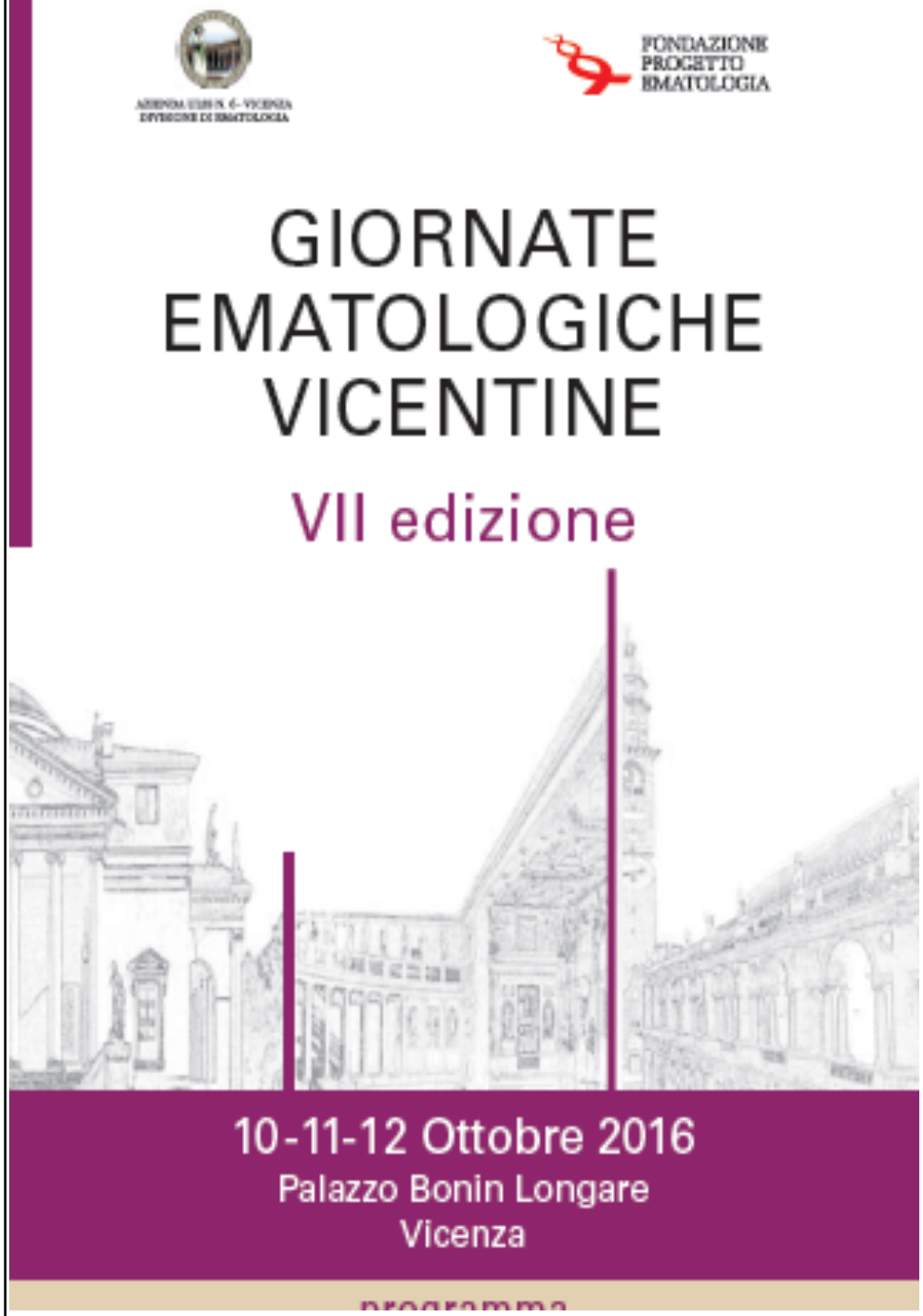


Vicenza
12 ottobre 2016

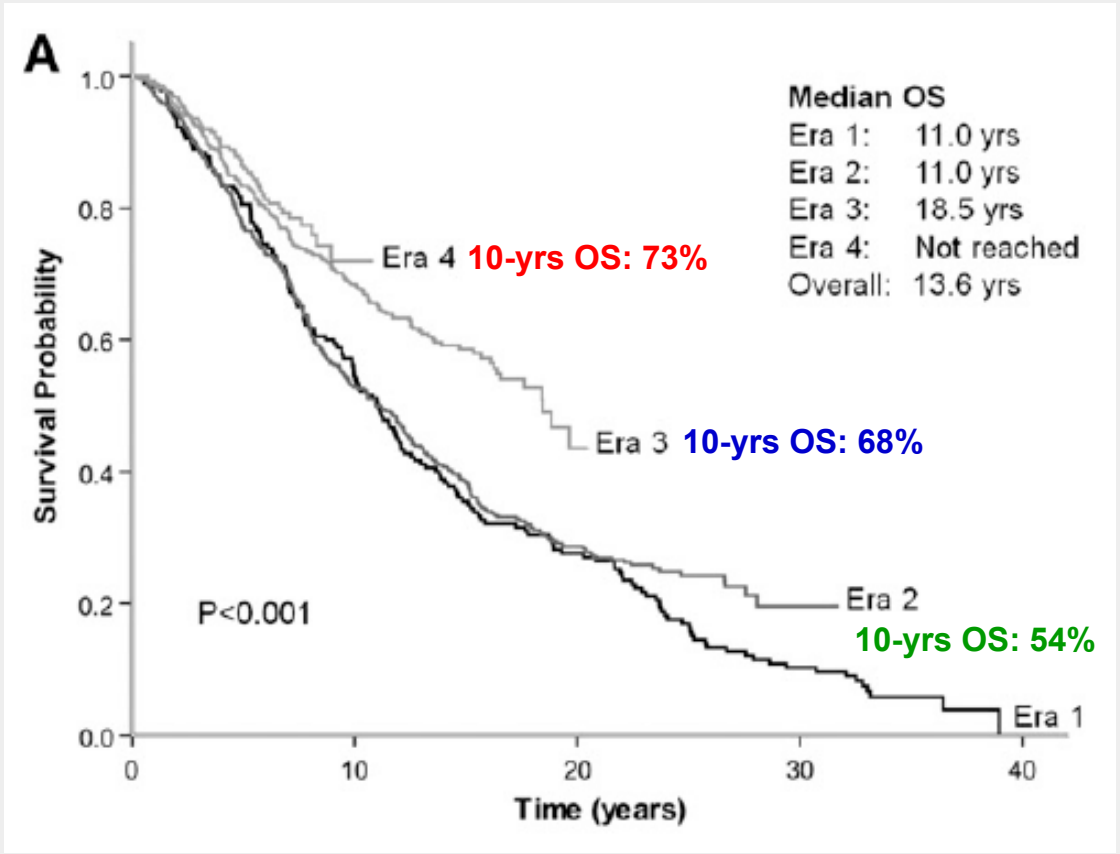
Nuovi farmaci e ruolo dell'autotrapianto nel linfoma follicolare

Barbara Botto

SC Ematologia
Città della Salute e della Scienza
Torino

Improvements in survival in FL during 4 decades: the Stanford University experience on 1334 pts

Era 1 (1960-1975): pre-anthracycline (median FU 11.1 yrs)
Era 2 (1976-1986): anthracycline (median FU 8.6 yrs)
Era 3 (1987-1996): aggressive chemotherapy/purine analogs (median FU 11.3 yrs)
Era 4 (1997-2003): Rituximab (median FU 6.1 yrs)



No plateau in any era

Tan D, et al: Blood 2013

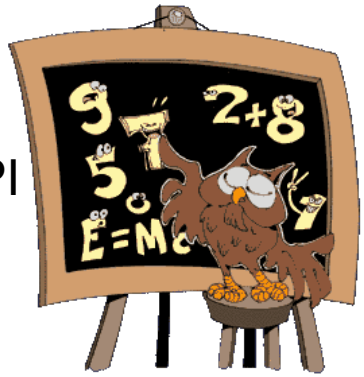
Relapsed Follicular lymphoma

Age and comorbidities: CGA

Previous tre

- HDT +ASCT
- RIT
- New MoAb
- New Biologic agents

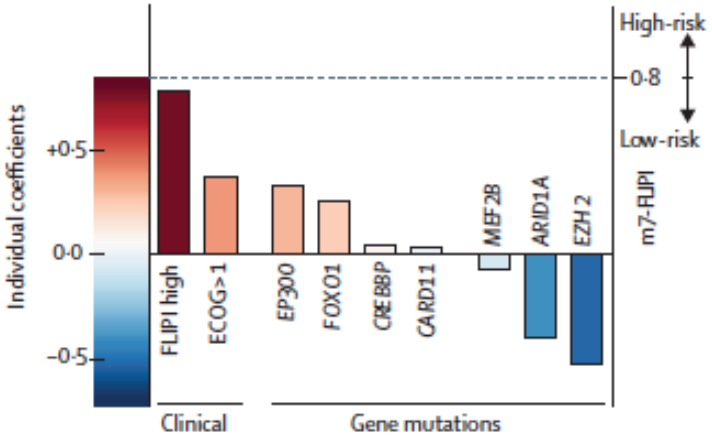
IPI



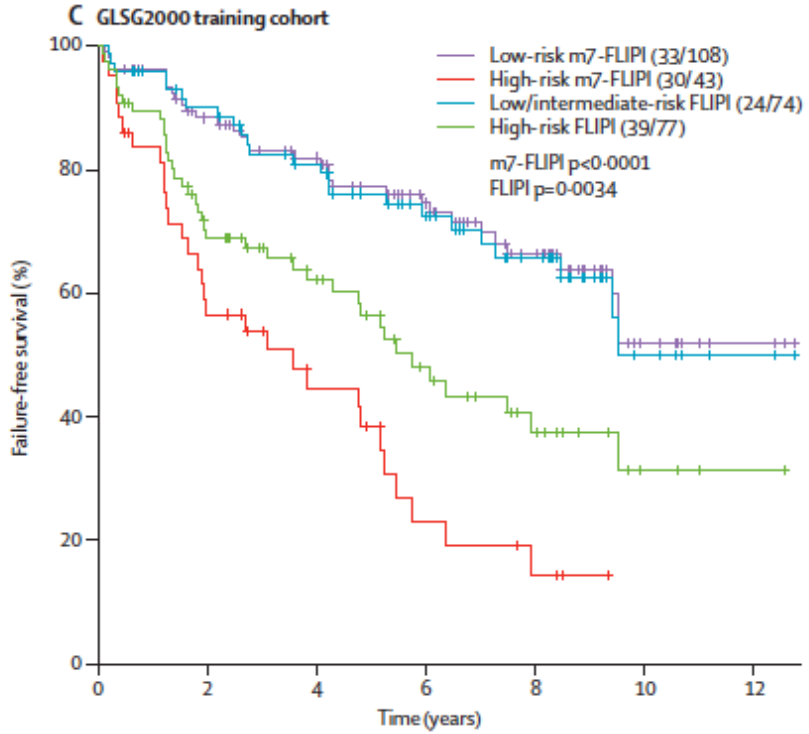
Quality of respons

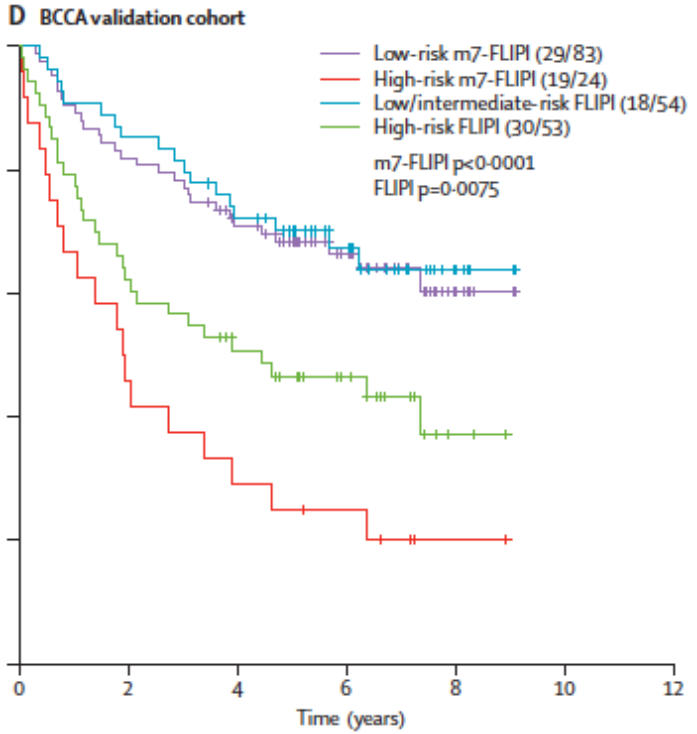
Time of relapse

Integration of gene mutations in risk prognostication for patients receiving first-line immunochemotherapy for follicular lymphoma: a retrospective analysis of a prospective clinical trial and validation in a population-based registry



151 follicular lymphoma biopsy specimens within 1 year before beginning (R-CHOP)

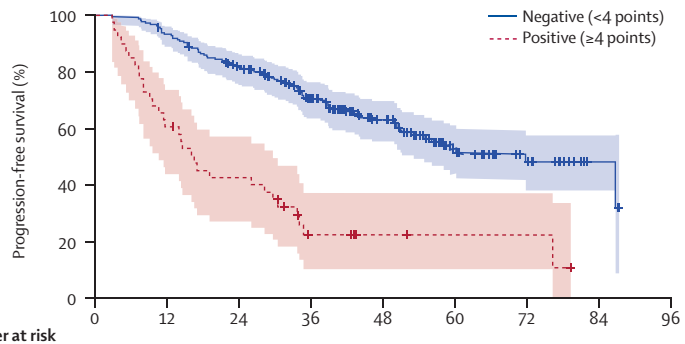




Pastore et al, Lancet Oncol 2015; 16: 1111–22

Prognostic value of PET-CT after first-line therapy in patients with follicular lymphoma: a pooled analysis of central scan review in three multicentre studies 246 patients centrally reviewed

A Progression-free survival according to PET scan score (cutoff ≥4)

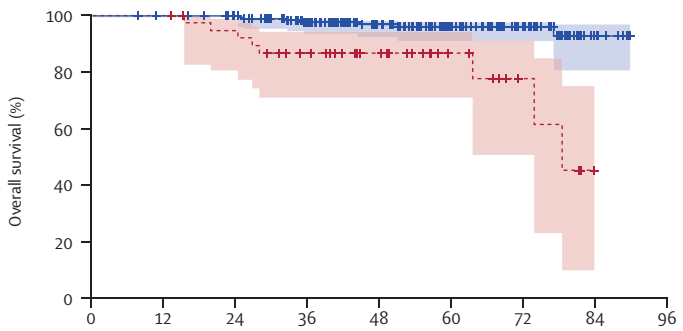


Number at risk

Negative	205	191	164	124	79	41	22	6	0
Positive	41	25	17	7	3	2	2	0	

	Events	Censored	Median survival (95% CI), months	Log-rank p value
Negative (n=205)	81 (40%)	124 (60%)	74 (54·7–NA)	<0·0001
Positive (n=41)	31 (76%)	10 (24%)	16·9 (10·8–31·4)	

B Overall survival according to PET scan score (cutoff ≥4)

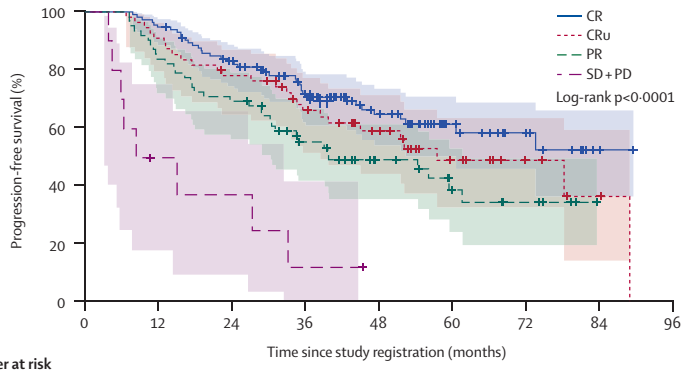


Number at risk

	205	203	197	168	124	77	45	10	0
	41	41	37	30	22	11	5	1	0

	Events	Censored	Median survival (95% CI), months	Log-rank p value
Negative (n=205)	7 (3%)	198 (97%)	NA (NA–NA)	<0·0001
Positive (n=41)	8 (20%)	33 (80%)	78·7 (74·1–NA)	

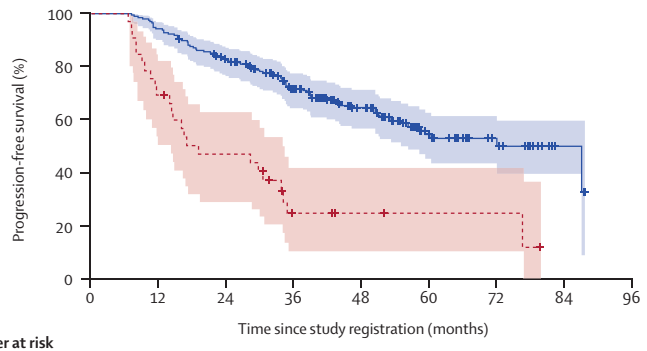
Progression-free survival according to IWC



Number at risk

CR	113	107	90	68	42	21	12	3	0
CRu	55	50	42	32	22	12	6	2	0
PR	62	52	43	28	17	10	6	1	0
SD+PD	10	4	3	1	0				

C Progression-free survival according to PET scan score (cutoff ≥4) in IWC responders



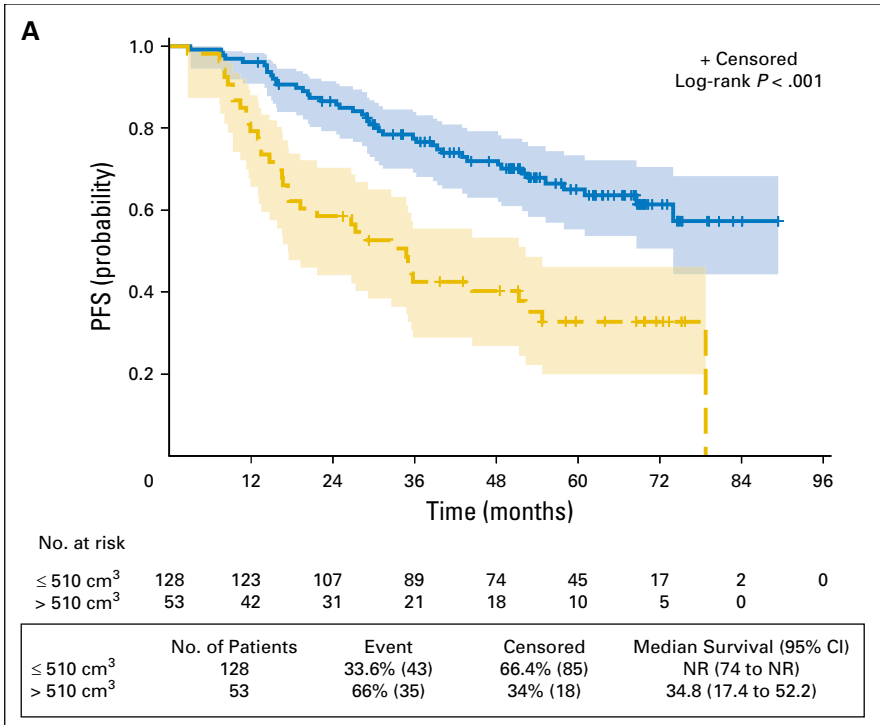
Number at risk

Negative	197	186	160	122	78	41	22	6	0
Positive	33	23	15	6	3	2	2	0	

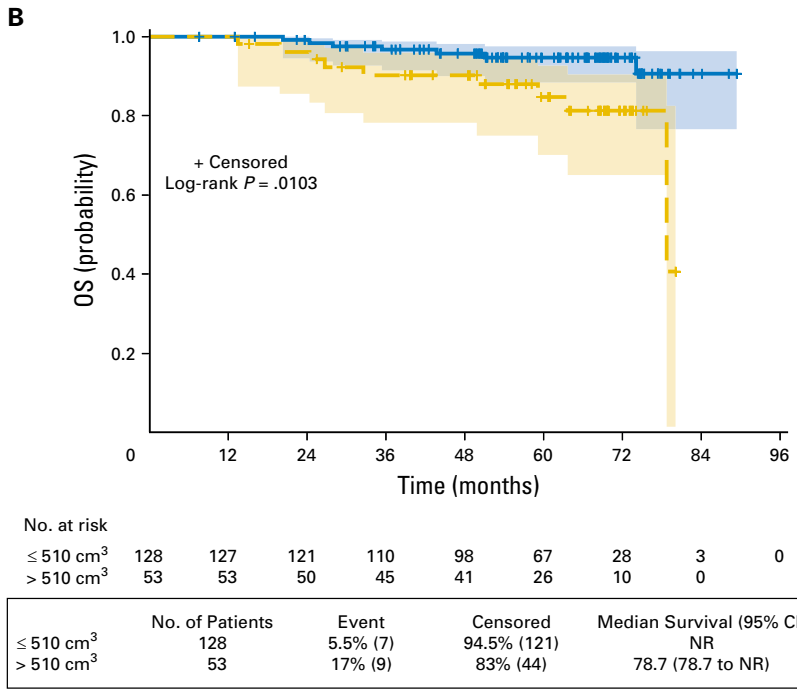
	Events	Censored	Median survival (95% CI), months	Log-rank p value
Negative (n=197)	75 (38%)	122 (62%)	89·5 (57·9–NA)	<0·0001
Positive (n=33)	24 (73%)	9 (27%)	19·6 (14·3–35·1)	

