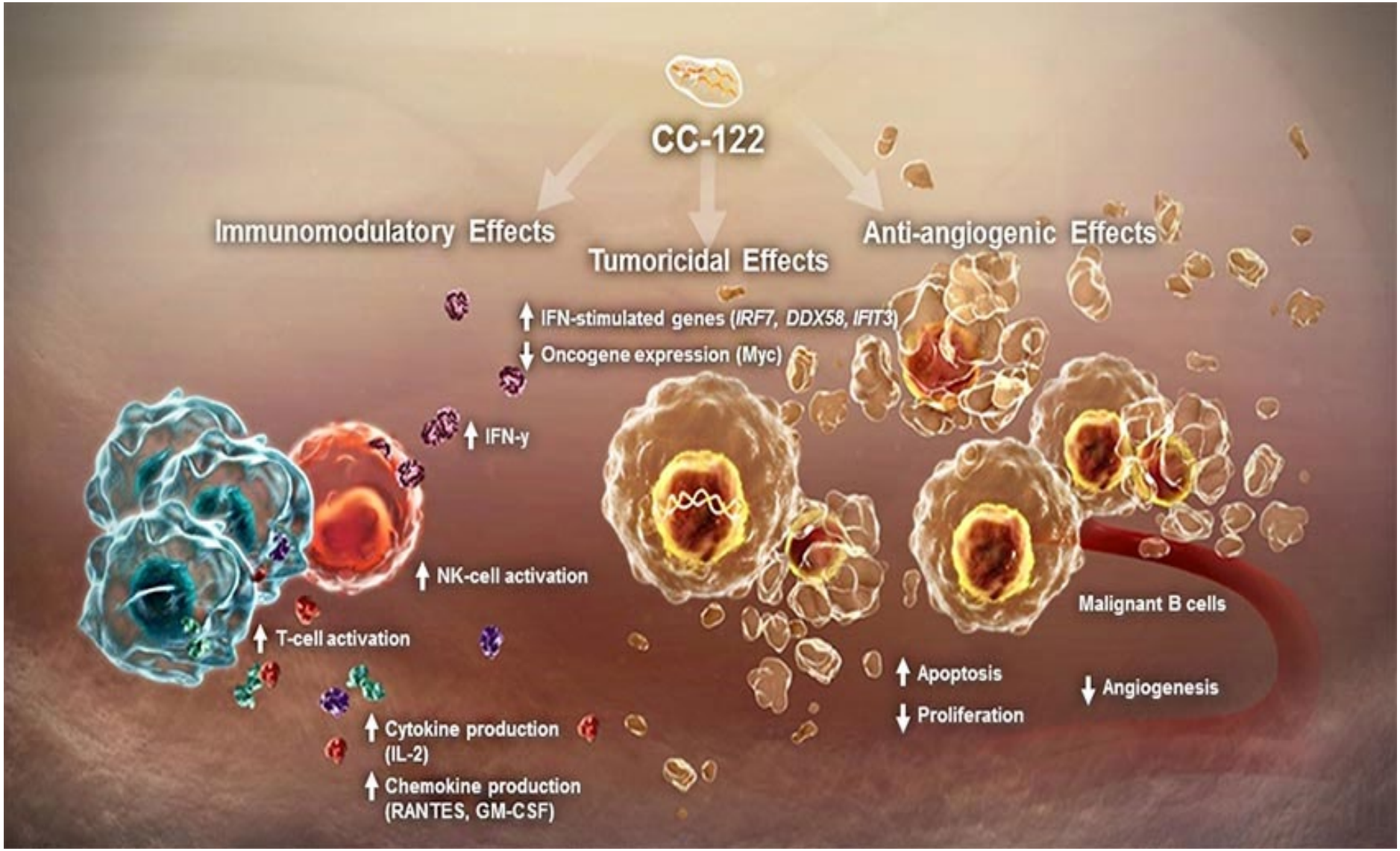
Leonard JP. *Blood (ASH annual meeting abstracts)*, 2018; 132: 445a

AUGMENT: A Phase III Randomized Study of Lenalidomide Plus Rituximab (R^2) vs Rituximab/Placebo in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma



Leonard JP. *Blood (ASH annual meeting abstracts)*, 2018; 132: 445a

4 - NEW IMMUNOMODULATORY DRUGS: AVADOMIDE (CC-122)



CC-122, a Novel Cereblon Modulating Agent, in Combination with Obinutuzumab (GA101) in Patients with Relapsed and Refractory (R/R) B-Cell Non-Hodgkin Lymphoma (NHL)

