

Highlights from EHA

Novità dall'EHA >> [Linfomi]

Relatore: **U. VITOLO**

27-28 ottobre 2008

Borgo S. Luigi – Monteriggioni (Siena)

LINFOMA NON HODGKIN

2

□ Studi biologici

□ Studi clinici

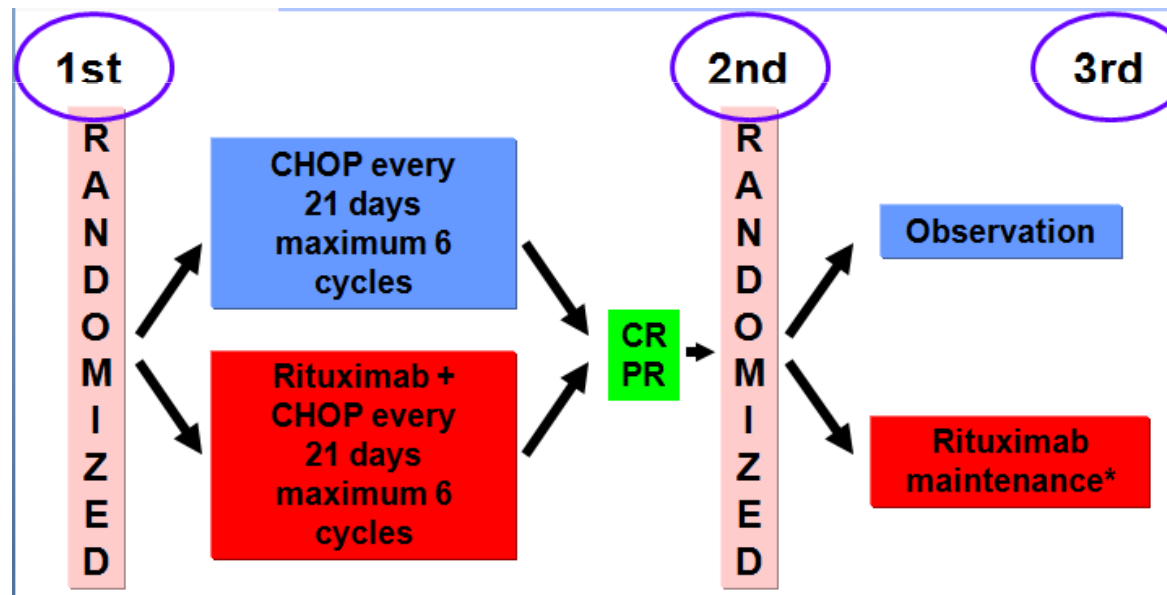
- ✓ NHL nodali
- ✓ NHL extranodali
- ✓ HD

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

Molecular screening in EORTC 20981 intergroup study

Conclusions as to Bcl2/IgH PCR analysis in relapsed/resistant FL

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Induction treatment

- ✓ Stronger decrease Bcl2 values with R-CHOP
- ✓ Bcl2 values at diagnosis do not predict response
- ✓ Initial Bcl2 positivity in BM: shorter PFS
- ✓ Improved PFS by R-CHOP mainly in Bcl2 negative group
- ✓ Bcl2 status in BM/PB after induction not useful as to PFS

Maintenance

- ✓ Improved PFS with R in Bcl2 negative (4-yr 55% vs 30%) and positive patients (4yr 45% vs 25%)
- ✓ Bcl2+ at end of maintenance predicts for rapid progression

Recommendations

- ✓ Initial Bcl2-IgH PCR useful in predicting PFS
- ✓ Bcl2-IgH PCR after maintenance might be useful
- ✓ Analyze cases for other Bcl2 breakpoints

Real-time quantitative PCR analysis for Bcl2/IgH in the phase III First-line Indolent Trial of 90Y-Ibritumomab Tiuxetan as consolidation of first remission in advanced-stage follicular lymphoma.

Goff LG, Summers KS, Iqbal SI, Kuhlman JK, Kunz MK, Louton TL, Hagenbeek AH, Lister TL, Rohatiner AR.

PCR Analysis of bcl-2

- ✓ Peripheral blood samples were collected at baseline to determine *bcl-2* PCR status; prior to Zevalin PCR analysis was repeated at study Week 14, Month 6, Month 12, Month 24, and yearly thereafter.

No. of patients converting from *bcl-2* PCR+ (after remission-induction treatment) to PCR- status post-randomization

	Control, n/N* (%)	Zevalin, n/N* (%)
Blood	21/59 (36)	61/68 (90)

CONCLUSIONS

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Zevalin consolidation significantly prolonged PFS by nearly 2.5 years in patients who were *bcl-2* PCR+ after remission-induction treatment

In patients treated with Zevalin consolidation, median PFS was similar in PCR+ and PCR- patient subgroups after remission induction treatment

In patients who become PCR- after remission-induction treatment, Zevalin does not result in improved PFS

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

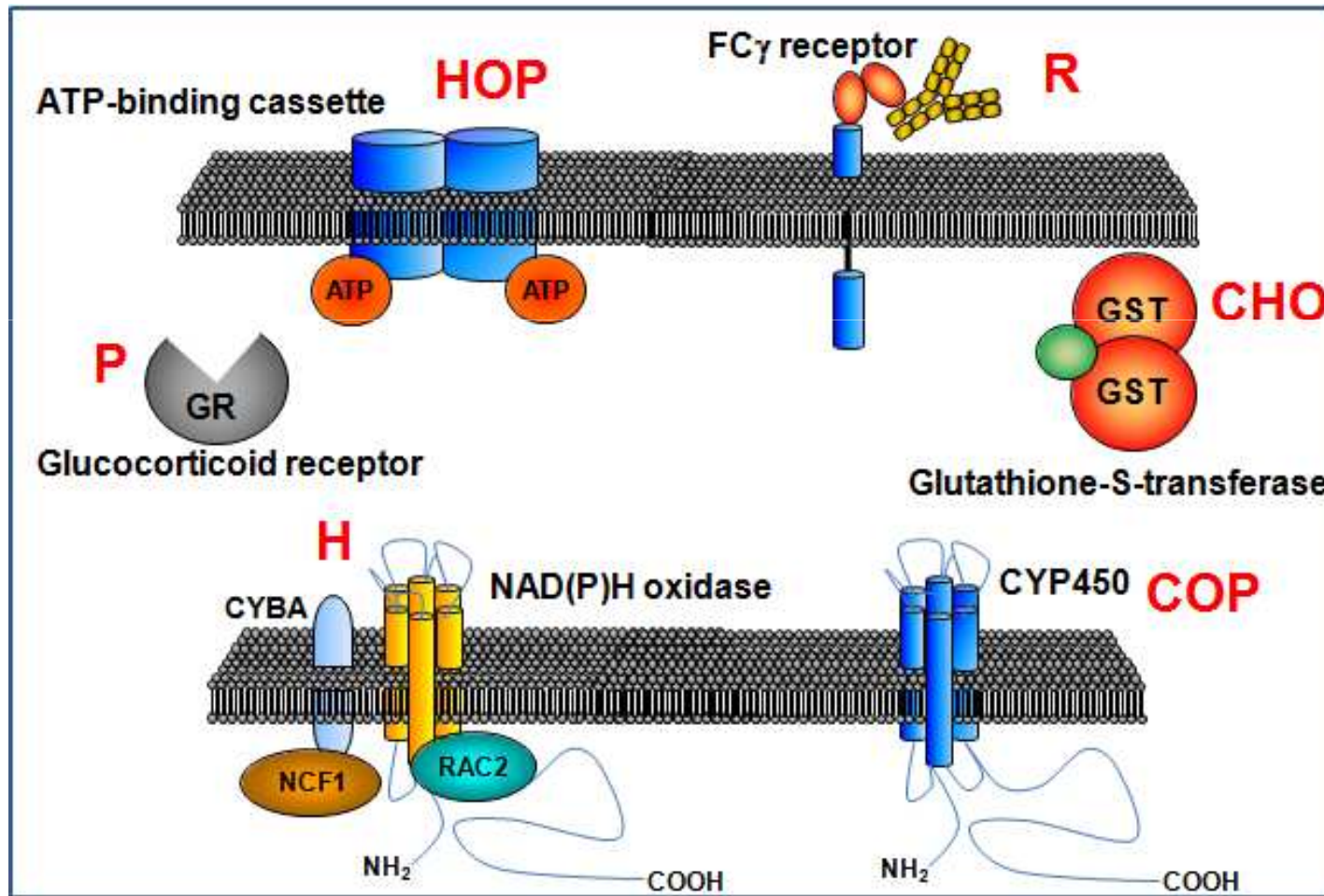
Rossi D, Rasi S, Franceschetti S, Capello D, Castelli A, De Paoli L, Ramponi A, Chiappella A, Pogliani EM, Vitolo U, Kwee I, Bertoni F, Conconi A, Gaidano G.

