Linfomi:

Report del gruppo di lavoro

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FONDAZIONE FIL ITALIANA LINFOMI

Linfomi: gruppo di lavoro

- Nadia Bisso Genova
- Catello Califano Salerno
- Tullio Calzamiglia Sanremo
- Andrea Camera Caserta
- Angela Lorenzi Verbania
- Laura Paris Bergamo
- Rossella Ribolla Brescia
- Anna Maria Bugli San Marino
- Francesca Rossi Milano
- Pietro Terrizzi Messina
- Daniela Venditti Roma
- Falcinelli Flavio Perugia
- Maria Pina Cabras Cagliari
- Marco Ladetto Alessandria
- Maurizio Martelli Roma
- Umberto Vitolo Torino

Linfomi: Report del gruppo di lavoro

- Is ASCT still the golden standard for MCL? how to challenge it in the future?

YOUNG PATIENTS PROBABLY NOT DESERVING ASCT

- ✓ Patients with major comorbidities
- ✓ Patients with limited stage MCL
- ✓ *Indolent MCL ????*
- ✓ Primary refractory patients

NOT YET

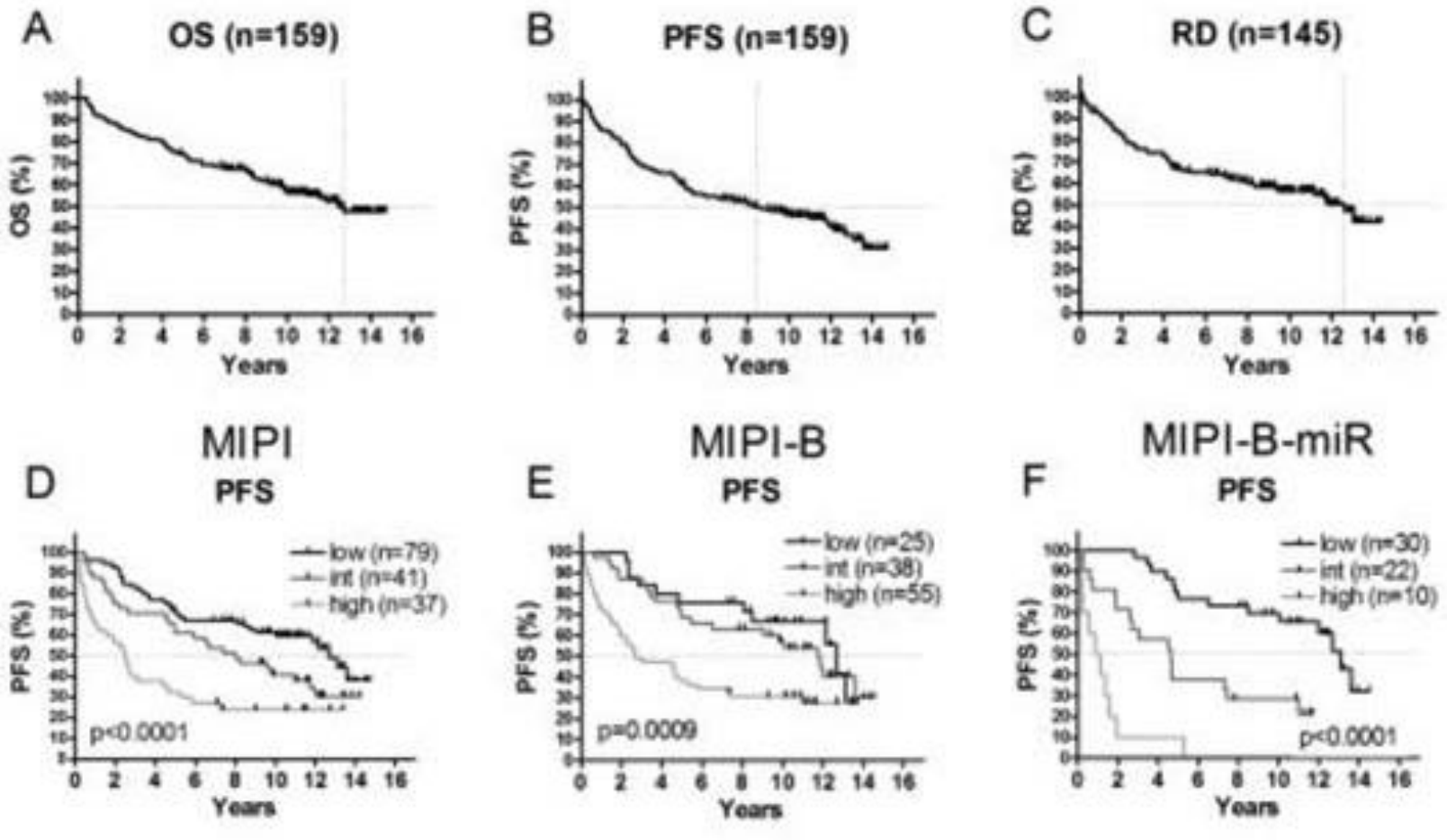
For specific prognostic subgroups….

Patients in whom treatment may be postponed (indolent MCL)

- *Long history of asymptomatic disease*
- *Non-nodal leukemic disease (++ spleen)*
- *Low proliferation rate*
- Hypermutated IGHV
- Noncomplex karyotypes
- *SOX11-negative*

Fernandez V, Cancer Res 2010
Seto M, Blood 2013
Ferrando A, Blood 2013
Vegliante et al, Blood 2013

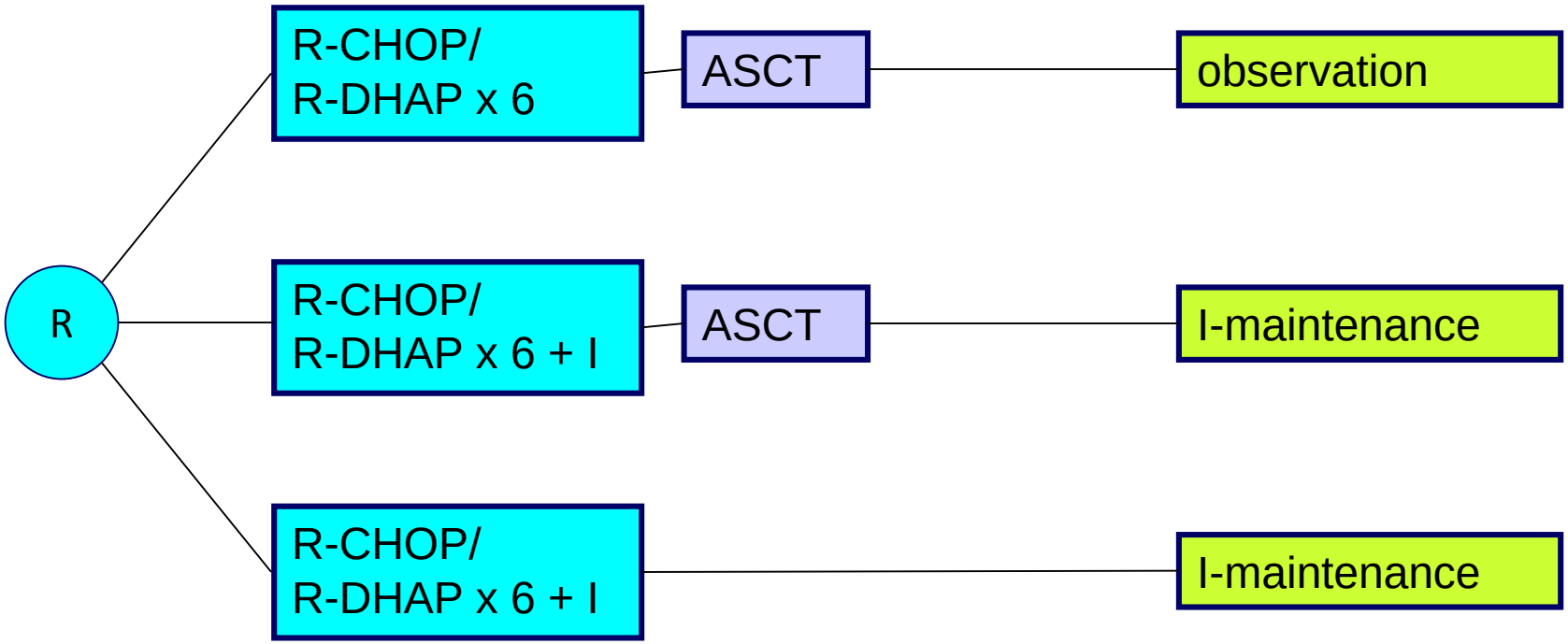
15-YEAR FOLLOW-UP OF THE NORDIC MCL2-TRIAL: DESPITE LONG-TERM RESPONSES LATE RELAPSES STILL OCCUR.



Eskeund CW S437 oral presentation

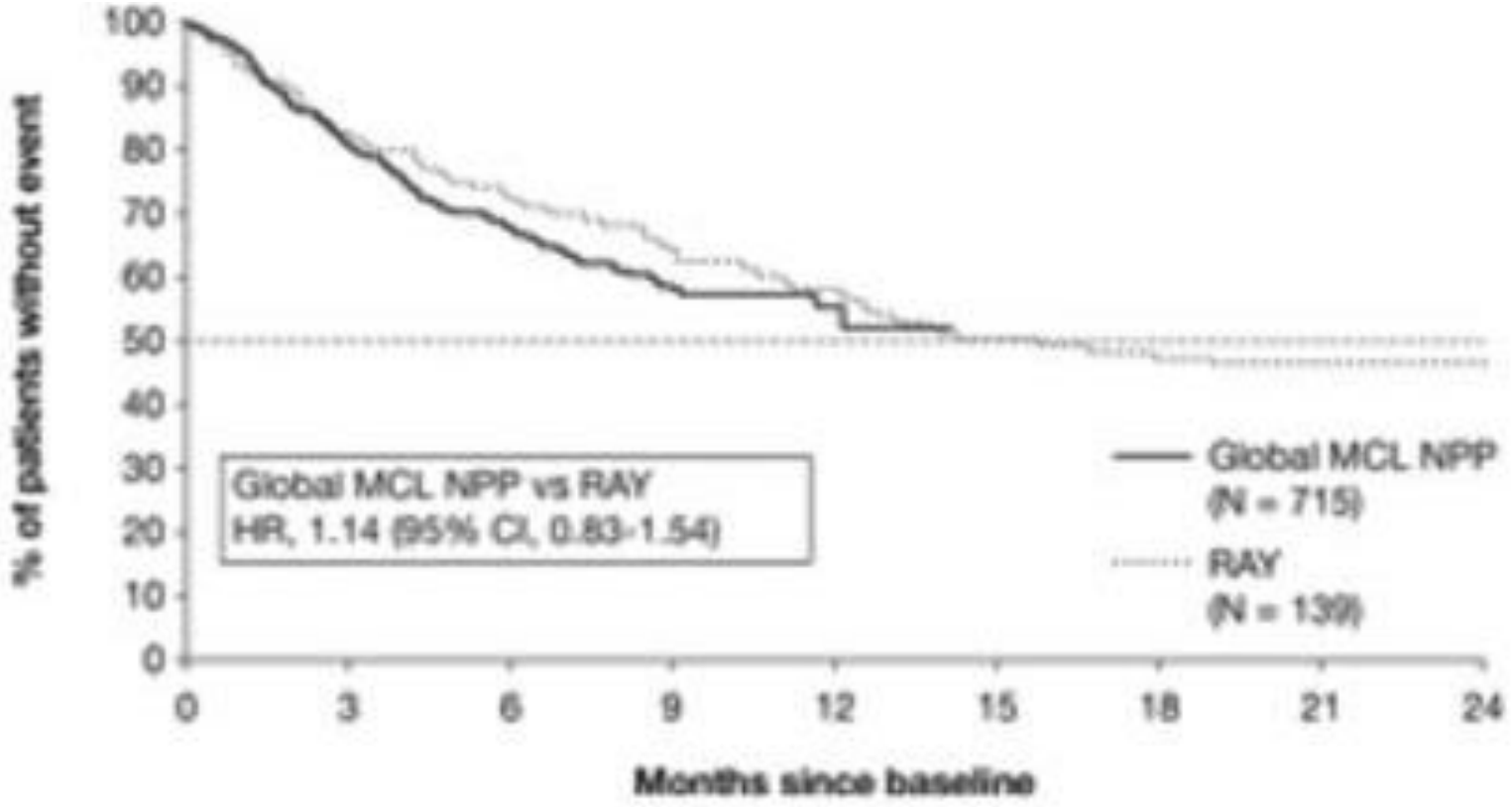
TRIANGLE Phase III Trial

MCL, 18 to 65 years old



on behalf of European MCL Network

REAL-WORLD EXPERIENCE OF IBRUTINIB IN >700 PATIENTS WITH MCL: DATA FROM A GLOBAL NAMED PATIENT PROGRAM



•NPP program to allow access to ibrutinib for eligible patients R/E MCL This program provides real-world data on estimated outcomes with ibrutinib across a large, global MCL population.

