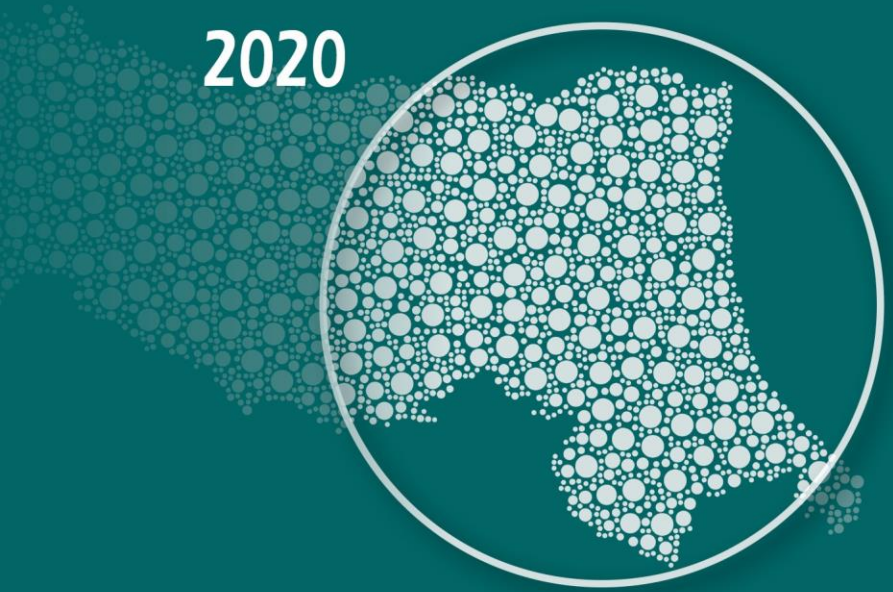


Progetto Ematologia Romagna

NOVITÀ NEI LINFOMI A BASSO GRADO

Introduzione

Alessandro Broccoli

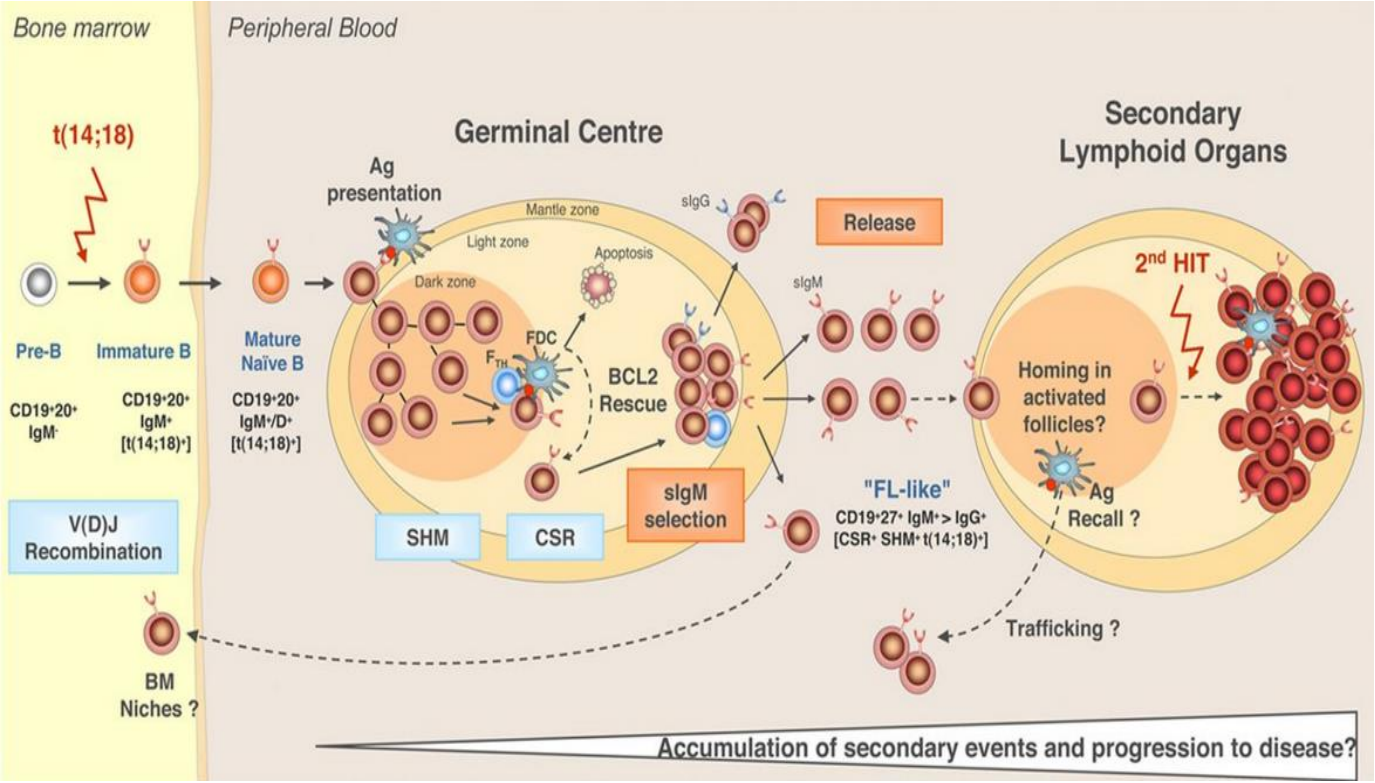
Istituto di Ematologia “L. e A. Seràgnoli” – Università di Bologna

LINFOMA FOLLICOLARE

- **Linfoma follicolare**: il paradigma di linfoma indolente.
- Malattia a lenta crescita, solo raramente caratterizzata da sintomi sistemici.
- Elevati tassi di risposta alla terapia standard di prima linea (chemioimmunoterapia) con tuttavia tendenza alla ricaduta o alla trasformazione.

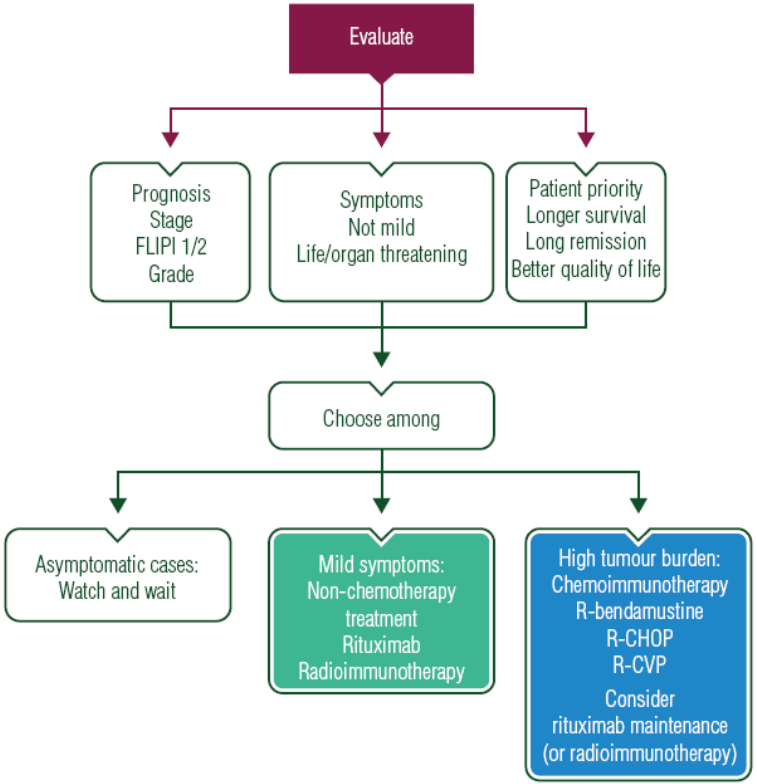
- **Stadio** (estensione di malattia limitata/diffusa): determina l'approccio iniziale al paziente (tipo di trattamento/quando trattare).
- **Malattia sintomatica (taglia di malattia o *tumor burden*)**: aspetto su cui si basa la decisione terapeutica (*watch and wait* / inizio di una chemioimmunoterapia).

PATOGENESI



Kahl BS. *Blood*, 2016; 127: 2055-2063

ELEMENTI DECISIONALI: APPROCCIO DI PRIMA LINEA

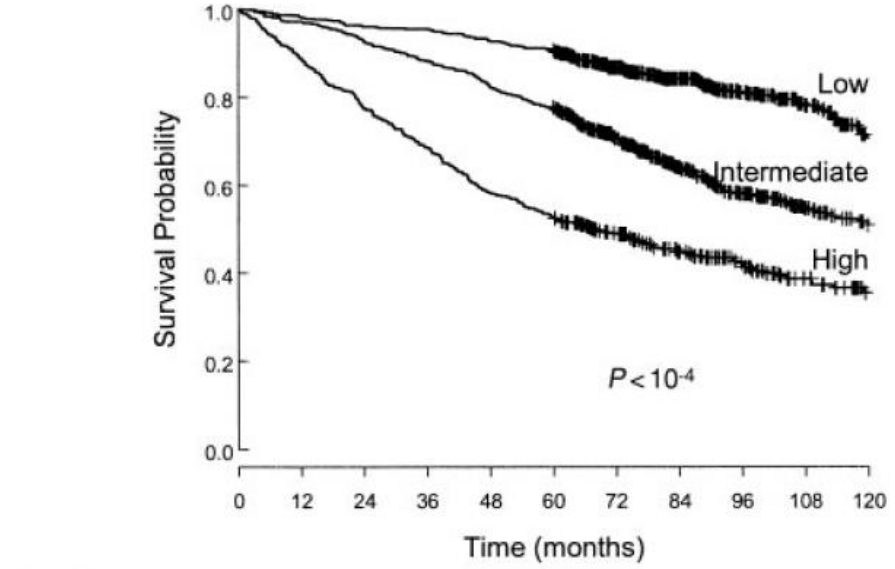


Dreyling M. *Ann Oncol*, 2016; 27(S5): v83-v90

FLIPI

Parameter	Adverse factor	RR	95% CI
Age	≥ 60 y	2.38	2.04-2.78
Ann Arbor stage	III-IV	2.00	1.56-2.58
Hemoglobin level	< 120 g/L	1.55	1.30-1.88
Serum LDH level	> ULN	1.50	1.27-1.77
Number of nodal sites	> 4	1.39	1.18-1.64

Risk group	Number of factors*	Distribution of patients, %	5-year OS, % (SE)	10-year OS, % (SE)	RR	95% CI
Low	0-1	36	90.6 (1.2)	70.7 (2.7)	1.0	NA
Intermediate	2	37	77.6 (1.6)	50.9 (2.7)	2.3	1.9-2.8
High	≥ 3	27	52.5 (2.3)	35.5 (2.8)	4.3	3.5-5.3



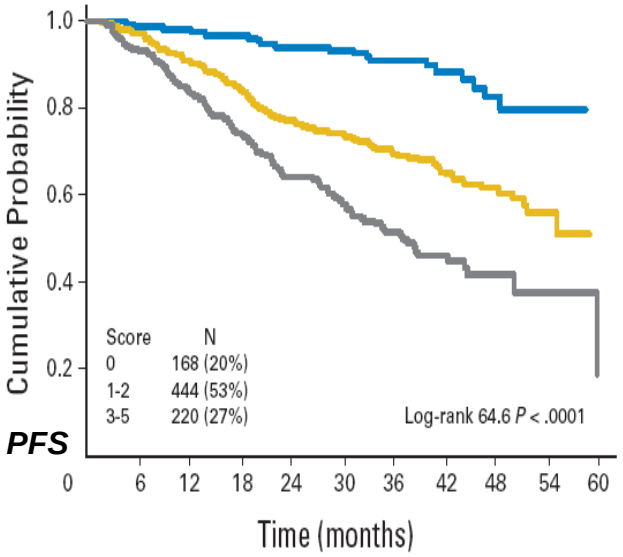
No. of Events											
Low	-	12	25	29	46	60	83	95	106	113	125
Intermediate	-	19	49	79	118	150	192	225	247	255	261
High	-	54	109	152	202	229	245	260	268	274	278

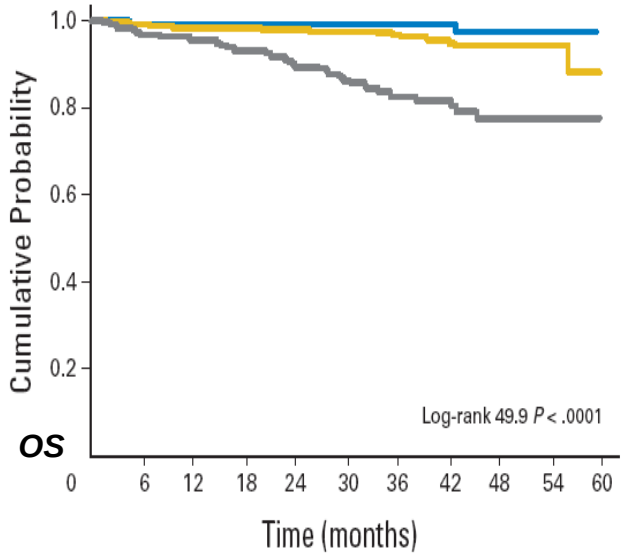
No. at Risk											
Low	641	629	616	612	595	581	450	337	241	157	93
Intermediate	670	651	621	591	552	519	385	263	178	108	68
High	484	430	375	332	282	255	193	139	98	56	33

Solal-Céligny P. *Blood*, 2004; 104: 1258-1265

FLIPI2

- β_2 microglobulina aumentata
- Coinvolgimento midollare
- Hb < 12 g/dL
- Età > 60 anni
- Diametro linfonodale > 6 cm



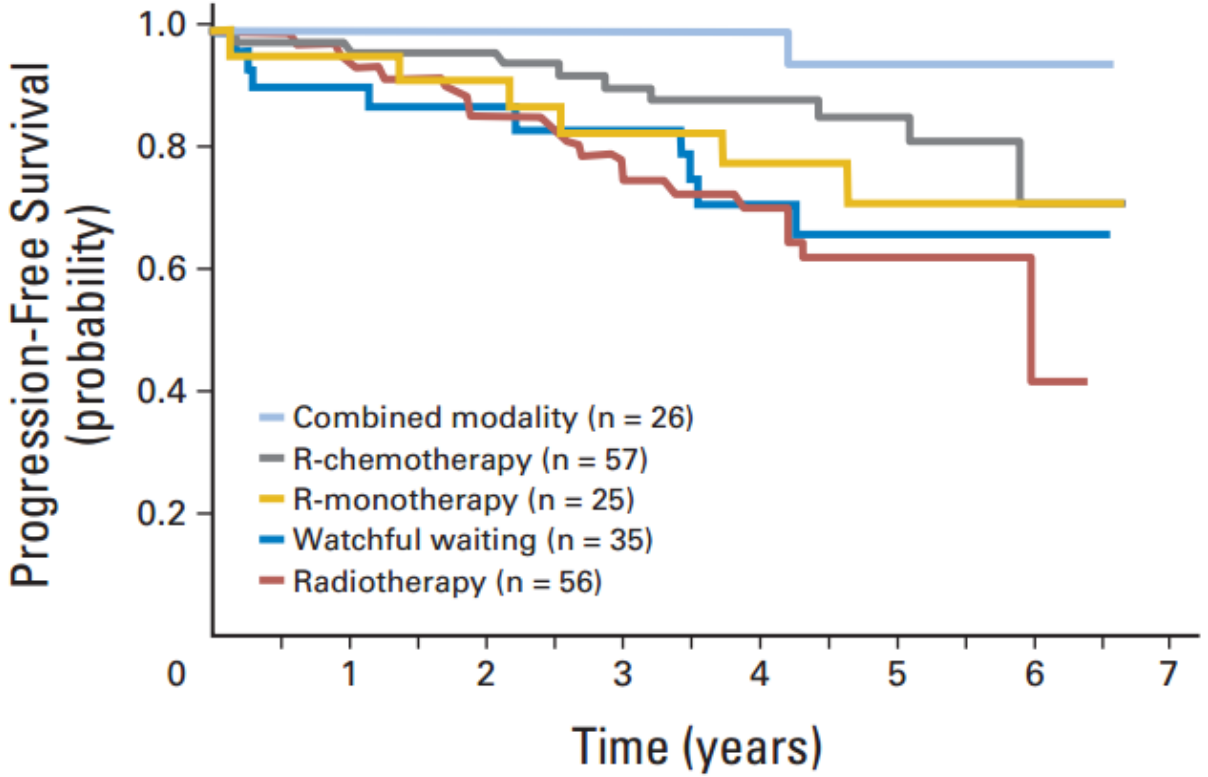


Outcome and Relative Risk of Progression According to Risk Group as Defined by FLIPI2 (N = 832)