Trotman J, S Luminari et al, Lancet Hematol 2014

Baseline Metabolic Tumor Volume Predicts Outcome in High–Tumor-Burden Follicular Lymphoma: A Pooled Analysis of Three Multicenter Studies 185 patients centrally reviewed



	No. of Patients	Event	Censored	Median Survival (95% CI)
≤ 510 cm^3	128	33.6% (43)	66.4% (85)	NR (74 to NR)
> 510 cm^3	53	66% (35)	34% (18)	34.8 (17.4 to 52.2)



	No. of Patients	Event	Censored	Median Survival (95% CI)
≤ 510 cm^3	128	5.5% (7)	94.5% (121)	NR
> 510 cm^3	53	17% (9)	83% (44)	78.7 (78.7 to NR)

Table 3. TMTV Association With PFS or OS

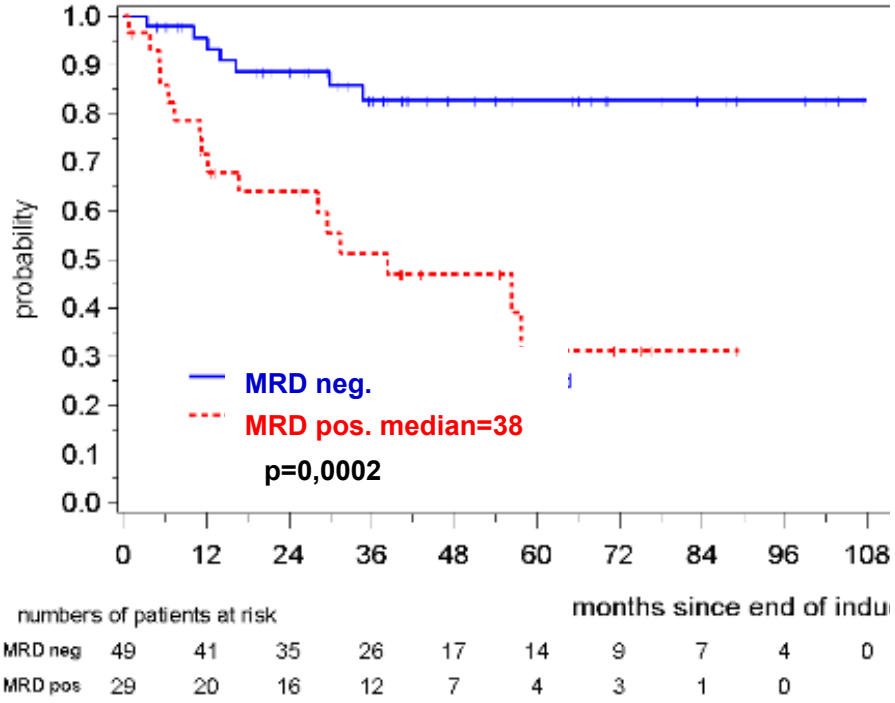
	PFS			OS		
	HR	95% CI	*P*	HR	95% CI	*P*
TMTV > 510 cm^3	**2.32**	**1.374 to 4.04**	**.002**			NS
β_2-microglobulin greater than ULN	1.68	1.01 to 3.04	.045			NS
TMTV > 510 cm^3	**2.46**	**1.49 to 4.70**	**.001**	**3.53**	**1.14 to 10.9**	**.029**
BMB positive	1.46	0.86 to 2.49	NS	2.04	0.55 to 7.55	NS
TMTV > 510 cm^3	**2.83**	**1.71 to 4.69**	**< .001**	2.71	0.89 to 8.22	.079
FLIPI score in two groups	1.05	0.64 to 1.73	NS	1.93	0.65 to 5.74	NS
TMTV > 510 cm^3	**2.25**	**1.34 to 3.78**	**.0021**			NS
FLIPI2 score in two groups	**2.17**	**1.32 to 3.58**	**.0024**			NS

NOTE. **Bold** indicates variable with $P < .05$; not significant (NS) corresponds to variables with $P > 0.1$. Data were adjusted for β_2-microglobulin, bone marrow involvement on biopsy (BMB), Follicular Lymphoma International Prognostic Index (FLIPI), or FLIPI2 and stratified by the factor "study."
Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TMTV, total metabolic tumor volume; ULN, upper limit of normal.

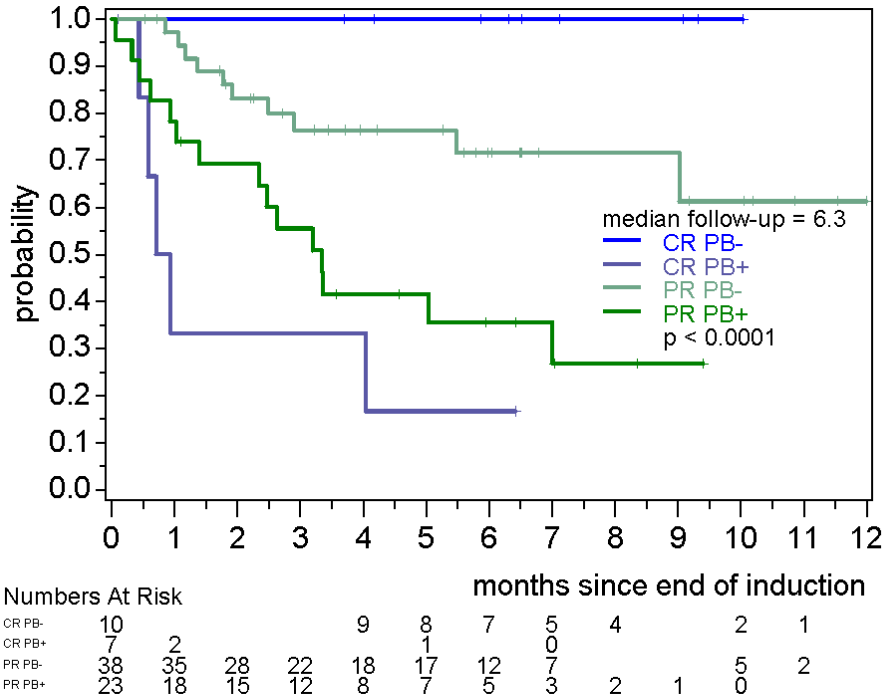
Meignan M et al, J Clin Oncol 2016

Prognostic relevance of MRD response after induction

PFS according to MRD response



PFS according to MRD status and clinical response



Multivariate Coxregression		
MR	HR 5,5 (95%CI 1.6-18.7)	p=0,0067
Rituximab	HR 1,4 (95% CI 0.45-4.4)	p=0,5524
ASCT	HR 0,08 (95% CI 0.01-0.62)	p=0,0158
FLIPI HR	HR 2 (95% CI 0.7-5.6)	P=0,1740

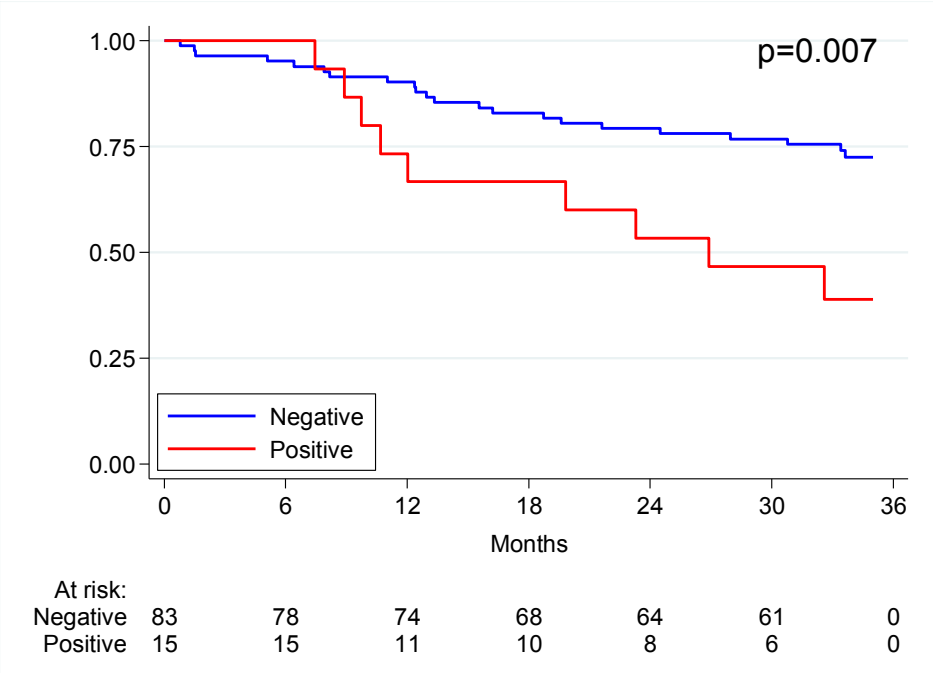
By courtesi of Christiane Pott

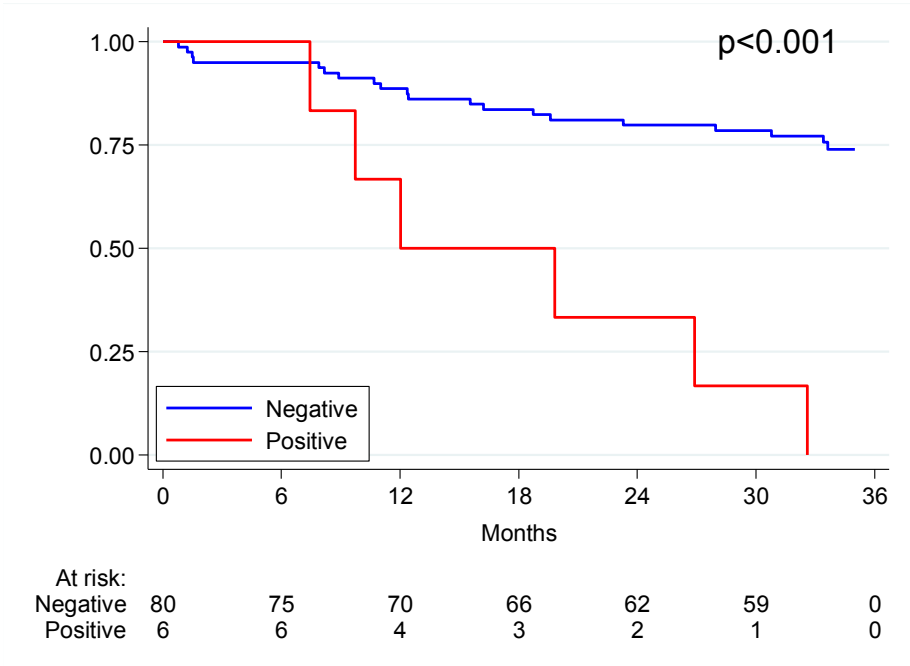
R-FND Elderly FL: Predictive value of MRD at the end of induction therapy

3-year PFS with a median follow-up of 34 months

N-PCR
72% vs 39%

RQ-PCR
74% vs NA





Ladetto M, Blood 2014

PET response and Minimal Residual Disease impact on Progression-Free Survival in Patients with Follicular Lymphoma

Luminari et al. Haematologica 2016

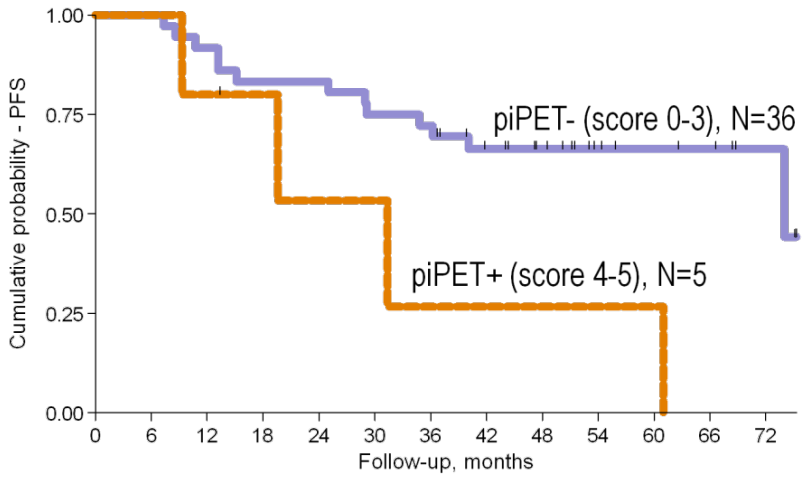
- Pts with centrally reviewed PET(5PS x3 with liver cutoff) (FOLL05; N=79)
- Baseline search for t(14;18)*(N=68)
- MRD analysis* on postinduction BM sample (N=41)

Table 1. Distribution of cases according to piPET and MRD

	MRD -	MRD+
piPET-	28 (68%)	8 (20%)
piPET+	2 (5%)	3 (7%)

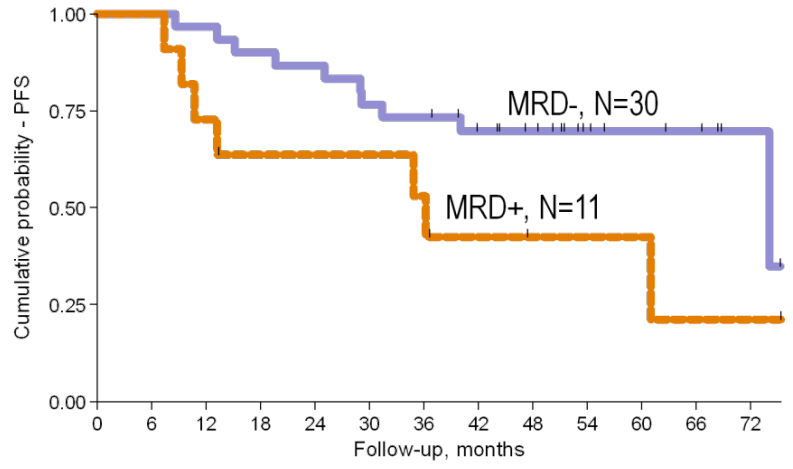
P = 0.110 K=.249(FAIR)

Figure 1.
PFS according to piPET



	HR	95%CI	P
piPET +	3.62	1.15-11.4	.028

Figure 2.
PFS according to MRD

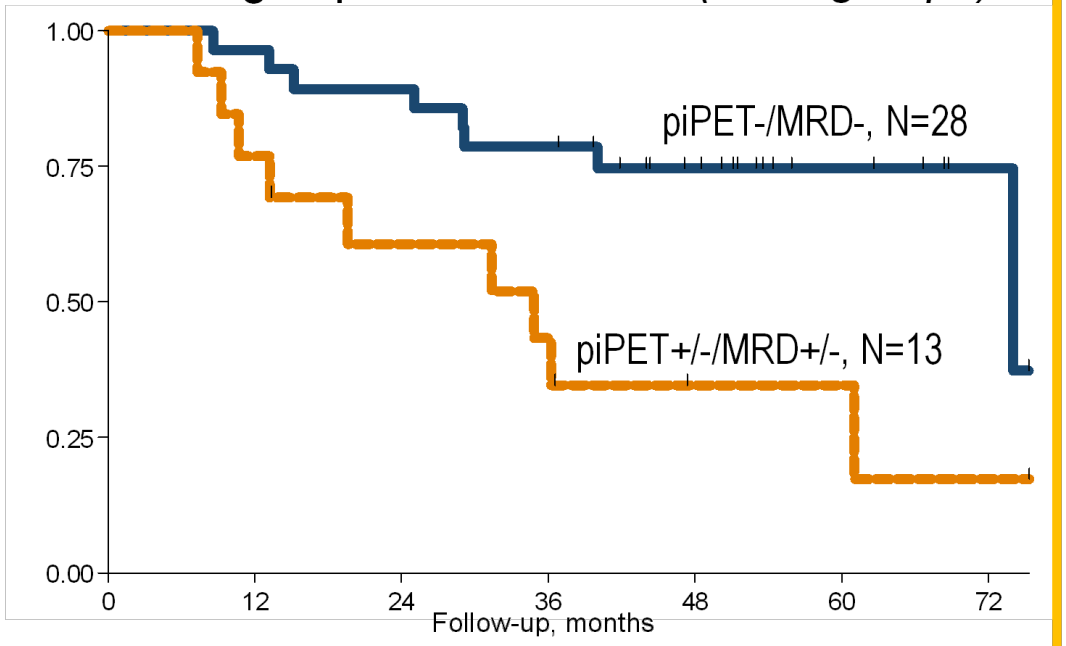


	HR	95%CI	P
MRD +	2.54	0.96-6.72	.060

(*) nested PCR for t(14:18) ch. translocation. All testS were performed within the FIL MRD network (Galimberti et al. Submitted)

PET RESPONSE AND MINIMAL RESIDUAL DISEASE IMPACT ON PROGRESSION-FREE SURVIVAL IN PATIENTS WITH FOLLICULAR LYMPHOMA

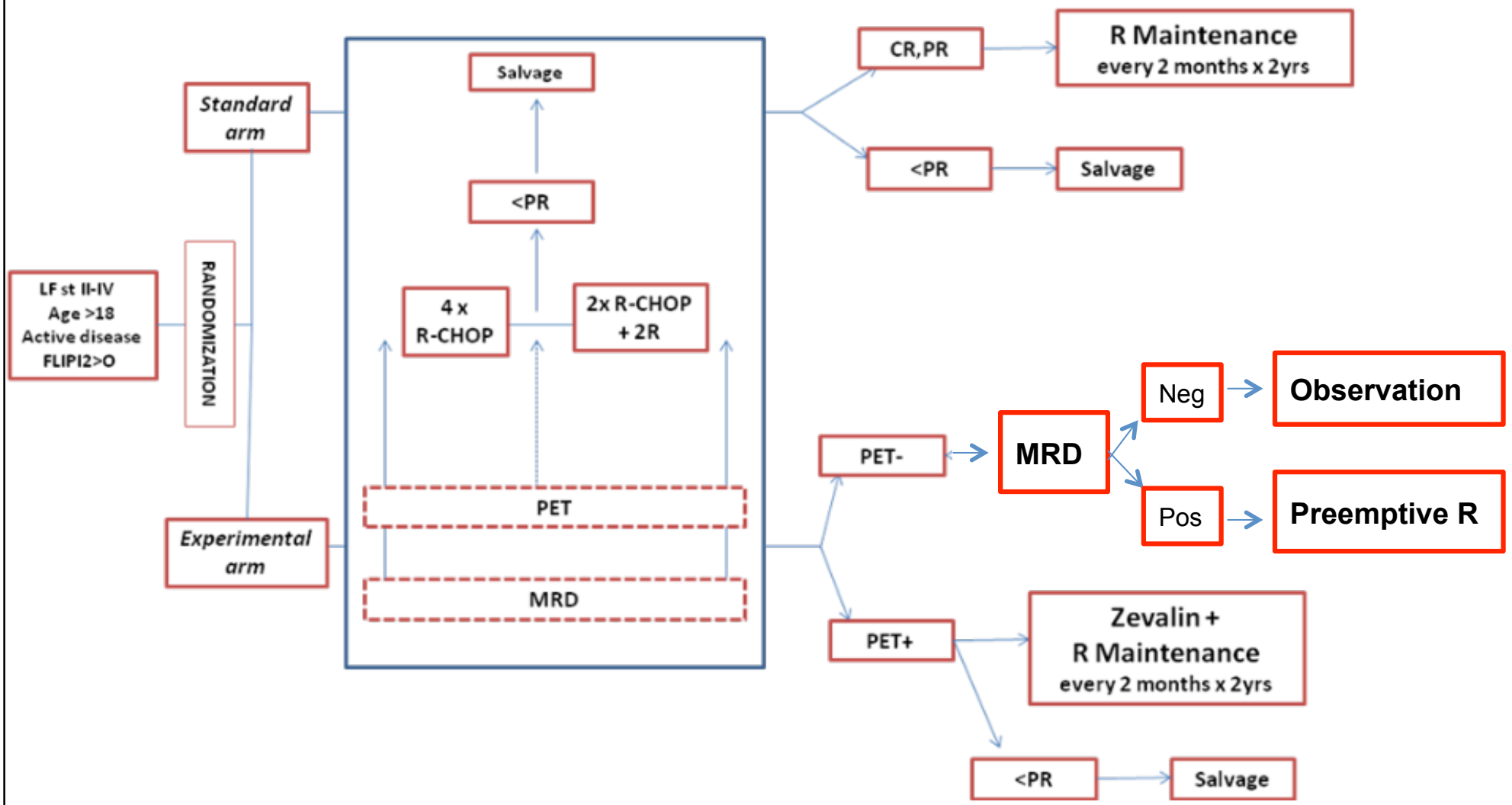
Figure 4.
PFS according to piPET and MRD *(2 subgroups)*



	HR	95%CI	P
piPET+/-/MRD+/-	3.42	1.31-8.95	.012

Luminari et al. Haematologica 2016

FOLL12 study: A phase III multicenter, randomized study comparing standard treatment with rituximab maintenance versus response adapted post-induction treatment as first line treatment in advanced follicular lymphoma.