Rule S et al S438 poster presentation

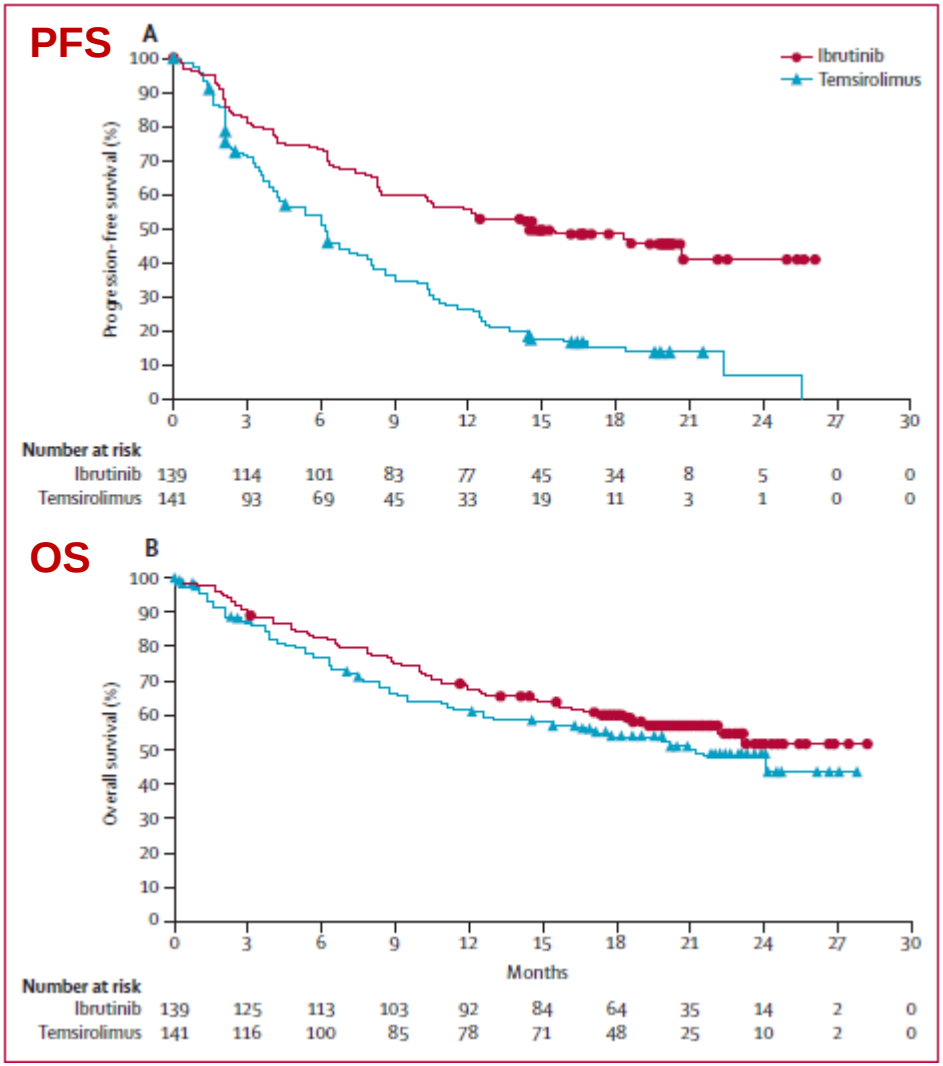
Open-Label, Phase 3 Study (MCL3001 Ray): Response and survival curves

Outcome, %	iBTK (n = 139)	Tems (n = 141)	*P* Value
ORR by IRC	71.9	40.4	< .0001
▪ CR	18.7	1.4	
▪ PR	53.2	39.0	
▪ SD	10.8	30.5	

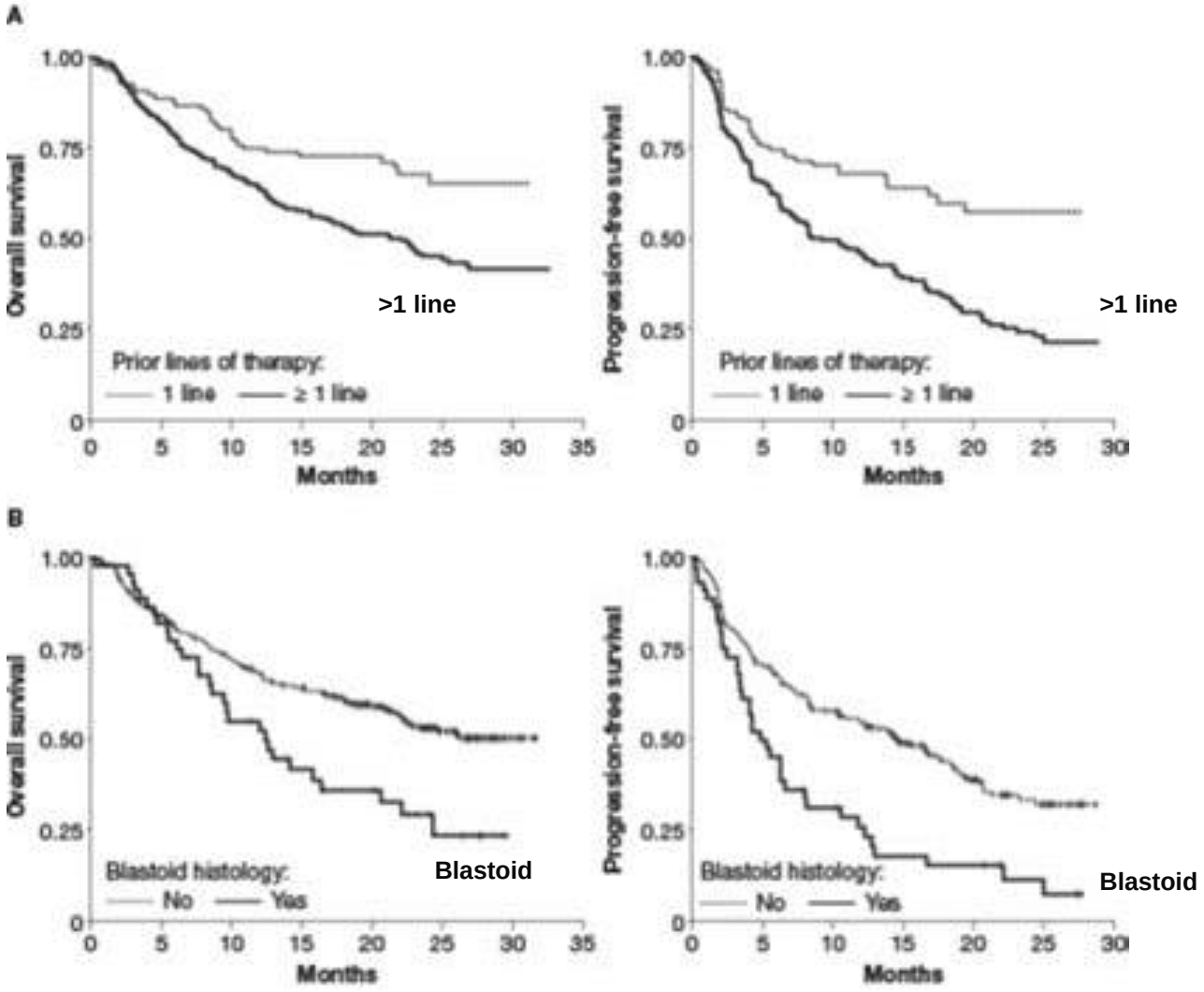
✓ *23% of pts treated with temsirolimus crossed over to ibrutinib at progression*

Median DoR:

✓ Not reached (95% CI: 16.2-NE) with ibrutinib vs 7.0 mos (95% CI: 4.2-9.9) for temsirolimus.

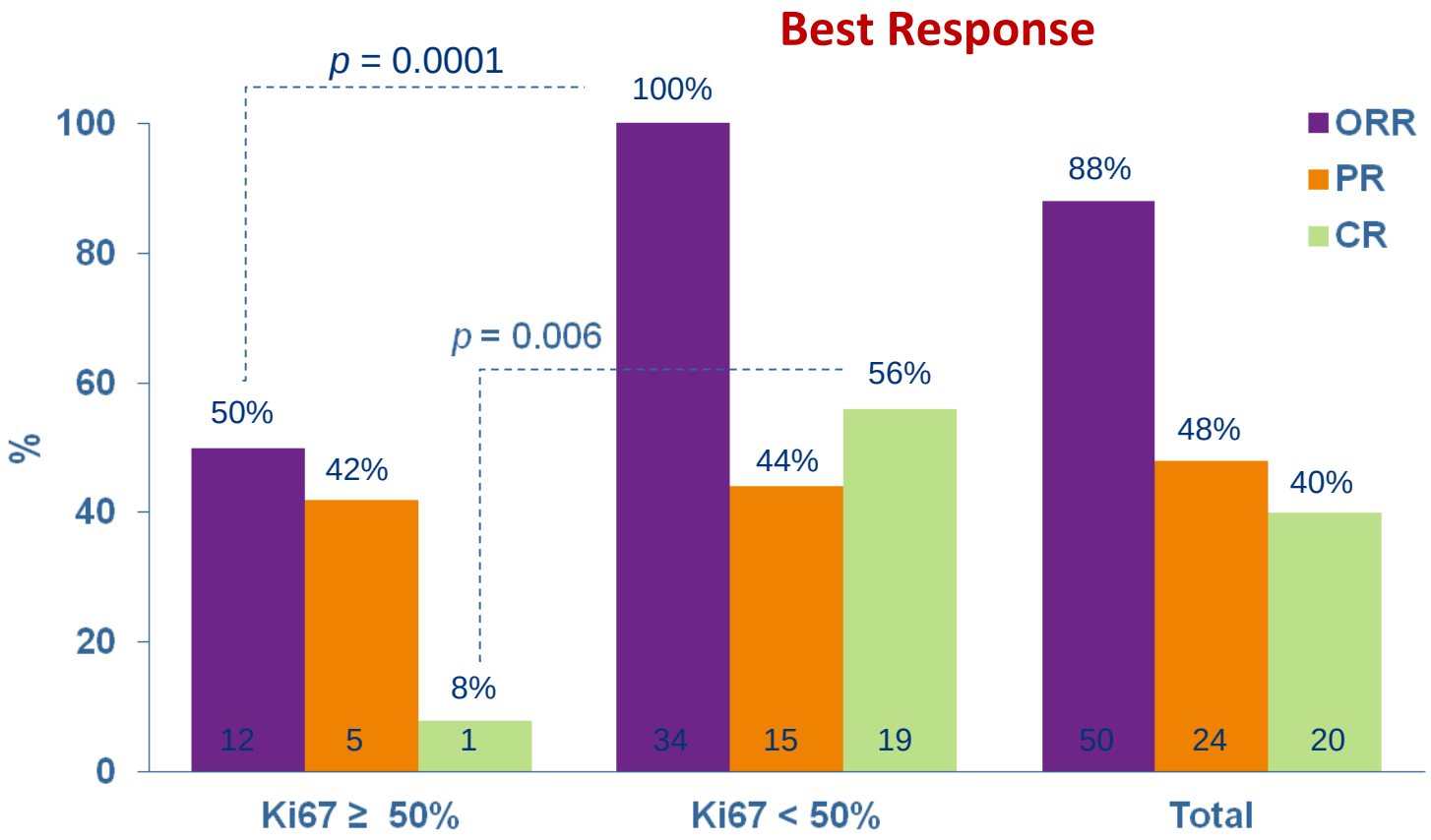


OVERALL SURVIVAL OUTCOMES IN PATIENTS WITH MCL TREATED WITH IBRUTINIB IN A POOLED ANALYSIS OF 370 PATIENTS FROM 3 INTERNATIONAL OPEN-LABEL STUDIES



Rule S et al S438 oral presentation

Ibrutinib And Rituximab Are An Efficacious And Safe Combination In Relapsed Mantle Cell Lymphoma: Preliminary Results From A Phase II Clinical Trial

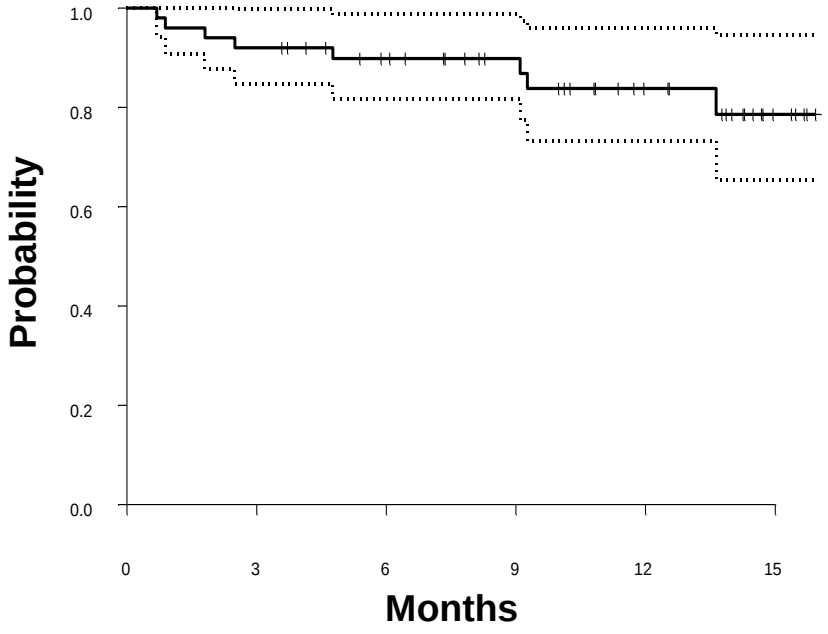


Ki67 N/A for 4 patients

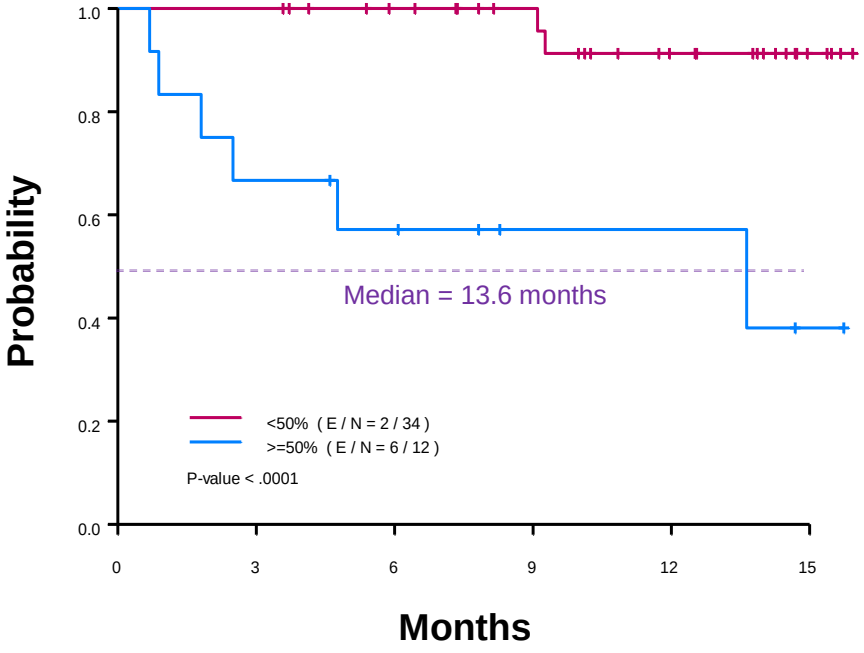
Wang ML et al. ASH 2014; Oral/Abstract 627

Progression Free Survival

Overall PFS (N=50)



PFS by Ki67



Median follow up 11 months (4-16 months)

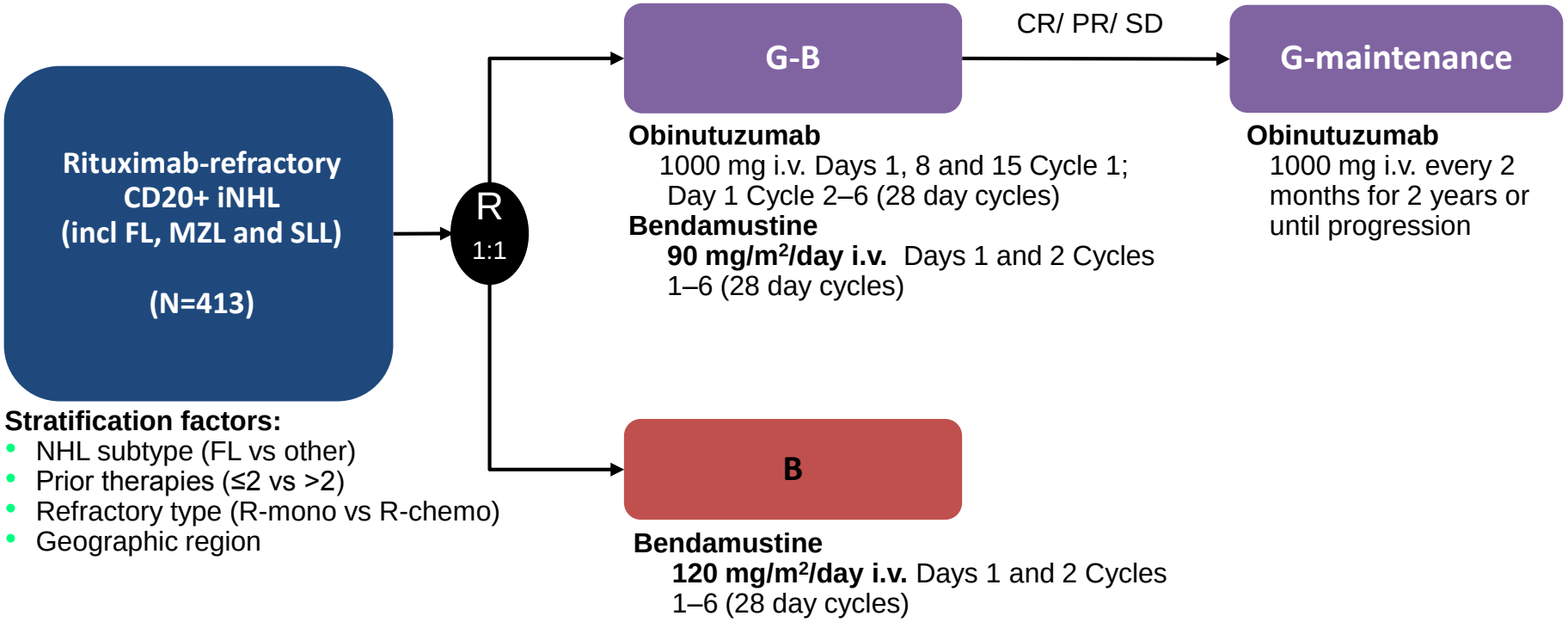
Wang ML et al. ASH 2014; Oral bstract 627

- Ibrutinib può essere considerato il gold standard della terapia di salvataggio del paziente con MCL refrattario o in prima recidiva di malattia?

