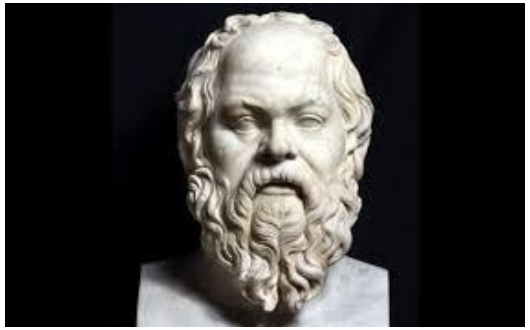
“Come tratterò il Linfoma follicolare nel 2020”

Luigi Rigacci
UOC Ematologia e Centro Trapianti Cellule Staminali
AO San Camillo Forlanini
Roma

FILOSOFEGGIARE DI SCIENZA



La cura dei linfomi follicolari è spesso un atteggiamento ’fideistico’,

Tutto quello che facciamo in un linfoma follicolare è sostanzialmente ‘giusto’

Il paziente assume un ruolo determinante nella scelta della terapia

Fermo restando un principio basilare PRIMUM NON NOCERE

LINFOMA FOLLICOLARE NEL 2020

- Heterogenous disease
- Varying prognosis (*clinical, laboratory and disease parameter*)
- Approximately 20% of FL patients have a high risk (HR) disease with significant reduction of their life expectancy (Casulo 2015, Maurer 2017)
- Incurable disease

- Prognosis has improved

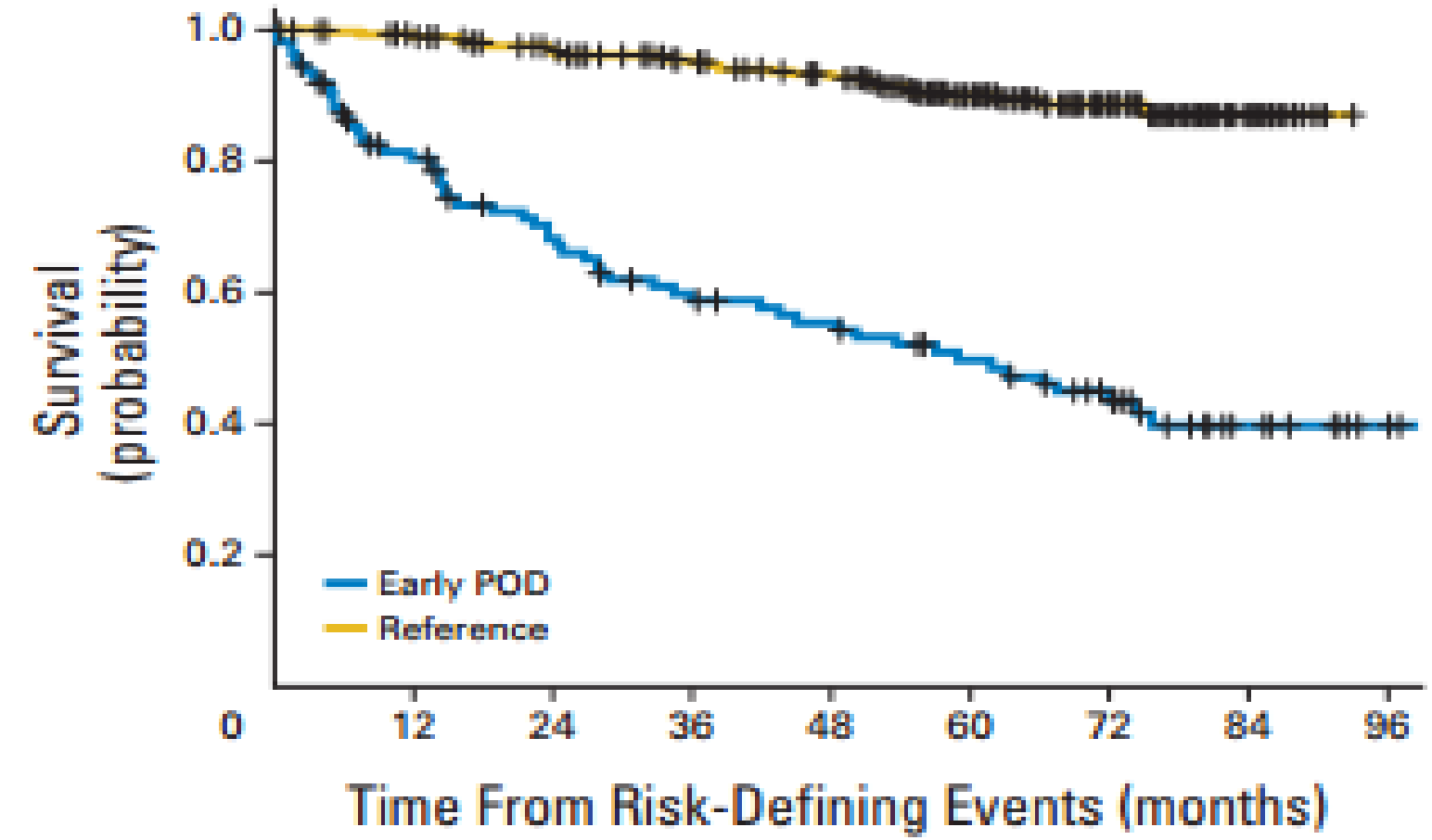
- Personalized approach: *disease biology*
  patient characteristics
  new therapies

The varying prognosis could be defined by RISK STRATIFICATION:

- **POD24**
- **FLIPI**
- **FLIPI2**
- **TMTV (+/- FLIPI2)**
- **M7-FLIPI**
- **23-gene expression-based**
- **Methabolic response (PET)**

TREATMENT DECISION CURRENTLY CANNOT BE DRIVEN BY AVAILABLE PROGNOSTIC MODELS .....BUT

LINFOMA FOLLICOLARE NEL 2020

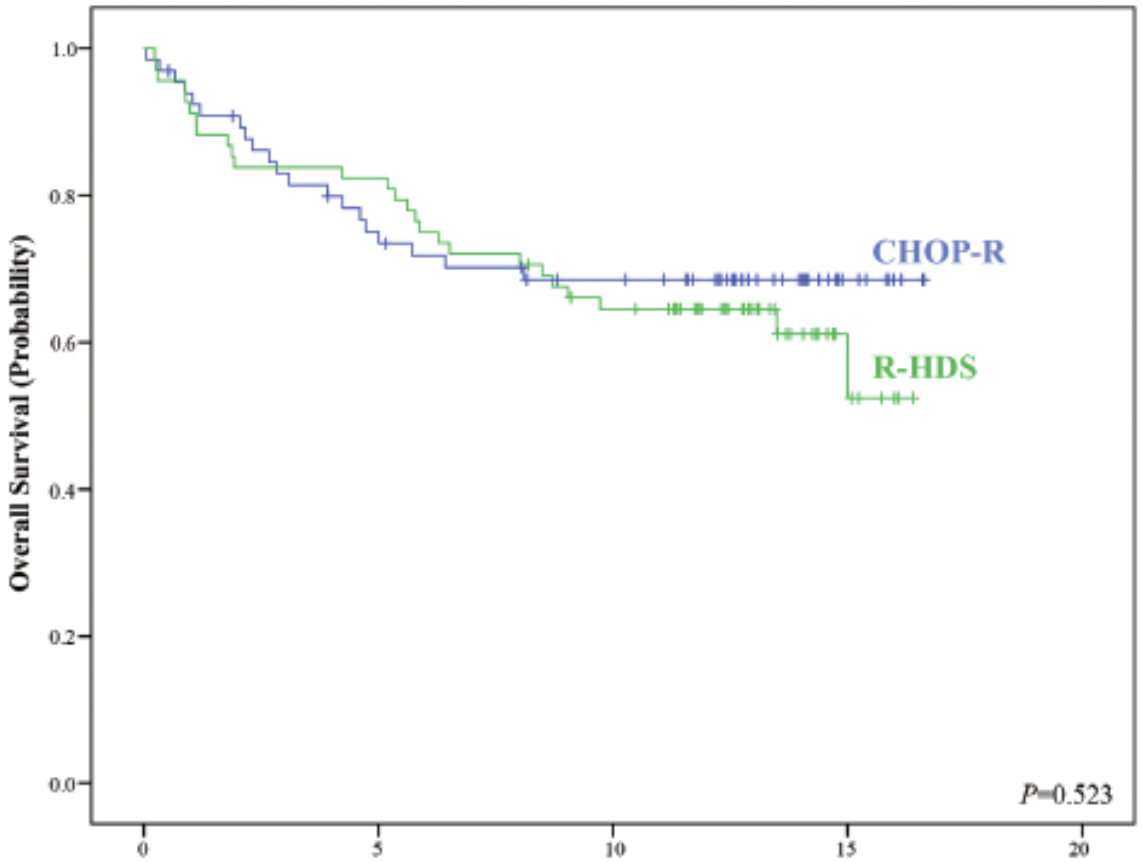


No. at risk									
Early POD	110	82	66	56	50	42	32	14	3
Reference	420	408	387	363	344	253	145	34	0

POD within 2 ys after RCHOP is associated with poor outcome (OS@5ys: 50%)

Casulo et al, JCO 2015

Incurable disease:



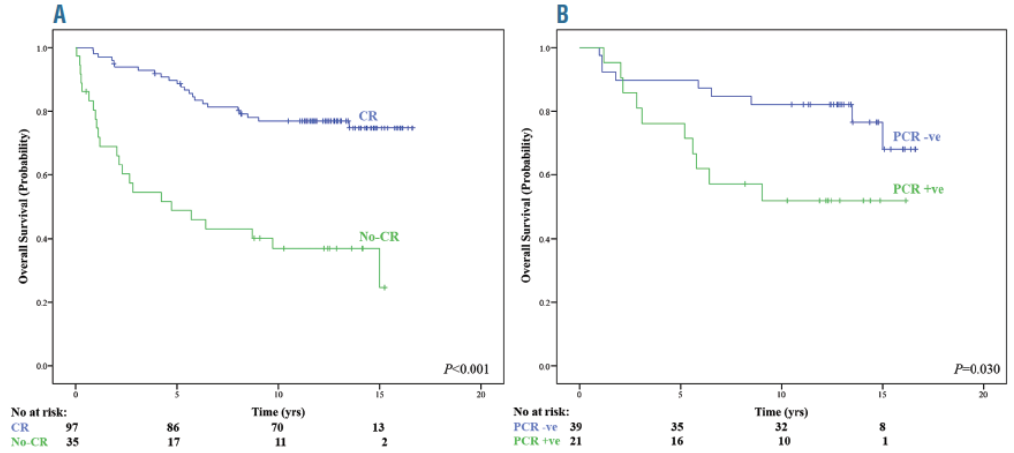
No at risk:				
CHOP-R	66	47	39	9
R-HDS	68	56	42	6

Prolonged survival in the absence of disease-recurrence in advanced-stage follicular lymphoma following chemo-immunotherapy: 13-year update of the prospective, multicenter randomized GITMO-IIL trial

Ferrata Storti Foundation

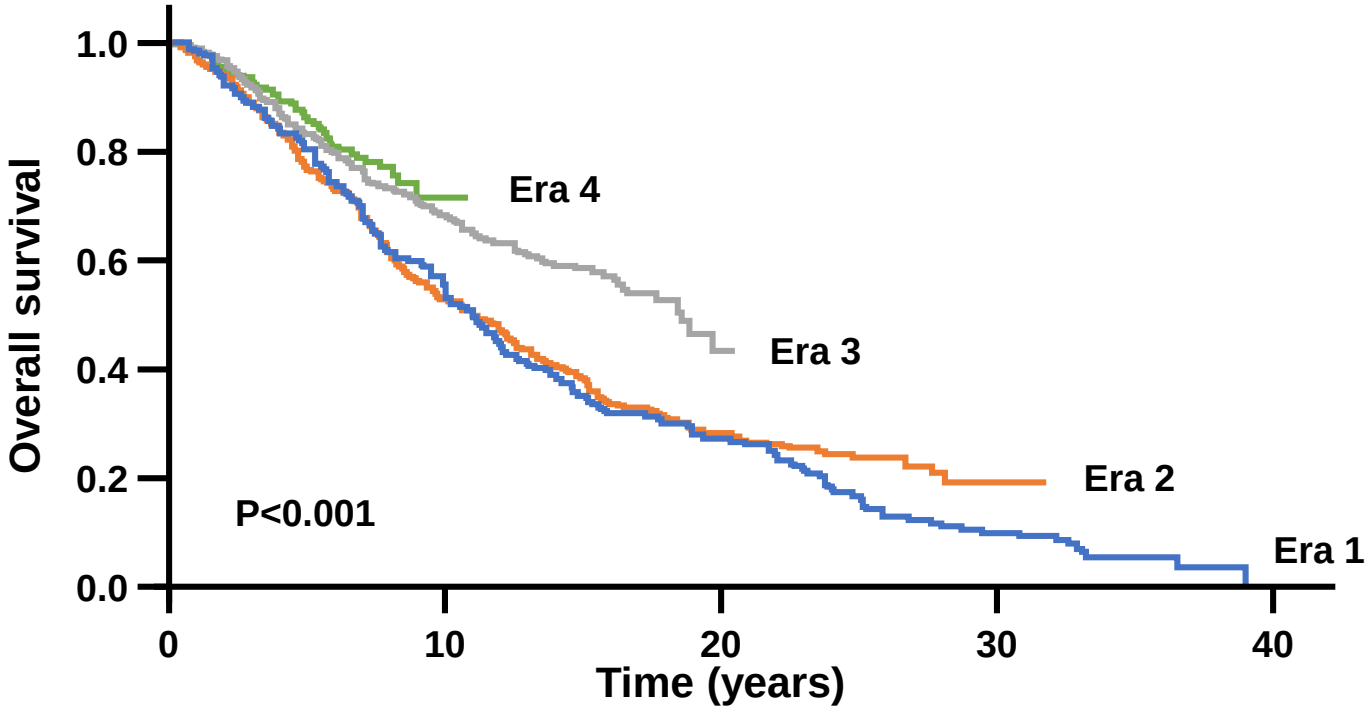
Riccardo Bruna,[1,8] Fabio Benedetti,[2] Carola Boccomini,[3] Caterina Patti,[4] Anna Maria Barbui,[5] Alessandro Pulsoni,[6] Maurizio Musso,[7] Anna Marina Liberati,[8] Guido Gini,[9] Claudia Castellino,[10] Fausto Rossini,[11] Fabio Ciceri,[12] Delia Rota-Scalabrini,[13] Caterina Stelitano,[14] Francesco Di Raimondo,[15] Alessandra Tucci,[16] Liliana Devizzi,[17] Valerio Zoli,[18] Francesco Zallio,[19] Franco Narni,[20] Alessandra Dondi,[21] Guido Parvis,[22*] Gianpietro Semenzato,[23] Francesco Lanza,[24*] Tommasina Perrone,[25] Francesco Angrilli,[26] Atto Billio,[27] Angela Gueli,[1] Barbara Mantoan,[28] Alessandro Rambaldi,[5,29] Alessandro Massimo Gianni,[1] Paolo Corradini,[17,29] Roberto Passera,[30] Marco Ladetto,[19] Corrado Tarella*[1,31]