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*)

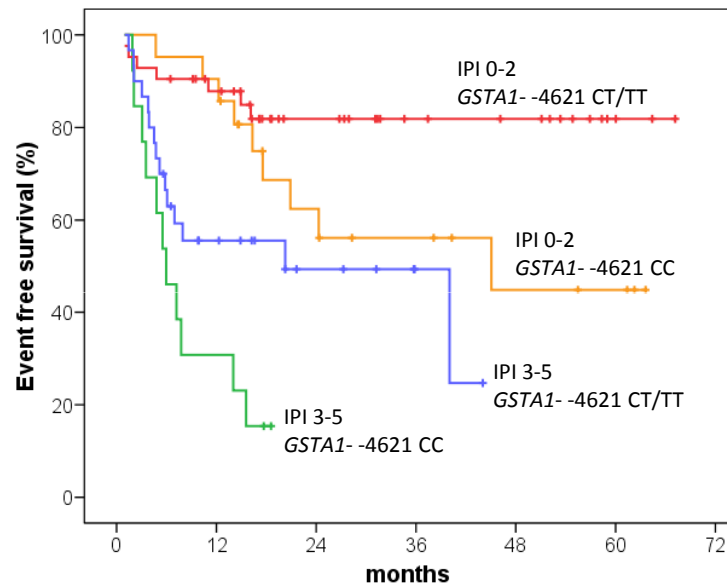
SNPs INVOLVED IN PHARMACOGENETICS of R-CHOP: 27 SNPs from 17 genes

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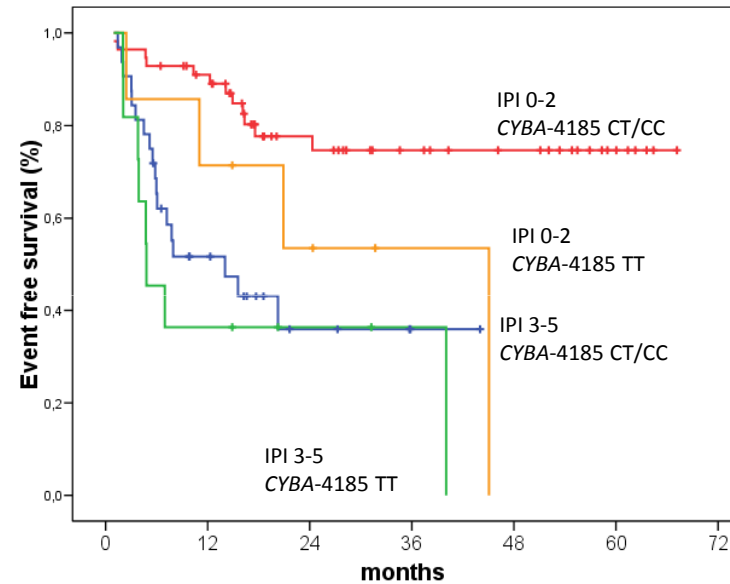


PHARMACOGENETIC SNPs MAY ADD PROGNOSTIC INFORMATION when COMBINED to IPI

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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%

CONCLUSIONS

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- ✓ Host SNPs CYBA-4185C>T affecting doxorubicin targeting and GSTA1- -4621C>T affecting alkylator detoxification are independent predictors of EFS in DLBCL treated with R-CHOP21
- ✓ NCF4- -368A>G, a SNP of the gene encoding the p40phox subunit of NADP(H) oxidase, has a protective effect against major toxicities
- ✓ Validation on independent DLBCL cohorts is needed

LINFOMA NON HODGKIN

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- Studi biologici

- Studi clinici

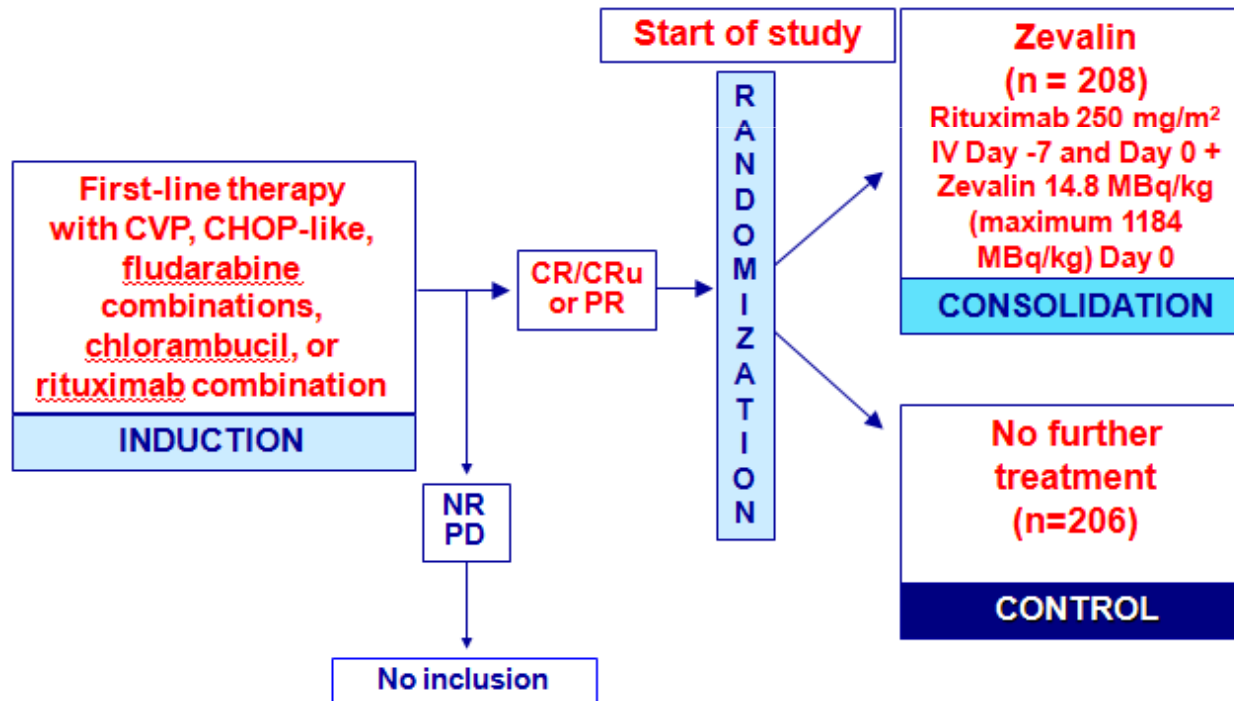
 - ✓ NHL nodali

 - ✓ NHL extranodali

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).

