FONDAZIONE ITALIANA LINFOMI

www.filinf.it

Luca Nassi

SCDU Ematologia
AOU Maggiore della Carità
Novara

FONDAZIONE ITALIANA LINFOMI

Relatore: Luca Nassi

www.filinf.it

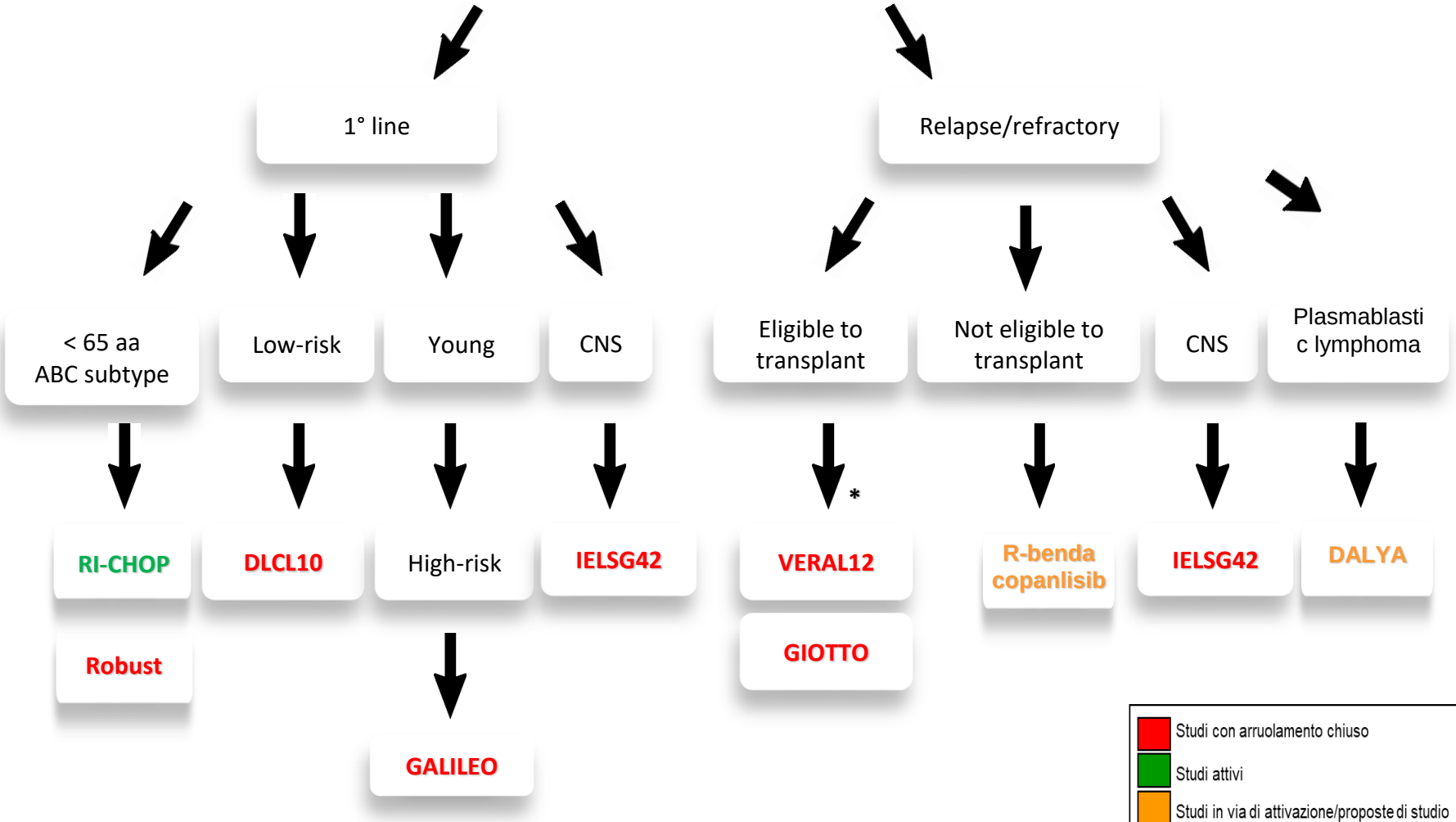
Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- **Posizione di dipendente in aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)**
- **Consulenza ad aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)**
- **Fondi per la ricerca da aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)**
- **Partecipazione ad Advisory Board (MSD, Takeda, Janssen)**
- **Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)**
- **Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)**