			PFS					
			3-Year		5-Year			
Risk Group	No. of Factors	Patients (%)	%	SE	%	SE	HR	95% CI
Low	0	20	90.9	2.4	79.5	5.0	1.00	—
Intermediate	1-2	53	69.3	2.4	51.2	5.7	3.19	2.00 to 5.15
High	3-5	27	51.3	3.7	18.8	13	5.76	3.53 to 9.40
High *v* intermediate							1.81	1.40 to 2.33

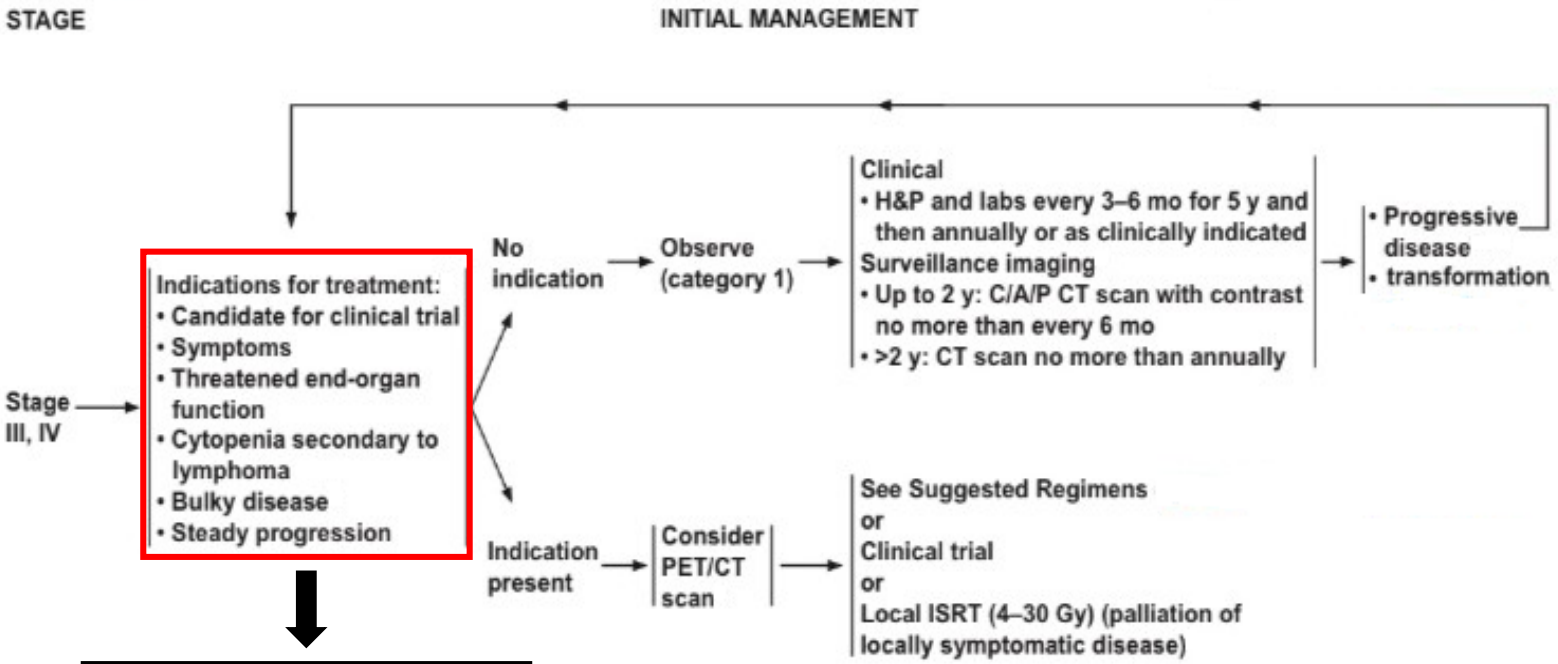
Federico M. *J Clin Oncol*, 2009; 27: 4555-4562

TERAPIA DI PRIMA LINEA (stadio iniziale)



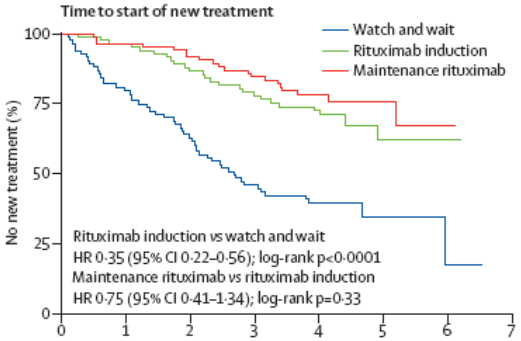
Friedberg JW. *J Clin Oncol*, 2012; 30: 3368-3375

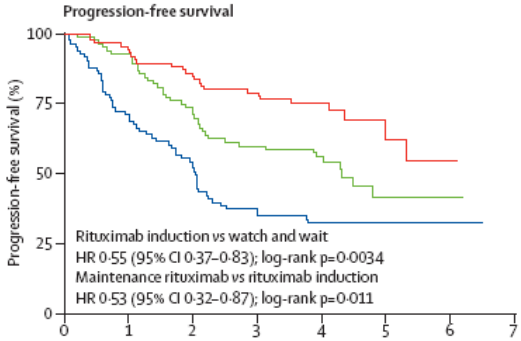
TERAPIA DI PRIMA LINEA (stadi avanzati)

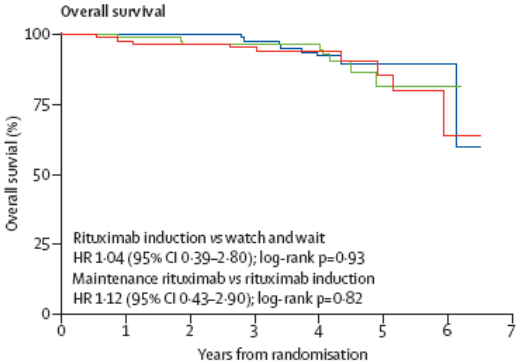


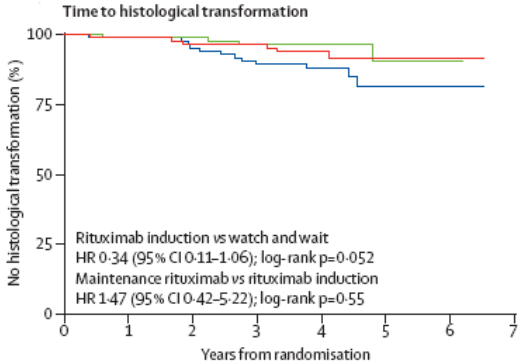
Tumor burden dictates the initial strategy of management

DECISIONI TERAPEUTICHE (ridotta taglia di malattia)





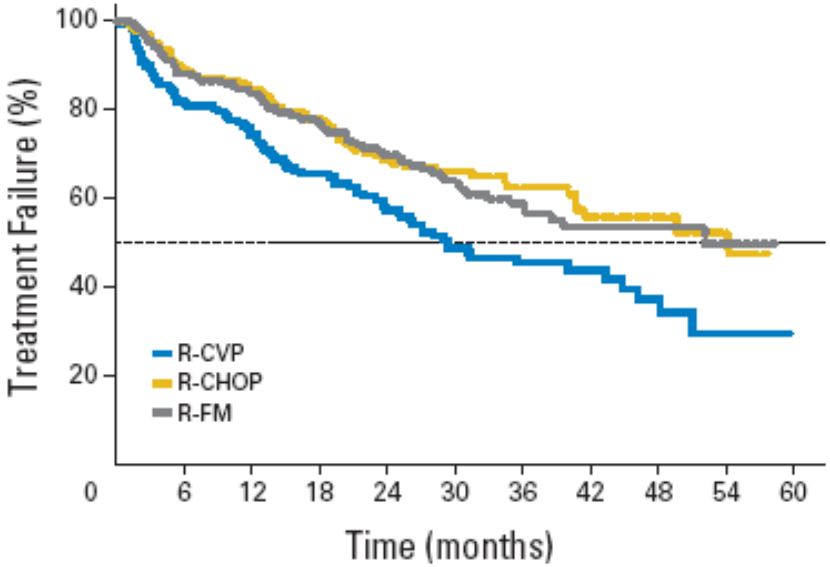




Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial

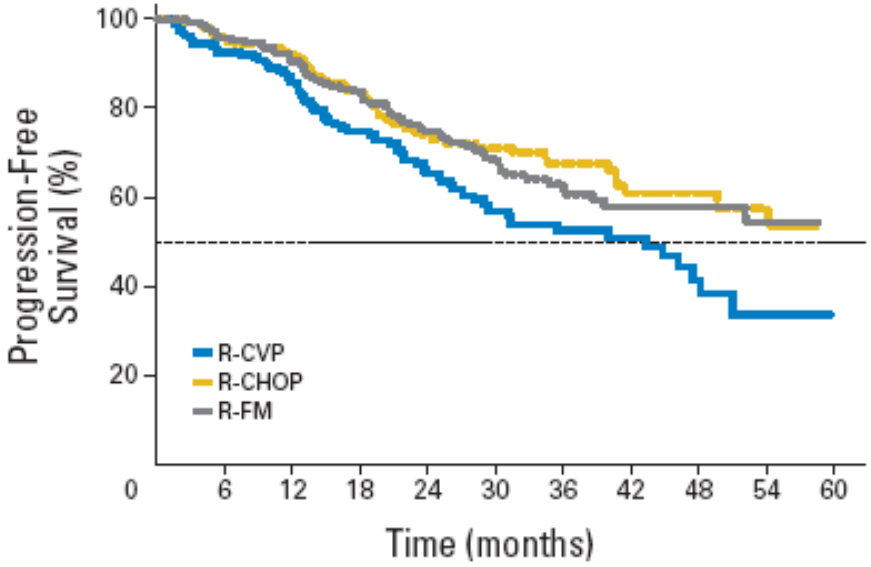
Ardeshna KM. *Lancet Oncol*, 2014; 15: 424-435

DECISIONI TERAPEUTICHE (elevata taglia di malattia)



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



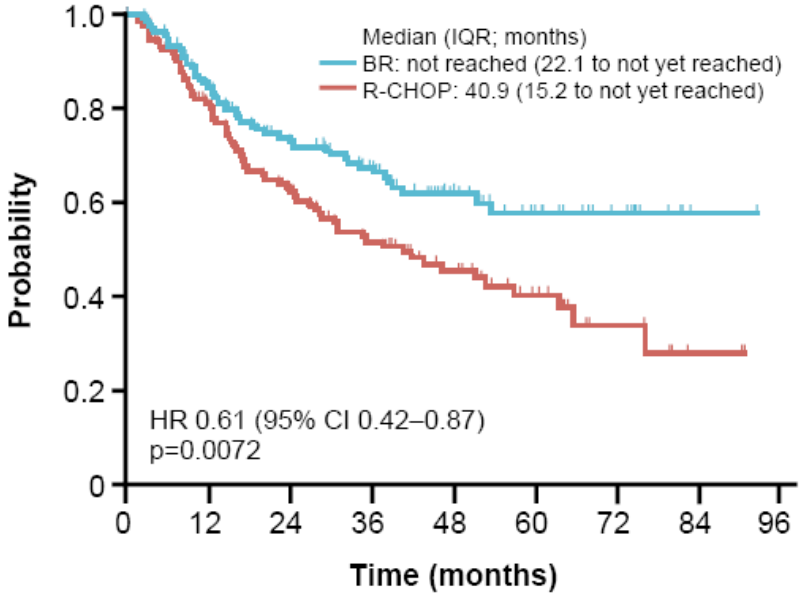
No. at risk

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

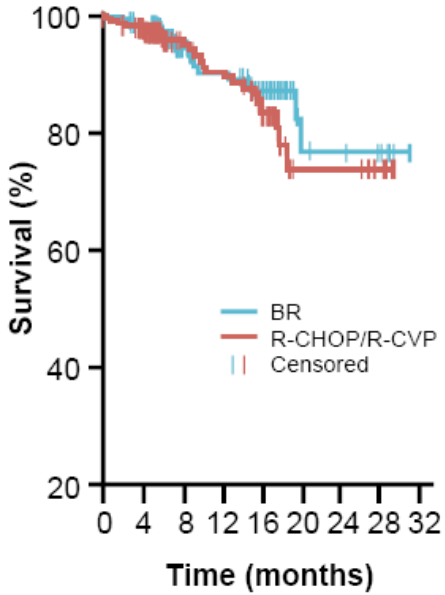
DECISIONI TERAPEUTICHE (elevata taglia di malattia)

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



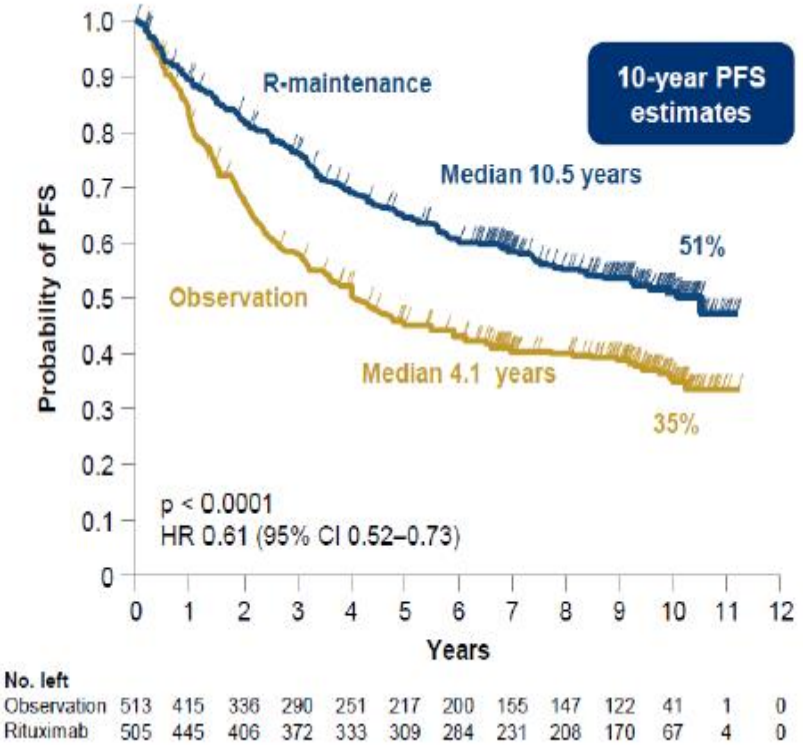
Rummel MJ. *Lancet*, 2013; 381: 1203-1210