Linfomi: Report del gruppo di lavoro

- Is ASCT still the golden standard for MCL? how to challenge it in the future?
- What is new in relapsed follicular lymphoma? Is benda-obinotuzumab a major step forward? Which are the alternatives?

OBINUTUZUMAB PLUS BENDAMUSTINE VERSUS BENDAMUSTINE ALONE IN PATIENTS WITH RITUXIMAB-REFRACTORY FOLLICULAR LYMPHOMA: RESULTS FROM THE GADOLIN STUDY



Stratification factors:

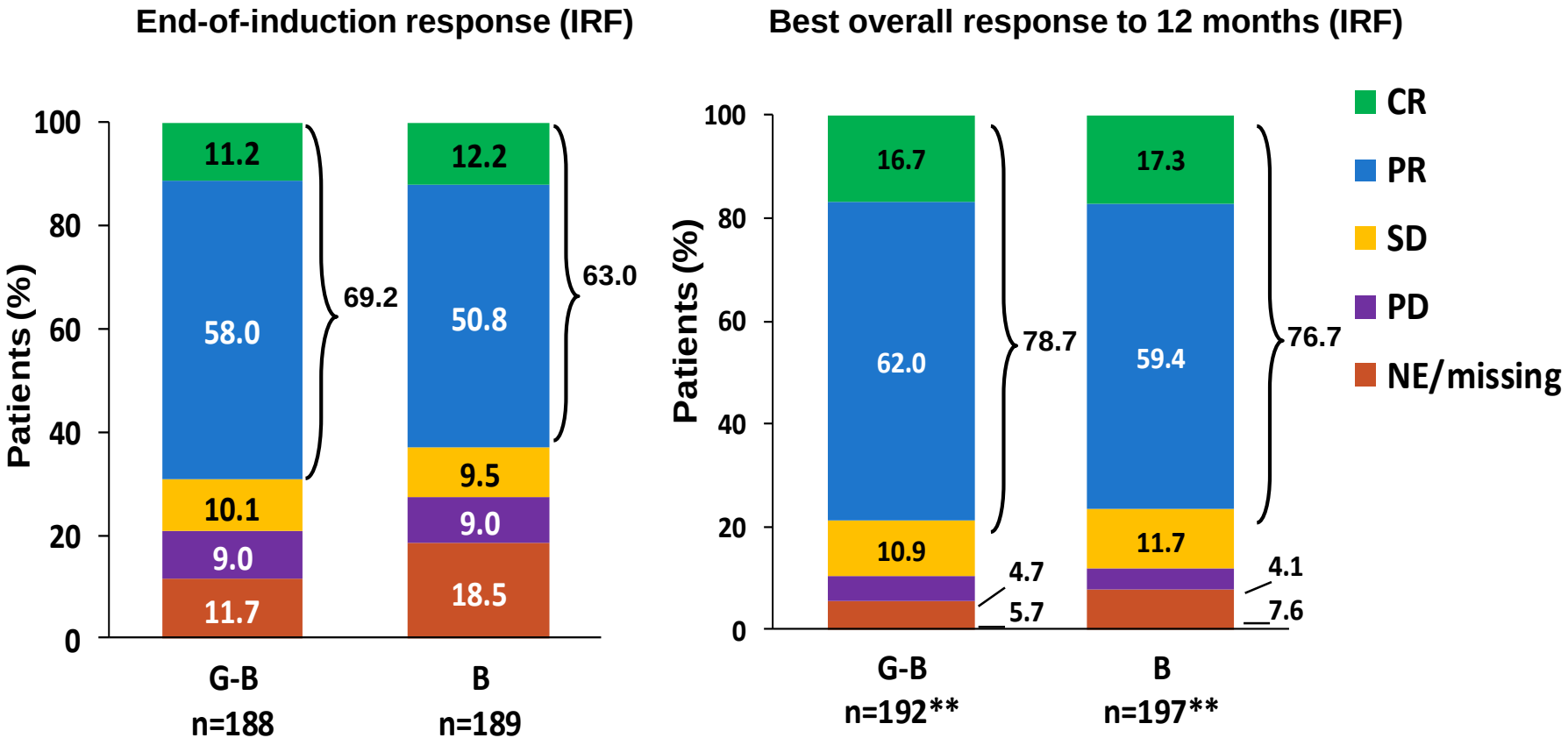
- NHL subtype (FL vs other)
- Prior therapies (≤2 vs >2)
- Refractory type (R-mono vs R-chemo)
- Geographic region

GADOLIN: Study design (NCT01059630)

- International, randomized, open-label study
- Response monitored by CT scan post-induction, then every 3 months for 2 years, then every 6 months

Trneny abs 440 Oral presentaion

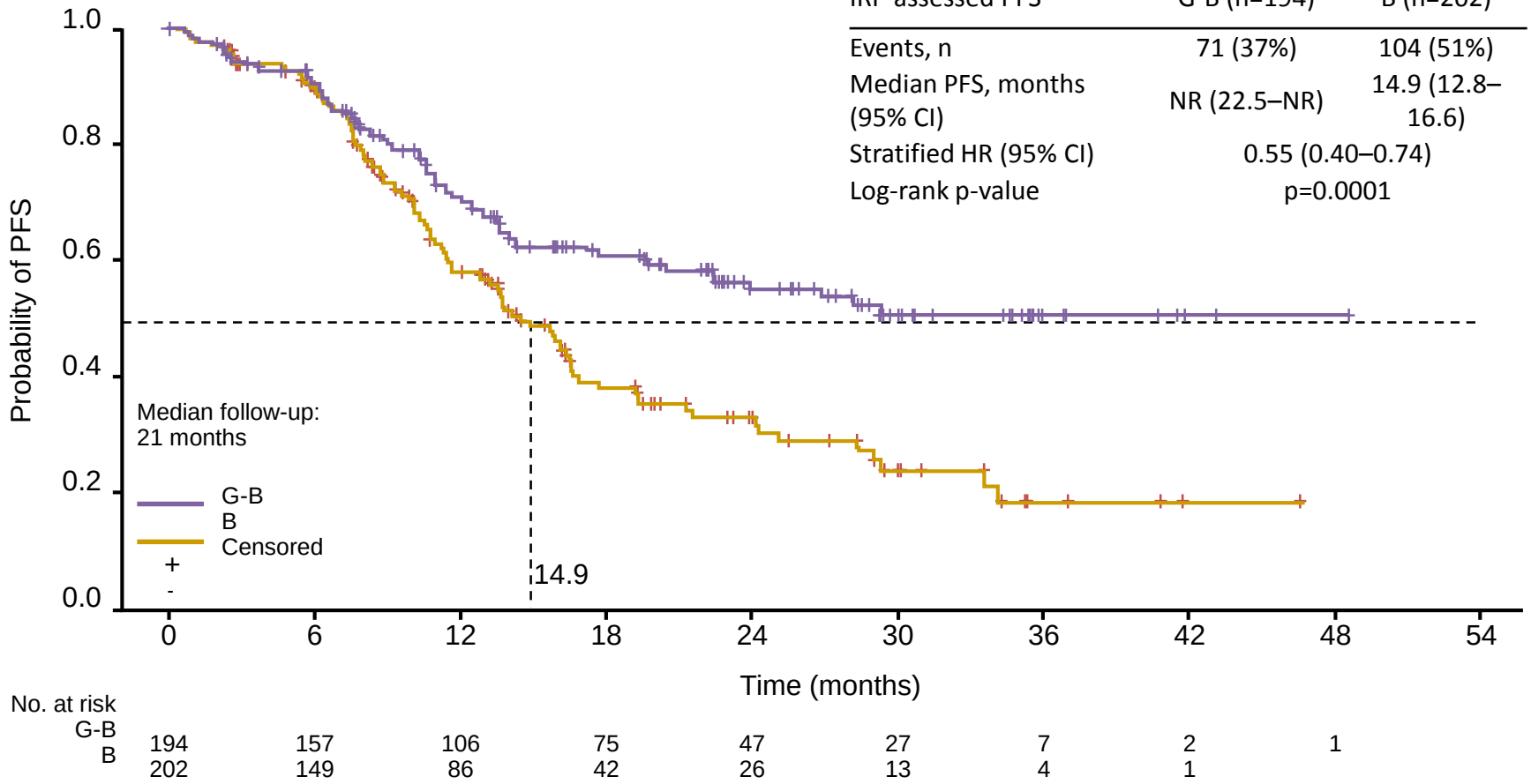
GADOLIN: Response to therapy



- 19 patients still in induction (G-B, n=6; B, n=13)*

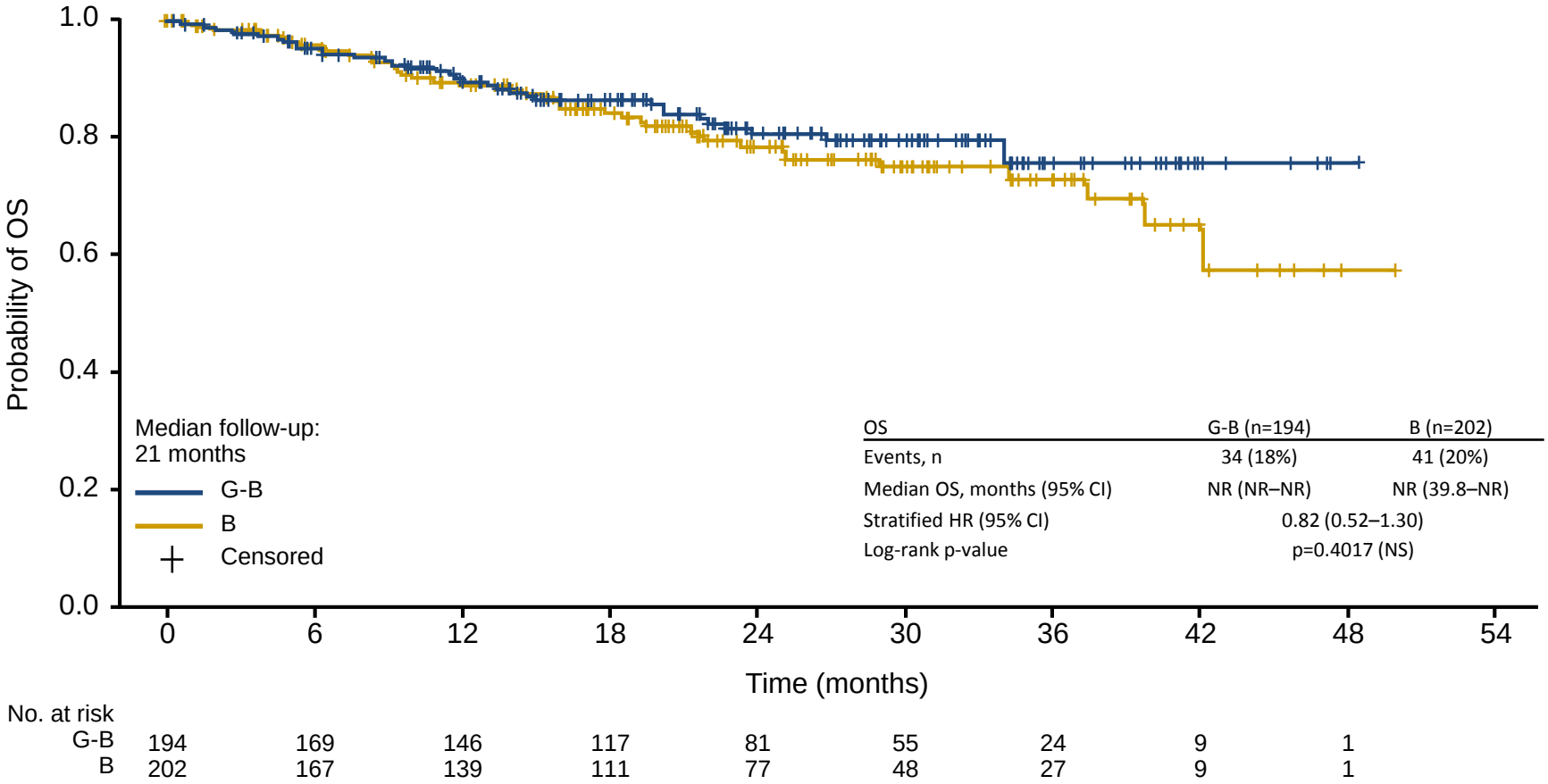
Sehn et al ASCO oral session

GADOLIN primary outcome: IRF-assessed PFS



IRF, independent radiology facility; HR, hazard ratio; CI, confidence interval; NR, not reached.

GADOLIN primary outcome: OS



- 34 (18%) patients died in the G-B arm vs 41 (20%) in the control arm
  - In the G-B arm, 22 (65%) deaths were due to disease progression vs 29 (71%) deaths in the B arm

ANALYSIS OF SECONDARY NEOPLASIAS AFTER HIGH DOSE THERAPY SUPPORTED BY ASCT IN FOLLICULAR LYMPHOMA PATIENTS. A LONG TERM FOLLOW-UP ANALYSIS FROM THE GELTAMO REGISTRY.