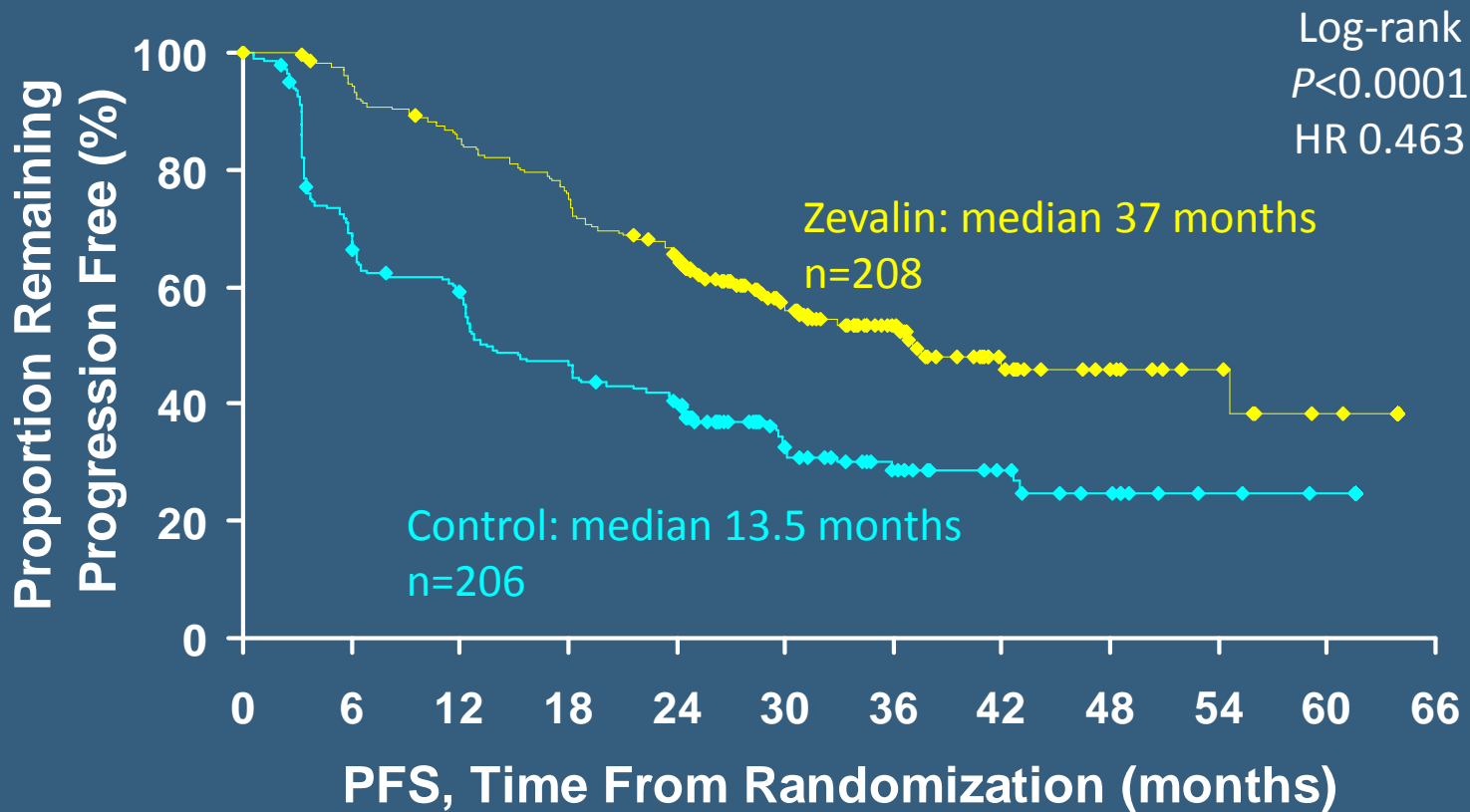
Radford JA, Morschhauser F, Van Hoof A, Vitolo U, Soubeyran P, Tilly H, Huijgens PC, Kolstad A, Kunz M, Hagenbeek A.

FIT Study Schema

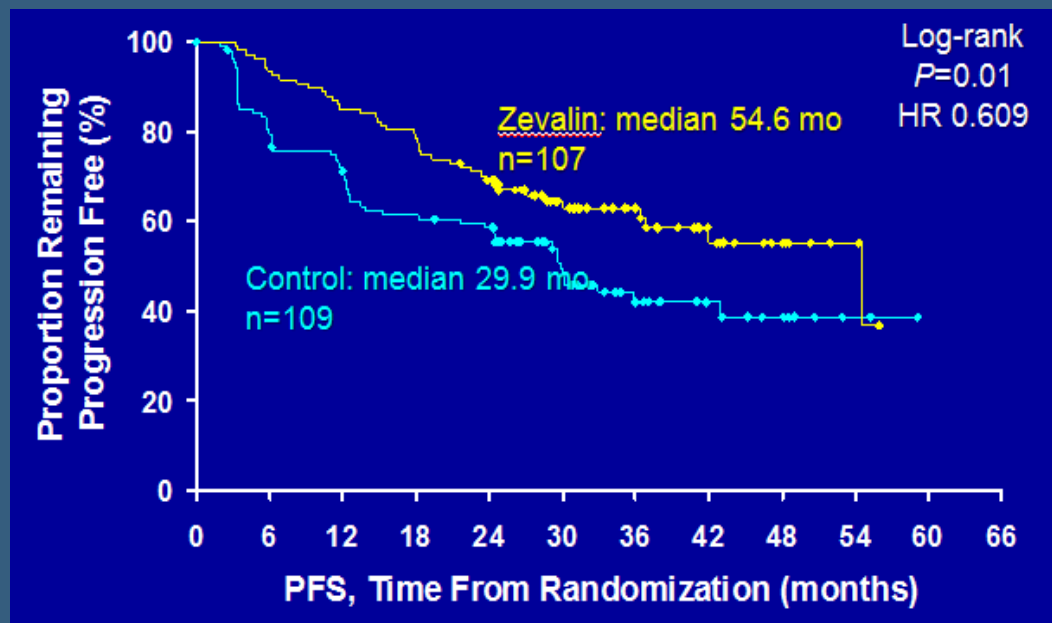


FIT Primary Endpoint: Median PFS in All Patients (median observation period: 3.5 years)

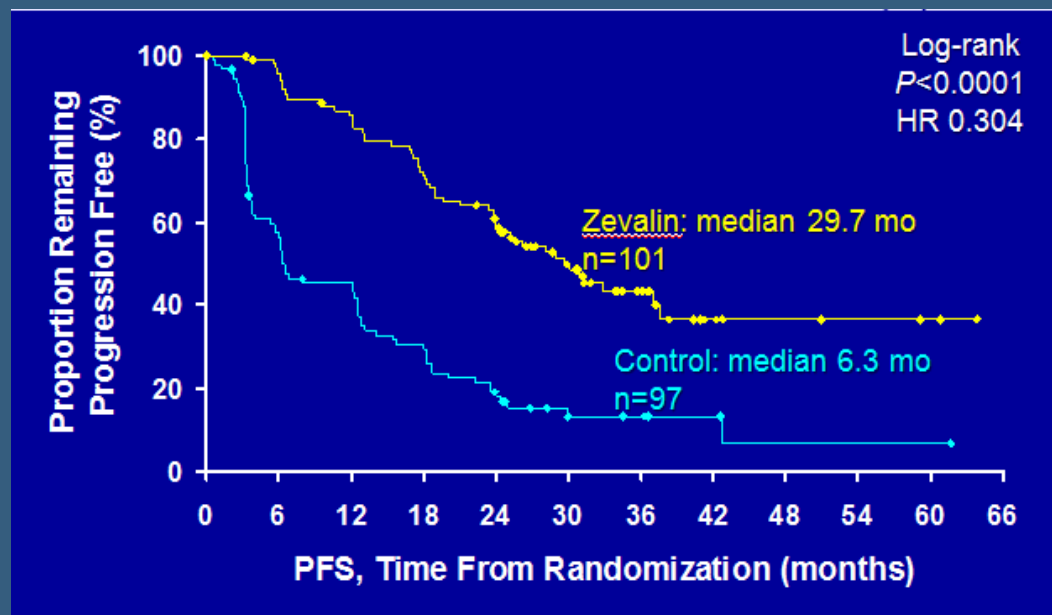
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FIT:
PFS in patients with
CR/CRu
after First-line Therapy



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



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.

