

## Highlights from EHA

Report dei gruppi di lavoro >>  
[ Linfomi ]

Relatore: **M. MARTELLI**

27-28 ottobre 2008

Borgo S. Luigi – Monteriggioni (Siena)

# Gruppo di lavoro

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[ Linfomi ]

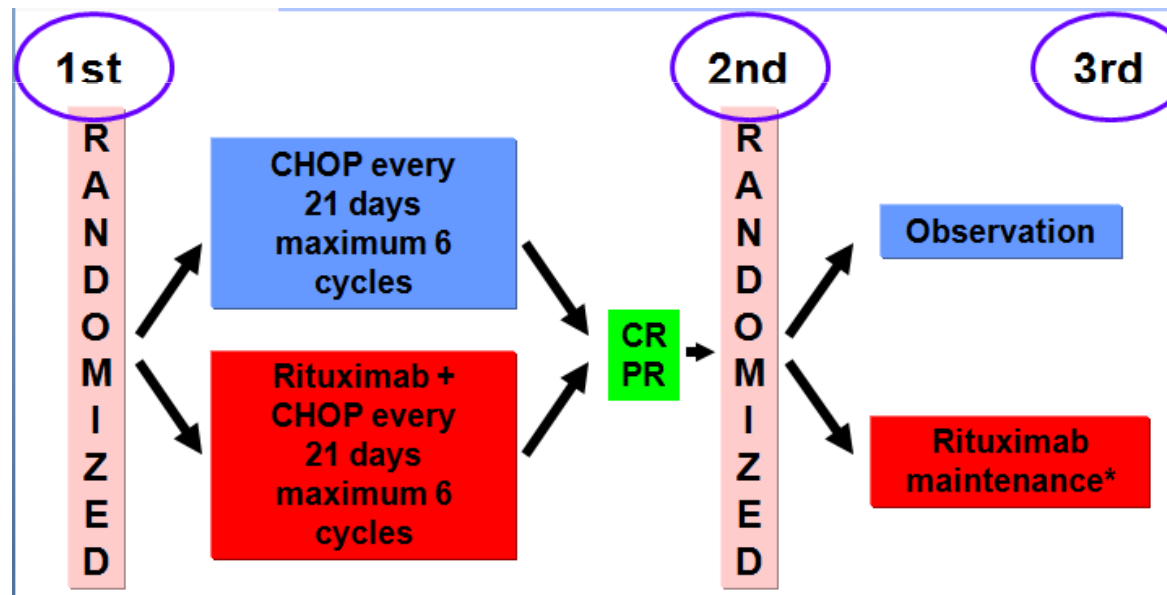
MASSIMILIANO CERGNUL	PAOLA PERFETTI
PAOLO DESSALVI	SERGIO STORTI
LAURA DOROTEA	SIMONE VOLTOLINI
ROBERTO MARRA	KATHRIN APRILE
LORELLA ORSUCCI	GIOVANNI CAMETTI

Bcl2/IgH PCR values at the end of induction are not predictive for progression free survival in relapsed/resistant follicular lymphoma.

Results from the EORTC20981 intergroup study.

Van der Reijden BA, Van Oers MHJ, Tönnissen E, Glabbeke M, Giurgia L, Klasa R, Marcus RE, Wolf M, Kimby E, Van t Veer M, Vranovsky A, Holte H, Hagenbeek A.

## Molecular screening in EORTC 20981 intergroup study



1. Before start induction therapy
2. End of induction therapy
3. End of 2 years maintenance or observation

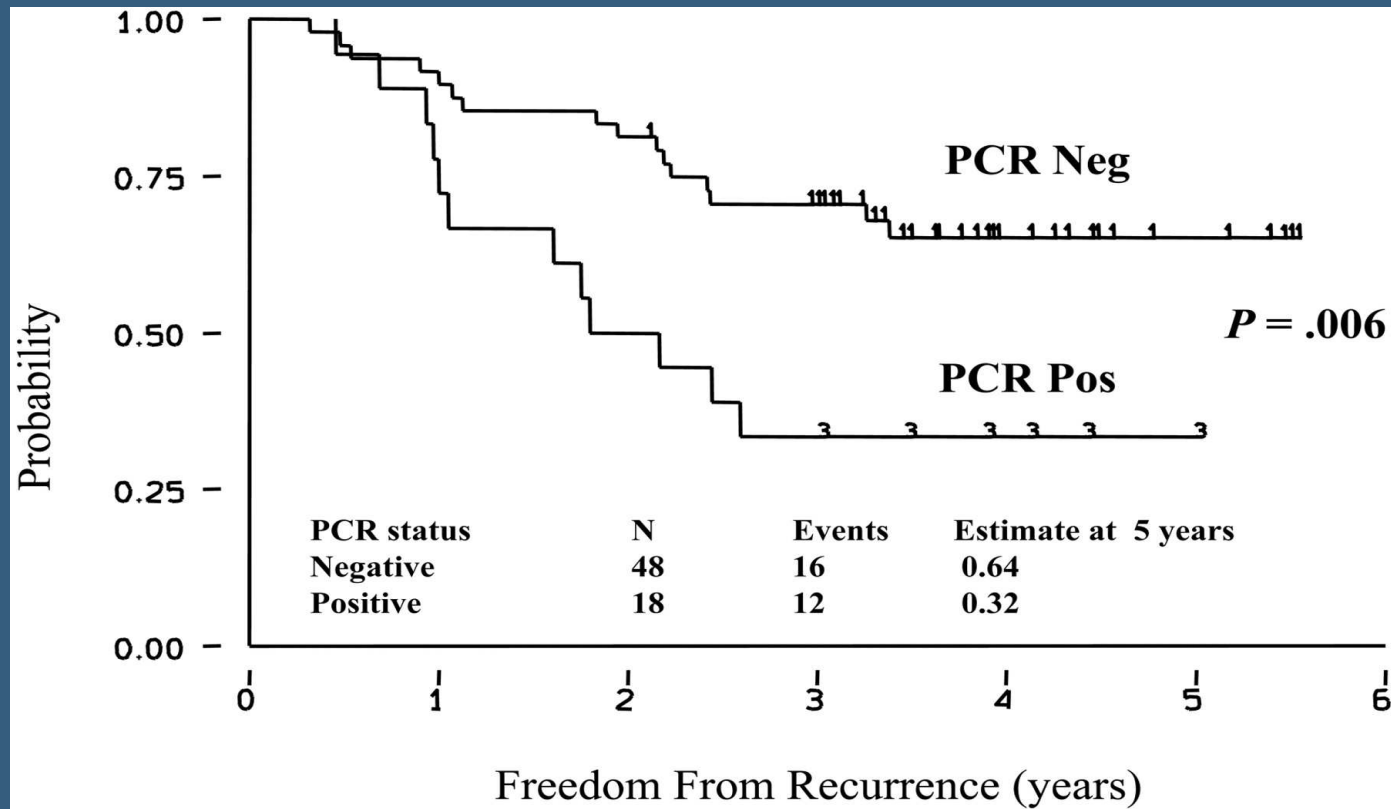
792 samples (peripheral blood and bone marrow) from 245 patients

# Report del gruppo di lavoro

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- Bcl-2 pos al termine della terapia di induzione non è predittivo per la PFS
- Vantaggio del mantenimento con Rituximab sia nei pazienti PCR neg e PCR pos dopo terapia d'induzione
- La prima conclusione è in contraddizione con i risultati di altri studi di fase II e III in pazienti con linfoma follicolare trattato con R-CHT.

## FFR according to minimal residual disease in the BM after treatment



Rambaldi, A. et al. Blood 2005;105:3428-3433

# PCR Status: 28 patients Bcl-2/VDJ+ at diagnosis: Clinical and molecular response

## PCR negative status

After FND Chemotherapy

10/27

Along with CR:

4/27 (15%)

Rituximab ±  
FND

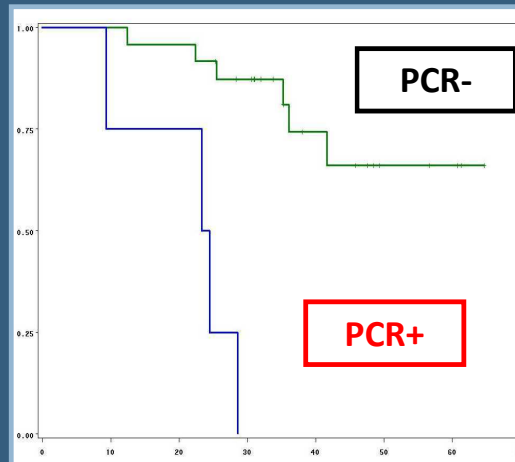


At the end of treatment

24/28

Along with CR:

24/28 (86%)



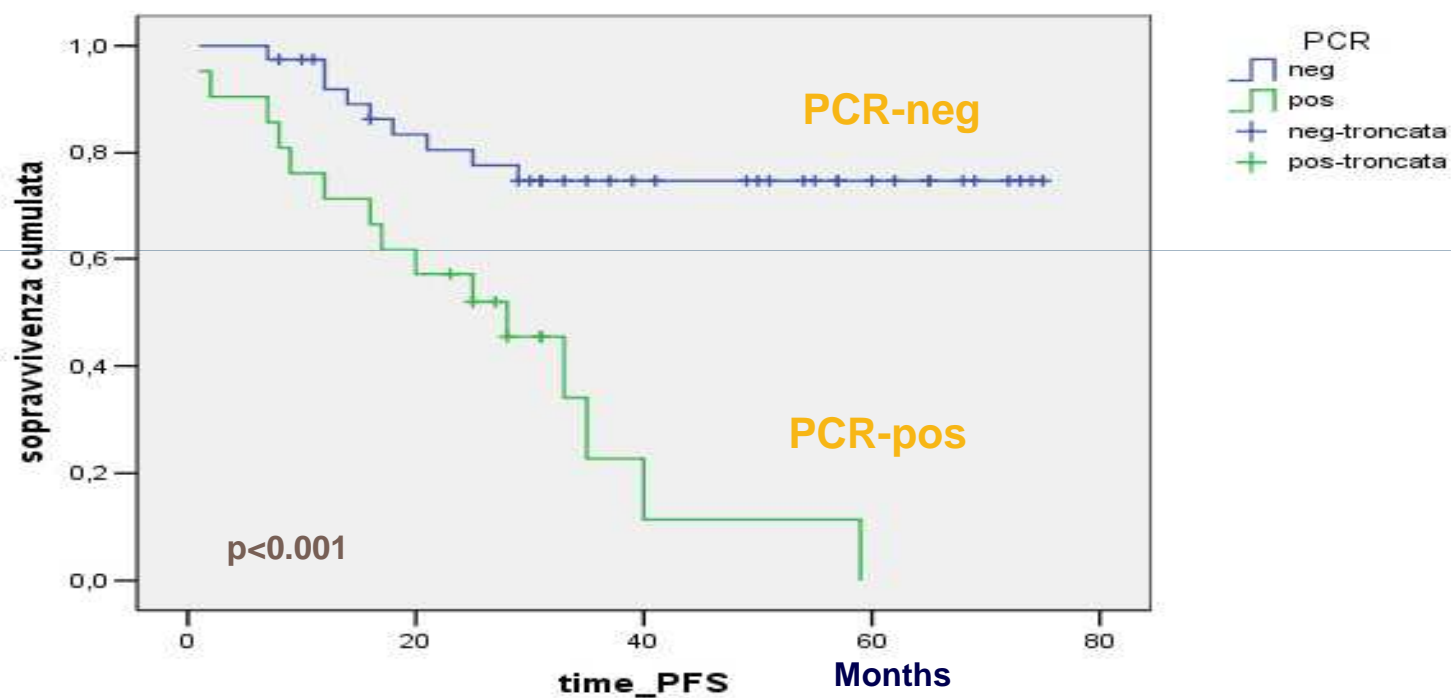
PCR - : Failures 6/24  
PCR + : Failures 4/4