Haematologica 2019
Volume 104(11):2241-2248



Taken together, these results indicate that an extensive disease response in FL may translate into both prolonged survival and in the long-term persistence of CR; a state that has been described as functional cure in other clinical settings. This in turn raises the issue of the curability of FL, at least in patients with a high-risk clinical presentation such as those selected in the present study.

Prognosis has improved: improvements in OS over multiple decades attribualble to effective new treatment options



Era	Year	N	Median OS (years)
1: Pre-anthracycline	1960–1975	180	11.0
2: Anthracycline	1976–1986	426	11.0
3: Aggressive chemo/purine analogues	1987–1996	471	18.5
4: Rituximab	1997–2003	257	Not reached

OS: overall survival

Tan D, *et al. Blood* 2013; 122:981–987.

WHICH APPROACH IN 2020 FOR:

- *Localized/limited stage disease*
- *Advanced disease*
- *Relapsed/refractory disease*
    - *Later and multiple relapsed disease*
    - *Early relapsed disease*

- *What about new prognostication models*
- *What about investigational therapies*

LOCALIZED/LIMITED STAGE

LINFOMA FOLLICOLARE NEL 2020

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

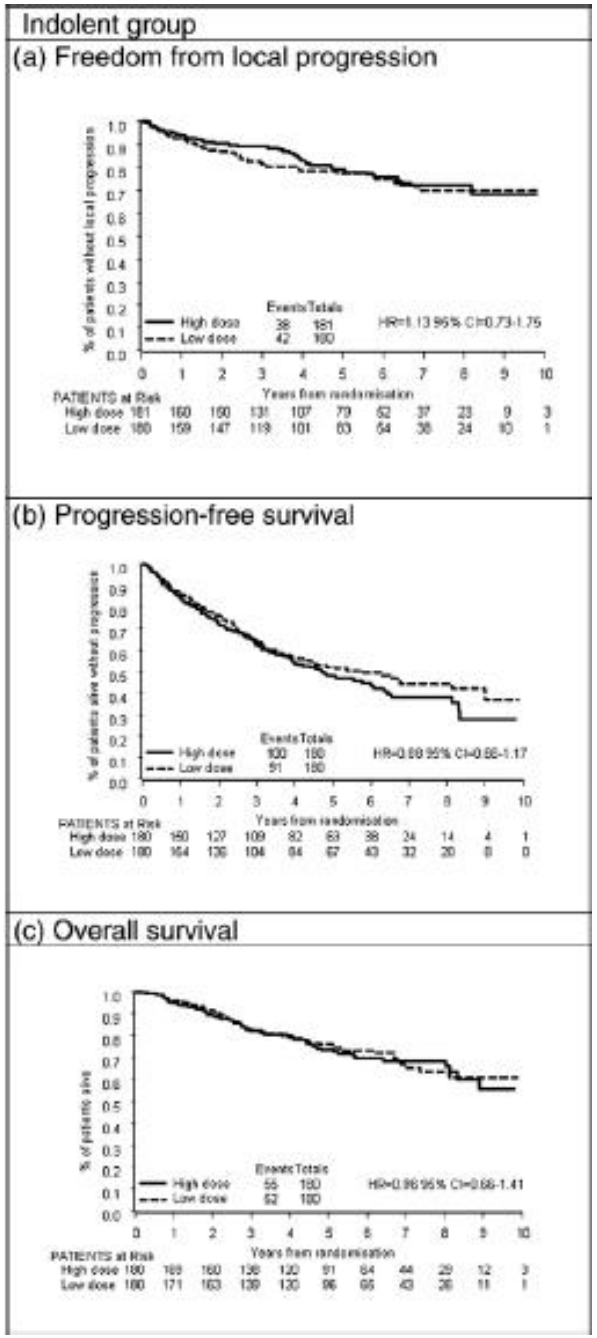
Phase III randomised trial

Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: A randomised phase III trial ☆,☆☆

Lisa Lowry [a], Paul Smith [a], Wendi Qian [b], Stephen Falk [c], Kim Benstead [d], Tim Illidge [e], David Linch [f], Martin Robinson [g], Andrew Jack [h], Peter Hoskin [i,*]

[a] Haematology Trials Group, University College London Cancer Trials Centre, UK; [b] MRC Clinical Trials Unit, London, UK; [c] Bristol Oncology and Haematology Centre, UK; [d] Department of Oncology, Cheltenham General Hospital, Gloucestershire, UK; [e] School of Cancer and Imaging Sciences, University of Manchester, UK; [f] University College London Cancer Institute, UK; [g] Academic Unit of Clinical Oncology, Weston Park Hospital, Sheffield, UK; [h] HMDS, St. James Institute of Oncology, Leeds, UK; [i] Mount Vernon Cancer Centre, Department of Clinical Oncology, London, UK

In conclusion, this large, randomised trial shows that doses of radiotherapy can safely be reduced to 24 Gy in indolent lymphoma and 30 Gy in more aggressive histological subtypes, without compromising local tumour control in the short- or long-term.

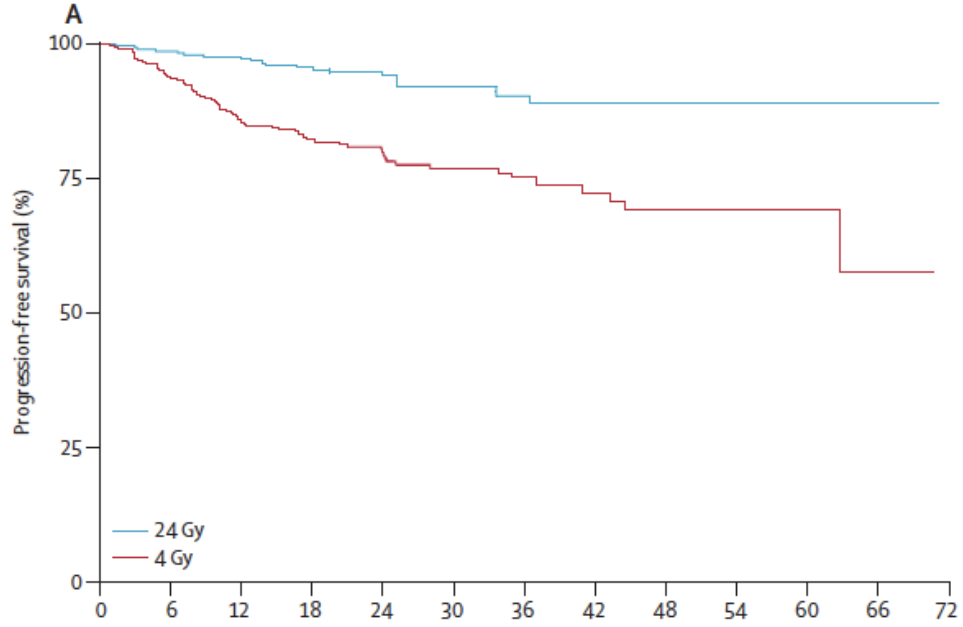


LINFOMA FOLLICOLARE NEL 2020

4 Gy versus 24 Gy radiotherapy for patients with indolent lymphoma (FORT): a randomised phase 3 non-inferiority trial

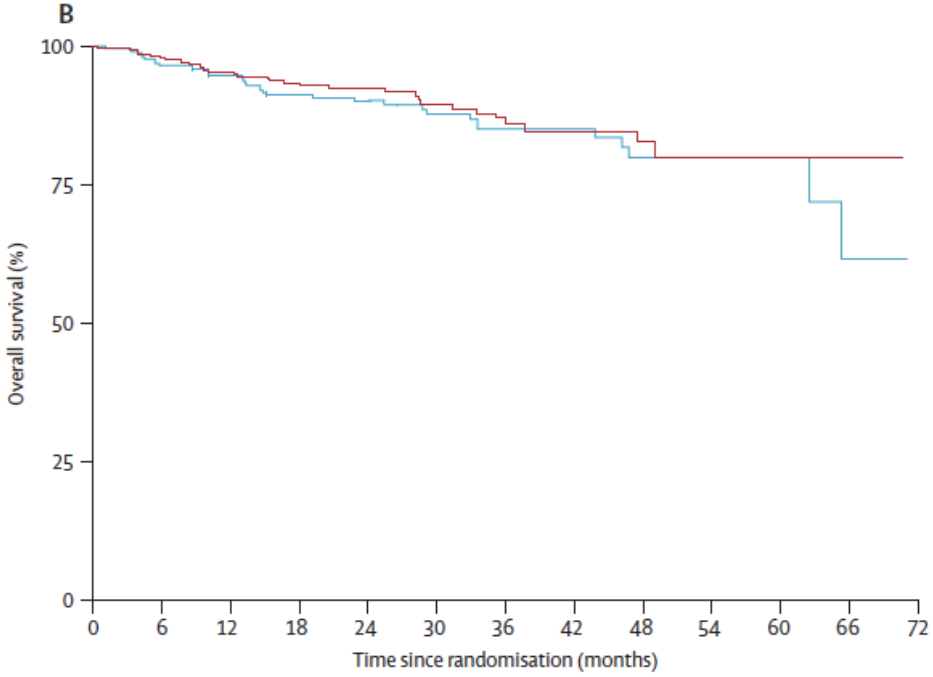
Peter J Hoskin, Amy A Kirkwood, Bilyana Popova, Paul Smith, Martin Robinson, Eve Gallop-Evans, Stewart Coltart, Timothy Illidge, Krishnaswamy Madhavan, Caroline Brammer, Patricia Diez, Andrew Jack, Isabel Syndikus