FONDAZIONE ITALIANA LINFOMI

www.filinf.it

DIFFUSE LARGE B-CELL LYMPHOMA DLBCL



Studi con arruolamento chiuso

Studi attivi

Studi in via di attivazione/proposte di studio

* Adesione su scelta del Centro

FONDAZIONE ITALIANA LINFOMI

FIL_RI-CHOP (ABC-DLBCL<65 y)

www.filinf.it

Phase II multicentric single arm study to evaluate the efficacy and safety of ibrutinib in combination to rituximab-CHOP followed by ibrutinib maintenance in untreated patients with Activated-B-Cell (ABC)-DLBCL at intermediate-high and high risk

Centro Coordinatore: Roma Sapienza

- (PI: Prof Maurizio Martelli)

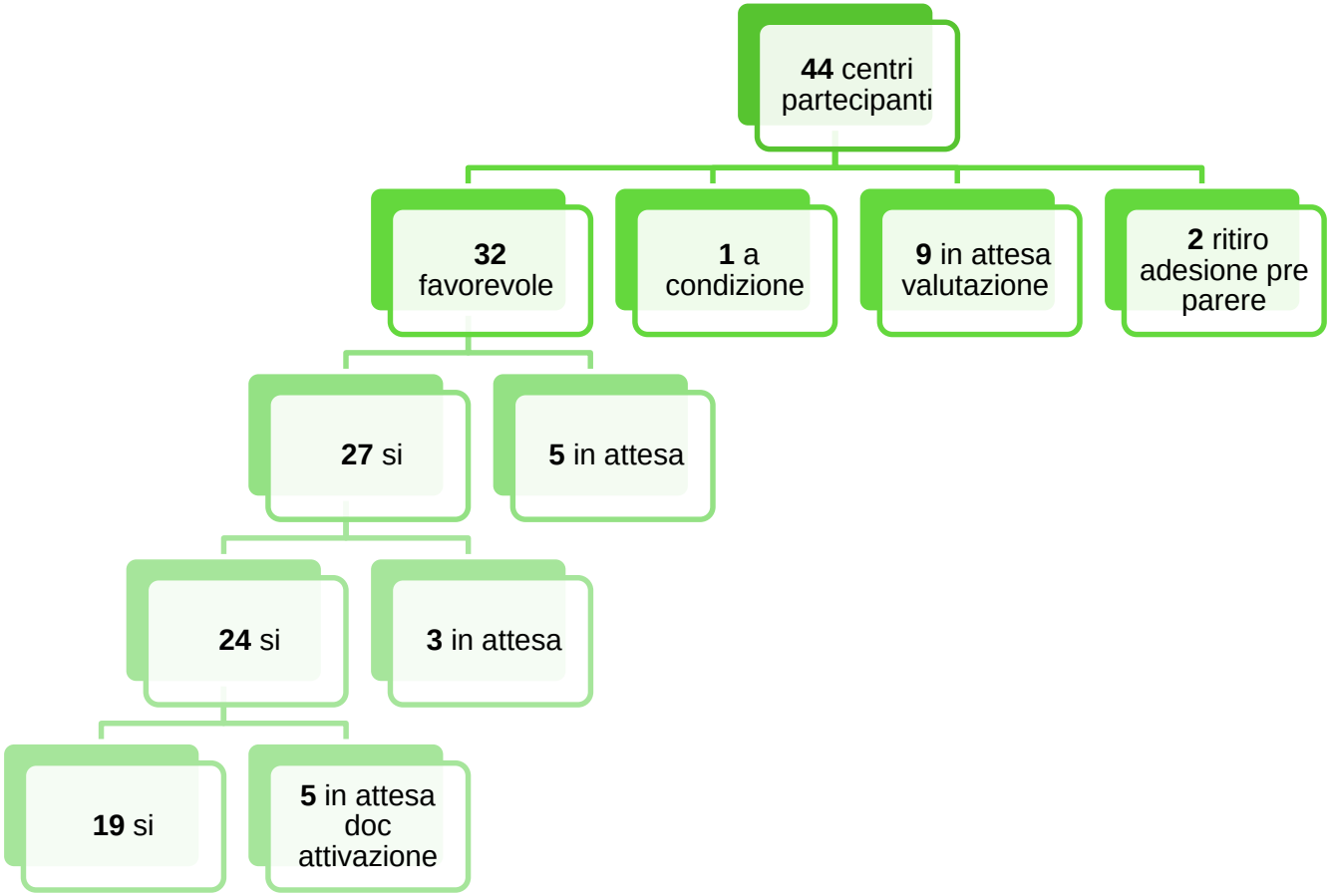
- Centri partecipanti: 42
- Arruolamento previsto: 90 pazienti
- Centri attivi/Centri partecipanti: 19/42
- Centri arruolanti/Centri attivi: 6*/19
- Pz screenati (step 1): 13/400
- Pz arruolati (step 2): 3/90