Vitolo EHA 2006

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

## PFS ACCORDING TO PCR-STATUS

Funzioni di sopravvivenza

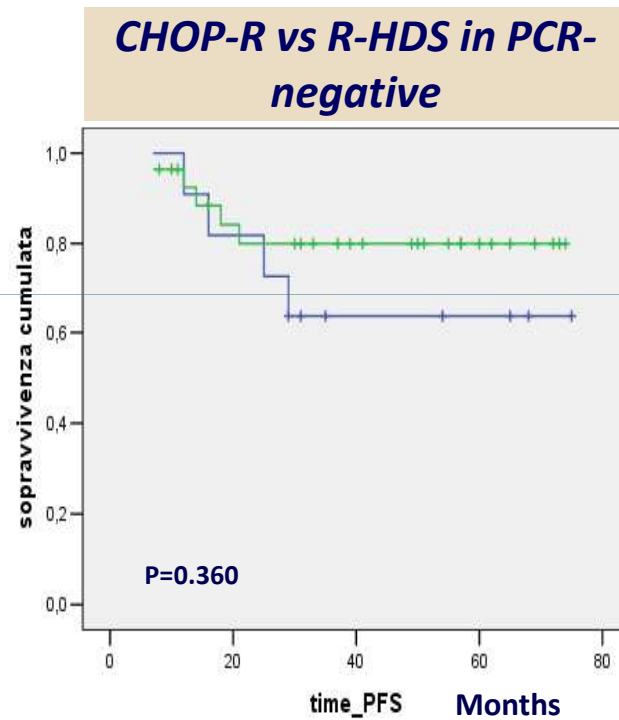


Ladetto et al ASH 2006

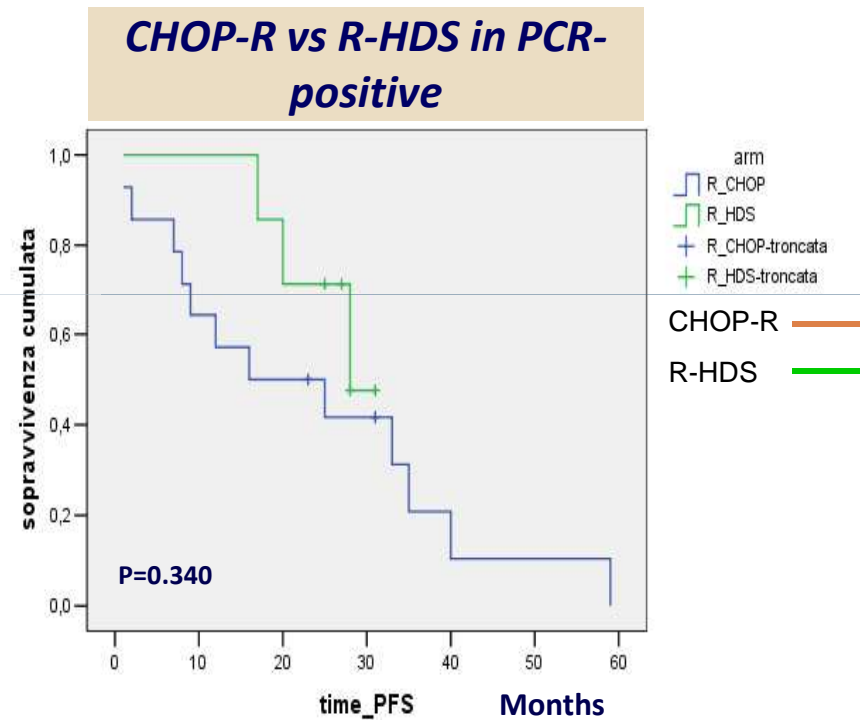
# R-HDS vs CHOP-R RANDOMIZED TRIAL EVALUABLE PATIENTS: 60

## PFS ACCORDING TO PCR-STATUS AND ARM

Funzioni di sopravvivenza



Funzioni di sopravvivenza



Ladetto et al ASH 2006

# Report del gruppo di lavoro

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- Lo studio prevedeva una valutazione molecolare centralizzata
- Nello studio EORTC si tratta di pazienti in ricaduta e non in prima linea
- Rispetto agli studi precedentemente pubblicati nell'esperienza dell' EORTC c'è la variabile mantenimento

The host pharmacogenetic background is an independent predictor of outcome and toxicity in DLBCL treated with R-CHOP21.

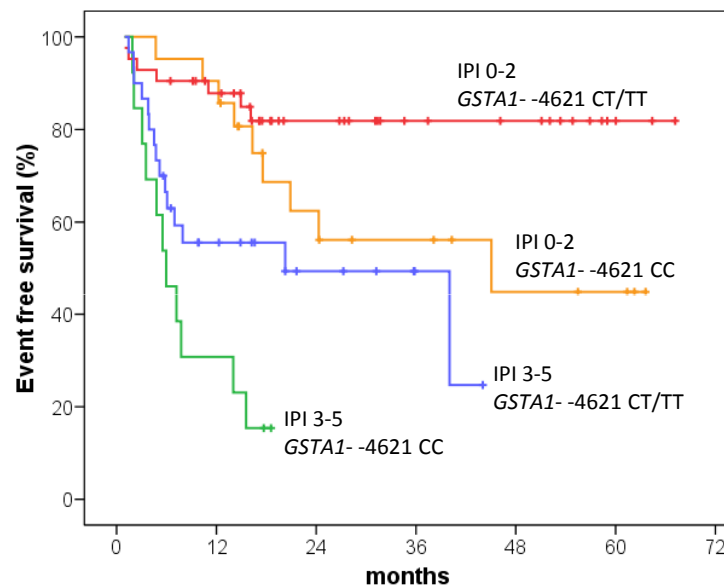
Rossi D, Rasi S, Franceschetti S, Capello D, Castelli A, De Paoli L, Ramponi A, Chiappella A, Pogliani EM, Vitolo U, Kwee I, Bertoni F, Conconi A, Gaidano G.

## DOES the PHARMACOGENETIC BACKGROUND of the HOST HAVE an IMPACT in DLBCL OUTCOME?

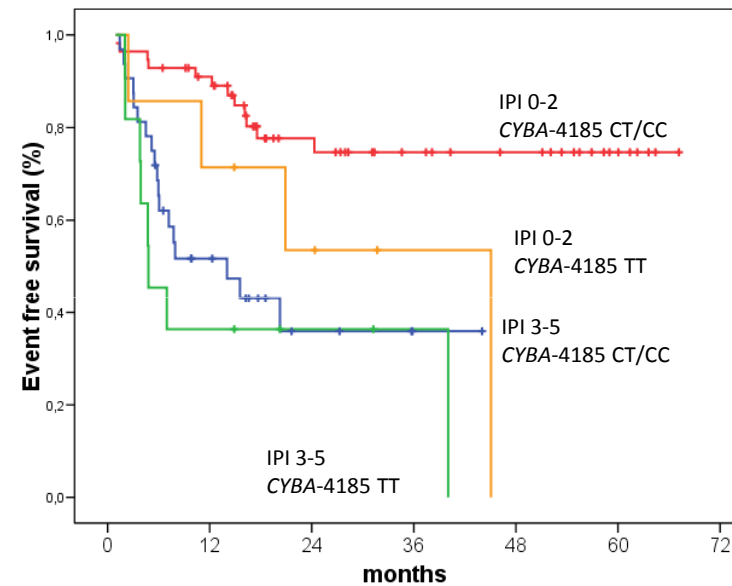
- ✓ The host pharmacogenetic profile may be traced to SNPs affecting drug metabolism, detoxification, cellular transport, and targeting
- ✓ In solid cancers and in ALL (*Cheek & Evans, Nat Rev Cancer 2006*), pharmacogenetic SNPs are responsible, in part, for interindividual variability in efficacy and toxicity of chemotherapy
- ✓ Scant information is available on the impact of pharmacogenetics as a predictor of outcome and toxicity in DLBCL (*Wojnowski et al, Circulation 112:3754, 2005*)

# PHARMACOGENETIC SNPs MAY ADD PROGNOSTIC INFORMATION when COMBINED to IPI

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	3-year EFS
IPI 0-2 and <i>GSTA1</i> -4621 CT/TT	81.9%
IPI 0-2 and <i>GSTA1</i> -4621 CC	56.2%
IPI 3-5 and <i>GSTA1</i> -4621 CT/TT	49.9%
IPI 3-5 and <i>GSTA1</i> -4621 CC	15.4%



	3-year EFS
IPI 0-2 and <i>CYBA</i> -4185 CT/CC	74.7%
IPI 0-2 and <i>CYBA</i> -4185 TT	53.6%
IPI 3-5 and <i>CYBA</i> -4185 CT/CC	35.9%
IPI 3-5 and <i>CYBA</i> -4185 TT	36.4%

# Report del gruppo di lavoro

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- Questi risultati dimostrano ulteriori limiti dell'IPI
- Necessità di validazione su ampi numeri e in studi randomizzati (DLCL04)
- Applicabilità e riproducibilità dei dati di farmacogenetica nella pratica clinica corrente.
- Futuro ruolo per una terapia personalizzata ( score prognostico clinico–biologico)

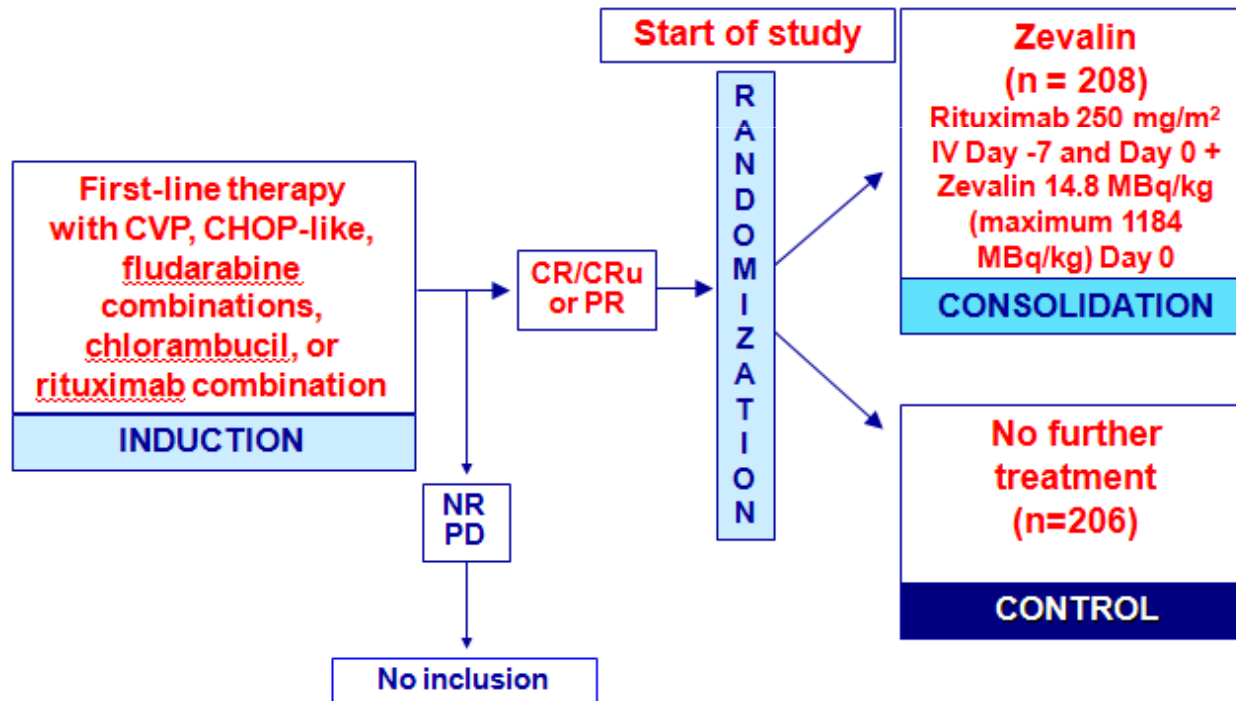
13

## Discussione

Results from the randomized phase 3 First-line Indolent Trial (FIT) of consolidation of first remission with 90Y-Ibritumomab Tiuxetan in advanced follicular non-Hodgkin's lymphoma (FL).