Lancet Oncol 2014; 15: 457–63



Number at risk

24 Gy	299	278	256	223	168	106	81	55	37	23	12	5	2
4 Gy	315	286	247	211	150	102	71	47	32	18	11	2	0



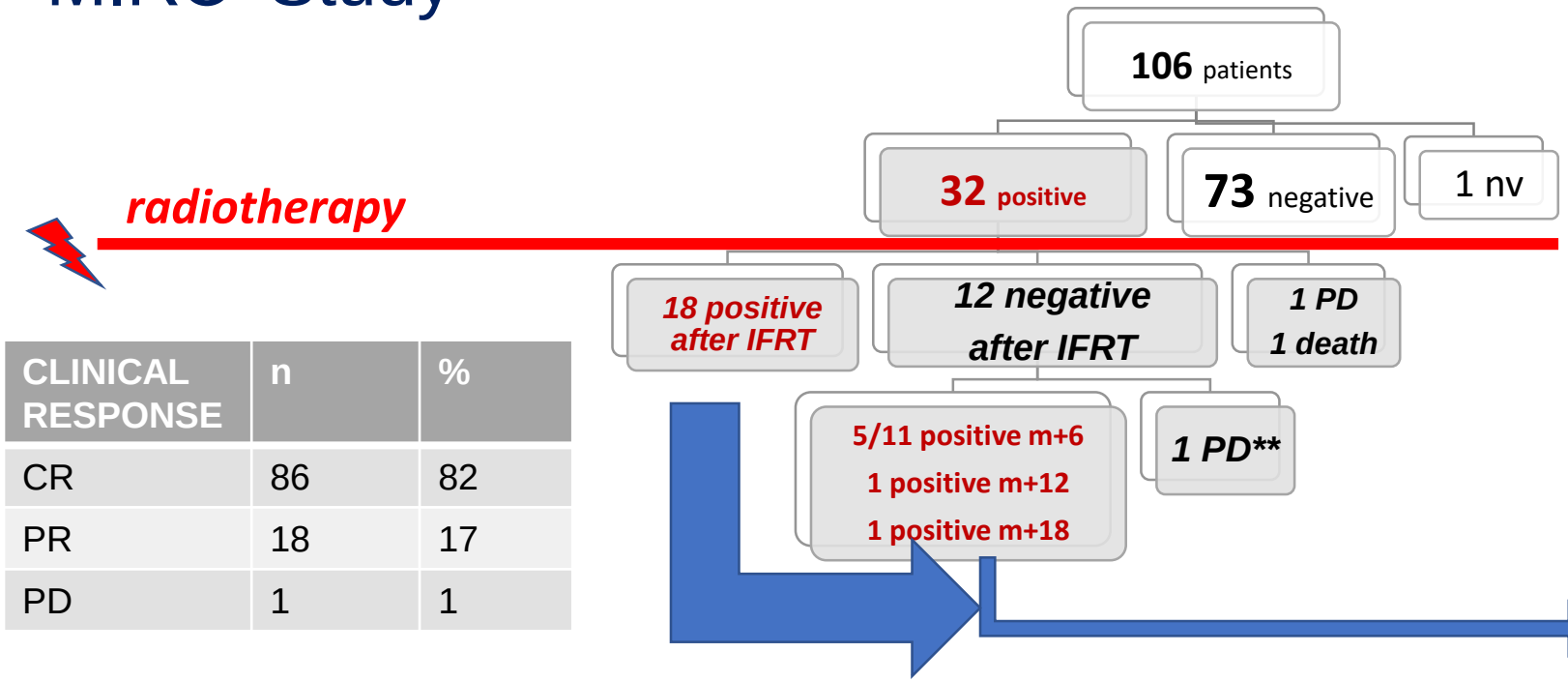
Number at risk

24 Gy	266	251	233	205	156	103	80	56	37	24	12	6	3
4 Gy	282	272	253	225	168	114	82	56	40	19	10	2	0

Interpretation

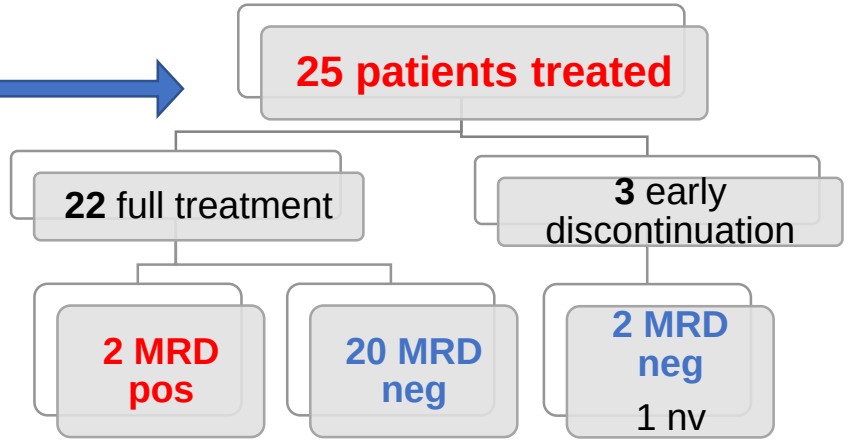
The results of this trial confirm that 4 Gy is effective in many patients but that it is inferior to 24 Gy in terms of time to local progression in both the radical and palliative setting when treating follicular lymphoma. Patients receiving radical radiotherapy for early stage follicular lymphoma should receive 24 Gy. 4 Gy has, however, a potential role as a simpler, shorter, and more pragmatic schedule in patients being treated for local control in the palliative setting, in which durable response might be less important.

MIRO' Study



CLINICAL RESPONSE	n	%
CR	86	82
PR	18	17
PD	1	1

After IFRT 18/30 (60%) patients remained MRD positive in BM and/or PB, and 12 (40%) became negative; of these, 7 converted positive over time



Ofatumumab treatment produced conversion to negative MRD in 20/22 (91%) fully treated patients;
Considering also cases with incomplete treatment in 22/24 (92%)
This result was significantly superior to the expected 50%*

Take home messagges in localized stages……..in 2020

- Radiotherapy 24 Gy is the standard for the cure
- Immunotherapy in bcl-2 positive patients could improve results
- Radiotherapy 4 Gy in selected cases with palliative/contenitive intent

- Watch and wait in highly selected cases

ADVANCED STAGE

LINFOMA FOLLICOLARE NEL 2020

GELF [60]	1. Tumor size: any site >7 cm or ≥ 3 sites >3 cm 2. B symptoms: yes 3. Spleen: below umbilical line 4. Compressive symptoms: yes 5. Pleural or peritoneal effusion: yes 6. Leukemic phase $>5 \times 10^9$/L 7. Neutropenia ($<1 \times 10^9$/L) or thrombocytopenia ($<100 \times 10^9$/L) due to disease	High tumor burden: ≥1 risk factors

Low tumor burden

High tumor burden

Low tumor burden

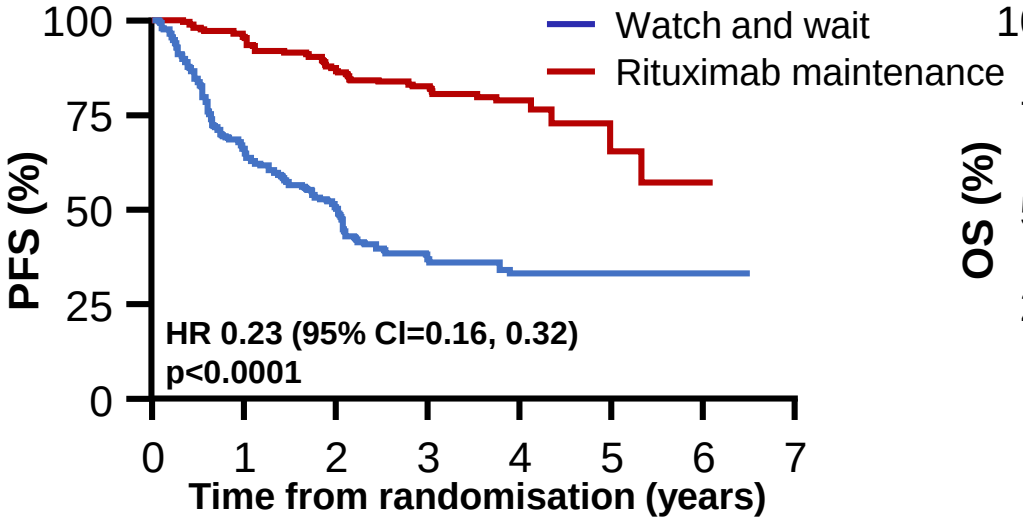
The aivailability of active and minimal toxic therapies it is a relavant issue

Is it Watch and Wait still viable?

First-line rituximab may delay disease progression compared with 'watch and wait'

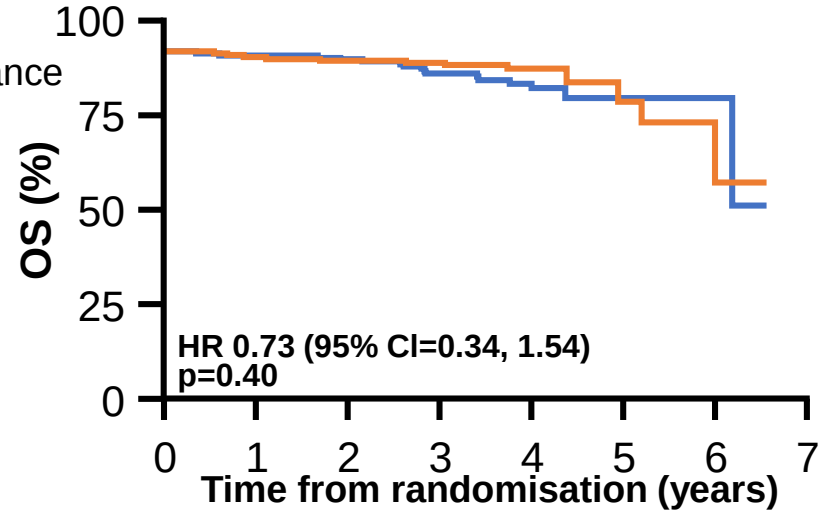
Low tumour burden, Stage III/IV

Randomised, Phase III study in previously untreated, advanced-stage, asymptomatic, non-bulky FL (N=463)



Number at risk

187	121	92	54	28	6	1	0
192	183	165	138	56	9	1	0



Number at risk

187	181	175	130	68	18	4	0
192	189	186	163	72	16	3	0

Ardeshna KM, et al. Lancet Oncol 2014; 15:424–435.

Is watch and wait still acceptable for patients with low-grade follicular lymphoma?

James O. Armitage[1] and Dan L. Longo[2]

[1]University of Nebraska Medical Center, Omaha, NE; and [2]Brigham and Women's Hospital, Harvard Medical School, Boston, MA

BLOOD, 9 JUNE 2016 • VOLUME 127, NUMBER 23

Table 1. Caveats for using watch and wait for patients with low-grade FL

• The patient should be asymptomatic
• The patient should not want therapy (after learning the data regarding watch and wait)
• The physician should be willing to observe the patient closely (ie, FL is cancer and occasionally progresses rapidly)
• Although not proven, the patient understands that delaying therapy might possibly adversely impact survival

High tumor burden

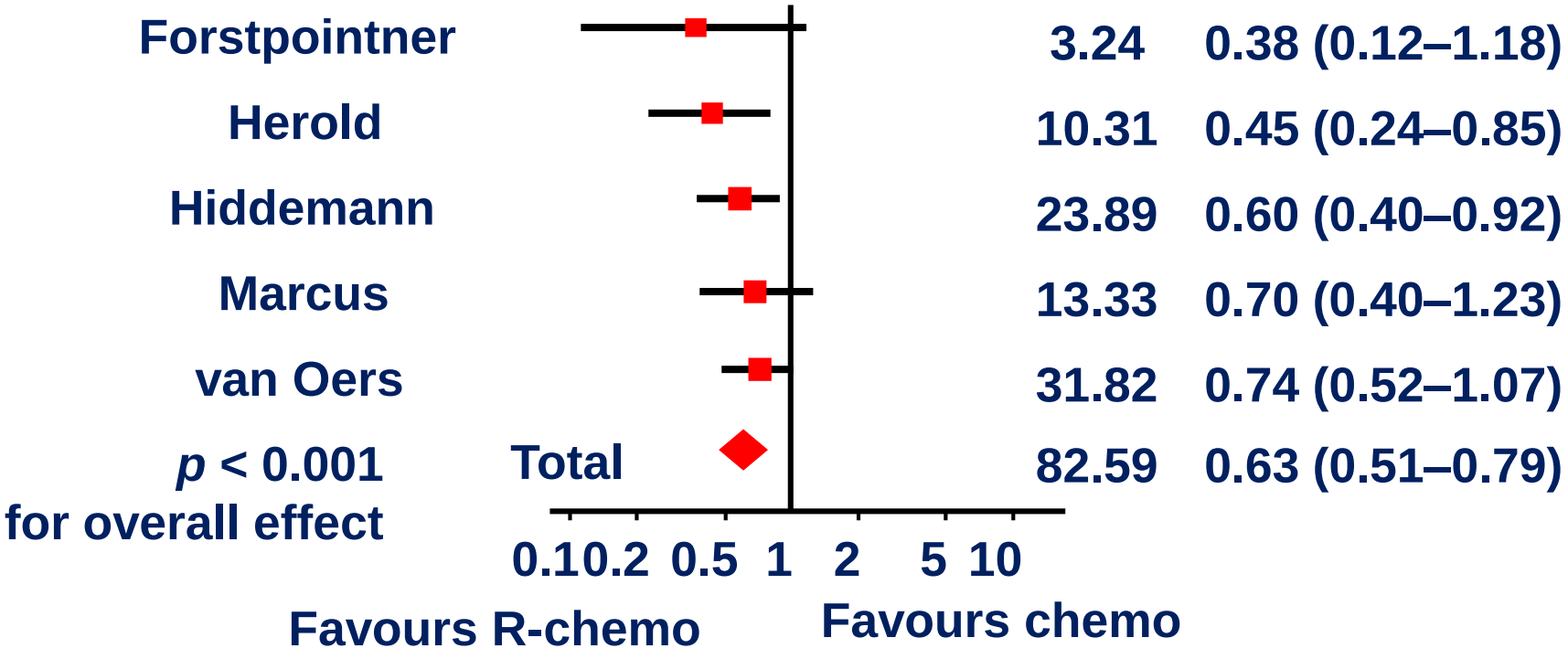
Current standard of care for advanced FL is chemoimmunotehrapy regimens including anti CD20 antibody

LINFOMA FOLLICOLARE NEL 2020

Study	Regimen	Follow-up	Overall survival (%)		*p*-value
			Control	Rituximab	
M39021[1] (Marcus)	CVP vs R-CVP	4 years	77	83	0.029
GLSG[2,3] (Hiddemann)	CHOP vs R-CHOP	5 years	84	90	0.0493
M39023[4,5] (Herold)	MCP vs R-MCP	4 years	74	86	0.0205
FL2000[6] (Salles)	CHVP/IFN vs R-CHVP/IFN	5 years	79	84	0.025 (high-risk pts)

