SABATI EMATOLOGICI DELLA ROMAGNA
Faenza 14 maggio 2016

Guarire un linfoma follicolare è possibile?
I guariti: passato, presente e futuro

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Hematology Department
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LINFOMA FOLLICOLARE

LE EMOPATIE **A. Ferrata**
“La linfoadenosi cronica aleucemica s’inizia in maniera subdola e può decorrere per un periodo discretamente lungo. La prognosi è sempre infausta, non essendo registrati finora casi di guarigione”

LEZIONI DI EMATOLOGIA **S. Tura**
“Il decorso può essere lento, ma l’esito è, nella maggior parte dei casi, fatale”

HEMATOLOGY **Williams**
“None of these therapies , however, is considered curative and most patients eventually relapse with recurrent disease”.

MALATTIE DEL SANGUE E DEGLI ORGANI EMOPOIETICI **G. Castoldi**
“I soggetti con linfoma a basso rischio rappresentano l’unico gruppo in cui la chemioterapia non determina nessun vantaggio in termini di sopravvivenza”

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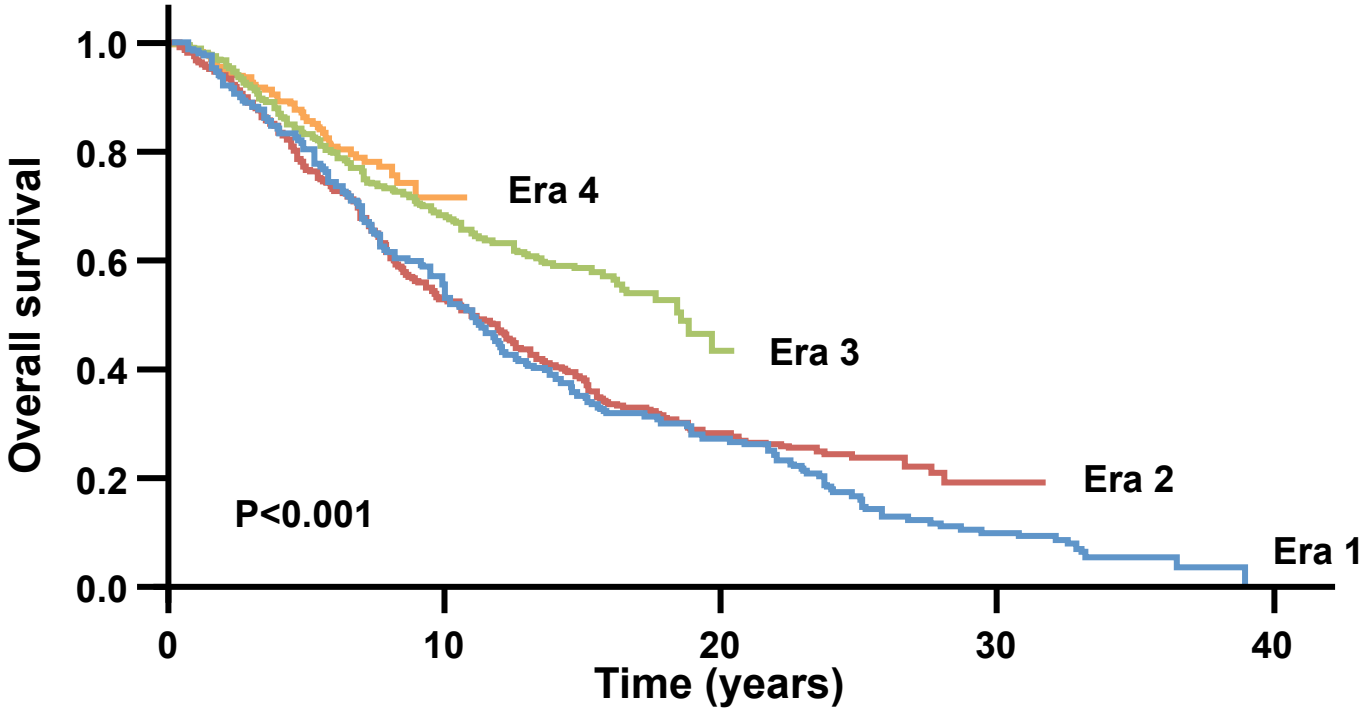
Tutti i manuali di ematologia nel capitolo sui linfomi follicolari iniziavano e iniziano con la frase: "i linfomi follicolari sono malattie non guaribili……" forse i prossimi non inizieranno più così

Affronterò i seguenti argomenti:

- Gli stadi localizzati sono guaribili !
- Low tumor burden FL come trattarli?
- Non tutti i linfomi follicolari sono uguali: come fare a distinguerli?
    - Indici prognostici (FLIPI, FLIPI2, M7FLIPI)
    - Malattia minima residua
    - PET/CT
- Le terapie ad alte dosi con supporto di staminali che ruolo hanno?
- Il Rituximab e gli altri anticorpi monoclonali, quale ruolo?
- La immuno-chemioterapia quanti FL guarisce?
- Le nuove terapie 'target'
- La induzione chemio-free, 'utopia'?

Improvements in OS over multiple decades attributable 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.

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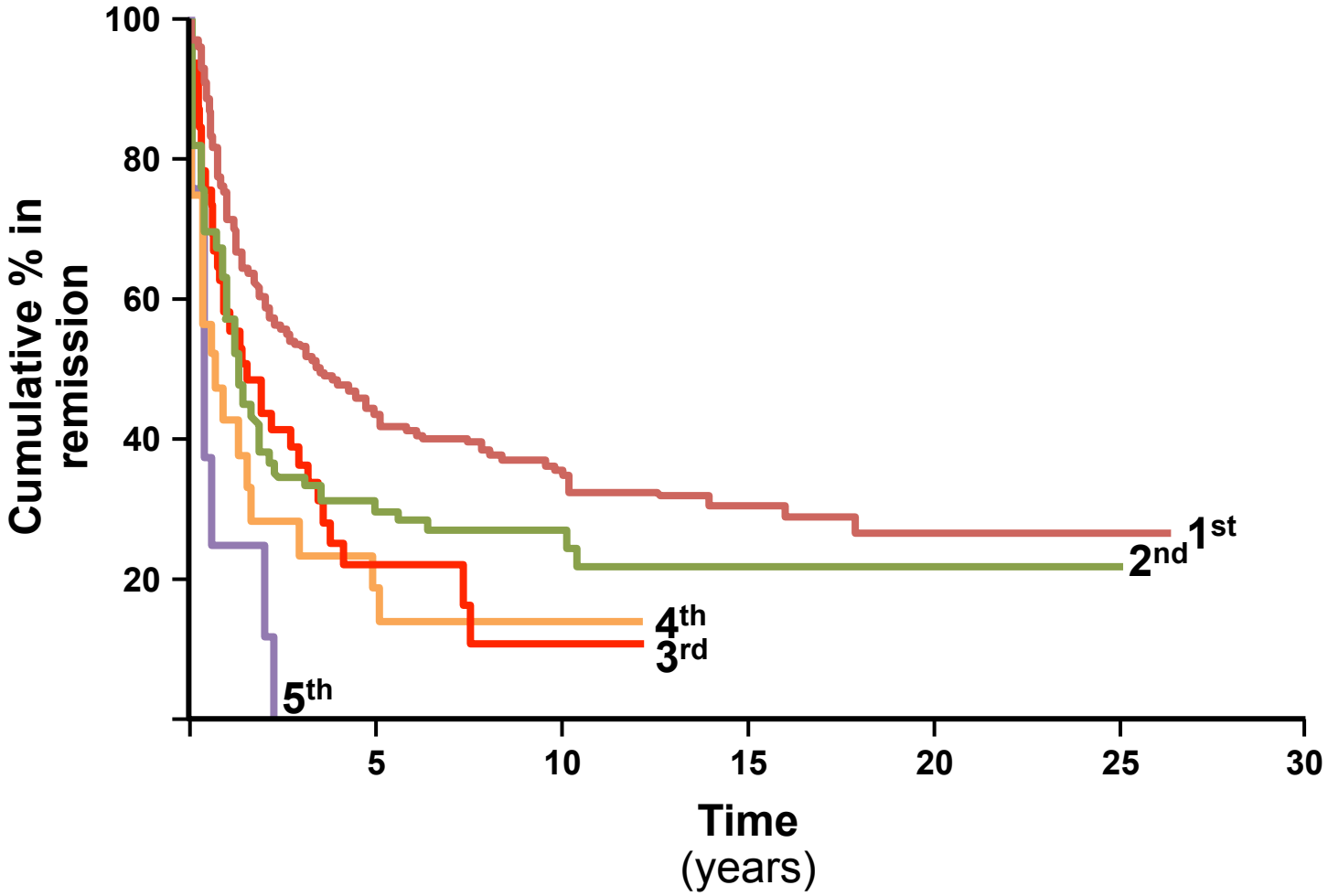
Important to remember the old data
FOLLICULAR LYMPHOMA: DURATION OF REMISSION

Outcome of treatment in patients with recurrent FL: 20-year study from a single centre



- Adapted from Johnson PWM A et al. J Clin Oncol 1995;13:140–147

Updated based on personal communication to speaker

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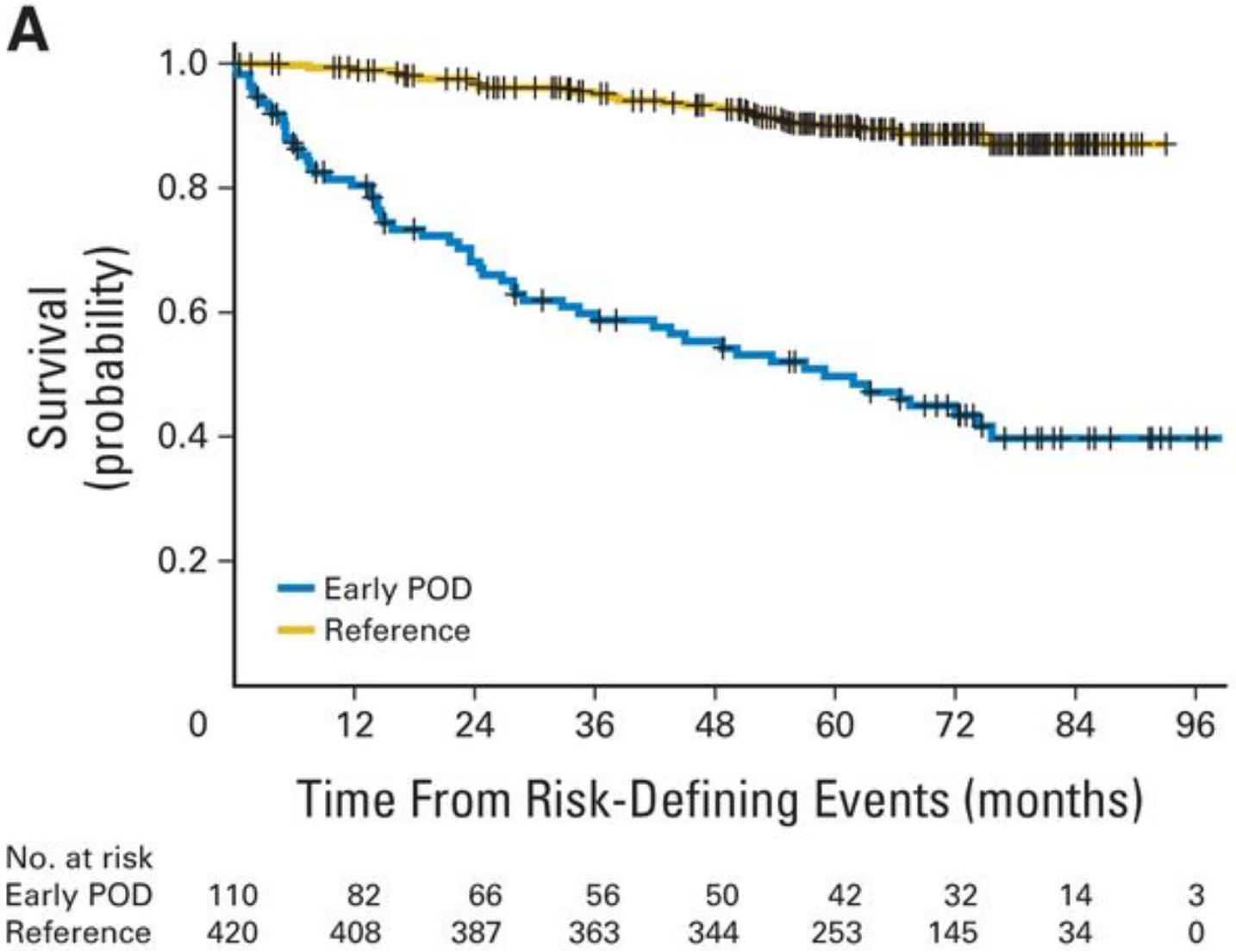
Early progression post R-CHOP portents a poor survival



Carla Casulo et al. JCO 2015;33:2516-2522

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Recommendations Patients with Stage I–II disease, a low tumor burden, and with documented contiguity of involved lymph-nodes treatable in the same radiotherapy field, should receive external involved field radiotherapy, at the dose of 24 Gy (quality of evidence, low; strength of recommendation, strong).

SIE-SIES-GITMO revised guidelines for the management of follicular lymphoma

Zinzani PL, Marchetti M, Billio A, Barosi G, Carella AM, Lazzarino M, Martelli M, Rambaldi A, Rigacci L, Tarella C, Vitolo U, Tura S.

SIE, SIES, GITMO revised guidelines

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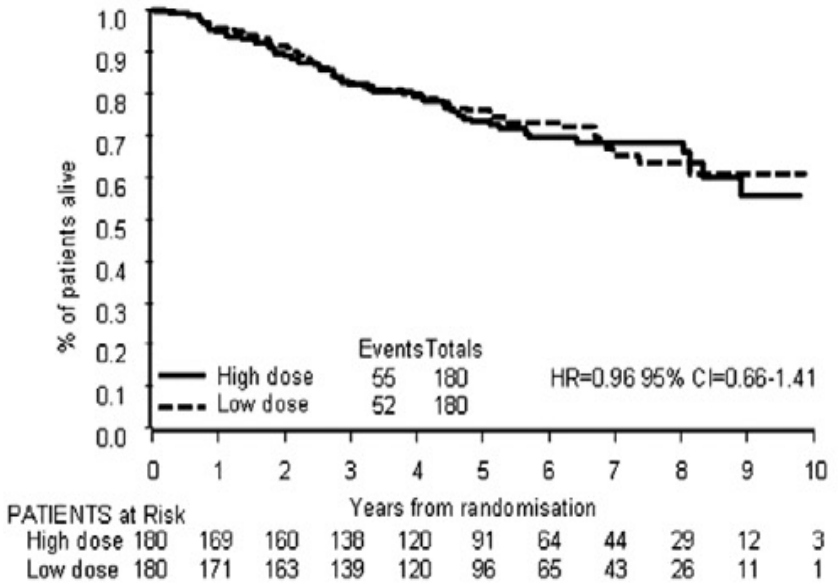
Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: A randomised phase III trial

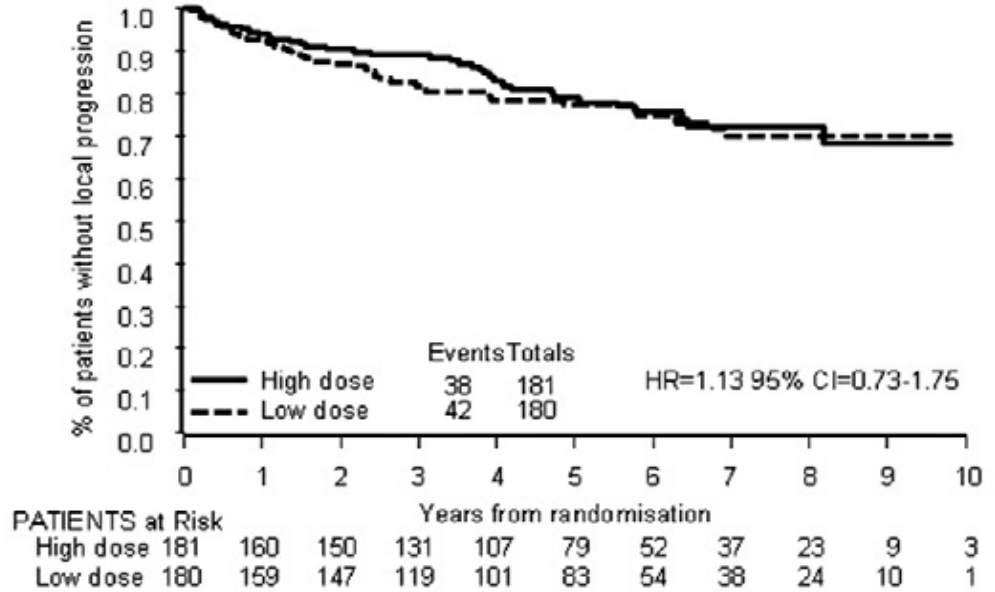
40-45 Gy in 20-23 fractions *vs* **24 Gy in 12 fractions**

361 cases of indolent lymphoma

Overall survival



Freedom from local progression



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Decision to initiate treatment is based on the assessment of tumour burden

GELF[1] criteria for high tumour burden[2]

- High tumour bulk defined by either[1]
  - Three distinct nodal sites, each ≥3 cm[1]
  - Single nodal site ≥7 cm[1]
  - Symptomatic splenic enlargement[1]
  - Cytopenias (leukocytes <1.0 x 10^9/L, and/or platelets <100 x 10^9/L)[1]
  - Circulating lymphoma cells (5 x 10^9/L)
  - Peritoneal ascites or pleural effusion[1]
- Presence of B symptoms[1]
- Serum LDH or β2-microglobulin above normal values[1]
- Performance status ≥1[1]

BNLI[3] criteria for high tumour burden[2]

- Progressive disease within 3 months of diagnosis[1]
- Vital organ involvement[1]
- Renal or liver infiltration[1]
- Bone lesions[1]
- B symptoms or pruritus[1]
- Cytopenias (haemoglobin <10 g/dL, leukocytes <3.0 x 10^9/L, platelets <100 x 10^9/L; related to marrow involvement)[1]

BNLI: British National Lymphoma Investigation; GELF: Groupe d'Etude des Lymphomes Folliculaires; LDH: lactate dehydrogenase

- 1. Brice P, *et al. J Clin Oncol* 1997; 15:1110–1117.
- 2. Smith SM. *Hematology Am Soc Hematol Educ Program* 2013; 2013:561–567.
- 3. Ardeshna KM, *et al. Lancet* 2003; 362:516–522.