Characteristics, n (%)		All Patients
		(N = 44)
Median (range) age, y		60.0 (26-81)
Age > 65 years		14 (32)
Male		29 (66)
ECOG PS	0	26 (59)
	1	18 (41)
Ann Arbor stage III/IV		33 (75)
Median (range) no. of prior systemic cancer therapies		3 (1-11)
Prior SCT		18 (41)
Rituximab refractory		22[a] (50)
NHL type	DLBCL	19 (43)
	FL	24 (55)
	MZL	1 (2)
Positive bone marrow involvement		10 (23)
Bulky disease		5 (11)

FLIPI, Follicular Lymphoma International Prognostic Index; IPI, International Prognostic Index; SCT, stem cell transplantation.
[a] 12 DLBCL, 9 FL, and 1 MZL

Michot JM. *Blood (ASH annual meeting abstracts)*, 2017; 130: 411a

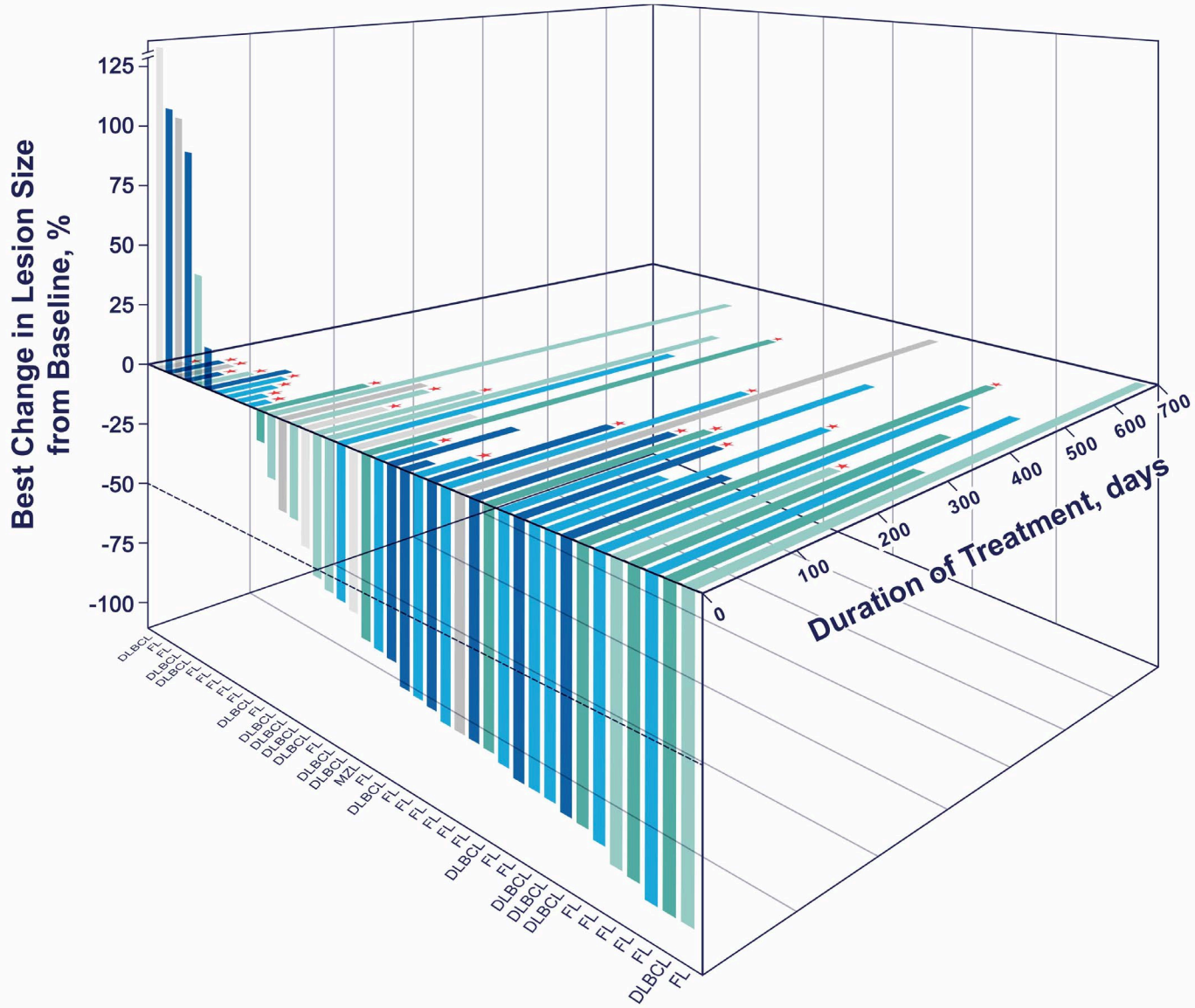
CC-122, a Novel Cereblon Modulating Agent, in Combination with Obinutuzumab (GA101) in Patients with Relapsed and Refractory (R/R) B-Cell Non-Hodgkin Lymphoma (NHL)