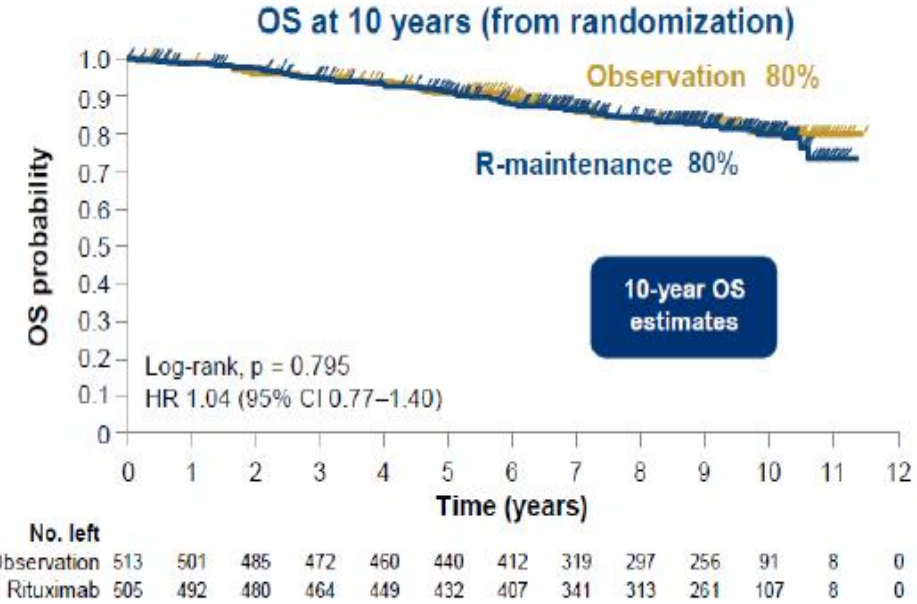
Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study



Flinn IW. *Blood*, 2014; 123: 2944-2952

MANTENIMENTO CON RITUXIMAB

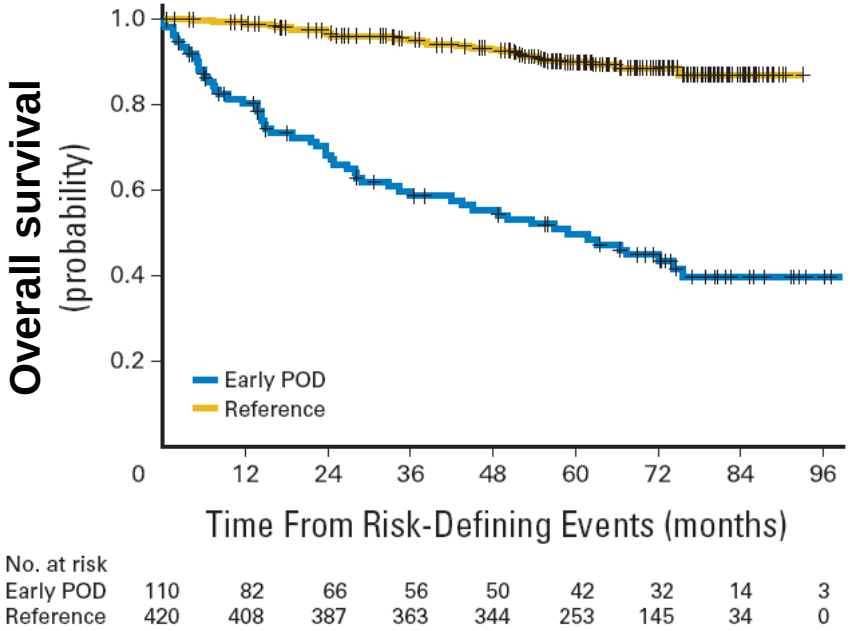




Salles G. *Lancet*, 2011; 377: 42-51 – Updated ASH 2017

SIGNIFICATO DELLA PROGRESSIONE PRECOCE

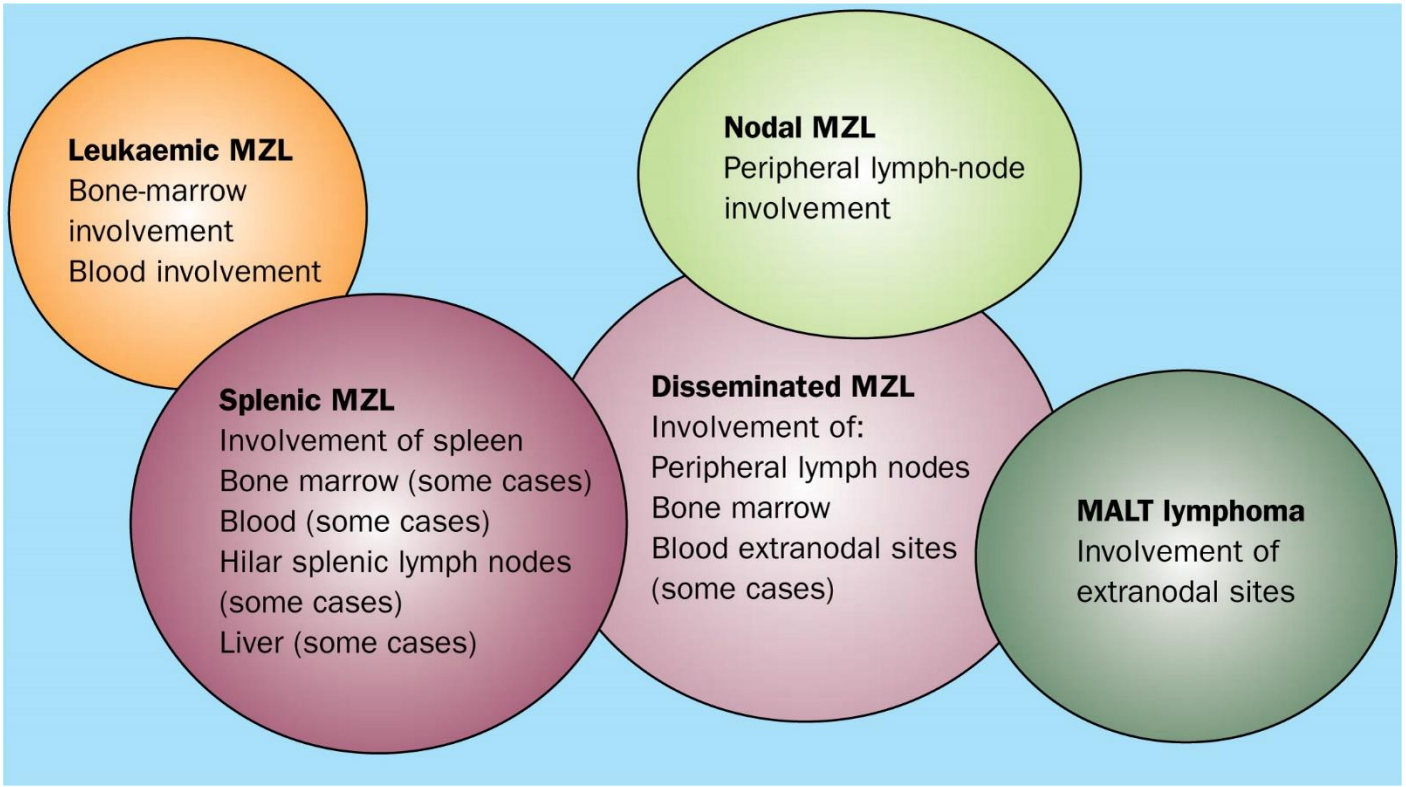
- 20-30% dei pazienti con linfoma follicolare mostra una progressione di malattia entro 24 mesi dalla terapia di induzione o di mantenimento.



Casulo C. *J Clin Oncol*, 2015; 33: 2516-2522

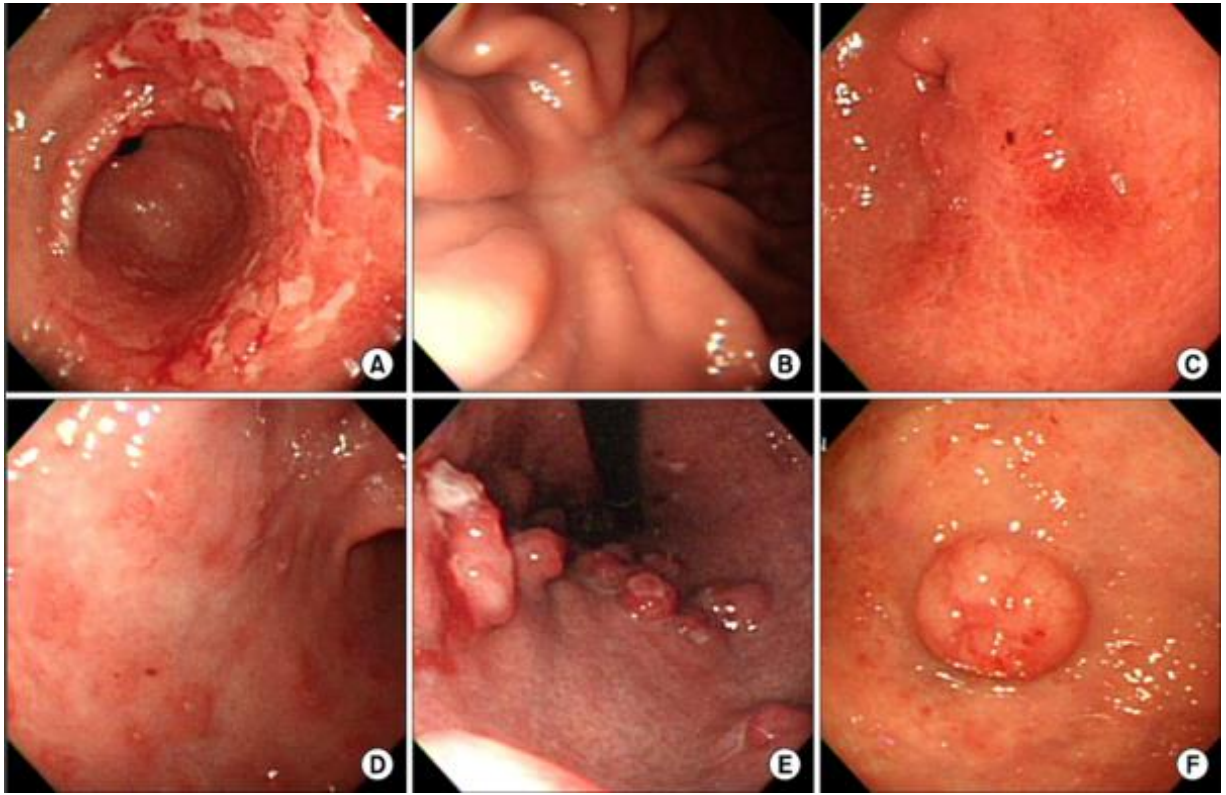
LINFOMI DELLA ZONA MARGINALE

CLASSIFICAZIONE CLINICA

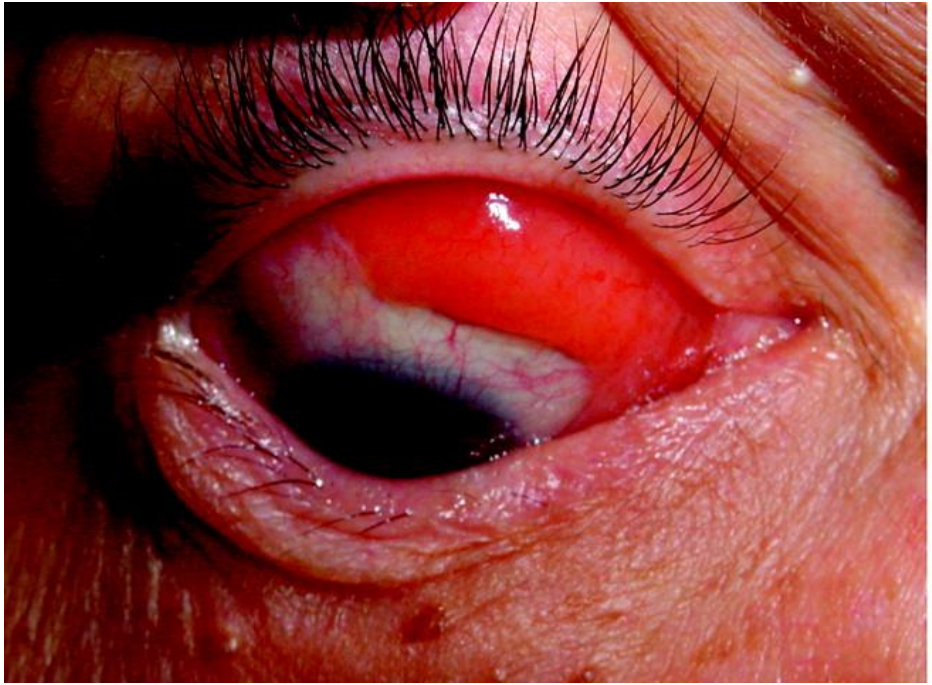


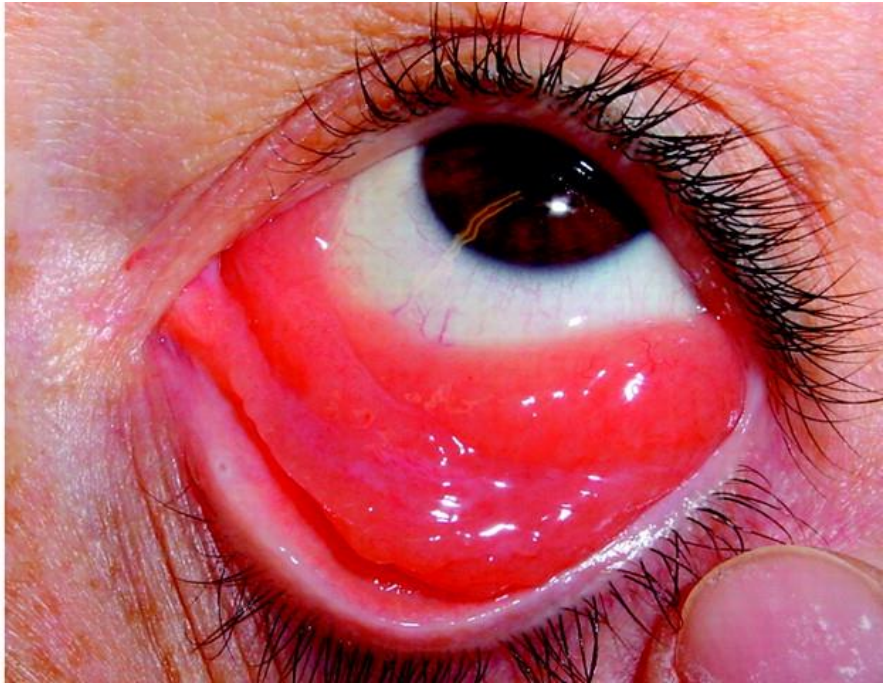
Thieblemont C. *Lancet Oncol*, 2003; 4: 95-103