1. *Marcus R, et al. J Clin Oncol 2008; 26(28): 4579-4586;*
2. *Hiddemann W, et al. Blood. 2005; 106(12): 3725-3732;*
3. *Buske C, et al. Blood. 2008; 112: Abstract 2599;*
4. *Herold M, et al.J Clin Oncol 2007; 25(15): 1986-1992; 5. Herold M, et al. Ann Oncol 2008; 19(Suppl 4): Abstract 329; 6. Salles G, et al. Blood. 2008; 112(13):4824–4831.*

R-CHEMOTHERAPY VS CHEMOTHERAPY META-ANALYSIS OF SURVIVAL: FL ONLY

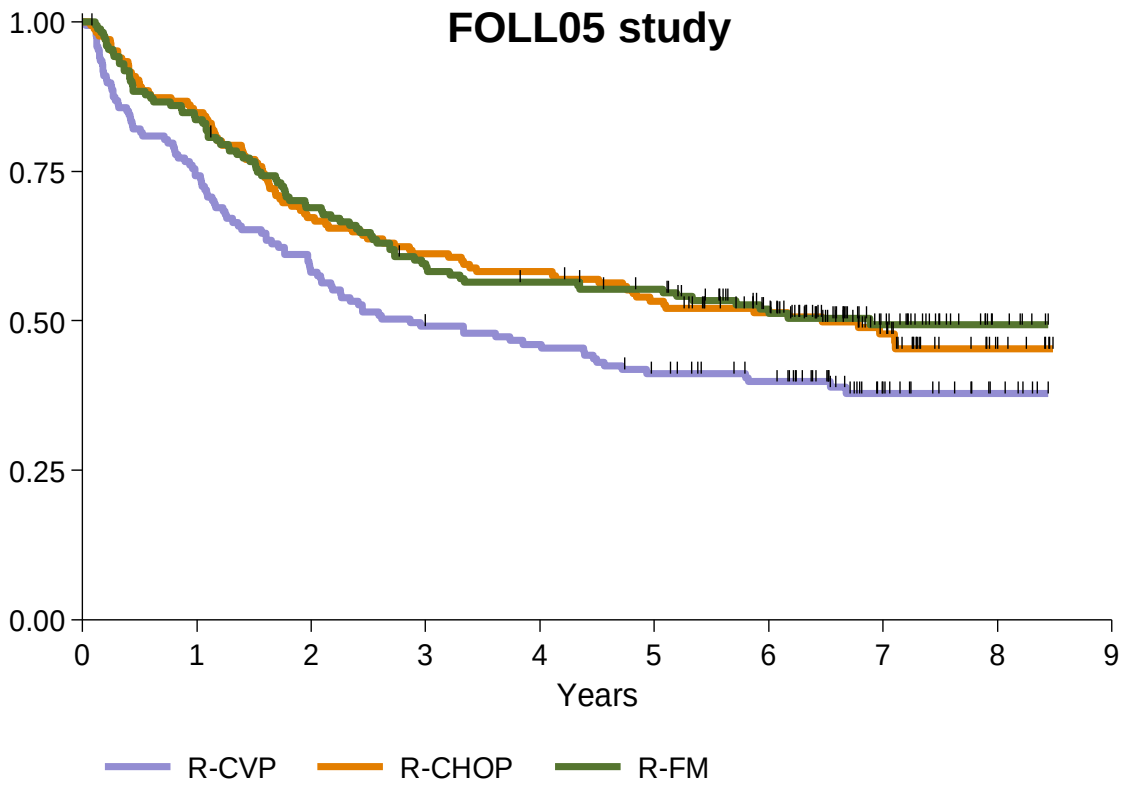


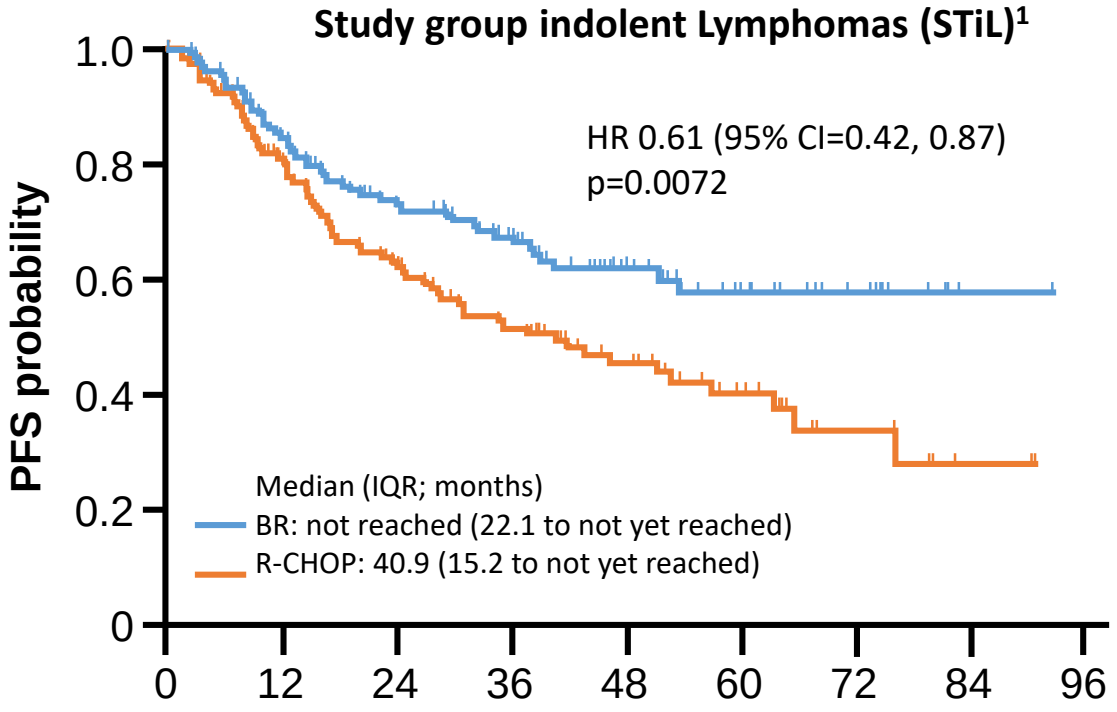
Adapted from Schulz H, et al. J Natl Cancer Inst 2007;

Sicuramente una immuno-chemioterapia.

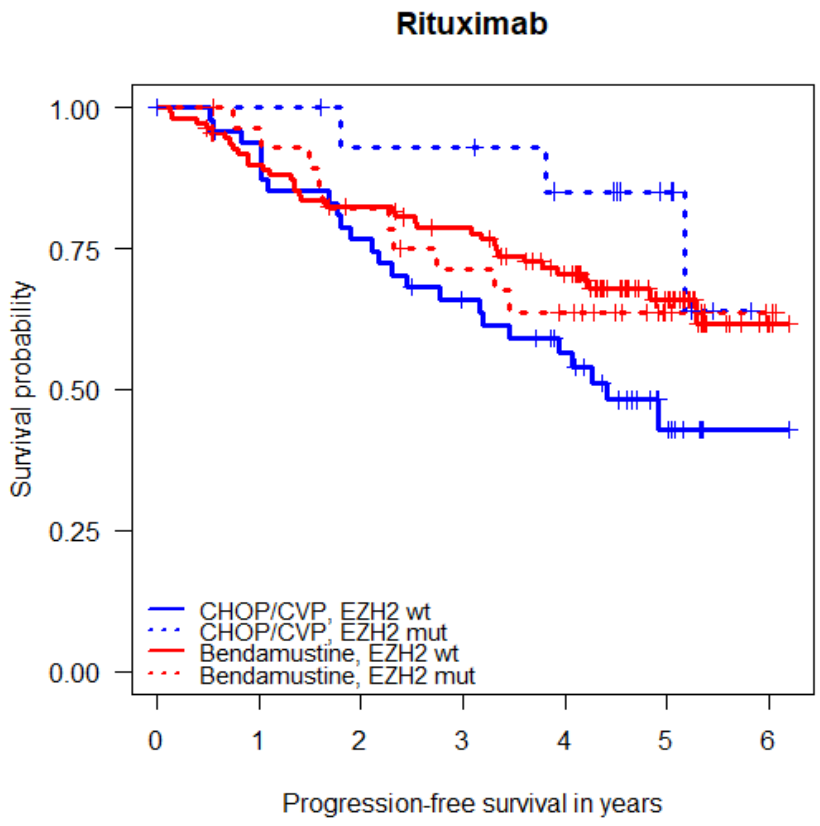
Ma quale chemioterapia e quale immunoterapia?

Quale chemioterapia

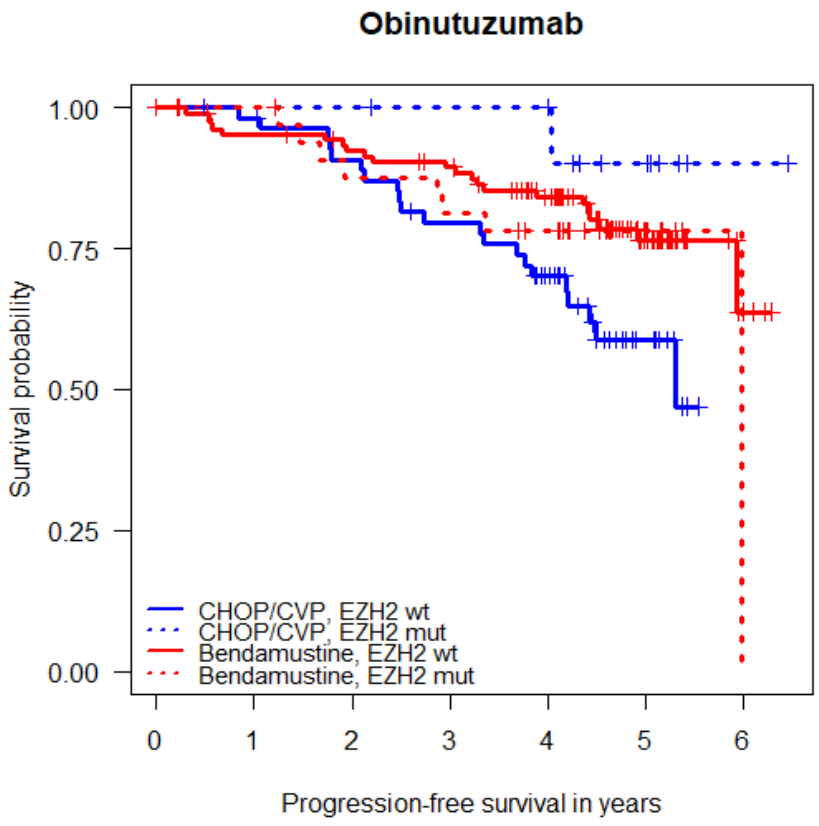




LINFOMA FOLLICOLARE NEL 2020



CHOP/CVP, EZH2 wt	49	44	36	29	22	8	1
CHOP/CVP, EZH2 mut	15	15	13	13	10	6	0
Bendamustine, EZH2 wt	111	97	87	80	63	29	2
Bendamustine, EZH2 mut	29	27	23	19	16	6	2

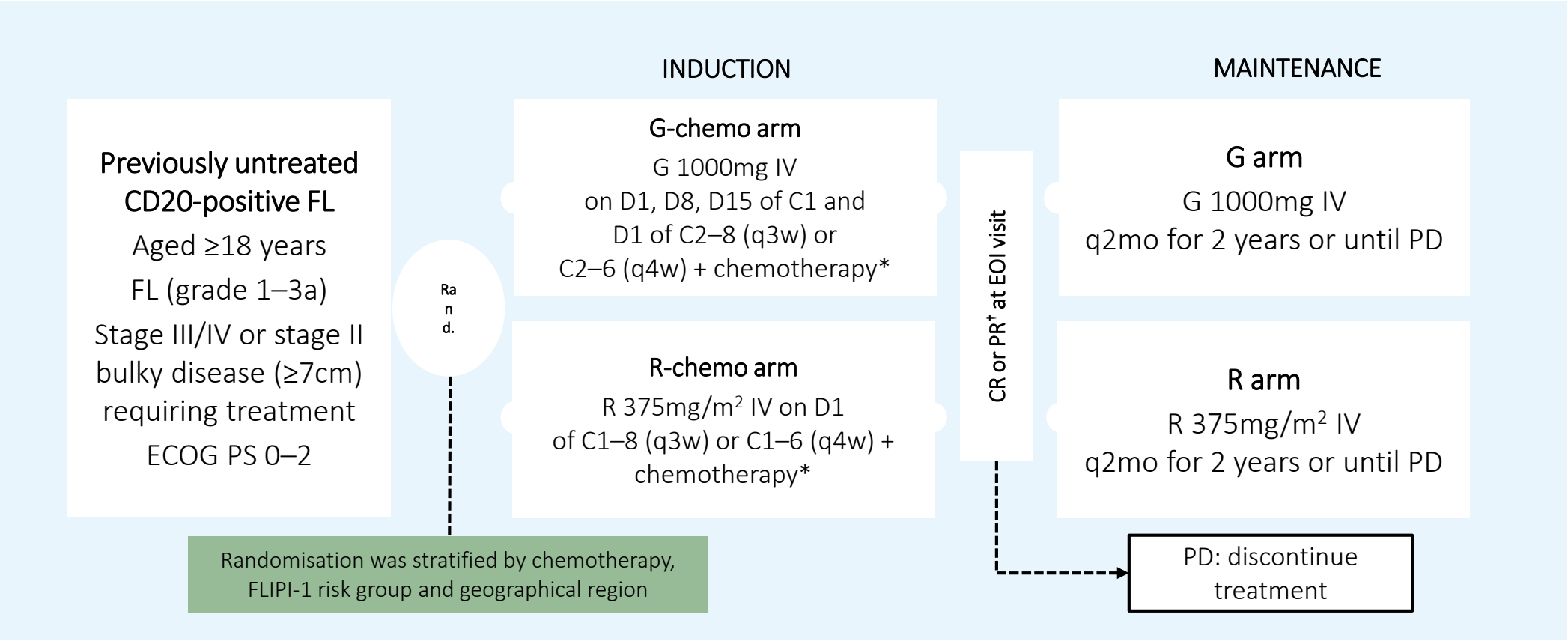


CHOP/CVP, EZH2 wt	56	54	49	42	31	10	0
CHOP/CVP, EZH2 mut	15	14	14	13	13	6	1
Bendamustine, EZH2 wt	109	100	95	90	74	33	3
Bendamustine, EZH2 mut	34	33	28	26	23	6	0