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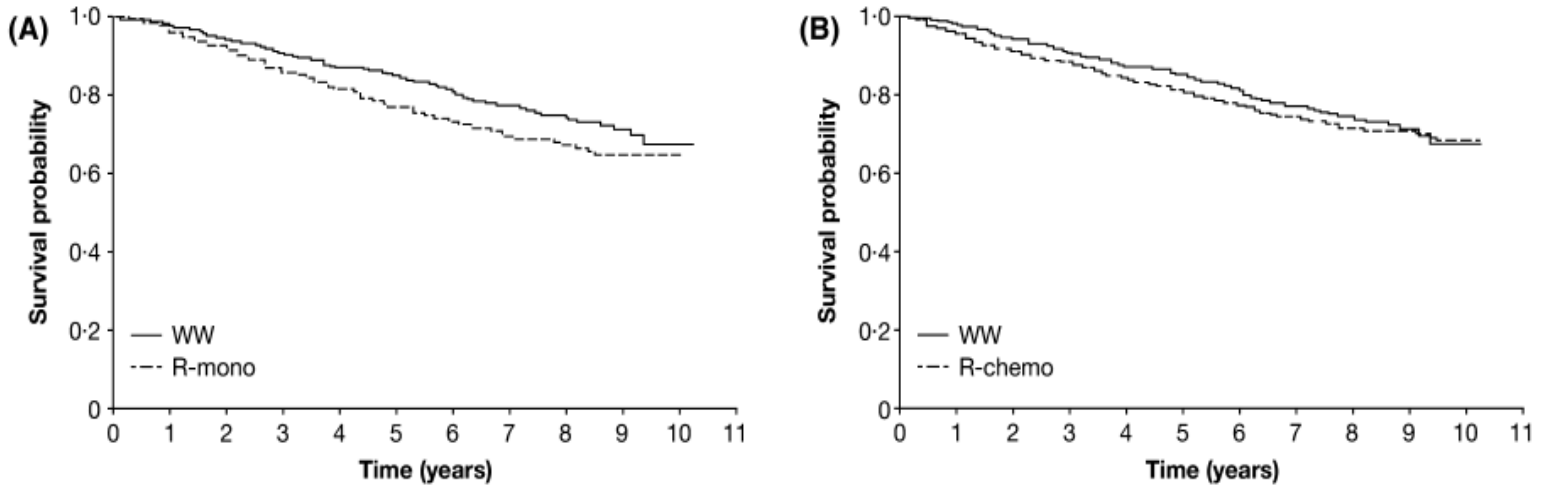
Watch & Wait

- 1754 patients diagnosed 2004-2007 in the United States (retrospective study)
  - initial watchful waiting (n=386)
  - initial rituximab monotherapy (n=296) better TtoCT
  - initial chemoimmunotherapy (n=1072) better PFS1, PFS2, .TtoNT
- 8-year overall survival estimates of 74%
- No differences between W/W, RTX and CT-RTX



"initial management with watchful waiting in the context of sequential therapy remains a viable option for FL patients in the modern era"

Nastoupil et al, BJH 2016

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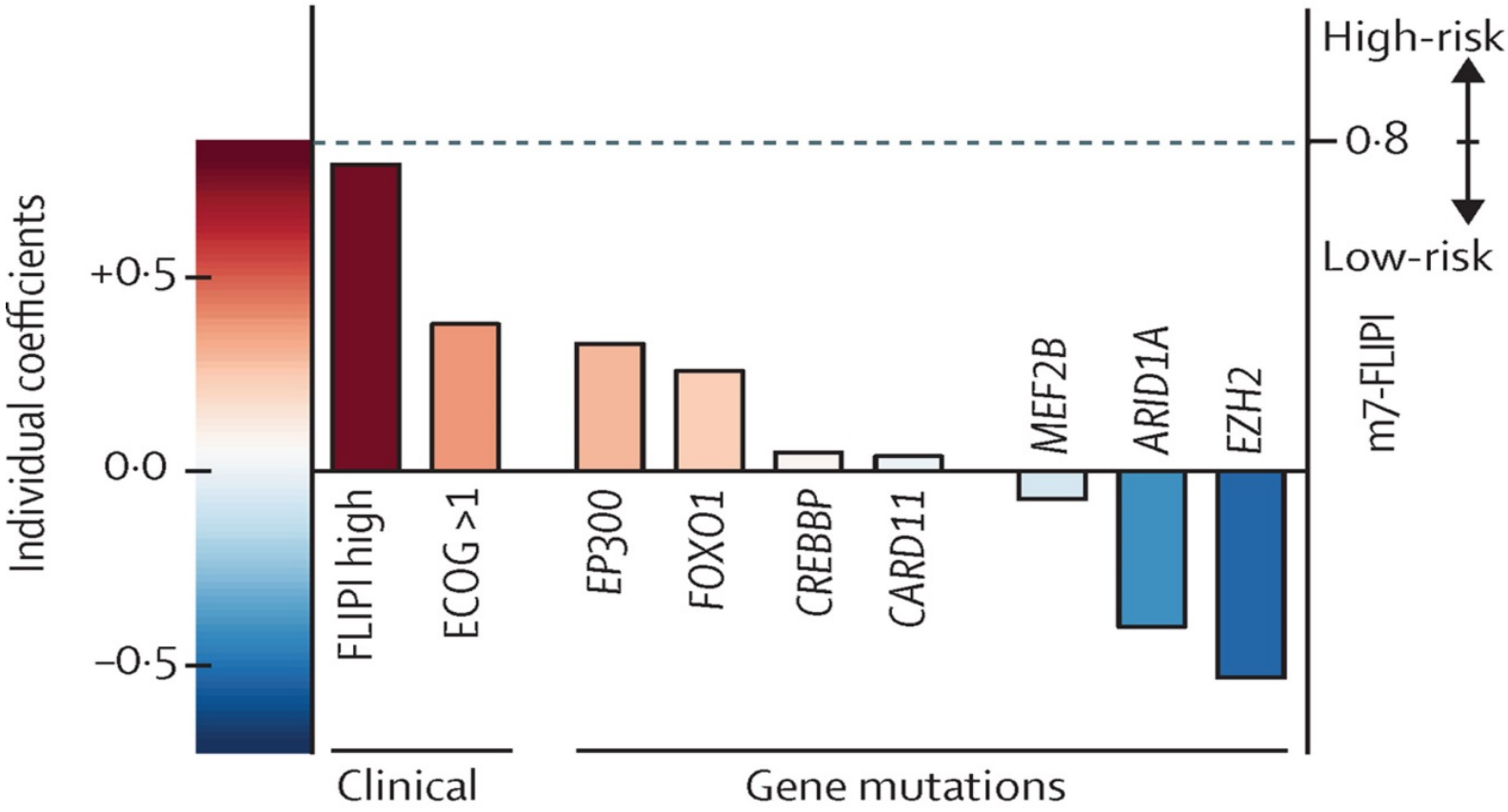
Current concepts in FL

- The identification patients at high risk of relapse is a critical goal of modern research in oncohematology and FL.
- Individual risk of relapse is estimated:
  - Before therapy: Prognostic scores (FLIPI and FLIP2), biomarkers, SNPs, GEP mol. signatures
  - After therapy: FDG-PET, CT-scan, MRD

Improving identification of poor risk groups: m7-FLIPI



Pastore et al. Lancet Oncol 2015

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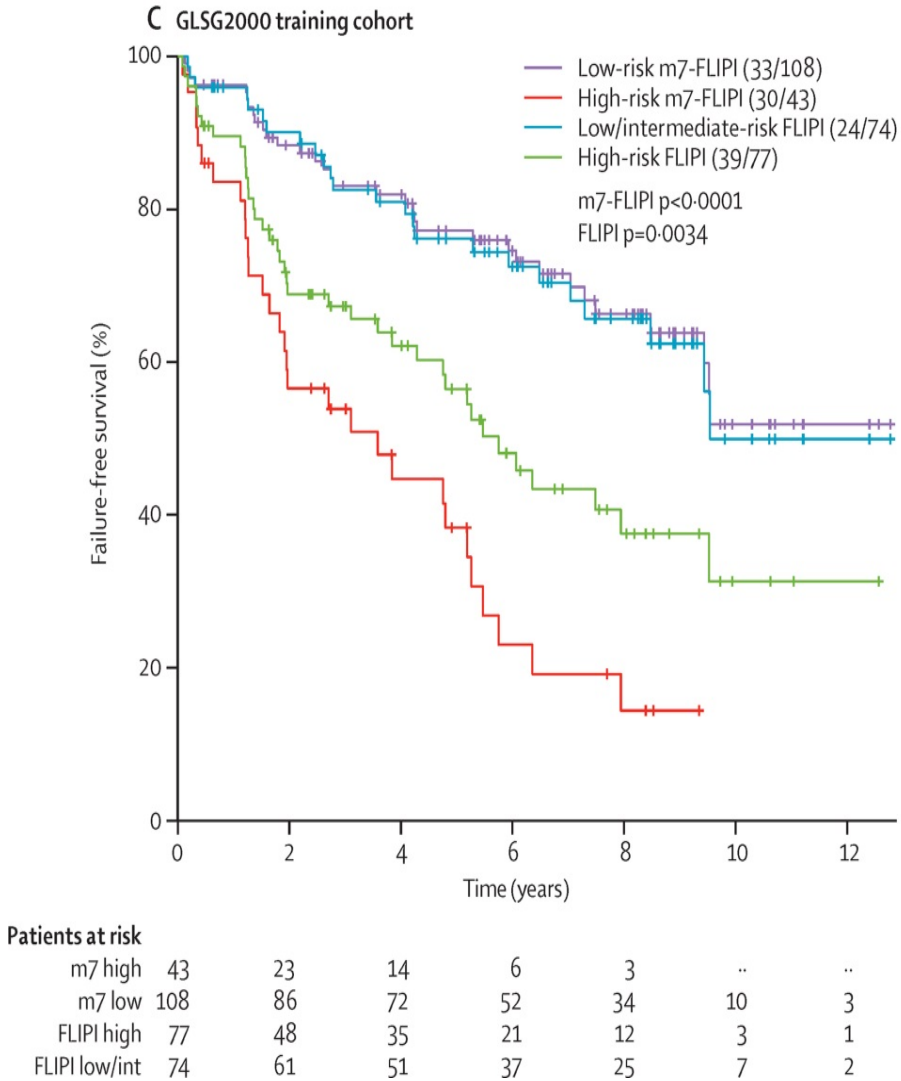
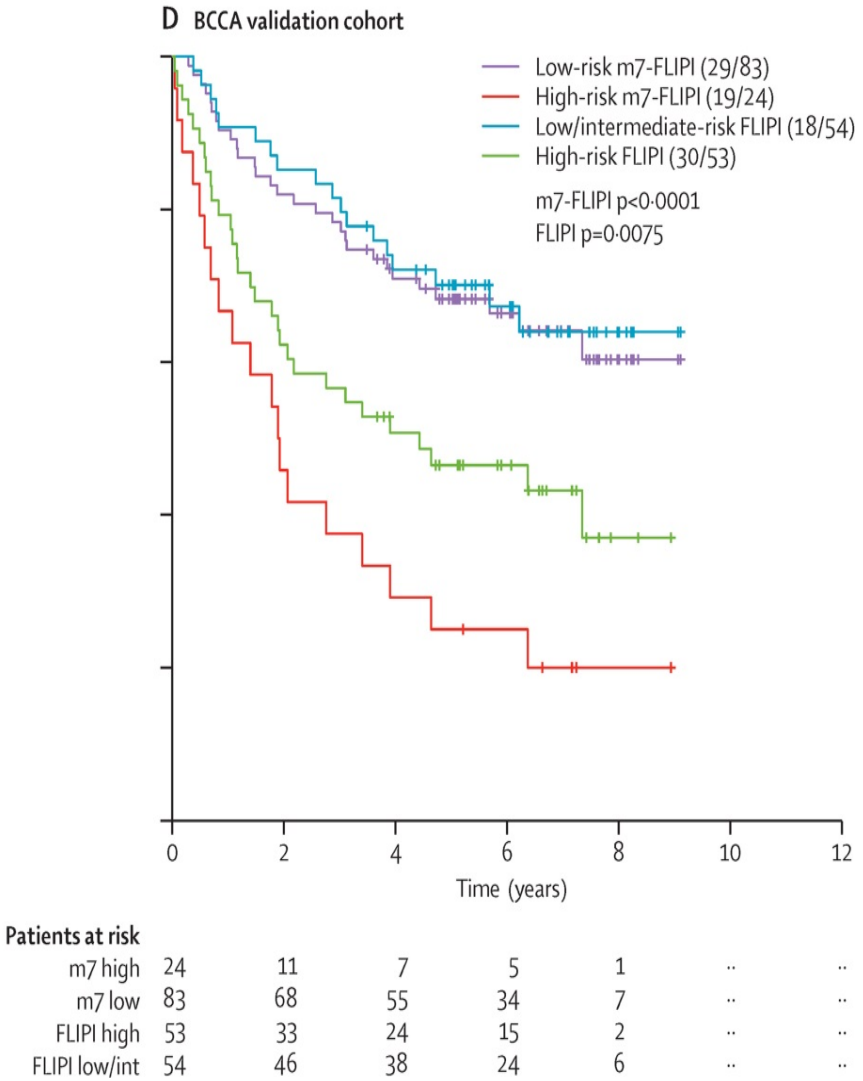
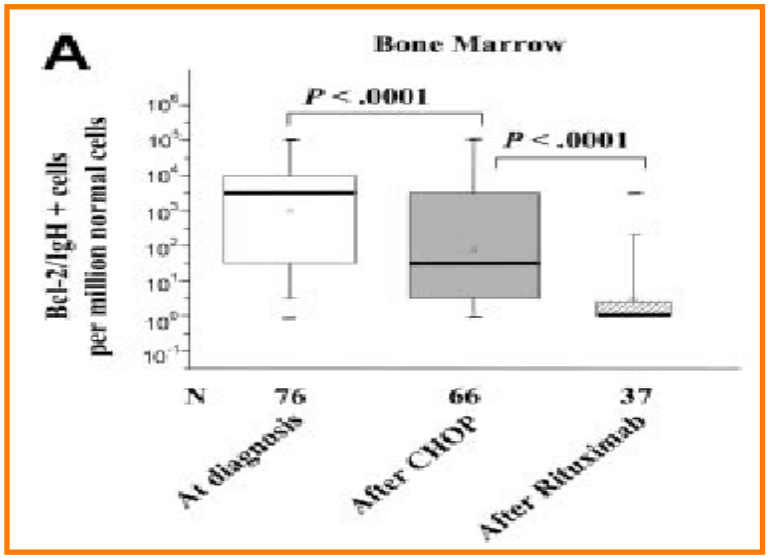
m7-FLIPI

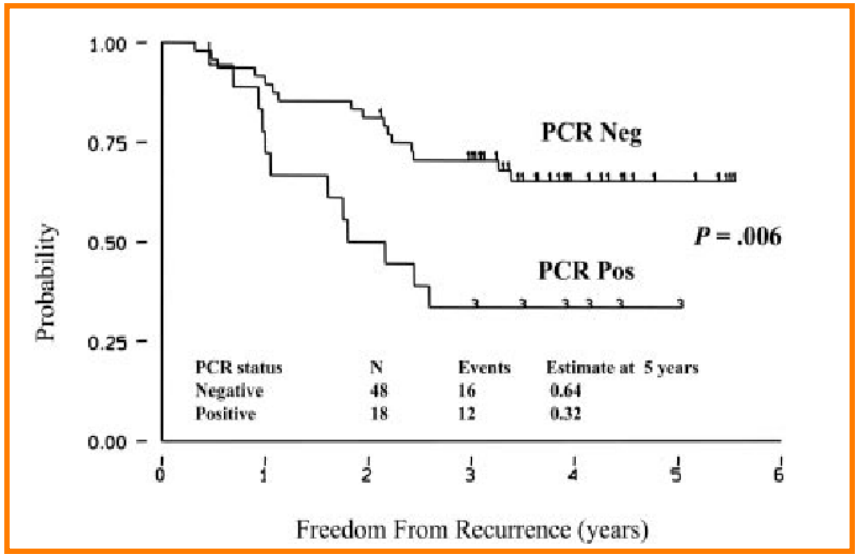




Pastore et al. Lancet Oncol 2015

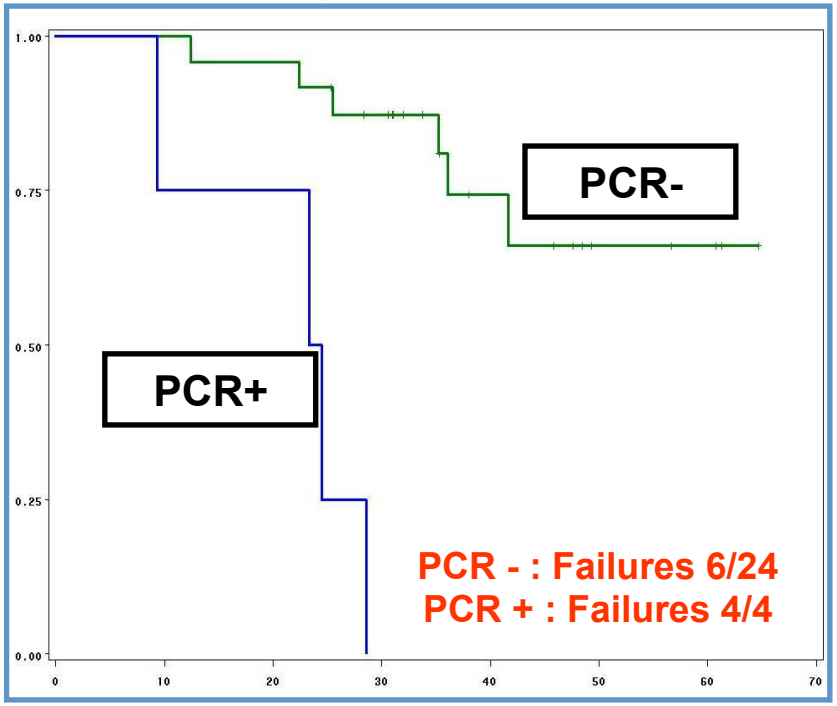
Persistent risk of relapse after R-chemotherapy: Role of molecular remission





Rambaldi et al. Blood, 2005

Sequential FND + rituximab in elderly untreated FL



Vitolo et al: Blood 2004;104(11):371a

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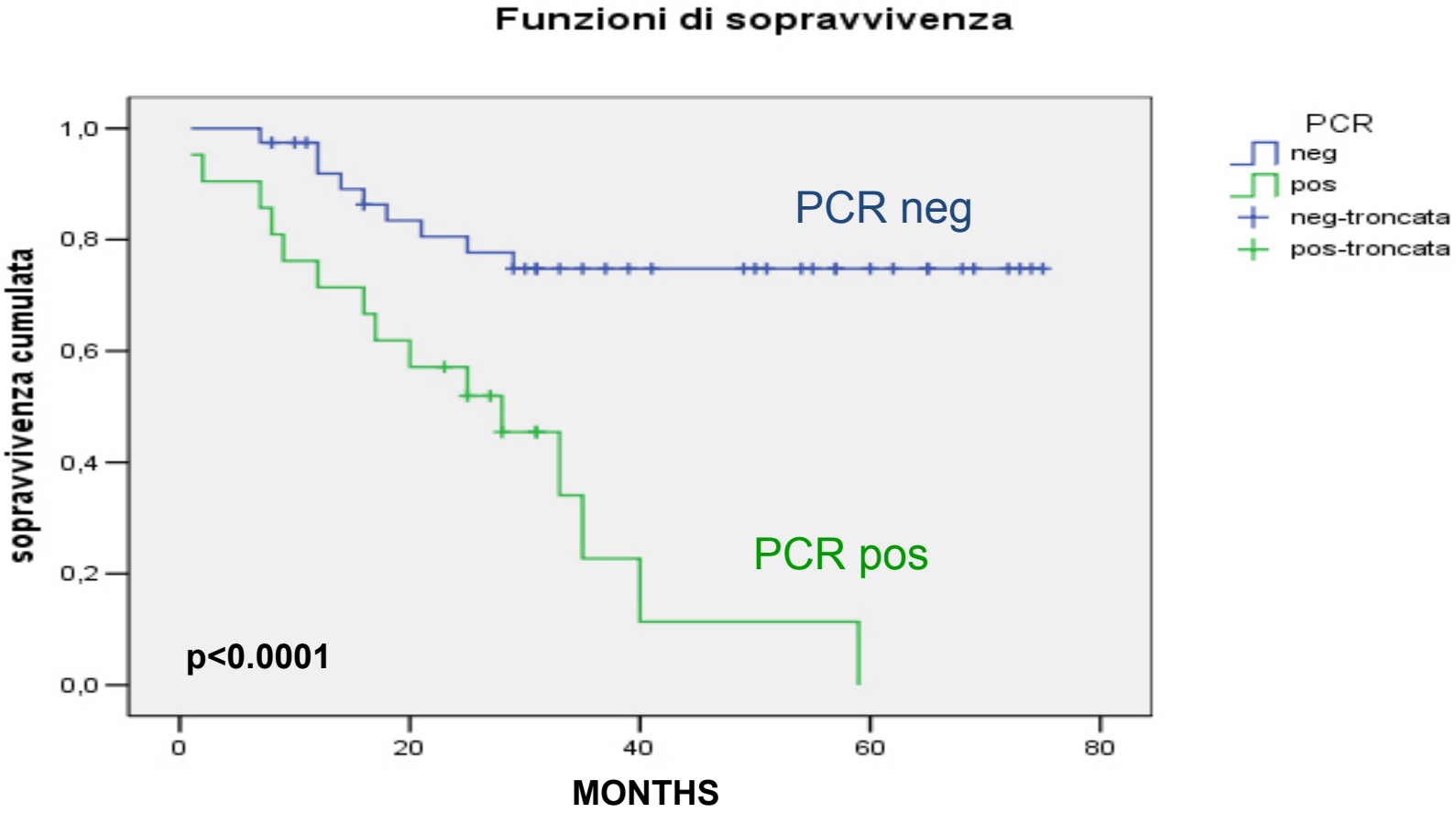
R-HDS vs CHOP-R RANDOMIZED TRIAL
EVALUABLE PATIENTS: 60