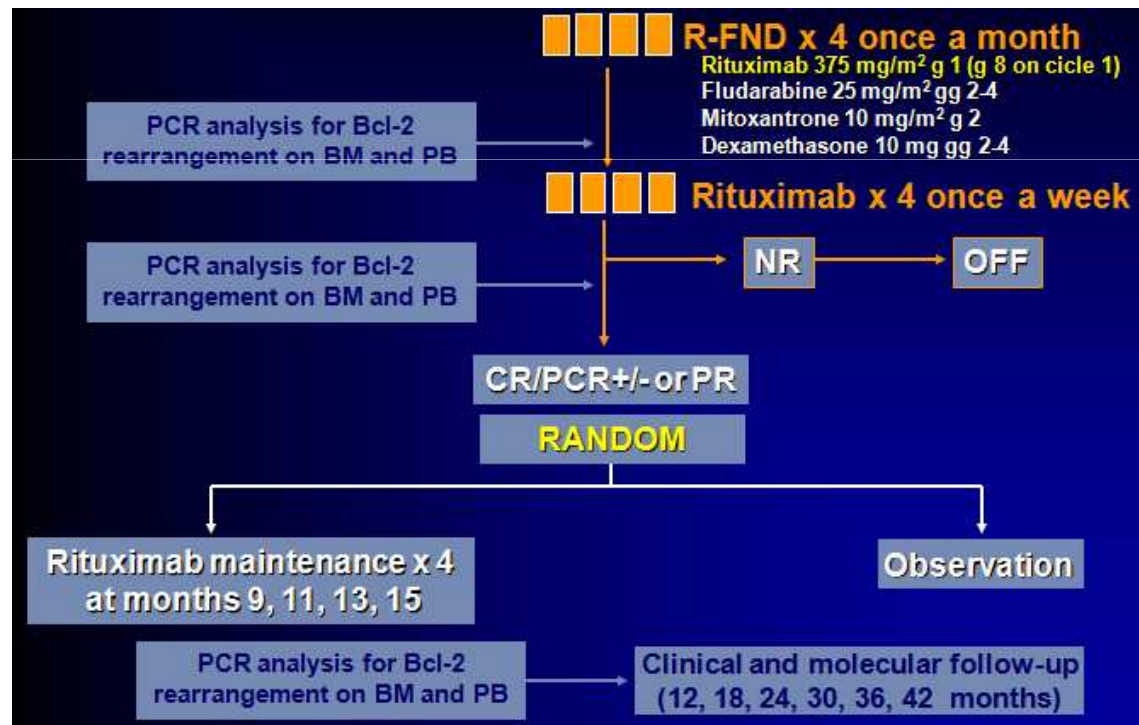
Vitolo U, Ladetto M, Boccomini C, Gamba E, Alvarez I, Baldini L, Ceccarelli M, Chiappella A, Corradini P, De Renzo A, Di Raimondo F, Gallamini A, Guarini A, Mantoan B, Martelli M, Naso V, Parvis G, Petrini M, Pinto A, Pozzi S, Pulsoni A, Rigacci L, Tarella C, Tucci A, Zaja F and Gallo E.



Study ML17638



IIL ID: IILFL04



CLINICAL RESPONSE TO TREATMENT

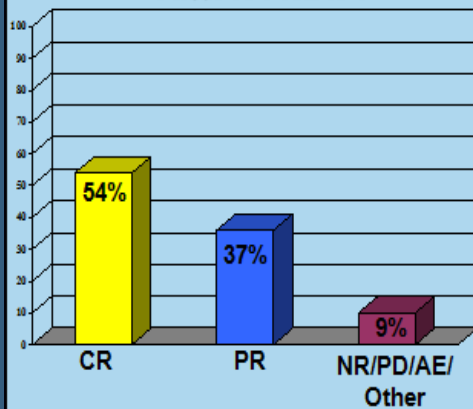
CLINICAL CHARACTERISTICS: 95 patients

Median age 65 years (range 60-75)

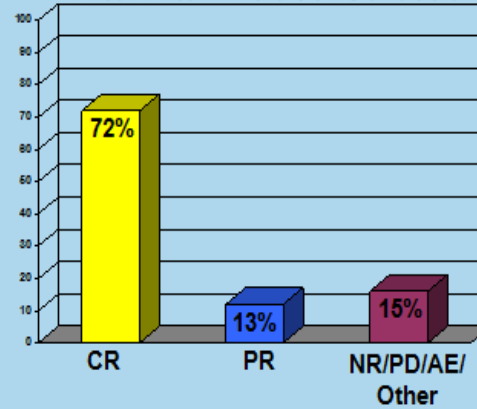
Sex M/F	38/57	B Symptoms	19%
Grade I/II	44/56%	LDH >normal	17%
Stage II/III/IV	14/16/70%	BM+	64%
FLIPI	Low	10%	
	Intermediate	30%	
	High	60%	

OVERALL RESPONSE RATE: 85%

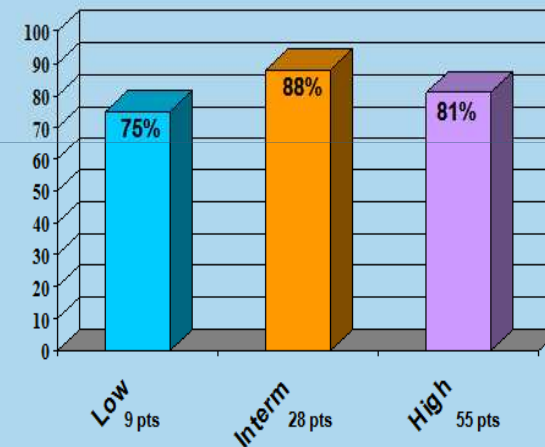
After R-FND x 4



After Rituximab consolidation



CR according to FLIPI



MOLECULAR RESPONSE TO TREATMENT

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

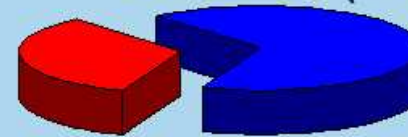
PCR negativity associated with CR

After R-FND x 4

After Rituximab consolidation

Bcl2-: 18/46 (39%)

Bcl2-: 31/46 (67%)



Qualitative PCR analysis



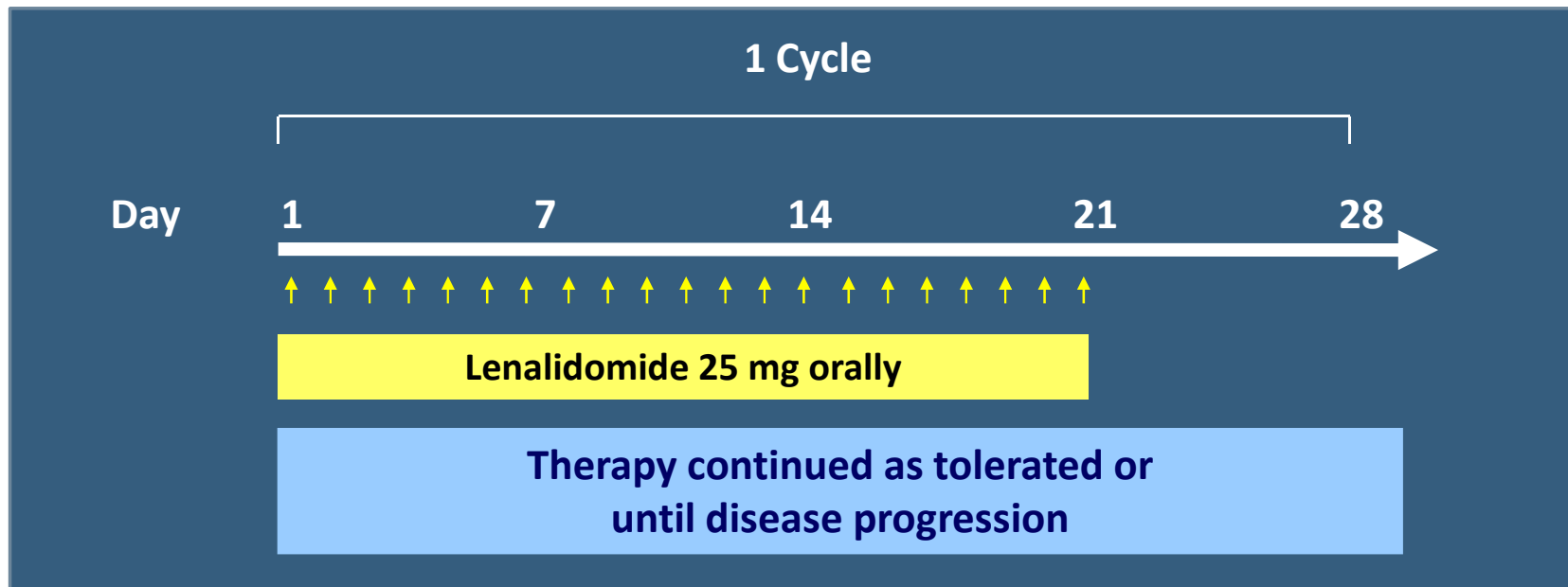
Oral Session
San Francisco
December 9, 2008