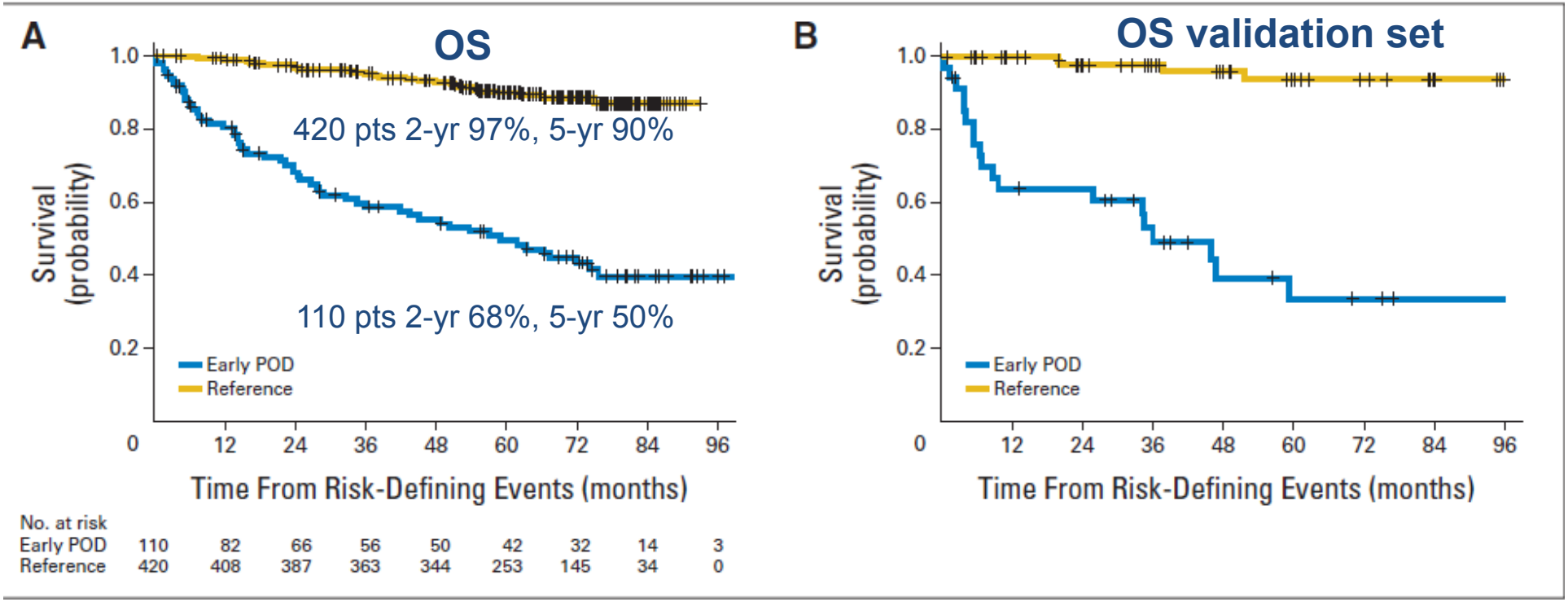
Principal Investigator: Massimo Federico

VOLUME 33 · NUMBER 23 · AUGUST 10 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

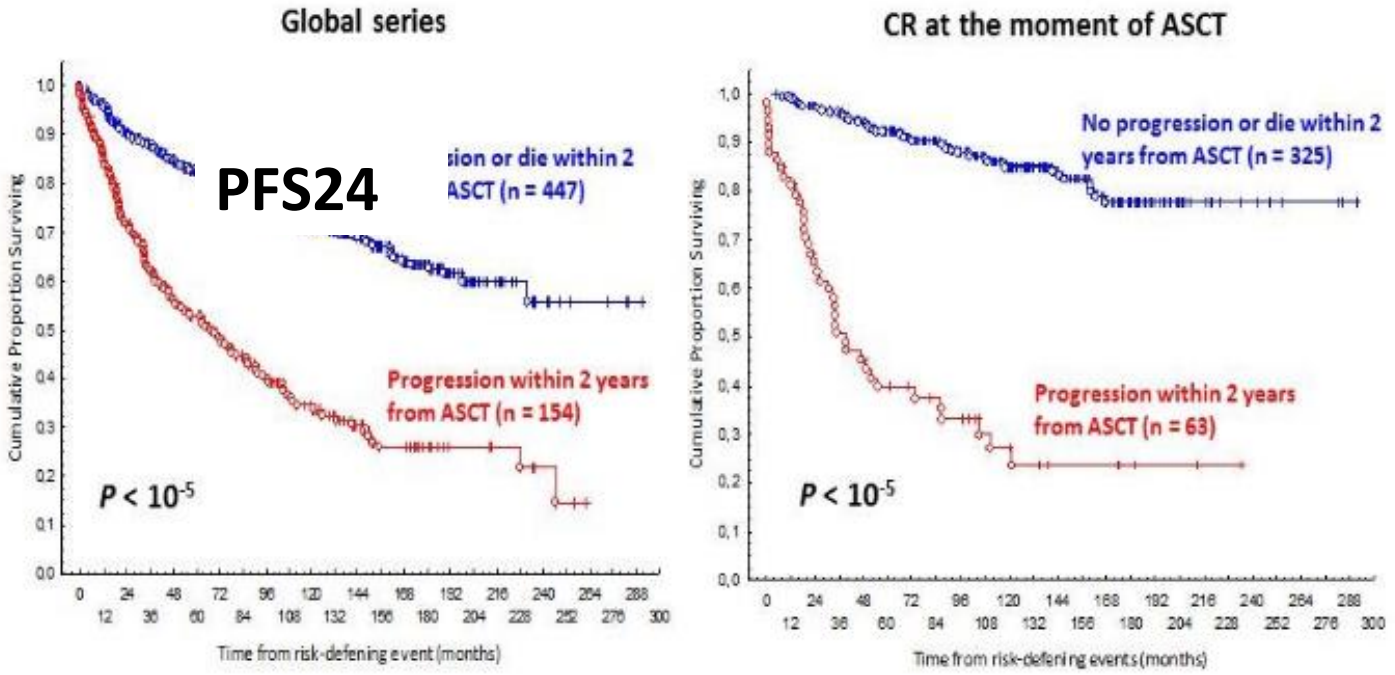
Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study



Casulo C et al, JCO 2015

Progression-Free Survival at 24 Months (**PFS24**) and Complete Response at 30 Months (**CR30**) from Autologous Stem Cell Transplantation (ASCT) Should be Used As Surrogates for OS in Follicular Lymphoma (FL) Patients

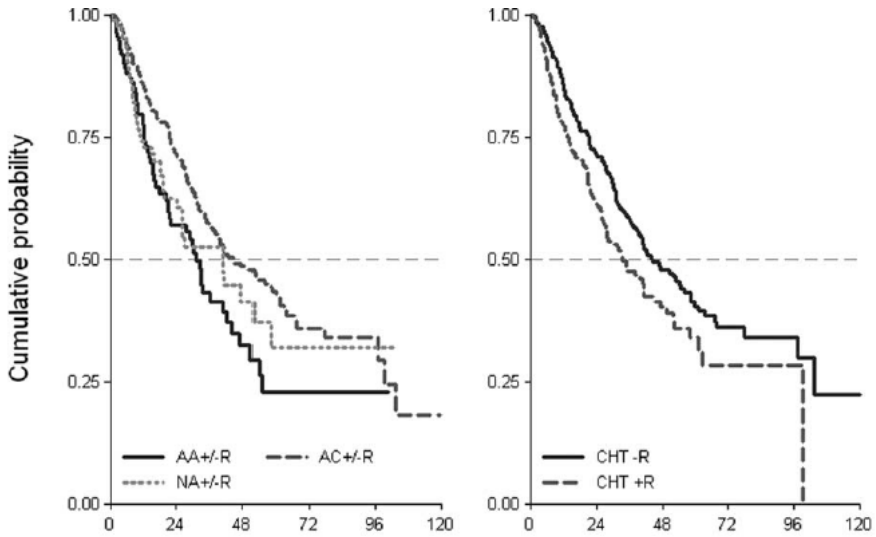
Objective: To assess if 2-year PFS (PFS24) is a feasible surrogate of OS in the setting of a very long follow-up series of FL patients treated with ASCT



626 FL patients intensified with auto (either 1st CR, PR or second line)

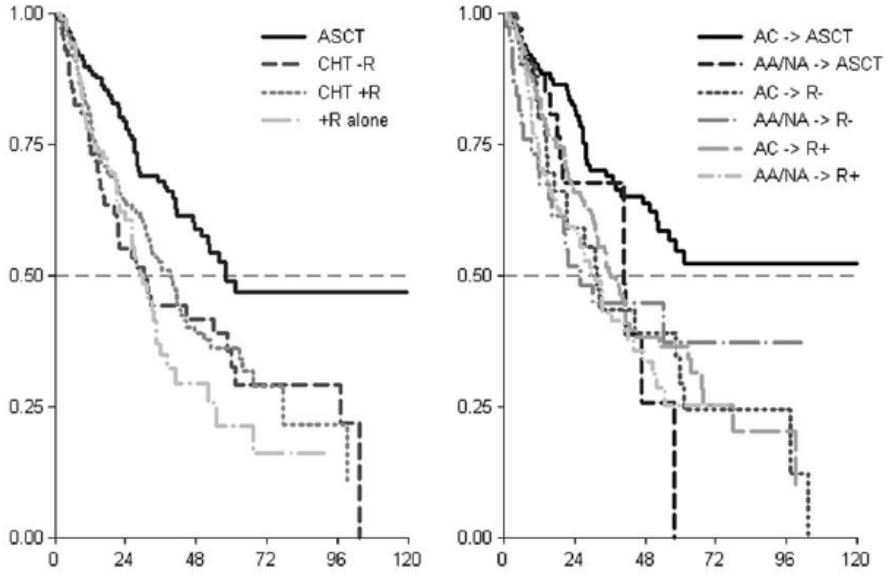
Ubieto AJ et al ASH 2015, ABSTR 521

The use of anthracycline at first-line compared to alkylating agents or nucleoside analogs improves the outcome of salvage treatments after relapse in follicular lymphoma
The REFOLL study by the Fondazione Italiana Linfomi



582 R/R FL in FIL centers

Time to next treatment duration after second-line therapy according to the type of first line chemotherapy received and to the use of Rituximab

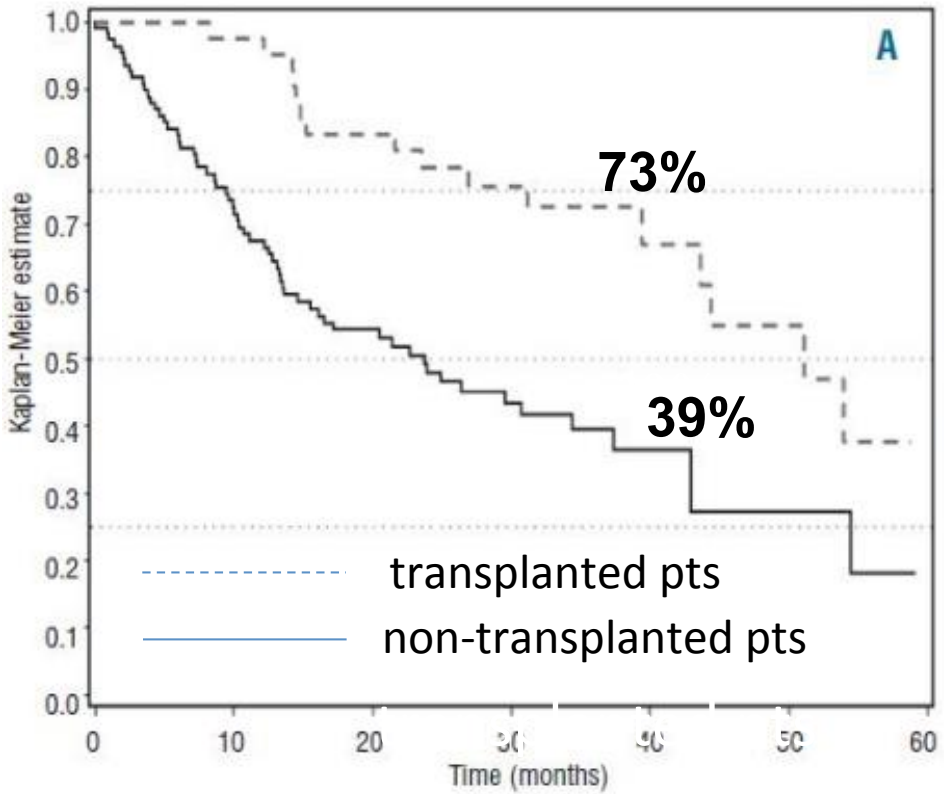


Time to next treatment duration after second-line therapy according to the type of treatment received and to the sequence of treatments

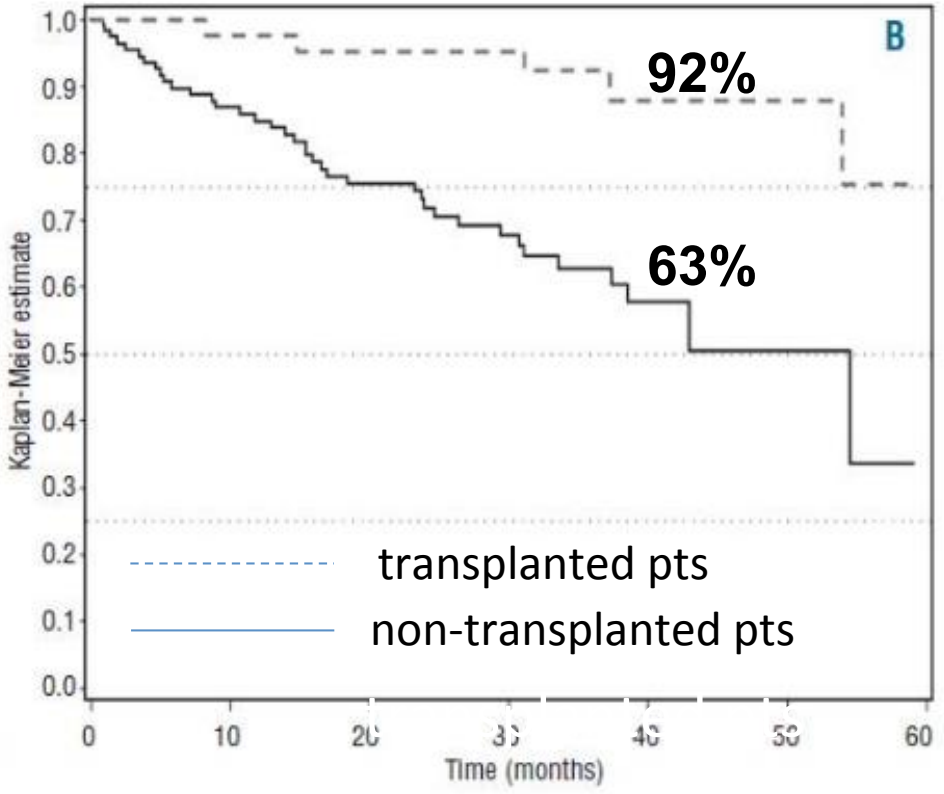
Rossi et al, Am J of Hematology, Vol. 90, No. 1, January 2015

Impact of the use of autologous stem cell transplantation at first relapse both in naive and previously rituximab exposed follicular lymphoma patients treated in the GELA/GOELAMS FL2000 study

3 yrs EFS



3 yrs OS

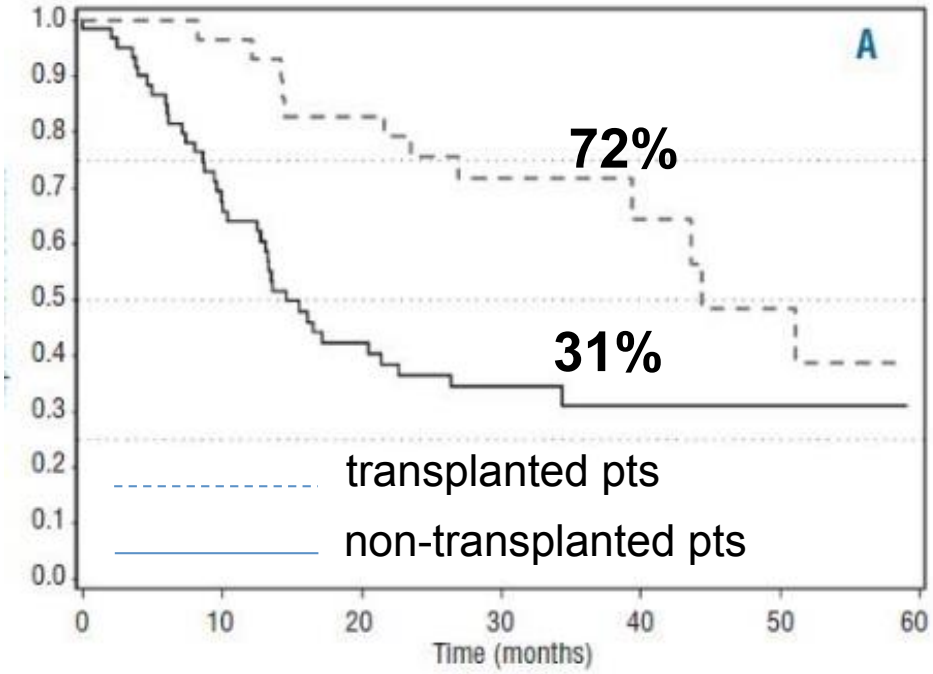


Le Gouill S et al. Haematologica 2011

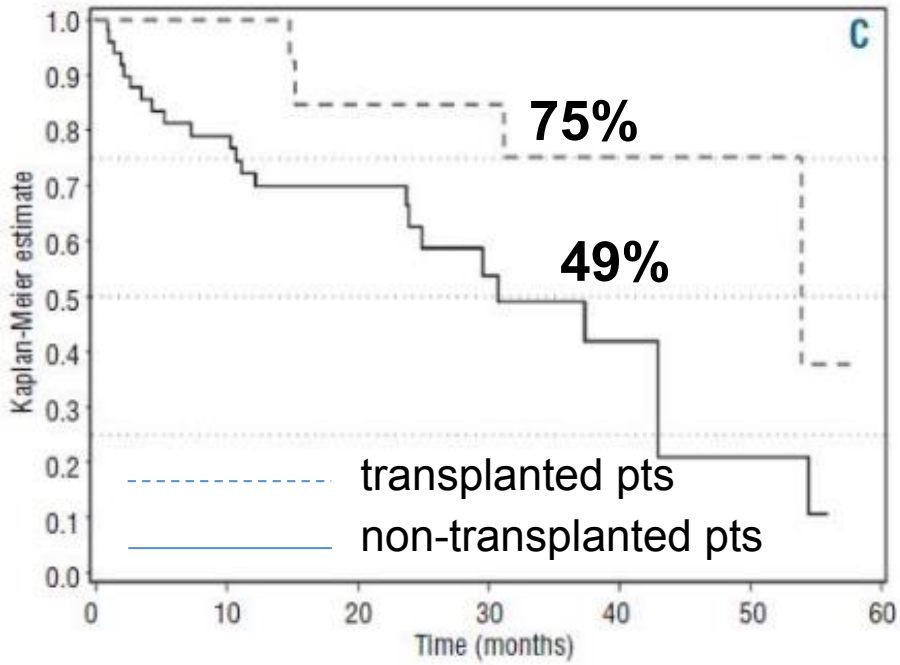
Impact of the use of autologous stem cell transplantation at first relapse both in naive and previously rituximab exposed follicular lymphoma patients treated in the GELA/GOELAMS FL2000 study