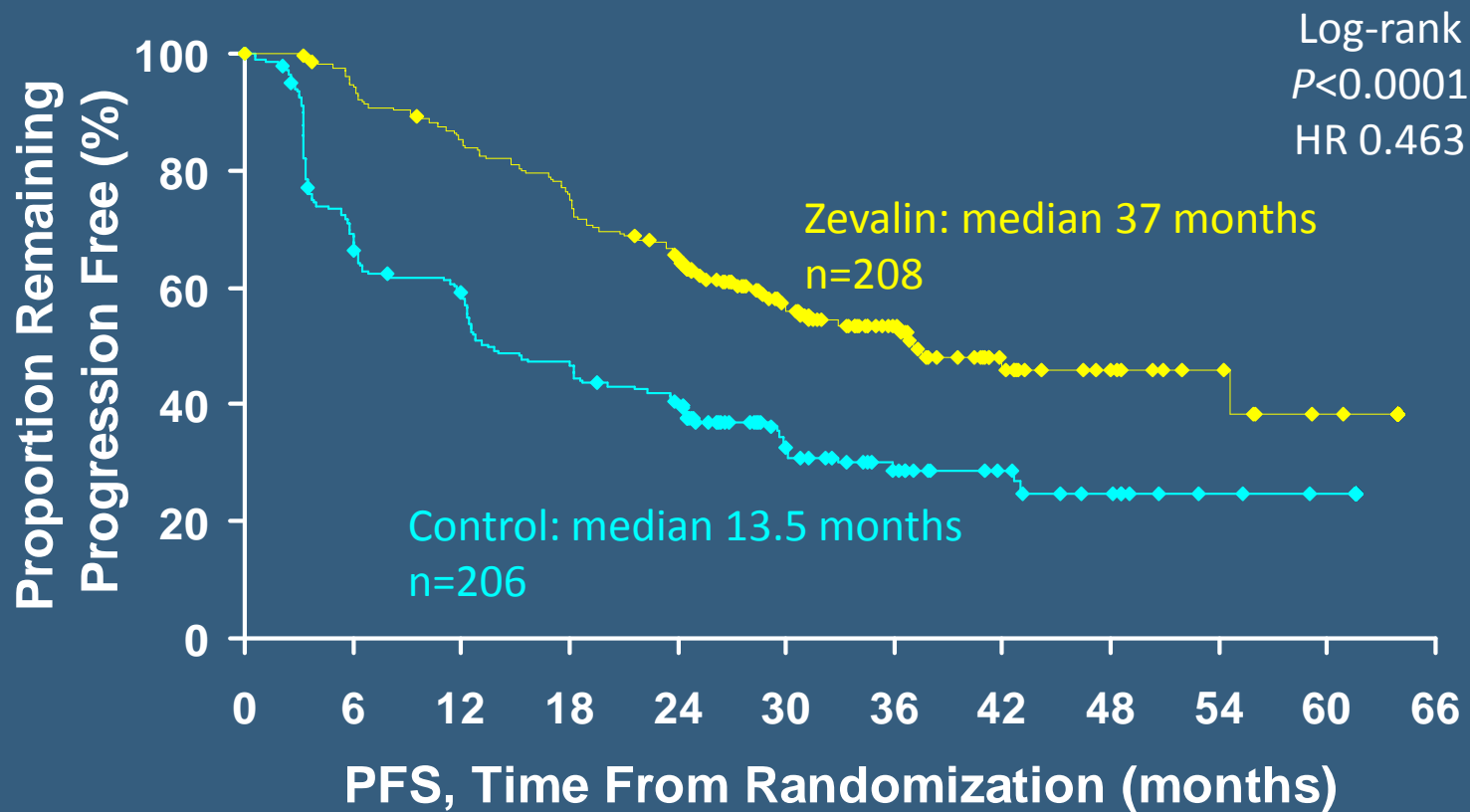
Radford JA, Morschhauser F, Van Hoof A, Vitolo U, Soubeyran P, Tilly H, Huijgens PC, Kolstad A, Kunz M, Hagenbeek A.

## FIT Study Schema

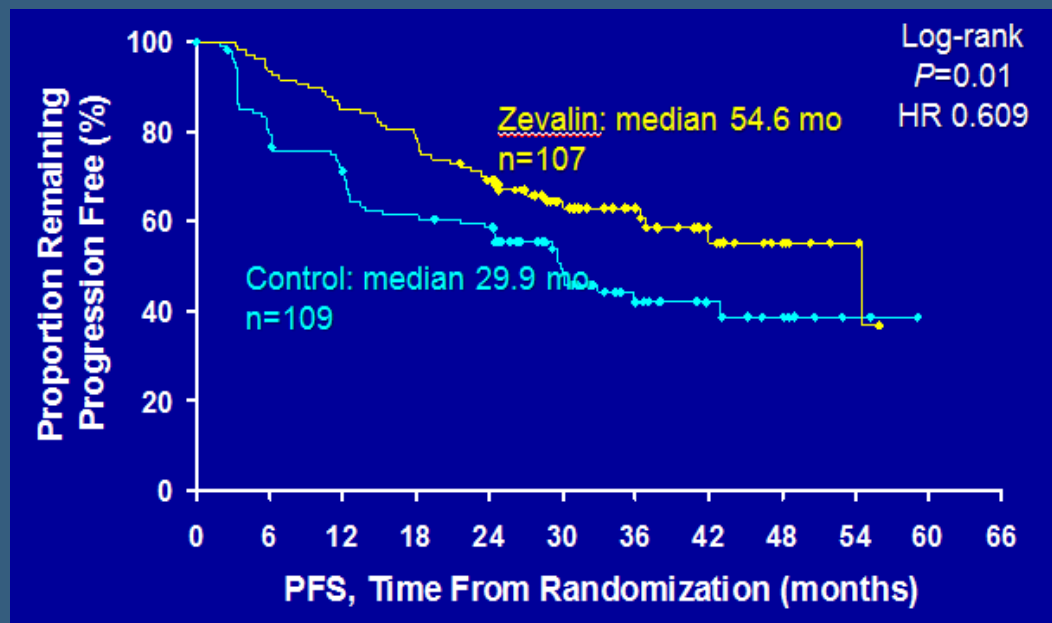


# FIT Primary Endpoint: Median PFS in All Patients (median observation period: 3.5 years)

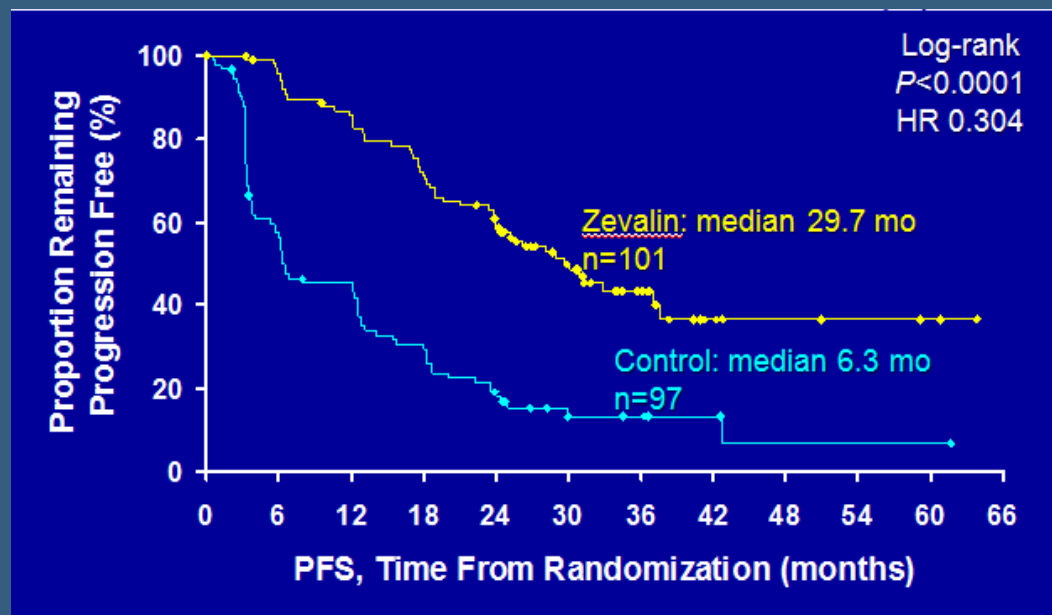
15

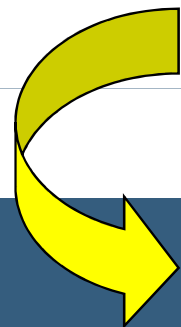
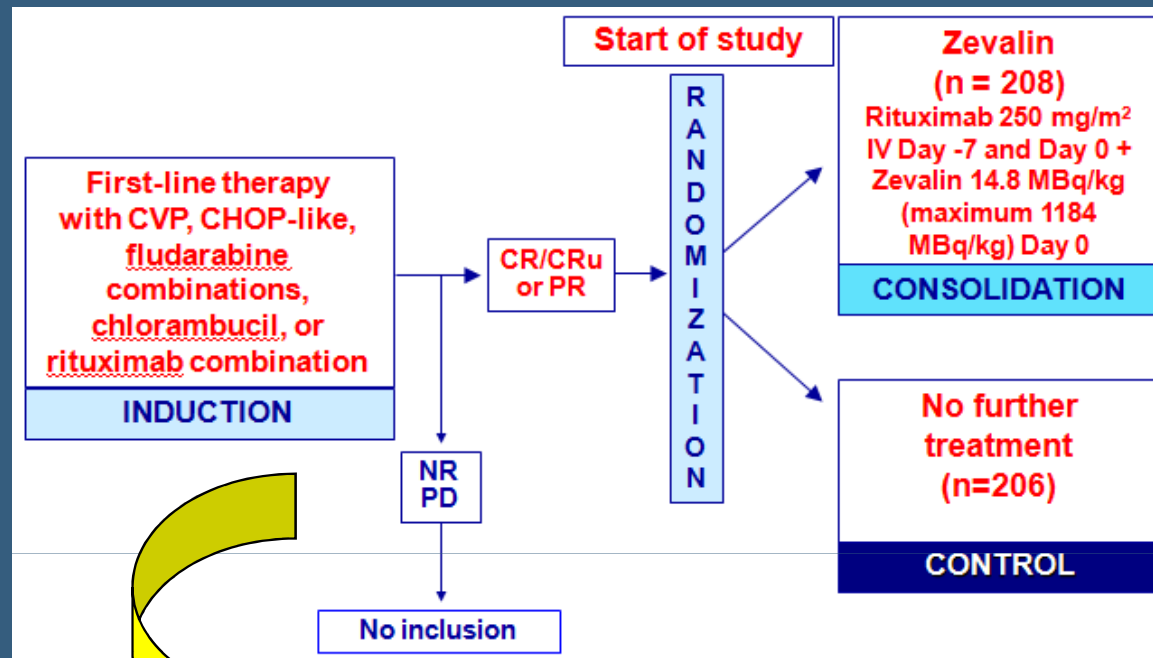


**FIT:**  
**PFS in patients with**  
**CR/CRu**  
**after First-line Therapy**



**FIT:**  
**PFS in patients with**  
**PR**  
**after First-line Therapy**





CVP	106
CHOP/ like	188
Flud. comb.	22
CHL	39
<b>Ritux. comb</b>	<b>59 (14%)</b>

# Report del gruppo di lavoro

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- La maggior parte dei pazienti (86%) ha ricevuto una terapia d'induzione senza Rituximab
- Questo può aver creato un vantaggio a favore del gruppo di pazienti consolidato con Zevalin rispetto al solo controllo.
- In futuro studio randomizzato (RITZ) pazienti con FL in recidiva: induzione con R-Chemo saranno randomizzati a Zevalin vs il solo controllo + Rituximab di mantenimento nei due bracci