LINFOMA MALT GASTRICO

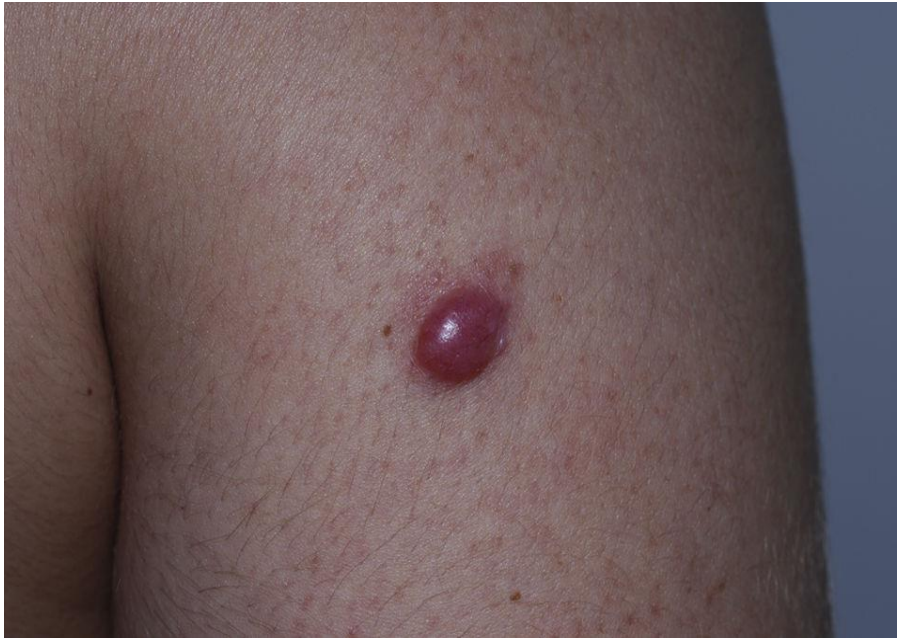


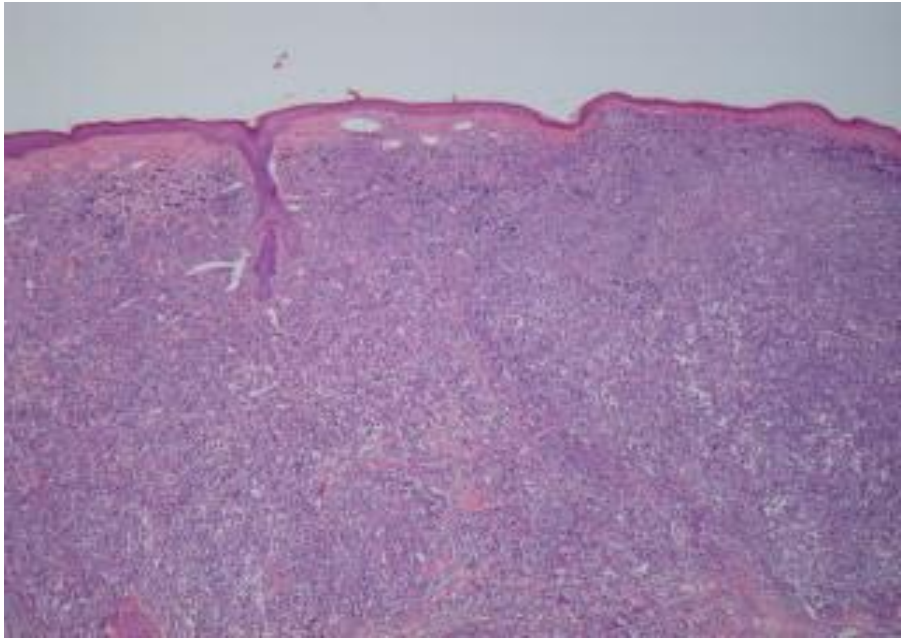
LINFOMA MALT DELLA CONGIUNTIVA



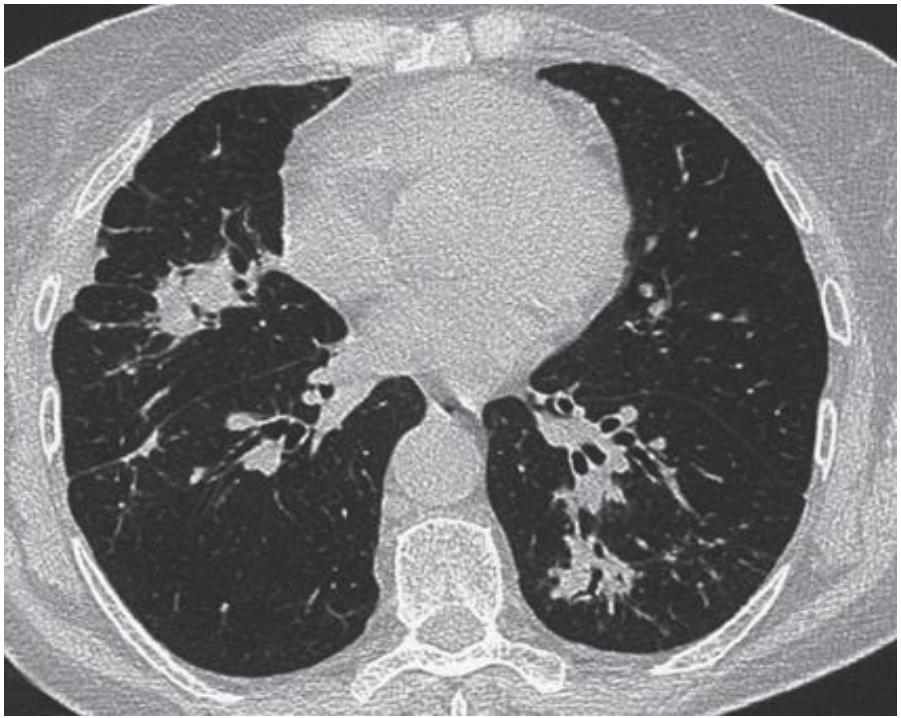


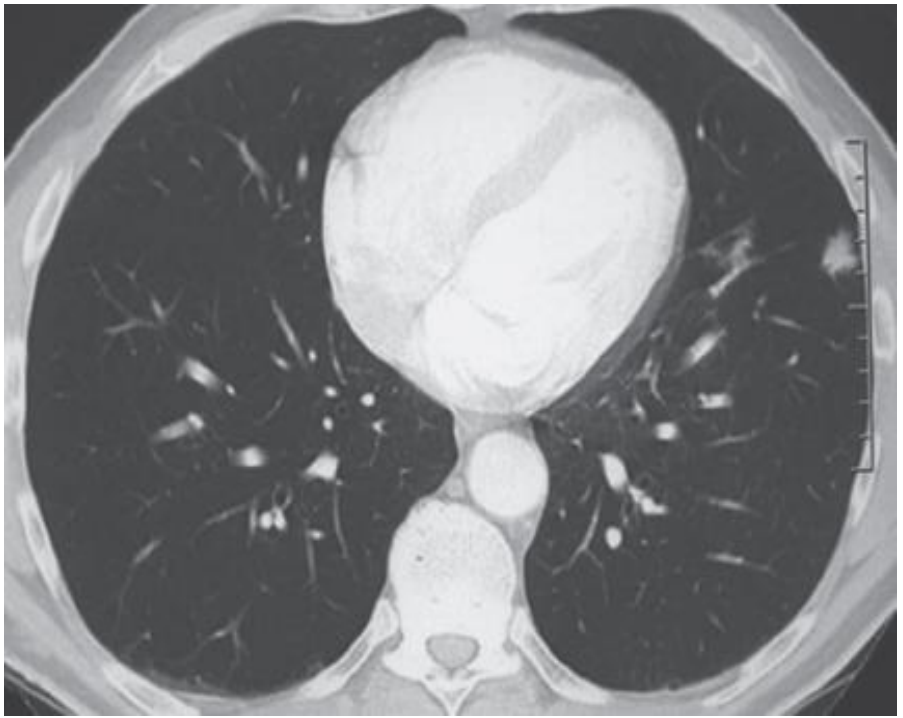
LINFOMA MALT CUTANEO





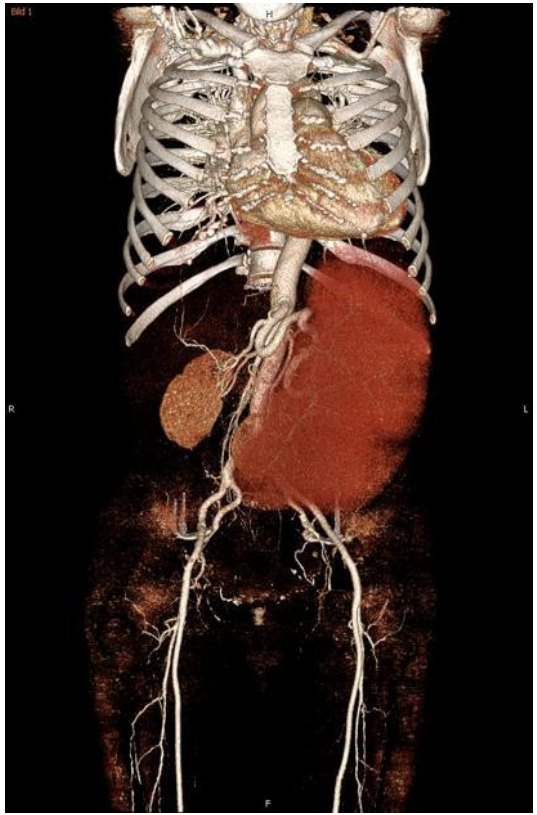
LINFOMA MALT AD INSORGENZA BRONCHIALE

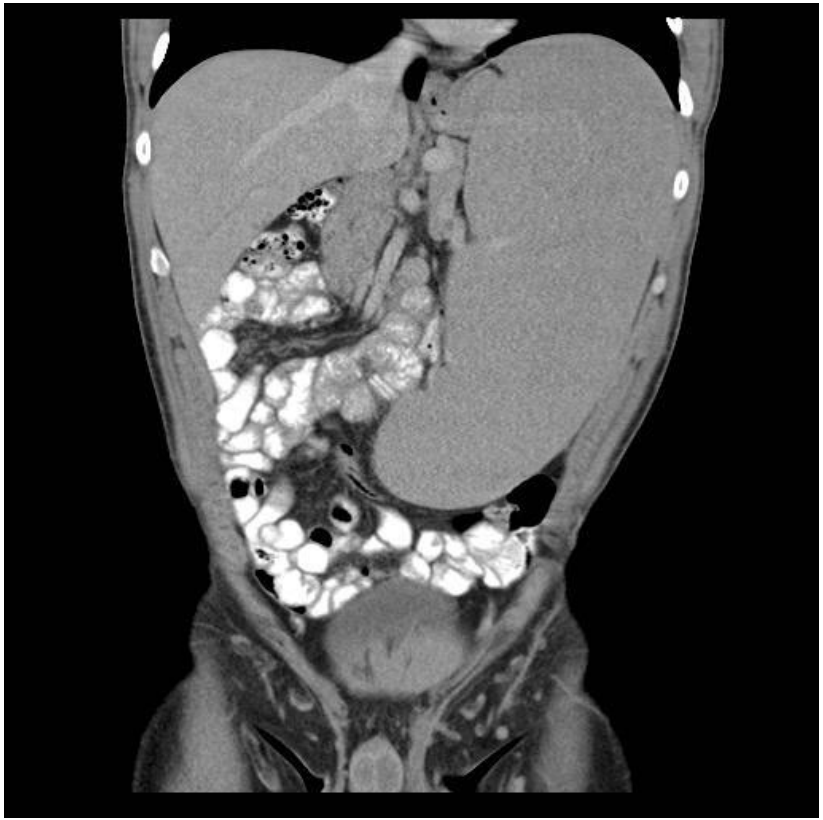




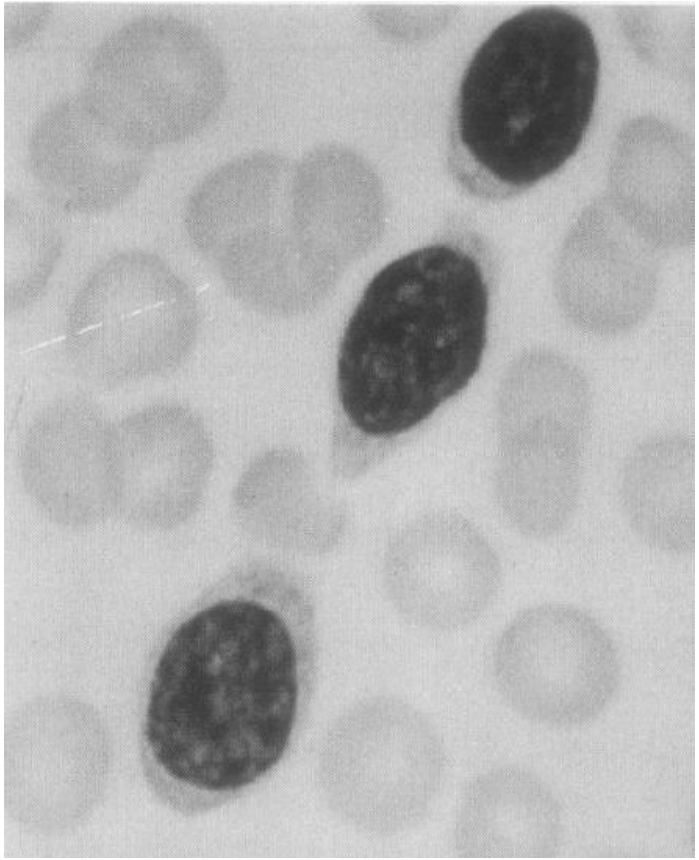
Zinzani PL. *Clin Lymphoma Myeloma Leuk*, 2007; 7: 566-572

LINFOMA MARGINALE SPLENICO





LINFOCITI VILLOSI

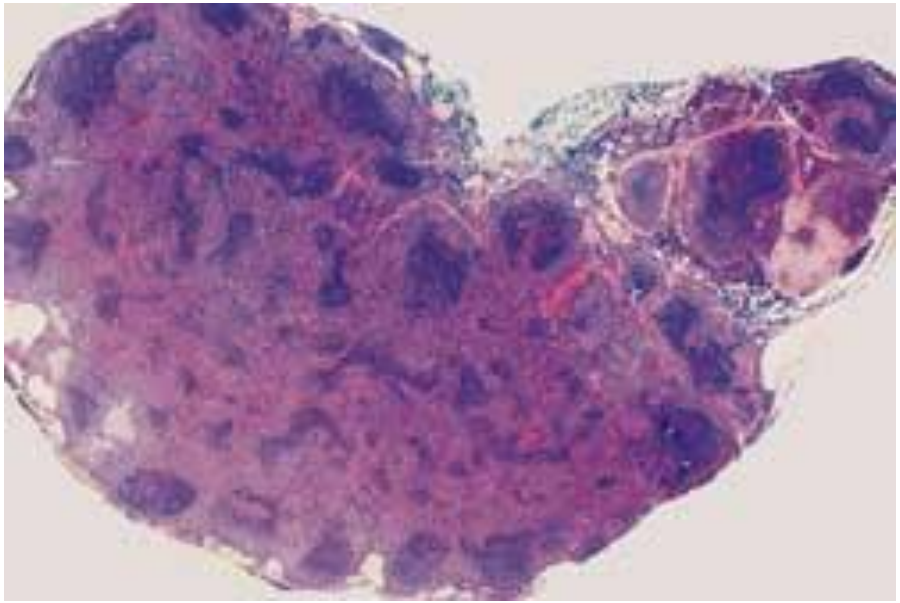


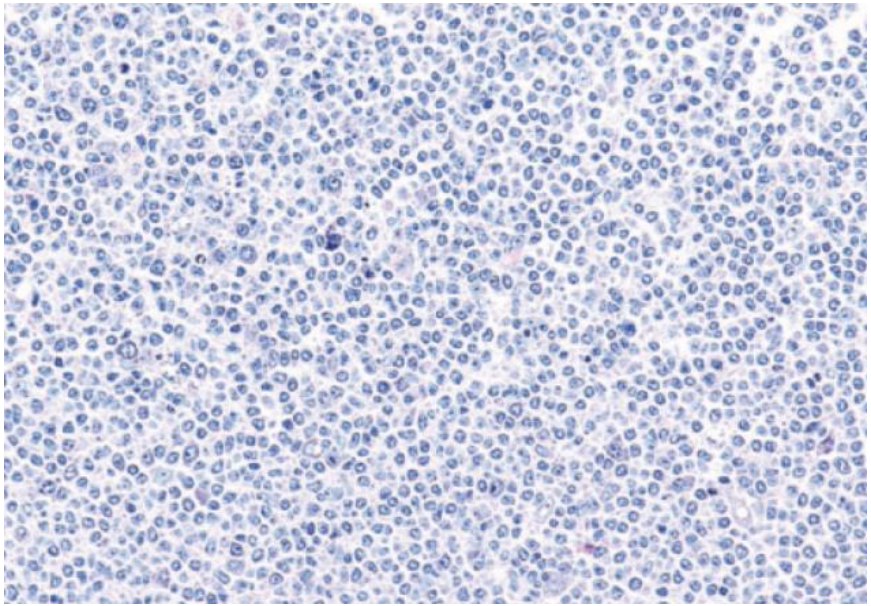
Splenic B cell lymphoma with circulating villous lymphocytes: differential diagnosis of B cell leukaemias with large spleens