Response by Histology	FL All (n = 24)	High-Risk (ER+DR)[a] (n = 13)	Not High-Risk (n = 11)
ORR, n (%)	20 (84)	10 (77)	10 (91)
CR	10 (42)	5 (39)	5 (46)
PR	10 (42)	5 (39)	5 (46)
SD	2 (8)	2 (15)	0
PD	2 (8)	1 (8)	1 (9)
Not evaluable/missing	0	0	0
mPFS (mo, 95% CI)[b]	16.2 (3.7-NR)	21.1 (2.9, NR)	16.2 (1.7-16.2)
6-mo PFS rate (%) (95% CI)[b]	67 (40-84)	71 (34-90)	61 (21-86)
mDOR (mo, 95% CI)[b]	19.4 (7.9-NR)	19.3 (1.9, NR)	NR

DR, double refractory; ER, early relapse.
[a]7 patients were both ER and DR; 6 patients were ER only.
ER and DR definitions:
•ER: Relapse within 2 years of initial diagnosis[1]
•DR: Refractory to rituximab (as monotherapy or in combination) and an alkylating agent[2]
[b]3 FL patients with PR were not evaluable for PFS or DOR at the data cutoff
Data cutoff was September 1, 2017.

Michot JM. *Blood (ASH annual meeting abstracts)*, 2017; 130: 411a

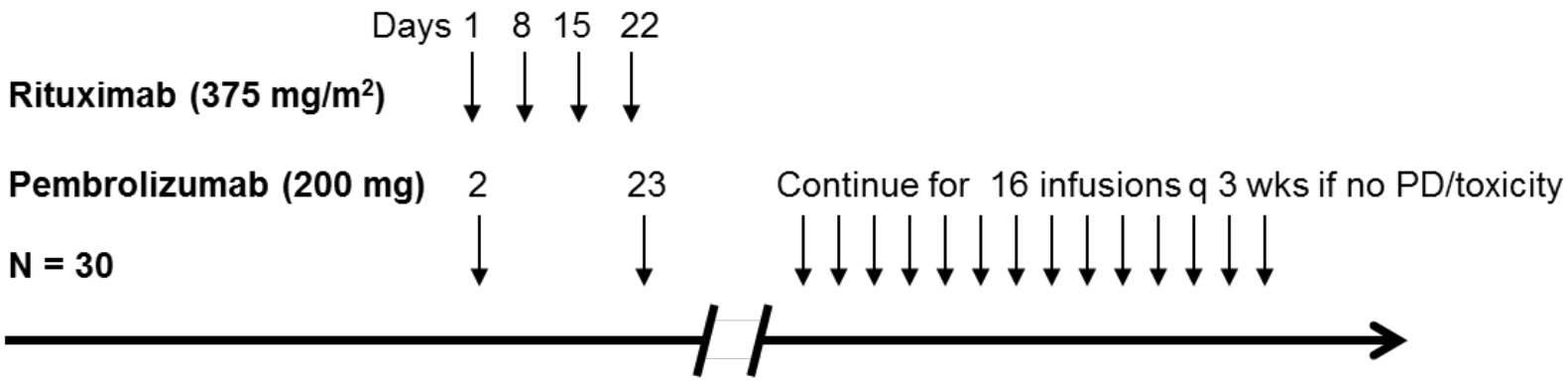
CC-122, a Novel Cereblon Modulating Agent, in Combination with Obinutuzumab (GA101) in Patients with Relapsed and Refractory (R/R) B-Cell Non-Hodgkin Lymphoma (NHL)



Michot JM. *Blood (ASH annual meeting abstracts)*, 2017; 130: 411a

5 - PEMBROLIZUMAB + RITUXIMAB

High Complete Response Rates with Pembrolizumab in Combination with Rituximab in Patients with Relapsed Follicular Lymphoma: Results of an Open-Label, Phase II Study



Response	Prior to day 1			day 64, q 12 wks x 1 yr, q 6 mos x 1 yr, and then annually until PD
Tumor Bx	Prior to day 1			
Blood (days)	Prior to day 1	8	23	43