**Brief chemoimmunotherapy with Rituximab R-FND ± Rituximab maintenance as first line treatment in advanced Follicular Lymphoma in elderly: preliminary analysis of a prospective randomized trial.**

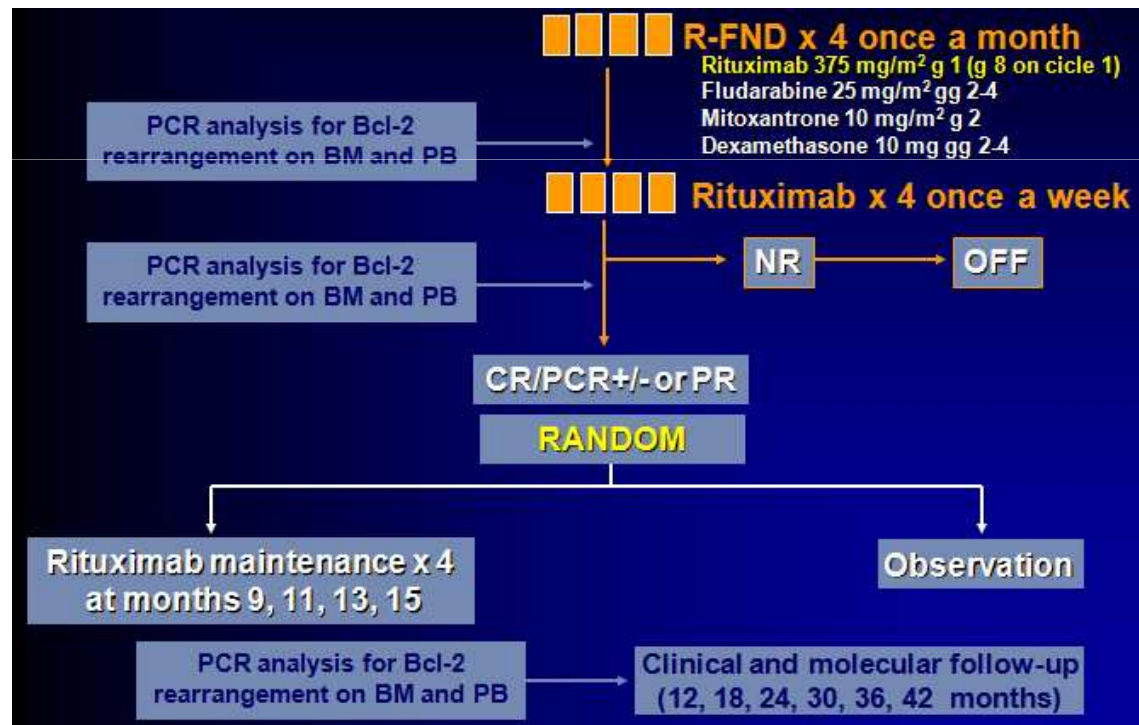
Vitolo U, Ladetto M, Boccomini C, Gamba E, Alvarez I, Baldini L, Ceccarelli M, Chiappella A, Corradini P, De Renzo A, Di Raimondo F, Gallamini A, Guarini A, Mantoan B, Martelli M, Naso V, Parvis G, Petrini M, Pinto A, Pozzi S, Pulsoni A, Rigacci L, Tarella C, Tucci A, Zaja F and Gallo E.



Study ML17638

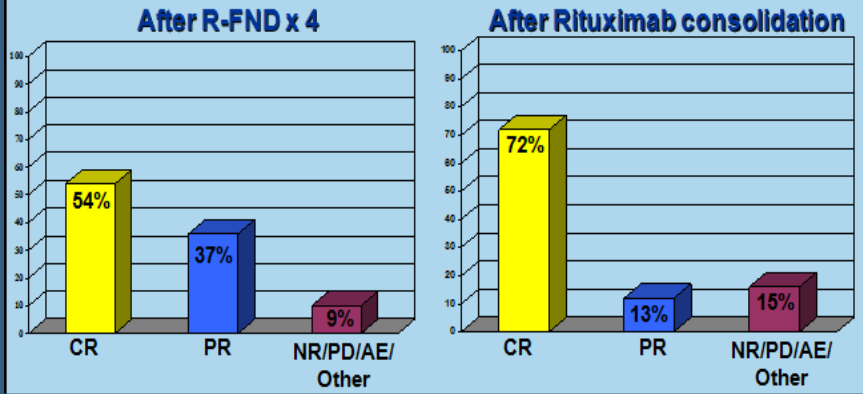


IIL ID: IILFL04



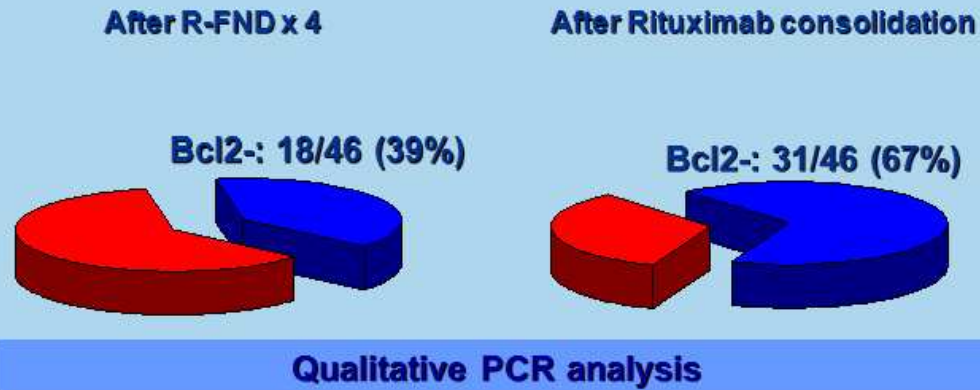
# MOLECULAR RESPONSE TO TREATMENT

OVERALL RESPONSE RATE: 85%



46 patients *Bcl2+* at diagnosis evaluable for clinical response

PCR negativity associated with CR



# Report del gruppo di lavoro

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- Alta percentuale di risposta clinica con tossicità moderata in pazienti anziani con FL con un trattamento di breve durata (R-FND x 4)
- L'aggiunta di Rituximab di consolidamento (R x 4) migliora significativamente la qualità della risposta clinica e molecolare
- Rappresenta il primo studio di fase III randomizzato, in pazienti anziani con FL, che pone il quesito della terapia di mantenimento con Rituximab dopo una terapia di prima linea standard R (8 dosi)-FND.

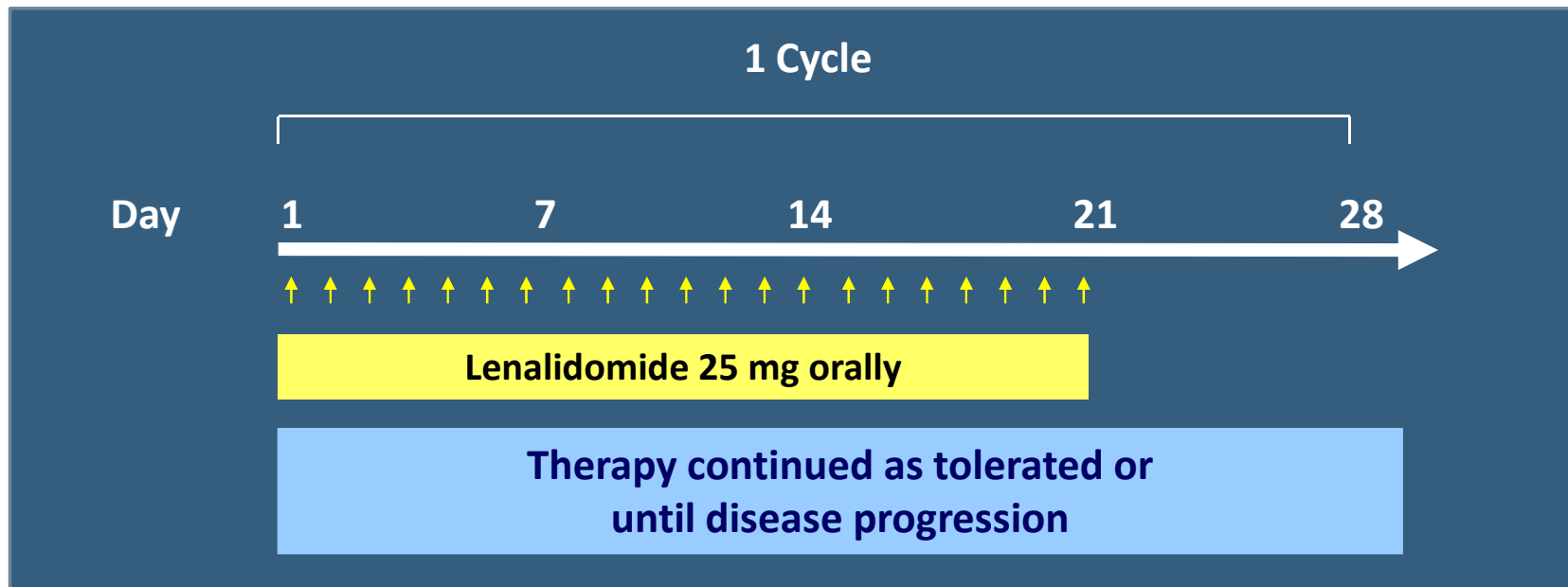
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## Discussione

## Results from an international study investigating the efficacy and safety of Lenalidomide in relapsed or refractory aggressive Non-Hodgkin's Lymphoma.

Haioun C, Reeder CB, Polikoff J, Chowhan NM, Esseeesee I, Greenberg R, Ervin-Haynes A, Pietronigro D, Zeldis JB, Witzig TE, Czuczman MS.

### Study Schema



## Response to Lenalidomide: 83 patients

<b>Objective Response</b>	<b>% (n)</b>
Overall Response	29% (24)
CR/CRu	6% (5)
PR	23% (19)
SD	19% (16)

## Response to Lenalidomide vs NHL histology

<b>Histology</b>	<b>Objective Response % (n/N)</b>
<b>Mantle cell</b>	<b>36% (8/22)</b>
Mantle cell post-Velcade	50% (3/6)
<b>Diffuse large B-cell</b>	<b>22% (11/49)</b>
Follicular lymphoma, Gr 3	33% (2/6)
Transformed lymphoma	50% (3/6)

## Preliminary results from phase II studies of lenalidomide oral monotherapy in NHL

Reference	No of pts	ORR (%)	Cr/Cru (%)	PFS	G 3-4 Toxicity (%)
PH Wiernik et al, ASCO 2007	41 relapsed/refractory NHL (MCL= 14)	14/41 (34) (MCL6/14;43%)	5/41 (12)	>239 days in Cru and >160 days in PR	Neutropenia=30 Thrombocytopenia =20
J M Tuscano et al, ASH, 2007	15 relapsed/refractory MCL	8/15 (53)	1/8 (12.5)	5.7 months	Neutropenia=46 Thrombocytopenia =20 Thromboembolism =13
MS Czuczman et al., ASCO 2008	46 relapsed/refractory NHL	13/46 (28)	NA	NA	Neutropenia=24 Thrombocytopenia =16
TM Habermann et al, ASCO 2008	136 relapsed/refractory NHL	88/136 (65)	NA	NA	Neutropenia=21 Thrombocytopenia =15 Pneumonia=4 Diarrhea=2