Characteristics		No.[a]	%
All patients		655	100
Median age, years (range)		47 (18-73)	
Sex: Male/ Female		330/ 325	50.4/ 49.6
FLIPI Score	Low	108	33
	Intermediate	120	36
	High	102	31
FLIPI 2 Score	Low	69	22
	Intermediate	118	38
	High	125	40
Disease Status at ASCT	CR	405	62
	PR	221	34
	Refractory disease	29	4
Anthracycline-containing first line therapy		460	76
Fludarabine-containing first line therapy		36	6
Only one therapy line before HDT/ASCT		183	28
Rituximab previous HDT, Yes/ No		184/ 436	30/ 70
Conditioning Regimen TBI based, Yes/ No		109/ 504	17/ 83
PBPC, Yes/ No		517/87	14.5/ 85.5

Abbreviations: BM: Bone Marrow, FLIPI: Follicular Lymphoma prognostic index, CR: Complete Response,PR: Partial Response, ASCT: Autologous Stem Cell Transplantation, HDT: High Dose Therapy, TBI: Total Body Irradiation, PBPC: Peripheral Blood Progenitor Cells.
a There are some missing data for several variables. No. of missing values can be directly derived for each variable by the equation: 655-(sum of available results)

CONCLUSIONS

Pts undergoing and ASCT are at an increased risk of developing a second malignancy, however, the incidence is not higher than that reported in other series.

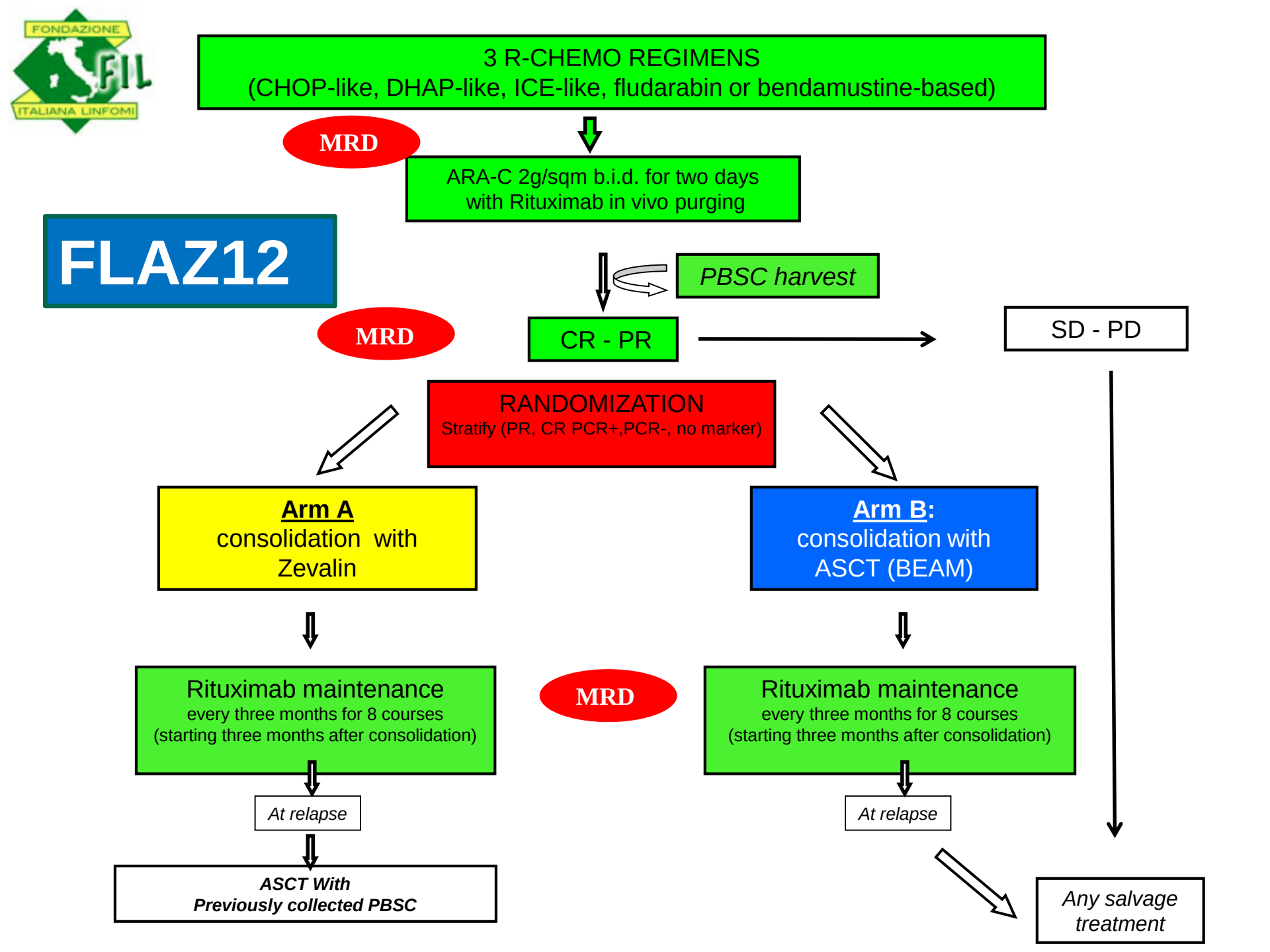
We suggest that, given the favorable survival obtained by HDT/ASCT makes not evident to what extent incidence of secondary neoplasia will diminish the benefit of HDT/ASCT in FL.

Ubieto et al 441 oral presentation

INTERIM ANALYSIS OF POST MARKETING SURVEILLANCE OF YTTRIUM-90 IBRITUMOMAB TIUXETAN IN JAPANESE PATIENTS WITH RELAPSED OR REFRACTORY INDOLENT B-CELL NHL OR MCL

CONCLUSIONS

The interim analysis of this surveillance confirms 90YIT is a tolerable and efficacious treatment option for pts with R/R B-cell NHL or MCL in Japan, demonstrating good benefit-risk balance consistent with the currently available international and Japanese data. (NCT01448928)


FONDAZIONE
FIL
ITALIANA LINFOMI
3 R-CHEMO REGIMENS
(CHOP-like, DHAP-like, ICE-like, fludarabin or bendamustine-based)
MRD
ARA-C 2g/sqm b.i.d. for two days
with Rituximab in vivo purging
FLAZ12
PBSC harvest
MRD
CR - PR
SD - PD
RANDOMIZATION
Stratify (PR, CR PCR+,PCR-, no marker)
Arm A
consolidation with
Zevalin
Arm B:
consolidation with
ASCT (BEAM)
Rituximab maintenance
every three months for 8 courses
(starting three months after consolidation)
MRD
Rituximab maintenance
every three months for 8 courses
(starting three months after consolidation)
At relapse
At relapse
ASCT With
Previously collected PBSC
Any salvage
treatment

Relapsed FL: Renoir

A randomized phase III multicenter trial assessing efficacy and toxicity of a combination of Rituximab and Lenalidomide (R2) vs Rituximab alone as maintenance after chemoimmunotherapy with Rituximab-Bendamustine for relapsed/refractory FL patients not eligible for autologous transplantation (ASCT).

RELAPSED/REFRACTORY
FOLLICULAR LYMPHOMA
NEED TO THERAPY

R-Bendamustine x 4 once a month
Rituximab 375 mg/m^2 day 0 or 1 (day 8 on cycle 1)
Bendamustine 90 mg/m^2 iv days 1-2

CR/PR → NR → OFF

Random

R2

Rituximab 375 mg/m2 day 1 q 90 days (8 cycles)
Lenalidomide (10 mg dd 1-21 q 28) (24 cycles)

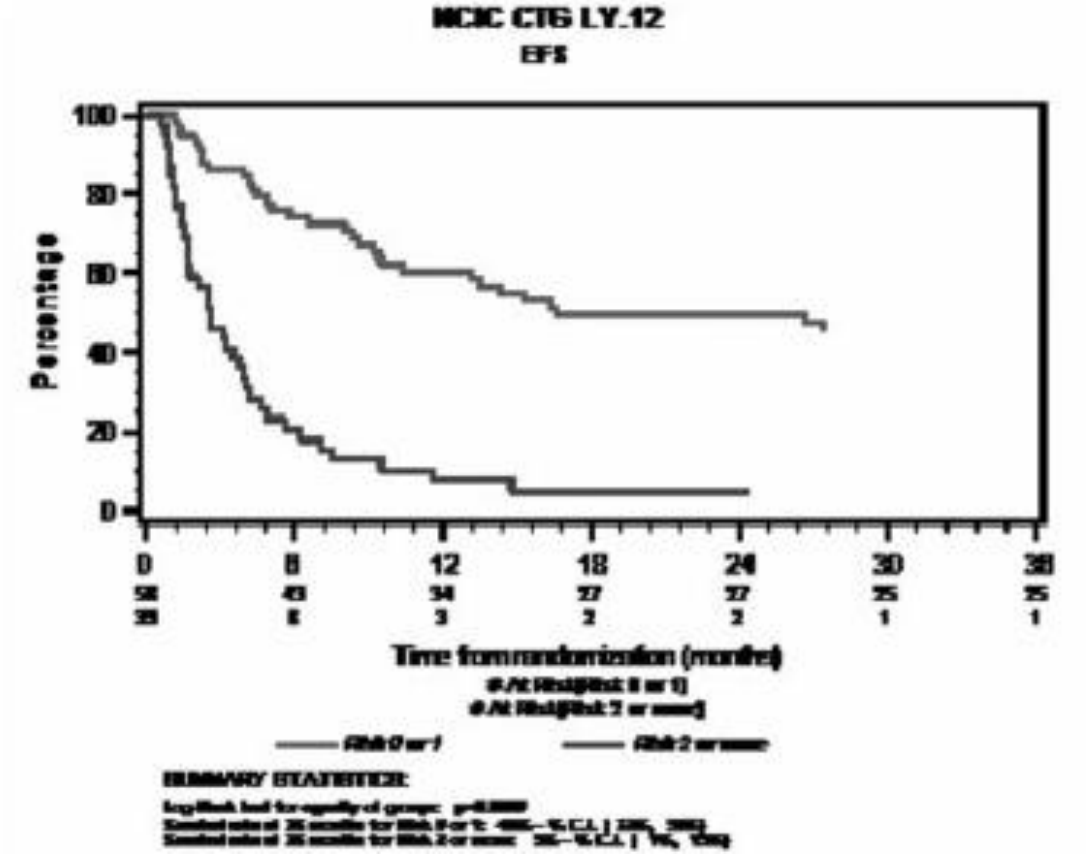
R alone

Rituximab 375 mg/m2 day 1 q 90 days (8 cycles)

Linfomi: Report del gruppo di lavoro

- Is ASCT still the golden standard for MCL? how to challenge it in the future?
- What is new in relapsed follicular lymphoma? Is benda-obinotuzumab a major step forward? Which are the alternatives?
- Ultra high-risk lymphoma patients: Can we identify them? and where shall we go for treatment?

A BIOCLINICAL PROGNOSTIC MODEL INCORPORATING MYC AND BCL2 PREDICTS OUTCOME TO SALVAGE THERAPY IN RELAPSED/REFRACTORY DLBCL: AN NCIC CTG LY12 CORRELATIVE SCIENCE STUDY.

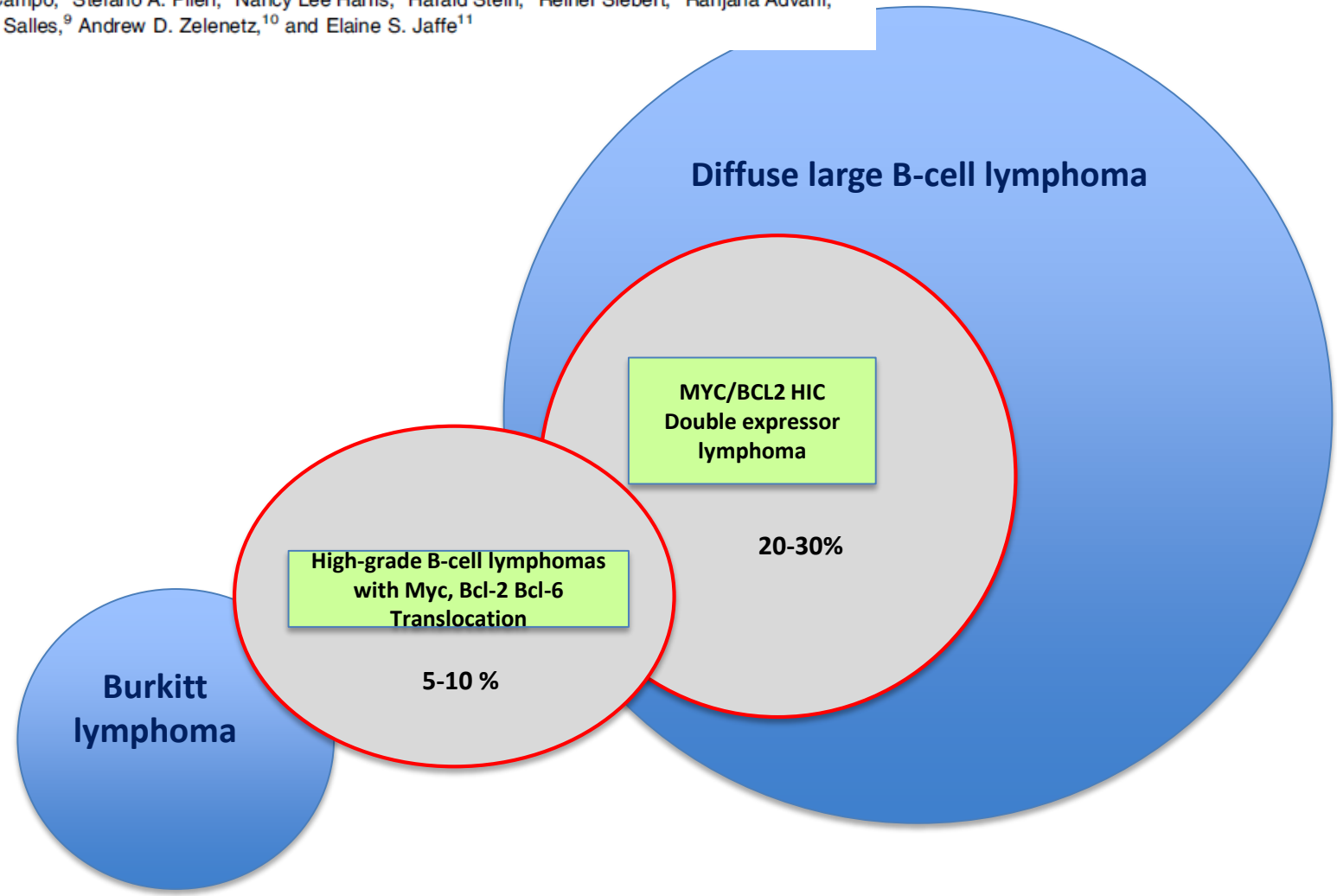


MYC and BCL2 expression, determined by IHC or Nanostring GEP, are independent poor prognostic factors for rrDLBCL, and dual expression predicts dismal prognosis.