*Inclusi screening failure

FONDAZIONE ITALIANA LINFOMI

FIL_RI-CHOP: Status di attivazione

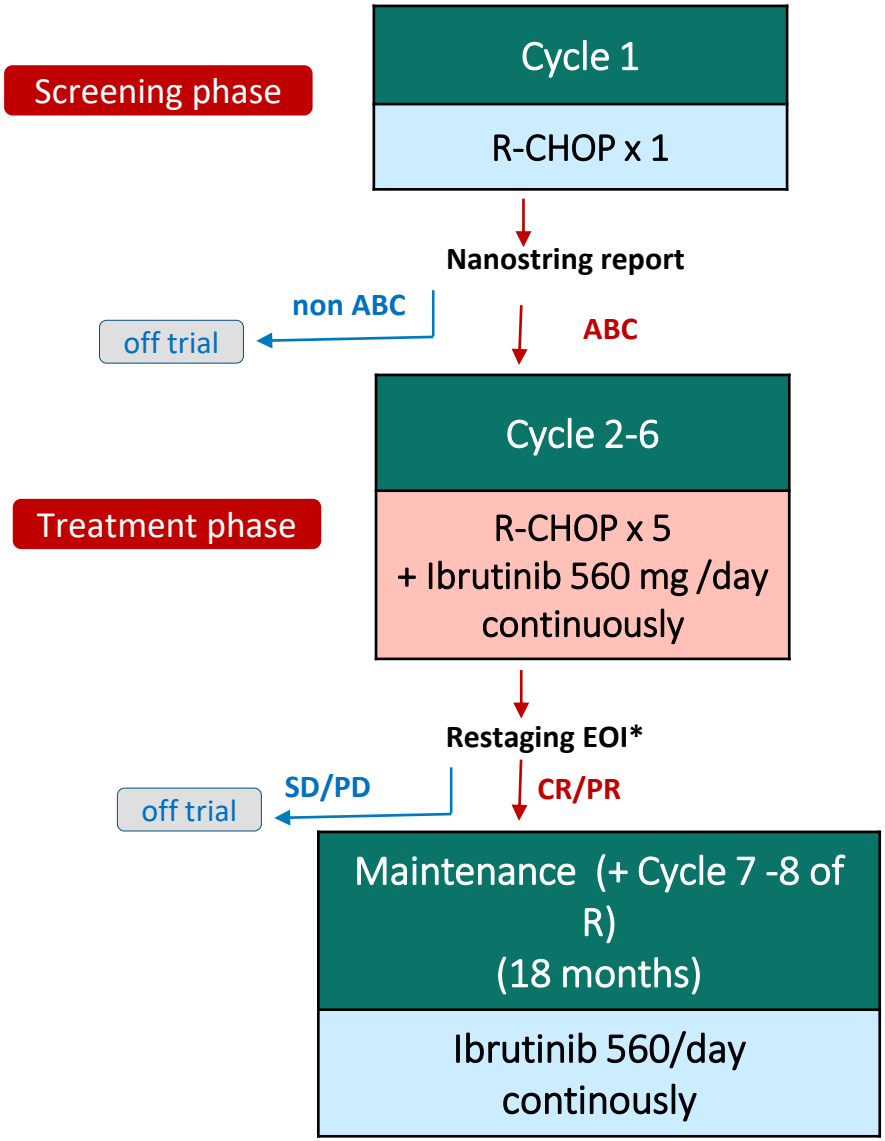
www.filinf.it



FONDAZIONE ITALIANA LINFOMI

FIL_RI-CHOP: Disegno dello Studio

www.filinf.it



Radiotherapy

- IFRT per local practice, such as for the treatment of a particular site of bulky disease (defined as ≥ 7.0 cm) or extranodal masses (bone, scrotum)
- As consolidation treatment, in all patients with focal PET positive residual disease, irrespective of initial tumor diameter

CNS prophylaxis

- For patients at high risk of CNS recurrence:

i.v. MTX x 2 cycles (q21 dd) : 3 g/m2 (with C7 e C8 R)

FONDAZIONE ITALIANA LINFOMI

FIL_RI-CHOP: Criteri inclusione ed esclusione

www.filinf.it

- Age 18-65 years old
- Histologically confirmed DLBCL
- ABC type defined by Lymph2Cx on the NanoString platform
- Previously untreated disease
- IPI score ≥ 2
- Ann Arbor stage II-IV
- Measurable disease ≥ 1.5 cm in the longest diameter, and measurable in 2 perpendicular dimensions
- Neutrophil count ≥ 1x10^9/L independent of GFs, PLT count ≥ 100000/mm3 (≥ 50000/mm3 if BM involvement)
- Creatinine ≤ 2xULN
- ALT or AST ≤ 3xULN
- Bilirubin ≤ 1.5 xULN (≤ 3xULN if Gilbert)
- Primary mediastinal B-cell Lymphoma (PMBCL)
- High grade B-lymphoma, NOS or double hit
- COO GCB after profiling
- LVEF < 50%
- HBsAg positive
- HBsAg negative, HBsAb positive and/or HBcAb positive with detectable viral DNA
- Active HCV infection
- HIV infectons
- History of stroke or intracranial hemorrage within the past 6 months
- Requirement of warfarin or equivalent vitamin K antagonists
- History of clinically relevant liver or renal insufficiency; significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, rheumatologic, hematologic, psychiatric, or metabolic disturbances

FIL_RI-CHOP: PO Arruolamento