## Wiernik et al; EHA 2008

### Phase II trial of Lenalidomide monotherapy in RR Aggressive NHL

<b>Pts(#)</b>	<b>49</b>
<b>Median age</b>	<b>65</b>
<b>Male</b>	<b>51 %</b>
<b>Median time from diagnosis</b>	<b>2.7 yrs</b>
<b>Median no. of prior therapies</b>	<b>4</b>
<b>Prior anthracyclines &amp; alkylating agents &amp; alkaloids &amp; rituximab</b>	<b>84%</b>
<b>At least 3 of the above</b>	<b>92%</b>

<b>IPI</b>	
<b>0-1</b>	<b>8 (16 %)</b>
<b>2</b>	<b>22 (45%)</b>
<b>3</b>	<b>13(27 %)</b>
<b>4-5</b>	<b>6 (12 %)</b>

## Wiernik et al; EHA 2008

### Aggressive NHL: Histology and Response Rate

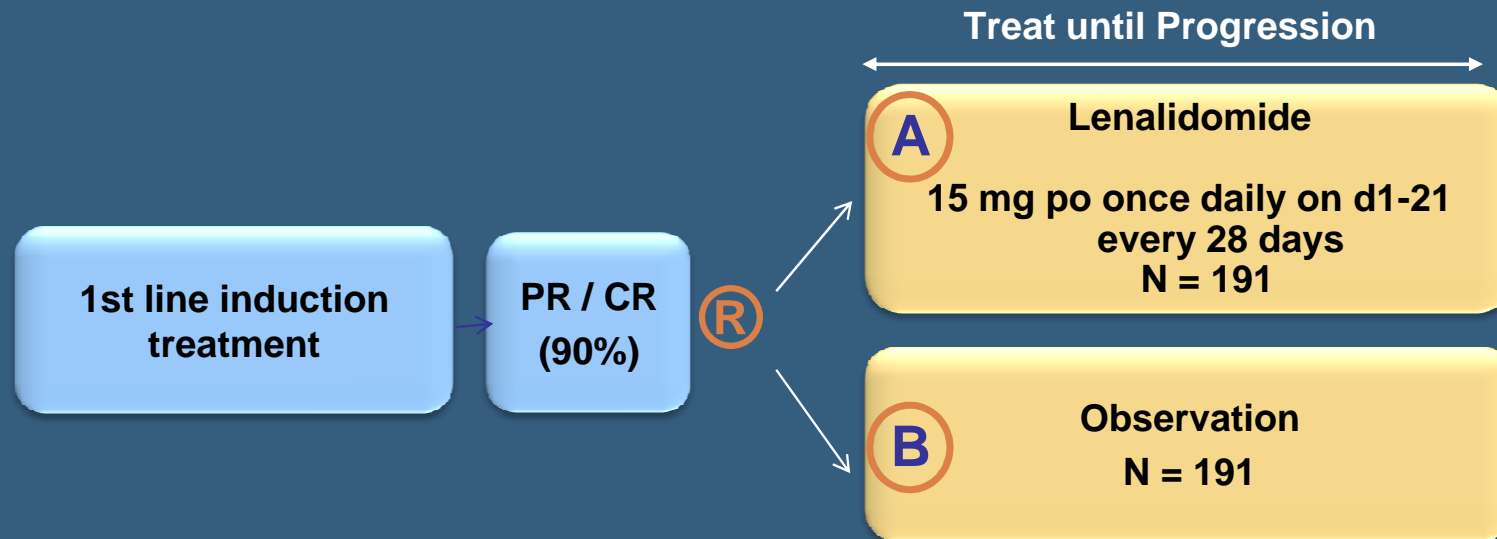
Histology		Response Rate according to Histology				
		CR	CRu	PR	ORR	SD
Aggressive NHL	49 (100%)	5	3	9	17 (35%)	12
DLBL	26 (53 %)	2	2	1	5 (19%)	8
FCL Grade 3	5 (10%)	0	1	2	3 (60%)	0
MCL	15 (31 %)	3	0	5	8 (53%)	2
TSF	3 (6%)	0	0	1	1 (33%)	2

# Report del gruppo di lavoro

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- Lenalidomide has activity in R-chemo resistant relapsed/refractory aggressive lymphoma.
- MCL seems more sensitive compared to other aggressive NHL
- Future prospective trials are needed to evaluate the real role of Lenalidomide in MCL and other aggressive NHL

## MCL 03: Study Design

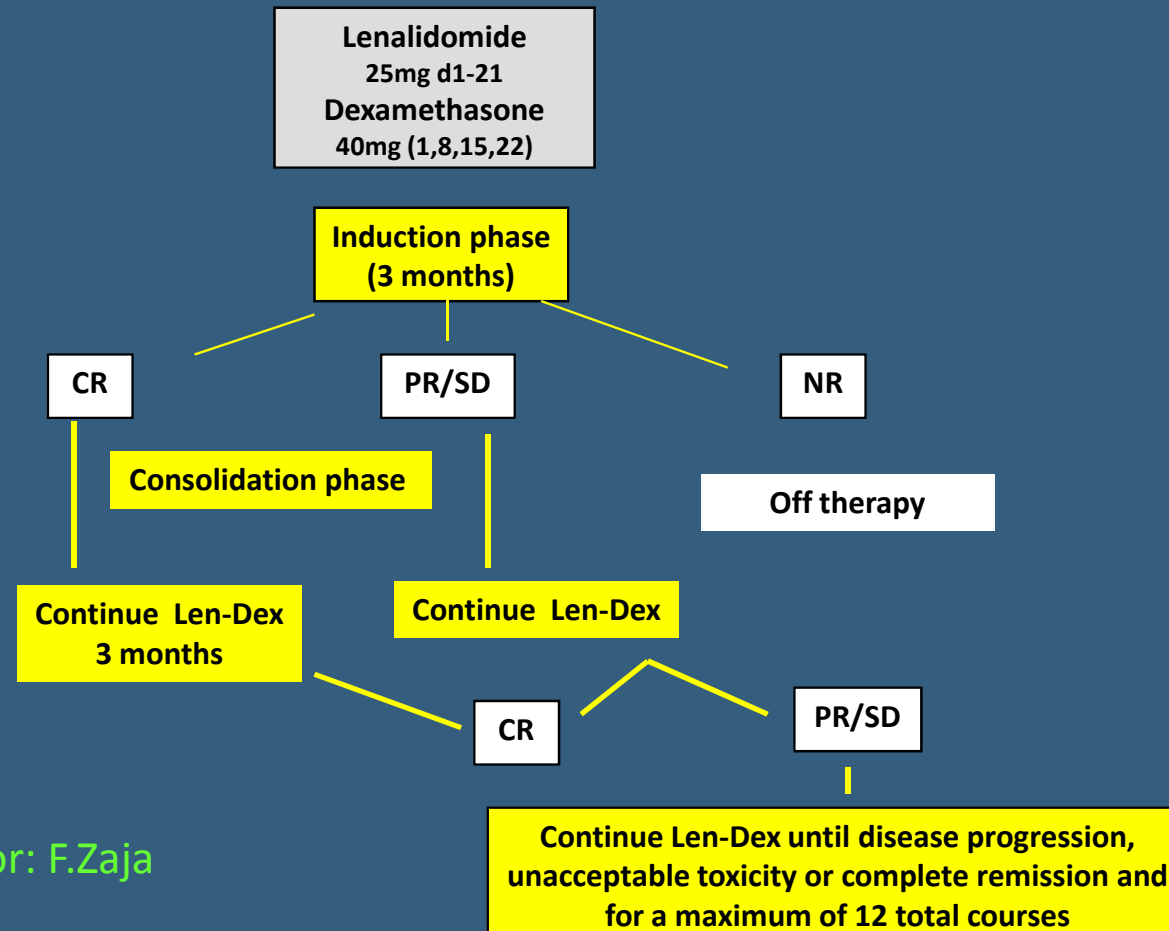


- Phase 3, 1:1 Randomized, comparative, observation-controlled
- Newly Diagnosed MCL Patients with PR or CR after Initial Chemotherapy
- Transplant ineligible (age, co-morbidities, patient decline)
- Global Participation in Study: Europe, US, other countries around the world



# Len-Dex MCL07 Phase II multicenter study

SALVAGE TREATMENT WITH LEN-DEX IN PATIENTS  
WITH RELAPSED/REFRACTORY  
MANTLE CELL LYMPHOMA

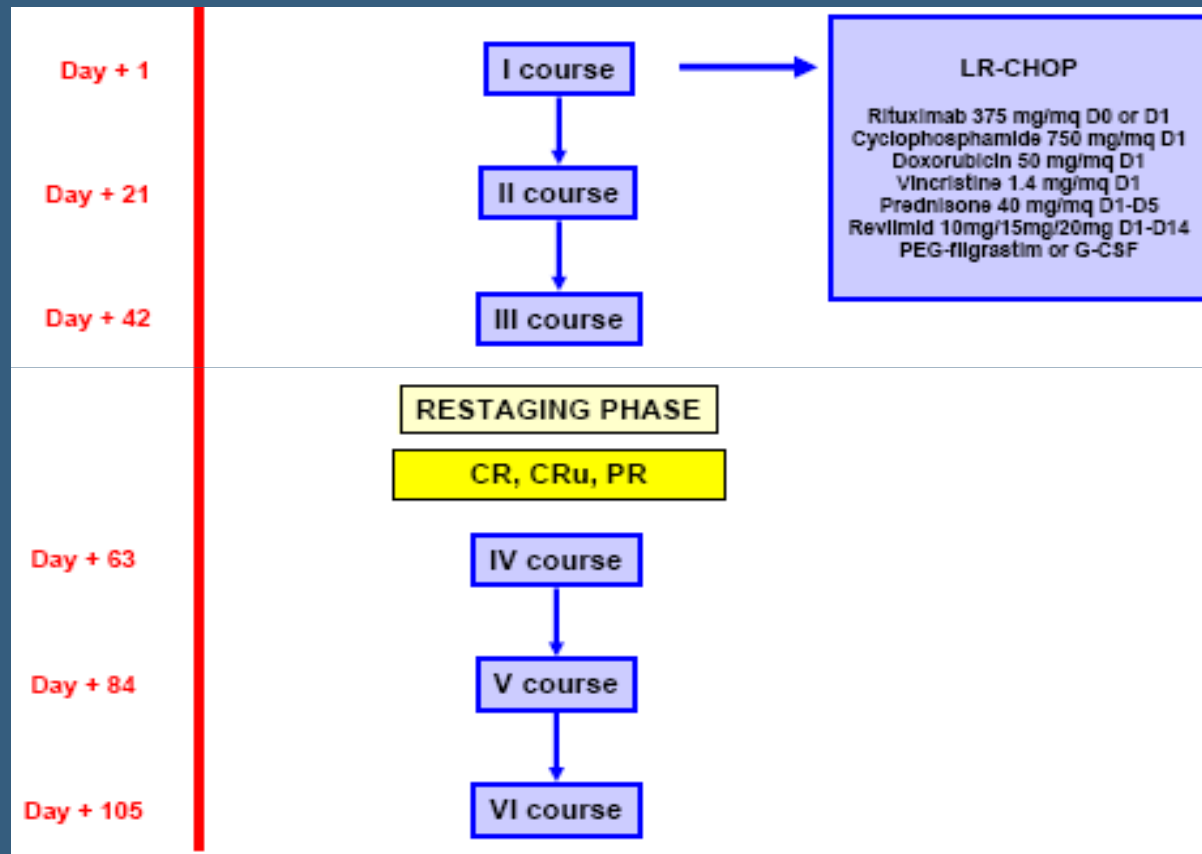


Principal Investigator: F.Zaja



## REAL07 – Revlimid in Elderly Aggressive Lymphoma

*Prospective multicenter phase I-II pilot trial to evaluate efficacy and safety of treatment with Lenalidomide plus R-CHOP21 (LR-CHOP21) for elderly patients with untreated Diffuse Large B-Cell Lymphoma (DLBCL)*