Brief Chemoimmunotherapy Rituximab (R)-FND +/- R Maintenance as First Line Treatment in Elderly Patients with Advanced Follicular Lymphoma (FL): Preliminary Analysis of a Prospective Randomized III Trial

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



83 patients

Adverse Event	Grade 3/4, n (%)
Neutropenia	35 (27)
Thrombocytopenia	20 (15)
Anemia	10 (8)
Fatigue	7 (5)
Leukopenia	7 (5)

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

Conclusions

- ✓ Lenalidomide has activity in relapsed/refractory aggressive NHL (poor prognostic group) with often limited salvage therapeutic options
- ✓ Lenalidomide allows anti-lymphoma activity in patients with R-chemo resistant disease
- ✓ Lenalidomide salvage therapy is “patient-friendly”: single oral dose regimen with a good safety profile
- ✓ Future research will help determine the optimal dose and schedule of lenalidomide either alone or in combination with other active agents

LINFOMA NON HODGKIN

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- Studi biologici

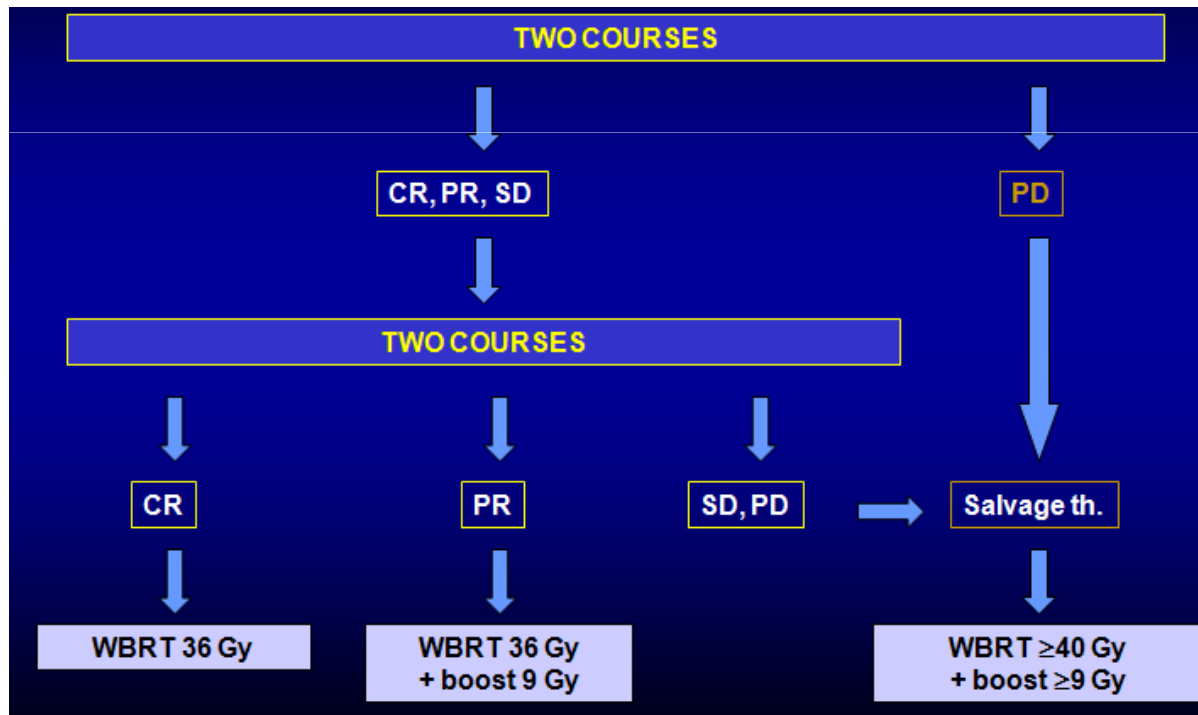
- Studi clinici

 - ✓ NHL nodali

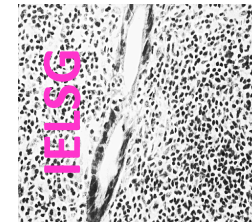
 - ✓ NHL extranodali

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



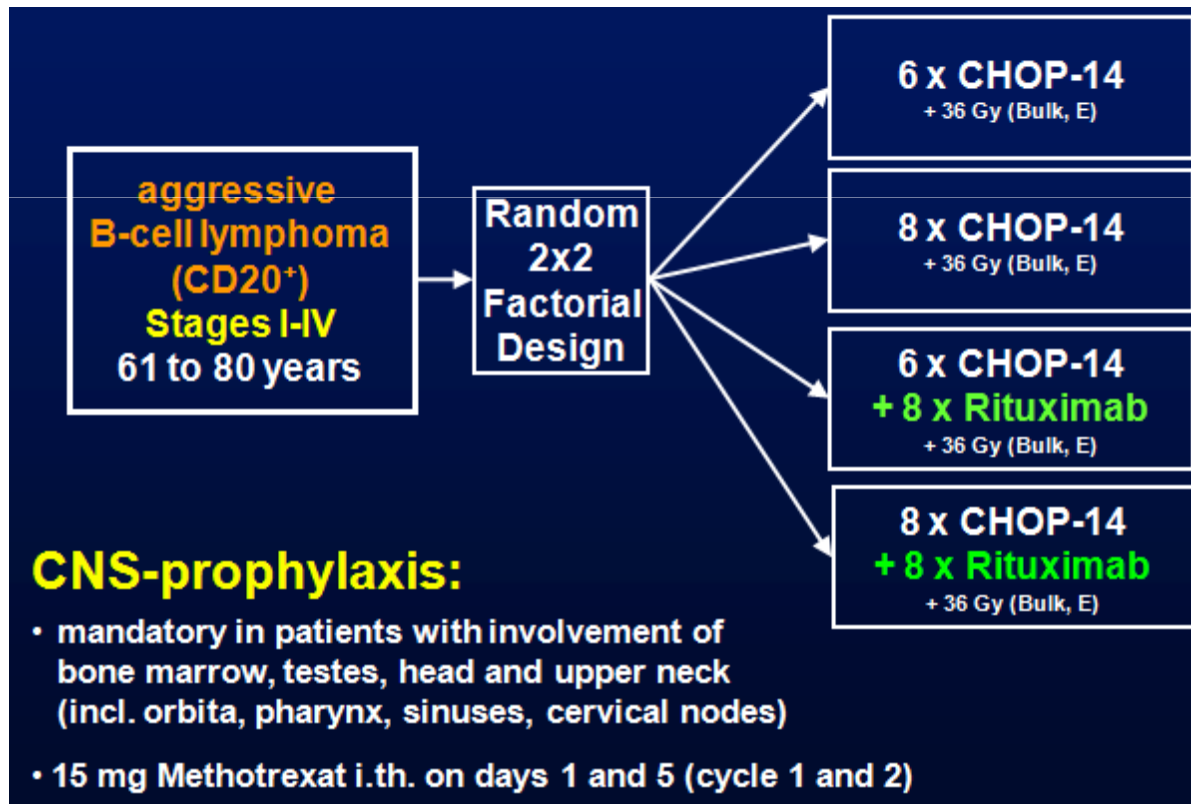
Survival curves

22

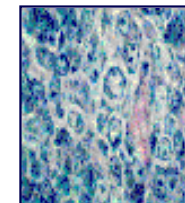


CNS recurrence in aggressive lymphoma treated with modern chemotherapy (CHOP-14) with or without Rituximab. An analysis of CNS-events in elderly patients treated in the RICOVER-60 trial of the German High-grade non-Hodgkin's lymphoma study group (DSHNHL).