PFS ACCORDING TO PCR-STATUS



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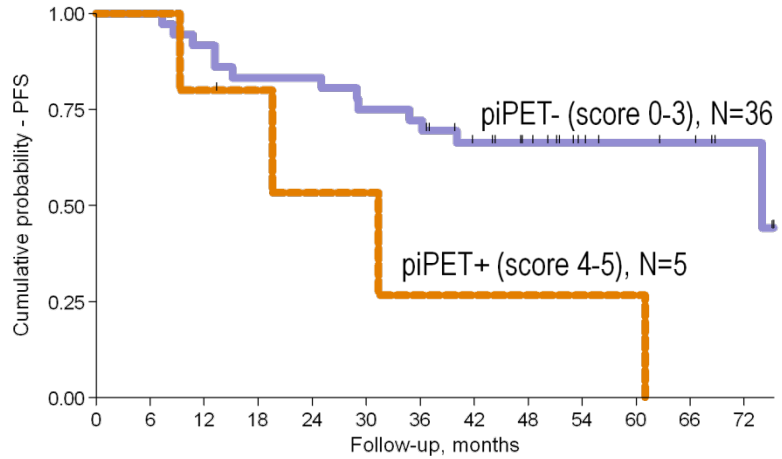
- **Pts with centrally reviewed PET(5PS x3 with liver cutoff) (FOLL05; N=79)**
- **Baseline search for t(14;18)*(N=68)**
- **MRD analysis* on postinduction BM sample (N=41)**

Table 1. Distribution of cases according to piPET and MRD

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

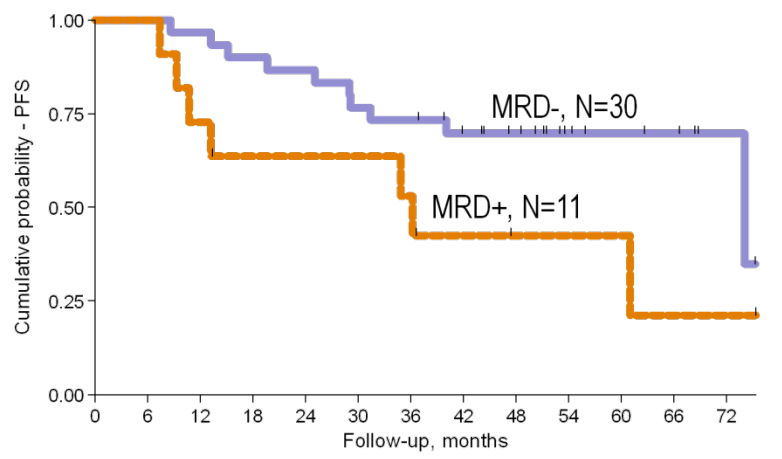
P = 0.110 K=.249(FAIR)

Figure 1.
PFS according to piPET



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

Figure 2.
PFS according to MRD

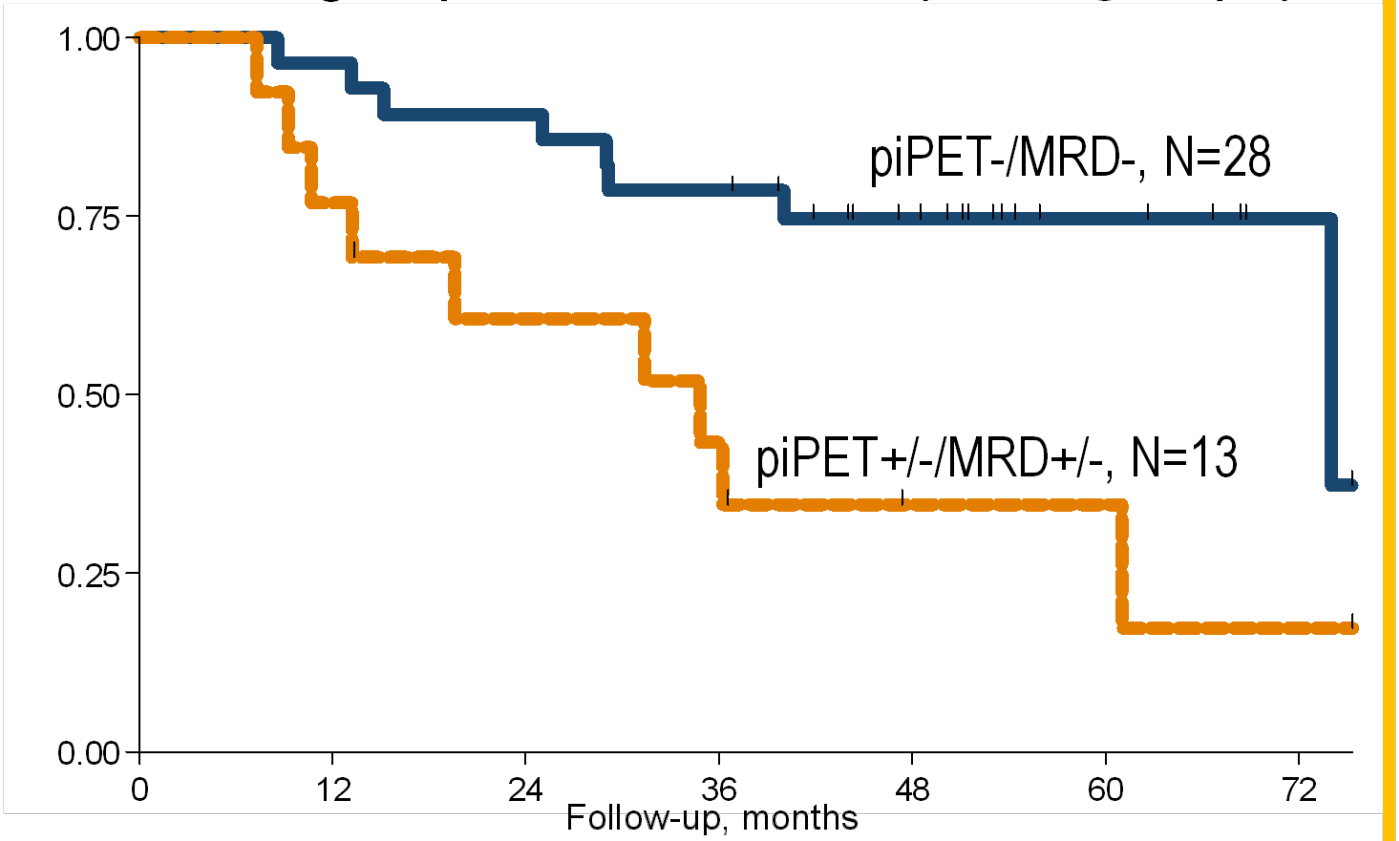


	HR	95%CI	P
MRD +	2.54	0.96-6.72	.060

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

Figure 4.

PFS according to piPET and MRD *(2 subgroups)*



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

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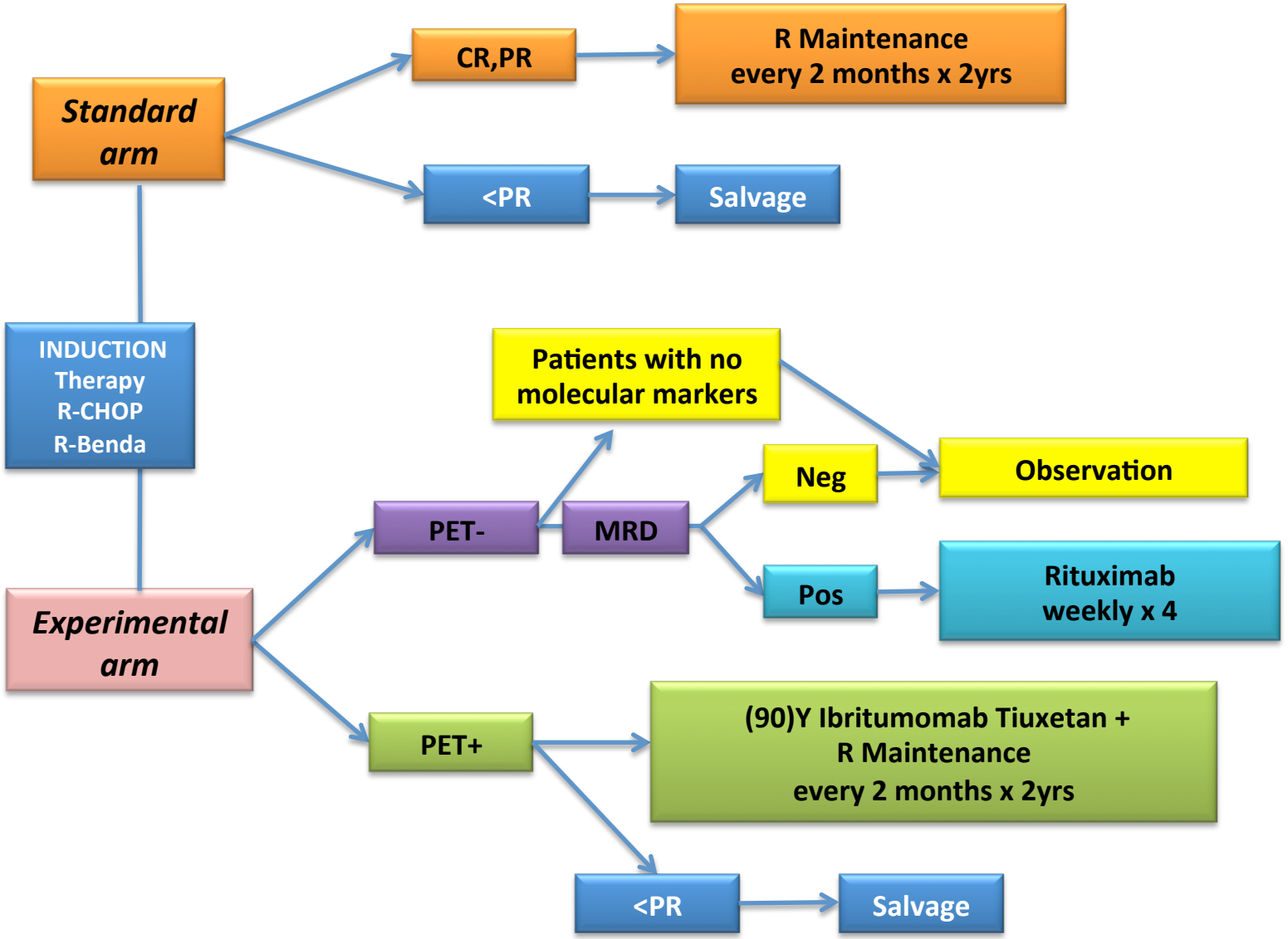
FIL-FOLL12



Non tutti i linfomi follicolari sono uguali,

Come fare a distinguerli?

Gli strumenti per distiguerli forse li abbiamo ma poi…….è utile una intensificazione o un cambio di terapia?

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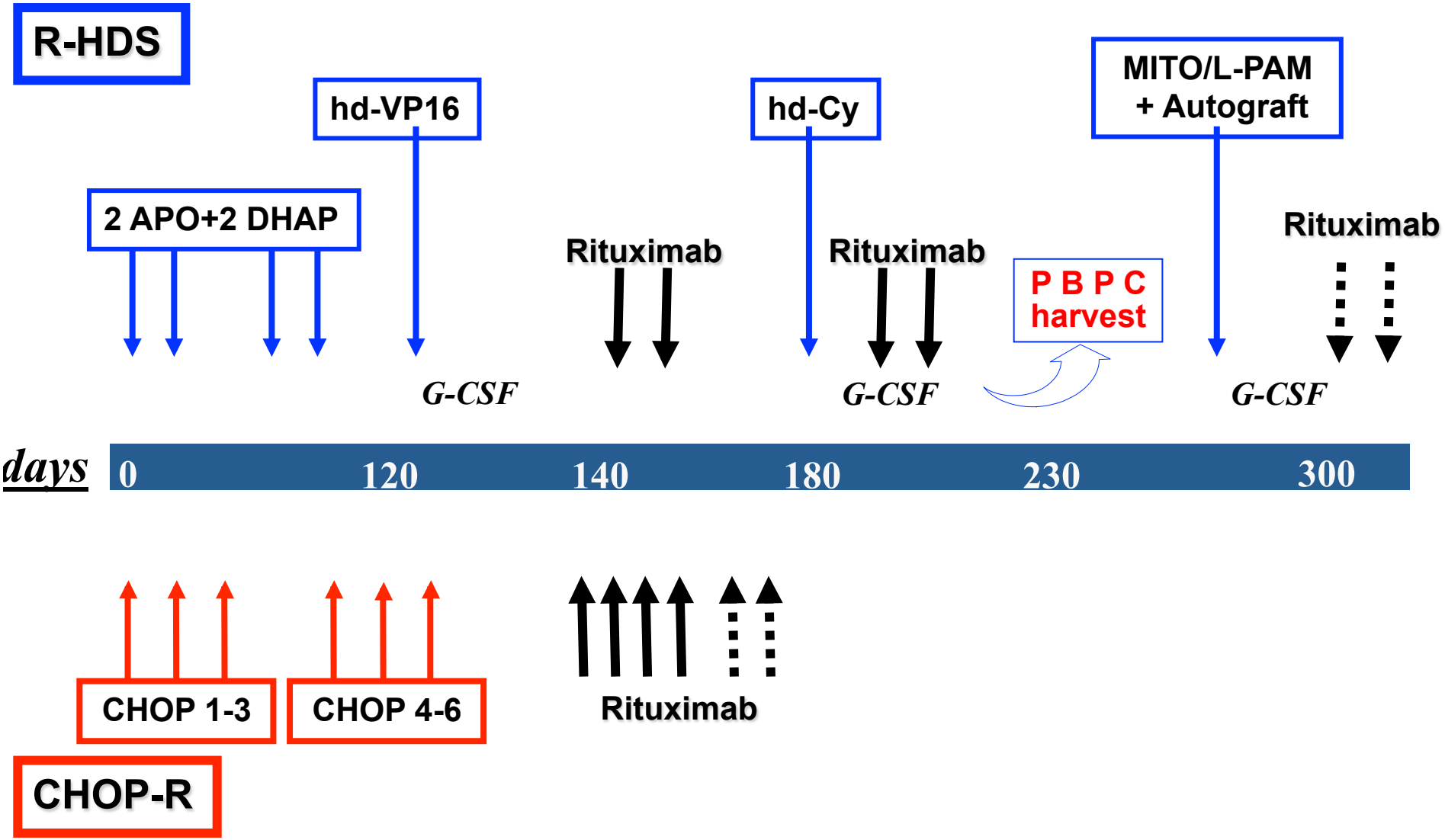
Treatment Schedules



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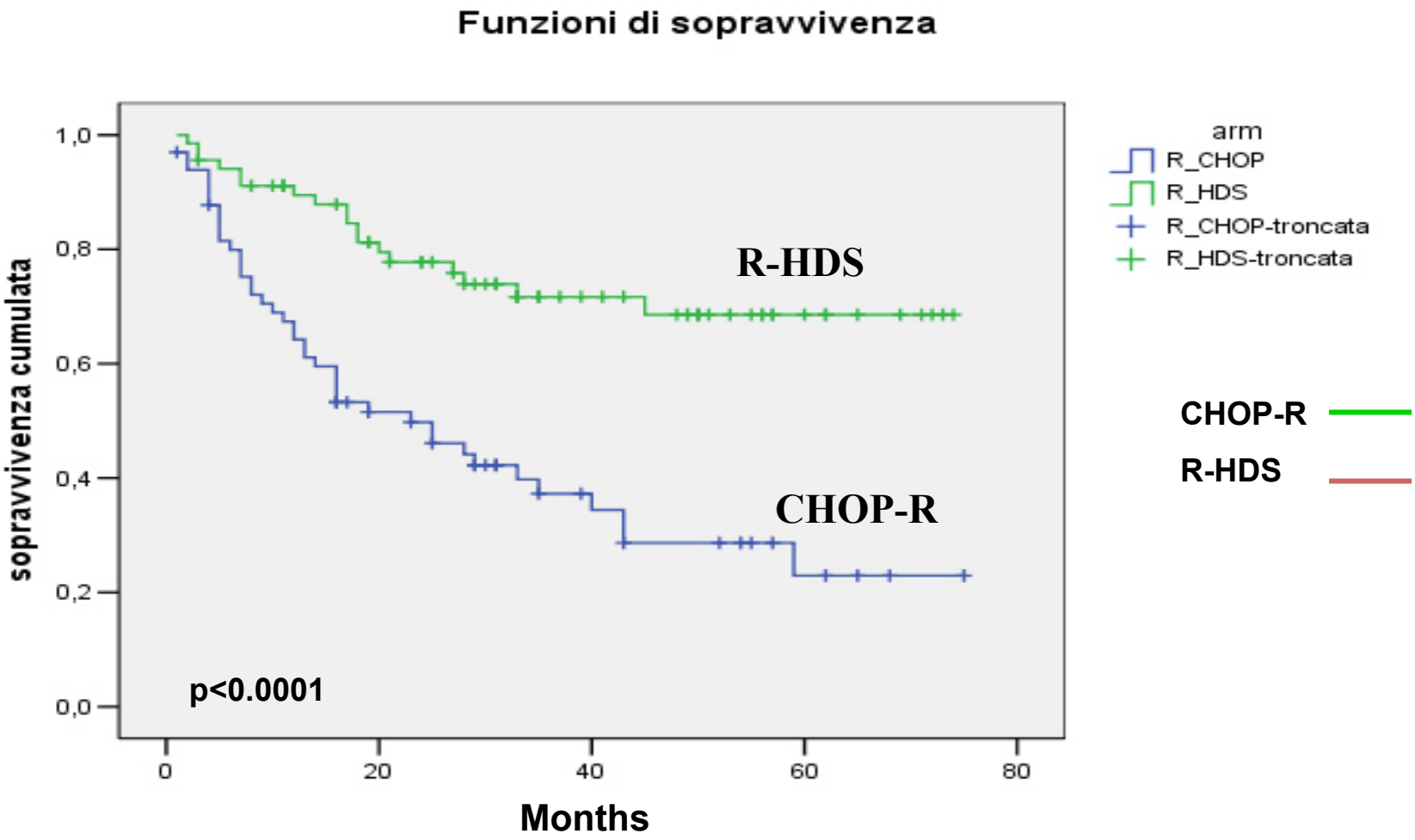
R-HDS vs CHOP-R RANDOMIZED TRIAL
EVALUABLE PATIENTS: 134