Patient outcome (EFS) according to rituximab up front or not

Rituximab naive pts



Rituximab treated pts



Le Gouill S et al. Haematologica 2011

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Patient outcome (OS) according to rituximab up front or not

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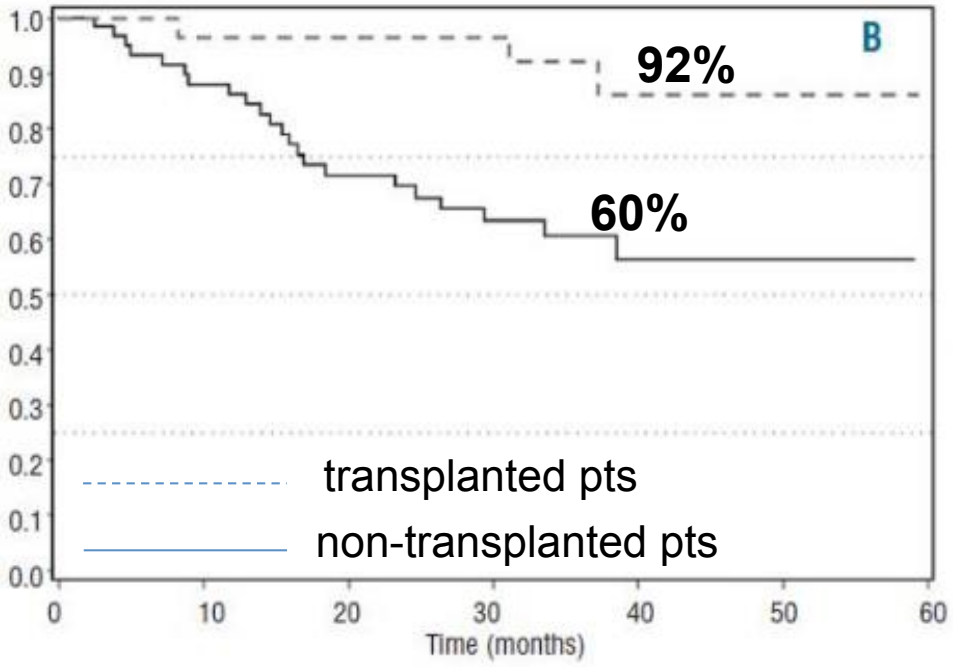
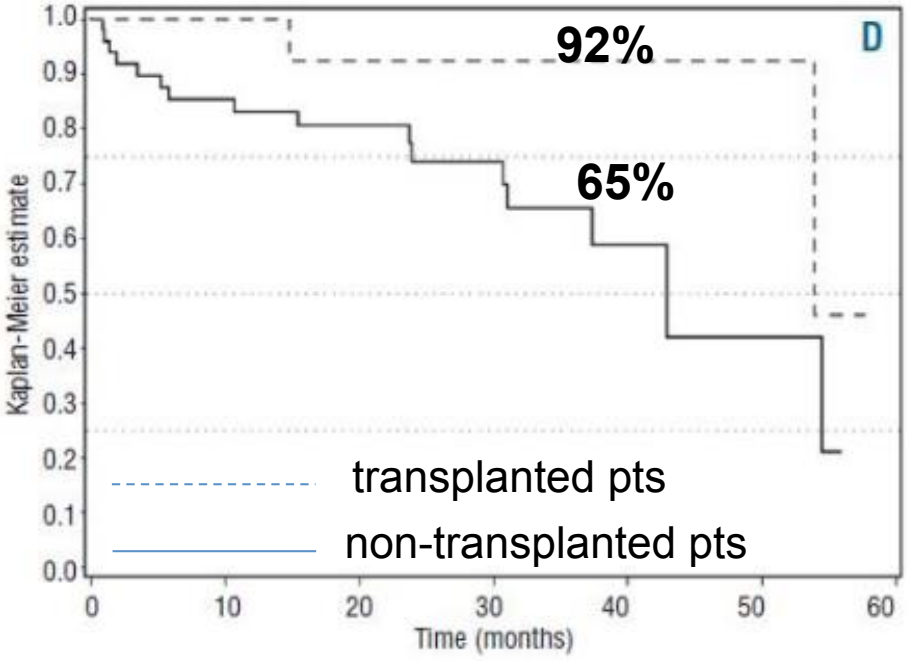


Rituximab treated pts

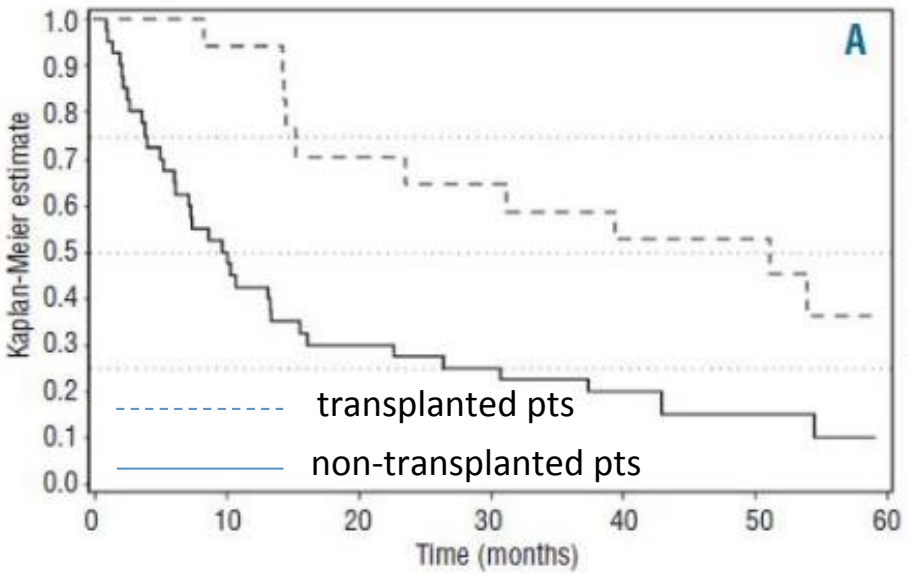


Le Gouill S et al. Haematologica 2011

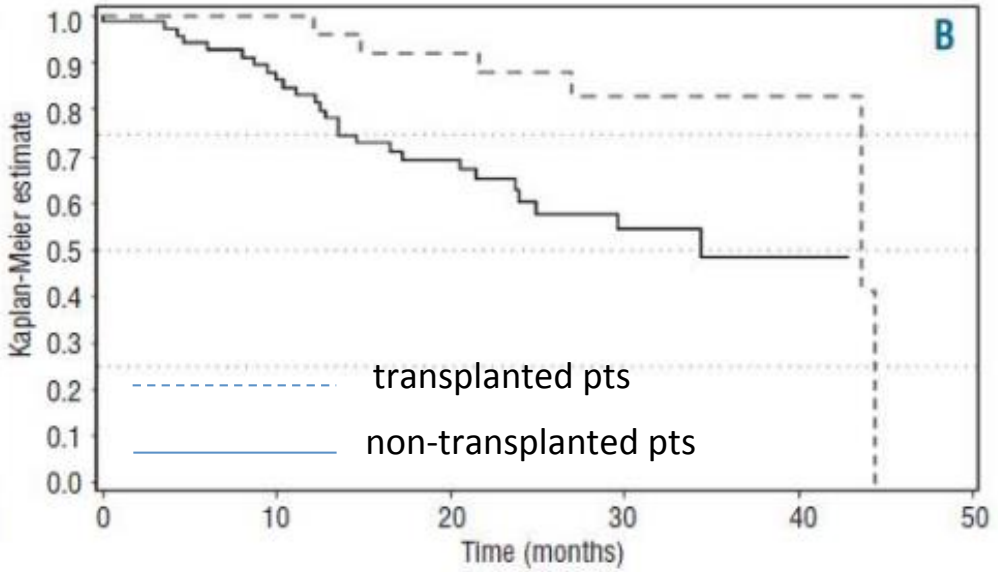
Impact of the use of autologous stem cell transplantation at first relapse both in naive and previously rituximab exposed follicular lymphoma patients treated in the GELA/GOELAMS FL2000 study

Patient outcome according to progression period and use of ASCT

primary refractory pts



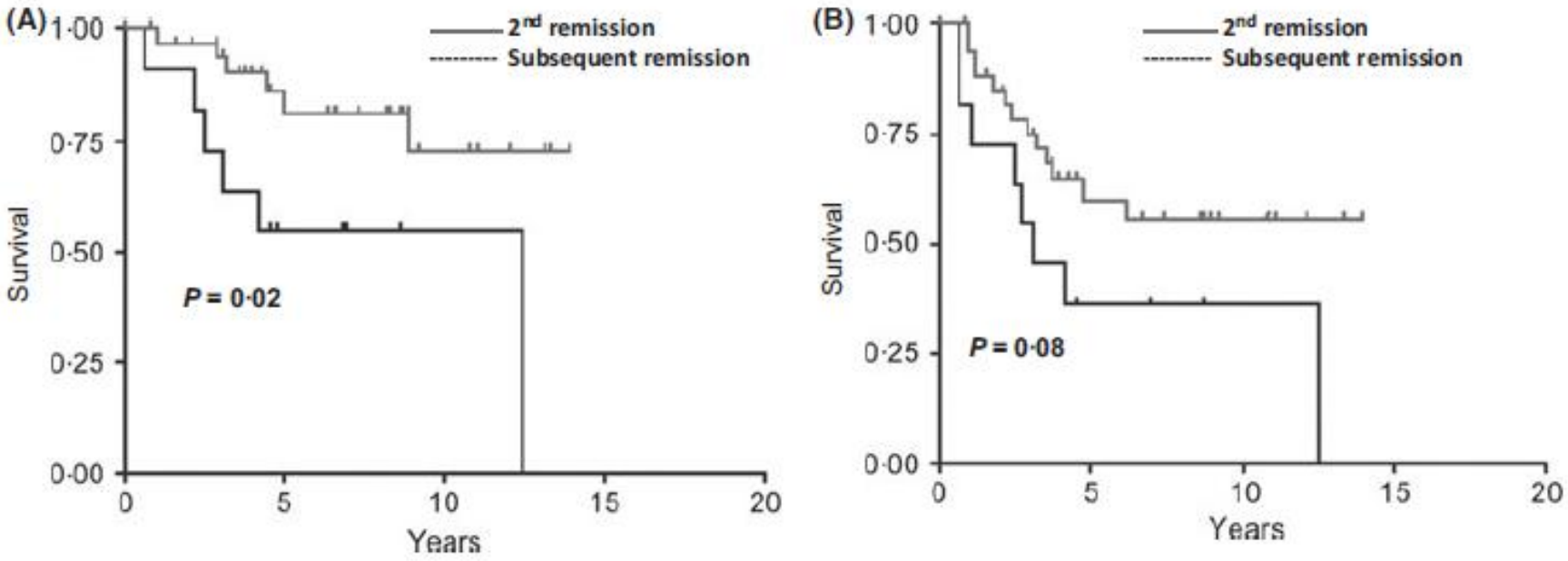
progressed/relapsed pts



Le Gouill S et al. Haematologica 2011

Autologous stem cell transplantation for follicular lymphoma is of most benefit early in the disease course and can result in durable remissions, irrespective of prior rituximab exposure

Single-centre experience on 70 FL pts (1988-2009)
Median follow-up: 6.8 yrs



Significant difference in OS comparing pts transplanted in 1st or 2nd remission vs later remission

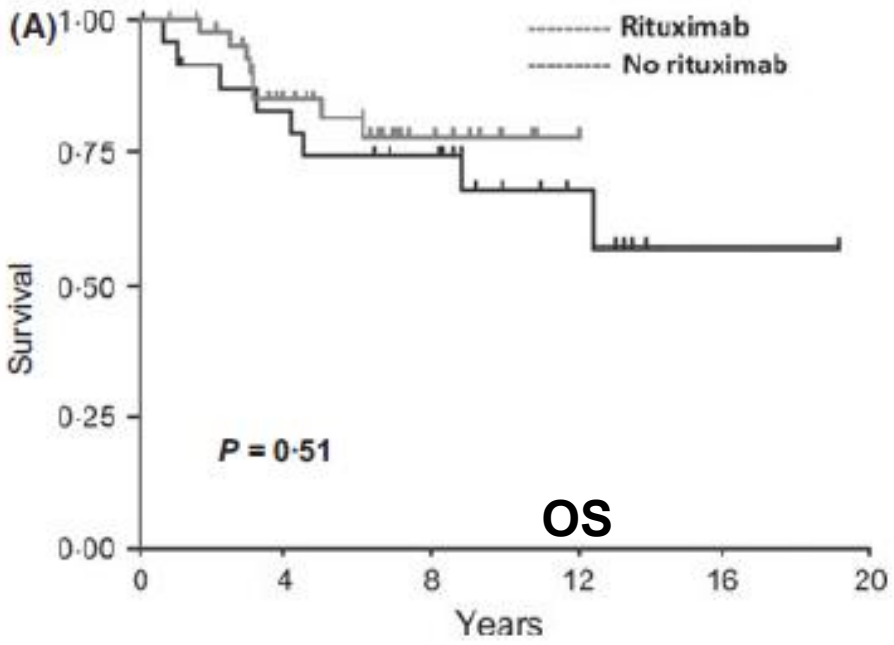
Plateau on PFS curves for pts transplanted in 1st or 2nd remission after 9.3 yrs and 6.4 yrs, respectively

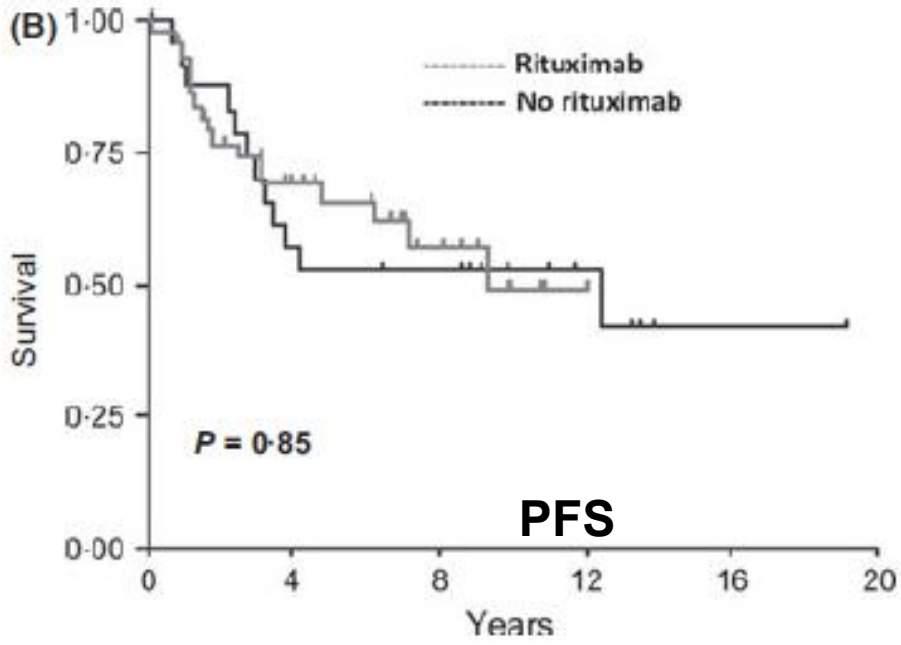
Kothari J, et al. BJH 2014

Autologous stem cell transplantation for follicular lymphoma is of most benefit early in the disease course and can result in durable remissions, irrespective of prior rituximab exposure

Single-centre experience on 70 FL pts (1988-2009 - London)

Median follow-up: 6.8 yrs



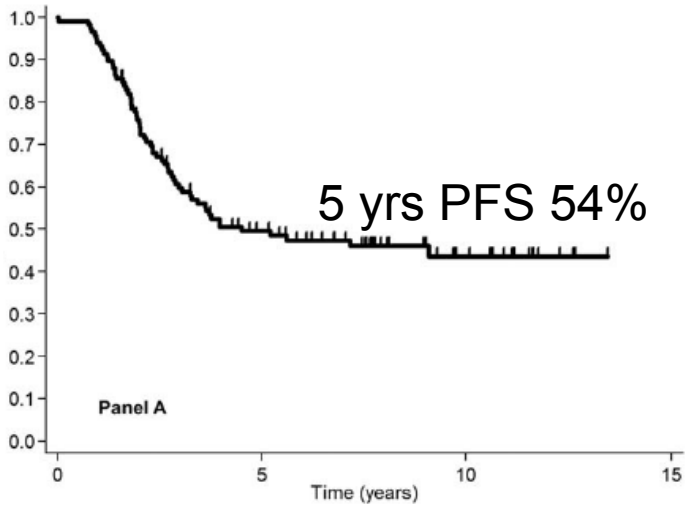


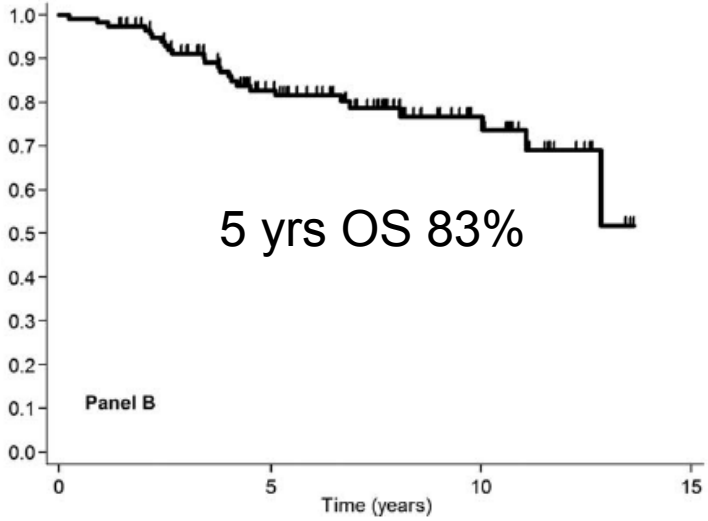
No differences in OS and PFS in those treated with Rituximab before ASCT vs those were not

Kothari J, Ardeshna KM et al: BJH 2014

Autologous stem cell transplantation with in vivo purged progenitor cells shows long-term efficacy in relapsed/refractory follicular lymphoma

- 112 relapsed/refractory FL treated with 4 CHOP/6 VACOP + 2 R-COP+ HD Ara-C+ ASCT
- CR 85%, PR 10%, PG/NR 5%
- Median FU 6.7 yrs, 54% still in CR
- 52/112 bcl2+ at enrollment, 29 bcl2- after ASCT