Stewart et al 479 oral presentation

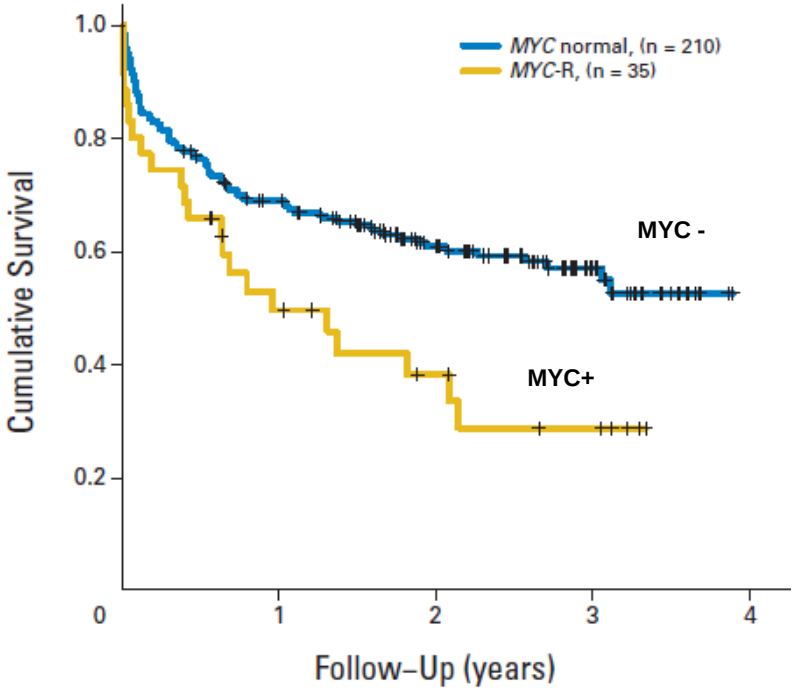
The 2016 revision of the World Health Organization classification of lymphoid neoplasms

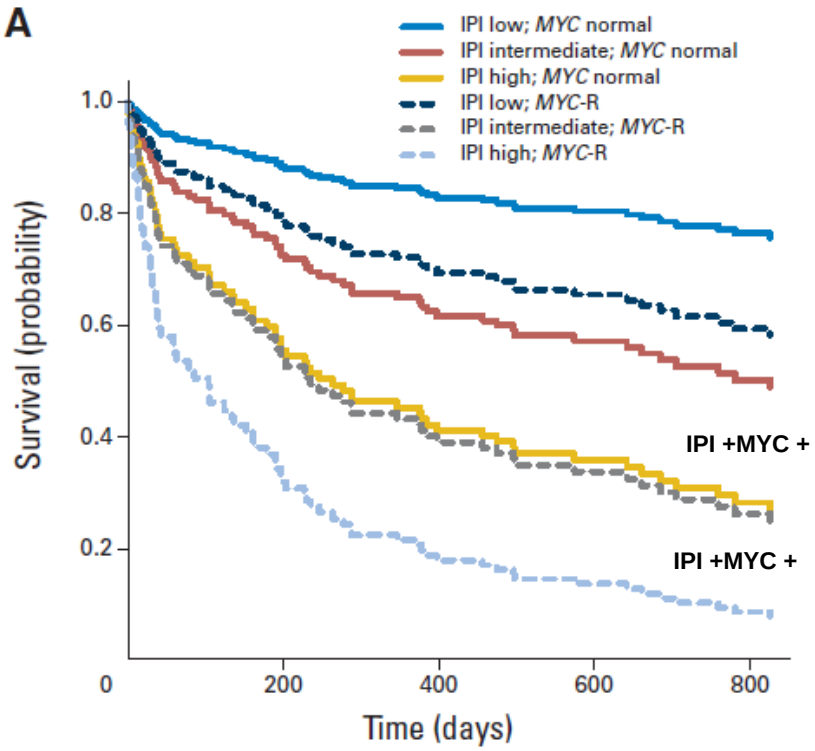
Steven H. Swerdlow,[1] Elias Campo,[2] Stefano A. Pileri,[3] Nancy Lee Harris,[4] Harald Stein,[5] Reiner Siebert,[6] Ranjana Advani,[7] Michele Ghielmini,[8] Gilles A. Salles,[9] Andrew D. Zelenetz,[10] and Elaine S. Jaffe[11]



Rearrangement of MYC in R-CHOP treated DLBCL

- **303 DLBCL previously untreated no follicular evidence.**
- **MYC, BCL6, t(14;18)/ BCL2 rearrangements**
- **245 evaluable, 35 (14%) MYC rearrangements of these 26 (74%) double HIT**

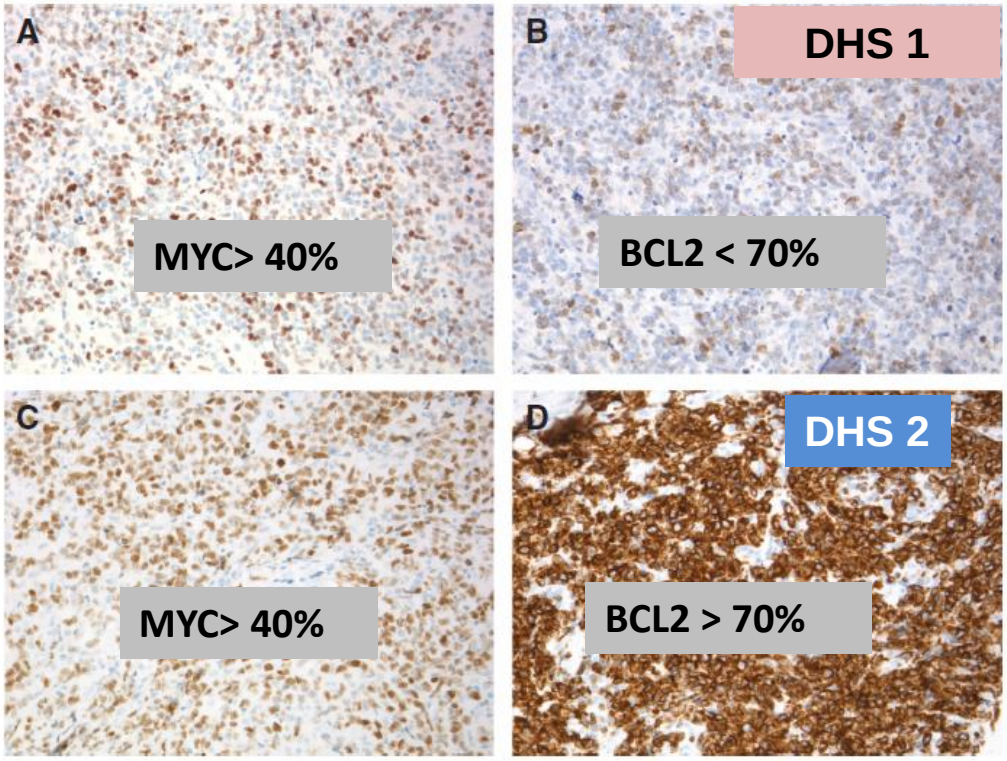




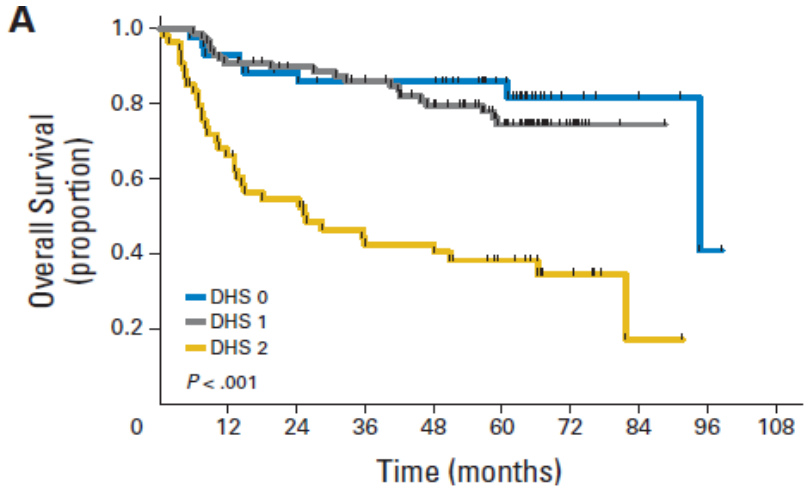
Barrans S. et al JCO 2010

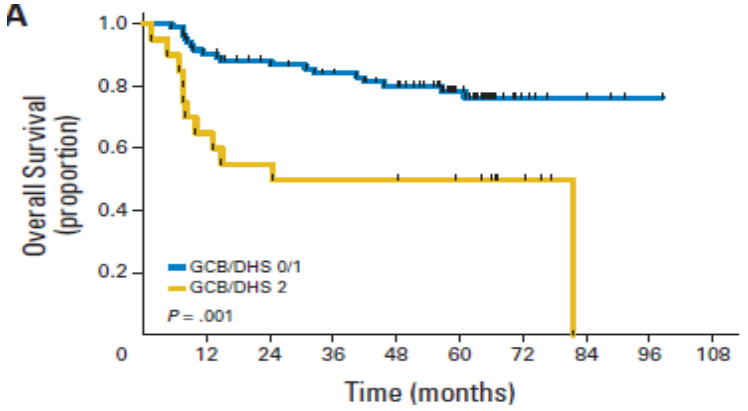
Immunohistochemical Double-Hit Score Is a Strong Predictor of Outcome in Patients With Diffuse Large B-Cell Lymphoma Treated With Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone

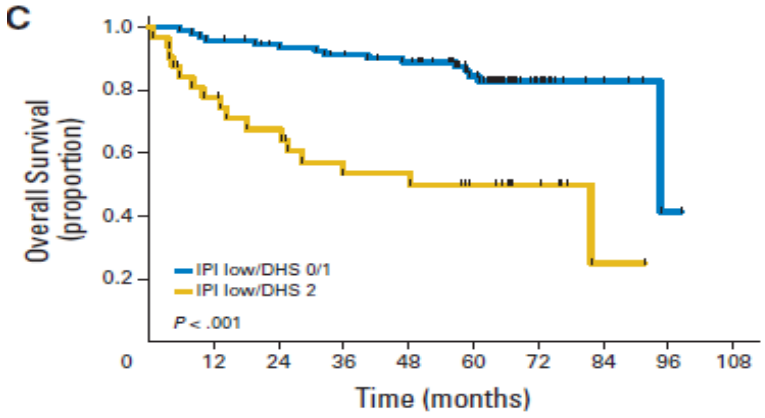
Tina Marie Green, Ken H. Young, Carlo Visco, Zijun Y. Xu-Monette, Attilio Orazi, Ronald S. Go, Ole Nielsen, Ole V. Gaidano, Torben Mourits-Andersen, Mikael Frederiksen, Lars Møller Pedersen, and Michael Boe Møller



DHS 2 = 29%







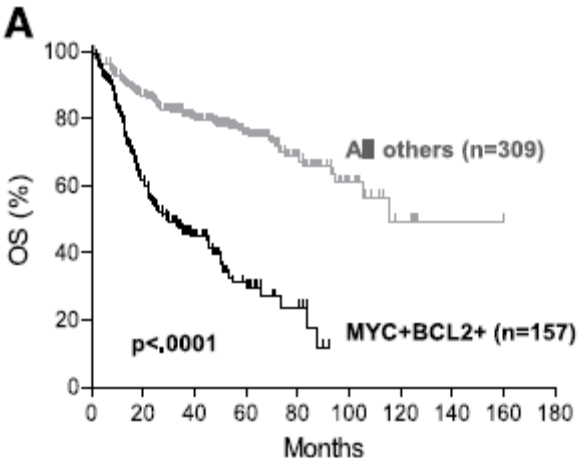
Green T.M et al JCO 2012

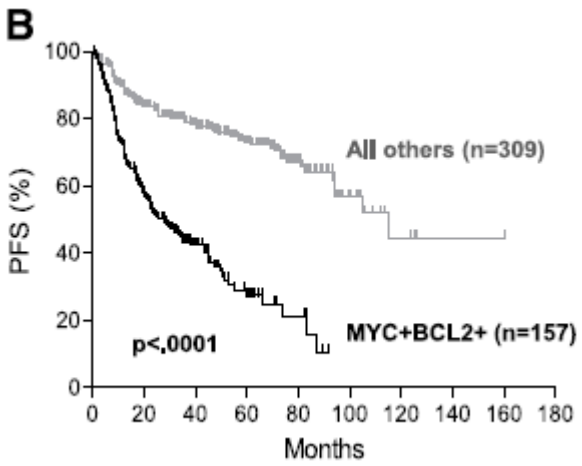
blood
2013 121: 4021-4031
Prepublished online February 28, 2013;
doi:10.1182/blood-2012-10-460063

MYC/BCL2 protein coexpression contributes to the inferior survival of activated B-cell subtype of diffuse large B-cell lymphoma and demonstrates high-risk gene expression signatures: a report from The International DLBCL Rituximab-CHOP Consortium Program

700 de novo DLBCL : 466 pts training and 234 validation set treated with R-CHOP

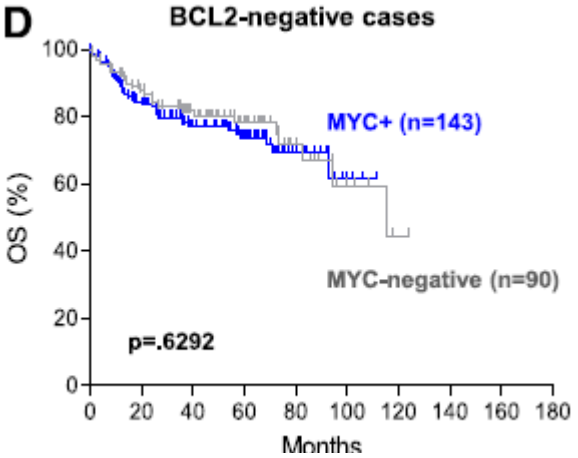
MYC/BCL2 protein coexpression predicts poor prognosis in DLBCL