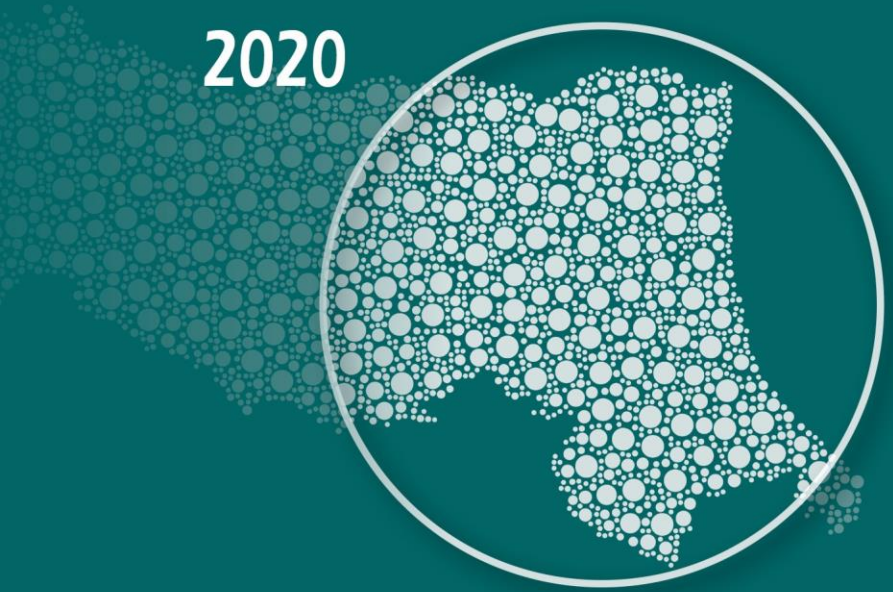
J V MELO,* U HEGDE,† A PARREIRA,* I THOMPSON,‡ I A LAMPERT,‡ D CATOVSKY*

Melo JV. *J Clin Pathol*, 1987; 40: 642-651

LINFOMA MARGINALE NODALE







Progetto Ematologia Romagna

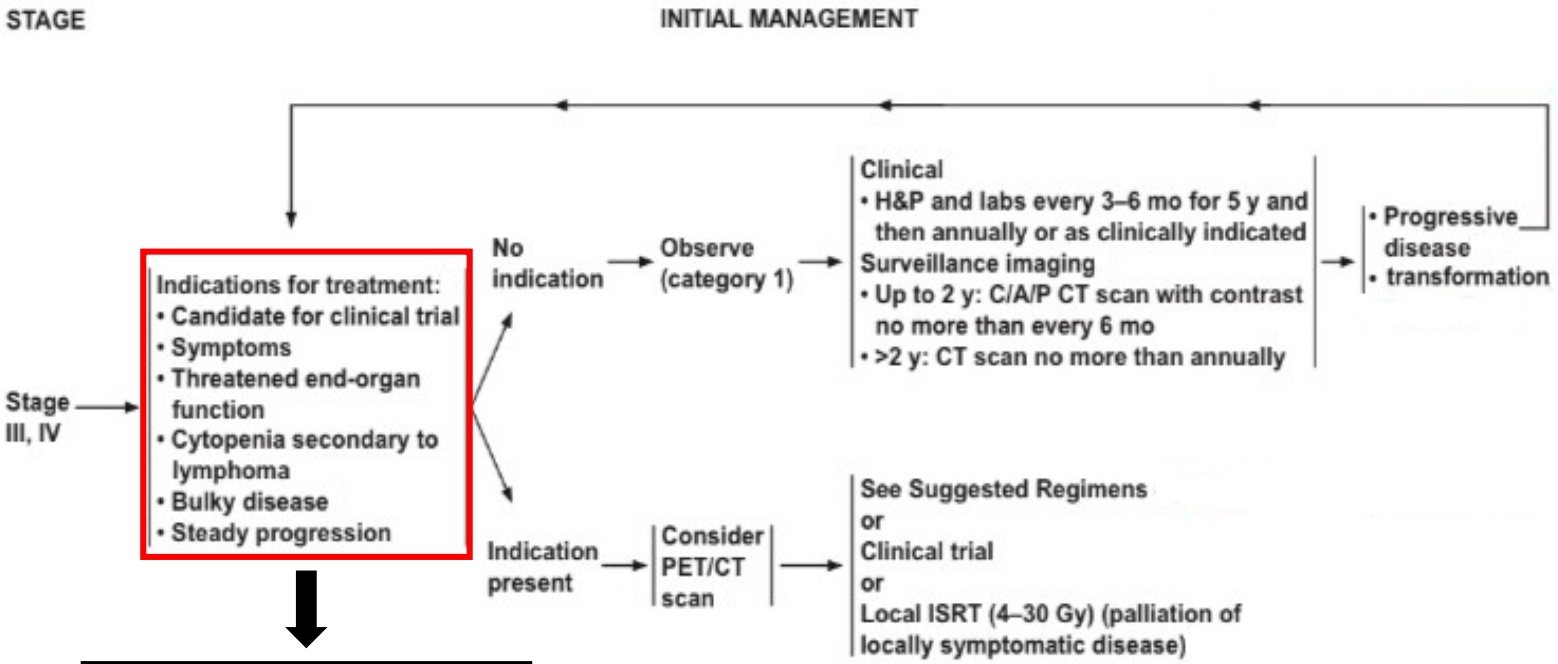
NOVITÀ NEI LINFOMI A BASSO GRADO

Linfoma follicolare

Alessandro Broccoli

Istituto di Ematologia “L. e A. Seràgnoli” – Università di Bologna

TERAPIA DI PRIMA LINEA (stadi avanzati)



Tumor burden dictates the initial strategy of management

TERAPIA DI PRIMA LINEA (stadi avanzati)

Terapie convenzionali

- Chemioimmunoterapia ± mantenimento
  - Rituximab + CHOP
  - Rituximab + CVP
  - Rituximab + bendamustina

Nuove strategie

- Chemioimmunoterapia ± mantenimento
  - Obinutuzumab + CHOP
  - Obinutuzumab + CVP
  - Obinutuzumab + bendamustina
- Farmaci immunomodulanti
  - Rituximab + lenalidomide (R^2)
  - Obinutuzumab + lenalidomide

TERAPIA DI PRIMA LINEA (stadi avanzati)

Terapie convenzionali

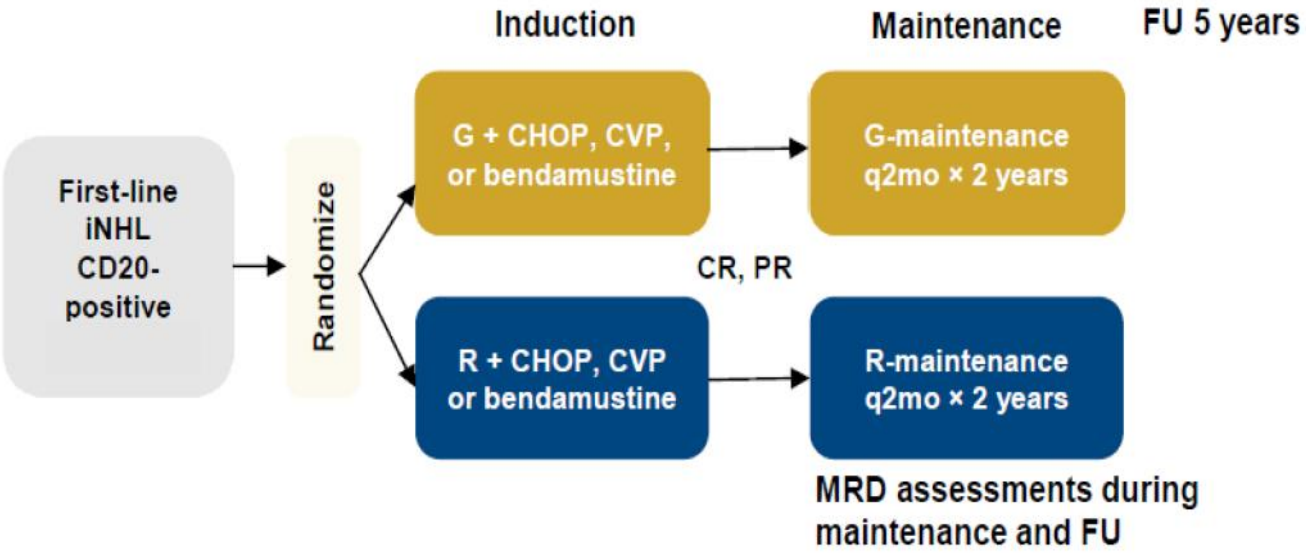
- Chemioimmunoterapia ± mantenimento
  - Rituximab + CHOP
  - Rituximab + CVP
  - Rituximab + bendamustina

Nuove strategie

- **Chemioimmunoterapia ± mantenimento**
  - **Obinutuzumab + CHOP**
  - **Obinutuzumab + CVP**
  - **Obinutuzumab + bendamustina**
- Farmaci immunomodulanti
  - Rituximab + lenalidomide (R^2)
  - **Obinutuzumab + lenalidomide**

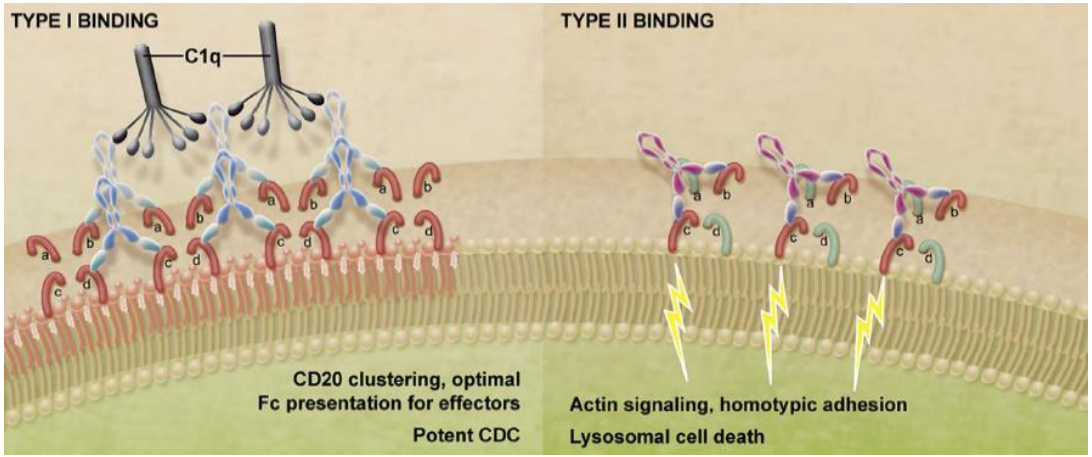
OBINUTUZUMAB-CHEMIOTERAPIA (1)

Obinutuzumab for the First-Line Treatment of Follicular Lymphoma



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

OBINUTUZUMAB-CHEMIOTERAPIA (2)



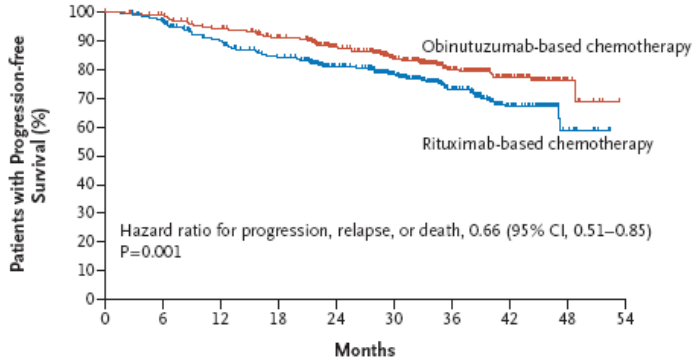
- **Tipo I**: legame con tetrameri adiacenti di antigene CD20 occupando tutti i siti disponibili; ridistribuzione del CD20 in *lipid rafts*; orientamento ottimale per attivazione del complemento tramite la via classica (C1q).
- **Tipo II**: legame all'interno dello stesso tetramero di antigene CD20; minore quota di anticorpo legato (*half-maximal binding capacity*); riarrangiamento di molecole di actina, attivazione di catepsine lisosomiali, generazione di radicali liberi dell'ossigeno (morte cellulare non-apoptotica).

Cragg MS. *Blood*, 2011; 118: 219-220

Table 1. Demographic and Disease Characteristics of the Patients at Baseline (Intention-to-Treat Population).

Characteristic	Obinutuzumab Group (N=601)	Rituximab Group (N=601)
Age — yr		
Median	60	58
Range	26–88	23–85
Weight — kg		
Median	75.0	74.0
Range	35.3–155.0	32.4–158.0
Body-surface area — m^2		
Median	1.8	1.8
Range	1.2–2.6	1.1–2.8
Male sex — no. (%)	283 (47.1)	280 (46.6)
Ann Arbor stage at diagnosis — no. (%)		
I	10 (1.7)	8 (1.3)
II	41 (6.8)	44 (7.3)
III	208 (34.6)	209 (34.8)
IV	339 (56.4)	336 (55.9)
Missing data	3 (0.5)	4 (0.7)
FLIPI risk status — no. (%)		
Low risk	128 (21.3)	125 (20.8)
Intermediate risk	224 (37.3)	223 (37.1)
High risk	249 (41.4)	253 (42.1)
B symptoms — no./total no. (%)	201/601 (33.4)	206/600 (34.3)
Bone marrow involvement — no./total no. (%)	318/592 (53.7)	295/598 (49.3)
Extranodal involvement — no. (%)	392 (65.2)	396 (65.9)
Bulk disease — no./total no. (%)	255/600 (42.5)	271/600 (45.2)
Time from initial diagnosis to randomization — mo		
Median	1.5	1.4
Range	0.1–121.6	0.0–168.1
Chemotherapy regimen — no. (%)		
Bendamustine	345 (57.4)	341 (56.7)
CHOP	195 (32.4)	203 (33.8)
CVP	61 (10.1)	57 (9.5)

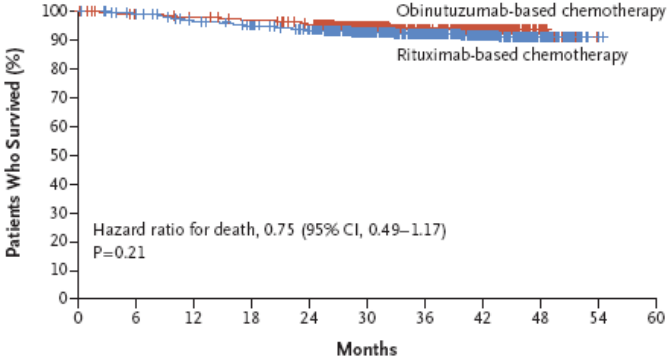
Progression-free Survival



No. at Risk

Obinutuzumab-based chemotherapy	601	570	536	502	405	278	168	75	13	0
Rituximab-based chemotherapy	601	562	505	463	378	266	160	68	10	0