PFS ACCORDING TO TREATMENT ARM

R-HDS vs CHOP-R



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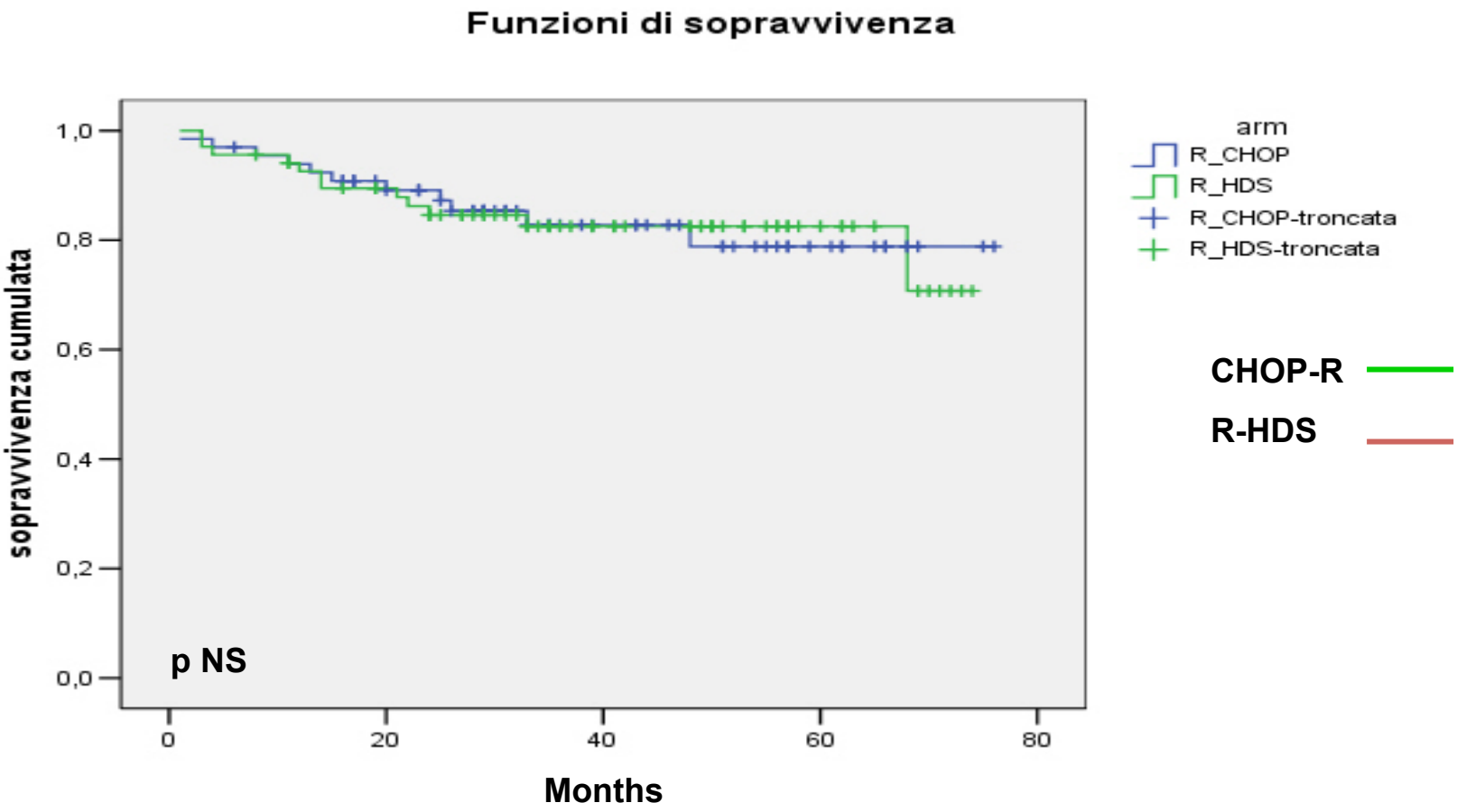
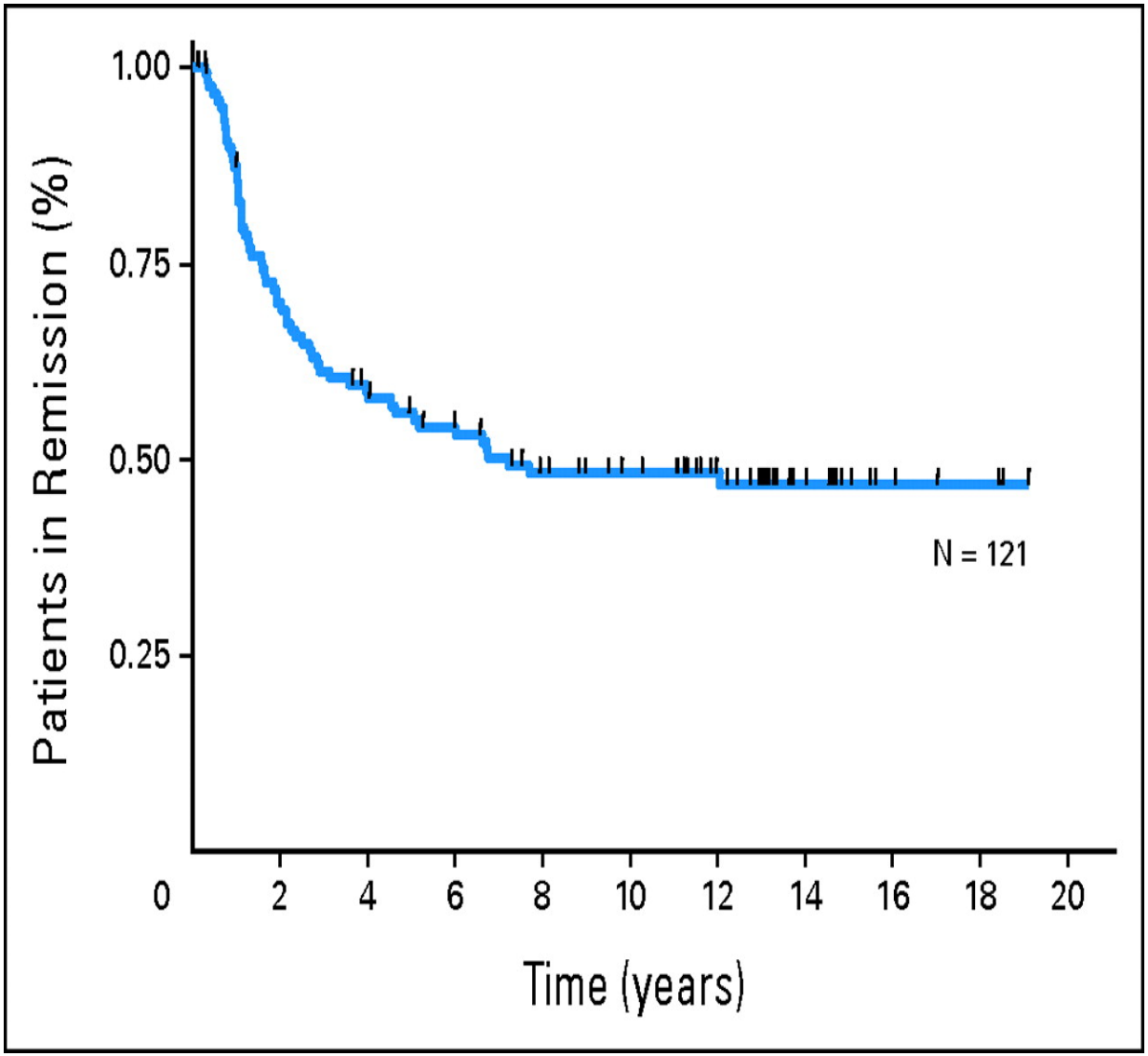
R-HDS vs CHOP-R RANDOMIZED TRIAL
EVALUABLE PATIENTS:134

OS ACCORDING TO TREATMENT ARM

OS R-HDS vs CHOP-R



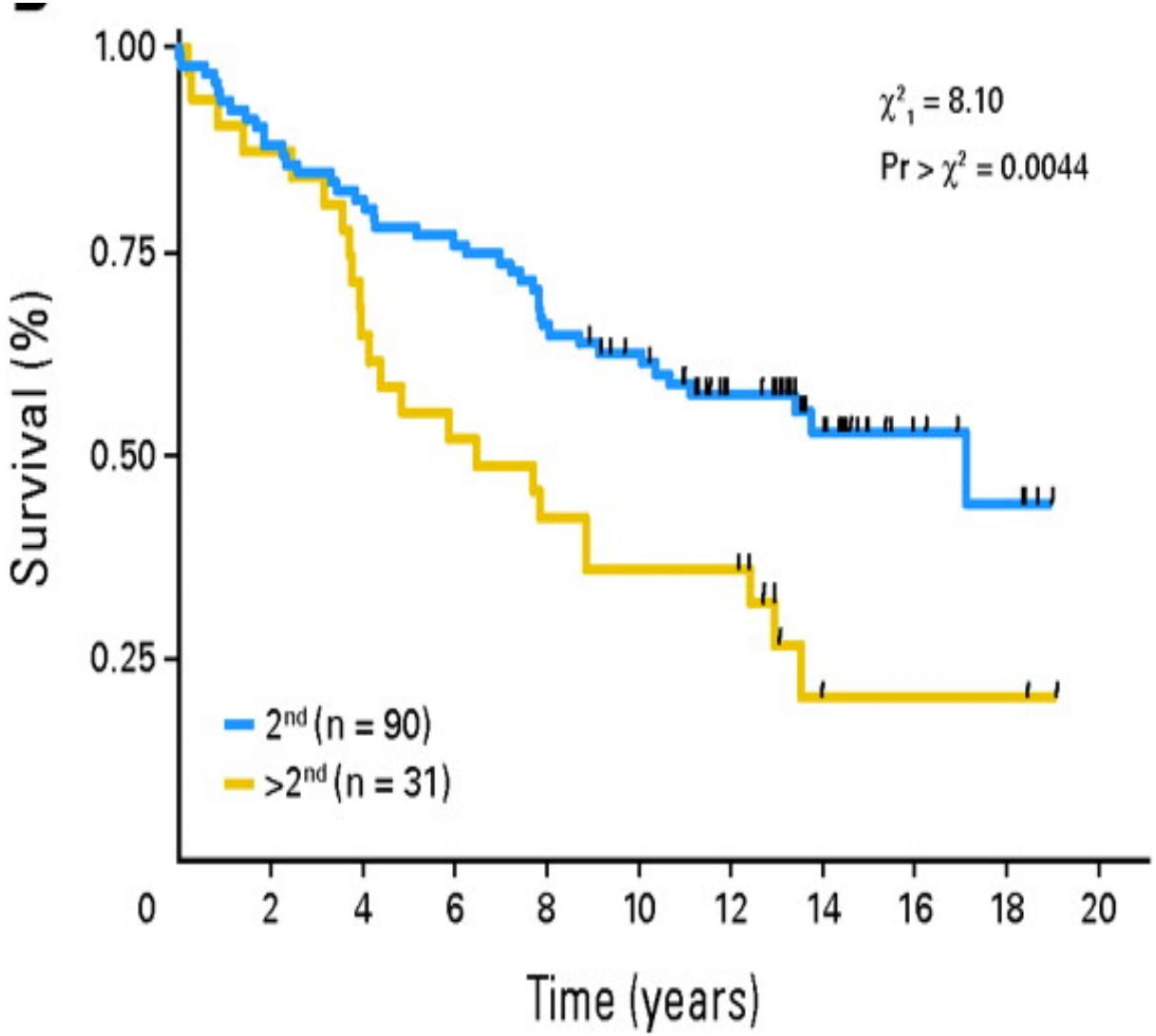
Auto in follicular lymphoma: Remission duration



Rohatiner et al. JCO 2007

Probably should do early in disease course…

Overall survival by remission number



Ama Z.S. Rohatiner et al. JCO 2007;25:2554-2559

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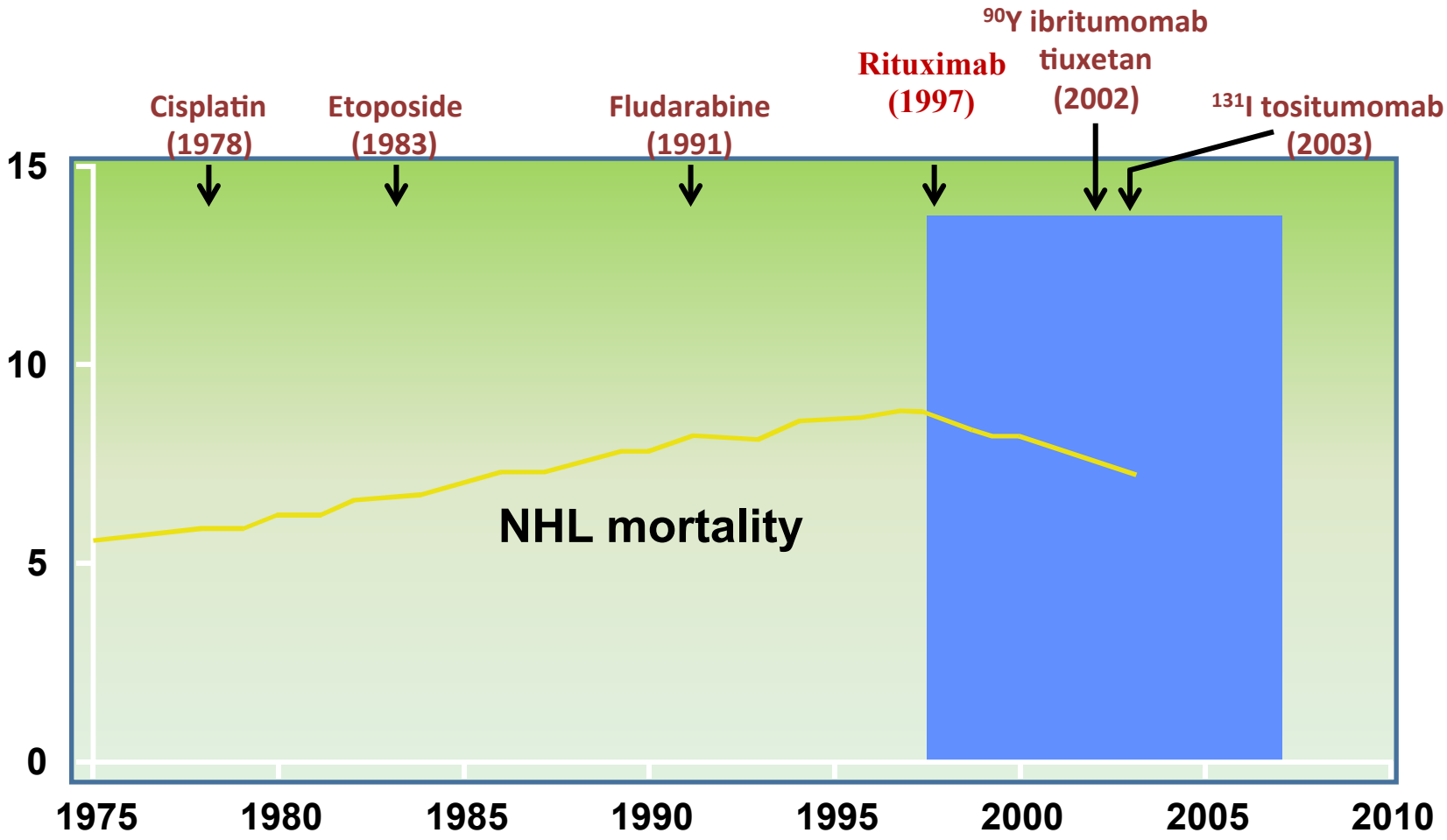
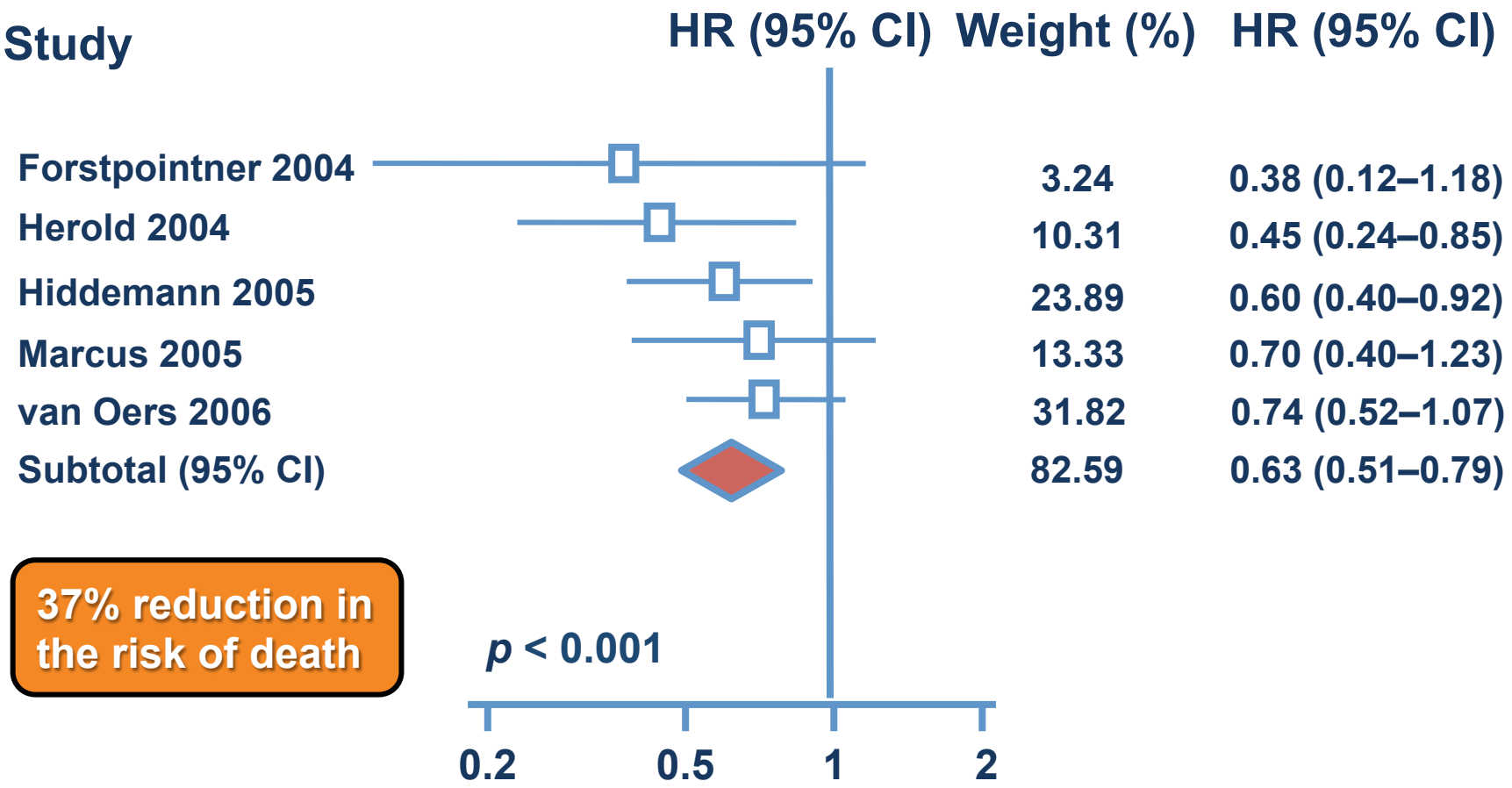
Immunotherapy has changed the clinical course of NHL



* Age-adjusted to 2000 US standard population

Adapted from Molina A. *Annu Rev Med* 2008; 59:237–250.

MabThera plus chemo consistently improves overall survival vs chemo alone in FL



Schulz H, *et al. J Natl Cancer Inst* 2007; 99:706–714.