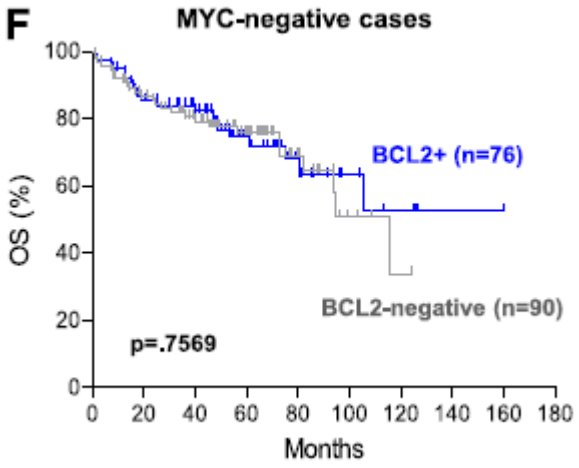




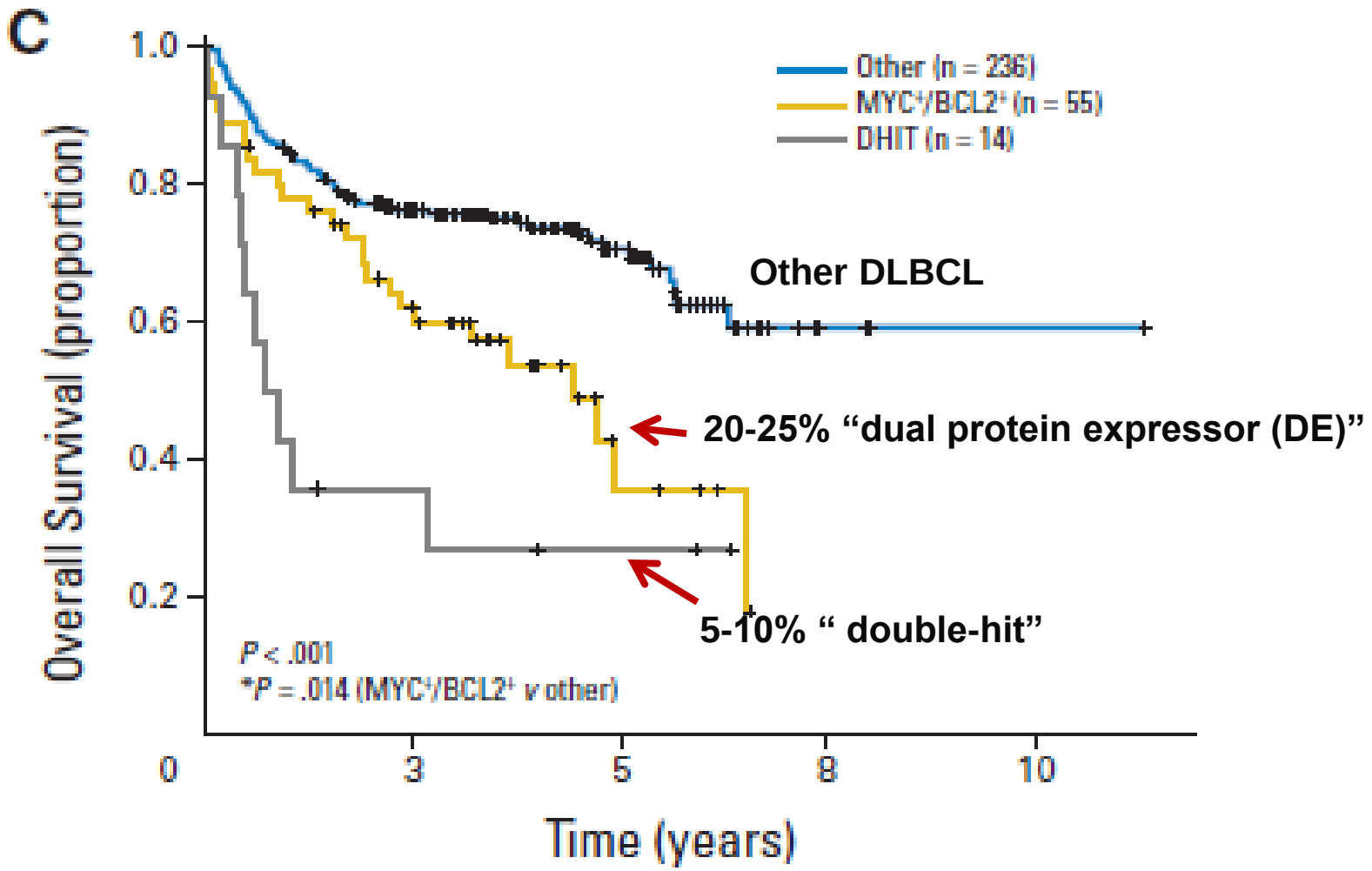
Prognostic impact of MYC or BCL2 protein expression was apparently due to the confounding effect of cases with MYC/BCL2 coexpression; when all cases with MYC/BCL2 were excluded neither MYC nor BCL2 protein expression significantly impacted OS

Hu et al. Blood 2013





Overall survival of patients with DLBCL according MYC and BCL2 translocation (DHIT) or MYC and BCL2 protein expression (DE)

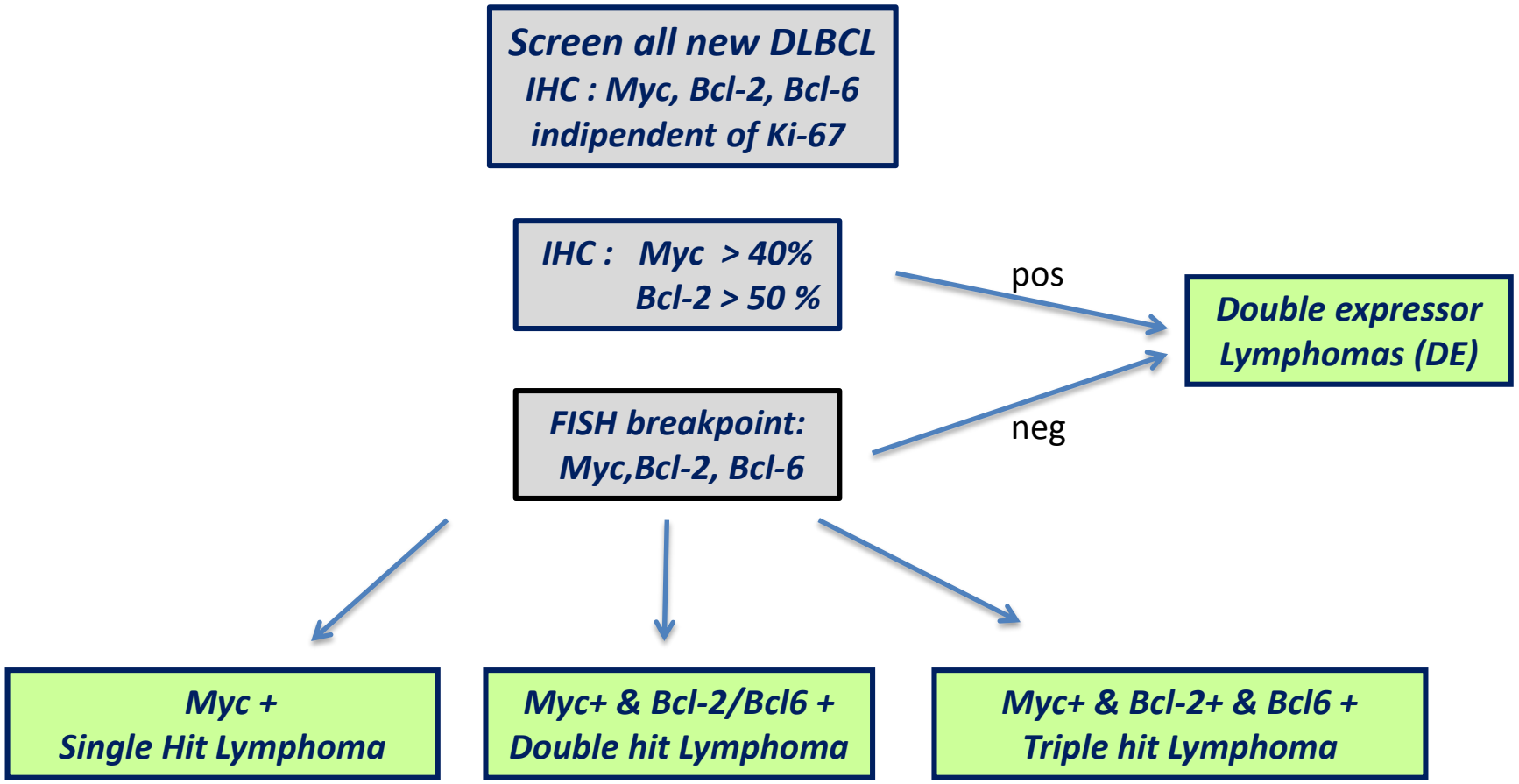


Johnson et al J.Clin. Oncol 2012

What we propose doing in Myc/DH pos DLBCL ?

First step:

Identification of patient at poor prognosis



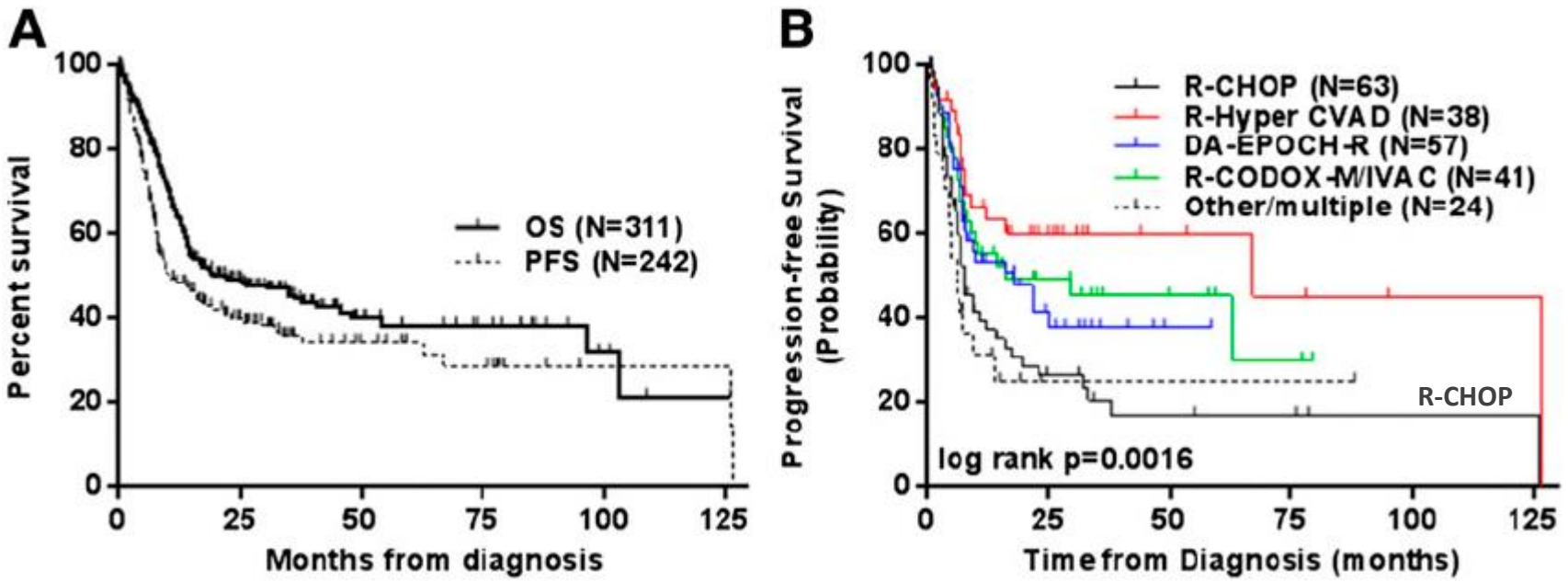
Linfomi: Report del gruppo di lavoro

- Nella vostra pratica clinica quale work-up nella diagnostica dei DLBCL viene impiegato ?

blood 2014 124: 2354-2361

CLINICAL TRIALS AND OBSERVATIONS

Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis



Petrich M, Gandhi M et al 2014

blood 2014 124: 2354-2361

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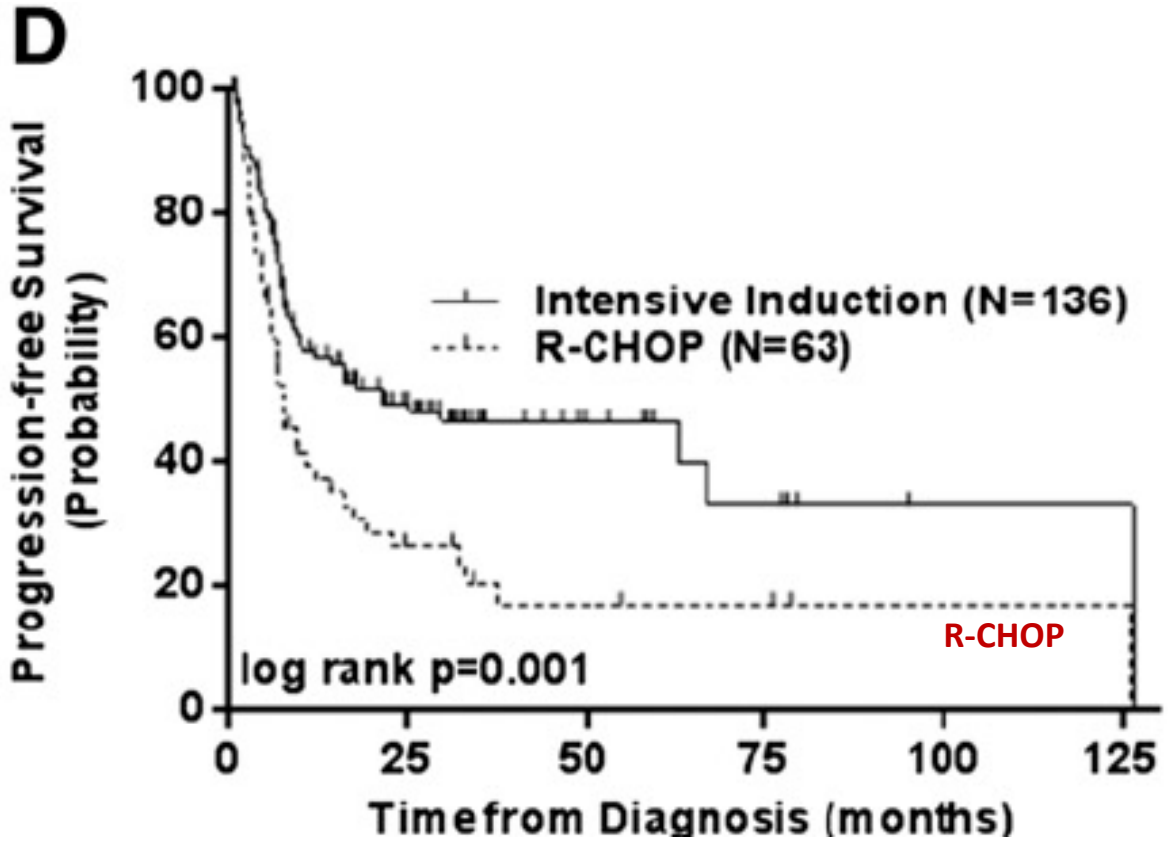