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



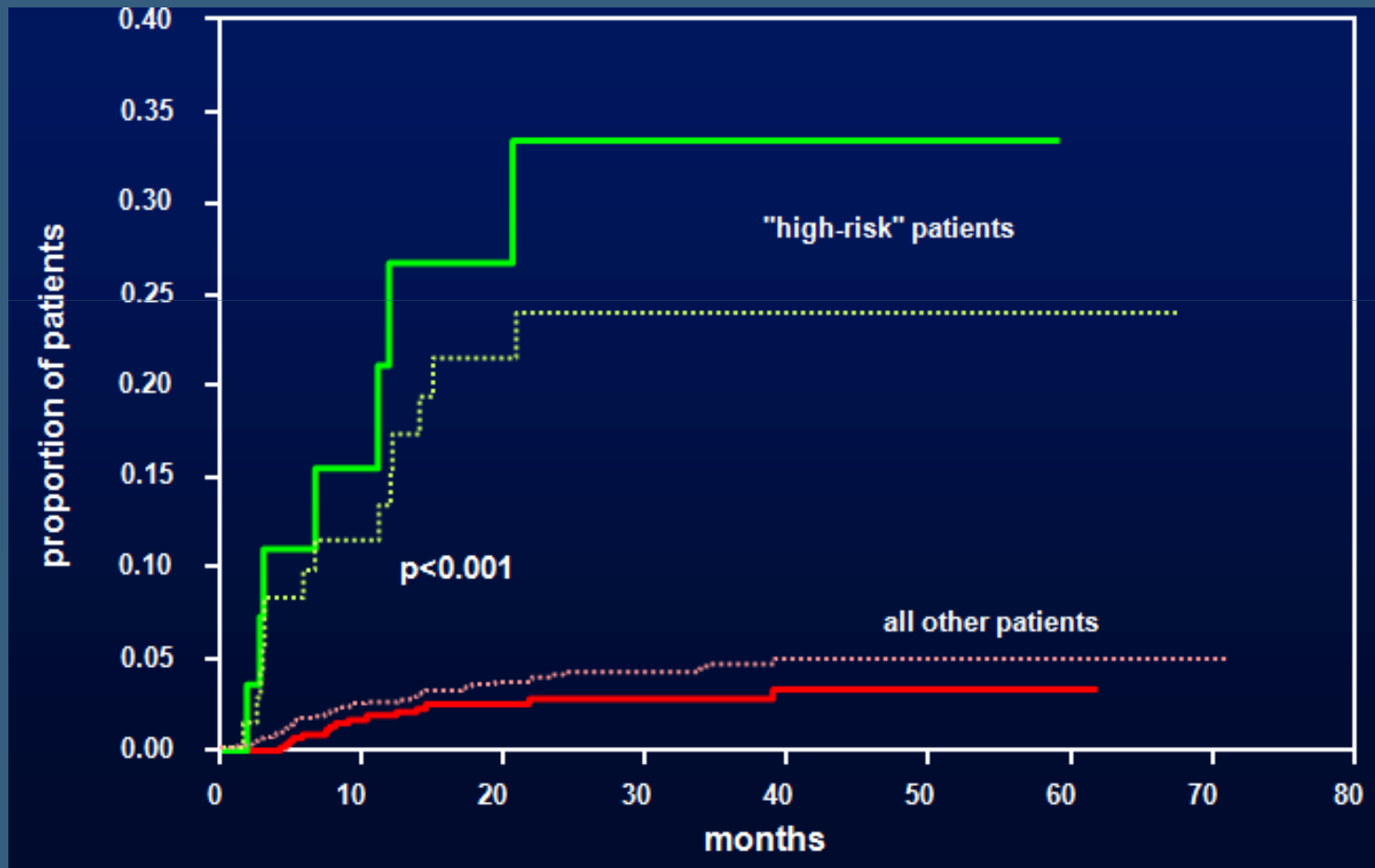
RICOVER-60



DSHNHL

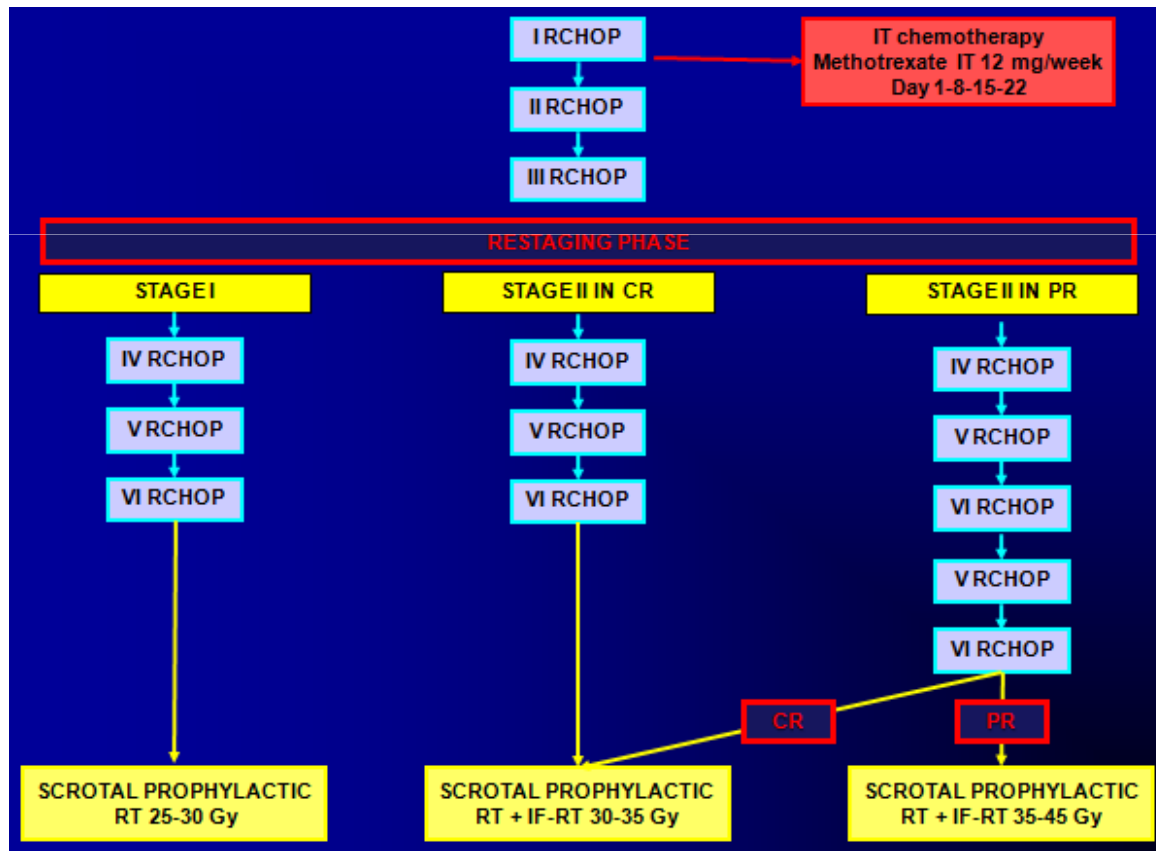
CNS events in RICOVER-60 trial "high-risk" patients with LDH > N, > 1 E-lesion, and ECOG > 1; all patients (---)/only patients with R-CHOP-14 (___)

24



Primary diffuse large B-cell lymphoma of the testis: improved outcome with Rituximab-CHOP with CNS and contralateral testis prophylaxis. Final results of IELSG 10 study.