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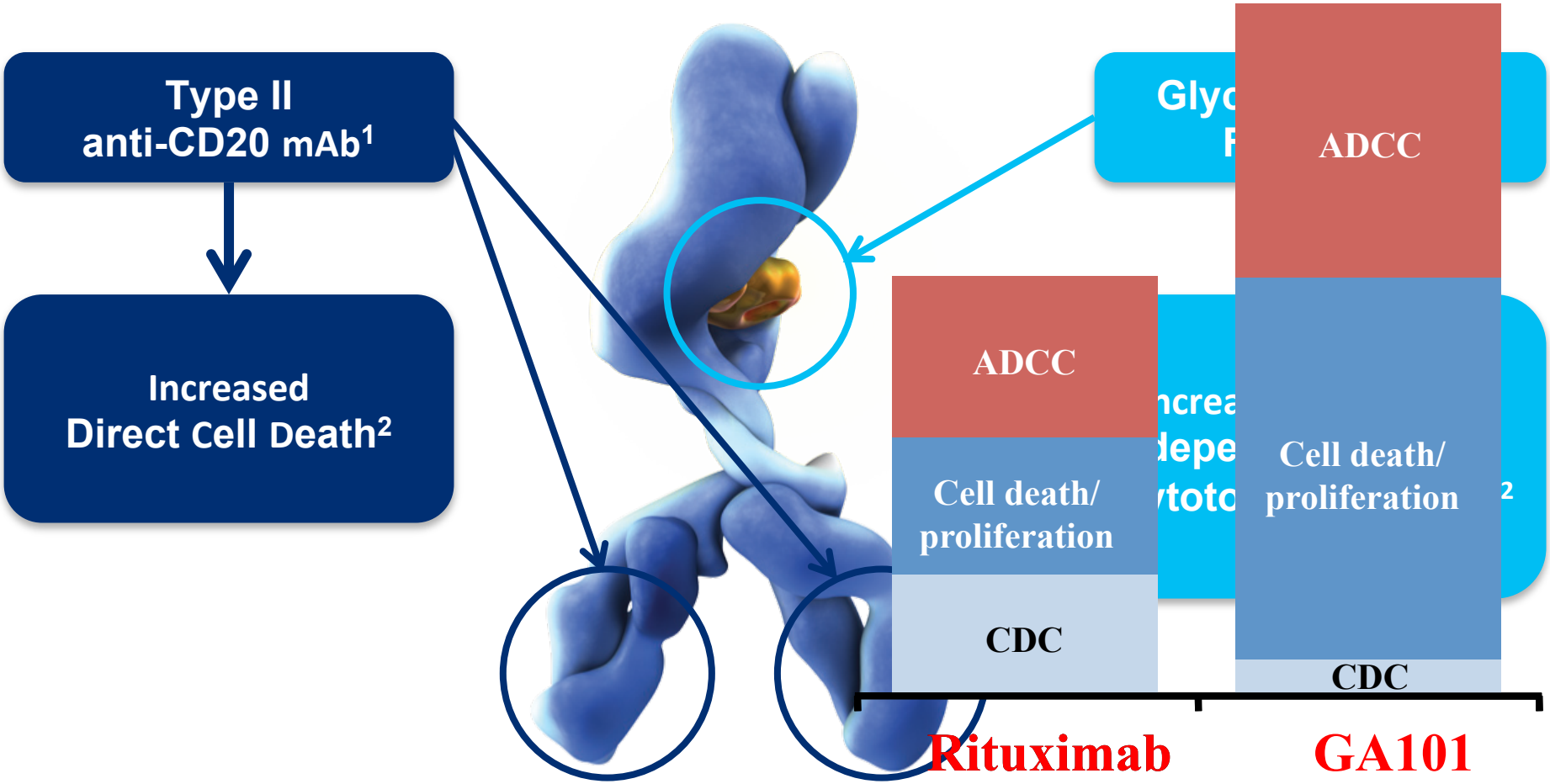
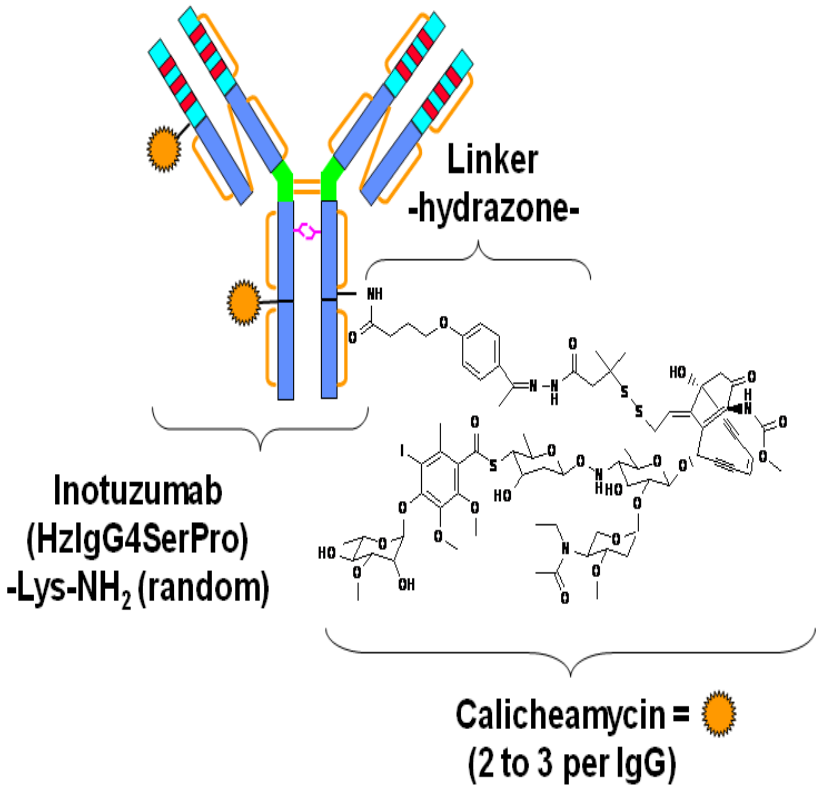
GA101: Designed for increased antibody-dependent cellular cytotoxicity (ADCC) and Direct Cell Death



Extensive clinical development program to evaluate the superiority of GA101 over rituximab in multiple head-to-head trials

1. Niederfellner G, *et al. Blood* 2011; 118:358–367. 2. Mössner E, *et al. Blood* 2010; 115:4393–4402.

Targeted chemotherapy in clinical development



Target CD22

Polatuzumab
Vedotin

Target CD79b

Goy A, et al. *Blood*. 2010;116(21): Abstract 430.

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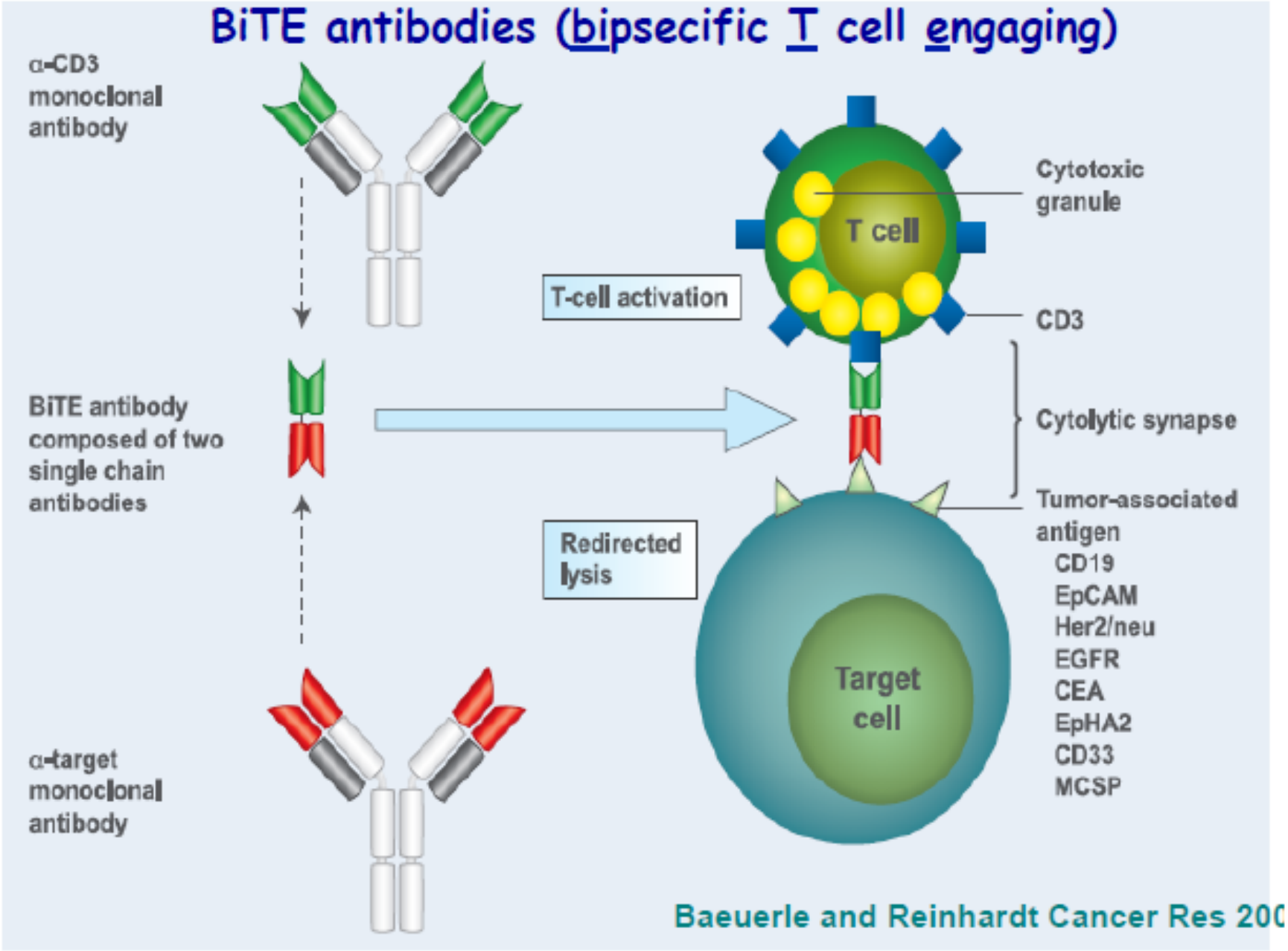

Clinical response in relapsed B-NHL pts to Blinatumomab (CD19xCD3)(Phase I-II study)

Blinatumomab dose levels (mg/m^2 per day)	Patients	Tumor regression (%)	Complete regression (disease)	Partial regression (disease)
0.0005, 0.0015, 0.005	12	0 (0)	0	0
0.015, 0.030	19	4 (21)	2 (MCL, FL)	2 (FL, CLL)
0.060	7	7 (100)	2 (MCL, FL)	5 (MCL, 4 FL)

Short half life and high efficacy:
Daily treatment with low doses lasting months

Bargou et al Science 2008

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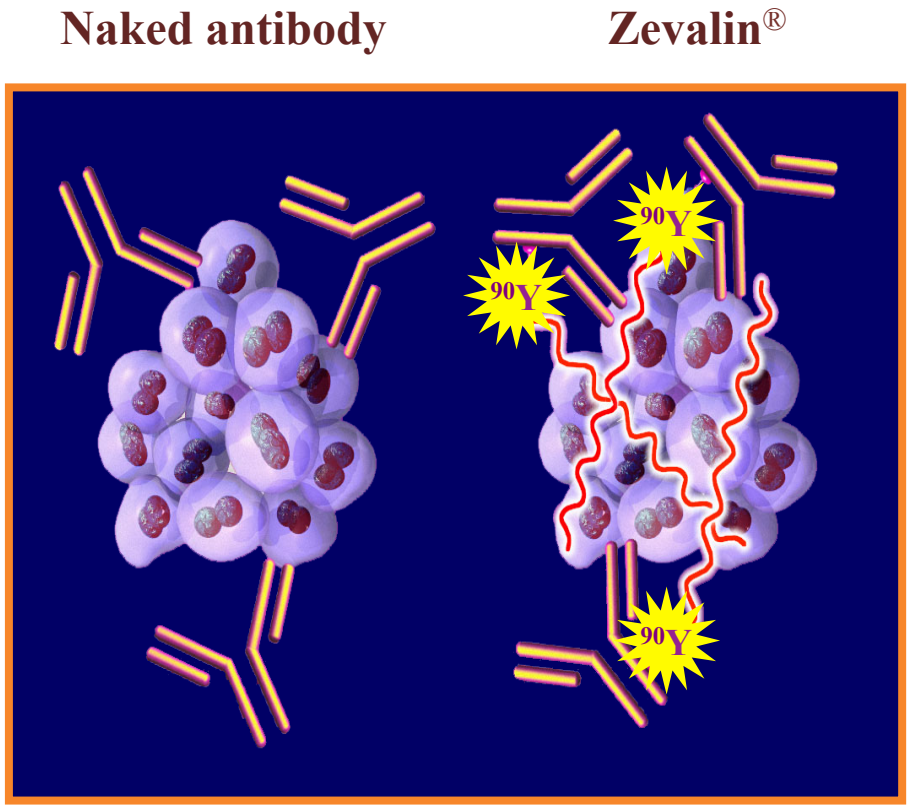
Advantages of Radioimmunotherapy (RIT)

Lymphoma cells are inherently sensitive to radiation

RIT delivers continuous low-dose radiation to tumour cells

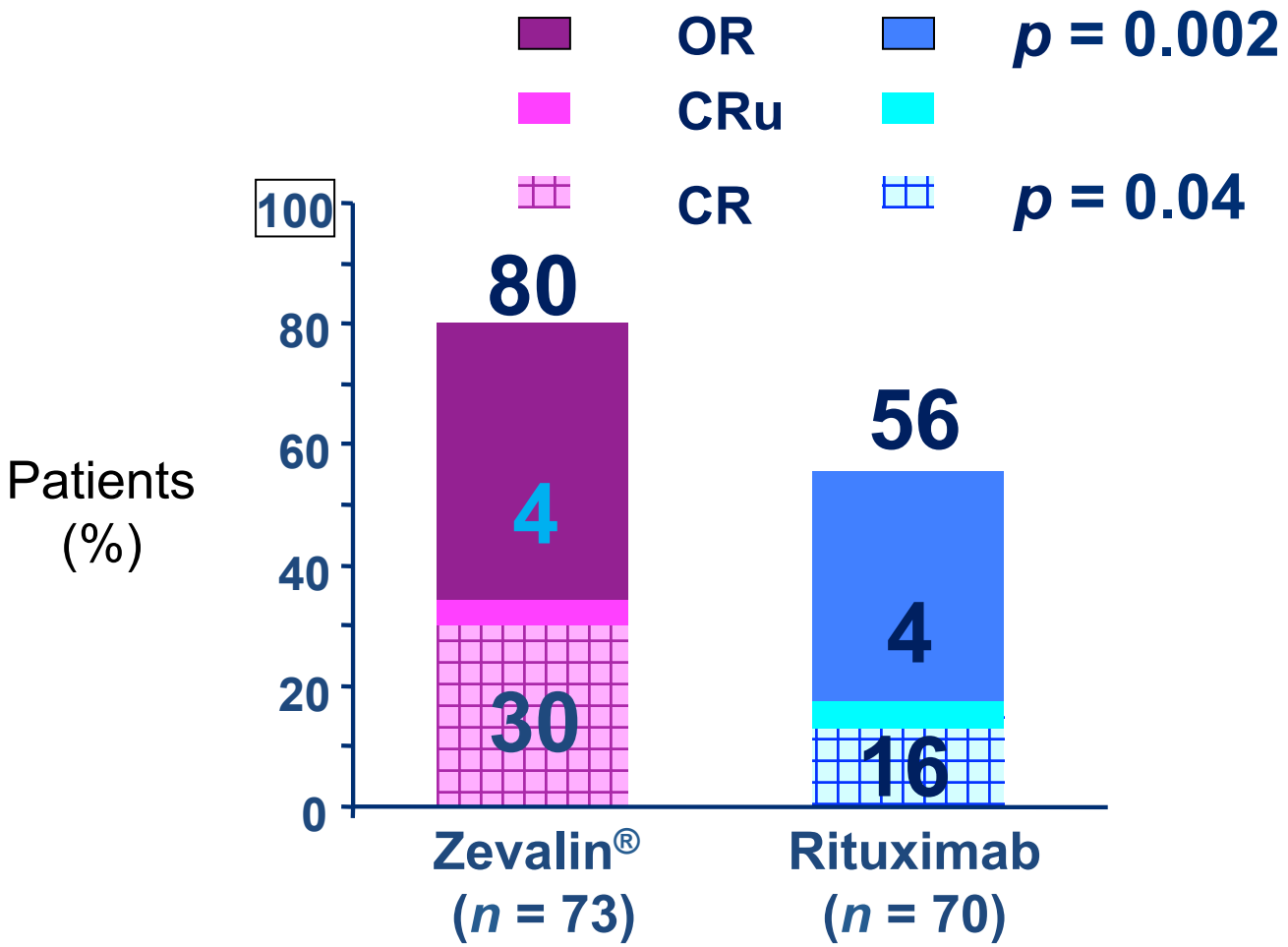
Targeted radiation of RIT also destroys neighbouring tumour cells by a 'cross-fire' effect



Illidge *et al*. *Br J Haematol* 2000;108:679-688

Press. *Semin Hematol* 2000;37(suppl 7):2–8
Krasner & Joyce. *Curr Pharma Biotech* 2001;2:341–349
Zelenetz. *Curr Opin Oncol* 1999;11:375–380

Zevalin® vs Rituximab Randomised Phase III Trial: Response Rates*



* Witzig *et al. J Clin Oncol* 2002; 20:2453–2463

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- Il Rituximab e gli altri anticorpi monoclonali, quale ruolo?
- **La immuno-chemioterapia quanti FL guarisce?**
- Le nuove terapie ‘target’
- La induzione chemio-free, ‘utopia’?

LINFOMA FOLLICOLARE

Esperienza AOU Careggi, Firenze

Tutti pazienti con diagnosi di linfoma follicolare (I-II e IIIa) diagnosticati fra il gennaio 2000 e il dicembre 2004, per avere almeno 10 anni di osservazione per i pazienti vivi

Abbiamo diviso la casistica in due gruppi:
Gruppo 1 costituito da pazienti mai recidivati o progrediti dopo la terapia di induzione durante il periodo di osservazione
Gruppo 2 costituito da pazienti recidivati o progrediti dopo la terapia di induzione durante il periodo di osservazione

146 pazienti identificati dal data base, 13 esclusi (8 persi follow-up, 5 non responsivi alla terapia di induzione)

133 pazienti valutabili

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	COHORT 1	COHORT 2
NR OF PATIENTS	48	85
MALE GENDER	22 (46%)	46 (54%)
FEMALE GENDER	26 (54%)	39 (46%)
AGE>60	21 (44%)	55 (65%)
STAGE I–II	21 (44%)	26 (30%)
STAGE III–IV	27 (56%)	59 (69%)
B SYMPTOMS	5 (10%)	20 (24%)
BULKY	8 (17%)	19 (22%)
EXTRANODAL INVOLMENT	10 (21%)	34 (40%)
FLIPI ≥3	14 (29%)	39 (46%)
FLIPI 2≥3	4 (8%)	16 (19%)
BOM +	9 (19%)	36 (42%)
β2-MICROGLOBULIN ↑	4 (8%)	24 (28%)
ANTRACYCLINE REGIMEN	37 (77%)	59 (69%)
FLUDARABINE REGIMEN	10 (21%)	14 (16%)
WATCH & WAIT or RT	1 (2%)	12 (14%)
RITUXIMAB TREATMENT:	37 (77%)	56 (66%)
– sequential	30 (63%)	40 (47%)
–concurrent	7 (15%)	15 (18%)
NO RITUXIMAB	11 (23%)	30 (35%)

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Per la sopravvivenza globale l'analisi **univariata**:

Beta2 microglobulina normale	p: 0.05
L'avere avuto Rituximab	p: 0.01
FLIPI < 3	p: 0.001

In analisi **multivariata** l'unico dato che mantiene significatività è l'aver fatto Rituximab

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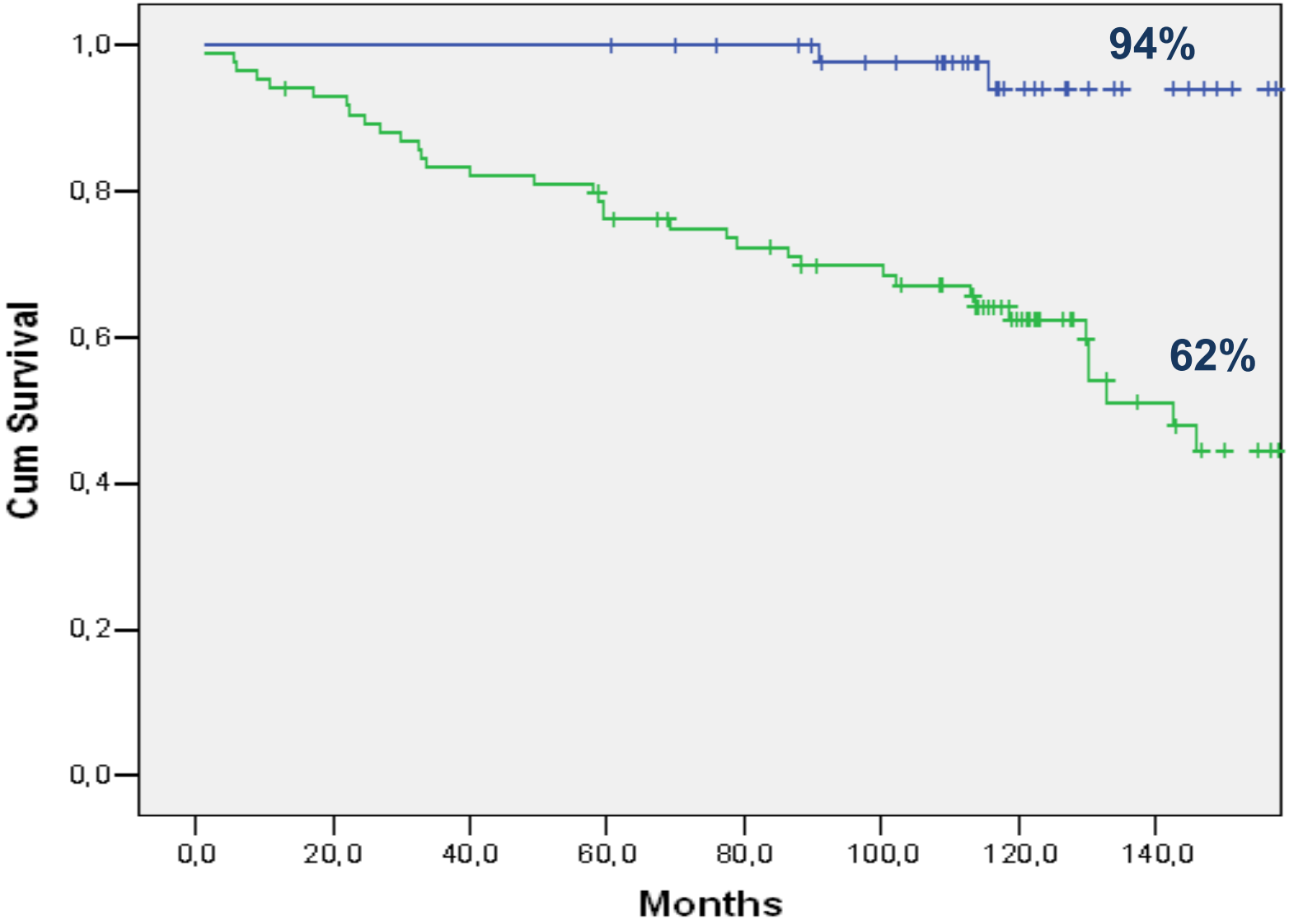
Sopravvivenza globale per gruppo



Gruppo 1: 94% Gruppo 2: 62% mediana osservazione 142 mesi (95% CI 125-180)

LINFOMA FOLLICOLARE

- Gli stadi localizzati sono guaribili !
- Low tumor burden FL come trattarli?
- Non tutti i linfomi follicolari sono uguali: come fare a distinguerli?
    - -Indici prognostici (FLIPI, FLIPI2, M7FLIPI)
    - -Malattia minima residua
    - -PET/CT
- Le terapie ad alte dosi con supporto di staminali che ruolo hanno?
- Il Rituximab e gli altri anticorpi monoclonali, quale ruolo?
- La immuno-chemioterapia quanti FL guarisce?
- **Le nuove terapie 'target'**
- La induzione chemio-free, 'utopia'?