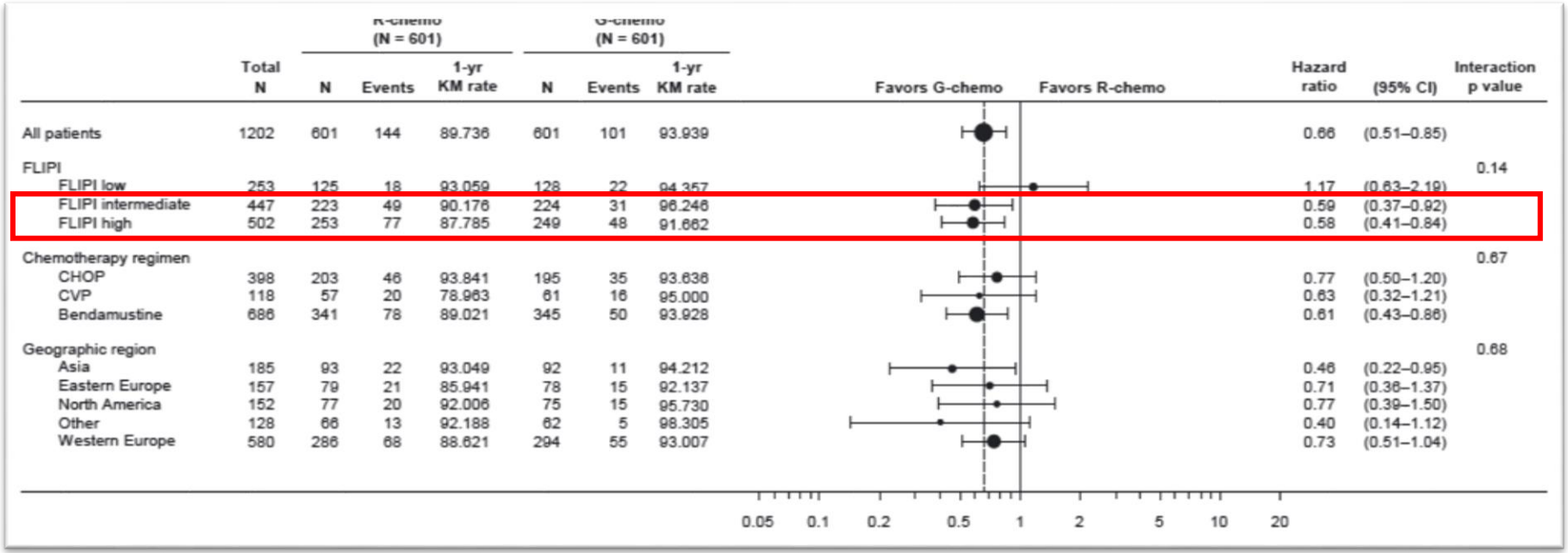
Overall Survival



No. at Risk

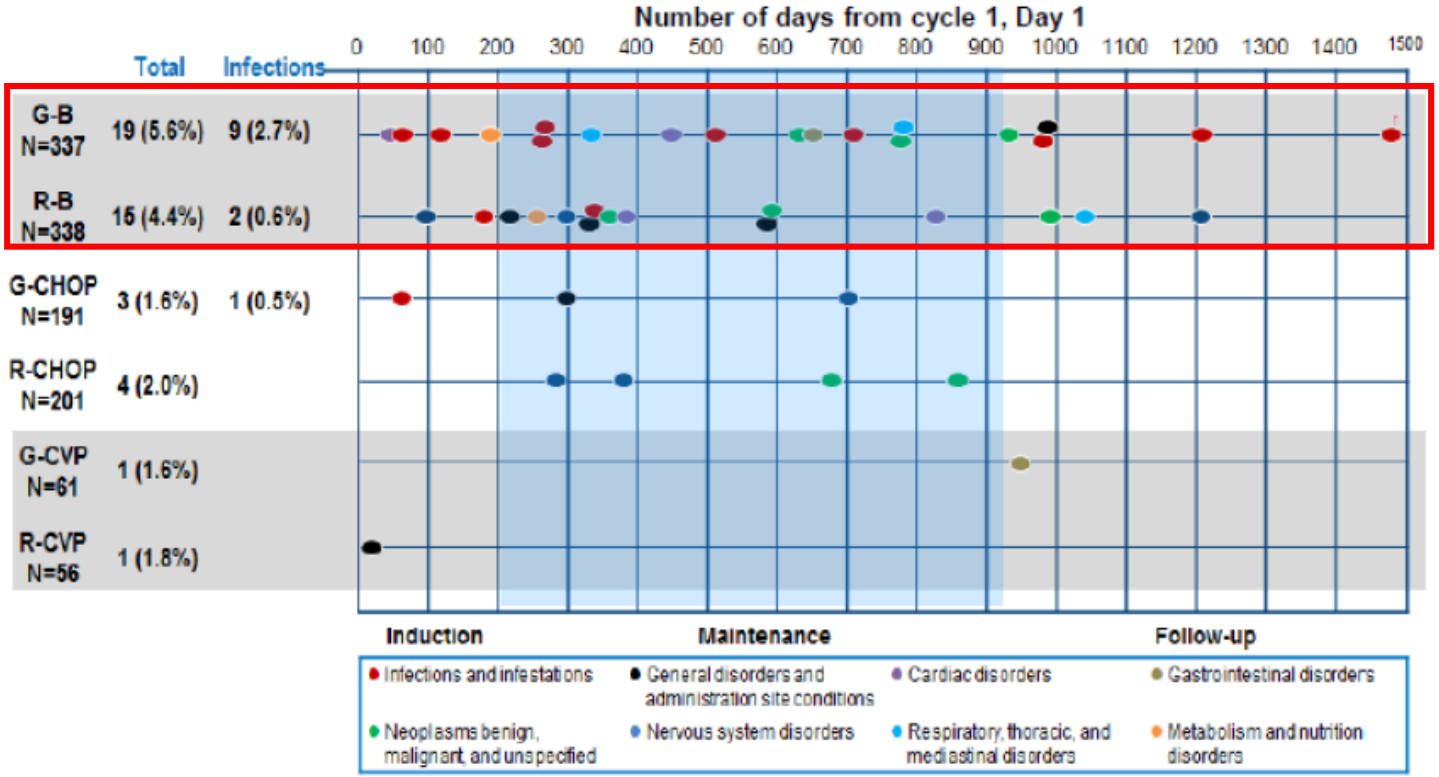
Obinutuzumab-based chemotherapy	601	584	573	563	549	416	271	161	55	0	0
Rituximab-based chemotherapy	601	588	566	549	527	399	265	160	58	2	0

OBINUTUZUMAB-CHEMIOTERAPIA (4)



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

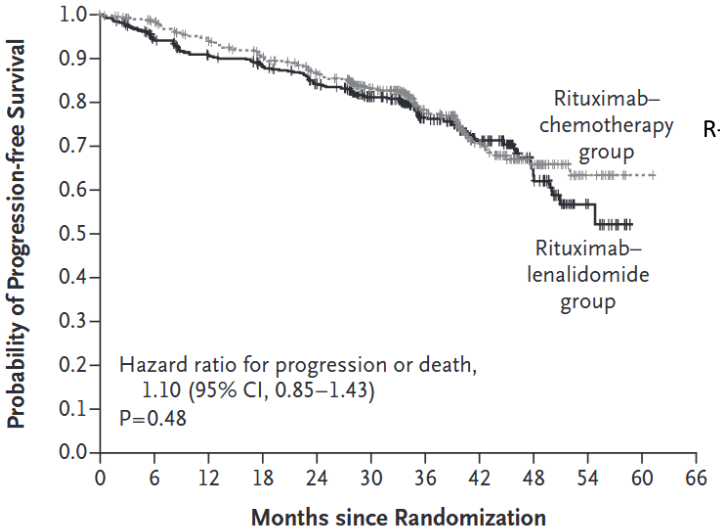
OBINUTUZUMAB-CHEMIOTERAPIA (5)



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

RITUXIMAB-LENALIDOMIDE

Rituximab plus Lenalidomide in Advanced Untreated Follicular Lymphoma



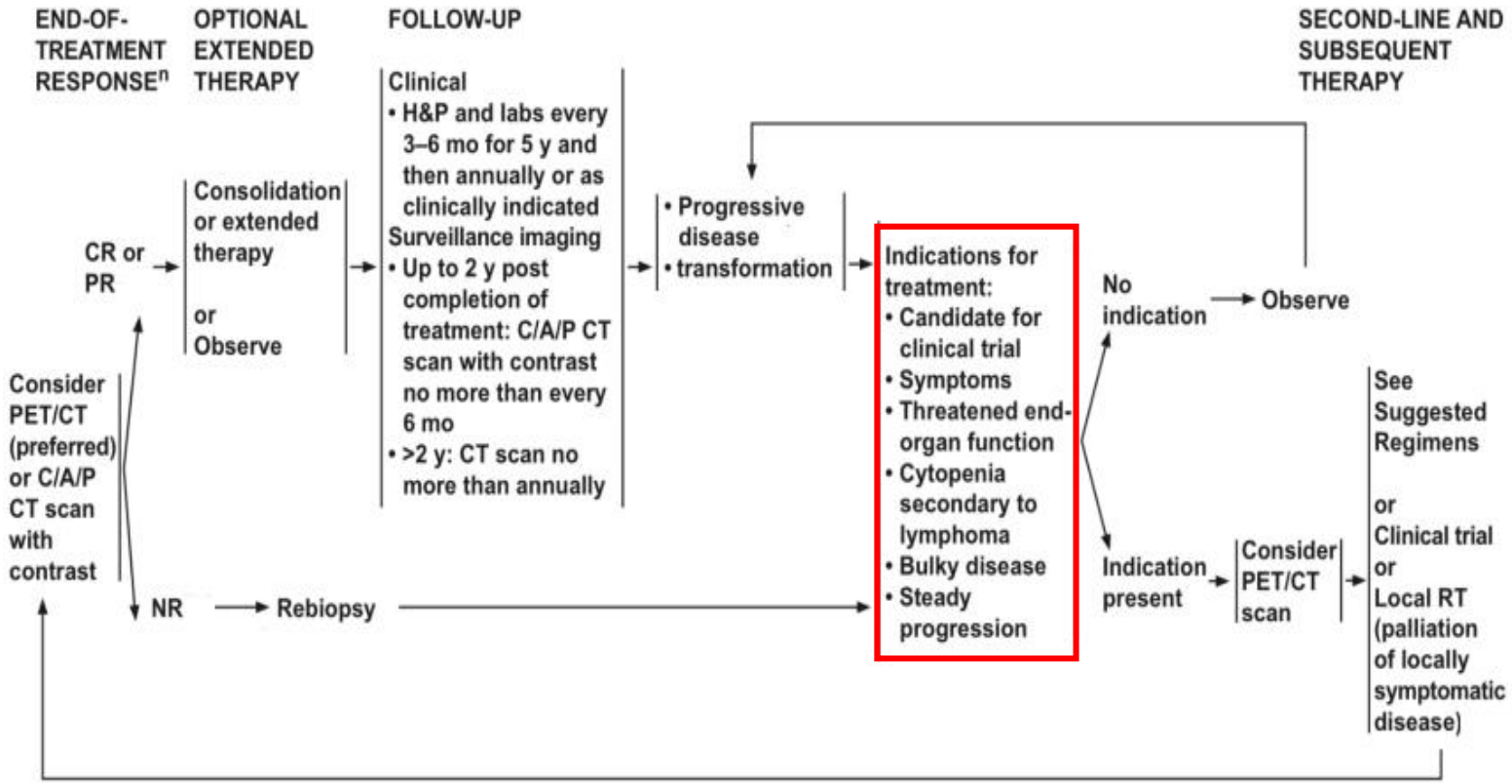
R-CHOP, R-Benda, R-CVP

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

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

TERAPIA NEL PAZIENTE RICADUTO-REFRATTARIO



TERAPIA NEL PAZIENTE RICADUTO-REFRATTARIO

Terapie convenzionali

- Rituximab ± mantenimento
- Chemioimmunoterapia ± mantenimento
- Obinutuzumab + bendamustina
- Radioimmunoterapia
- Radioterapia
- Trapianto autologo
- Trapianto allogenico

Nuove strategie

- PI3K inibitori
  - idelalisib
  - copanlisib
  - duvelisib
- Farmaci immunomodulanti
  - Rituximab + lenalidomide (R^2)
- Trials clinici con nuovi farmaci
  - Radioimmunoconiugati
  - Tazemetostat
  - Linfociti T-CAR
  - Anticorpi bispecifici
  - Anticorpi anti-eat me

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  - Anticorpi bispecifici
  - Anticorpi anti-eat me

IDELALISIB (1)

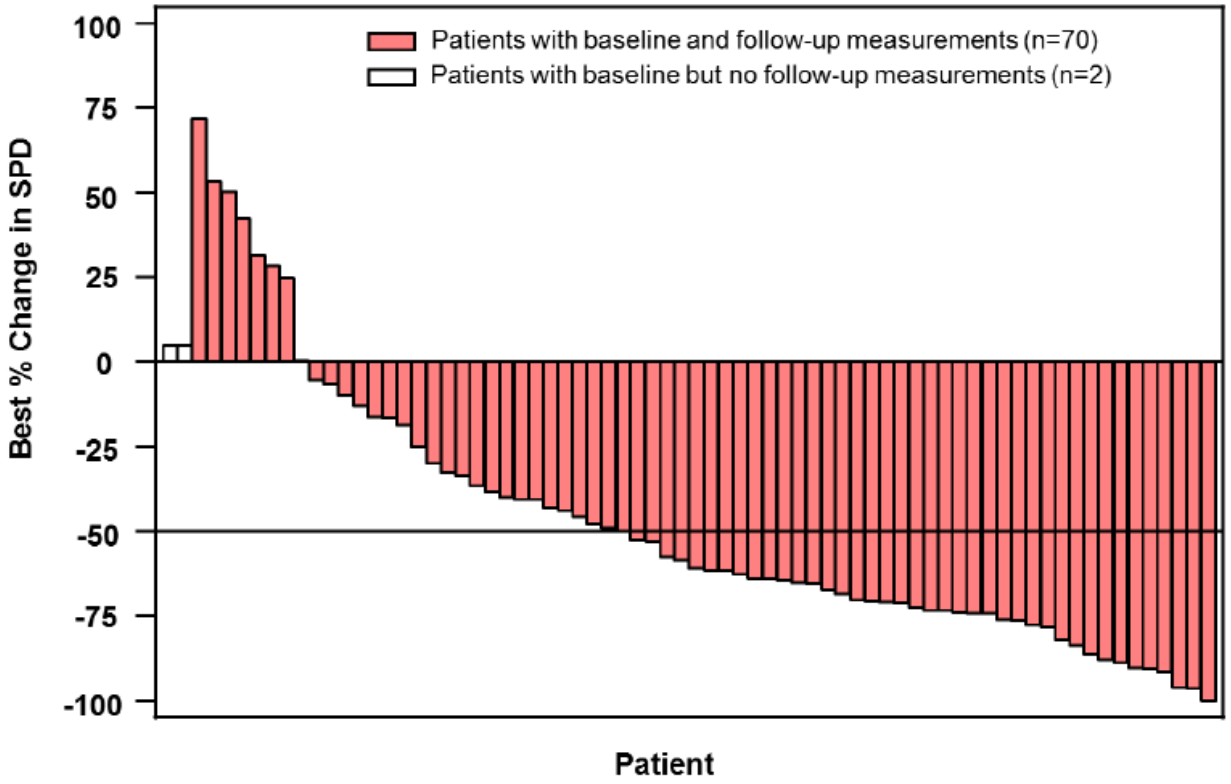
Characteristic (N = 72)	Patients
Median (range) age, y	62 (33–84)
Men, n. (%)	39 (54.2)
White, n. (%)	64 (88.9)
FL grade, n. (%)	
1	21 (29.2)
2	39 (54.2)
3a	12 (16.7)
Disease burden, n. (%)	
Stage III or IV	60 (83.3)
Elevated LDH†	21 (29.2)
Bulky disease‡	16 (22.2)
FLIPI risk score at baseline, n. (%)	
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