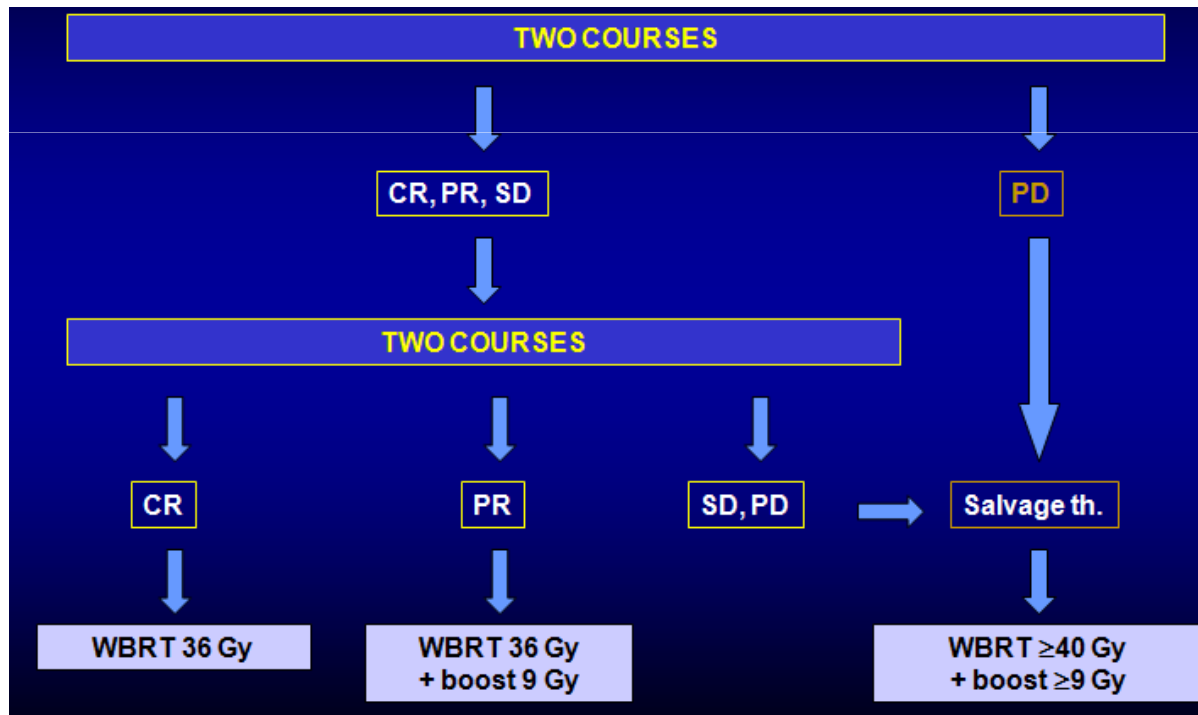
Principal Investigators: U.Vitolo G.Rossi

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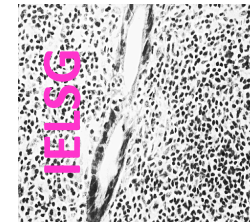
## Discussione

Randomized phase II trial on primary chemotherapy (CHT) with high-dose methotrexate (Mtx) alone or associated with high-dose cytarabine (AraC) for patients with primary CNS lymphoma (PCNSL).

Ferreri AJM, Foppoli M, Martelli M, Pangalis G, Frezzato M, Cabras G, Fabbri A, Corazzelli G, Ilariucci F, Rossi G, Soffietti R, Stelitano C, Vallisa D, Zaja F, Zoppegno L, Aondio G, Annibaldi O, Balzarotti M, Brandes A, Fajardo J, Gómez H, Guarini A, Pinotti G, Rigacci L, Uhlmann C, Ponzoni M, Reni M, Zucca E, and Cavalli F.



Study  
Schema  
IELSG 20



# Survival curves

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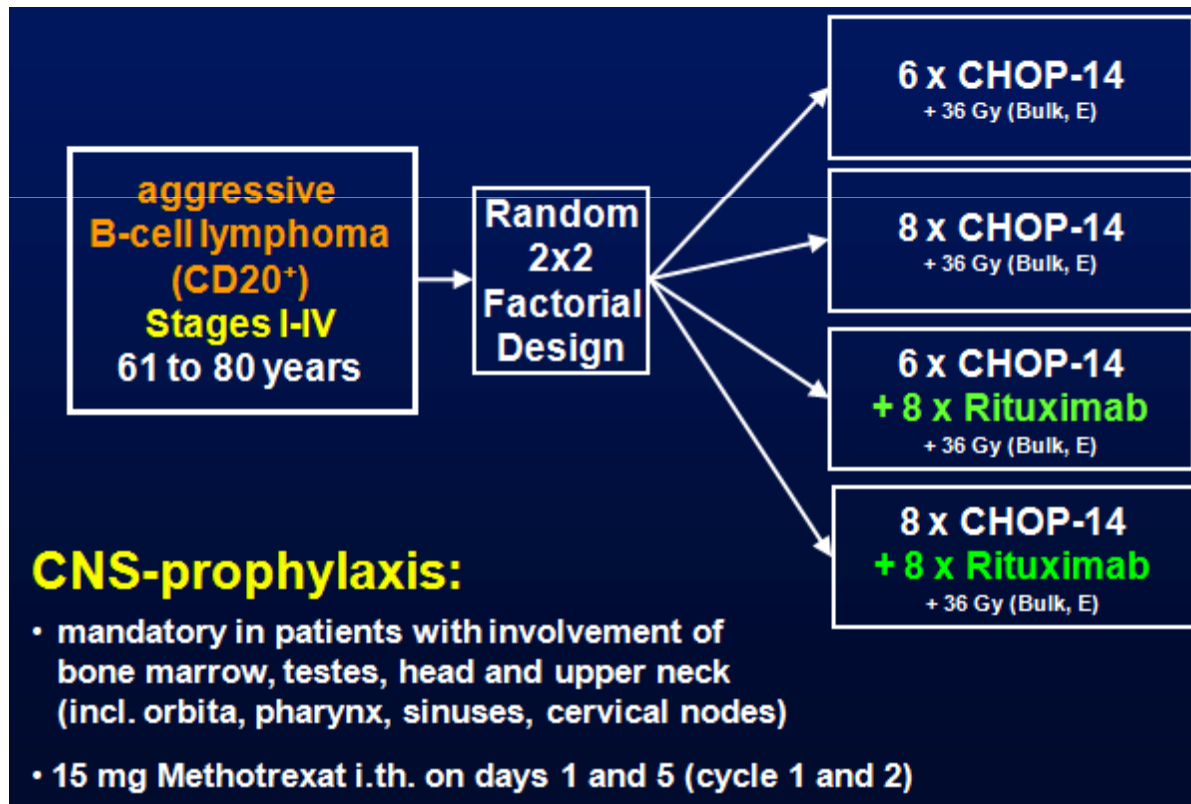
# Report del gruppo di lavoro

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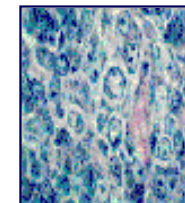
- This is the first randomized trial on PCNSL first- line therapy who has completed the accrual
- MTX/Ara-C is more active and effective than MTX alone in newly diagnosed PCNSL.
- Survival benefit justify the higher risk of toxicity
- MTX+ Ara-C may be considered the control arm for future randomized trial

CNS recurrence in aggressive lymphoma treated with modern chemotherapy (CHOP-14) with or without Rituximab. An analysis of CNS-events in elderly patients treated in the RICOVER-60 trial of the German High-grade non-Hodgkin's lymphoma study group (DSHNHL).

Schmitz N, Boehme V, Zeynalova S, Lengfelder E, Reiser M, Steinhauer H, Clemens M, Nickenig C, Loeffler M, Pfreundschuh M.

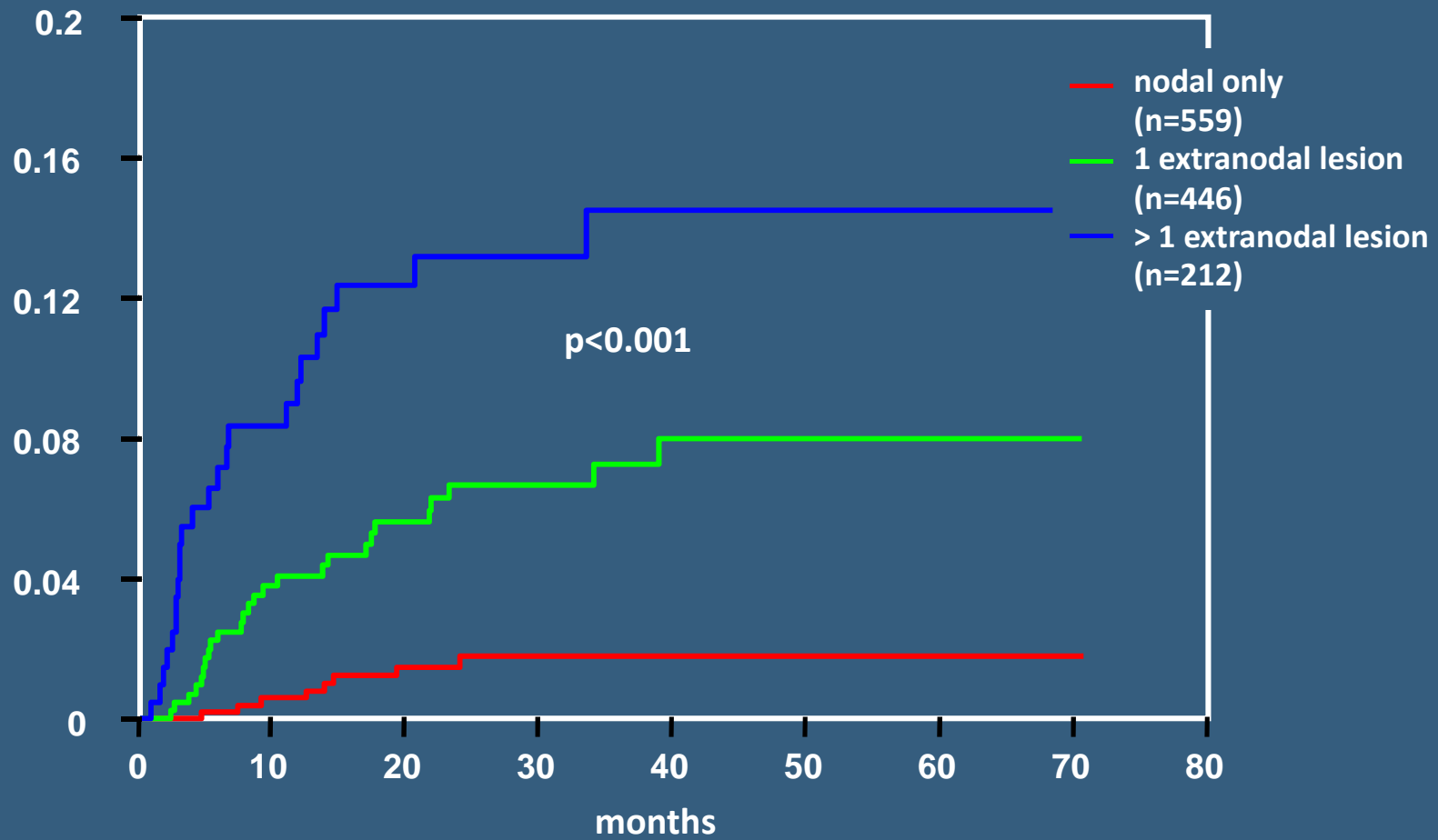


RICOVER-60



DSHNHL

## CNS events in the RICOVER-60 trial extranodal disease and time to CNS recurrence



## CNS events in the RICOVER-60 trial multivariate analysis

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<b>risk factor</b>	<b>RR</b>	<b>p - value</b>	<b>95% CI</b>
LDH > UNV	1.5	0.146	(0.9; 2.7)
B-symptoms	1.9	0.025	(1.1;3.3)
Extranodal > 1	3.4	< 0.001	(2.0; 5.8)