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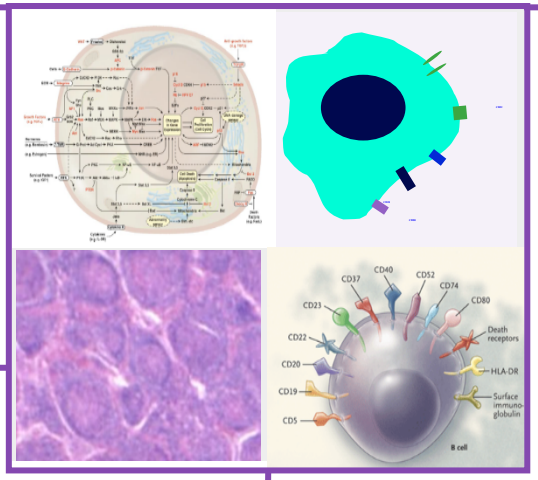
Microenvironment

- **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

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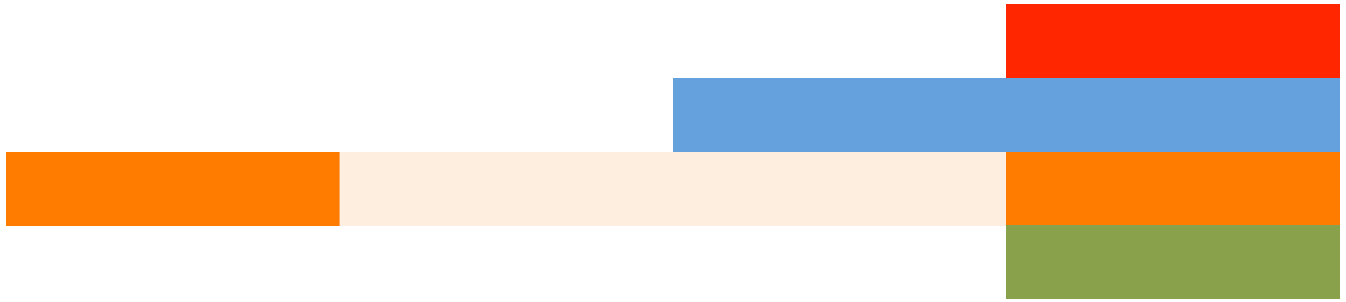
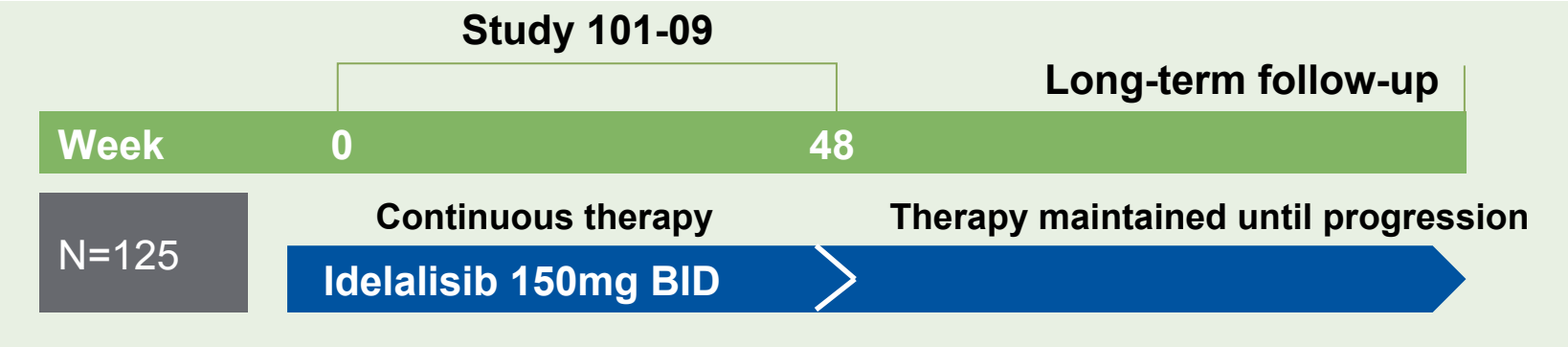
INHIBITORS OF PI3K

Class I PI3K Isoform	α	β	γ	δ
Expression	**Ubiquitous**	**Ubiquitous**	**Leukocytes**	**Leukocytes**
	Insulin signaling Mutated in solid tumours	Platelet activation Neutrophil function Insulin signaling	Mast cell activation Innate immunity Immune tracking	B and T cell activation Fc receptor signaling



Idelalisib in Double-Refractory iNHL

- **Phase II single-arm monotherapy study in patients with R/R iNHL**
- **Accrual completed October 2012**
- **Tumour assessments:**
  - Week 0, 8, 16, 24, 36 and 48, then every 12 weeks thereafter
  - Evaluated by independent review committee (IRC)
    - 2 radiologists with adjudication, if needed, and clinical review
- **Primary endpoint:** Overall response rate (ORR)
- **Secondary endpoints:** Duration of response (DOR), progression-free survival (PFS), safety



Gopal A *et al.* ASH 2014, Abstract #1708

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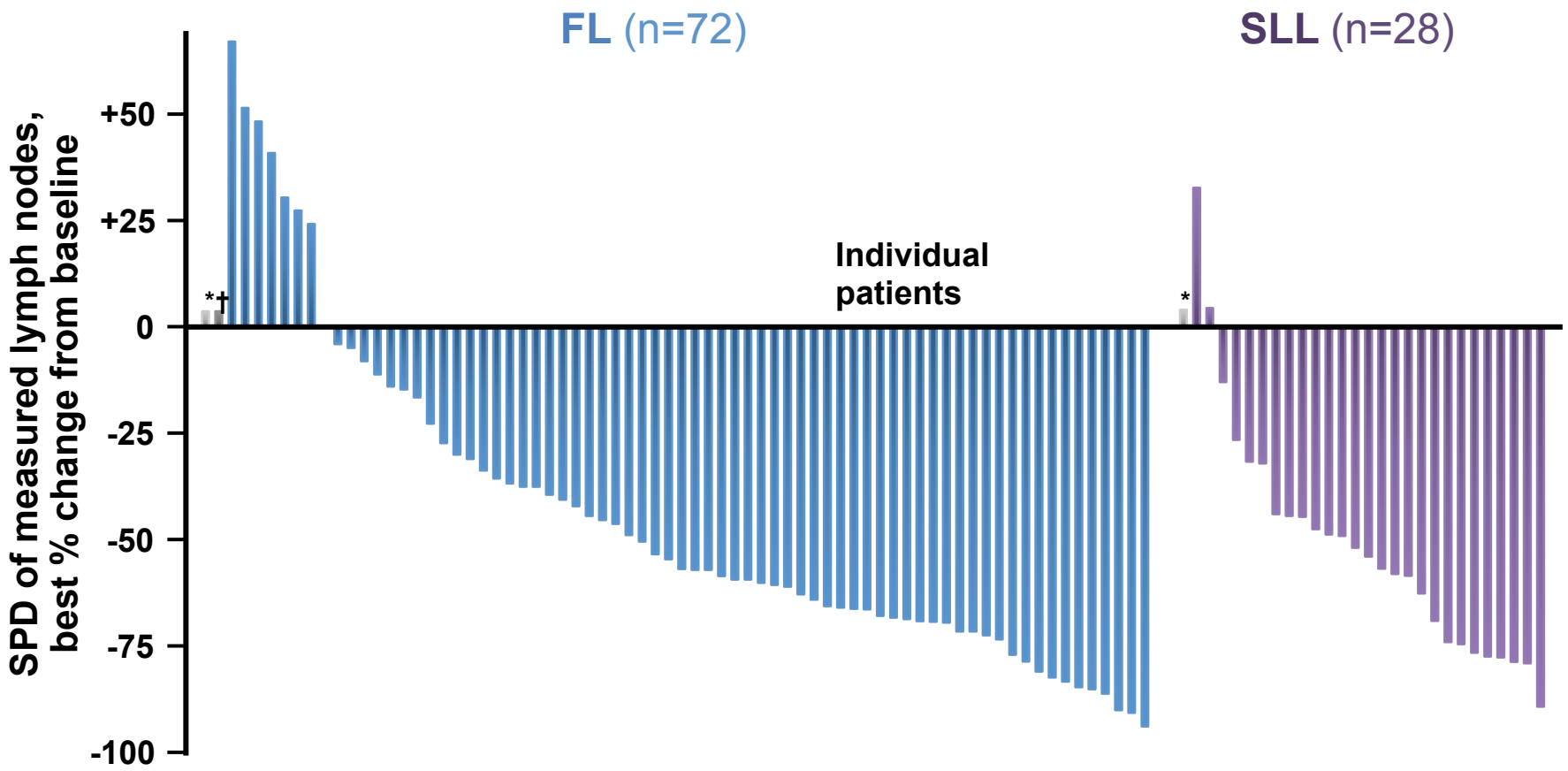
LYMPH NODE RESPONSE BY DISEASE SUBGROUP



3 patients had no post baseline computed tomographic scan evaluation; *2 of these patients were not evaluable
†1 had progressive disease by lymph node biopsy.
‡Criterion for lymphadenopathy response (Cheson BD *et al. J Clin Oncol* 2007;25:579–86)

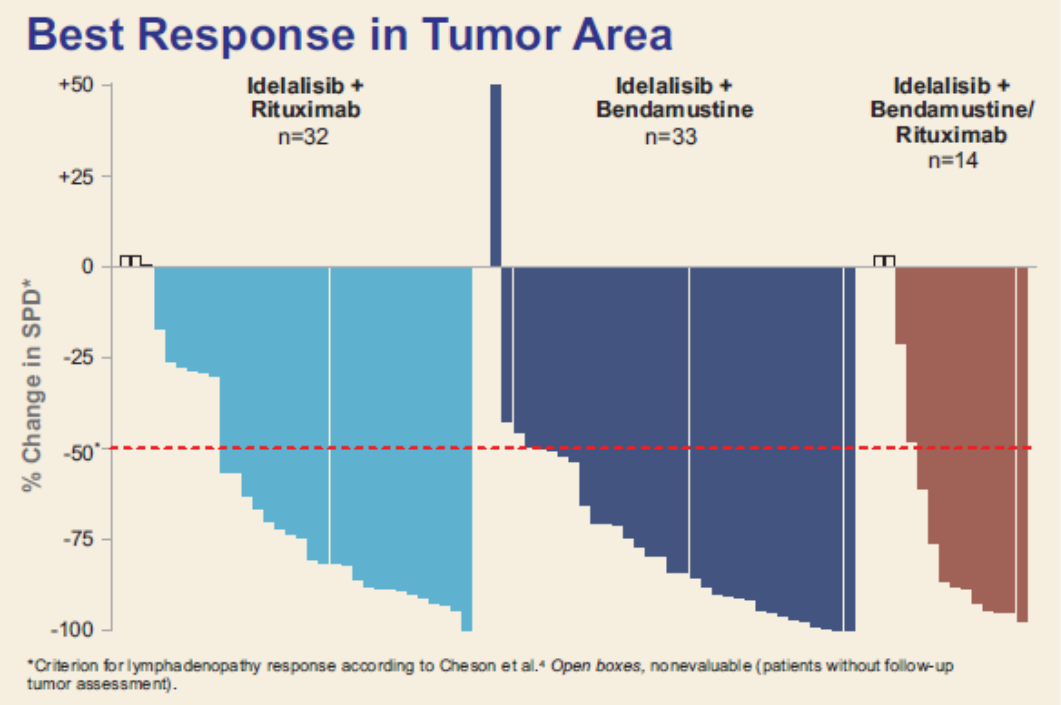
Gopal A et al. ASH 2014, Abstract #1708

In combination…

GS-1101
Rituximab weekly x8

GS-1101
Bendamustine 90mg/m2
day 1+2 x6

GS-1101
Bendamustine 90mg/m2
day 1+2 x6
Rituximab day 1 each cycle

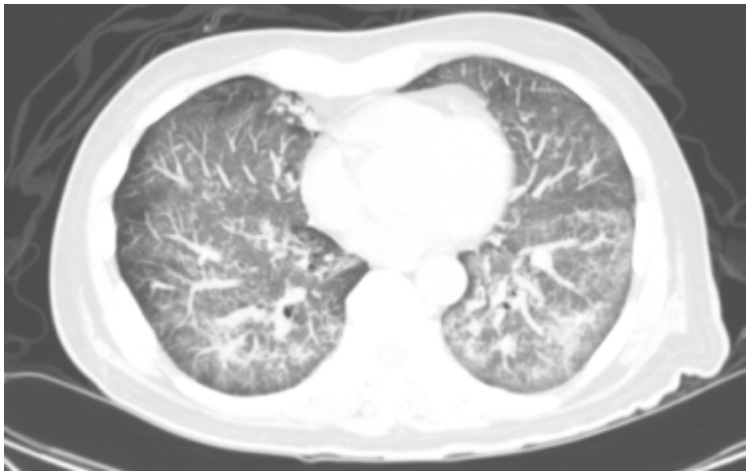


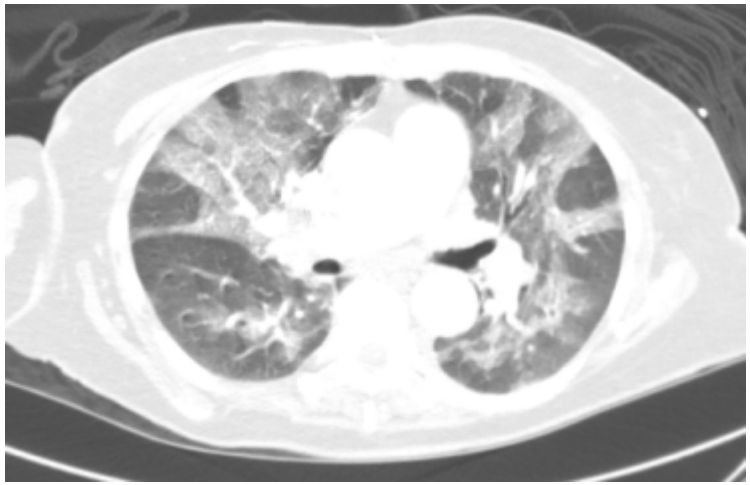
Emerging new toxicity data

de Vos et al ASH 2014

Toxicity of combinations

- 12 of 66 patients (18%)
- Median onset (range): 86 d (51–149)
- Prodrome included cough, fever, and hypoxia
  - 5 patients required ventilatory support
- Chest CT infiltrates characterized as ground-glass opacities
- Infectious etiology not identified
- Responded to steroid treatment
- No significant difference in entospletinib or idelalisib exposure between patients experiencing pneumonitis and others





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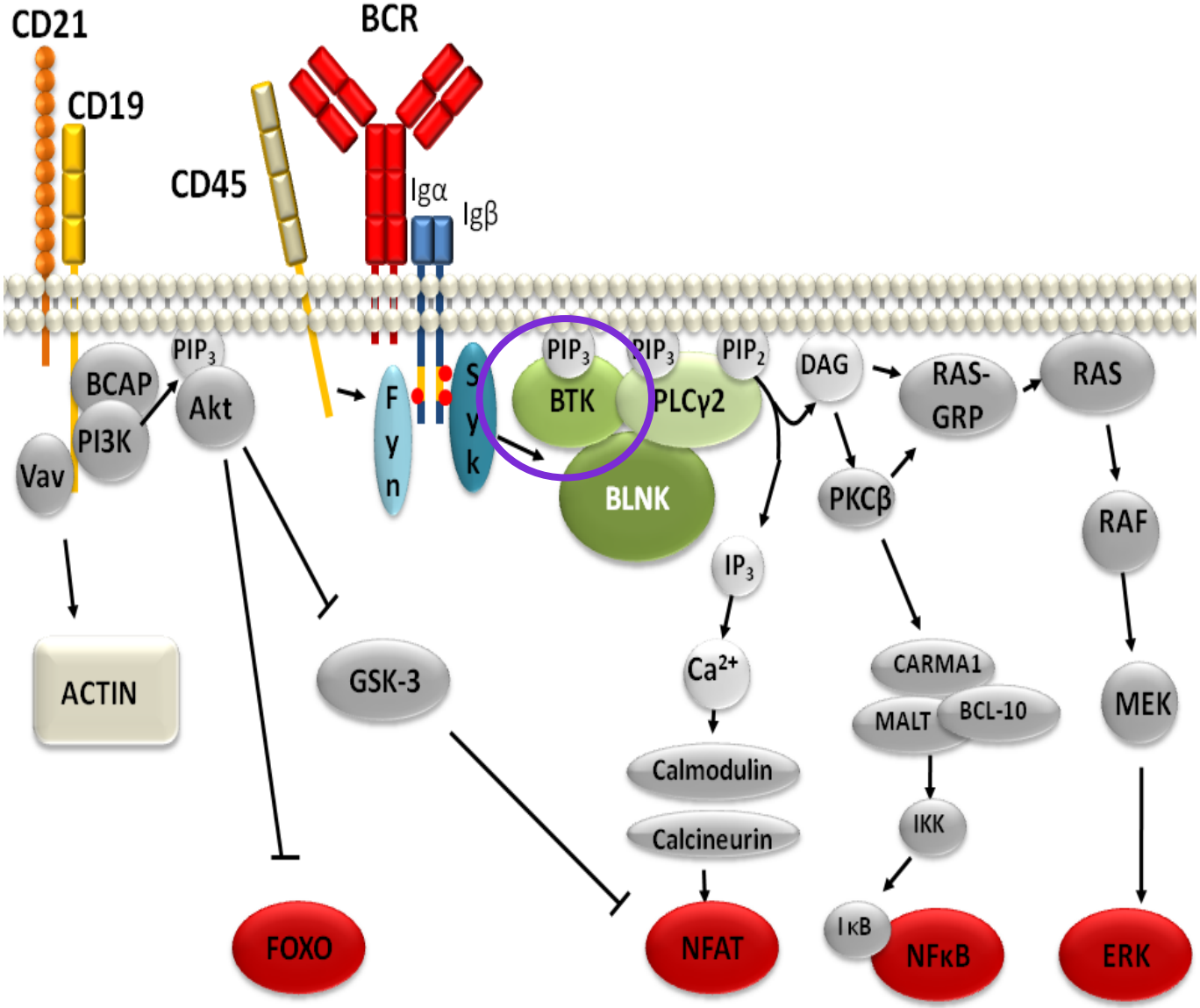
INHIBITING BTK…