www.filinf.it

Step 1: Screening Phase (circa 400 pazienti)

- Registrazione del paziente in CRF (assegnazione codice) dopo firma consenso
- Invio agli Uffici Studi FIL della Dichiarazione di idoneità Step 1 firmata dal Medico che ottiene il Consenso Informato del paziente alla fase di Screening
- Invio agli Uffici Studi FIL della copia debitamente anonimizzata del referto istologico
- Compilazione CRF dell'evento Screening e CRF Inclusion/Exclusion (dati clinici) Step1

- **Centralizzazione materiale bioptico (inclusione in paraffina) e campioni biologici**

Step 2: Treatment for ABC-DLBCL patients (90 pazienti)

- Dopo conferma centralizzata diagnosi di ABC-DLBCL
- Compilazione CRF Inclusion/Exclusion (dati istopatologici - 2nd Registration)
- Invio agli Uffici Studi FIL della Dichiarazione di idoneità Step 2 firmata dal Medico che ottiene il Consenso Informato del paziente alla partecipazione allo studio

FONDAZIONE ITALIANA LINFOMI

FIL_RI-CHOP: Campioni biologici

www.filinf.it

- **Saliva invio campione solo al baseline**
- **Sangue venoso periferico (1 provetta siero + 3 BCT) e urine**

Timepoint	Patients
Baseline	*All screened patients (400)*
Cycle 2 Day 1	*All ABC patients*
Cycle 3 Day 1	*All ABC patients*
3-4 wks after last induction cycle start	*All ABC patients*
At restaging 12 mos after maintenance start	*Only ABC patients in CR/PR after induction*
Follow-up: at restaging 6 mos after the EOT	*Only ABC patients in CR/PR after induction*
Early withdrawal (any time)	*All ABC patients*
Relapse/PD (any time)	*All ABC patients*

La FIL fornisce i kit per la raccolta del materiale biologico

FIL_RI-CHOP: Revisione PET

www.filinf.it

I centri PET partecipanti allo studio devono avere effettuato preventivamente il Clinical Trial Qualification (CTQ) tramite il Core Lab.