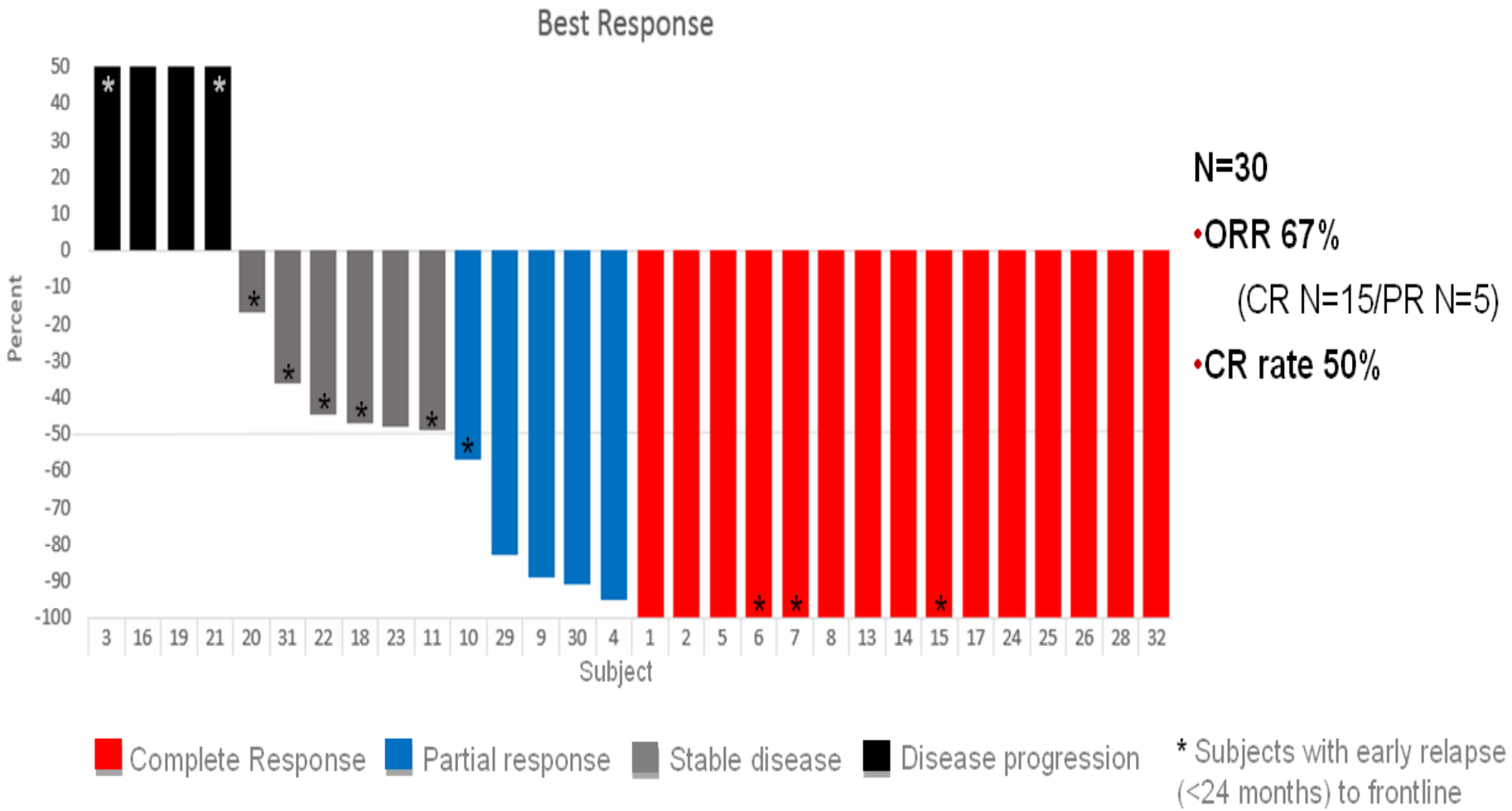
Nastoupil LJ. *Blood (ASH annual meeting abstracts)*, 2017; 130: 414a

High Complete Response Rates with Pembrolizumab in Combination with Rituximab in Patients with Relapsed Follicular Lymphoma: Results of an Open-Label, Phase II Study

Characteristic		N= 30 (% or Range)
Age	Median	64 (43-84) yrs
Sex	Male	17 (57%)
	Female	13 (43%)
ECOG PS	0	22 (73%)
	1	8 (27%)
FLIPI	Low	8 (27%)
	Intermediate	16 (53%)
	High	6 (20%)
Stage	II	4 (13%)
	III/IV	8/18 (27%/60%)
GELF	High	15 (50%)
Prior Therapy	Median	1 (1-4)
	Prior chemo	22 (73%)
PFS last therapy	Median	28 (3-162) months
	PFS < 2 yrs, last line	13 (43%)
	PFS < 1 yr, last line	5 (17%)
1st line	Early Relapse (< 2 yrs)	11 (37%)