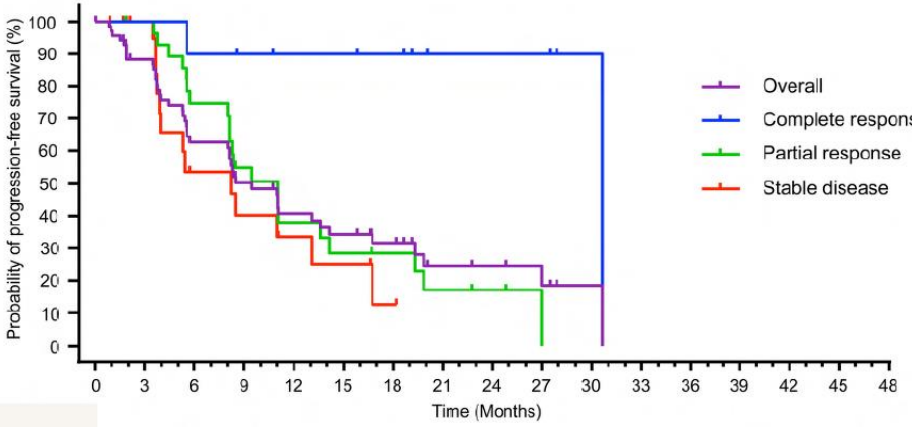
IDELALISIB (2)

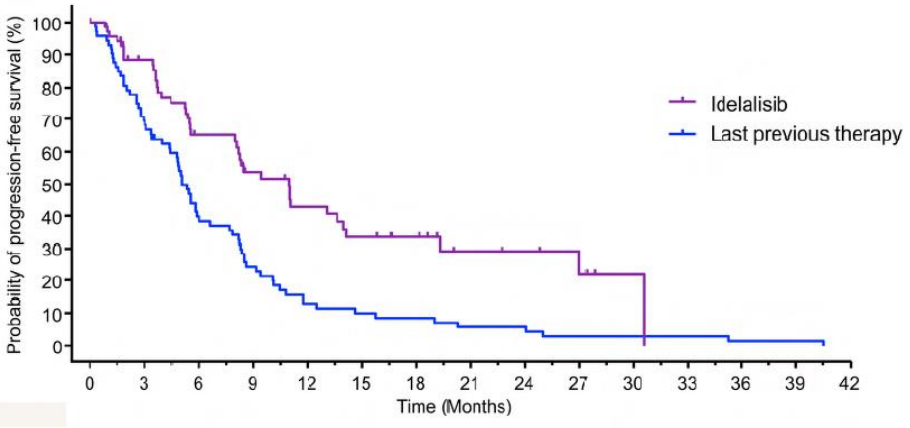
ORR 55,6%
CR 13,9%
PR 41,7%
SD 31,9%



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

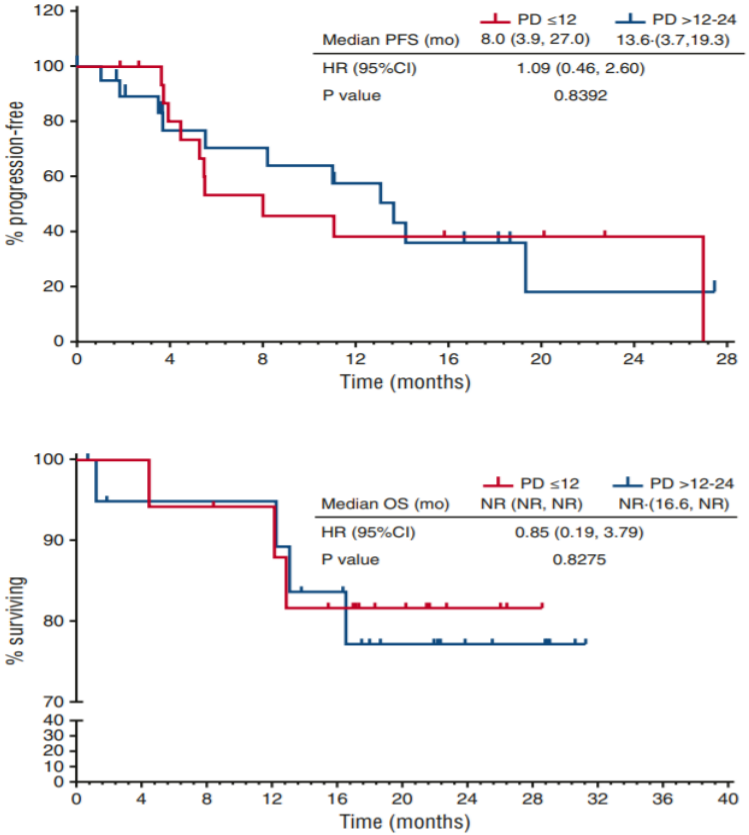
IDELALISIB (3)

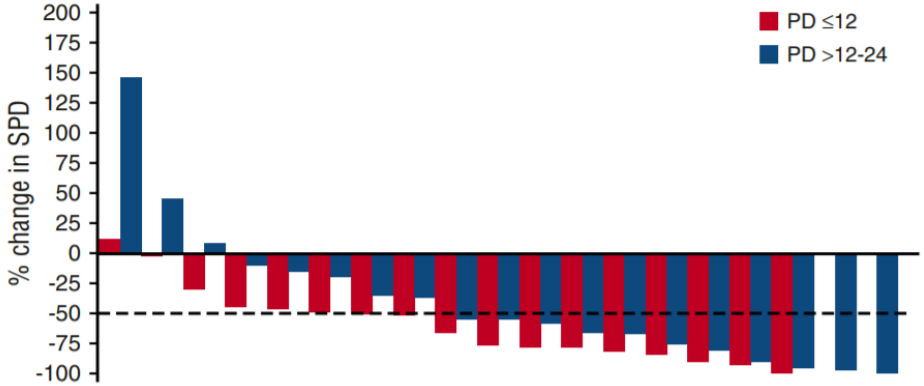




Salles G. *Haematologica*, 2017; 102: e156-e159

IDELALISIB (4)





Gopal AK. *Blood*, 2017; 129: 3037-3039

COPANLISIB (1)

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).

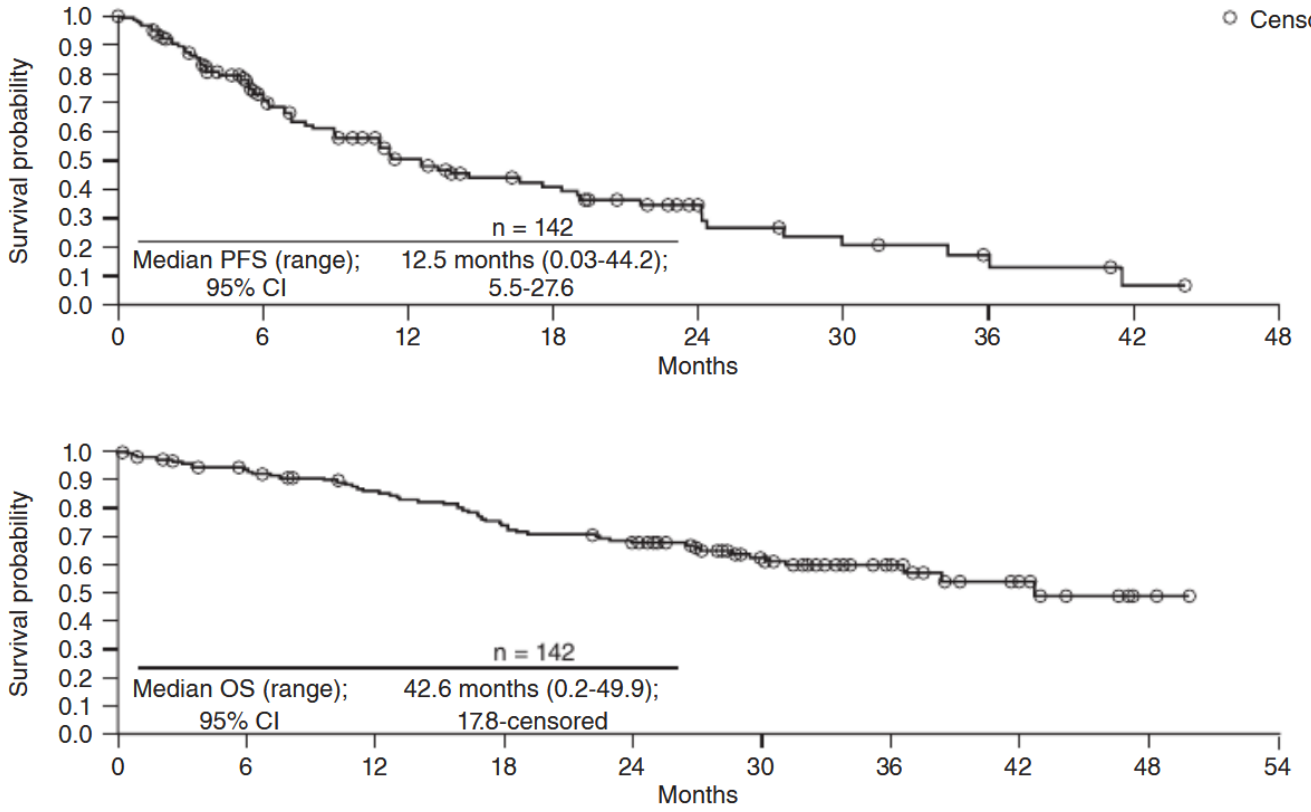
‡Of the full analysis set of 142 patients, data for 11 (8%) were not available for the analysis of the primary efficacy variable (objective response rate).

§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.

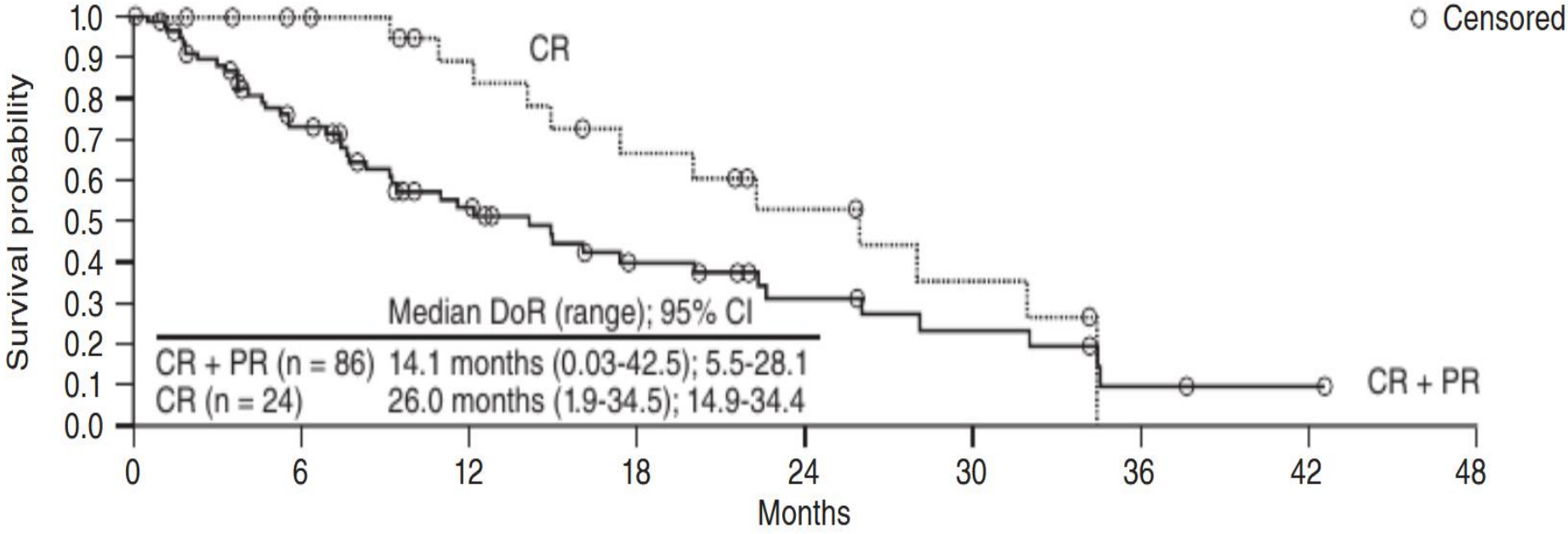
Dreyling M. *J Clin Oncol*, 2017; 35: 3898-3905

COPANLISIB (2)



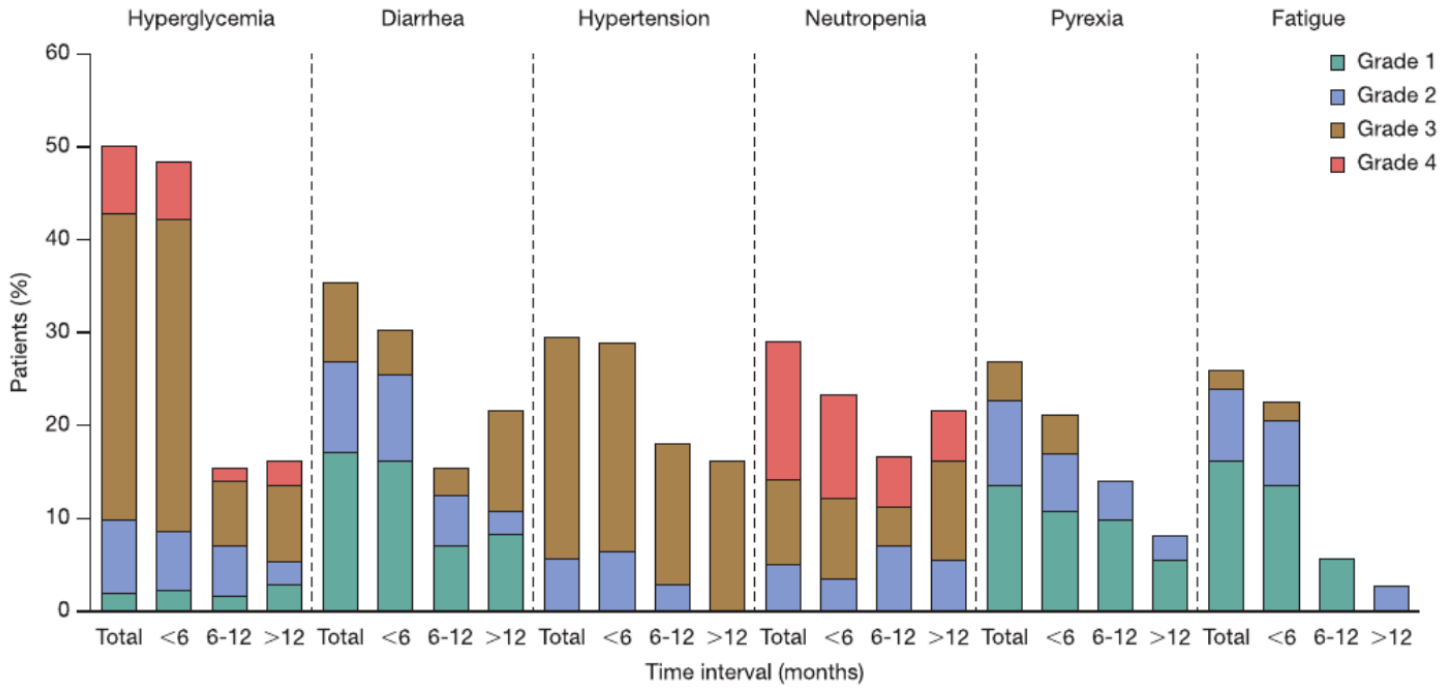
Dreyling M. *Am J Hematol*, 2019; in press

COPANLISIB (3)