# Profilassi SNC per DLBCL

## Linee Guida SIE, SIES, GITMO

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- Prophylaxis of CNS relapse should be performed in patients with involvement of specific extranodal sites such as the: testis, paranasal sinuses, hard palate, orbit, paravertebral masses and bone marrow. (Grade B)
- Prophylaxis of CNS relapse should be considered in patients with an High-IPI score reflecting **involvement of more than one extranodal site and increased LDH.** ( Grade B)

*Barosi G, Carella A, Lazzarino M, Marchetti M, Martelli M, Rambaldi A.  
Tarella C., Vitolo U, Zinzani PL and S.Tura . Haematologica 2006*

## Conclusioni studio RECOVER 60

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- Intrathecal prophylaxis in “high risk” patients significantly reduces the incidence of CNS recurrence
- Rituximab significantly reduced incidence of CNS recurrence
- In this study the cumulative risk of CNS disease did not significantly differ, if given or not given i.th MTX, in patients who receive R-CHOP
- Intrathecal MTX not recommended if patients receive R-CHOP

## Site of CNS disease, initial response after (R-)CHOP-14 and type of CNS relapse

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type of CNS involvement	no. of patients (% of all CNS events)	response after end of therapy (%)	with concurrent systemic relapse
parenchymal	38 (65.5%)	CR 15 (39%) PR 4 (11%) PD 18 (47%) unk. 1 (3%)	7 3 7 1
meningeosis lymphomatosa	15 (25.9%)	CR 4 (27%) PD 9 (60%) TRD in PD 2 (13%)	– 2 2
intracerebral and meningeal	5 ( 8.6%)	CR 1 (20%) PD 3 (60%) unk. 1 (20%)	1 1 –
<b>all</b>	<b>58 (100%)</b>	<b>CR 20 (34%)</b> <b>no CR 38 (66%)</b>	<b>24 (41%)</b>

# Report del gruppo di lavoro

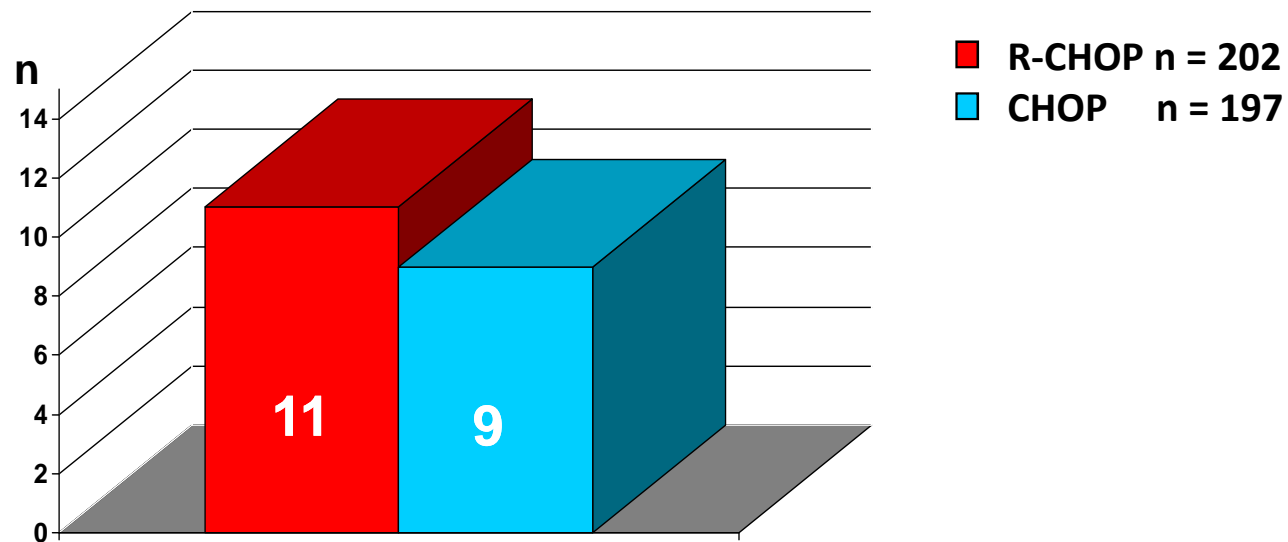
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- L'attività di Rituximab è da inquadrare maggiormente nella sua attività globale di riduzione della recidiva nel più che ad un effetto mirato sul SNC.
- La non necessaria profilassi intratecale in pazienti trattati con R-CHOP dovrà essere confermata in altri trials
- Lo studio di fase III del GELA ha portato a risultati diversi

## Recidiva al SNC nel linfoma aggressivo

**Rituximab è inefficace!!**

studio LNH 98-5: CHOP vs R-CHOP



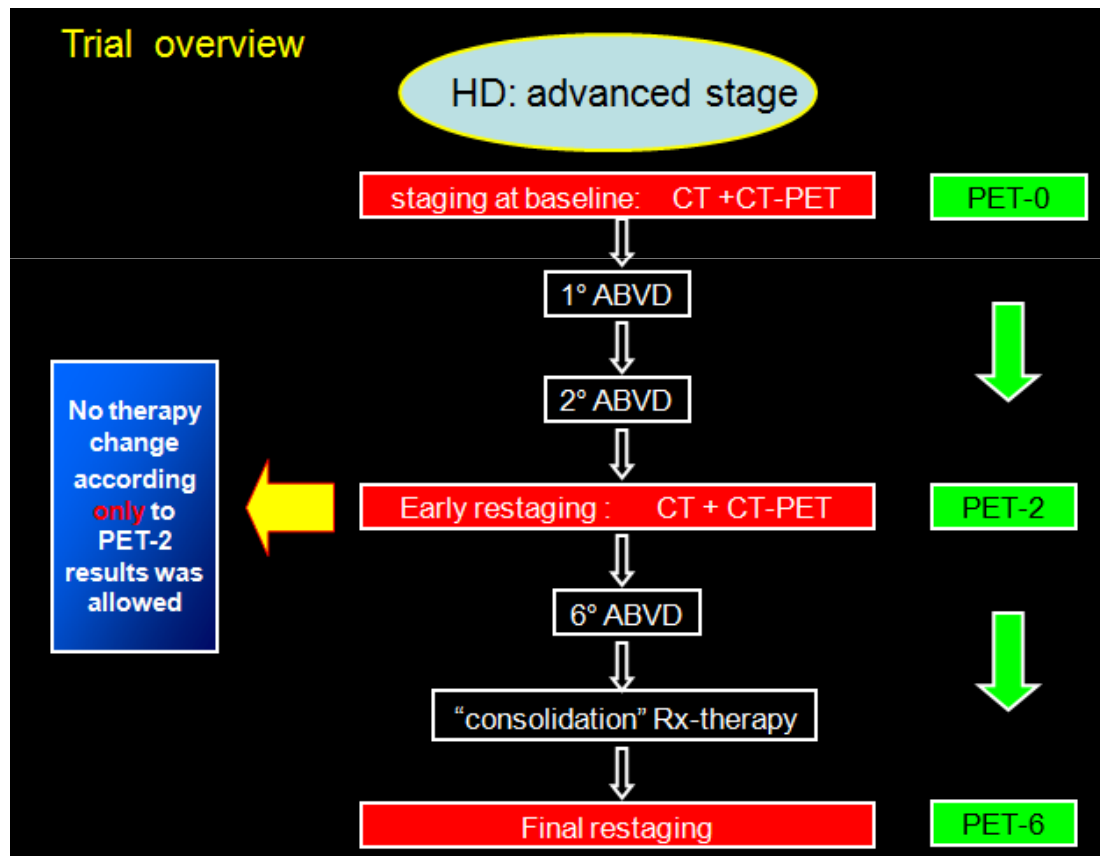
*P. Feugier et al. Ann. Oncol, 2004*

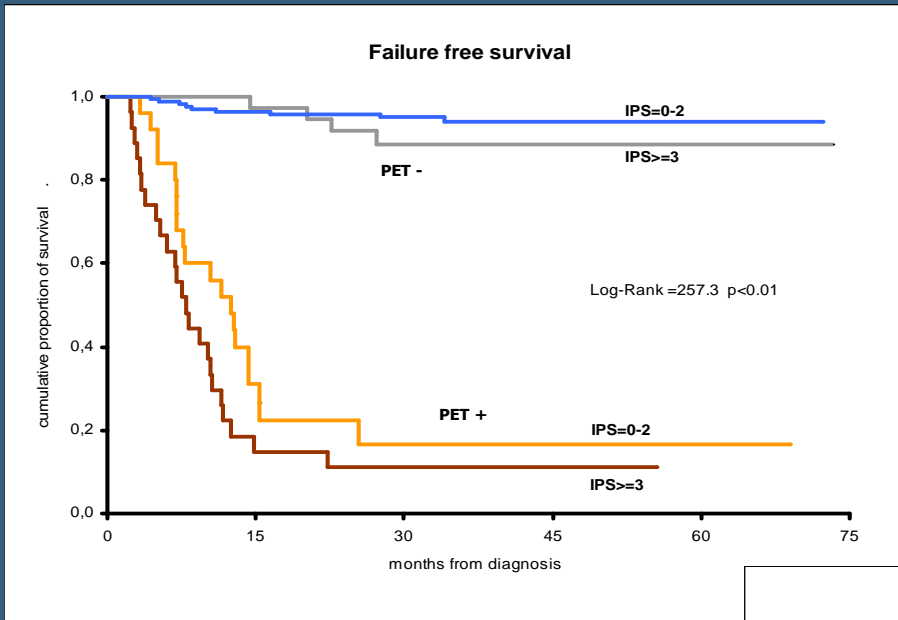
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## Discussione

## Early Interim FDG-PET in advanced-stage Hodgkin Lymphoma (HL). Long-term results of the Italian-Danish cooperative study.

Gallamini A, Hutchings M, Rigacci L, Specht L, Merli F, Hansen M, Patti C, Loft A, Di Raimondo F, D'Amore F, Biggi A, Pregno P, Stelitano C, Sancetta R, Trentin L, Luminari S, Iannitto E, Viviani S, Pierri I, Torchio P, Levis A.