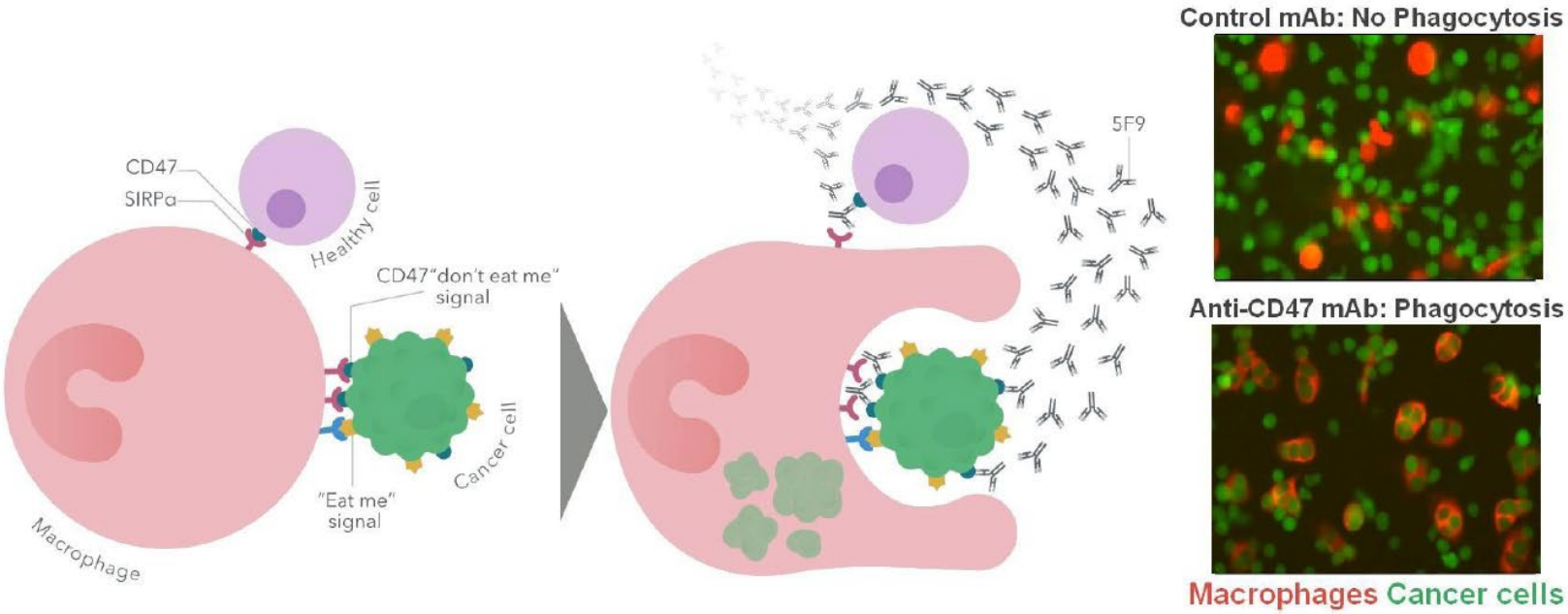
Nastoupil LJ. *Blood (ASH annual meeting abstracts)*, 2017; 130: 414a

High Complete Response Rates with Pembrolizumab in Combination with Rituximab in Patients with Relapsed Follicular Lymphoma: Results of an Open-Label, Phase II Study



Nastoupil LJ. *Blood (ASH annual meeting abstracts)*, 2017; 130: 414a

6 - MACROPHAGE IMMUNE CHECKPOINT INHIBITOR (ANTI-"EAT-ME")