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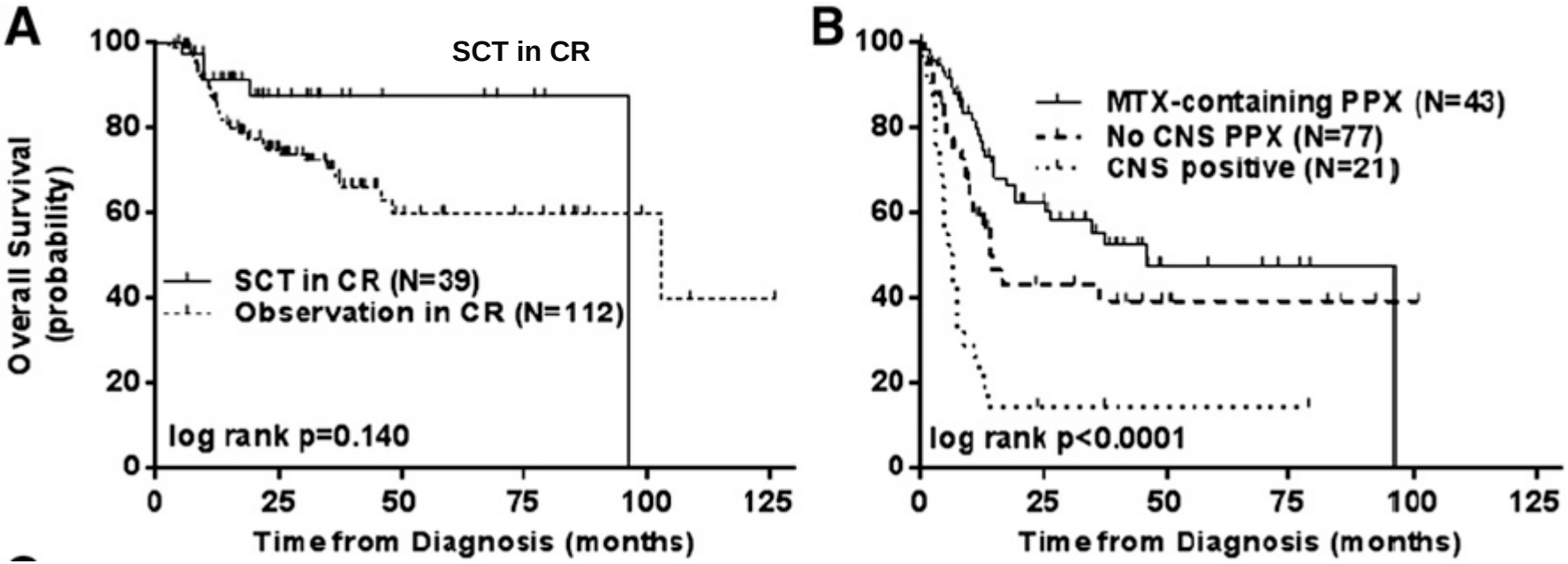
Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis



Petrich M, Gandhi M et al 2014

Linfomi: Report del gruppo di lavoro

- Nella vostra pratica clinica quale work-up nella diagnostica dei DLBCL viene impiegato ?
- Il trattamento dei DLBCL-DE e dei DLBCL-DH è diversificato rispetto al classico DLBCL (R-CHOP) ?
- Nei DLBCL-DH impiegate ASCT come terapia di consolidamento?

VOLUME 33 · NUMBER 26 · SEPTEMBER 10 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Prognostic Significance of Diffuse Large B-Cell Lymphoma Cell of Origin Determined by Digital Gene Expression in Formalin-Fixed Paraffin-Embedded Tissue Biopsies

Pts 344 R-CHOP

David W. Scott, Anja Mottok, Daisuke Ennishi, George W. Wright, Pedro Farinha, Susana Ben-Neriah, Robert Kridel, Garrett S. Barry, Christoffer Hother, Pau Abrisqueta, Merrill Boyle, Barbara Meissner, Adele Telenius, Kerry J. Savage, Laurie H. Sehn, Graham W. Slack, Christian Steidl, Louis M. Staudt, Joseph M. Connors, Lisa M. Rimsza, and Randy D. Gascoyne

Characteristic	ABC DLBCL (n = 108)	GCB DLBCL (n = 189)	Unclassified DLBCL (n = 38)	*P* (ABC *v* GCB)
Age, years				.30
Median (range)	66.5 (16-86)	62 (16-92)	60.5 (20-87)	
Sex, No. (%)				.31
Male	71 (66)	113 (60)	25 (66)	
Female	37 (34)	76 (40)	13 (34)	
B symptoms, No. (%)				.61
Absent	66 (62)	122 (65)	22 (58)	
Present	40 (38)	65 (35)	16 (42)	
Missing	2	2	0	
Bulk (> 10 cm), No. (%)				.54
Absent	82 (77)	135 (74)	28 (74)	
Present	24 (23)	47 (26)	10 (26)	
Missing	2	7	0	
Disease stage, No. (%)				.61
Limited	32 (30)	61 (33)	10 (26)	
Advanced	75 (70)	125 (67)	28 (74)	
Missing	1	3	0	

ABC=108 (31%) **GCB=189 (55%)** **Unclassicable=38 (11%)**

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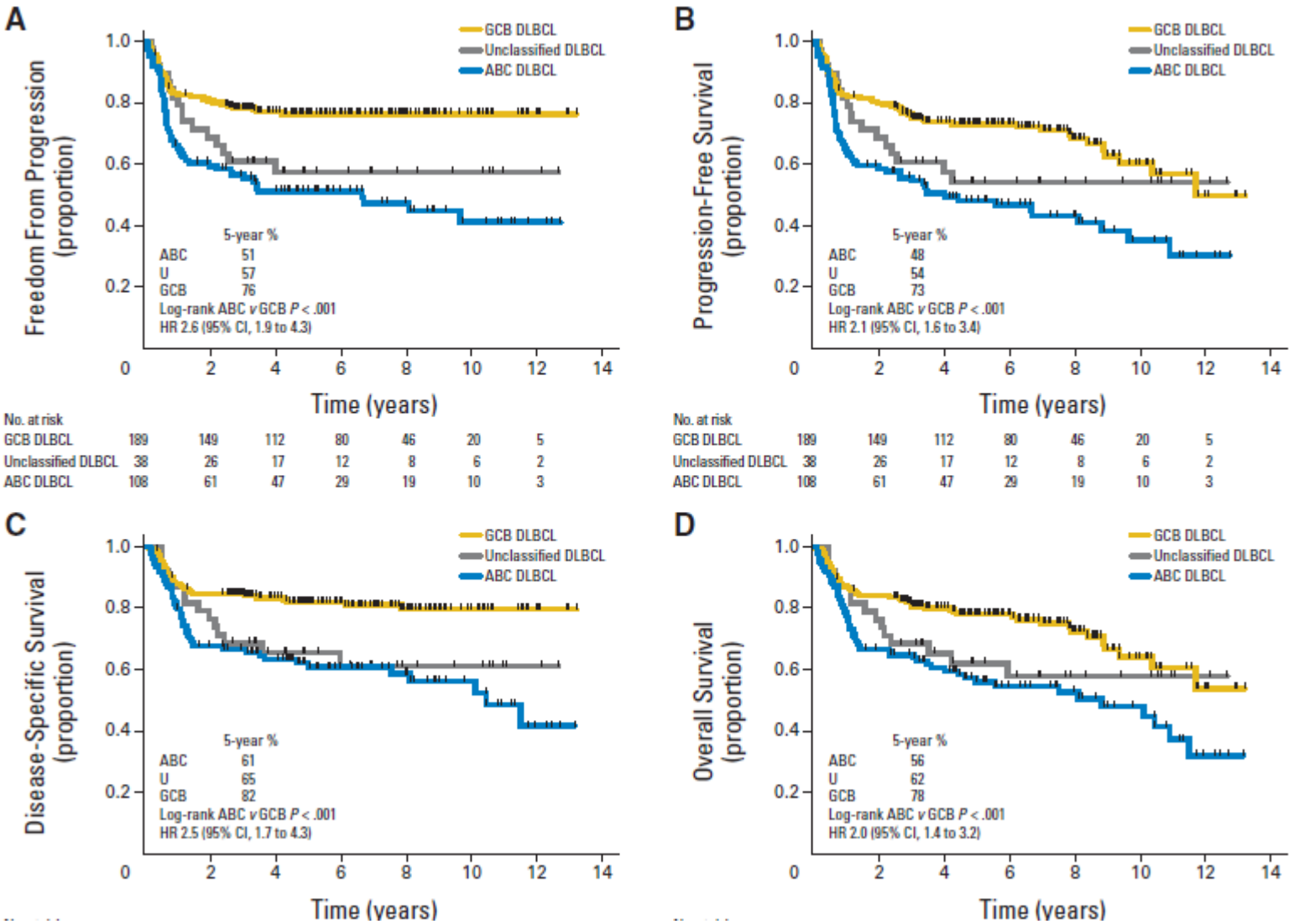
ORIGINAL REPORT



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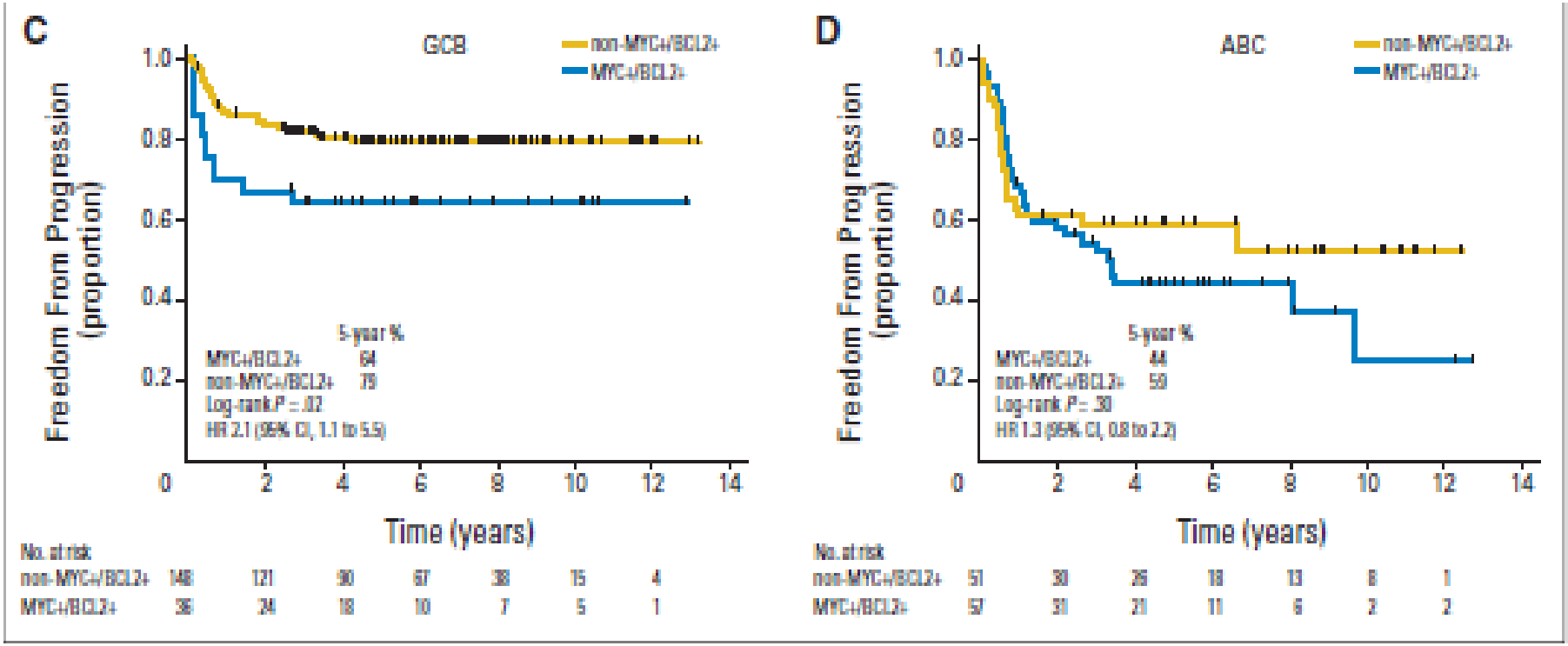
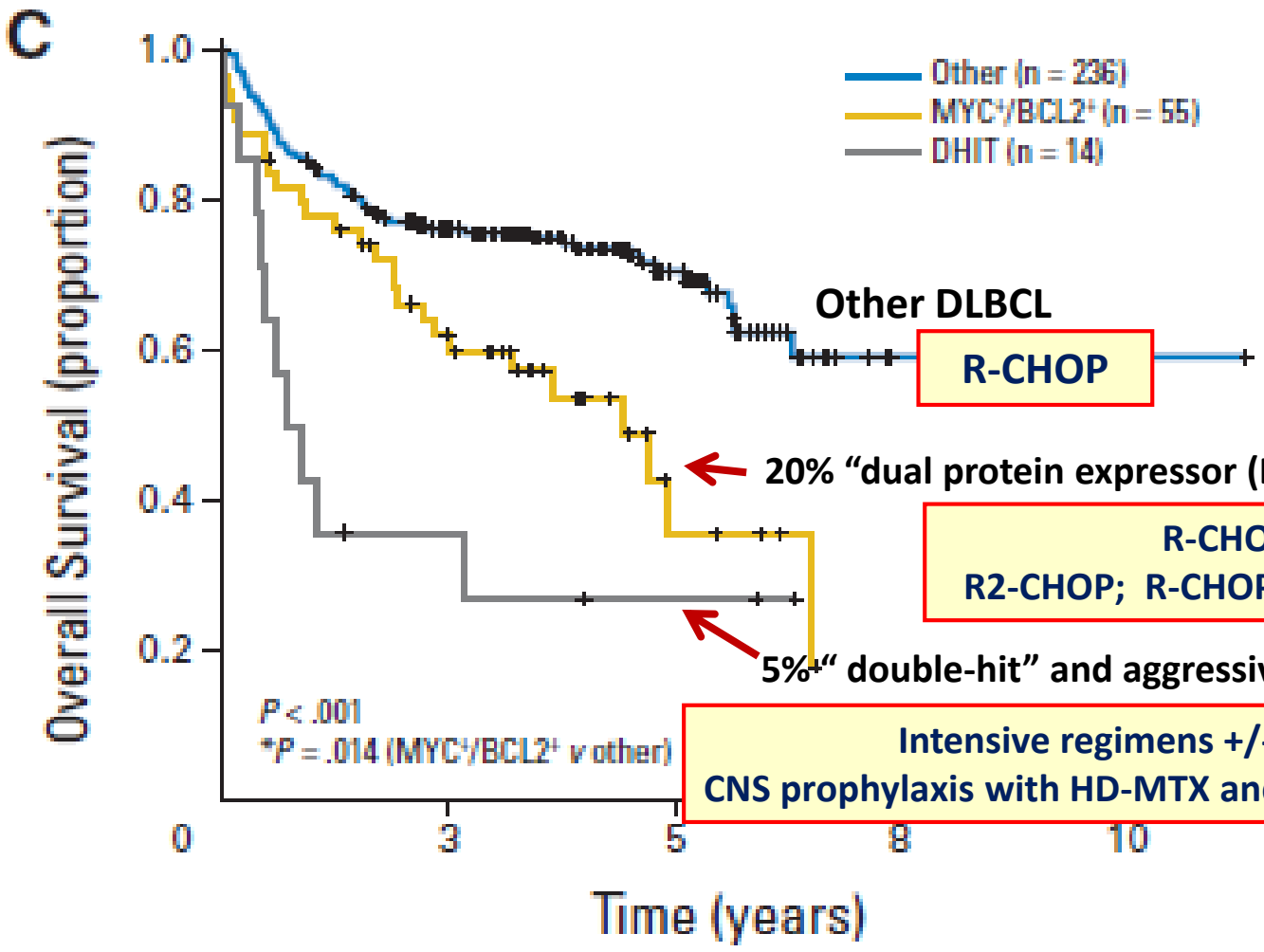


How I treat Myc/DH and DE pos DLBCL ?