LINFOMA FOLLICOLARE

IBRUTINIB MONOTHERAPY IN R/R FL: PHASE 2 CONSORTIUM (P2C) TRIAL

Relapsed/refractory FL, n=40
560mg OD until PD or unacceptable toxicity

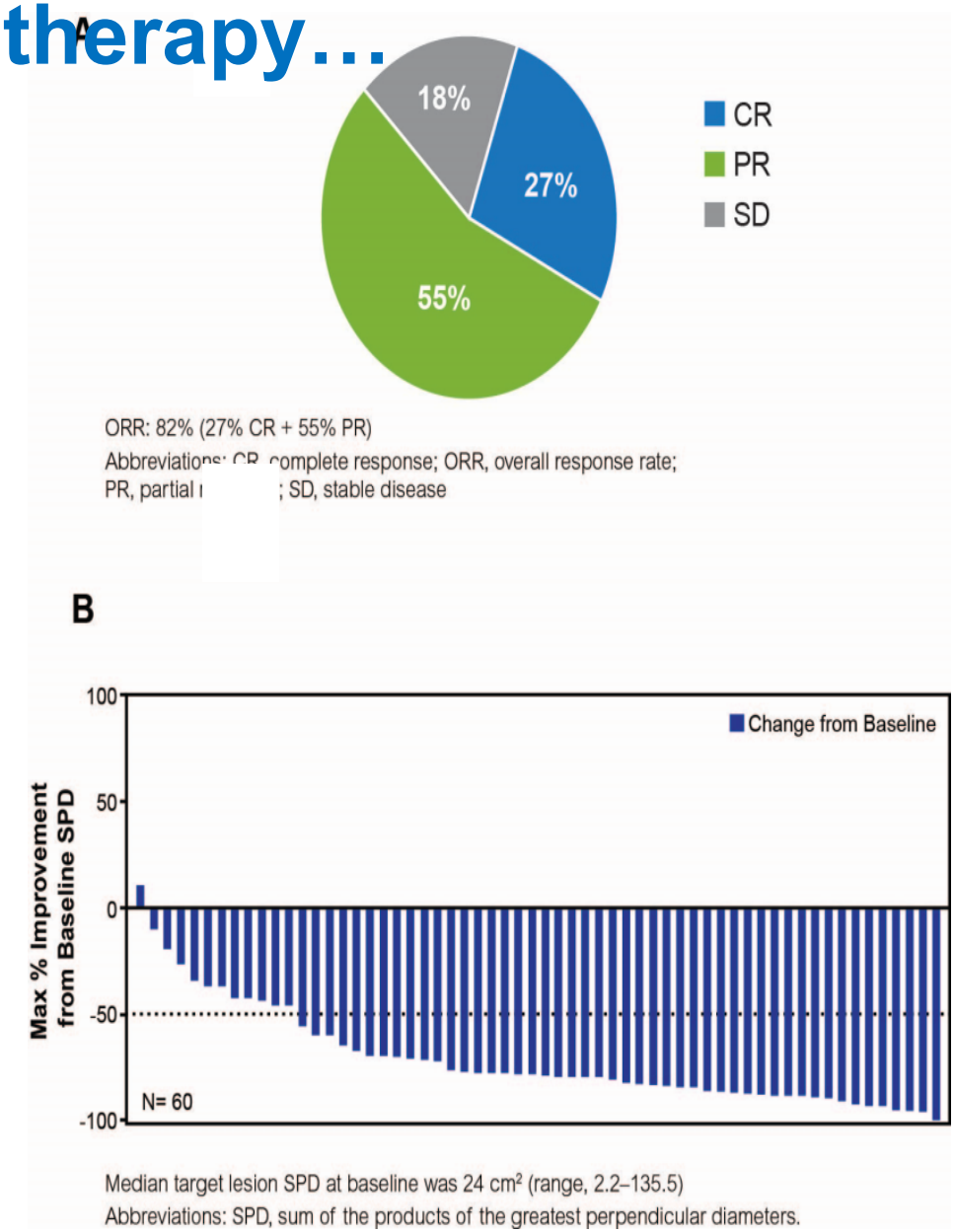
Baseline characteristics	
FLIPI ≥3	55%
Rituximab refractory	45%
Previous stem cell transplant	20%
Refractory to last therapy	36%
Median number of prior therapies (range)	3 (1–11)

Summary of outcomes at median follow up of 6.5 months	
ORR	30% (1 CR)
Patients exhibiting tumour size reduction	65%
Median time to response (range)	2.4 months (1.8–12.9)
Response – Rituximab refractory – Rituximab sensitive	 2/18 (11%) 8/19 (42%) [p=0.06]
Median PFS (95% CI)	9.9 months (6–NR)

Bartlett NL et al. ASH 2014 Abstract #800

Front line therapy…

- FL (Grade 1, 2 and 3a, stage II-IV disease) received oral ibrutinib 560 mg once daily until progressive disease (PD) or unacceptable toxicity + rituximab 375 mg/m2 IV once weekly for 4 doses
- Primary endpoint ORR
- 28% of patients discontinued ibrutinib (AEs: 12%; PD: 8%; patient decision: 5%; and investigator decision: 3%).
- Median PFS, OS, and DOR are not reached as a result of a small number of PD (n=5) and death (n=1) events

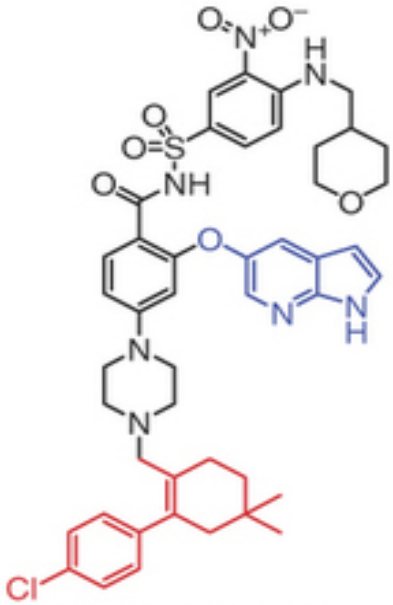


Fowler et al. ASH 2015

BCL-2 Inhibition (Gerecitano et al. ASH 2015)

Bcl-2 highly expressed in FL

GDC-0199 oral active Bcl-2 inhibitor (lack BCLXL activity: plts ↓)
Phase I dose escalation
200-1200 mg cohorts
N=109
FL =29
AEs: diarrhoea (44%), fatigue (44%) Nausea (33%),
Tumour lysis in 1 patient each with DLBCL and MCL
FL CR =10 pts. (34%); PR = 3 pts. (10%)

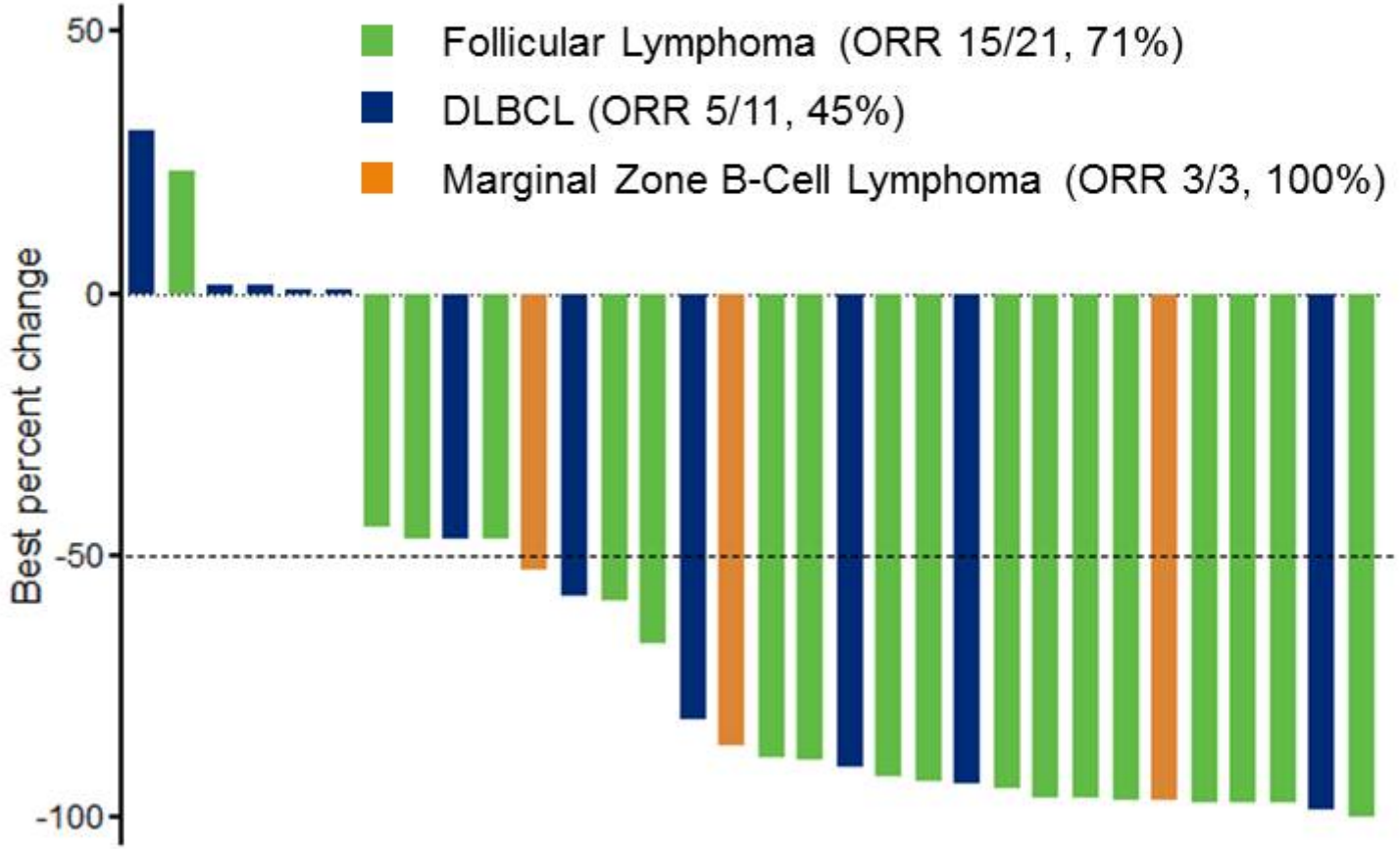


GDC-0199

Best response on venetoclax, n (%)	DLBCL n=34	DLBCL-RT n=7	Follicular Lymphoma n=29
Overall response rate (ORR)	5 (15)	3 (43)	10 (34)
CR	3 (9)	0	3 (10)
PR	2 (6)	3 (43)	7 (24)
SD	9 (26)	2 (29)	18 (62)
PD	18 (53)	1 (14)	1 (3)
Discontinued prior to assessment	1 (3)	1 (14)	0
Not evaluable [a]	1 (3)	0	0

[a] Data entry error; response is PR

Best Percent Change from Baseline in Nodal Size



n=3 did not have post-baseline tumor assessment
As of January 9, 2015

Adapted from the de Vos presentation at European Hematology Association on 12 June 2015

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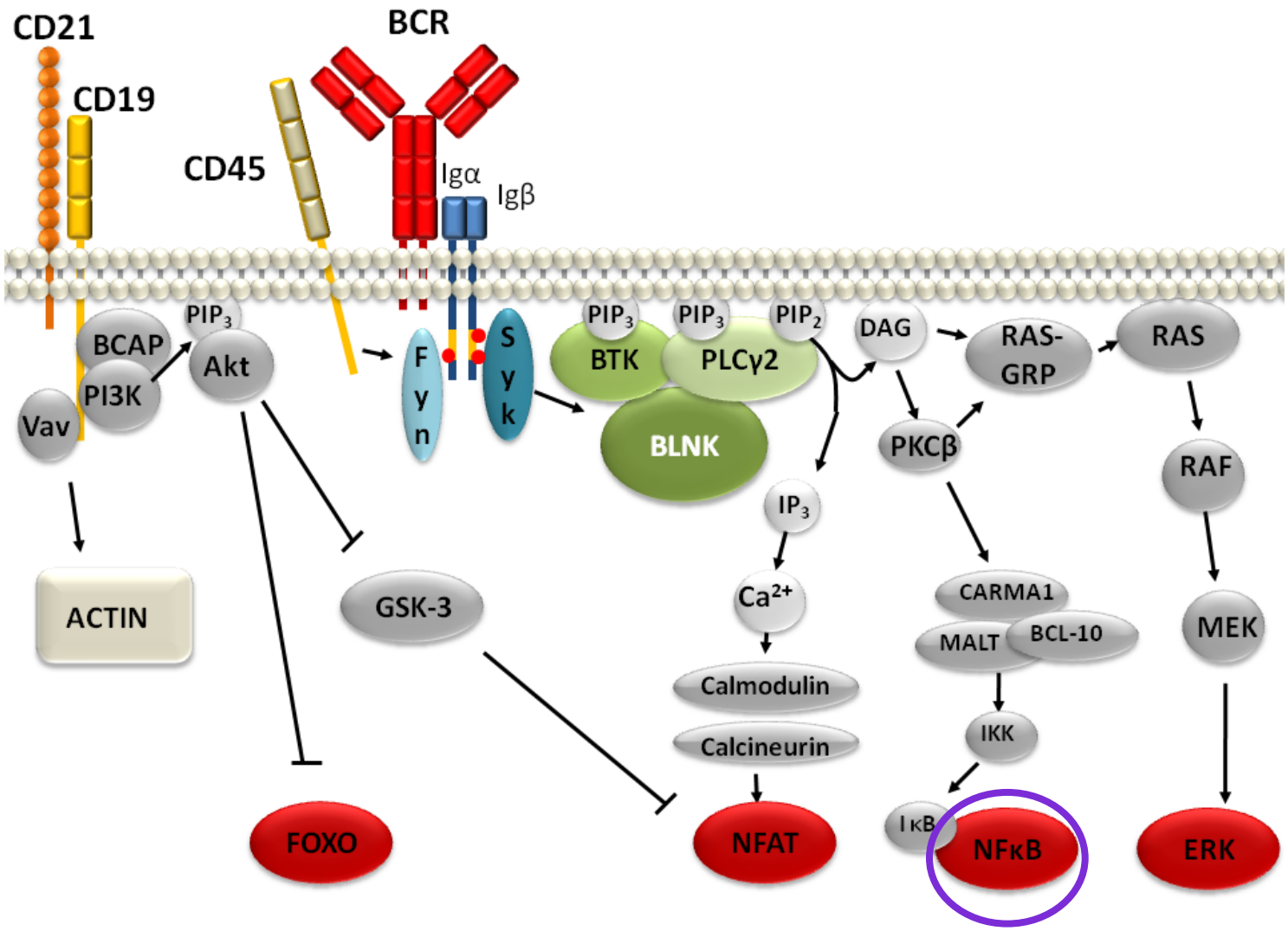
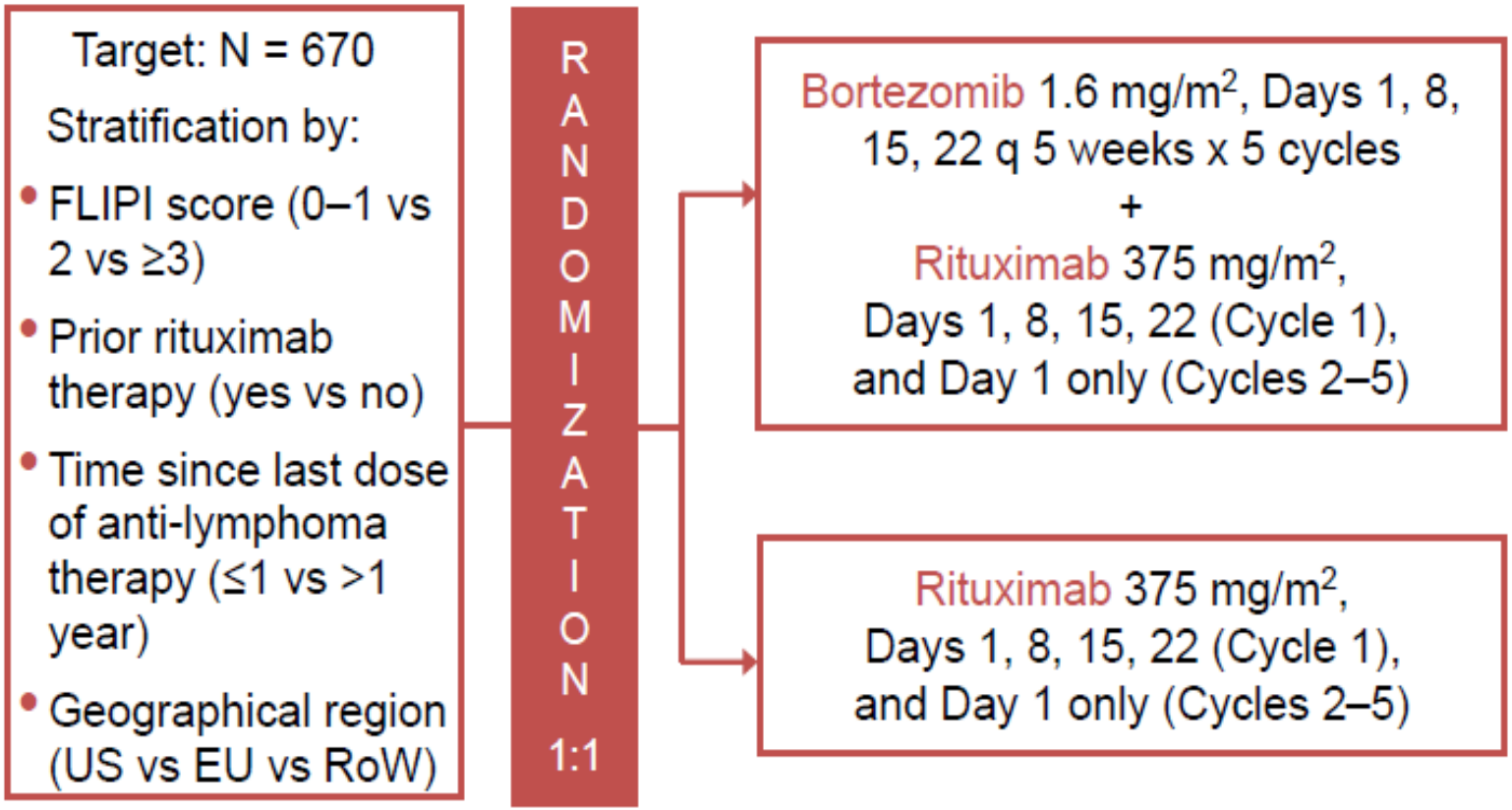
NF-κB