In presenza di EZH2 mutato la scelta della CHOP sembra ‘vincente’

Quale immunoterapia

International, open-label, randomised Phase III study in 1L pts



Primary endpoint

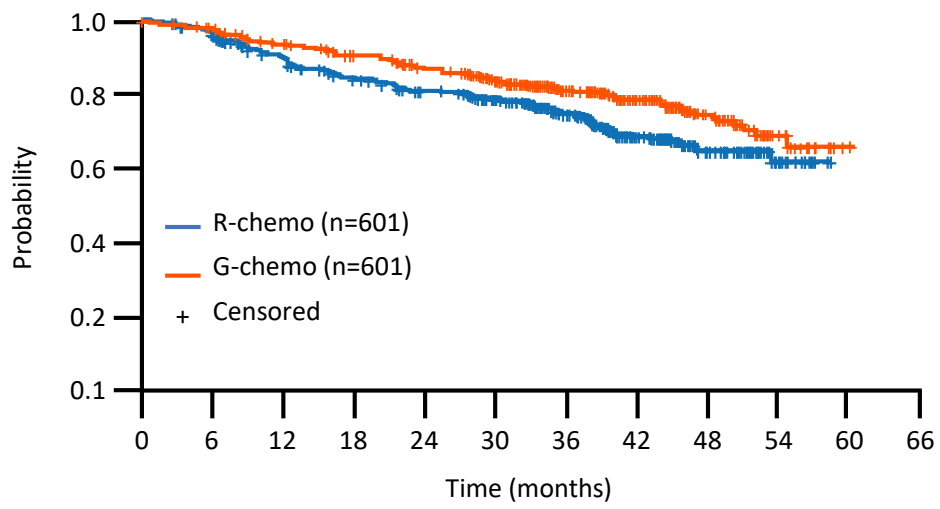
- PFS (INV-assessed)

Secondary endpoints

- PFS (IRC-assessed)
- OS, EFS, DFS, DoR, TTNALT
- ORR/CR at EOI (+/– FDG-PET)
- Safety
- PROs

Quale immunoterapia

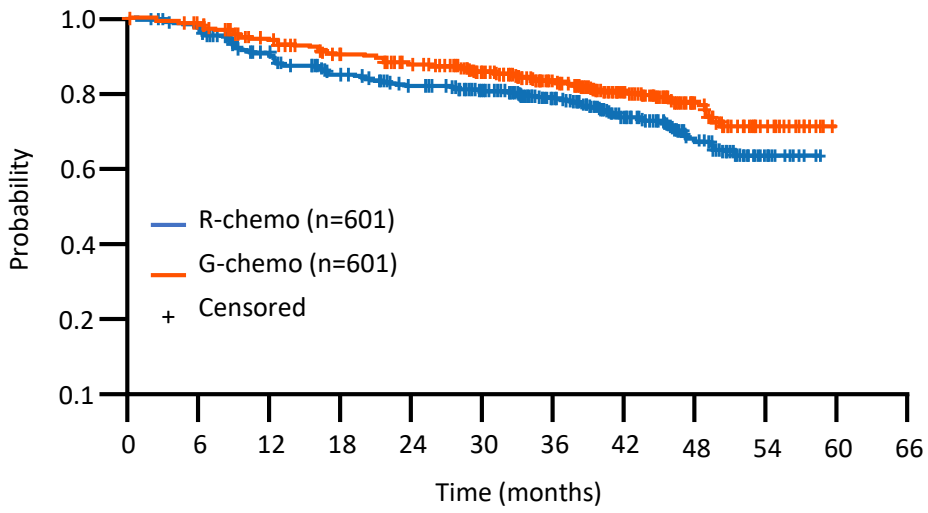
INV-assessed PFS



No. of patients at risk

G-chemo	601	561	505	464	438	396	267	149	77	18	
R-chemo	601	569	535	505	478	420	291	176	85	25	1

IRC-assessed PFS



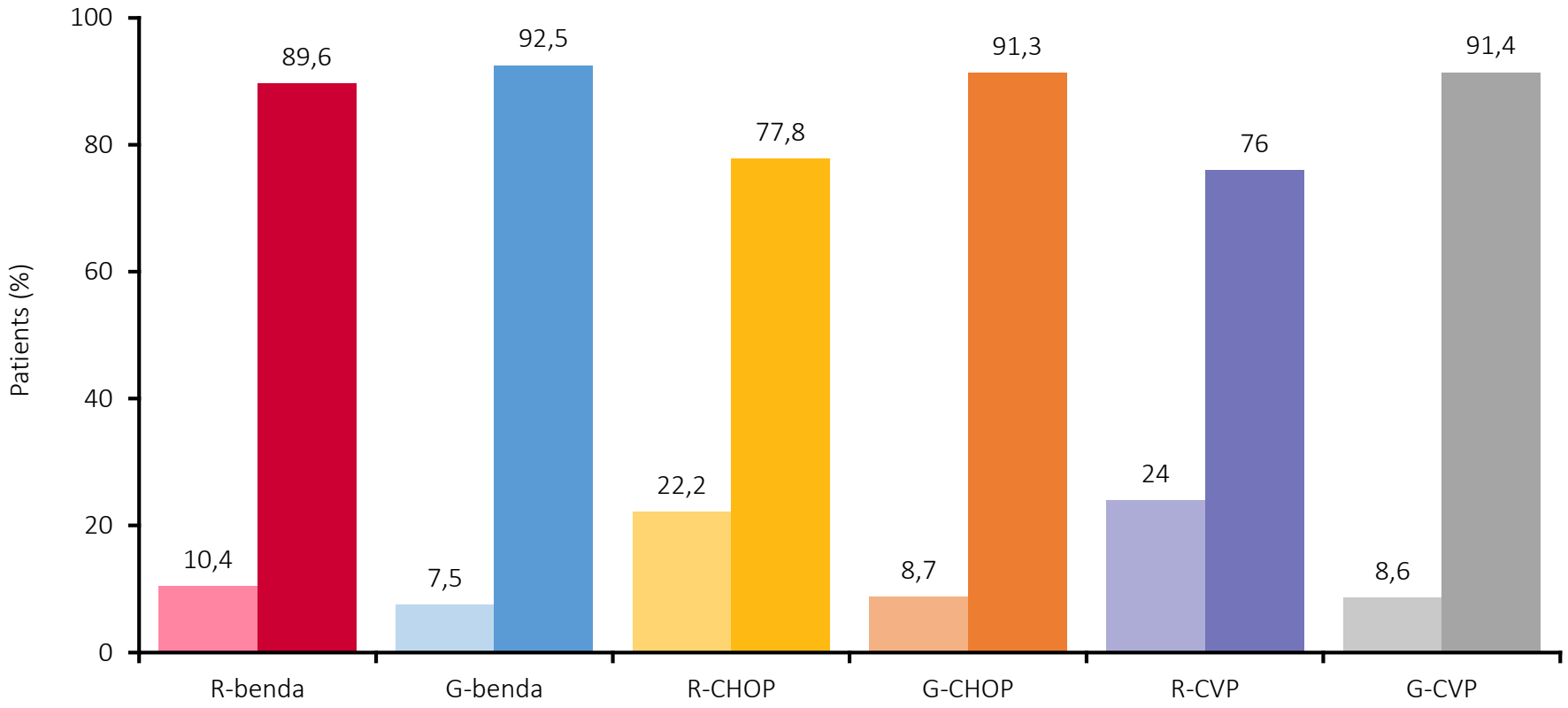
No. of patients at risk

G-chemo	601	563	502	463	438	394	271	151	73	16
R-chemo	601	571	532	497	476	414	287	179	79	22

	R-chemo, n=601	G-chemo, n=601
3-yr PFS, % (95% CI)	75.0 (71.0, 78.5)	81.5 (77.9, 84.6)
HR (95% CI), p-value†	0.68 (0.54, 0.87), p=0.0016	

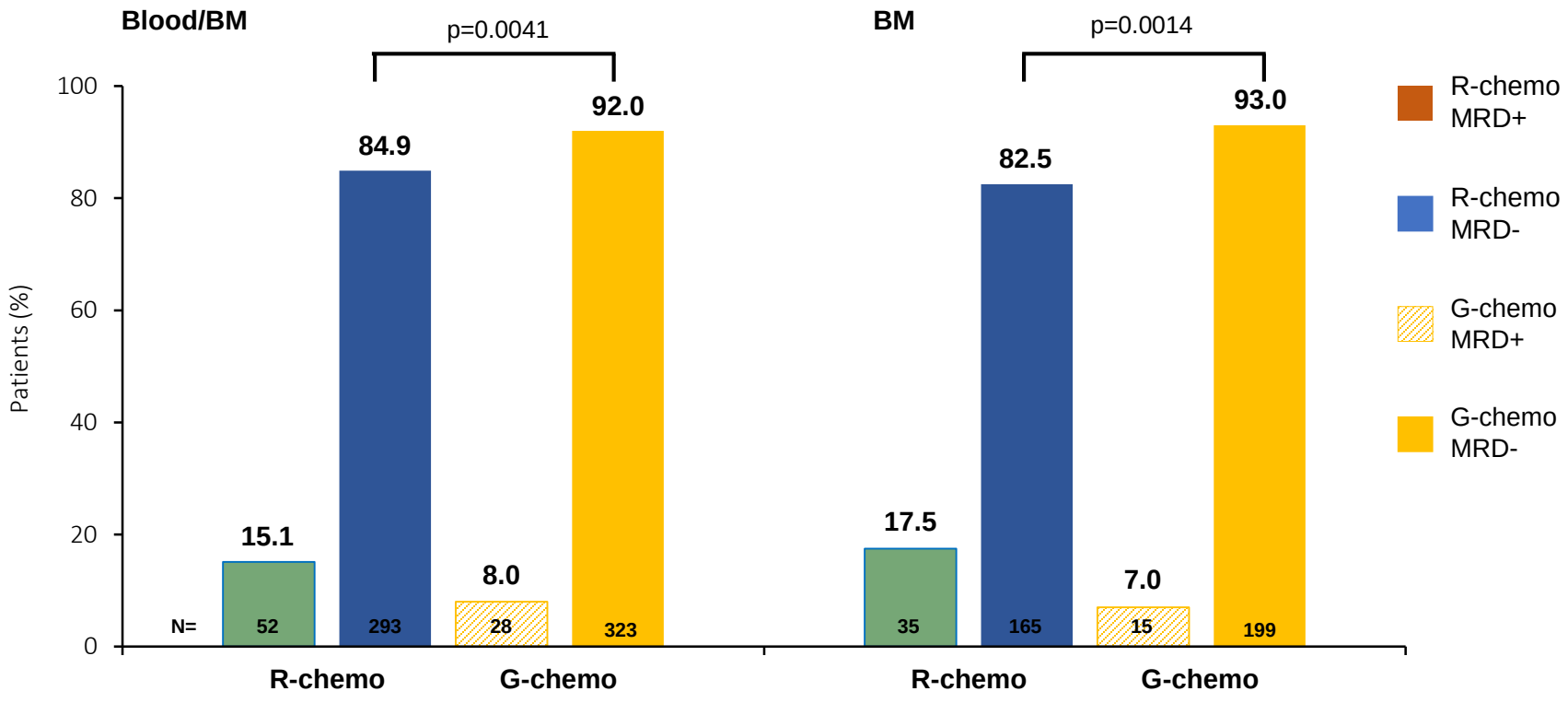
	R-chemo, n=601	G-chemo, n=601
3-yr PFS, % (95% CI)	78.9 (75.2, 82.1)	83.4 (79.9, 86.3)
HR (95% CI), p-value†	0.72 (0.56, 0.93), p=0.0118	