Other DLBCL

R-CHOP

20% "dual protein expressor (DE)"

R-CHOP +X
R2-CHOP; R-CHOP+IBR; R-CHOP +?

5% " double-hit" and aggressive DLBCL NOS

Intensive regimens +/- ASCT
CNS prophylaxis with HD-MTX and HD-ARAC and IT

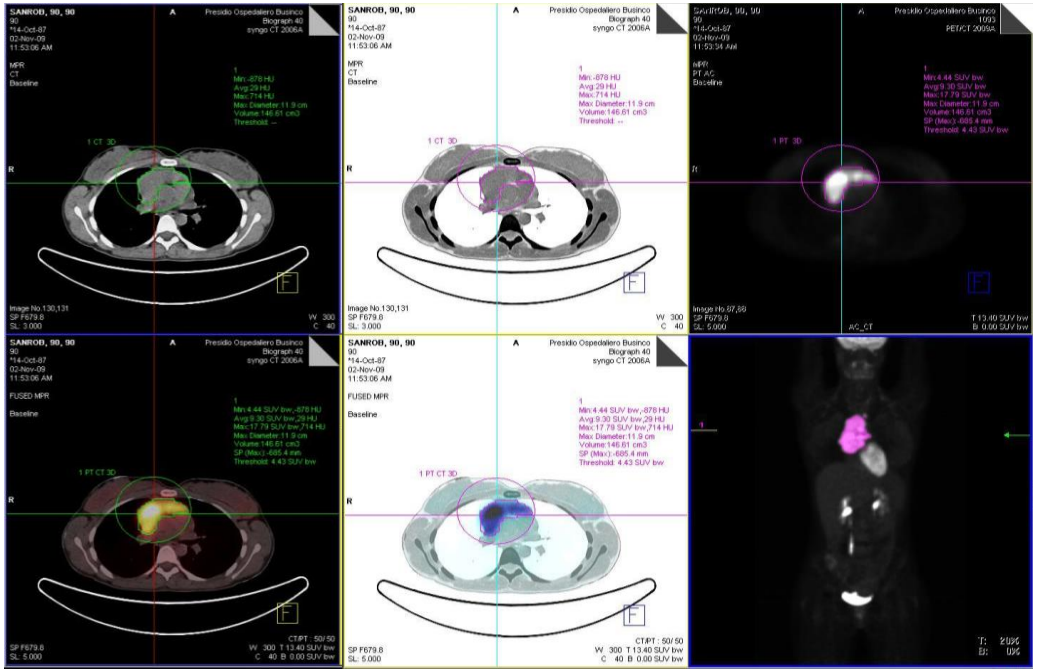
BASELINE TOTAL METABOLIC VOLUME (TMTV) PREDICTS THE OUTCOME OF PATIENTS WITH ADVANCED HODGKIN LYMPHOMA (HL) ENROLLED IN THE AHL2011 LYSA TRIAL

Olivier Casasnovas Abstract: S105 Oral Presentation

Functional and quantitative PET parameters

- Assessment of the prognostic value of
  - maximum Standard Uptake Value (**SUVmax**)
  - metabolic tumor volume (**MTV**)
  - total lesion glycolysis (**TLG**)

  - **SUV max, MTV** and **TLG** were measured following a standard protocoL



BASELINE TOTAL METABOLIC VOLUME (TMTV) PREDICTS THE OUTCOME OF PATIENTS WITH ADVANCED HODGKIN LYMPHOMA (HL) ENROLLED IN THE AHL2011 LYSA TRIAL

	High TMTV	Low TMTV	PET-2 pos	PET- 2 neg
2yrs PFS	81%	93%	76%	92%

	Low TMTV PET2 neg	High TMTV PET 2 pos	Low TMTV PET-2 pos HighT MTV PET- 2 neg
2yrs PFS	94%	61%	88%

The combination of MTV and PET2 allows identifying 3 subsets of HL pts with significantly different outcome that may help clinician to better tailor therapy.

Olivier Casasnovas Abstract: S105 Oral Presentation

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Utility of baseline 18FDG-PET/CT functional parameters in defining prognosis of primary mediastinal (thymic) large B-cell lymphoma

Luca Ceriani,[1] Maurizio Martelli,[2] Pier Luigi Zinzani,[3] Andrés J. M. Ferreri,[4] Barbara Botto,[5] Caterina Stelitano,[6] Manuel Gotti,[7] Maria Giuseppina Cabras,[8] Luigi Rigacci,[9] Livio Gargantini,[10] Francesco Merli,[11] Graziella Pinotti,[12] Donato Mannina,[13] Stefano Luminari,[14] Anastasios Stathis,[1] Eleonora Russo,[2] Franco Cavalli,[1] Luca Giovanella,[1] Peter W. M. Johnson,[15] and Emanuele Zucca[1]

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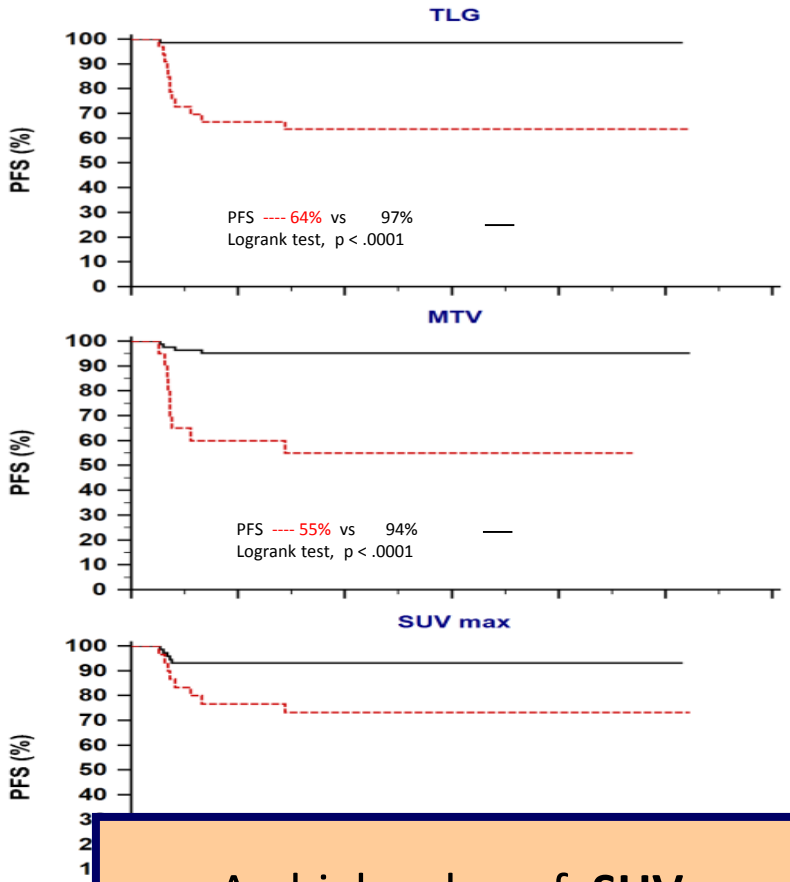
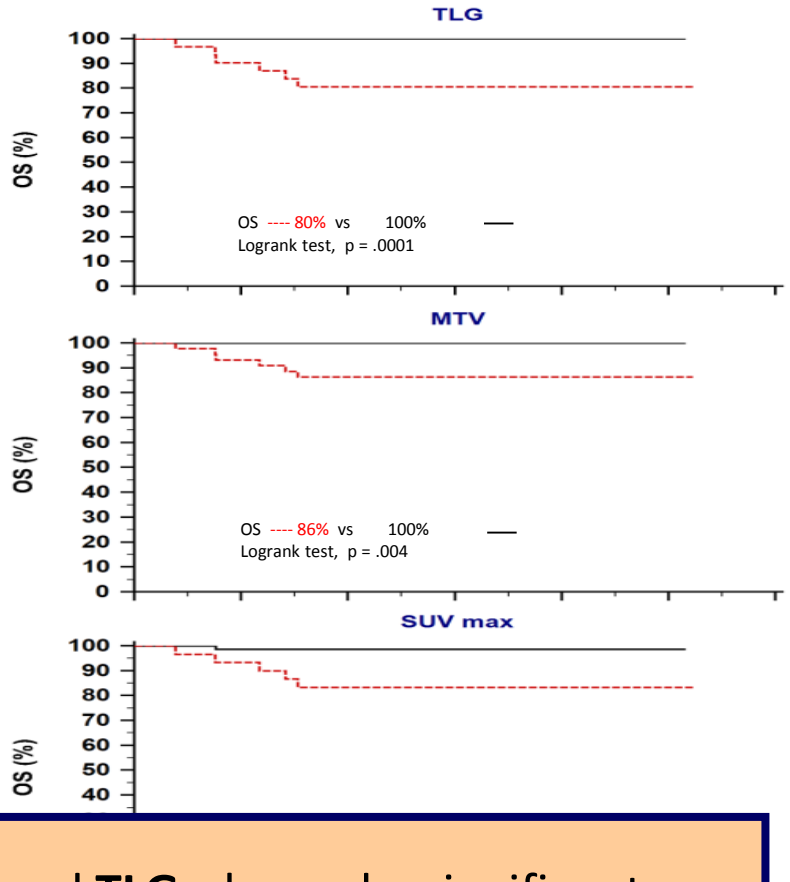
Prognostic value of the baseline functional PET parameters in PMBCL





An high value of **SUVmax**, **MTV** and **TLG** showed a significant prognostic impact for PFS at ***univariate analysis***

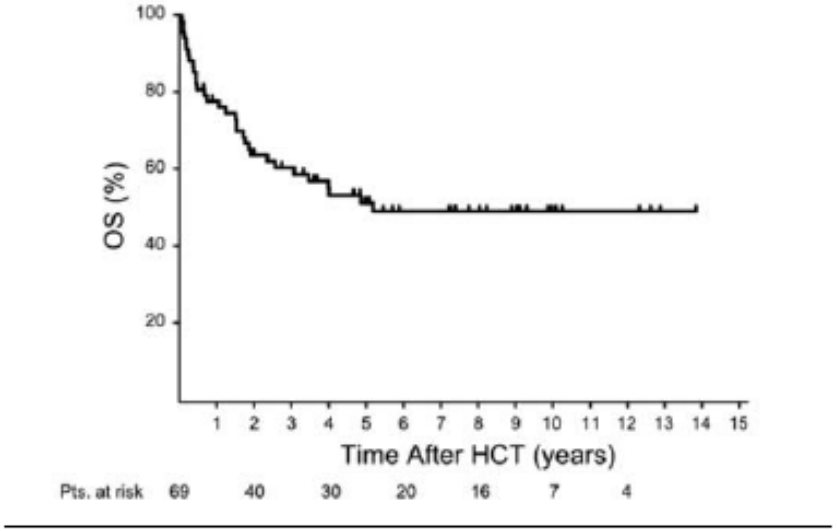
- Nella vostra pratica clinica I parametri quantitativi ***SUV max, MTV,TLG*** vengono riportati nella valutazione della PET basale ?

- Questi parametri potranno essere considerati nel futuro un valido e riproducibile fattore prognostico nella pratica clinica del paziente con HD e LNH?

ALLOGENEIC STEM CELL TRANSPLANTATION AND BRENTUXIMAB VEDOTIN IN RELAPSED/REFRACTORY HODGKIN LYMPHOMA: A MULTICENTER EXPERIENCE

DISCUSSION

Allo-HCT is a feasible and effective option for RR HL. In our series, the disease status at HCT was the main predictor of outcomes, primarily relapse. Furthermore, BV showed efficacy as a bridge to allo- HCT as well as post allo-HCT rescue.



Festuccia M et al 796 oral presentation

Linfomi: Report del gruppo di lavoro

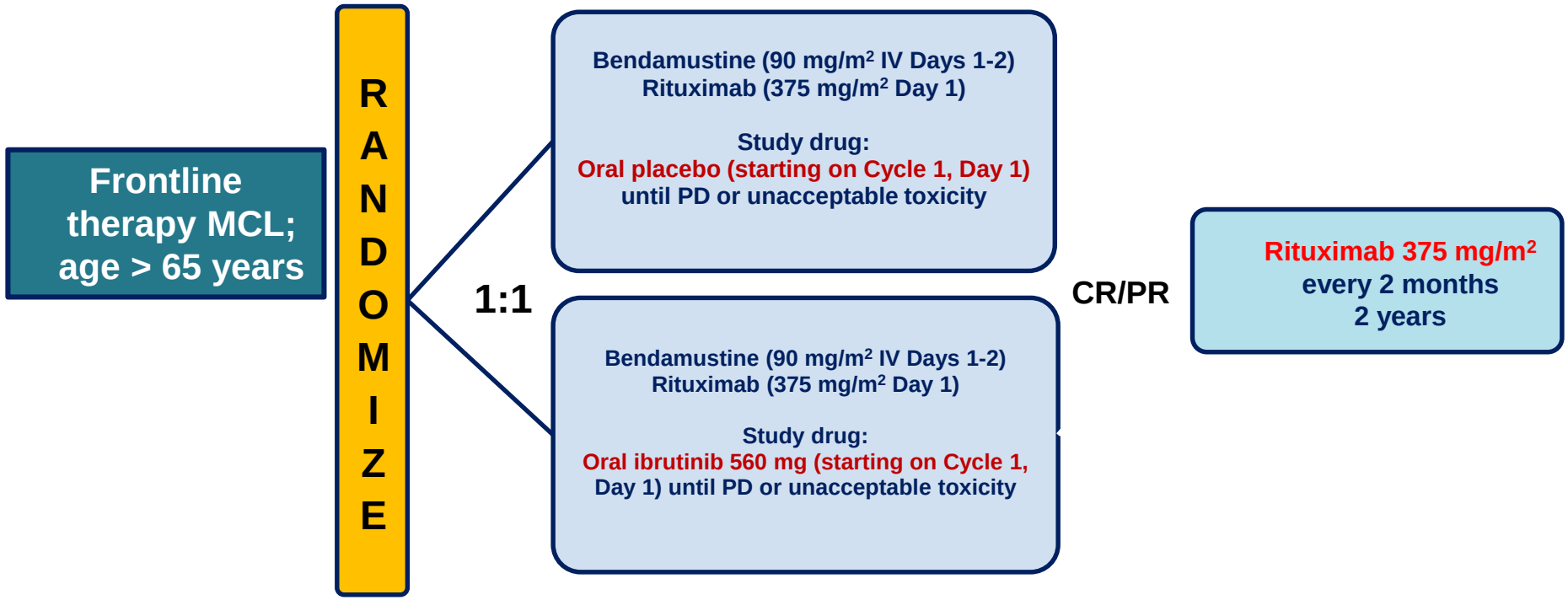
- Allo ASCT è la terapia standard del paziente con HD recidivato post ASCT?
- Aplo vs allo ASCT ?
- Brentuximab è considerato terapia bridge o post Allo ASCT ?

Grazie per la cortese attenzione ……

MCL3002 - study design (SHINE study)

Phase 3, randomized, double-blind, placebo-controlled study

N=520



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