Cosa inviare?

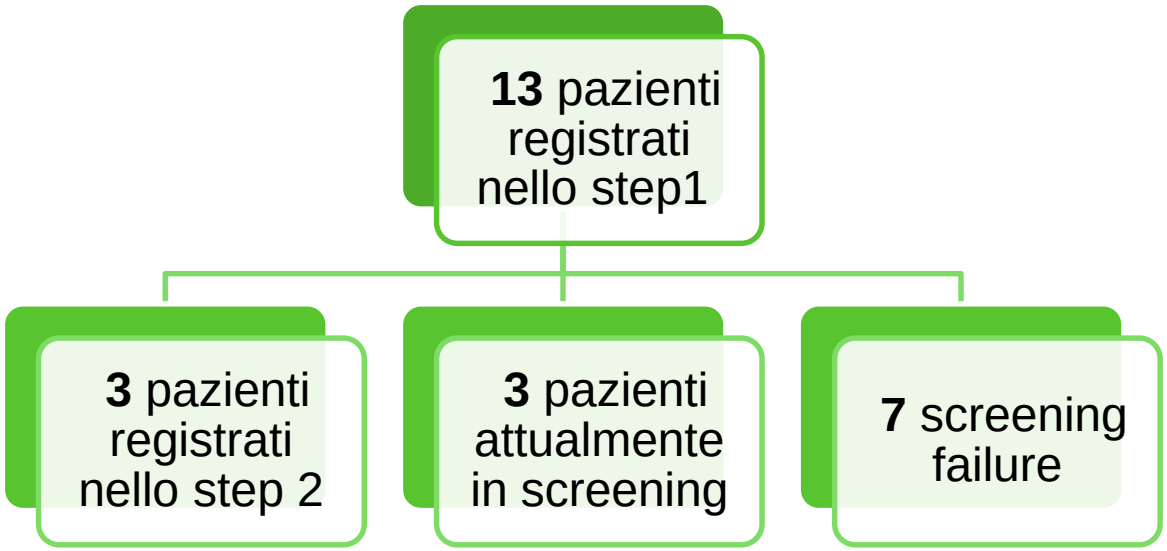
- **Baseline** (PET-0)
- **End of Induction** (PET-EOI) 3-4 settimane dopo l'inizio del sesto ciclo d RCHOP21 in combinazione con Ibrutinib o nel momento in cui il trattamento viene interrotto per qualsiasi ragione.
- **Mantenimento** (PET-3M) dopo 3 mesi di mantenimento con Ibrutinib solo per i pazienti in RP a fine induzione

Le immagini PET anonimizzate, in formato DICOM, complete di peso e altezza del paziente, e raccolte in una cartella compressa, sono caricate sulla piattaforma web WIDEN:

https://trials.widen.it/richop

Comunicazione dei risultati:
-PET-EOI: invio mail automatica dall'indirizzo no-reply@widen.it agli Uffici Studi FIL e ai Centri.
-PET-3M: blinded, nessuna comunicazione ai centri.

FIL_RI-CHOP: Arruolamento



- ✓2 DLBCL non ABC
- ✓2 diagnosi non confermate
- ✓Non compliance
- ✓FEV< 50%
- ✓Materiale istologico scarso

FONDAZIONE ITALIANA LINFOMI

IELSG45 FIORELLA Trial

www.filinf.it

Randomized Phase II Trial on Fitness- and Comorbidity- Tailored Treatment in Elderly Patients with Newly Diagnosed Primary CNS Lymphoma

Centro Coordinatore: IRCCS Ospedale San Raffaele

Prof. Andrés Ferreri

- **Centri partecipanti:** 47 in 6 differenti Nazioni (Denmark, Finland, Germany, Israel, Italy, Switzerland). **In Italia 28** centri partecipanti.
- **Centri attivi in Italia: 8/28**
- ***First Patient In*: 18/06/2019**
- **Pazienti arruolati in Italia: 1** (IRCCS Ospedale San San Raffaele)
- **Pazienti arruolati**: 2/208