Vitolo U, Zucca E, Martelli M, Chiappella A, Balzarotti M, Benevolo G, De Masi P, Filippi A, Gospodarowicz MK, Lopez-Guillermo A, Martinelli G, Merli F, Perrone T, Pregno P, Sarris AH, Storti S and Cavalli F.

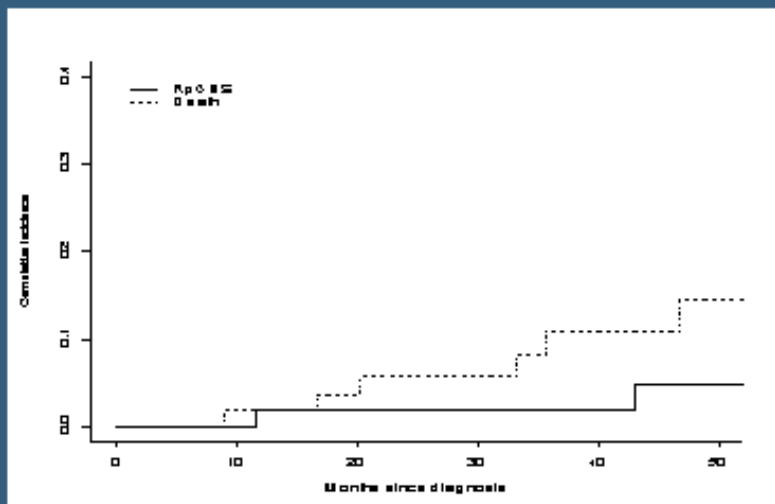
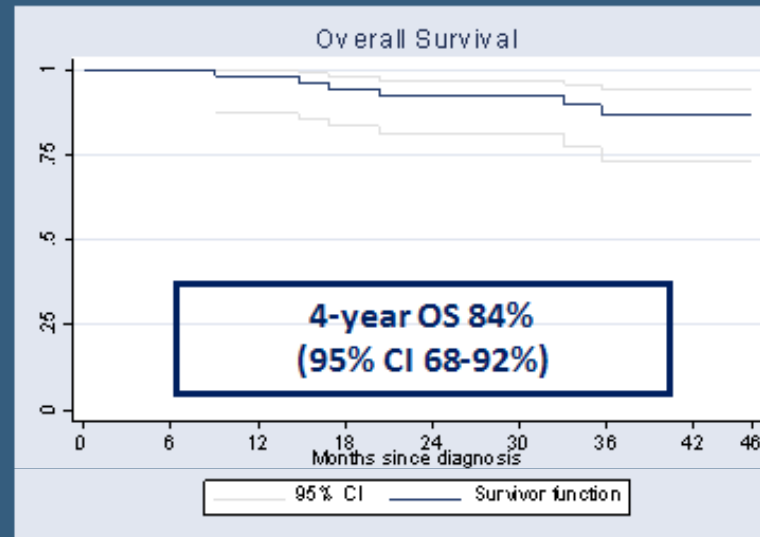
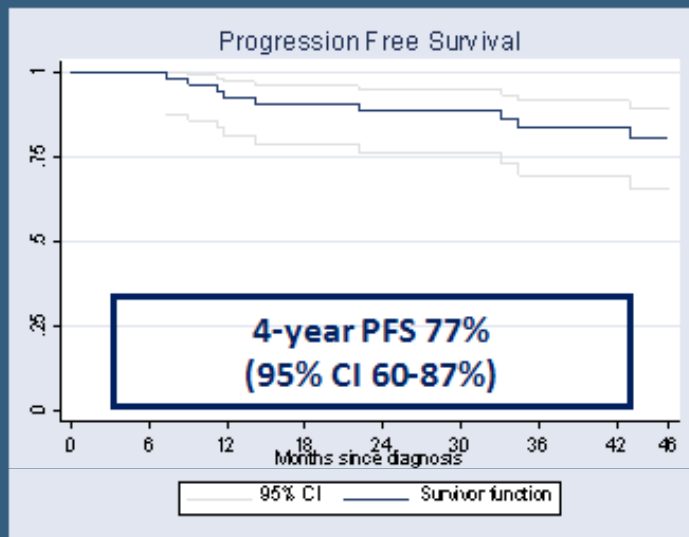


Study Schema IELSG 10



IELSG 10: Survival and CSN recurrence

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**Risk of CNS recurrence
at 4-years: 5%
(95% CI 0-12%)**

**No contralateral testis
relapse**

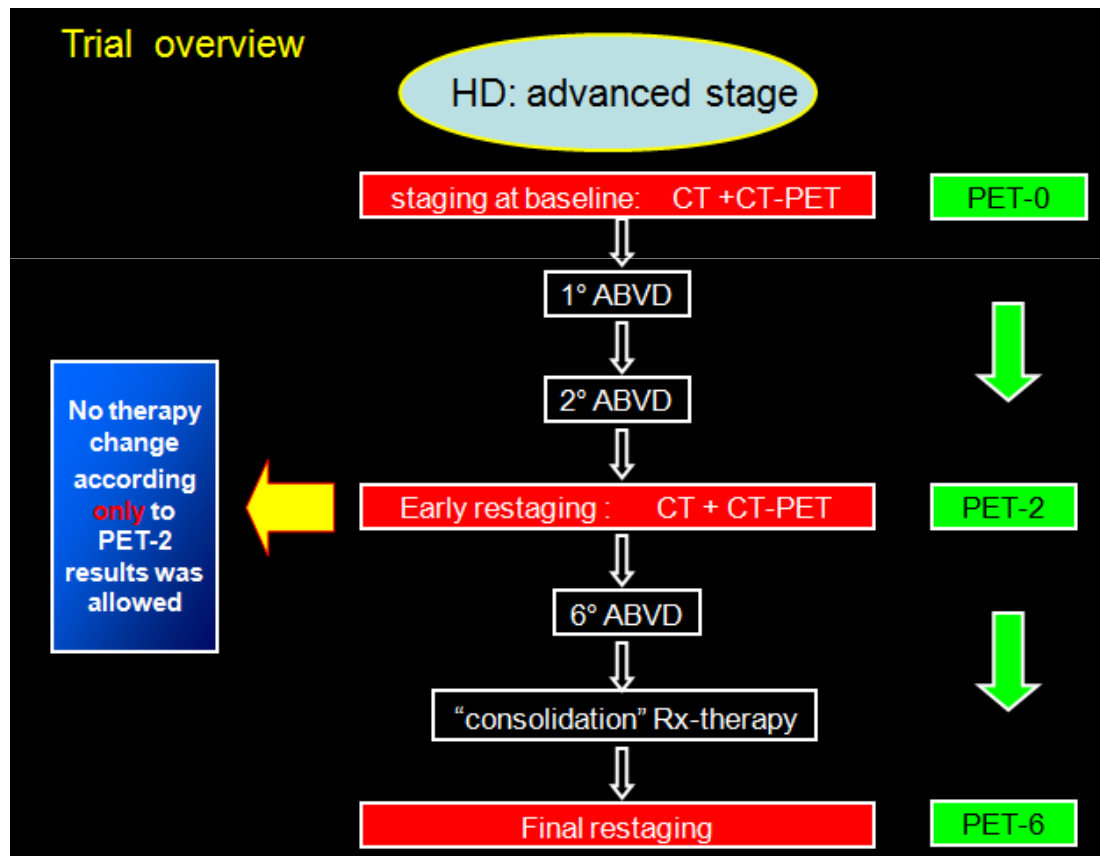
LINFOMA DI HODGKIN

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- **Significato prognostico della PET**
- **Allotrapianto**