Quale immunoterapia



MRD at the end of induction

Quale immunoterapia



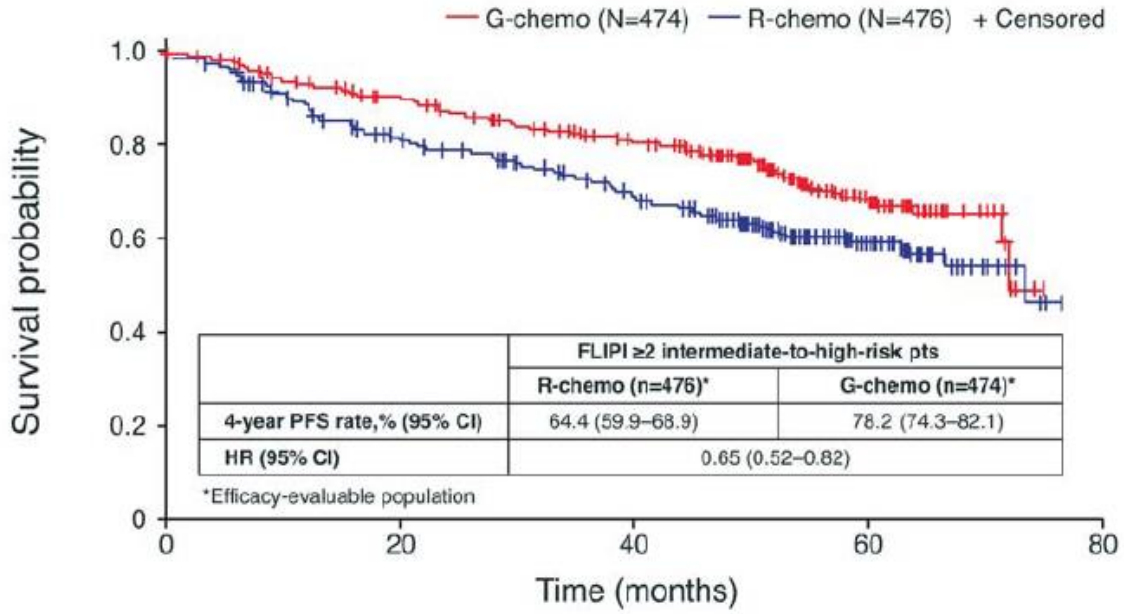
MRD status by compartment at end of induction

Quale immunoterapia

The treatment effect on PFS appeared to be different between pts with FLIPI <2 and FLIPI ≥2

PFS markedly improved in the FLIPI ≥2 pts (n=952) treated with G-chemo vs R-chemo (**HR=0.65** [95% CI: 0.52–0.82])

Figure. PFS (investigator assessed) in FLIPI ≥2 intermediate-to-high-risk pts



	FLIPI ≥2 intermediate-to-high-risk pts	
	R-chemo (n=476)*	G-chemo (n=474)*
4-year PFS rate,% (95% CI)	64.4 (59.9–68.9)	78.2 (74.3–82.1)
HR (95% CI)	0.65 (0.52–0.82)	

*Efficacy-evaluable population

Number at risk				
R-chemo 476	362	292	97	0
G-chemo 474	399	337	96	0

CI, confidence interval; FLIPI, Follicular Lymphoma International Prognostic Index; G-chemo, obinutuzumab plus chemotherapy; HR, hazard ratio; PFS, progression-free survival; pts, patients; R-chemo, rituximab plus chemotherapy

Quale immunoterapia

Fewer POD24 events occurred in FLIPI ≥2 pts treated with G-chemo vs pts treated with R-chemo with a 1-HR based risk reduction of 52.9% (95% CI: 31.9–67.4).

Overall population	vs.	pts FLIPI≥2
- 46%		- 52.9%

These data suggest that patients with FLIPI ≥2 have a better risk-benefit profile with G-chemo vs R-chemo, than those with FLIPI<2.

Defining a Hi-Risk population in Follicular Cell Lymphoma

Pre-upfront treatment models

Patient & disease as the 'probes'

- Clinical data at presentation
- Genetics/cytogenetics
- Gene Expression Profiling
- Combined models

Post-upfront treatment models

- ***Treatment as the 'probe'***
- Response *'mode'*
  i. timing, quality & duration
  ii. MRD
- Event *'mode'*
  i. Disease-related events
  ii. Treatment-related events
- Imaging *'mode'* (EOT)
- Gene Expression Profiling

Pre-upfront treatment models

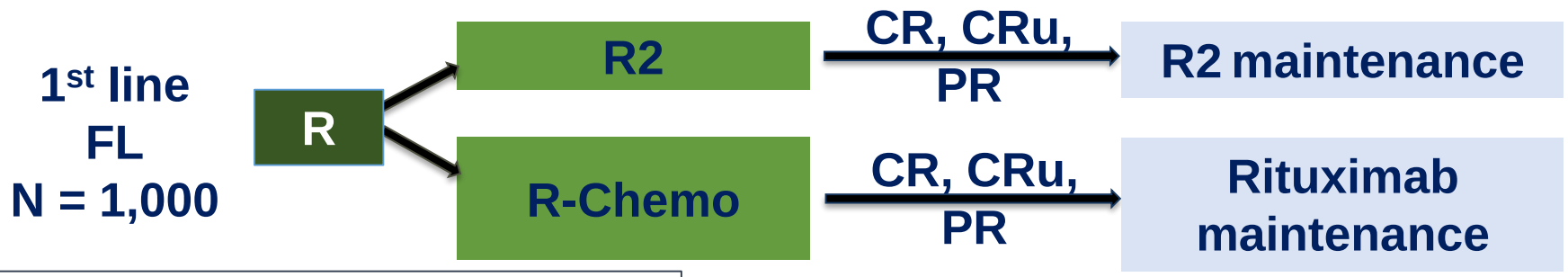
FLIPI ci può essere utile nella scelta dell'anticorpo

La genetica del linfoma può esserci utile nella scelta della chemioterapia

RELEVANCE: PHASE III STUDY DESIGN

(RITUXIMAB AND LENALIDOMIDE VERSUS ANY CHEMOTHERAPY, FL-001)

International, multicentre, randomized study



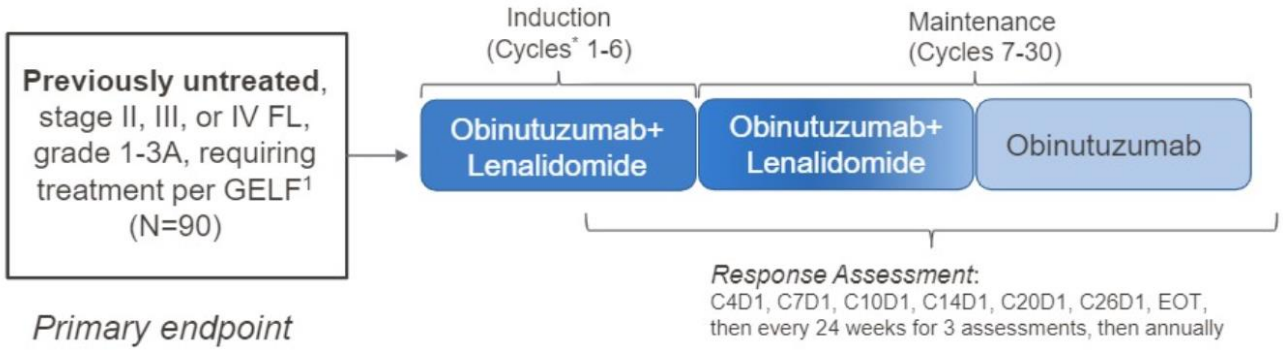
- R-Chemo
  - investigator choice of R-CHOP, R-CVP, R-B
- Lenalidomide
  - 20 mg × 6 cycles, if CR then 10 mg

- Co-primary endpoints
  - CR/CRu rate at 120 weeks
  - PFS

	R^2 (513)	R-Chemo (517)
CR/Cru at 120 W		
By IRC/INV	48%/55%	53%/58%
PFS 3 years	77%	78%
OS at 3 years	94%	94%

LINFOMA FOLLICOLARE NEL 2020

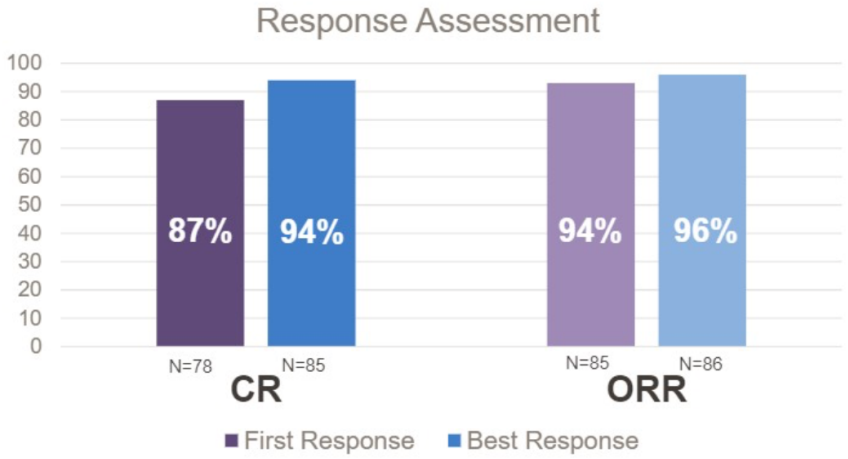
Study Design: Obinutuzumab + Lenalidomide in FL



Primary endpoint

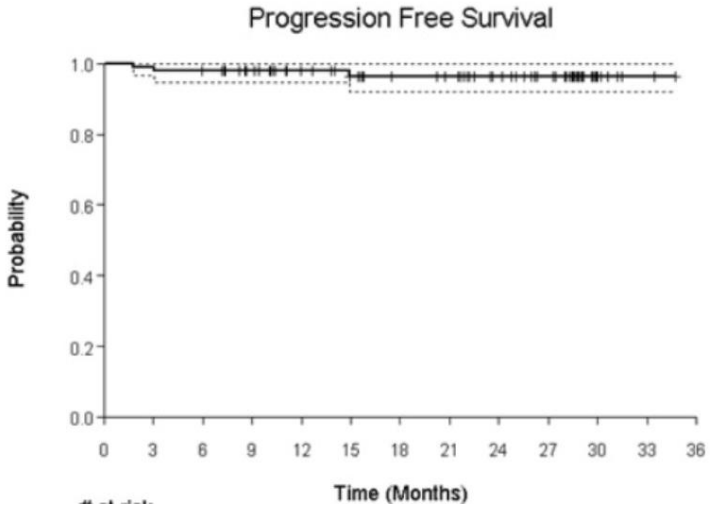
- Progression-free survival (PFS) at 2 years

Obinutuzumab + Lenalidomide Response



Obinutuzumab + Lenalidomide PFS

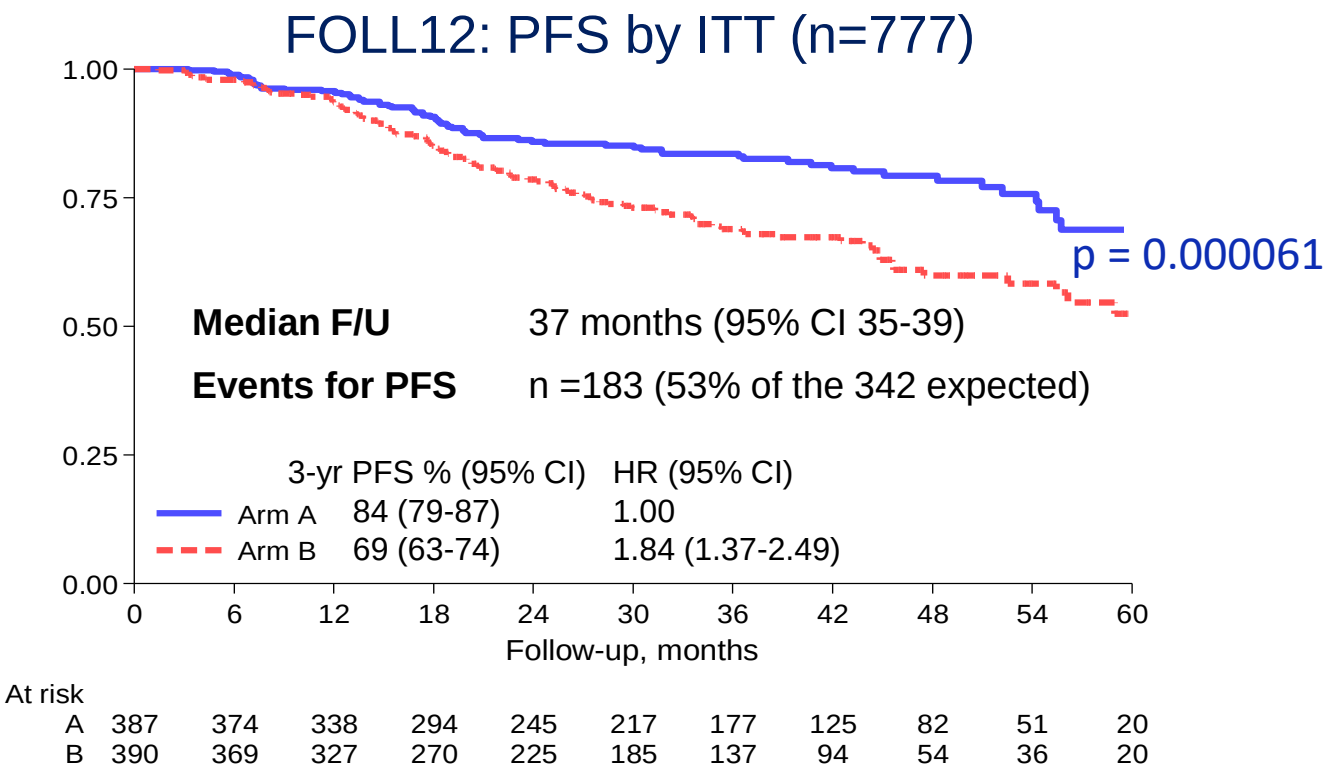
- With a median follow up of 25 months (range 6-35 months), the 2-year PFS estimate is 96% (95% CI 92-100%)