Target population

- Age ≥70 years
- Pts not eligible for high-dose chemotherapy supported by autologous stem cell transplant
- ECOG PS ≤3

End point primario

A 2-years Progression Free Survival (PFS)

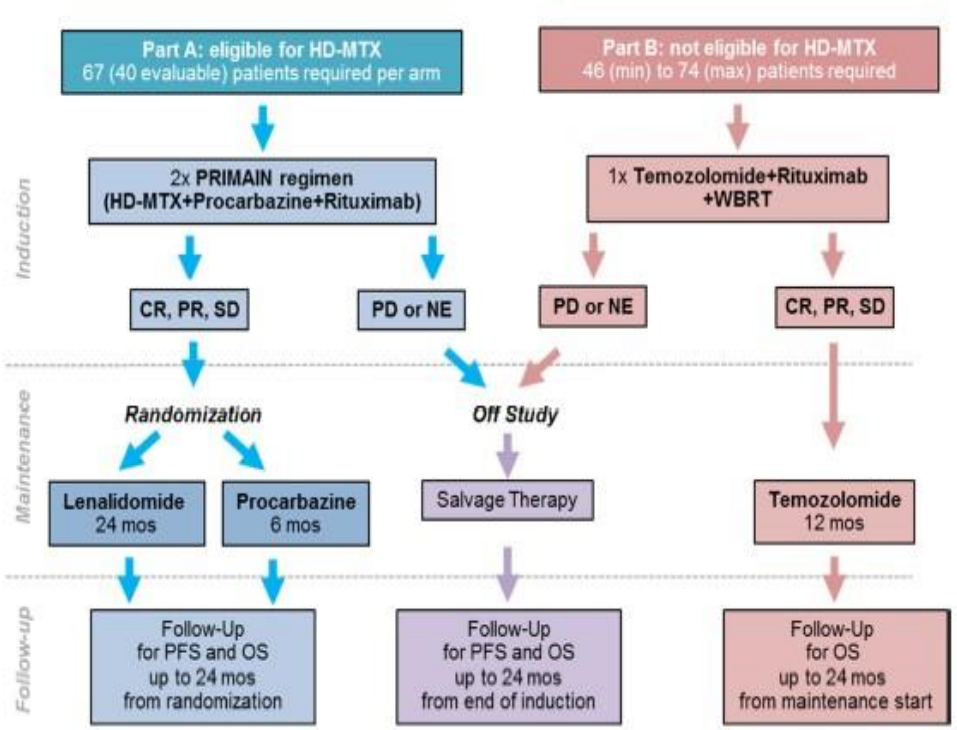
IELSG45 Disegno Studio

All PCNSL pts ≥ 70 years old

Trial registration

Eligible for therapy (PS ≤3 – Not eligible for ASCT)

Ineligible for therapy



ONLY DATA COLLECTION

Part A

To compare the efficacy and tolerability of a new oral lenalidomide maintenance treatment with that of the oral procarbazine maintenance currently in use.

Part B

To evaluate the efficacy and tolerability of concomitant chemo-immunoradiotherapy administered as induction treatment followed by temozolomide maintenance.

FONDAZIONE ITALIANA LINFOMI

www.filinf.it

STUDI IN CORSO DI APERTURA

FONDAZIONE ITALIANA LINFOMI

www.filinf.it

Multicentric single arm phase II trial to investigate the efficacy (in terms of PFS) of the combination regimen Rituximab–Bendamustine in association with Copanlisib in patients affected by relapsed refractory DLBCL, not eligible to HDC and ASCT or to CART-Cell or relapsed after intensified regimens.