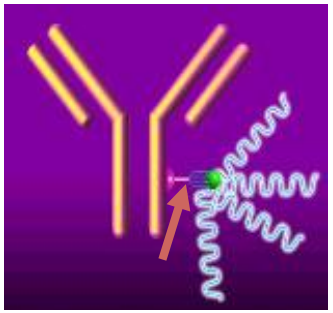


In univariate analysis, PFS influenced by FLIPI at relapse and by CR before ASCT

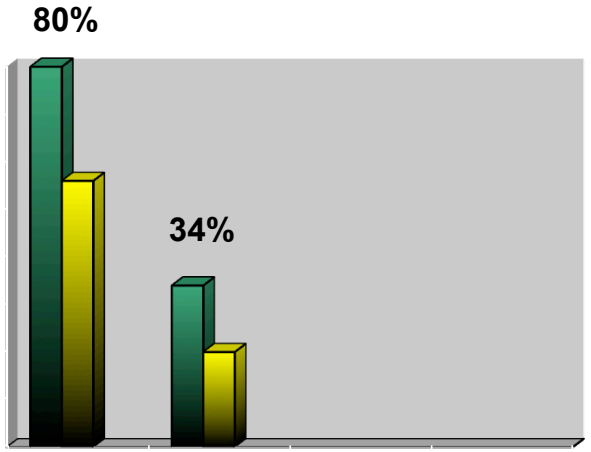
In multivariate analysis only FLIPI

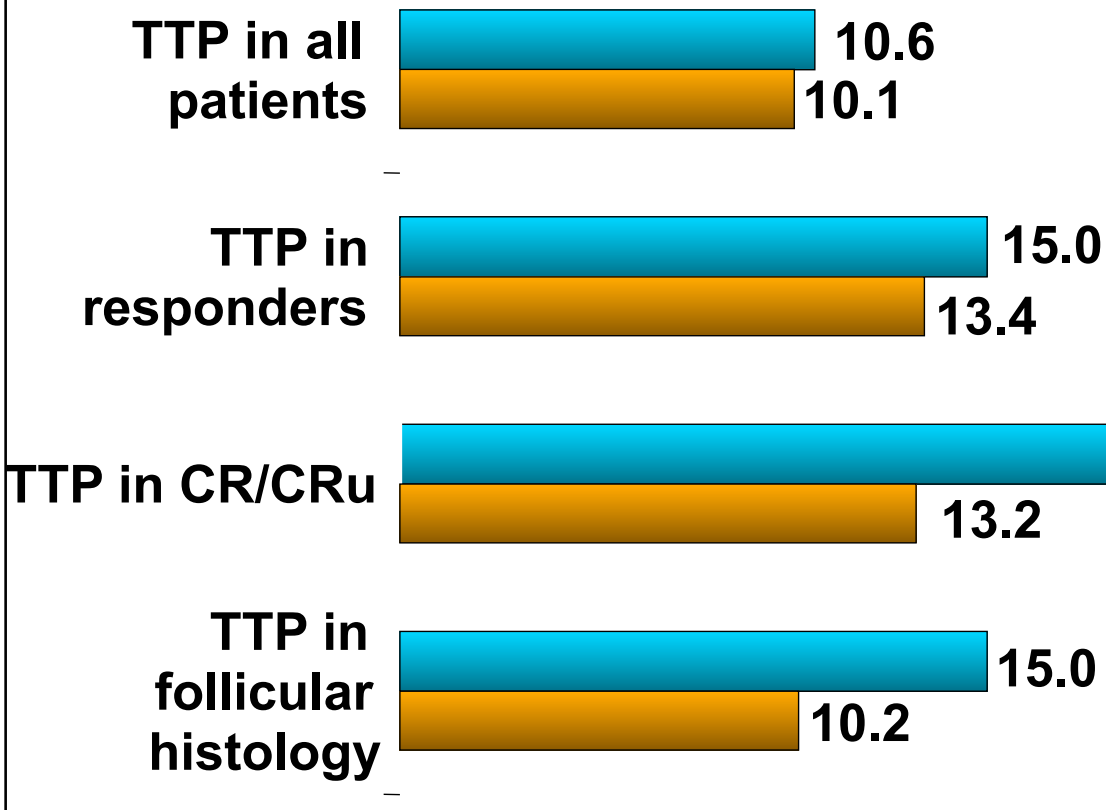
L Arcaini, Am J of Hematology, Vol. 90, No. 3, 2015

Zevalin® vs Rituximab nei pazienti recidivati o refrattari



143 pazienti Rituximab naïve; 80% FL



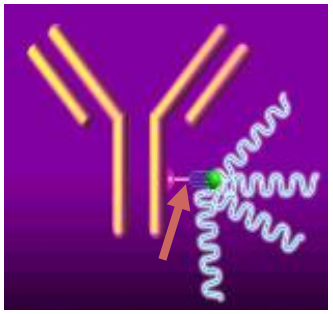


■ Zevalin®: 73 patients

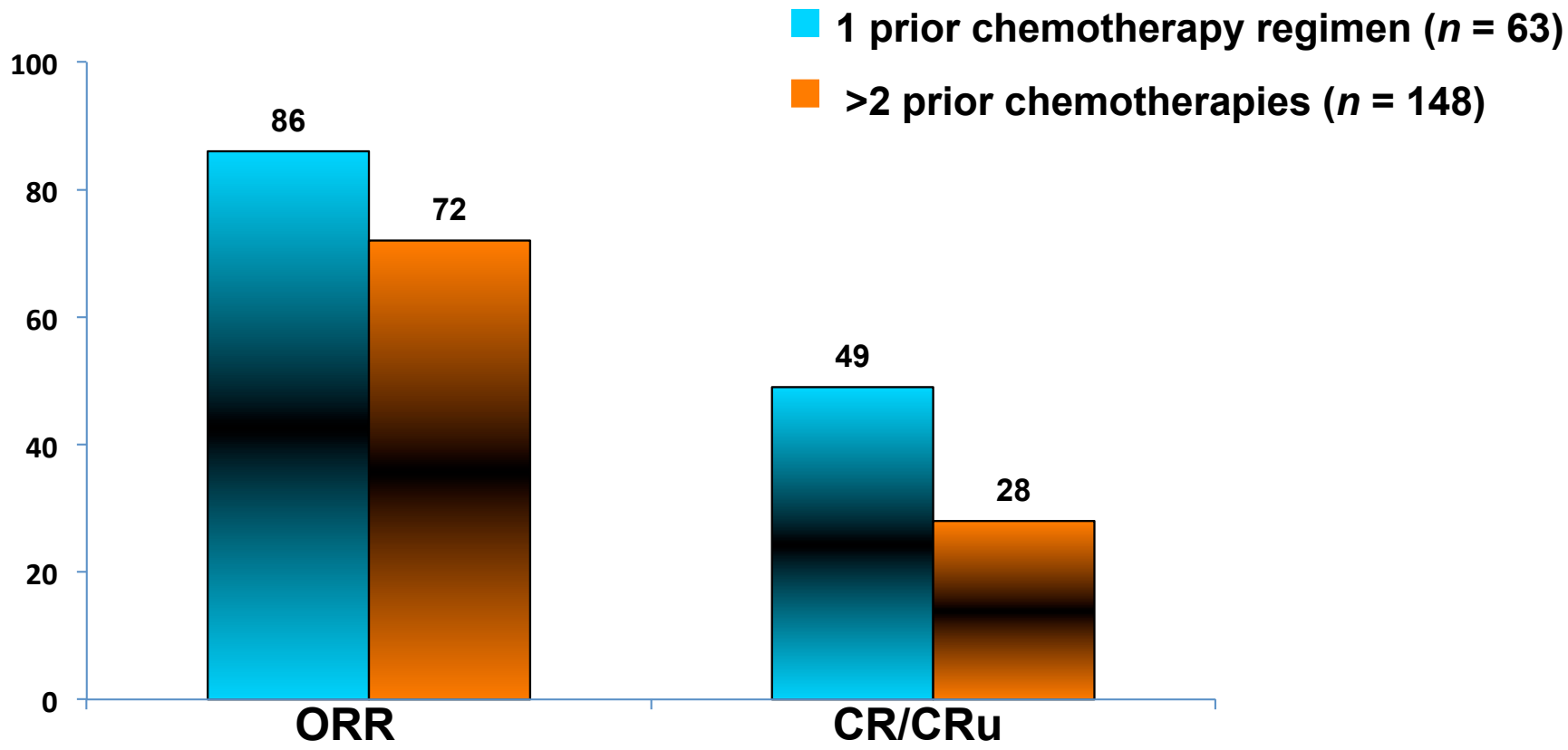
■ Rituximab: 70 patients

Gordon LI, et al: Clin Lymphoma 2004

Zevalin®: razionale dell'uso precoce in recidiva



211 pts relapsed/refractory low-grade, follicular or transformed NHL



Emmanouilides C, et al: Leukemia Lymphoma 2006

Yttrium-90 Ibritumomab Tiuxetan as a Single Agent in Patients With Pretreated B-Cell Lymphoma: Evaluation of the Long-Term Outcome

Pts. Characteristics	(N = 57)
Median Age, Y. (Range)	53 (33-78)
M / F	24 / 33
Follicular Lymphoma	53
Median prev. Therapies	3 (1-9)

RESULTS: 57 Patients, median FU 48 mo.

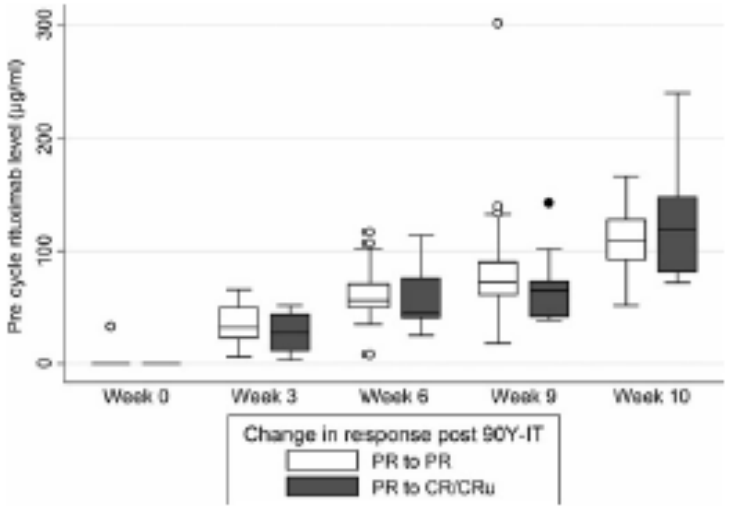
ORR	53 / 57 93 %
CR	40 / 57 70 %
Median pretreatments of CR pts =	3 (2-5) (11 pts > 4 diff. Chemoimmunother)
CCR	26 / 40 = **65 % of CR pts / 46% of total pts**

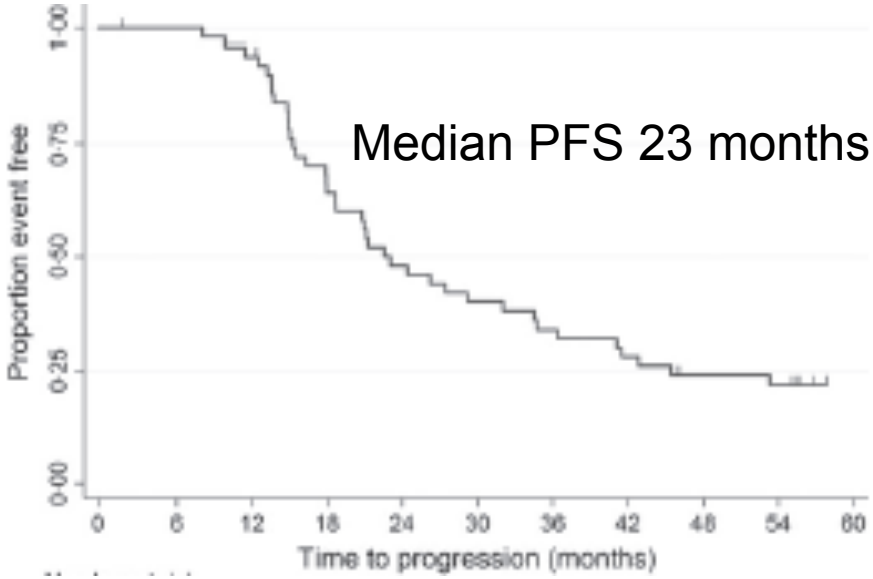
Zinzani et al. Clinical Lymphoma, Myeloma & Leukemia August 2010

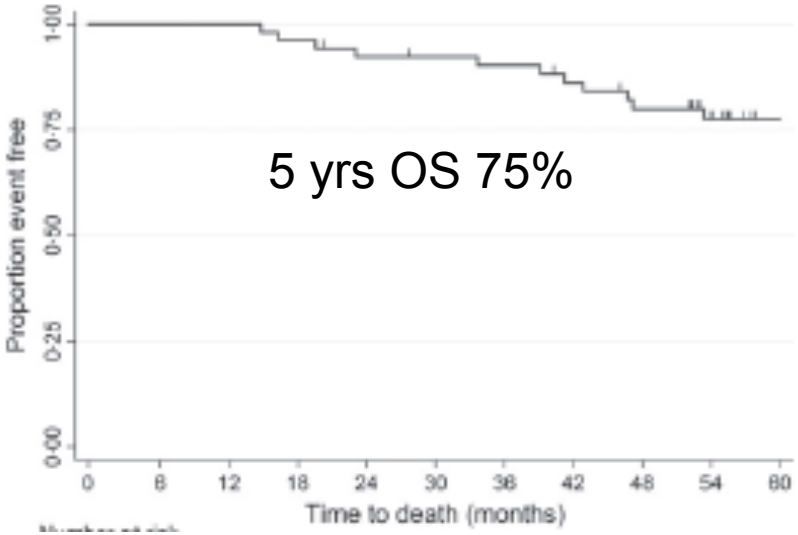
Short duration immunochemotherapy followed by radioimmunotherapy consolidation is effective and well tolerated in relapsed follicular lymphoma: 5-year results from a UK National Cancer Research Institute Lymphoma Group study

52 relapsed/refractory FL:

- 3 R-CHOP/R-CVP
- RIT standard dose
- ORR 98% CR 30%
- Median FU 5 years

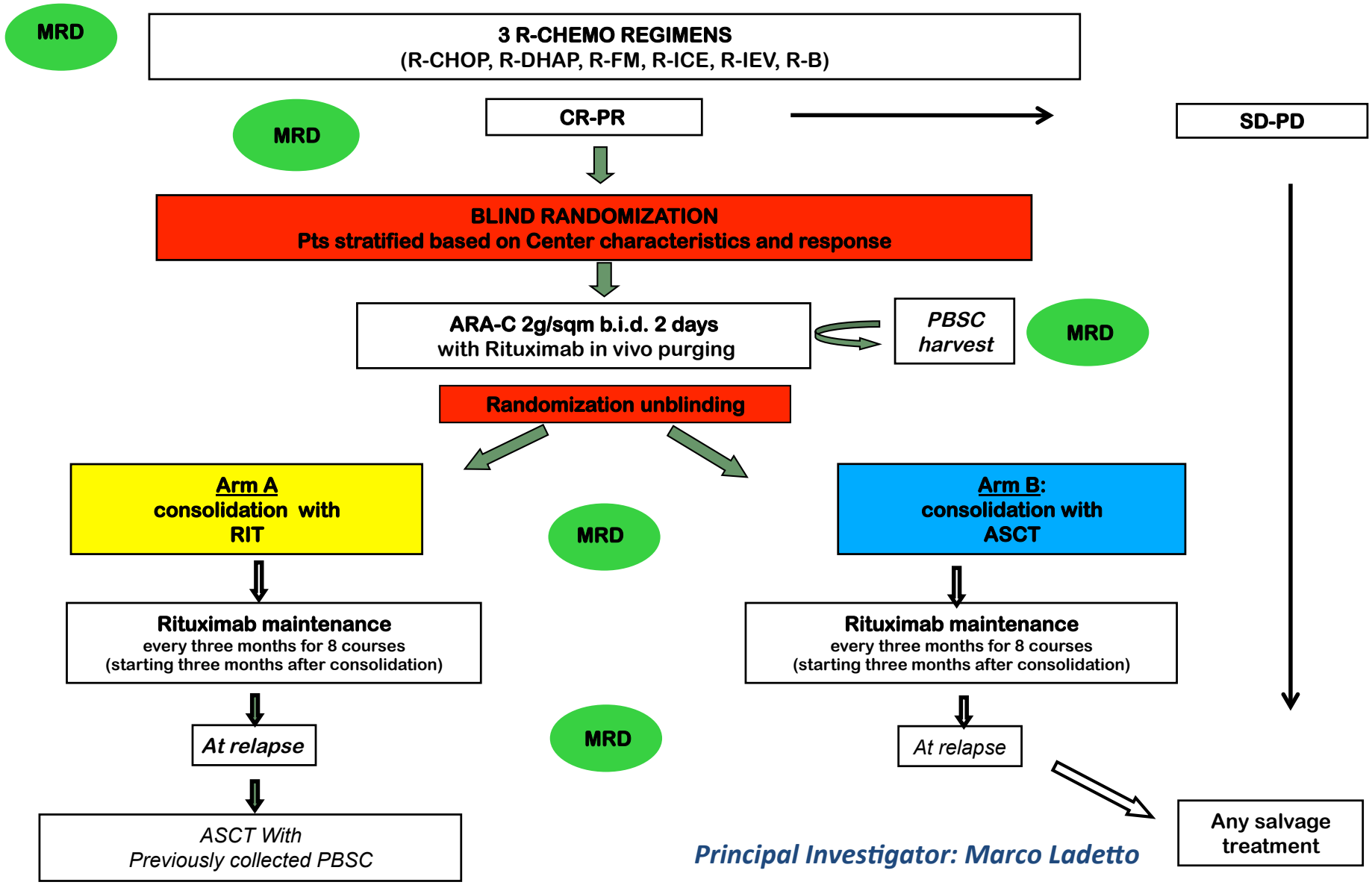




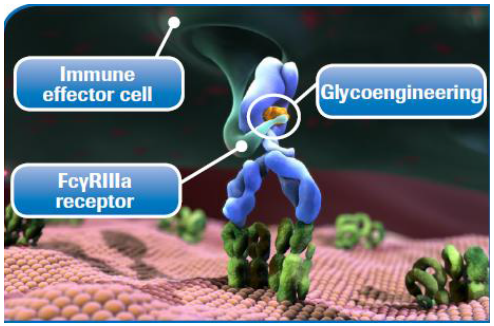


Illidge T, BJ Haematol, 2016, 173, 274–282

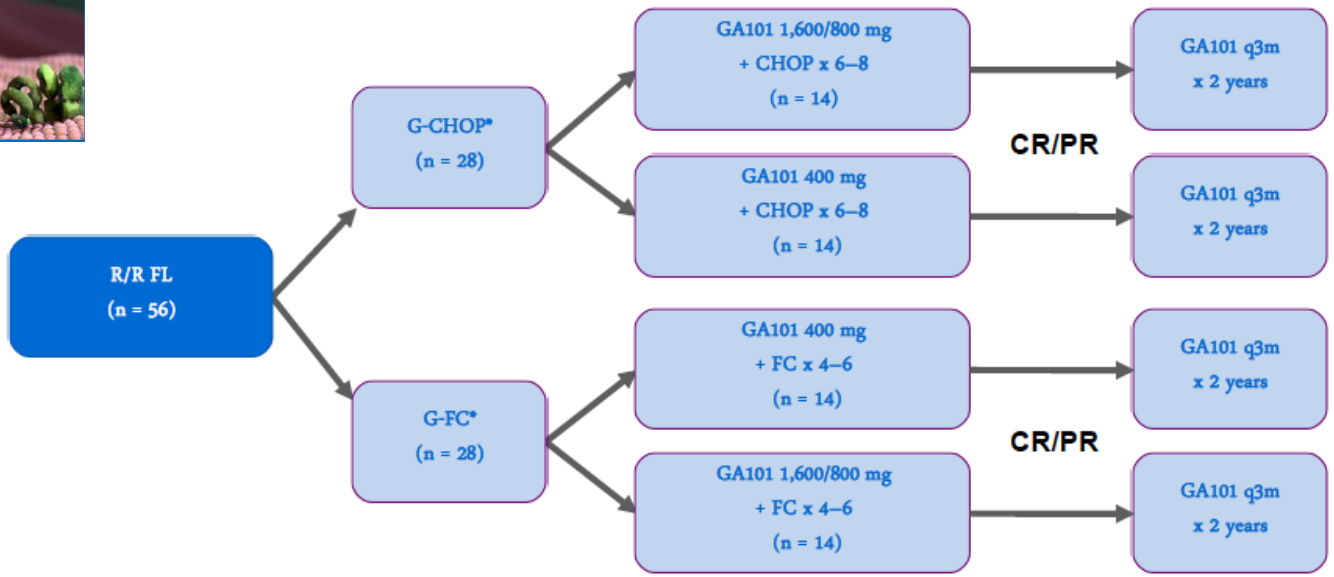
High risk relapsed FL: FLAZ-12 STUDY DESIGN