Bortezomib..better use of biomarkers



Treatment duration: 25 weeks in each arm
8 doses of rituximab in each arm

Coiffier el al. Lancet Oncology, Volume 12, Issue 8, 2011, 773 - 784

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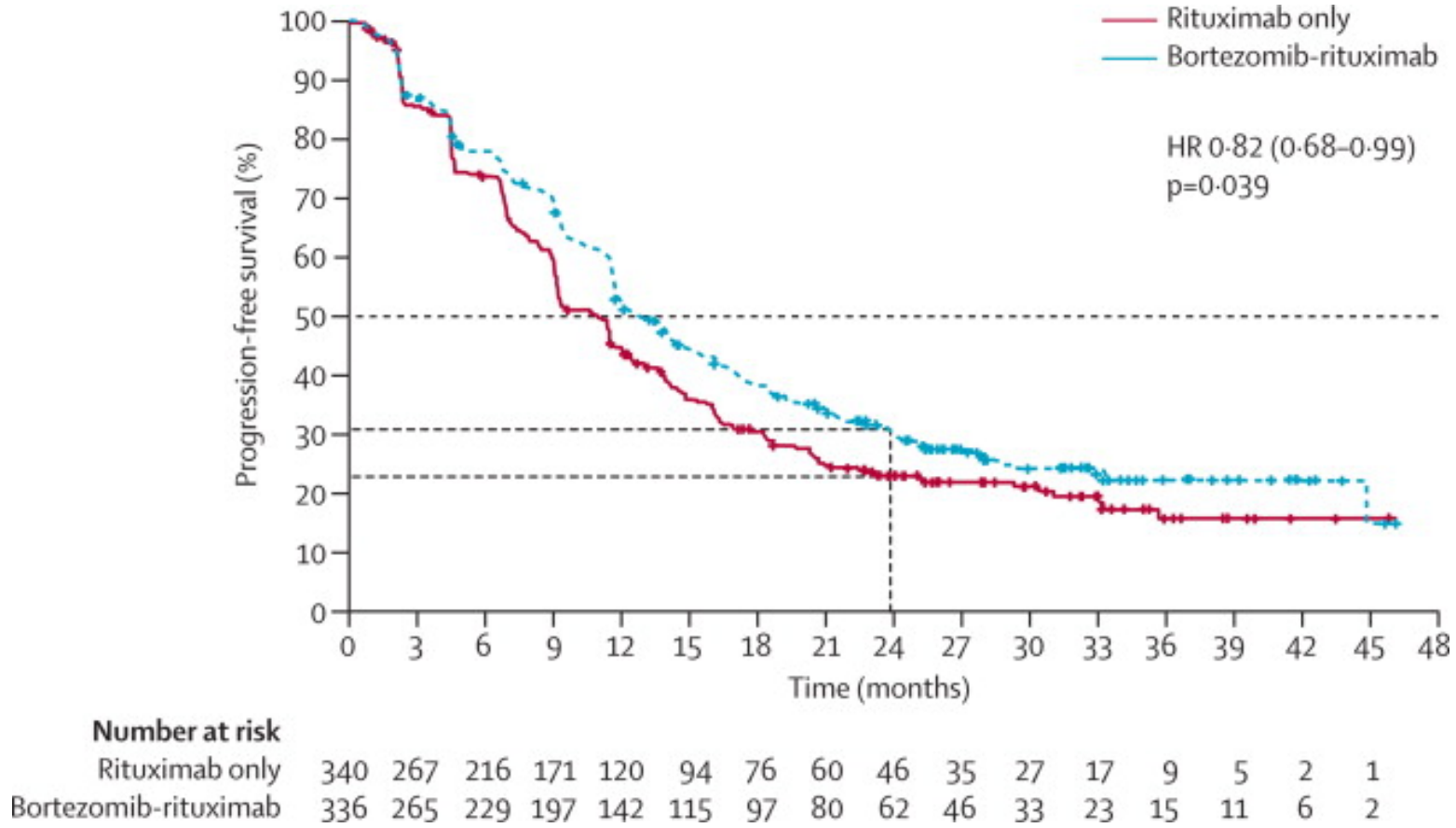
Progression-free survival per IRC.

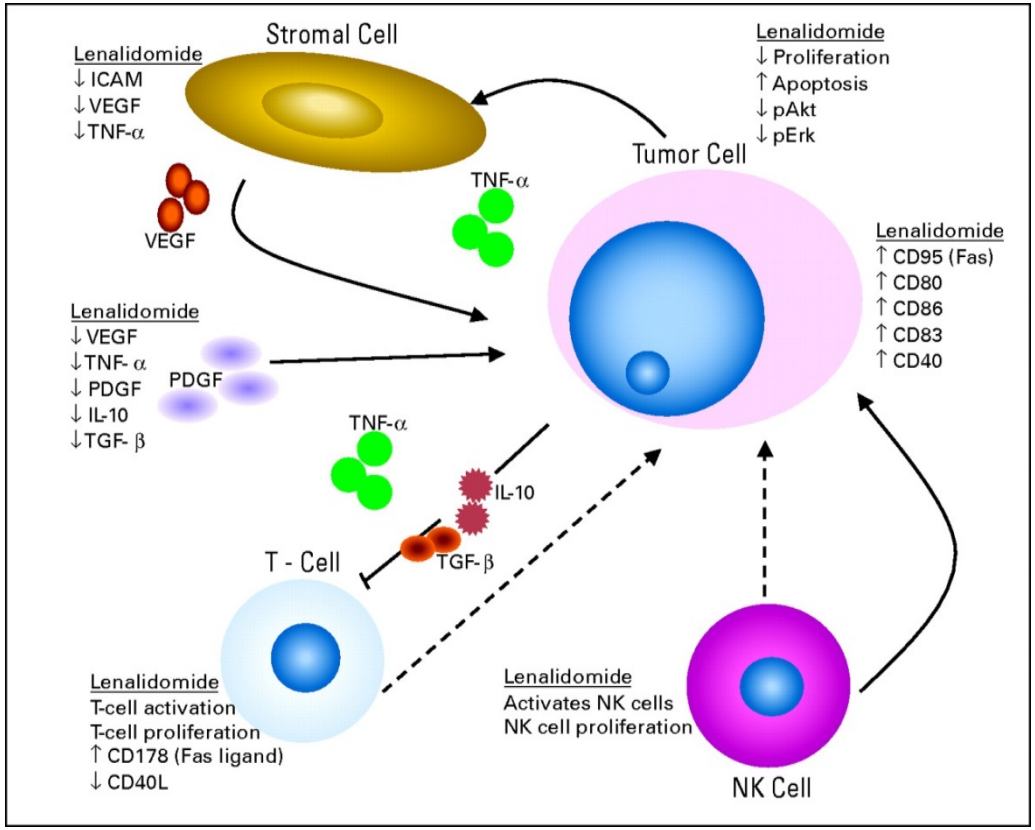


Median PFS 110 mo (R)
vs 12.8 mo (R+B)

Coiffier el al. Lancet Oncology, Volume 12, Issue 8, 2011, 773 - 784

Lenalidomide

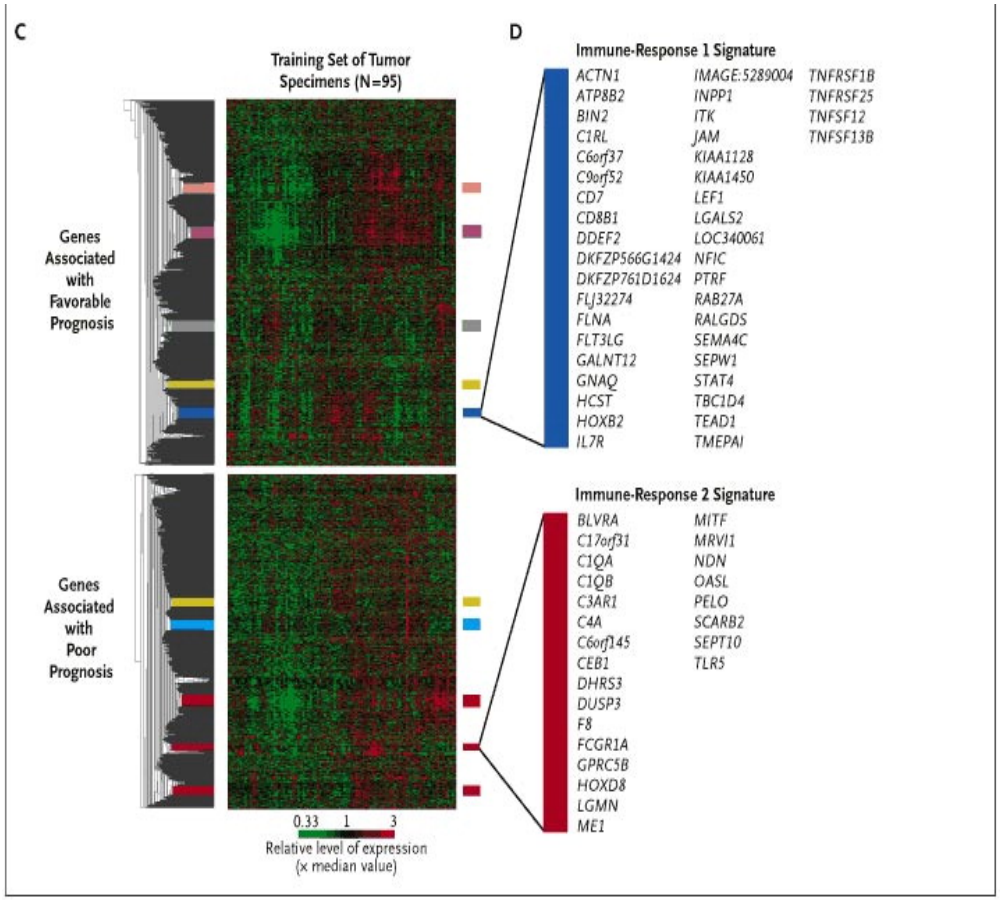
- **Immunomodulatory properties**
- **Modulation of both cellular and cytokine tumour cell microenvironment**
- **Activates T cell and NK response to tumour cell**
- **Down regulates pro-survival cytokines**
- **Approval in myeloma**



Chanan-Khan, A. A. et al. J Clin Oncol; 26:1544-1552 2008

Exhausted T-cells: Will there be a role?

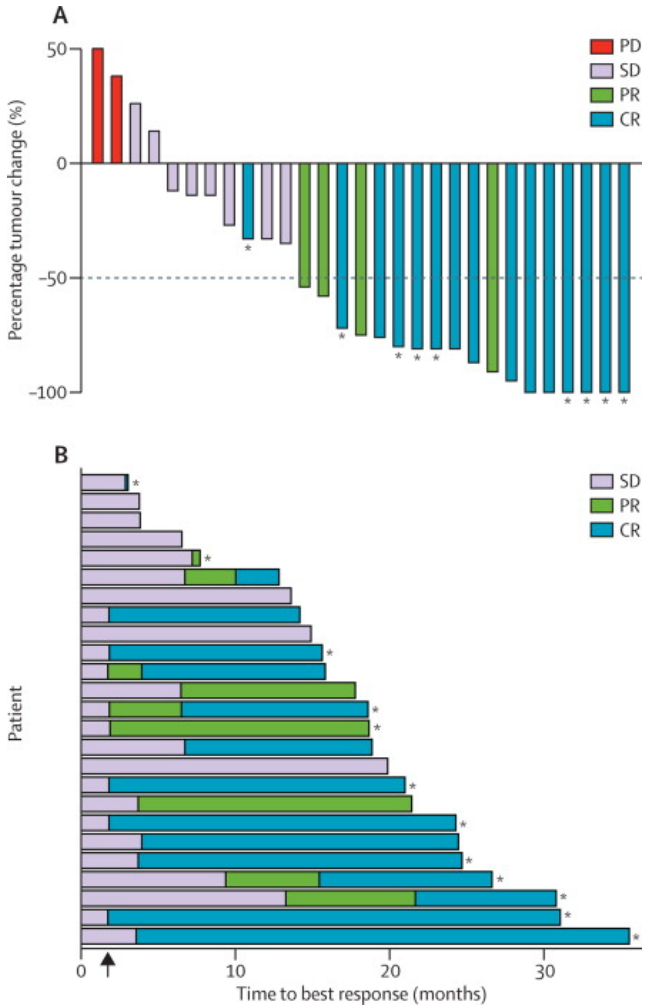
- **Important interplay between malignant cells and microenvironment.**
- **Natural induction of antitumour immune response in FL**
- **…eventually ineffective. Immune escape or immune checkpoints**



Dave SS et al. N Engl J Med 2004;351:2159-2169.

Pidilizumab

- Humanised IgG-1 targets PD1
- Pidilizumab (4 + 8 infusions) and rituximab (4 infusions) combination study in FL
- n=32
- Median number of prior therapies 1 (1-4)
- Time since last therapy 23.8 mo (9.8-76.1)
- 66% ORR (in 29 evaluable)
- 15 pts (52%) CR



Westin et al. Lancet Oncology, Volume 15, Issue 1, 2014, 69 - 77

LINFOMA FOLLICOLARE

- Gli stadi localizzati sono guaribili !
- Low tumor burden FL come trattarli?
- Non tutti i linfomi follicolari sono uguali: come fare a distinguerli?
    - -Indici prognostici (FLIPI, FLIPI2, M7FLIPI)
    - -Malattia minima residua
    - -PET/CT
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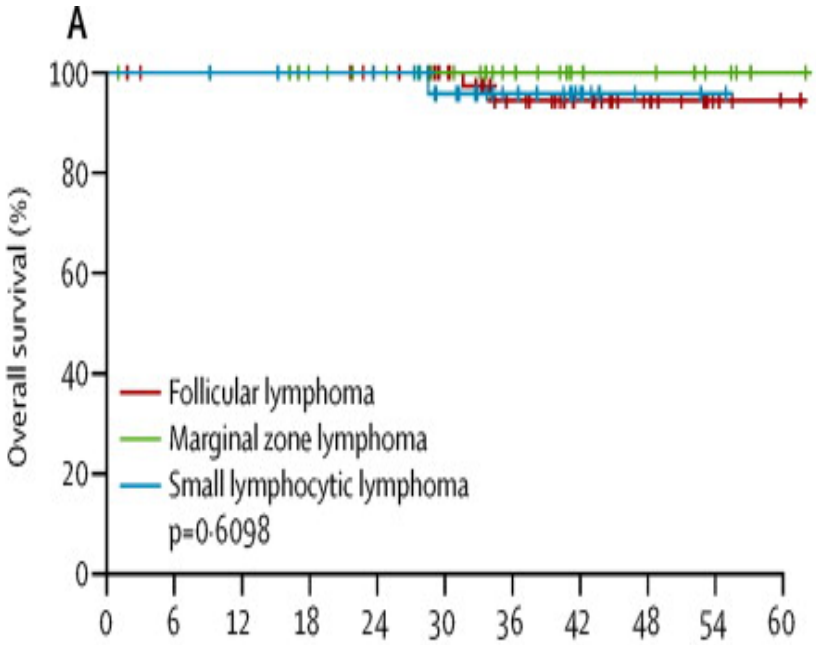
- **La induzione chemio-free, ‘utopia’?**

The R^2 regimen (Fowler at al. Lancet Oncol 2014)

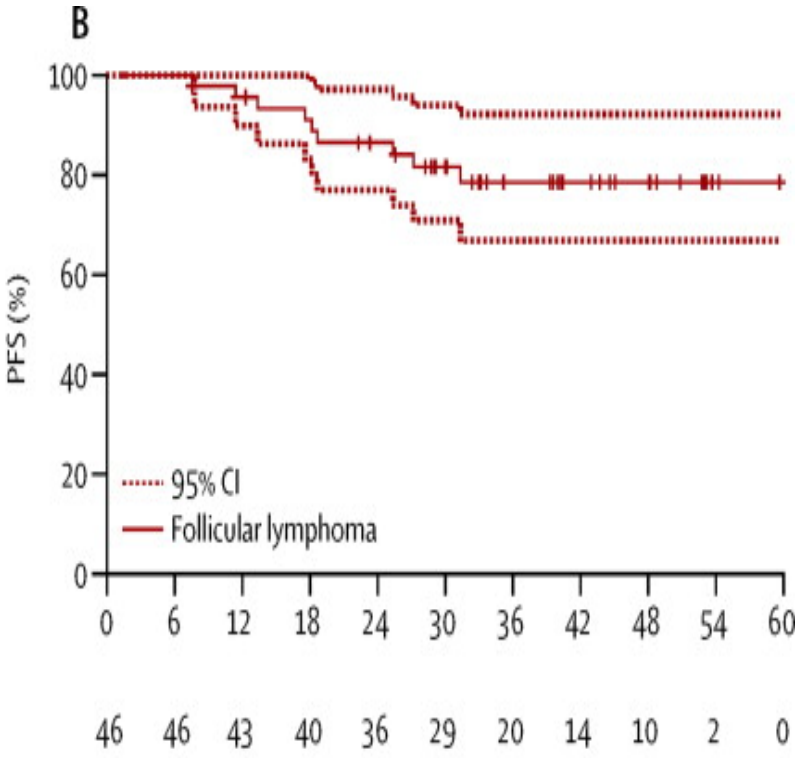
%	ORR	CR/CR(u)	PR	SD	PD
Follicular (n=46)	98	87	11	2	0
Small lymphocytic (n=30)	80	27	53	13	7
Marginal zone (n=27)	89	67	22	11	0
All (n=103)	90	64	26	8	2

Overall survival



Number at risk											
Follicular lymphoma	50	48	48	48	45	40	30	20	13	4	1
Marginal zone lymphoma	30	30	29	26	24	20	15	9	8	5	1
Small lymphocytic lymphoma	30	29	29	28	27	21	14	8	2	1	0

Progression-free survival: Follicular lymphoma



Will chemo free be better? RESORT

Fowler et al Lancet Oncol 15 (12), 2014, 1311-1318

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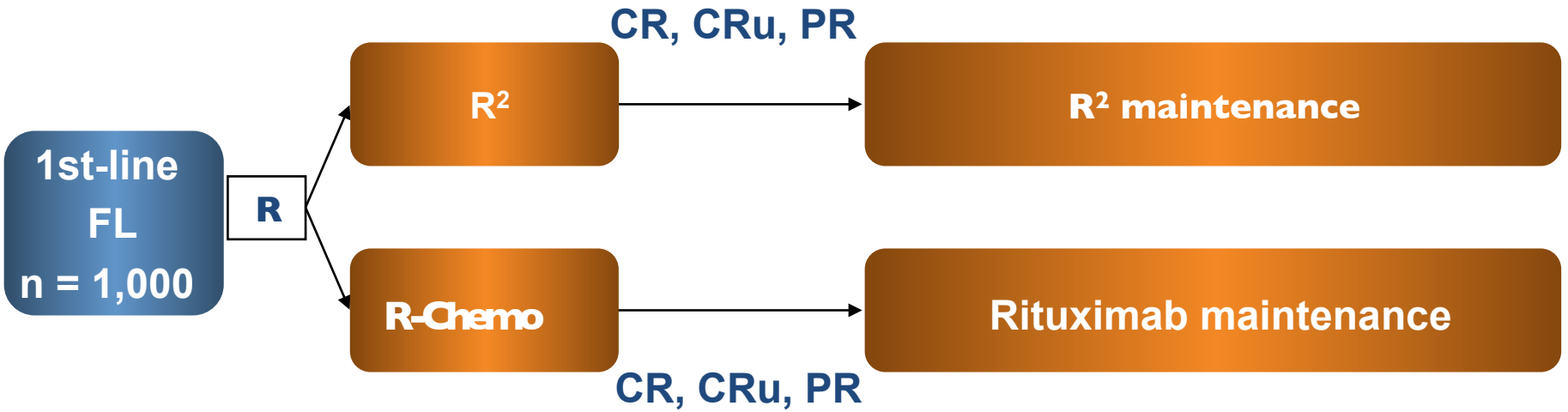
RELEVANCE : phase 3 study design

(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

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- *lo stadio 1 è potenzialmente guaribile*
- *il watch and wait è una terapia*
- *quando si inizia un trattamento il programma deve essere 'completo e curativo'*
- *preferire i nuovi farmaci in particolare i nuovi anticorpi e/o nuovi farmaci biologici*
- *non escludere mai il paziente dalle decisioni*

LINFOMA FOLLICOLARE

- *di linfoma follicolare si può guarire*
- *le guarigioni in passato erano sporadiche*
- *l'avvento del rituximab sia nell'induzione*

che nel mantenimento ha aumentato le possibilità di guarigione

- *le nuove terapia che 'colpiscono' selettivamente i meccanismi di linfomagenesi*

in una patologia così poco aggressiva saranno e terapie di elezione per ottenere sempre più guarigioni.


GRAZIE