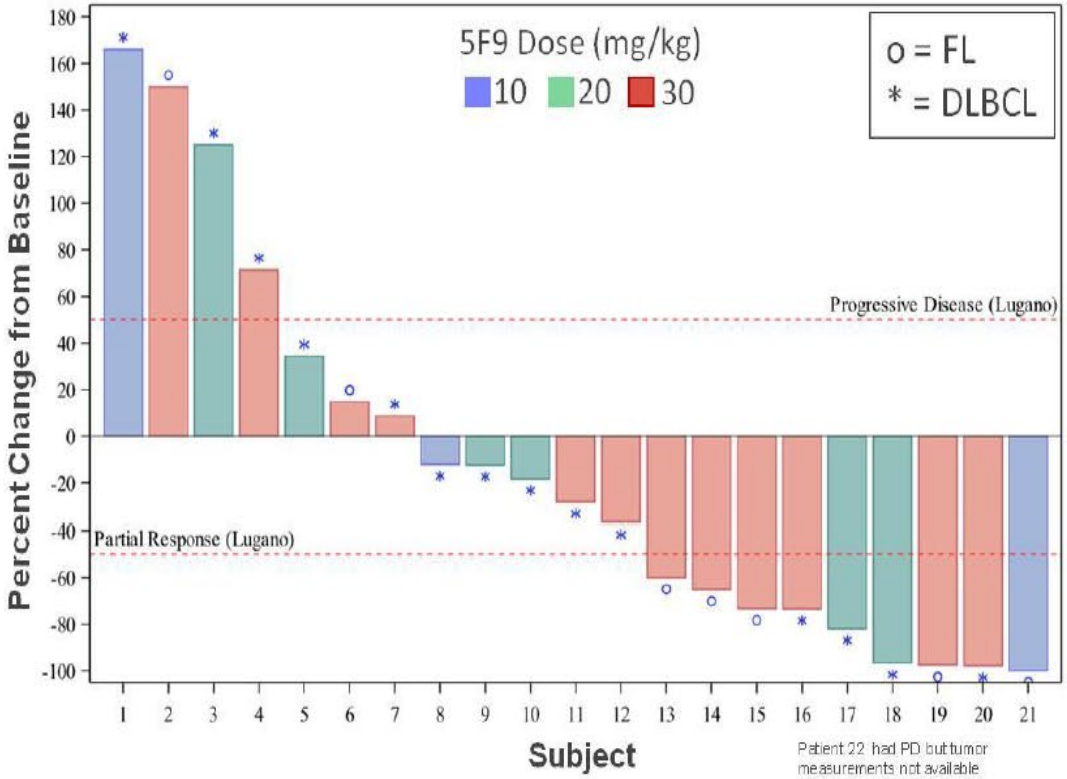
- 5F9 is a humanized IgG4 antibody against CD47, a don't eat me signal, that induces tumor cell phagocytosis
- 5F9 eliminates cancer cells through blockade of CD47 to its binding partner SIRP-alpha on macrophages
- Cancer cells express pro-phagocytic (eat me) signals while most normal cells do not; this allows 5F9 to selectively eliminate cancer cells
- 5F9/CD47 blockade induces anti-tumor activity in over 25 tumor models

Advani R. *N Engl J Med*, 2018; 379: 1711-1721

CD47 Blockade by Hu5F9-G4 and Rituximab in Non-Hodgkin's Lymphoma

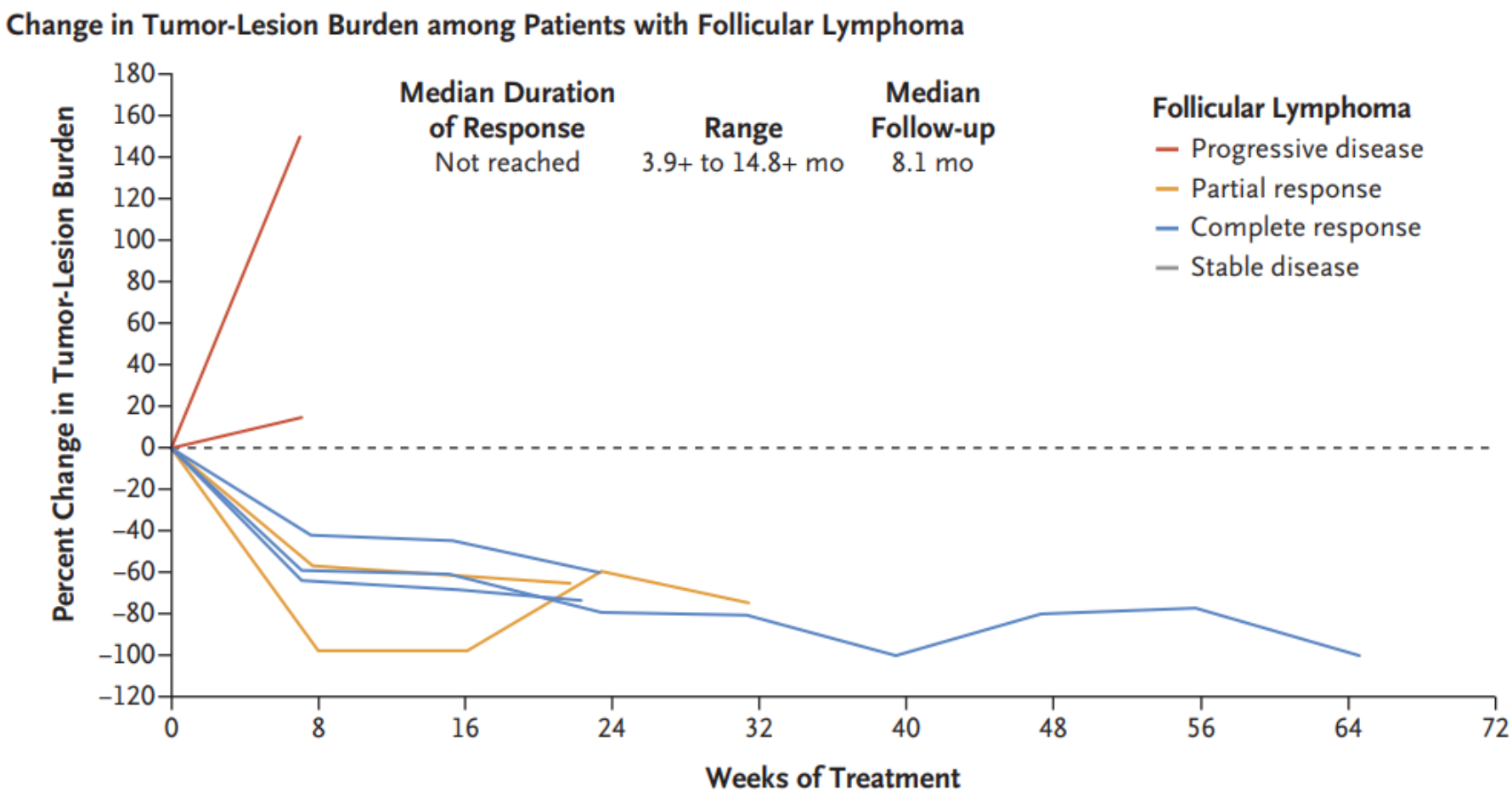
	Phase 1b		
Response	All patients n=22	DLBCL n=15	Follicular Lymphoma n=7
Objective Response Rate (ORR)	11 (50%)	6 (40%)	5 (71%)
Partial Response (PR)	3 (14%)	1 (7%)	2 (29%)
Complete Response (CR)	8 (36%)	5 (33%)	3 (43%)
Disease control rate (CR+PR+SD)	14 (64%)	9 (60%)	5 (71%)