Principal Investigator: Marco Ladetto



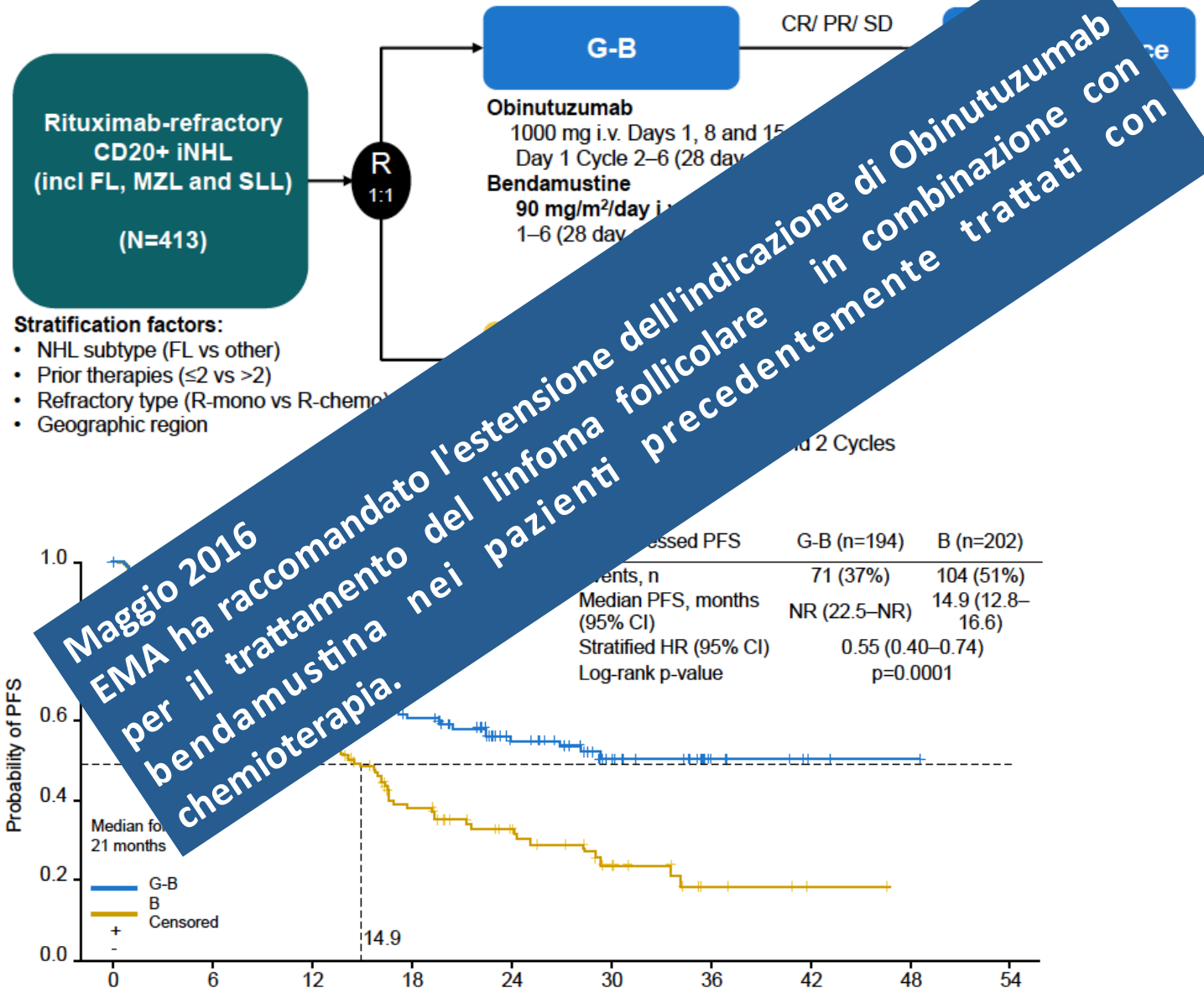
Obinotuzumab GAUDI Phase Ib in R/R FL



	Patients, n (%)	
Response	G-CHOP (n = 28)	G-FC (n = 28)
Overall response	27 (96.4)	26 (92.9)
Complete response	11 (39.3)	14 (50.0)
Partial response	16 (57.1)	12 (42.9)
Stable disease	1 (3.6)	0
Progressive disease	0	1 (3.6)
No response assessment	0	1 (3.6)

Radford J, et al; Blood 2013

Phase III Obinotuzumab GADOLIN



Sehn L, Lancet Oncol. 2016 Aug;17(8):1081-93

Is it possible to abrogate the chemoimmunotherapy?

- Rituximab-Lenalidomide?
- Anti-PD1?
- PI3K-inhibitors?
- Anti-BCL2?
- Drug-coniugated antibodies?
- BTK inhibitors?

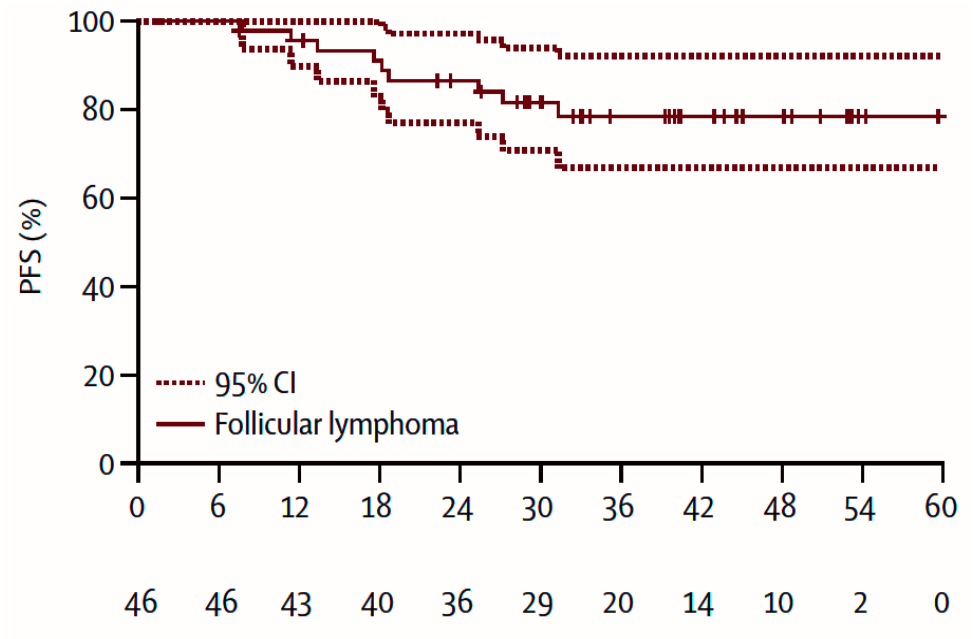
Clinical studies of lenalidomide or lenalidomide + rituximab in patients with relapsed/refractory FL

Regimen	Reference	Patient population	n	ORR (%)	CR (%)
Lenalidomide monotherapy	Witzig et al[1]	Relapsed/refractory FL	22	27	9
	Witzig et al[2]	Relapsed/refractory FL grade III	19	42	11
Lenalidomide + rituximab combination	Dutia et al[3]	Relapsed FL (33% rituximab refractory)	16	86	50
	Ahmadi et al[4]	Rituximab refractory FL + MCL	15	53	33

1. Witzig TE, et al. J Clin Oncol. 2009;27(32):5404-5409; 2. Witzig TE, et al. Ann Oncol. 2011;22(7):1622-1627;
3. Dutia M, et al. Ann Oncol. 2011;22(suppl 4): Abstract 306); 4. Ahmadi T, et al. Blood. 2009;114: Abstract 1700.

Frontline Combination of Lenalidomide and Rituximab (R2) for FL: Clinical Response

	SLL (N = 24)	Marginal (N = 24)*	Follicular (N = 45)*	All patients Eval (N = 93)	All patients ITT (N = 100)
ORR, n (%)	20 (83)	21 (88)	**44 (98)**	85 (91)	85 (85)
CR/Cru	6 (25)	16 (67)	**38 (85)**	60 (65)	60 (60)
PR	14 (59)	5 (21)	**6 (13)**	25 (27)	25 (25)
SD, n (%)	2 (8)	3 (13)	**1 (2)**	6 (6)	6 (6)
PD, n (%)	2 (8)	0	**0**	2 (2)	2 (2)



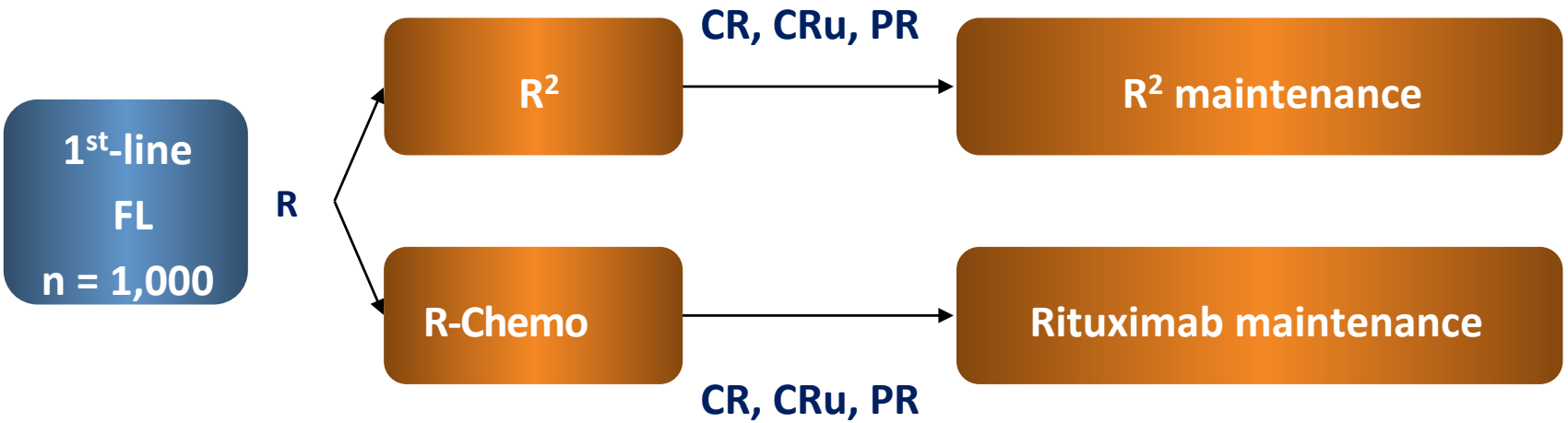
*7 patients inevaluable for response:

- 5 due to adverse event in cycle 1
- 1 due to non-compliance
- 1 due to withdrawal of consent

Fowler N, et al. Lancet Oncol 2014

RELEVANCE: Phase 3 Study Design (Rituximab and LEnalidomide Versus ANy ChEmotherapy, FL-001)

International, multi-centre, randomized study (Frank Morchhauser, Nathan Fowler)



- R-Chemo
  - investigator choice of R-CHOP, R-CVP, R-B
- Lenalidomide 20 mg x 6 cycles, if CR then 10 mg
- Co-primary end-points
  - surrogate end-point: CR/CRu rate at 1.5 years
  - PFS

NCT01476787. Available from: http://clinicaltrials.gov. Accessed March 2012.

Relapsed FL not elegible for ASCT: Renoir study

PCR analysis for Bcl-2 rearrangement on PB/ BM

REALPSED/REFRACTORY FOLLICULAR LYMPHOMA NEED TO THERAPY

R-Bendamustine x 4 once a month

Rituximab 375 mg/m^2 day 0 or 1 (day 8 on cycle 1)
Bendamustine 90 mg/m^2 iv days 1-2

Restaging and PCR analysis for Bcl-2 rearrangement on PB/ BM

CR/PR → **NR** → **OFF**

Random

R2

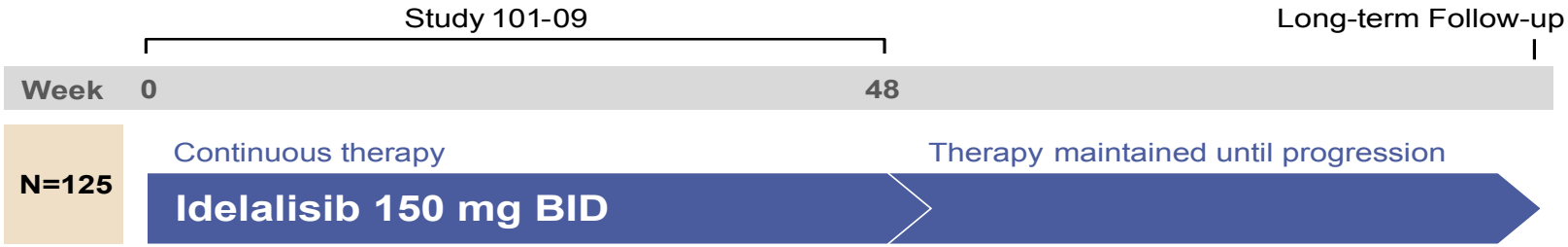
Rituximab 375 mg/m2 day 1 q 90 days (8 cycles for 2 years)
Lenalidomide (10 mg dd 1-21 q 28) (24 cycles for 2 years)

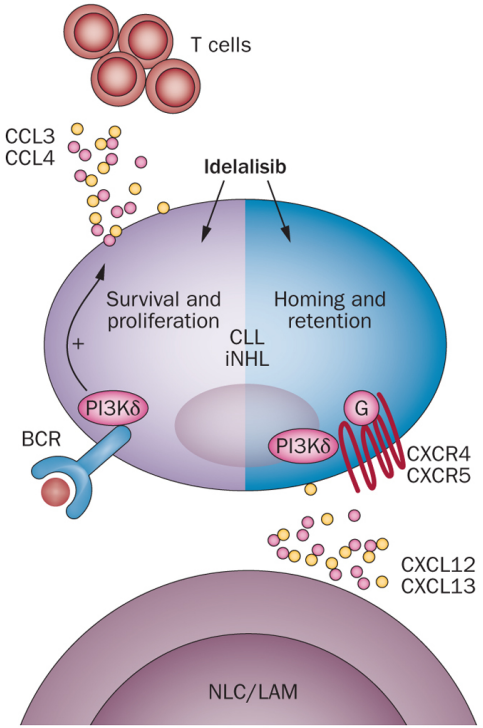
R alone

Rituximab 375 mg/m2 day 1 q 90 days (8 cycles for 2 years)

Clinical and molecular follow-up months 12, 18, 24 and 30 (end of study)

Phase 2 Study of PI3K-Delta Inhibitor Idelalisib in Patients With Double (Rituximab and Alkylating Agent)–Refractory Indolent B-Cell Non-Hodgkin Lymphoma: 125 patients

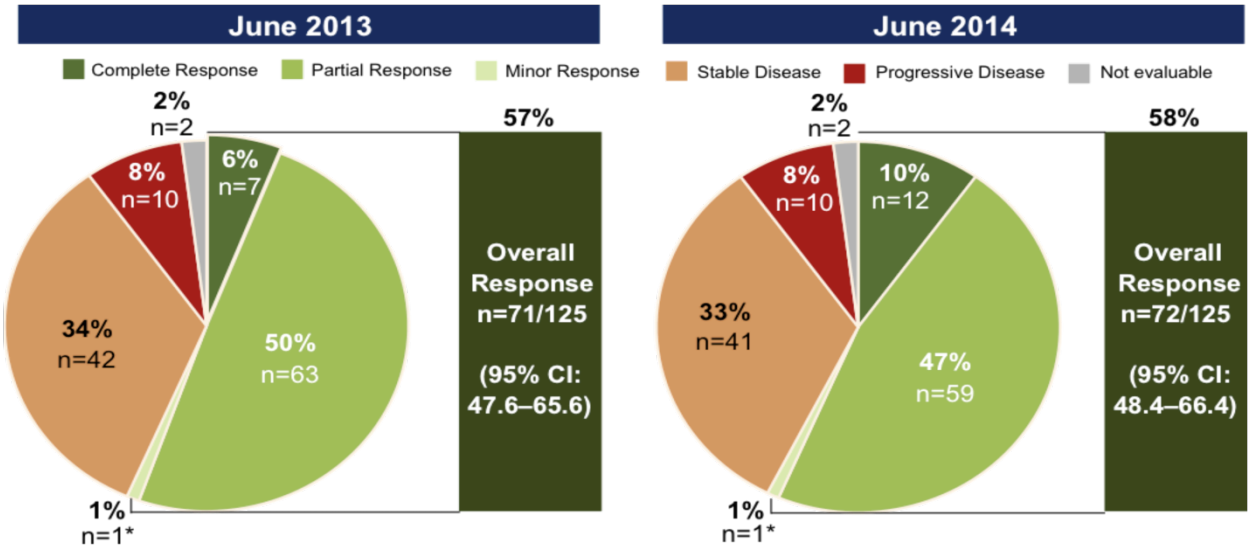




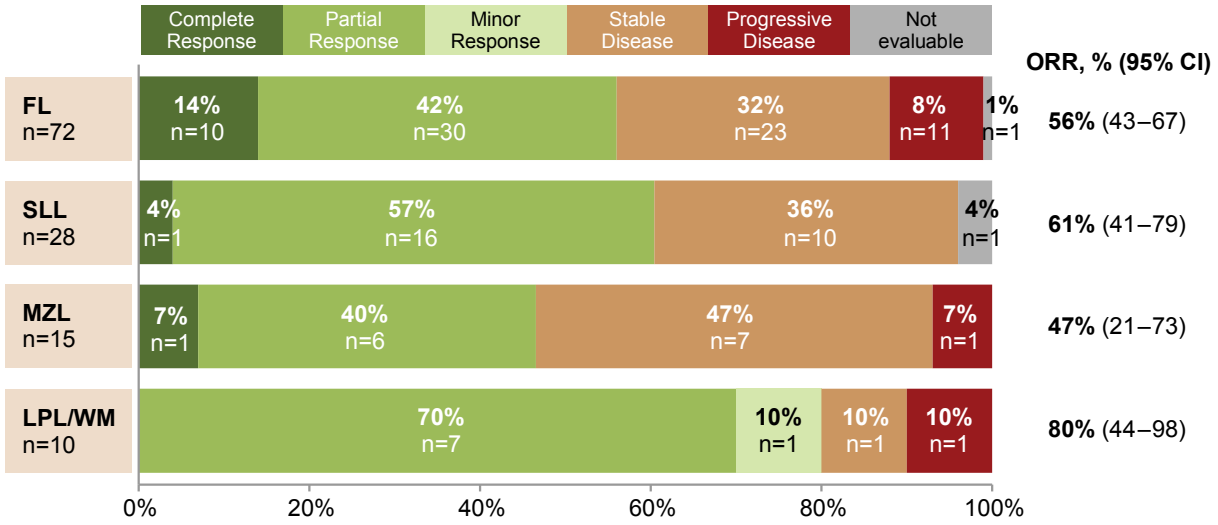
Baseline Patient Characteristics	N=125
Male/female, n (%)	80/45 (64/36)
Median age, y (range)	64 (33–87)
Disease type, n (%)	
FL	72 (58)
SLL	28 (22)
MZL	15 (12)
LPL/WM	10 (8)
Lactate dehydrogenase >ULN, n (%)	38 (30)
Bulky disease [>7 cm], n (%)	33 (26)
Neutropenia [ANC <1500 cells/μL], n (%)	17 (14)
Anemia [Hb <10 g/dL], n (%)	19 (15)
Thrombocytopenia [platelets <75,000/μL], n (%)	10 (8)
Refractory to > 2 regimens	99 (79)

Gopal A, et al. N Eng J Med 2014

Phase 2 Study of PI3K-Delta Inhibitor Idelalisib in Patients With Double (Rituximab and Alkylating Agent)–Refractory Indolent B-Cell Non-Hodgkin Lymphoma: 125 patients