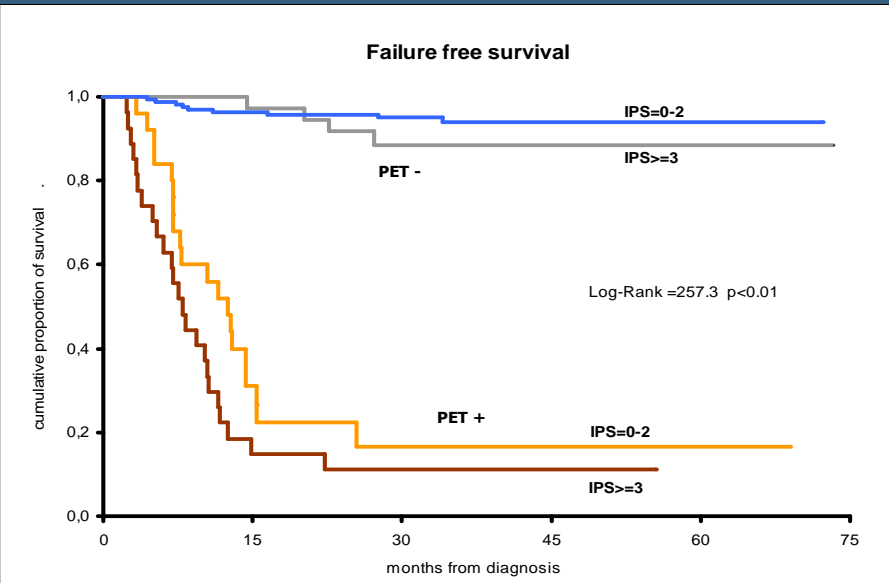
Early Interim FDG-PET in advanced-stage Hodgkin Lymphoma (HL). Long-term results of the Italian-Danish cooperative study.

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.



Intergruppo
Italiano Linfomi

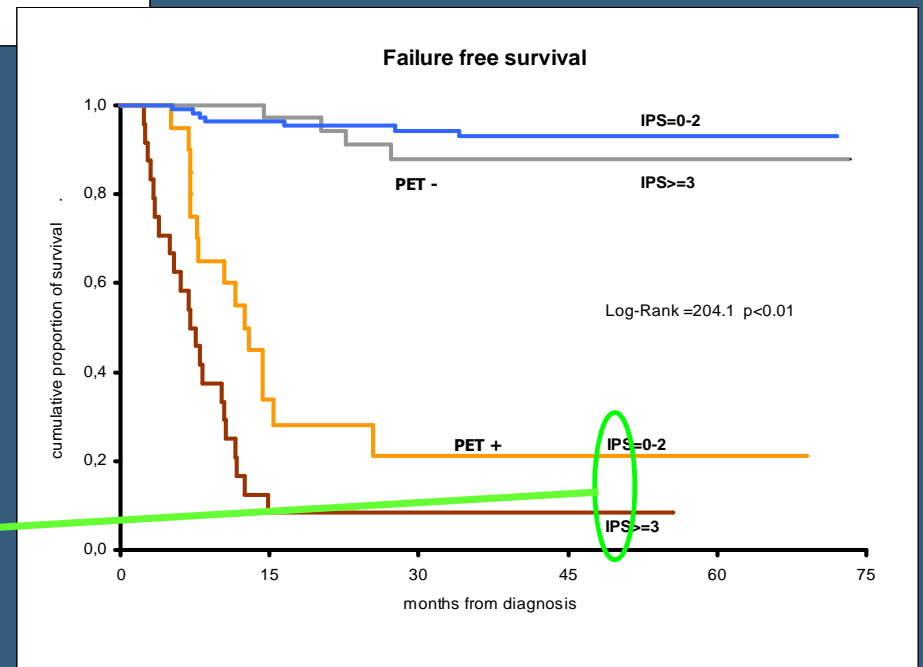




FFS: PET-2 vs IPS stage IIA-IVB

FFS: PET-2 vs IPS stage IIB-IVB

P < .05, log rank 6.0



LINFOMA DI HODGKIN

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- **Significato prognostico della PET**

- **Allotrapianto**

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:

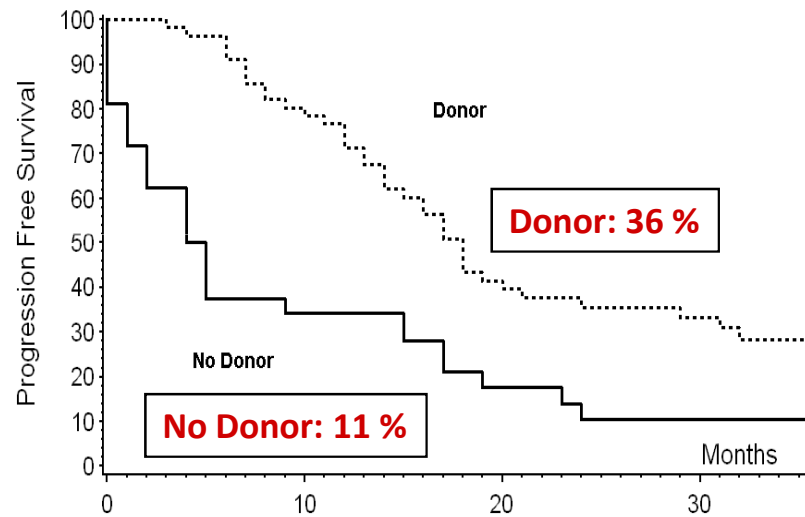
60 had a donor and received RIC allo-SCT

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

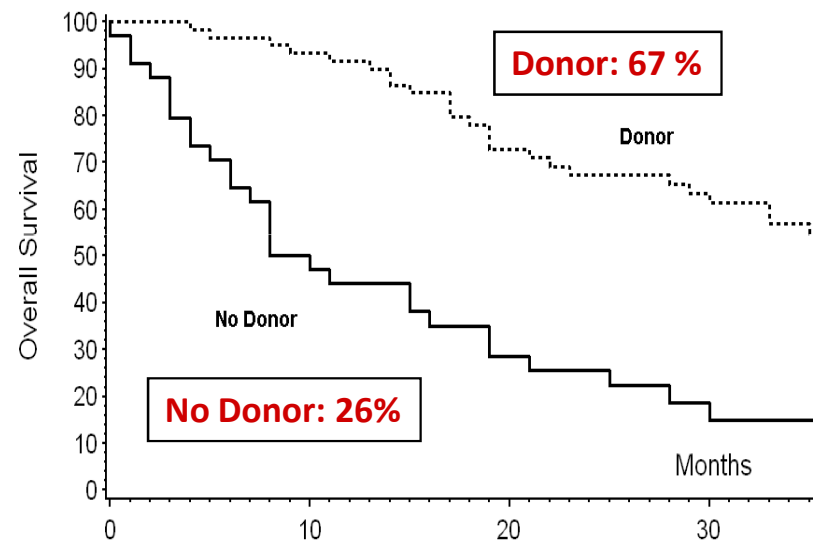
All of them received CT and/or RT

2-year PFS and OS donor vs no donor

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PFS at 2 years p value: <0.001



OS at 2 years p value: <0.001

CONCLUSIONS

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- ✓ RIC allo-SCT seems an effective salvage treatment for a fraction of patients failing a HDC
- ✓ NRM is low (15%)
- ✓ The main problem remains the relapse after allo
- ✓ This is a retrospective study and results showed should be considered preliminary
- ✓ It is time to build up prospective randomized studies, introducing allogeneic transplantation early in the course of disease.