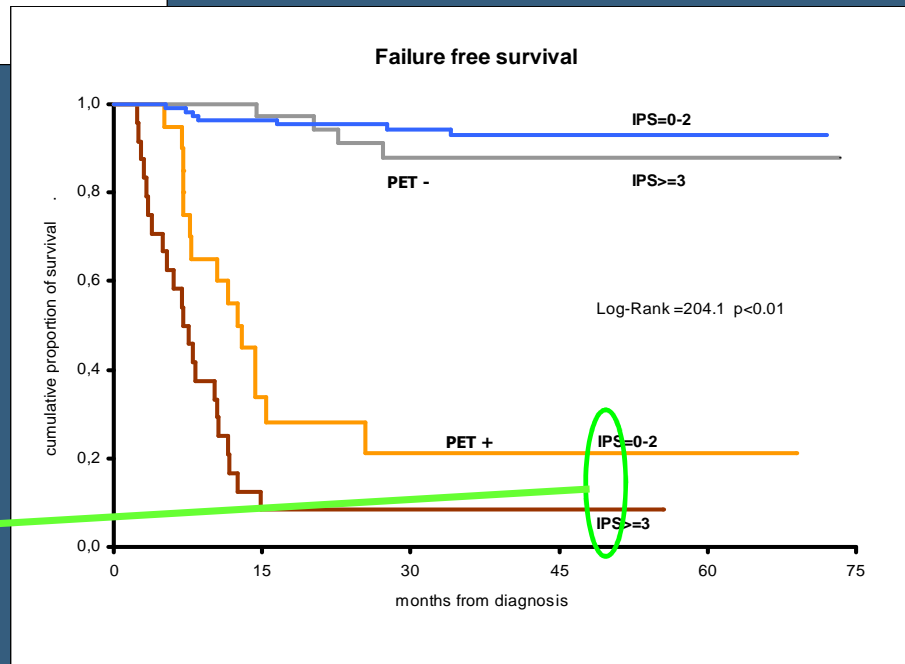




**FFS: PET-2 vs IPS stage IIA-IVB**

**FFS: PET-2 vs IPS stage IIB-IVB**

**P<.05, log rank 6.0**



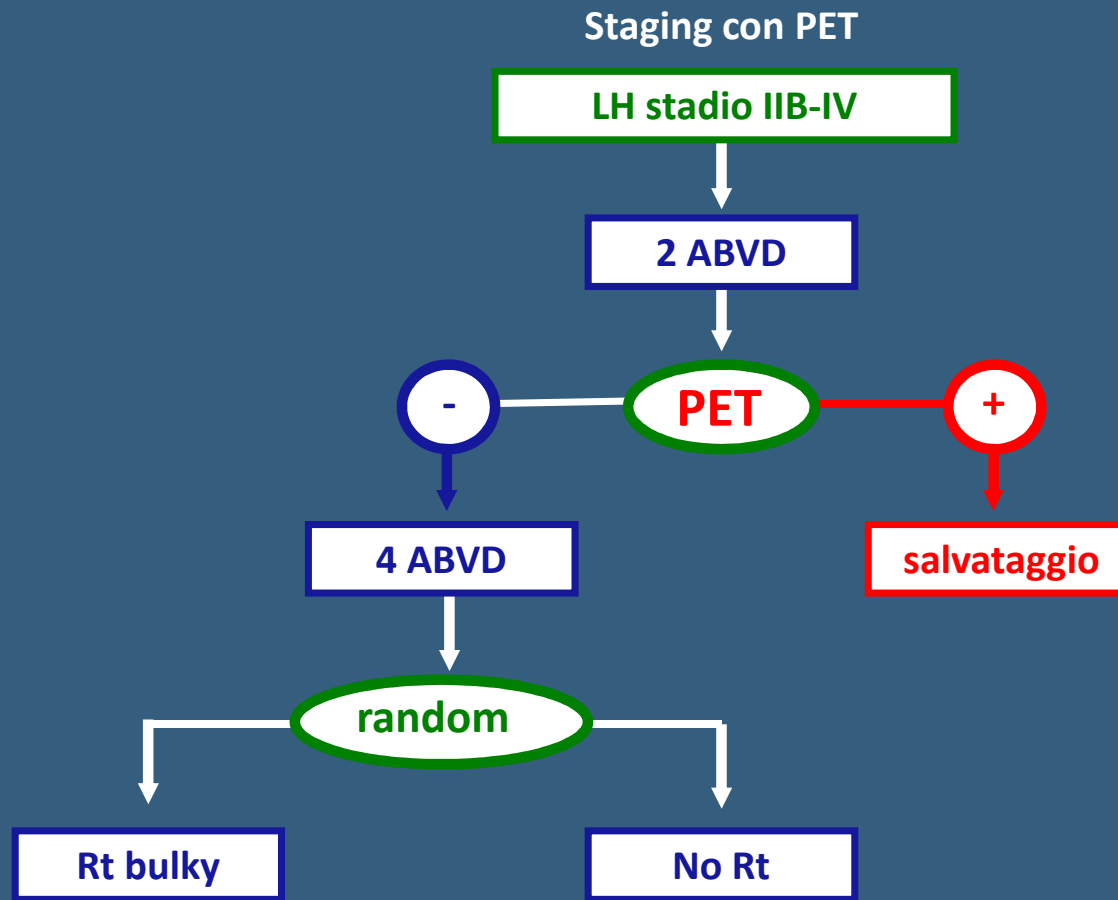
# Report del gruppo di lavoro

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- PET-2 plays the main prognostic role in HD.
- PET-2 is able to predict the majority of treatment failure.
- ABVD treated PET-2 positive are subset of patients with a very poor outcome requiring an early aggressive therapy



# Studio prospettico HD avanzati IIL



Allogeneic stem cell transplantation after RIC regimen prolongs the survival in patients with Hodgkin lymphoma (HL) relapsed after high-dose chemotherapy (HDC): a retrospective study based on donor availability.

L. Castagna A.



## Rationale and design of the study

The role of allo-SCT in the clinical practice is still quite controversial. GITMO centers were asked for reviewing all HL patients fulfilling the following criteria:

1. Relapse or progression after HDC
2. HLA typing performed after the failure to perform a salvage RIC allo-SCT

94 patients have a complete data set so far and thus were analyzed:

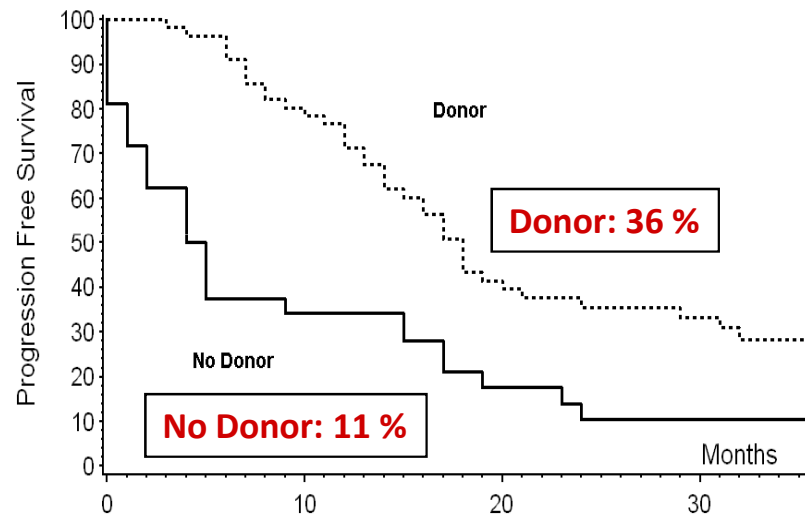
60 had a donor and received RIC allo-SCT

34 did not have a donor and were treated according to the common policy of each center

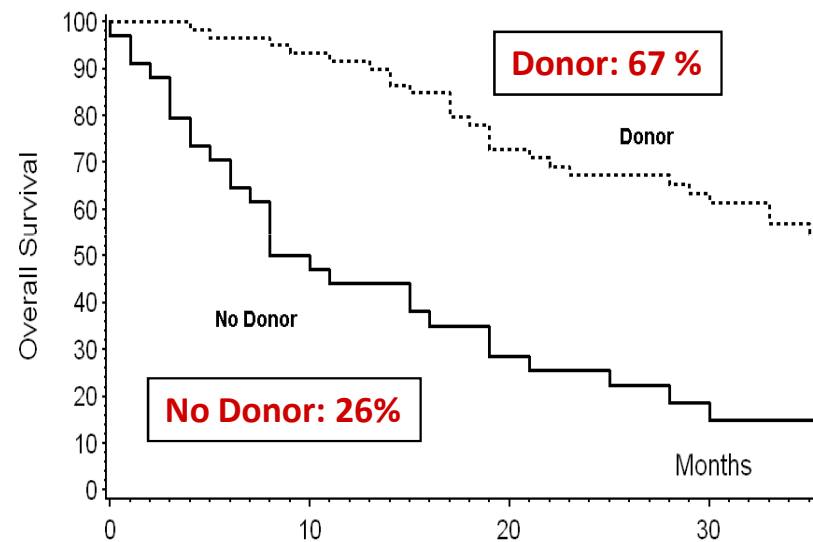
All of them received CT and/or RT

## 2-year PFS and OS donor vs no donor

50



**PFS at 2 years  $p$  value:  $<0.001$**



**OS at 2 years  $p$  value:  $<0.001$**

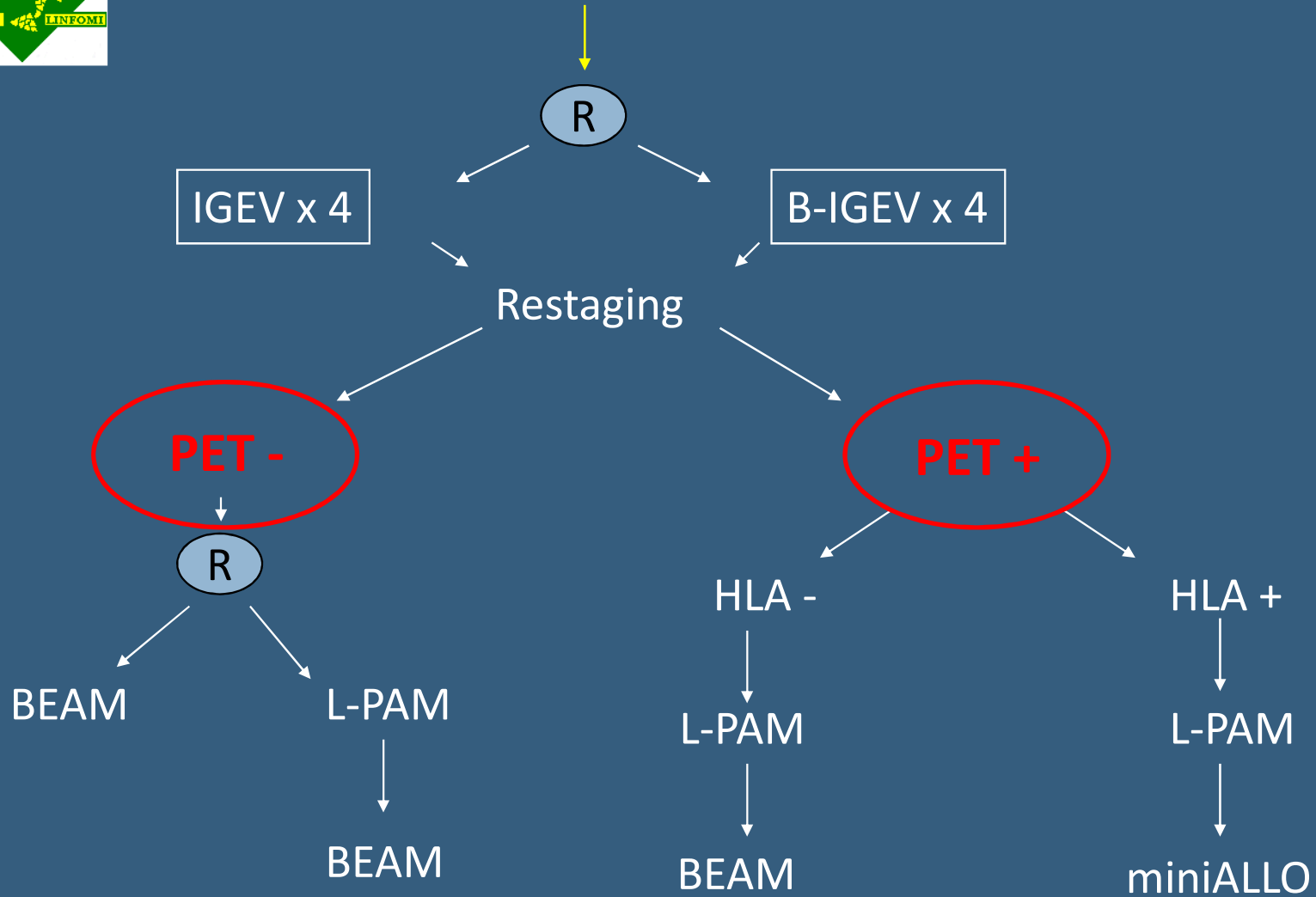
# Report del gruppo di lavoro

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- ❑ RIC allo-SCT is an effective salvage treatment with a low TRM (12 %)
- ❑ The results should be considered preliminary considering the retrospective study
- ❑ Prospective trials should be considered RIC-allo SCT early in the course of disease



## Studio prospettico HDrecidiva/ refrattario



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## Discussione