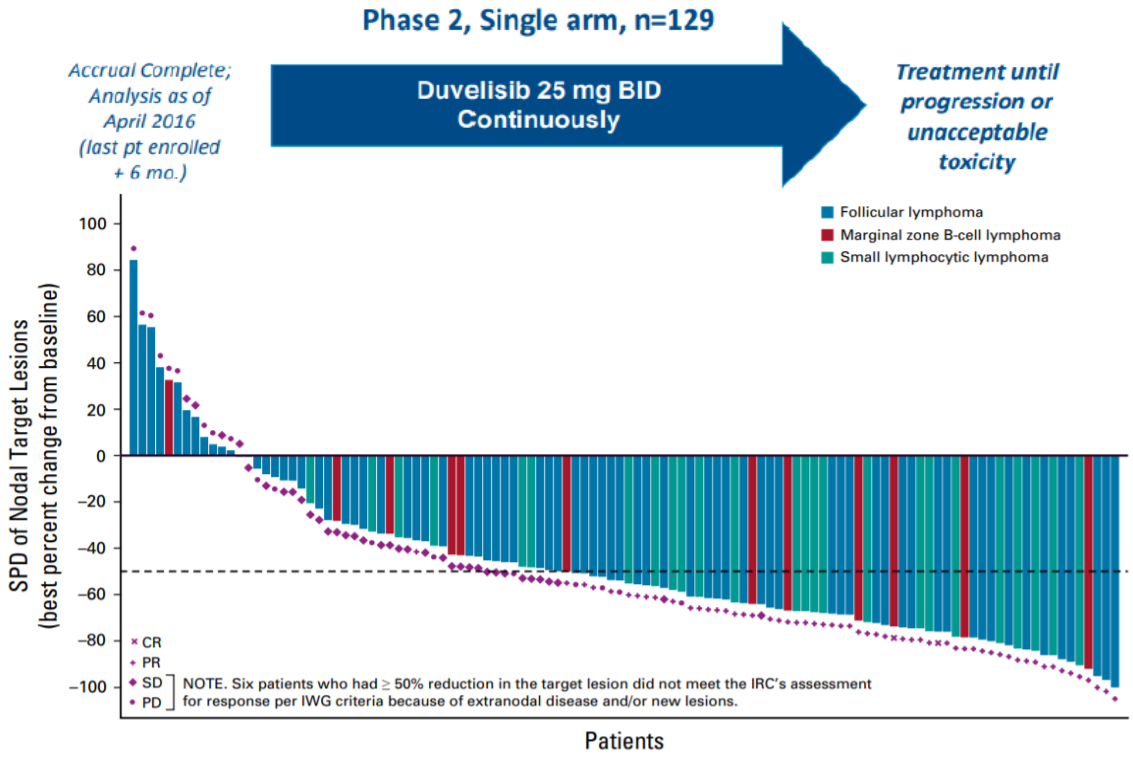
Dreyling M. *Am J Hematol*, 2019; in press

COPANLISIB (5)



Dreyling M. *Am J Hematol*, 2019; in press

DUVELISIB (1)



Flinn IW. *J Clin Oncol*, 2019; 37: 912-922

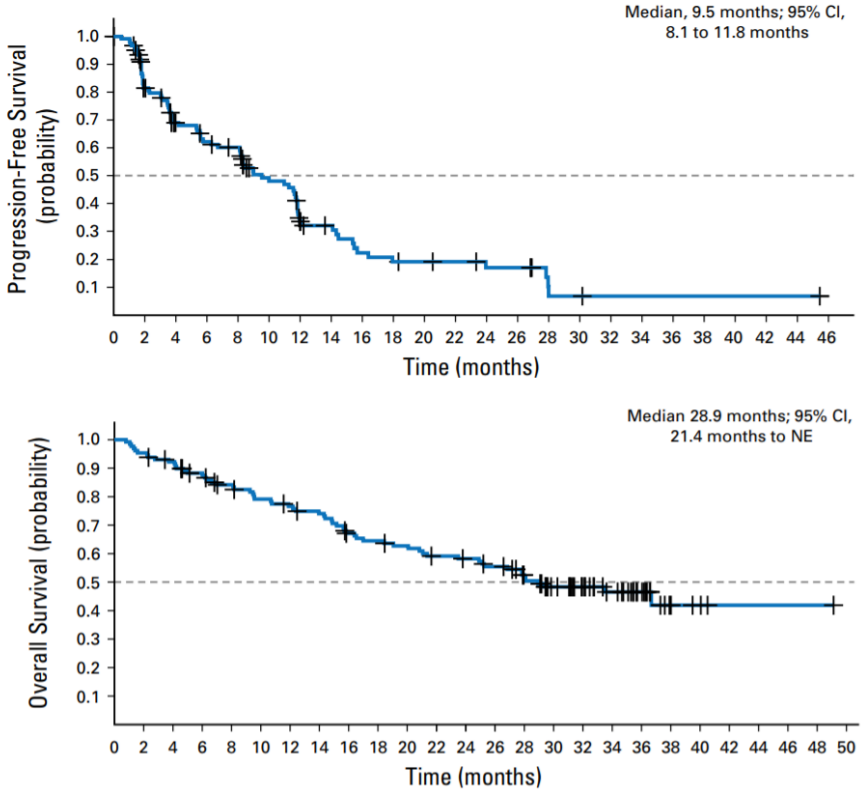
DUVELISIB (2)

Efficacy	Response by IRC, No. (%)	Response by Investigator, No. (%)
All patients (N = 129)		
ORR (CR + PR)	61 (47.3)	77 (59.7)
95% Exact binomial CI	38.4 to 56.3	50.7 to 68.2
Best response		
CR	2 (1.6)	4 (3.1)
PR	59 (45.7)	73 (56.6)
SD	42 (32.6)	38 (29.5)
PD	18 (14.0)	8 (6.2)
Unknown	7 (5.4)	6 (4.7)
No evidence of disease*	1 (0.8)	0
Median DOR by IWG, months	10.0	10.0
95% CI	6.3 to 10.5	6.5 to 12.5
Median PFS, months	9.5	10.0
95% CI	8.1 to 11.8	8.3 to 11.7
Median OS, months	28.9	
95% CI	21.4 to NE	
Median TTR, months	1.87	1.87
Range	1.4-11.7	1.0-12.3

Efficacy	Response by IRC, No. (%)	Response by Investigator, No. (%)
Follicular lymphoma (n = 83)		
ORR (CR + PR)	35 (42.2)	44 (53.0)
95% Exact binomial CI	31.4 to 53.5	41.7 to 64.1
Best response		
CR	1 (1.2)	2 (2.4)
PR	34 (41.0)	42 (50.6)
SD	29 (34.9)	28 (33.7)
PD	14 (16.9)	7 (8.4)
Unknown	5 (6.0)	4 (4.8)

Flinn IW. *J Clin Oncol*, 2019; 37: 912-922

DUVELISIB (3)



Flinn IW. *J Clin Oncol*, 2019; 37: 912-922

TERAPIA NEL PAZIENTE RICADUTO-REFRATTARIO

Terapie convenzionali

- Rituximab ± mantenimento
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  - **Rituximab + lenalidomide (R^2)**
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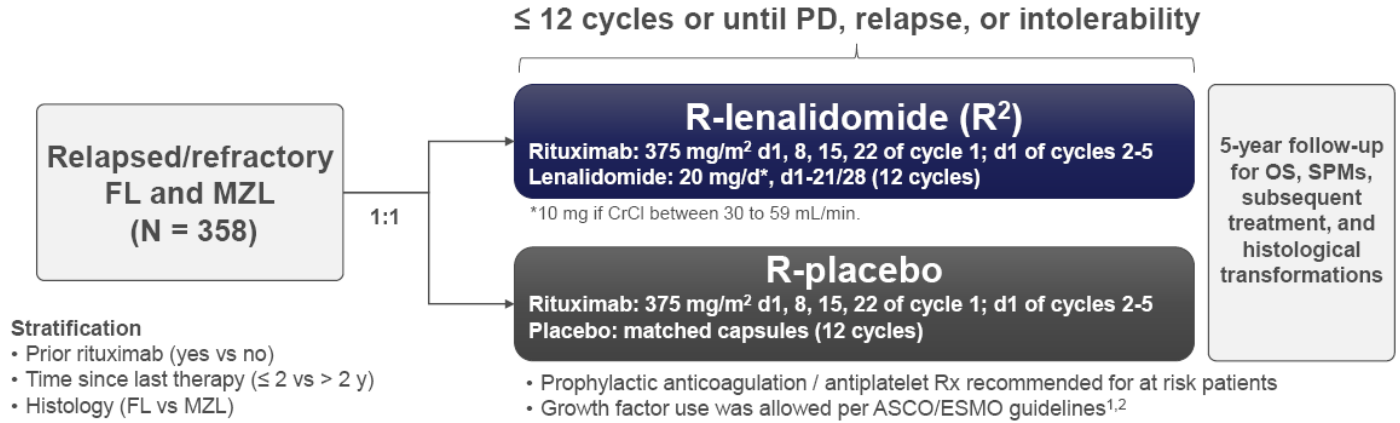
  - Radioimmunoconiugati
  - Tazemetostat
  - Linfociti T-CAR
  - Anticorpi bispecifici
  - Anticorpi anti-eat me

RITUXIMAB-LENALIDOMIDE (1)

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



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)

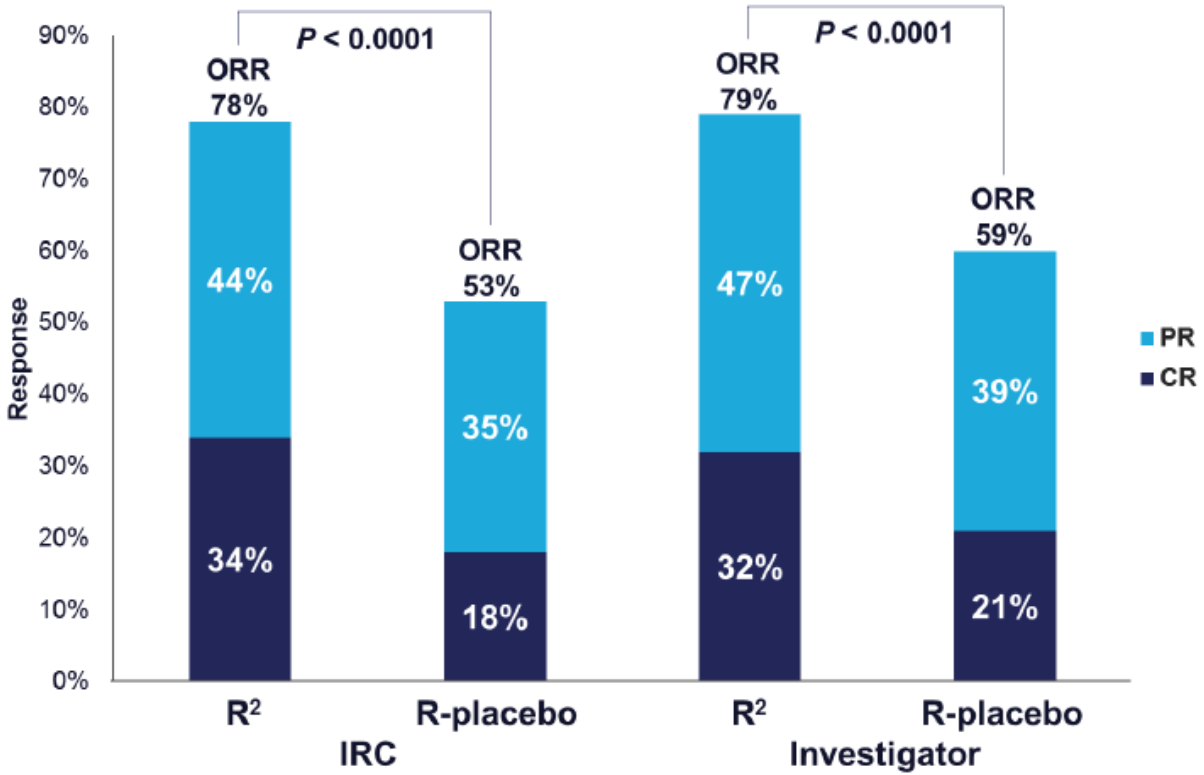
Leonard JP. *J Clin Oncol*, 2019; 37: 1188-1199

RITUXIMAB-LENALIDOMIDE (2)

Characteristic, n (%)		R² (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)

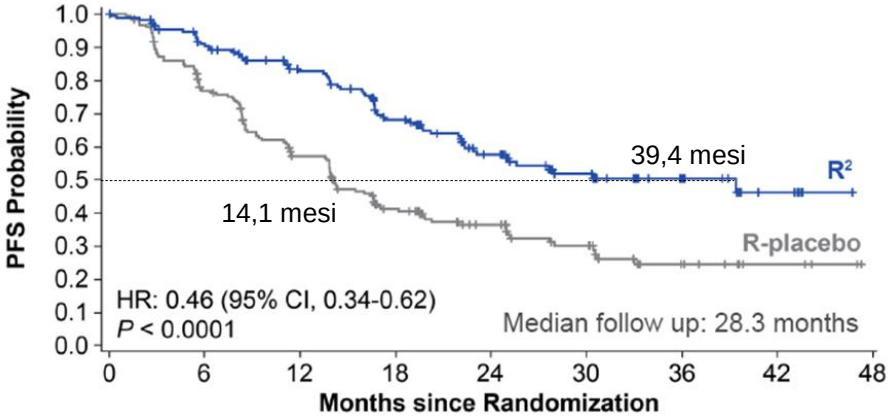
Leonard JP. *J Clin Oncol*, 2019; 37: 1188-1199

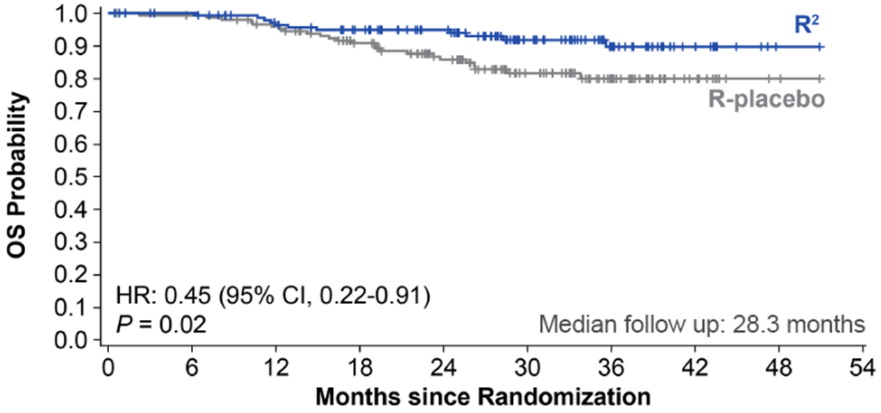
RITUXIMAB-LENALIDOMIDE (3)



Leonard JP. *J Clin Oncol*, 2019; 37: 1188-1199

RITUXIMAB-LENALIDOMIDE (4)





Leonard JP. *J Clin Oncol*, 2019; 37: 1188-1199

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  - **Linfociti T-CAR**
  - Anticorpi bispecifici
  - Anticorpi anti-eat me

	Pz	ORR %	CR %	mPFS (mesi)	mOS (mesi)	
Idelalisib **Copanlisib** **Duvelisib**	72 104 83	56 58 44	14 14 2	11 13 10	N.R. 43 29	Idelalisib: approvato in Italia. Applicabili dalla 3ª linea. Dati su attività nei pazienti POD24. Risposte limitate. Tossicità rilevante. Profilassi raccomandate.
R²	178	78	34	39	N.R.	Non ancora approvato in Italia (FDA). Approccio chemo-free. Applicabile dalla 2ª linea. Risultati promettenti.
Beta-lutin	57	65	28	—	—	Risultati preliminari.
Tazemetostat (EZH2^{mut})	45	~ 60	~ 12	14	N.R.	Recente approvazione FDA. Attività nei pazienti POD24. Buona tolleranza.
Axi-cel	80	95	81	24	N.R.	Risultati preliminari. CRS 77% (grado ≥ 3: 7%) Neurotossicità 55% (grado ≥ 3: 15%)