Data cutoff April 2018



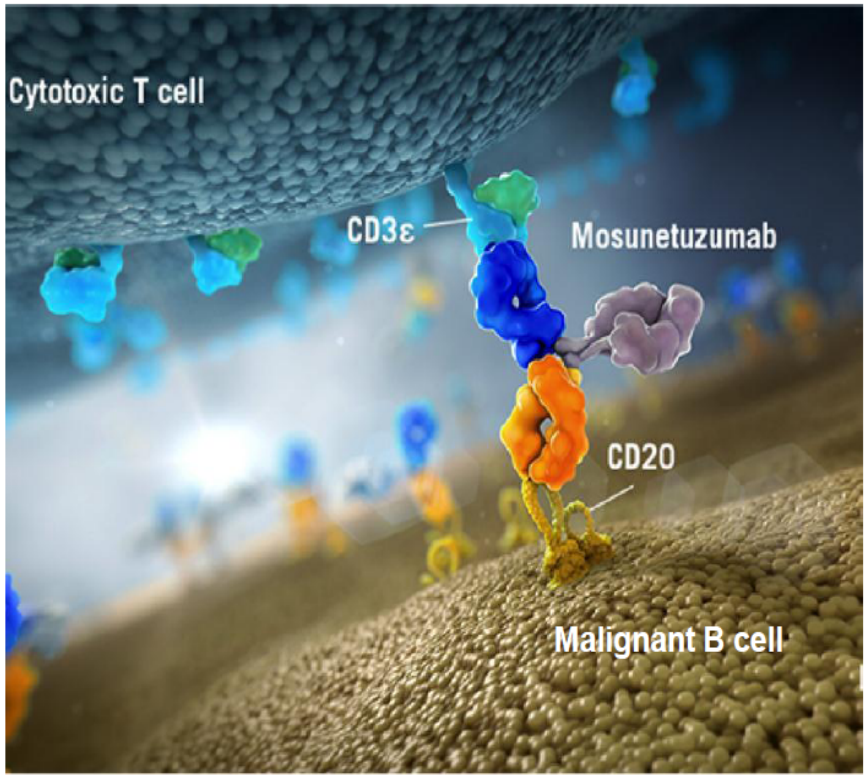
Advani R. *N Engl J Med*, 2018; 379: 1711-1721