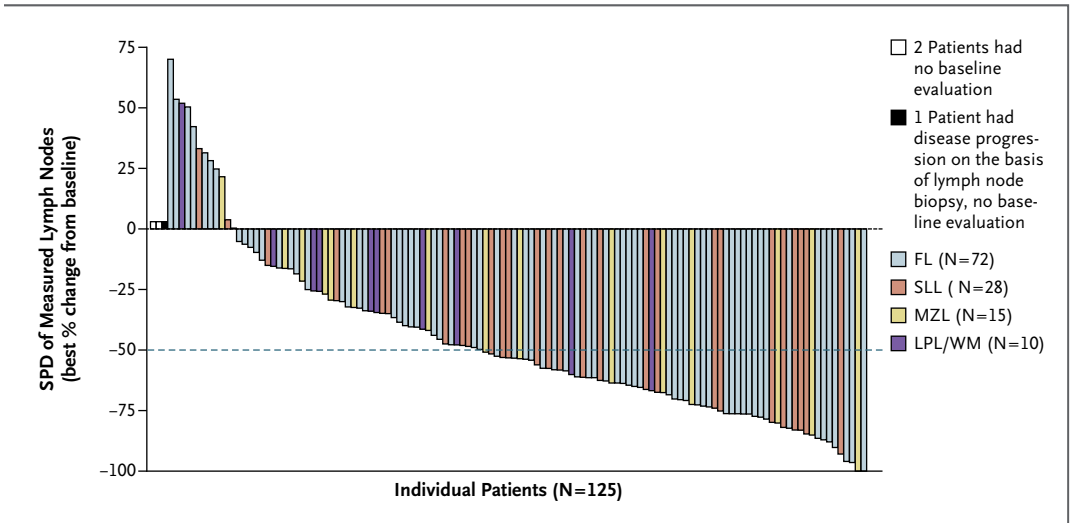


Overall Response Rate By Disease Subgroups: 2014

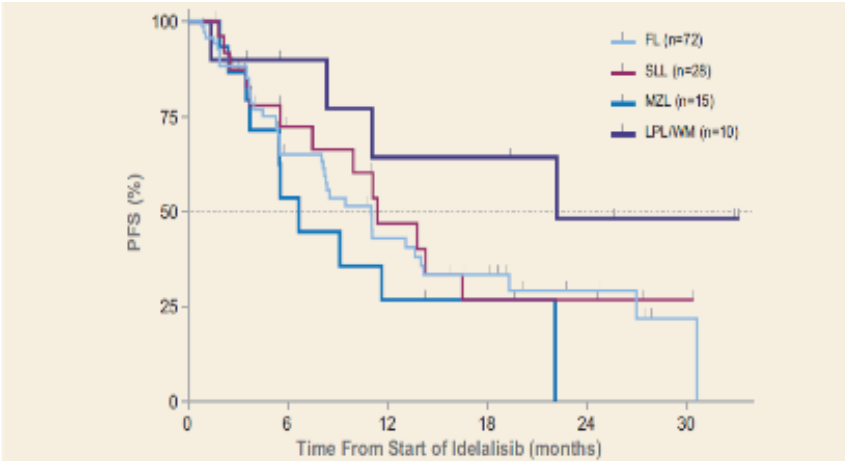


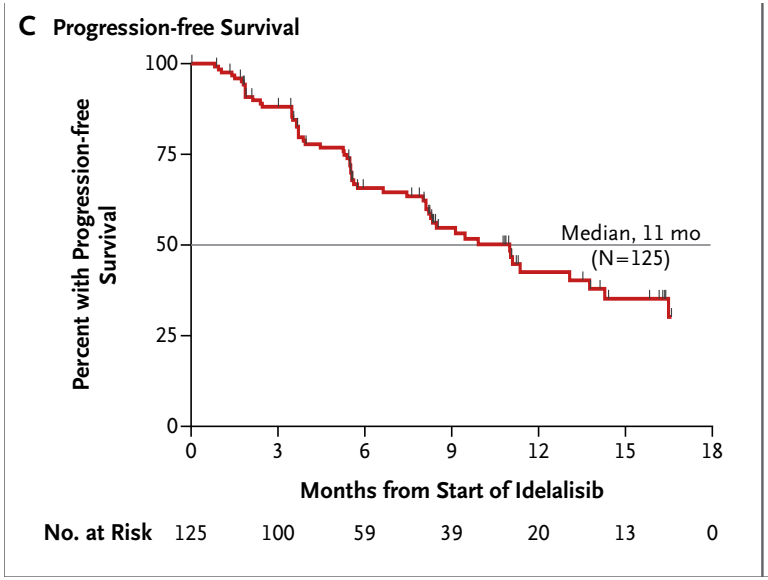
Gopal A, et al. N Eng J Med 2014

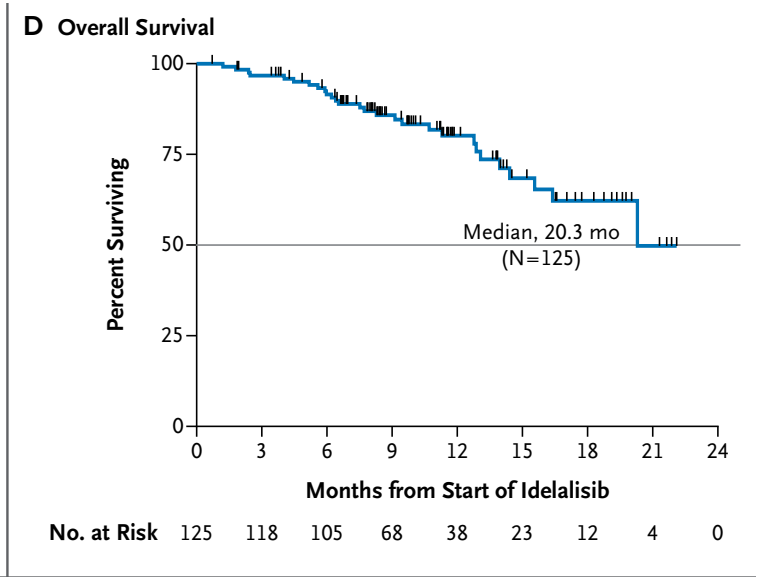
Phase 2 Study of PI3K-Delta Inhibitor Idelalisib in Patients With Double (Rituximab and Alkylating Agent)–Refractory Indolent B-Cell Non-Hodgkin Lymphoma: 125 patients



By Disease Group







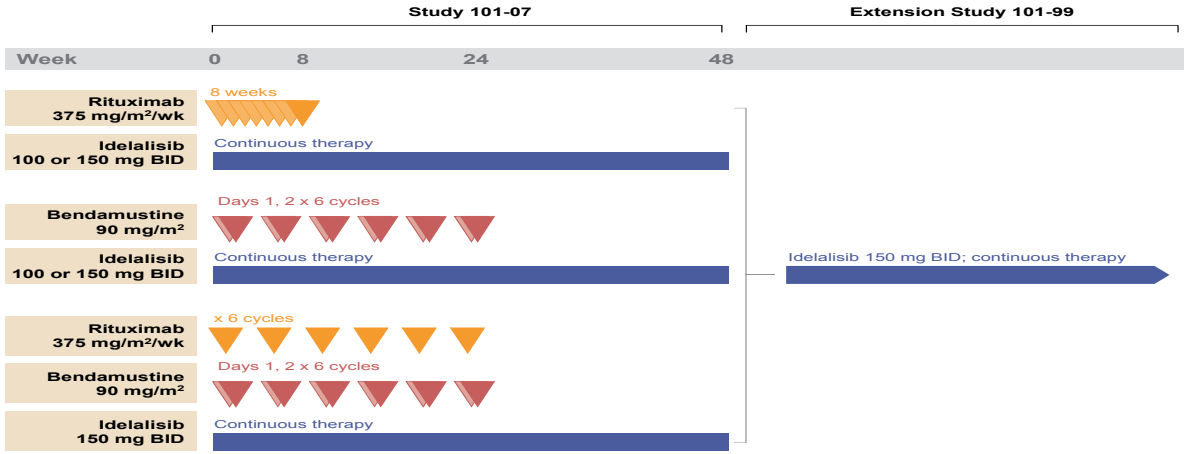
Gopal A, et al. N Eng J Med 2014

Adverse Events Occurring in >20% of Patients

Patients, n (%)	All Patients, N=79	
	All Grades	Grade ≥3
Pyrexia	43 (54)	2 (3)
Nausea	35 (44)	0
Fatigue	34 (43)	3 (4)
Diarrhea/colitis	31 (39)	12 (15)
Rash	30 (38)	7 (9)
Cough	28 (35)	0
Insomnia	18 (23)	0
Pneumonia	17 (22)	15 (19)
Upper respiratory infection	16 (20)	1 (1)
Laboratory Abnormalities		
ALT/AST elevation	44 (56)	13 (16)*
Neutropenia	44 (56)	32 (41)
Anemia	37 (47)	8 (10)
Thrombocytopenia	33 (42)	6 (8)

Gopal A, et al. N Eng J Med 2014

Idelalisib in Combination With Rituximab, Bendamustine, or Both, in Recurrent Indolent Non-Hodgkin Lymphoma: Phase 1/2 Results: 79 patients



- 3 non-randomized treatment groups; treatment regimen based on investigator's discretion
- Patients enrolled from April 2010 to May 2012 (US only)

Patient Characteristics	All Patients N=79	Idelalisib +		
		Rituximab n=32	Bendamustine n=33	Bendamustine/ Rituximab, n=14
Median age, y (range)	61 (37–84)	65 (40–84)	59 (37–80)	56 (48–76)
Bulky adenopathy, %*	48	50	52	36
Refractory disease, %†	42	34	39	64
Median prior therapies, n (range)	3 (1–11)	4 (1–11)	3 (1–10)	3 (1–7)
Rituximab	98	94	100	100
Alkylating agent	86	91	82	86
Anthracycline	53	56	49	57
Bendamustine	32	44	21	29
Purine analog	25	22	33	14

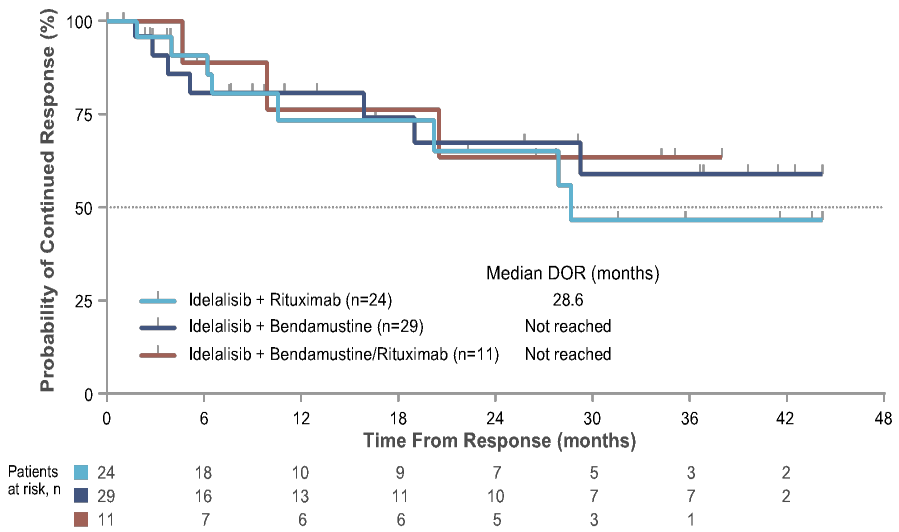
Sven De Vos et al ASH 2015

Idelalisib in Combination With Rituximab, Bendamustine, or Both, in Recurrent Indolent Non-Hodgkin Lymphoma: Phase 1/2 Results: 79 patients

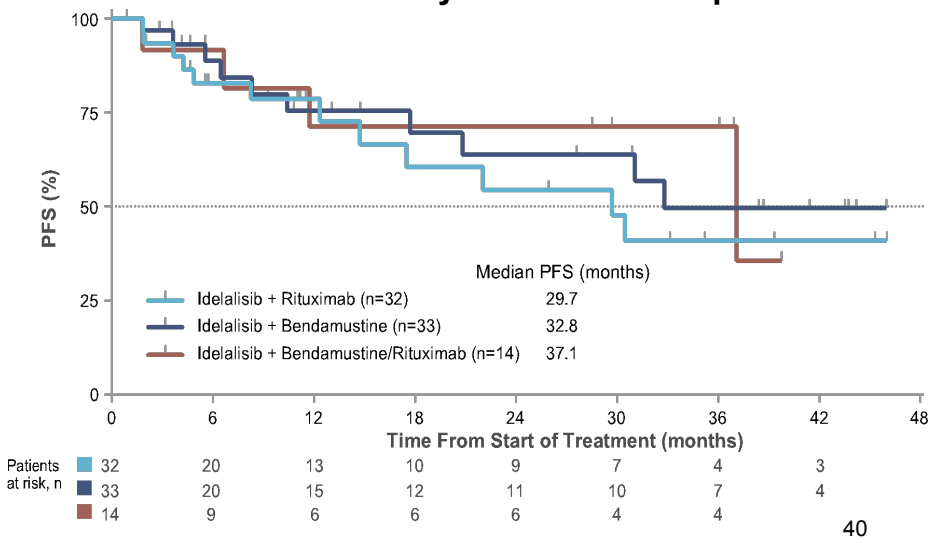
Best Overall Response Rate by Treatment Group

Patients, n (%)	All Patients N=79	Idelalisib +		
		Rituximab n=32	Bendamustine n=33	Bendamustine / Rituximab n=14
ORR, n (% [95% CI])*	64 (81 [71–89])	24 (75 [57–89])	29 (88 [72–97])	11 (79 [49–95])
Complete response	25 (32)	7 (22)	12 (36)	6 (43)
Partial response	39 (49)	17 (53)	17 (52)	5 (36)
Stable disease	7 (9)	4 (13)	3 (9)	0
Progressive disease	4 (5)	2 (6)	1 (3)	1 (7)
Not evaluable	4 (5)	2 (6)	0	2 (14)

DOR by Treatment Group

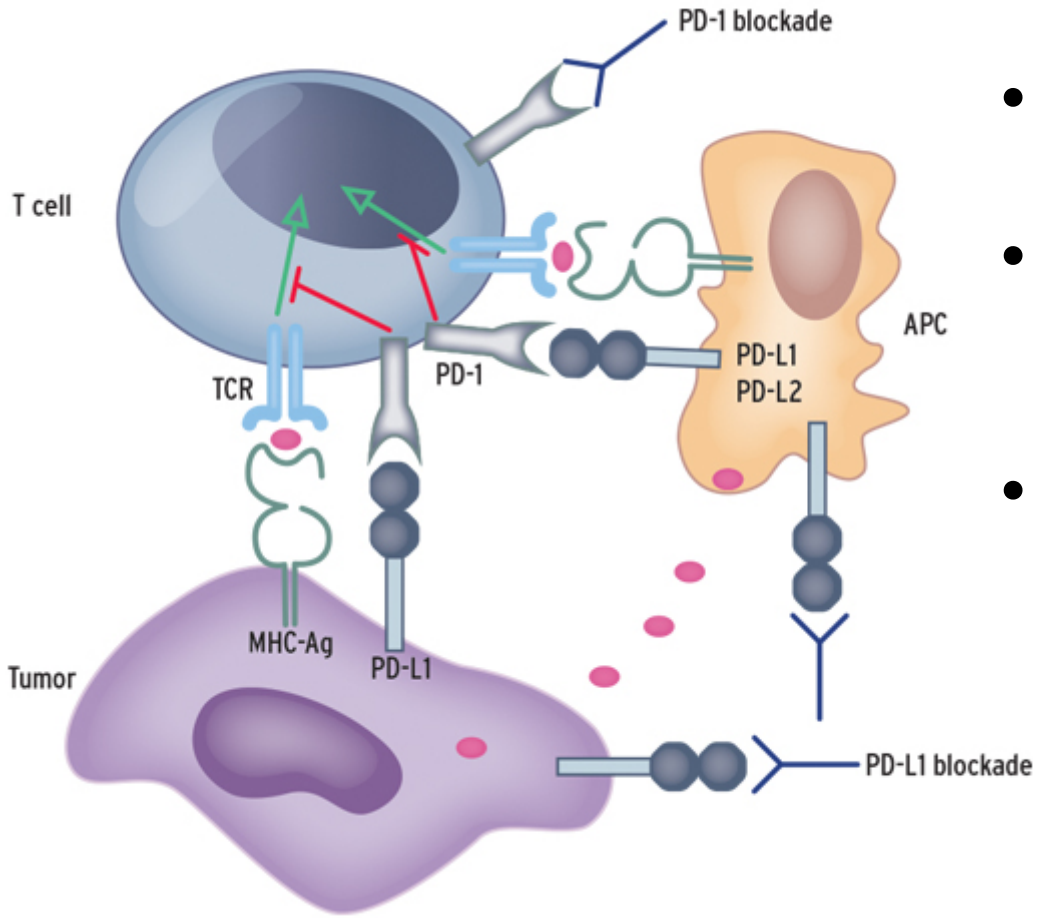


PFS by Treatment Group



Sven De Vos et al ASH 2015

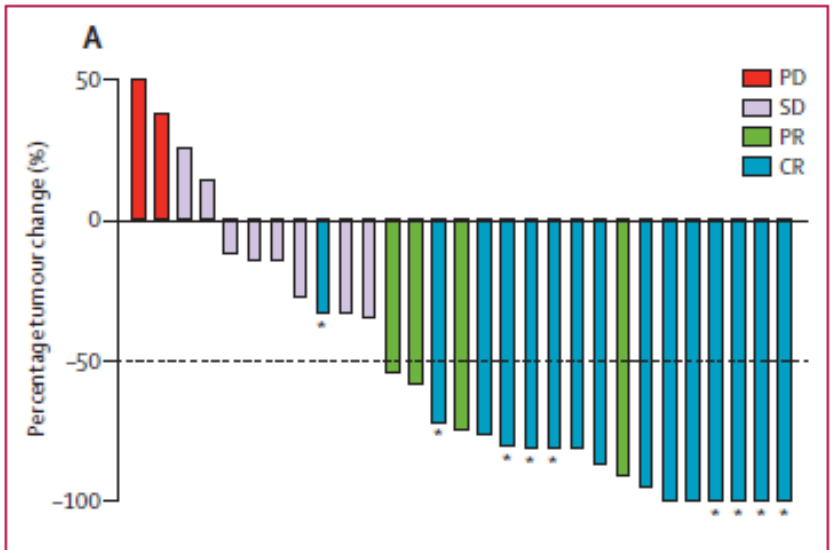
PD-1 Pathway and Immune Surveillance

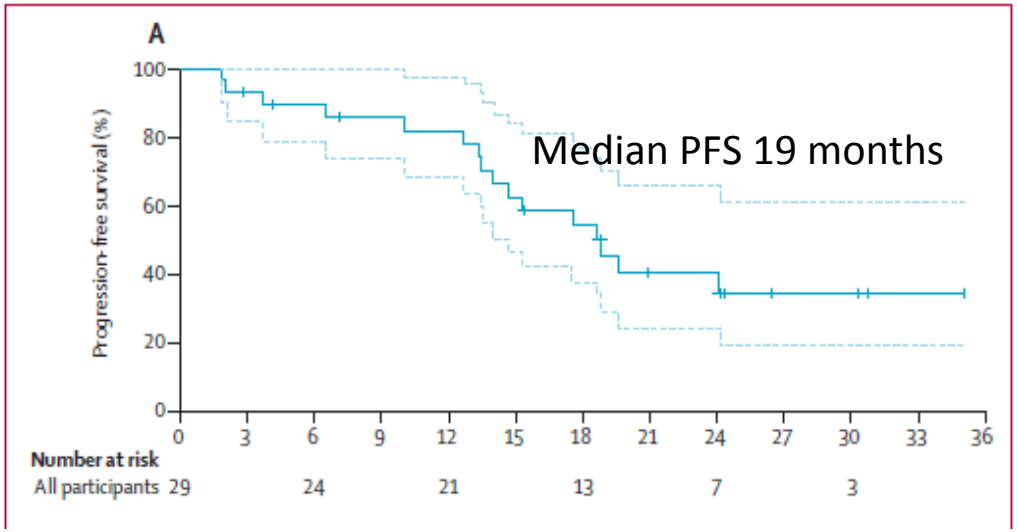


- PD-1 is expressed on the surface of activated T cells
- Its ligands, PD-L1 and PD-L2, are overexpressed in certain tumor cells
- Binding of PD-1 to its ligands inhibits T-cell activation, allowing tumors to evade the immune response

Safety and Activity of PD1 Blockade by Pidilizumab in Combination with Rituximab in Patients with Relapsed Follicular Lymphoma: a Single Group, Open-label, Phase 2 Trial