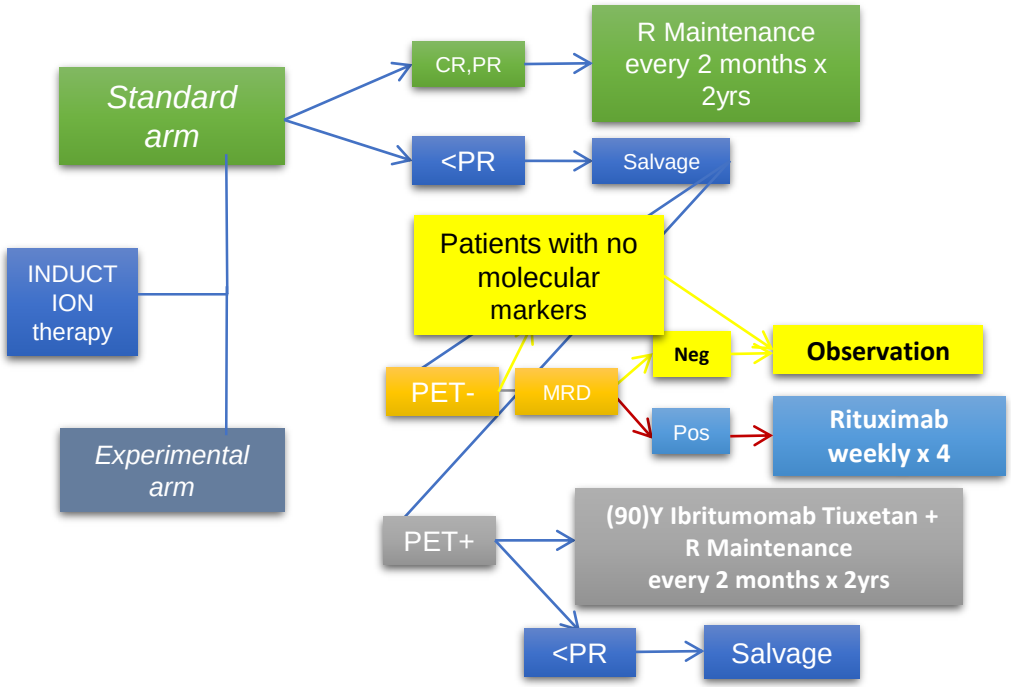


- Obinutuzumab in combination with lenalidomide was associated with early and very high complete response rates.
- Though limited by short follow-up (median follow-up 25 months), 2-year PFS estimates are very promising.
- The toxicity profile was manageable with few episodes of grade 3 or higher toxicity and no deaths have been observed to date.
- This phase II study suggests the combination of obinutuzumab and lenalidomide in previously untreated, high tumor burden FL results in favorable efficacy and safety profile warranting further study.

MD Anderson ASH 2019

Anti-CD20 maintenance





- A Complete Metabolic Response is good news
- A Complete Molecular Response is good news
- However, not enough to omit a 2 year rituximab maintenance

Take home messagges in advanced stages……..in 2020

- In low tumor burden WW is still a viable option, even if less toxic therapy……
- In high tumor burden immunochemotherapy is the standard
- It is possible to use more effective antibody (Obinutuzumab) according to clinical parameters (FLIPI)
- It is possible to chose CHOP according to genetic alteration (more than clinical behaviours), no more 'fideistic' attitude
- Chemo-free strategy will come soon (patients' selection)
- Maintenance can not be omitted

RELAPSED/REFRACTORY DISEASE

Post-upfront treatment models

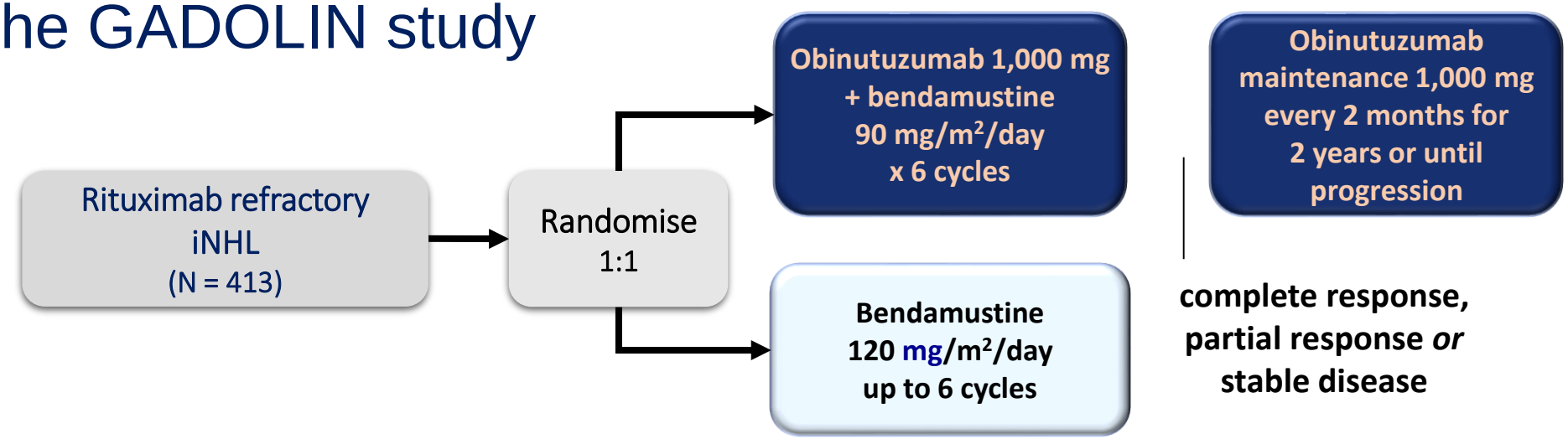
POD24 come indice di ‘aggressività’ della malattia

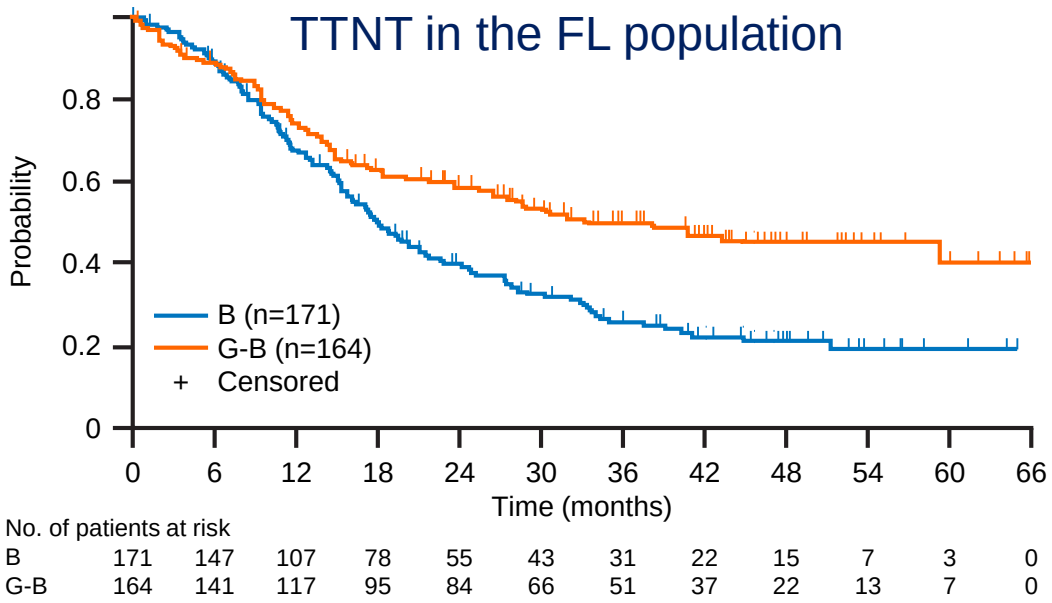
Risposta alla terapia MDR e Methabolic Response

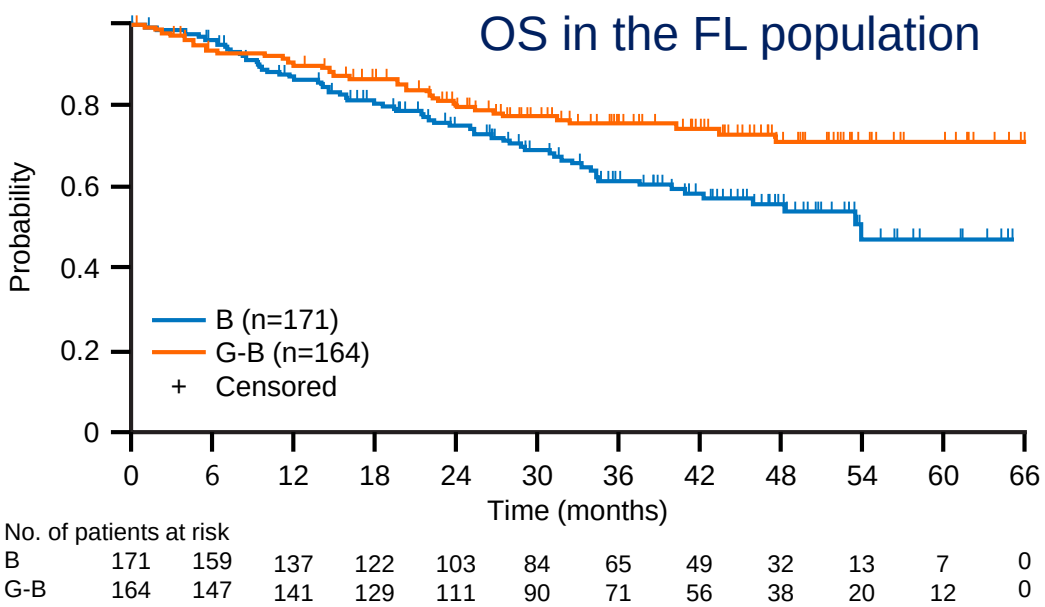
Paradigm of relapsed/refractory

Age >65 years		Age <65 years	
Early relapse (POD24)	**Late relapse (no POD24)**	**Early relapse (POD24)**	**Late relapse (no POD24)**
R^2/R-chemotherapy +/– R maintenance	Watch and Wait	ASCT	Watch and Wait
R^2	R^2/R-chemotherapy +/– R maintenance	R-chemotherapy +/– R maintenance	R^2/R-chemotherapy +/– R maintenance
Radioimmunotherapy	R^2	R^2	Radioimmunotherapy
R monotherapy	R monotherapy	Radioimmunotherapy	R monotherapy
	Radioimmunotherapy	Allo-transplant	

the GADOLIN study





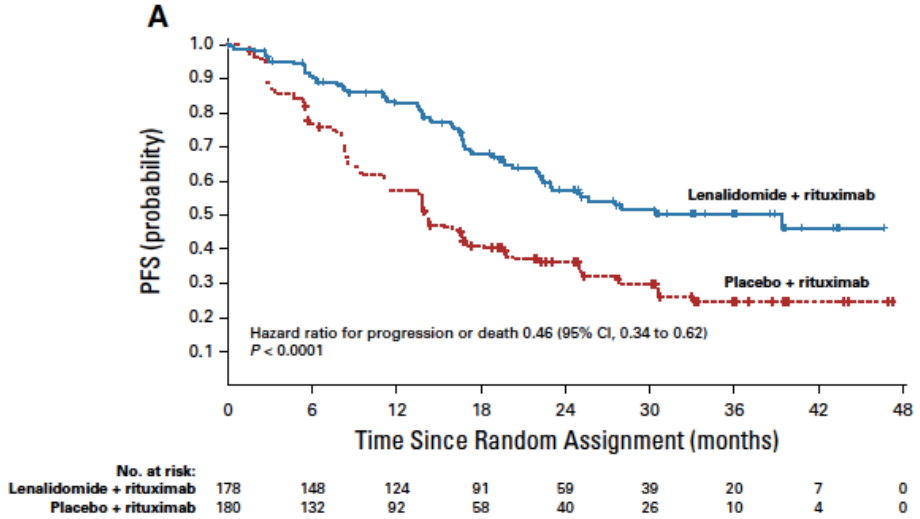


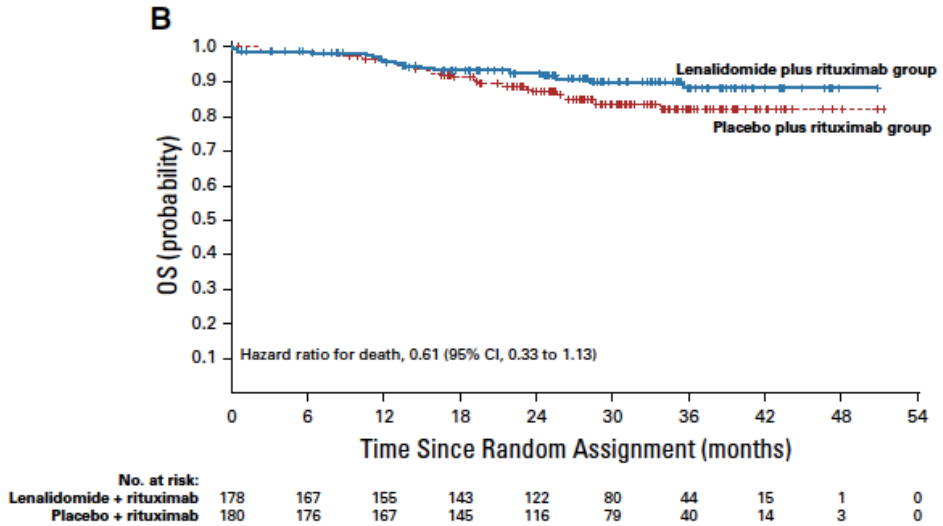
The GADOLIN study demonstrates a significant improvement in OS in the G-B arm (42% risk reduction in FL patients)

AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma

John P. Leonard, MD[1]; Marek Trneny, MD[2]; Koji Izutsu, MD[3]; Nathan H. Fowler, MD[4]; Xiaonan Hong, MD[5]; Jun Zhu, PhD[6]; Huilai Zhang, MD[7]; Fritz Offner, MD, PhD[8]; Adriana Scheliga, MD[9]; Grzegorz S. Nowakowski, MD[10]; Antonio Pinto, MD[11]; Francesca Re, MD[12]; Laura Maria Fogliatto, MD, PhD[13]; Phillip Scheinberg, MD[14]; Ian W. Flinn, MD, PhD[15]; Claudia Moreira, MD[16]; José Cabeçadas, MD[17]; David Liu, MD, PhD[18]; Stacey Kalambakas, MD[18]; Pierre Fustier, PhD[19]; Chengqing Wu, PhD[18]; and John G. Gribben, MD, DSc[20]; for the AUGMENT Trial Investigators

J Clin Oncol 37:1188-1199. © 2019 by American Society of Clinical Oncology





The magnitude of efficacy differences between the two treatments is clinically meaningful and suggests that lenalidomide plus rituximab should replace rituximab monotherapy as a standard of care for patients with relapsed or refractory indolent NHL.

LINFOMA FOLLICOLARE NEL 2020

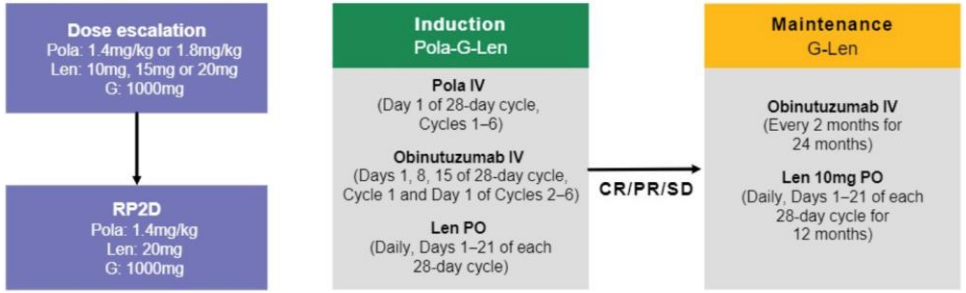
Polatuzumab vedotin plus obinutuzumab and lenalidomide in patients with relapsed/refractory follicular lymphoma: primary analysis of the full efficacy population in a Phase Ib/II trial

Catherine Diefenbach,[1] Brad Kahl,[2] Lalita Banerjee,[3] Andrew McMillan,[4] Fiona Miall,[5] Javier Briones,[6] Raul Cordoba,[7] Jamie Hirata,[8] YiMeng Chang,[9] Lisa Musick,[8] Pau Abrisqueta[10]

[1]Perlmutter Cancer Center at NYU Langone Health, New York, NY, USA; [2]Division of Oncology, Washington University, St Louis, MO, USA; [3]Oncology Centre, Maidstone and Tunbridge Wells NHS Trust, Kent, United Kingdom; [4]Centre for Clinical Haematology, Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom; [5]Department of Haematology, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom; [6]Department of Hematology, Hospital Santa Creu i Sant Pau, Barcelona, Spain; [7]Fundacion Jimenez Diaz University Hospital, Madrid, Spain; [8]Genentech, Inc., South San Francisco, CA, USA; [9]F. Hoffmann-La Roche Ltd, Mississauga, Canada; [10]Hospital Vall Hebron, Barcelona, Spain

Study design

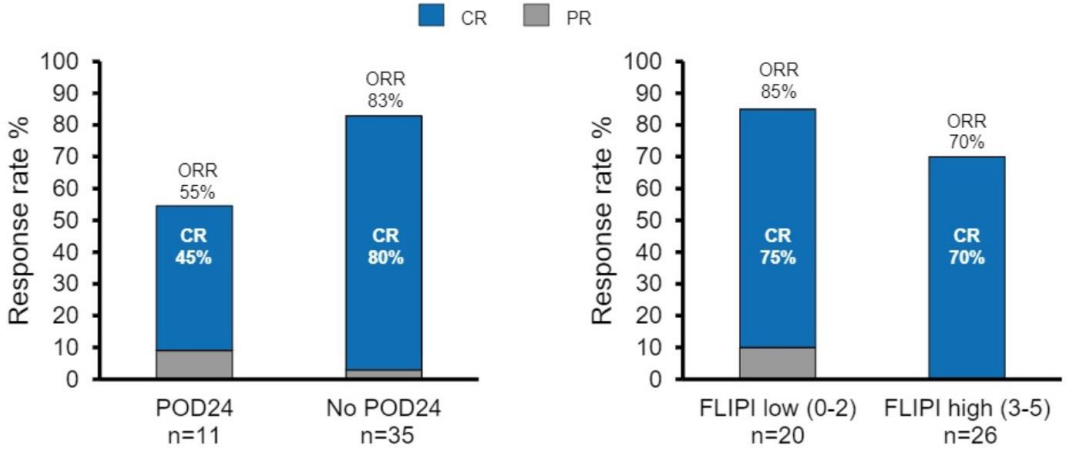
Open-label, single-arm, Phase Ib/II study in patients with R/R FL



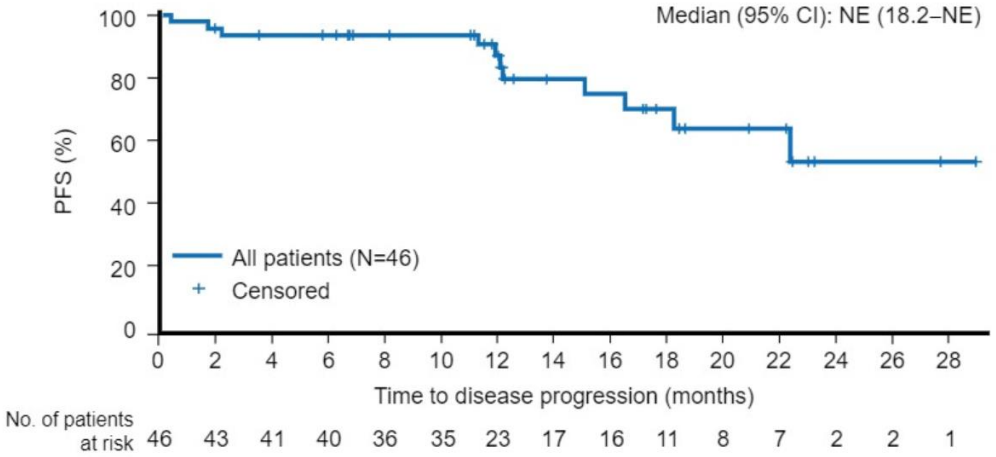
Primary efficacy endpoint:
CR at EOI, as determined by the IRC, on the basis of PET-CT scans (by Modified Lugano 2014 criteria)

Subgroup analysis

POD24 and FLIPI high



Kaplan-Meier curve of PFS



- Median PFS remains immature
- 12-month PFS[1] = 83.4% (CI: 70.85–95.96); median duration of follow-up = 15.1 months

Diefenbach C. ASH 2019

INVESTIGATIONAL THERAPIES

Microenvironment

Lenalidomide

T-cell exhaustion

Actionable mutations

EZH2
E7438

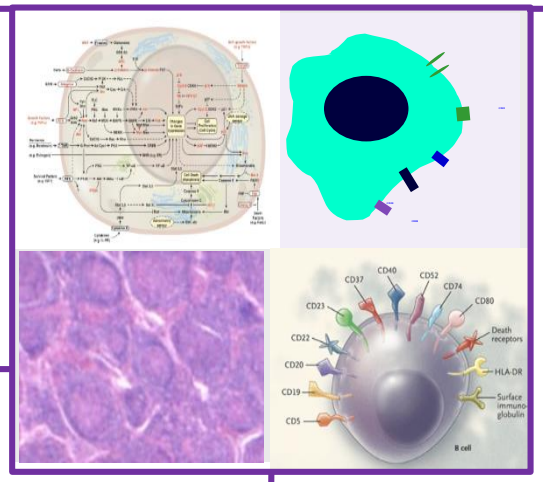
CD79a/b
AEB071

Proteosome inhibitors
Bortezomib

Bcl-2 family inhibitors
ABT-263

Survivin inhibitors
YM155

Syk inhibitors
Fostamatinib + others



Pathways

mTOR inhibitors
Everolimus
Temsirolimus

PI3K inhibitors
Idelalisib
Copanlisib
Duvelisib
TGR-1202

Btk inhibitors
Ibrutinib
ONO/GS-4059
ACP-196

Hsp 90 inhibitors
KW 2478

Surface markers

Anti CD20 moAb
Ofatumumab
GA-101

Anti CD40 moAb
Dacetuzumab

Anti CD22
Epratuzumab
Inotuzumab Ozogamicin
polatuzumab

HDAC inhibitors
Vorinostat
Panobinostat

PKC inhibitors
Enzastaurin

Aurora kinase inhibitors

Nedd8-activating enzyme inhibitors
MLN4924

Leading Molecular Targets and Drugs in Lymphoma

Pathway	Target	Drug	Response Rate					
			DLBCL	**FL**	**MCL**	**SLL/CLL**	**T-Cell**	**HL**
PI3K/AKT/mTOR	mTOR	Everolimus	30%	50%	32%	18%	63%	42%
		Temsirolimus	36%	56%	38%	10%	-	-
	AKT	MK2206	0%	25%	9%	(50%)	0%	20%
	PI3K-δ	Idelalisib	-	57%	40%	72%	-	12%
		TGR-1202	11%	42%	33%	63%	-	13%
	PI3K-γδ	Duvelisib	0%	67%	67%	54%	33%	33%
	PI3K-αδ	Copanlisib	25%	46%	71%	67%	50%	-
		BKM120	12%	25%	23%	-	-	-
B Cell Receptor (BCR)	Syk	Fostamatinib	22%	10%	11%	55%	0%	-
	Btk	Ibrutinib	26%	28%	75%	67%	-	-
Apoptosis	Bcl-2	Venetoclax	15%	34%	75%	77%		
Immune checkpoint	PD1	Nivolumab	36%	40%	-	-	-	87%
		Pambrolizumab	-	-	-	-	-	66%

Younes et al, Nature Rev Clin Oncol 2017

We are waiting for……..

- Epigenetic alterations inhibitors: HDAC, EZH2
- Immune checkpoint inhibitors
- Chimeric antigen receptor T cell therapy
- Bispecific antibodies

Take home messagges in relapsed/refractory……..in 2020

- In high risk young patients (POD24) ASCT is still a viable option
- New antibody play an important role in Rituximab refractory patients either in induction or in manteinance
- Immunotherapy without chemotherapy (lenalidomide + anti-CD20) is a valid option
- New therapy (PI3K inhibitor, anti-bcl2, anti-BTK) as bridge to allogeneic transplant (?)
- We are waiting for new options (ICP, CAR-T, BITEs)

CONCLUSIONS: PROSPECTS FOR 2020

SELECTING THE MOST APPROPRIATE TREATMENT FOR A PATIENT:

- Identify high risk patient
- Novel therapies
- Identify predicitive biomarkers of progression, response and resistence

AVAILABILITY OF A CLINICAL USEFUL TOOL TO IDENTIFY PATIENTS WITH HIGH-RISK DISEASE:

- Integration of molecular, clinical, imaging parameters to define prognosis

SPECIFIC GENETIC AND EPIGENETIC ABERRATION IN AN INDIVIDUAL PATIENT ARE NOT CURRENTLY ACCOUNTED FOR MANAGEMENT:

- Better understanding of disease biology may reveal new therapeutic options to obtain targeted therapies mached to individual disease

Grazie!