CD47 Blockade by Hu5F9-G4 and Rituximab in Non-Hodgkin's Lymphoma



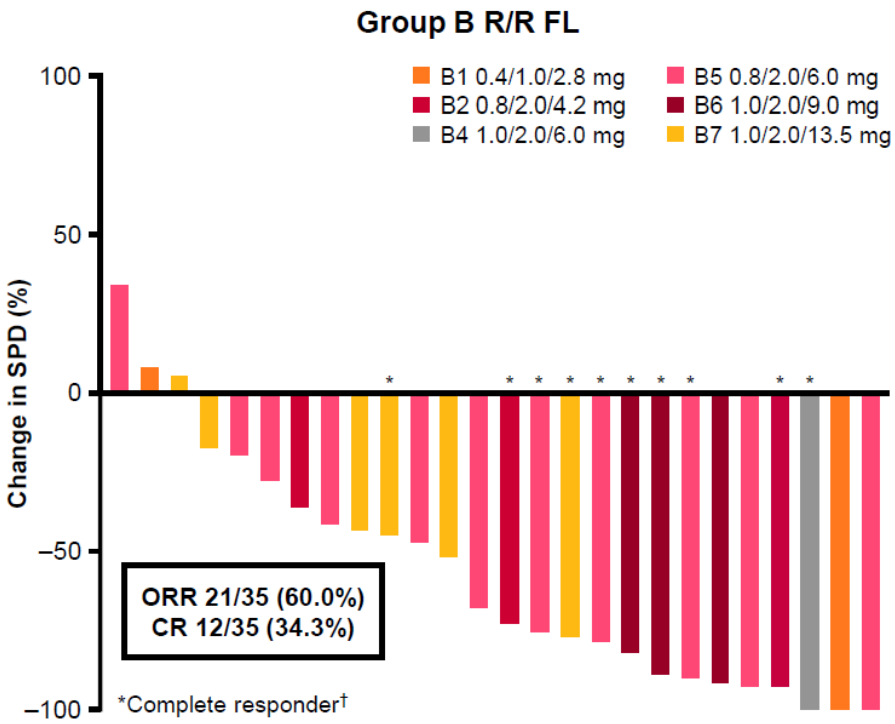
Advani R. *N Engl J Med*, 2018; 379: 1711-1721

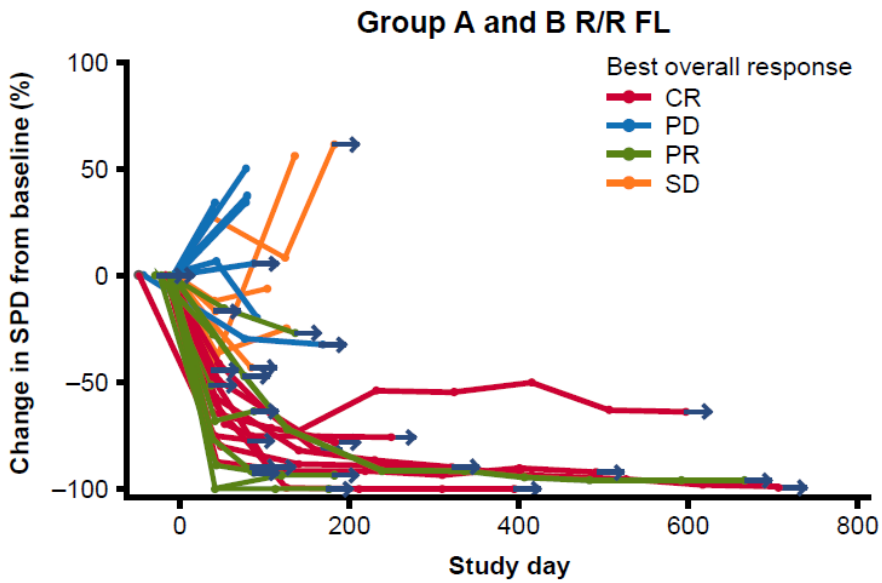
Mosunetuzumab: a bispecific anti-CD3/CD20 antibody



- **Mechanism of action**
  - Redirects T-cells to engage and eliminate malignant B-cells
  - Conditional agonist: T-cell activation dependent on B-cell engagement
  - Amino-acid substitution (N297G) to inactivate ADCC and avoid destruction of engaged T cells
- **Full-length humanized IgG1 antibody**
  - Longer half-life than fragment-based drug formats
  - PK properties enable QW to Q3W dosing
  - Does not require *ex-vivo* T-cell manipulation
  - Off the shelf, readily available treatment

Mosunetuzumab, a Full-Length Bispecific CD20/CD3 Antibody, Displays Clinical Activity in Relapsed/Refractory B-Cell Non-Hodgkin Lymphoma (NHL): Interim Safety and Efficacy Results from a Phase 1 Study





- Median duration of CR: not reached
- Median duration of follow-up for CR: 330 days (range 54–788 days)

Data cut-off date: 17 August 2018

†Complete response, assessed by the investigator with or without positron emission tomography, marked for efficacy-evaluable patients (when SPD data available).

Budde LE. *Blood (ASH annual meeting abstracts)*, 2018; 132: 399a