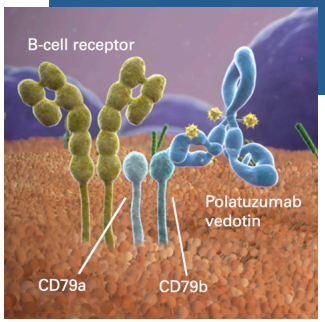
- Single arm phase 2 study: 32 patients
- Pidilizumab (3.0 mg/kg) every 4 weeks x 4 doses + rituximab administered weekly x 4 doses
  - Rituximab was started 2 weeks after 1st dose of pidlizumab
  - Up to 8 additional doses of pidilizumab every 4 weeks could be administered to patients whose disease did not progress on above
  - Median number infusion: 10
  - ORR 66% , CR 52%



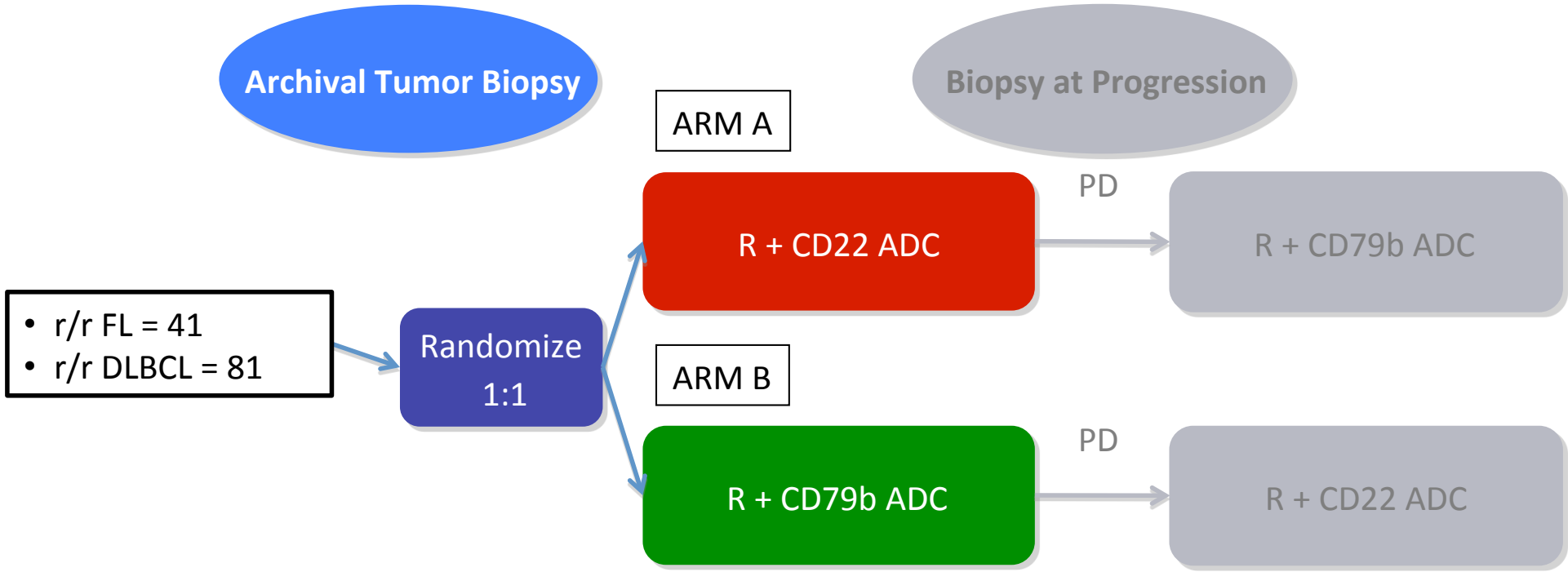


Westin J, Lancet Oncol. 2014 January ; 15(1): 69–77

Anti-CD79b Antibody-Drug Conjugate (ADC): DCDS4501A Polatuzumab Vedotin



Preliminary Results of a Phase II Randomized Study (ROMULUS) of antiCD22 ADC DCDT2980S or antiCD79 ADC DCDS4501A Plus Rituximab in Patients with Relapsed/Refractory NHL



Rituximab (R) (375 mg/m^2) + ADC (2.4 mg/kg) administered in every-21-day cycles up to one year

Morschhauser F, et al. EHA 2014

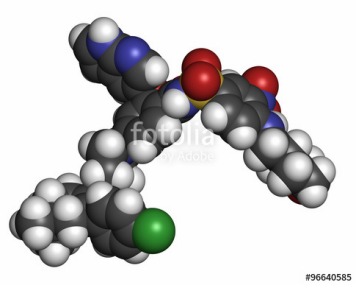
Anti-CD79b Antibody-Drug Conjugate (ADC): DCDS4501A Polatuzumab Vedotin

Preliminary Results of a Phase II Randomized Study (ROMULUS) of antiCD22 ADC DCDT2980S or antiCD79 ADC DCDS4501A Plus Rituximab in Patients with Relapsed/ Refractory NHL

RESPONSE ANALYSIS	DLBCL		FL	
	R+CD22 ADC (N=42)	R+CD79b ADC (N=39)	R+CD22 ADC (N=21)	R+CD79b ADC (N=20)
ORR, n (%)	**24 (57%)**	**22 (56%)**	**13 (62%)**	**14 (70%)**
CR	10 (24%)	6 (15%)	2 (10%)	8 (40%)
PR	14 (33%)	16 (41%)	11 (52%)	6 (30%)
SD	3 (7%)	4 (10%)	6 (29%)	6 (30%)
PD	7 (21%)	11 (30%)	1 (5%)	0
Not evaluable	8 (19%)	2 (5%)	1 (5%)	0
Median DOR, mo (95%CI)	6.0 (2.9-12.2)	**NR (2.6-NR)**	5.8 (2.6-10.1)	**NR (5.7-NR)**

Morschhauser F, et al. EHA 2014

A Phase 1 Study of **Venetoclax** (ABT-199 / GDC-0199) Monotherapy in Patients with Relapsed/Refractory Non-Hodgkin Lymphoma



Venetoclax is a selective, potent, orally bioavailable BCL-2 inhibitor

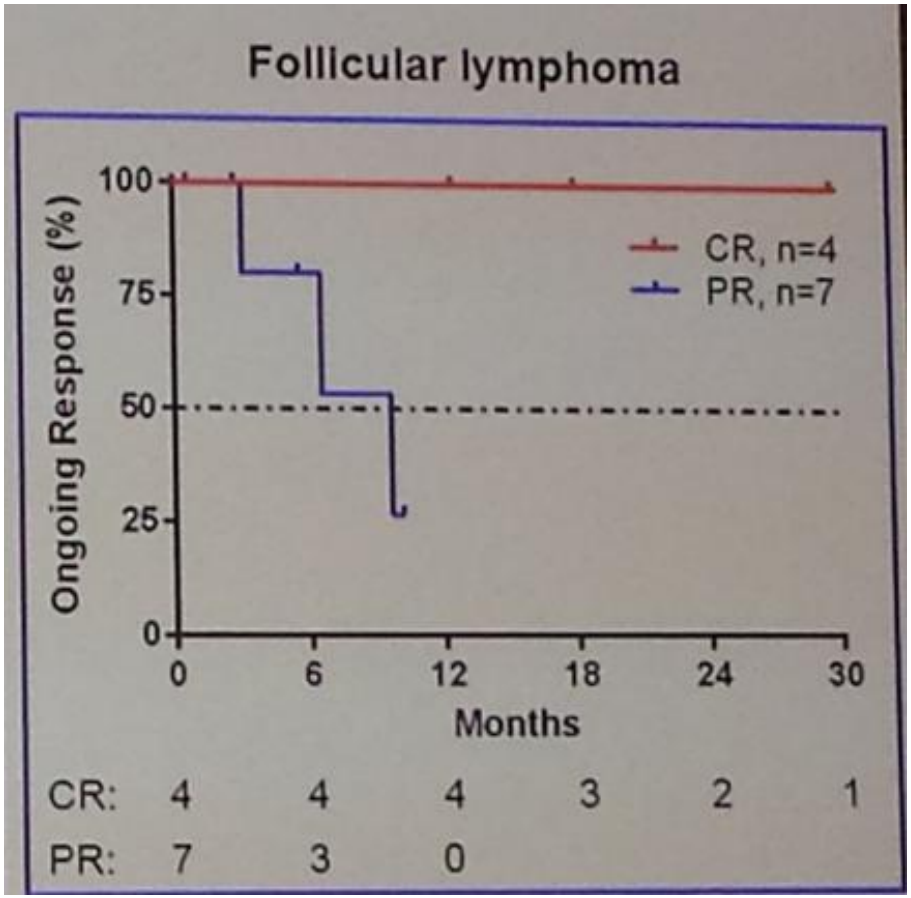
Venetoclax was administered once-daily. Stepwise, intrapatient dose ramp-up to mitigate the risk of tumor lysis syndrome (200 to 1200 mg in 3 weeks)

Characteristic, n	
Age, years	Med (ran
Prior therapies	Med
	Ritu
Bulky nodes	>5 c
	>10
LDH	> U Nor

Best Objective Response, n (%)	All N=106	MCL n=28	FL n=29	DLBCL n=34
Overall Response	47 (44)	21 (75)	11 (38)	6 (18)
CR	14 (13)	6 (21)	4 (14)	4 (12)
PR	33 (31)	15 (54)	7 (24)	2 (6)
SD	32 (30)	5 (18)	17 (59)	8 (24)
PD	23 (22)	1 (4)	1 (4)	19 (56)

Gerecitano JF et al ASH 2015, ABSTR 254

A Phase 1 Study of **Venetoclax** (ABT-199 / GDC-0199) Monotherapy in Patients with Relapsed/Refractory Non-Hodgkin Lymphoma



Median DOR 10 months (1-30)

5% discontinued due to AE.

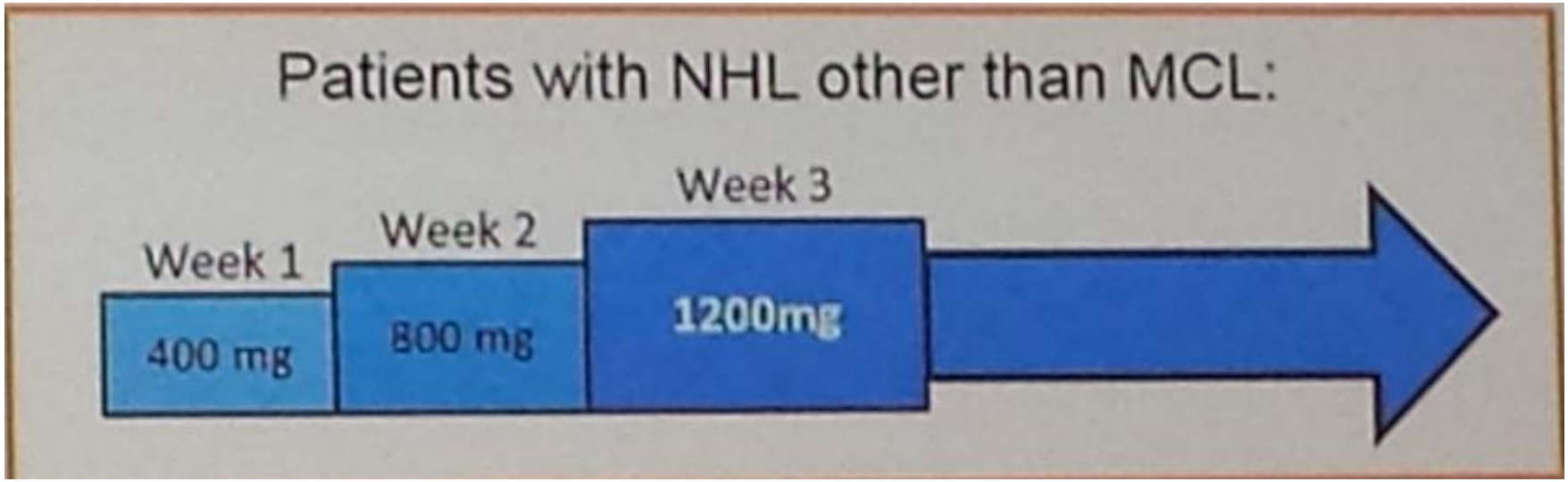
Treatment emergent-AEs of any grade: diarrhea and fatigue (each 44%), nausea (33%) and vomiting (23%), anemia (14%).

SAE in ≥2 pts were hyponatremia (4%), and dehydration, diarrhea, and febrile neutropenia (each 3%).

No new events of laboratory TLS and no pts had clinical TLS.

Gerecitano JF et al ASH 2015, ABSTR 254

A Dose-Escalation Study of **Venetoclax (ABT-199/GDC-0199) in Combination with Bendamustine and Rituximab** in Patients with Relapsed or Refractory Non-Hodgkin's Lymphoma.



3, 7, or 28 consecutive days of each 28-day cycle

- <u>Ongoing phase 1, open-label, dose-escalation study, with BR standard dose</u>
- Patients had a median of 3 (range: 1–8) prior therapies.
- Most common grade 3/4 AEs (≥10%) during combination therapy were neutropenia (32%, FN 9%), lymphocyte count decrease (26%), thrombocytopenia (21%), anemia (15%), and leukopenia (13%). G-CSF encouraged (febrile neutropenia 9%).
- MTD not reached (1200 ongoing). ORR 78% (CR 30%) in 27 FL.

De Vos S et al ASH 2015, ABSTR 255

Long-Term Follow-up and Analysis of Dose Groups with **Ibrutinib** in Relapsed **Follicular Lymphoma**

Patient Characteristics and Efficacy (8+8)		
	Low dose (MAX420mg)	**Higher dose** (>420mg*)
Median age, yrs (range)	57 (48-70)	62.5 (41-71)
Median no. of prior therapies	3 (1-4)	2 (1-5)
FLIPI score, % (low / interm/ high)	25 / 38 / 38	13 / 38 / 50
Median treatment duration, months (range)	3.8 (0.5-11.1)	12.4 (0.2-61.5)
ORR, n (%) CR, n (%)	2 (25) 0 (0)	5 (63) 3 (38)
Median DOR, months (range)	3.4 (1.8-4.9)	12.3 (4.8-51.3)
10-month PFS, %	35.7	70
Median OS, months (95% CI)	NR	NR

Higher doses associated with increased response rates and prolonged PFS.
No increase of AEs or cumulative toxicity.

Single-agent ibrutinib at 560 mg/day in pts with R/R FL is ongoing (Bartlett Blood 2014), and in chemoimmunotherapy refractory FL.

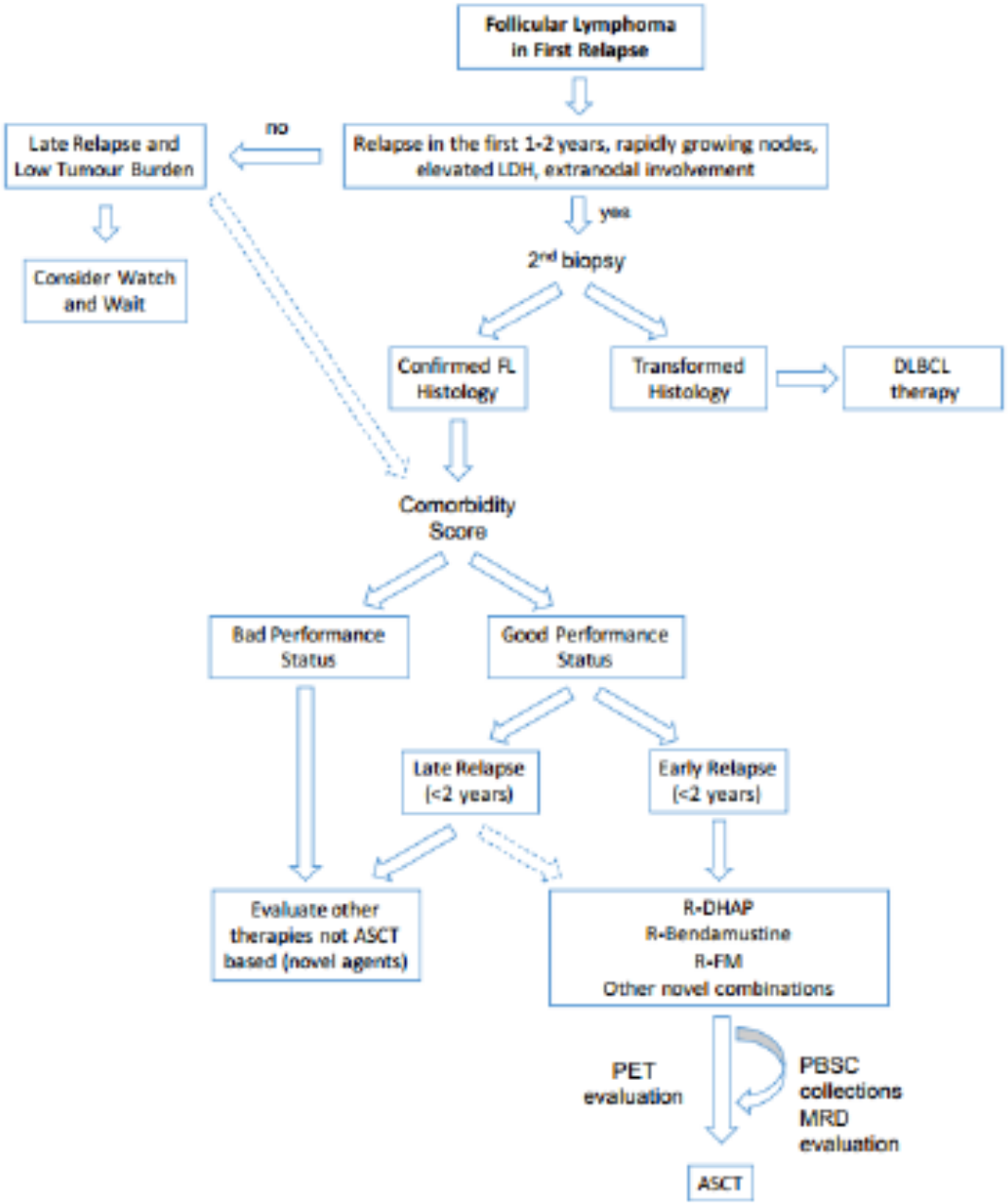
*≥8.3 mg/kg/day

Fowler N et al, ASH 2015, ABSTR 2706

Conclusions

- A personalized treatment is now feasible and it is worthy to be tested with different tools such as:
  - PET and MRD analysis allow a better assessement of the quality of response
  - Duration of response
  - No impact of prior Rituximab treatment
- Chemo-free regimens are available with promising results however require a more prolonged treatment (for all life?), higher cost and may have unexpected toxicities
- Until now, no novel drugs or combinations have shown superior or non inferior clinical outcome compared to the results of ASCT
- Transplant based treatments are affected by signficant toxicities and require carefully and multidisciplinar evaluation.

Conclusions



Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

High tumor burden
Outside clinical studies

	< 65 yrs	> 65 yrs
Relapse/progression	Dependent on first-line regimen and remission duration • Chemoimmunotherapy + rituximab maintenance (every 3 months, up to 2 years) • Alternatively, radioimmunotherapy • In early relapses, discuss high-dose consolidation with ASCT[b]	Dependent on first-line regimen and remission duration • Chemoimmunotherapy (e.g BR, R-CHOP, R-CVP) +/- rituximab maintenance (every 3 months, up to 2 years) • Alternatively, radioimmunotherapy
Later relapse/progression	Dependent on prior regimens and remission duration • Chemoimmunotherapy (long prior remission) + rituximab maintenance (if not previously applied) • In early relapses, discuss high-dose consolidation with ASCT[b] • Radioimmunotherapy or rituximab monotherapy • Idelalisib (double refractory cases) • In selected cases, discuss allogeneic transplantation	Dependent on prior regimens and remission duration • Chemoimmunotherapy (long prior remission) + rituximab maintenance (if not previously applied) • Radioimmunotherapy or rituximab monotherapy • Idelalisib (double refractory cases)

- High-dose chemotherapy with ASCT prolongs PFS and OS and should be considered, especially in patients who experience short-lived first remissions
- New approaches, including lenalidomide–rituximab and additional inhibitors of the B-cell signalling pathway, have proved active in phase II studies, but to date their benefit has yet to be confirmed in randomised phase III studies.
- The PI3K inhibitor idelalisib has been registered in double-refractory FL

Dreyling et al, Ann Oncol Volume 27 | Supplement 5 |September 2016