PRINCIPAL INVESTIGATOR: Umberto Vitolo, Torino, Italy
CO-PI: Grzegorz S. Nowakowski, Rochester, MN, USA

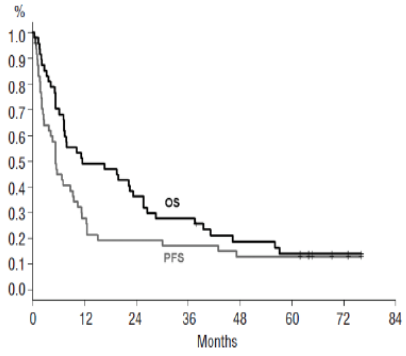
WRITING COMMITTEE AND SCIENTIFIC SUPPORT:
U. Vitolo, G. Nowakowski, A. Chiappella, T. Witzig, M. Novo, A. Castellino, G. Ciccone, M. Balzarotti, M. Martelli, M. Spina.

Background and Rationale

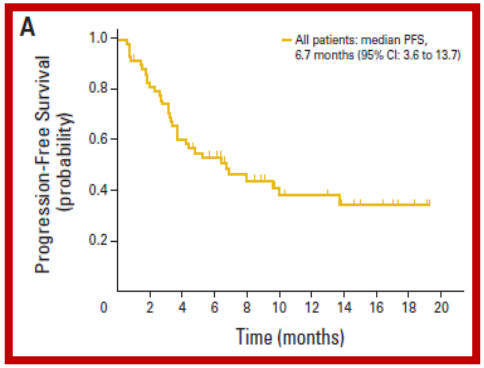
www.filinf.it

REGIMEN	N	Median age	ORR %	CR %	PFS	Reference
R-GEMOX	49	69	46	38	5-yrs 12.8%	Mounier N, Haematol 2013
R-Bendamustine	59	67	63	37	Median 6.7 mo	Ohmachi K, L Clin Oncol 2013
	55	76	50	28	Median 8.8 mo	Arcari A, Leuk Lymphoma 2015
	39	71	33	20	Median 2.0 mo	Sehn L, ePub JCO 2019 (st. arm)
Pixantrone	70	60	37	20	Median 5.3 mo	Pettengel R, Lancet Oncol 2012
Lenalidomide	49	65	35	12	Median 4 mo	Wiernik PH, JCO 2008

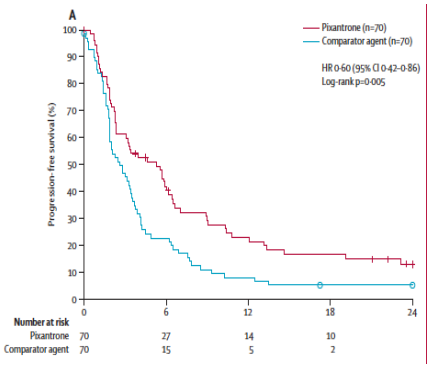
R-GEMOX



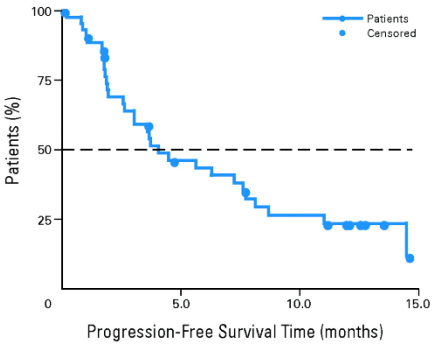
R-BENDAMUSTINE



PIXANTRONE



LENALIDOMIDE



Background and Rationale

www.filinf.it

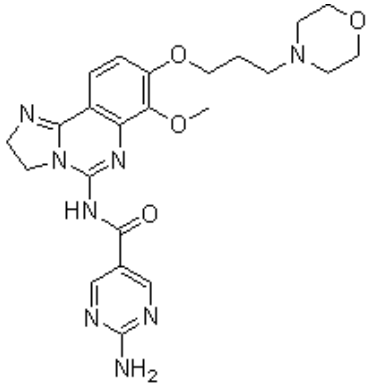
Copanlisib (BAY 80-6946)

pan-Class I PI3K inhibitor, predominant activity against the ⟨ and ™ isoforms

PI3Kδ isoform: B-cell signaling, development and survival

PI3K⟨ isoform upregulation may contribute to resistance mechanism in lymphoma cells

metabolized by the cytochrome P450 (CYP) 3A4 and CYP1A1: lower risk for clinical drug-drug interactions in combination regimens



R/R Indolent lymphoma:

- Single-agent: ORR of 59%, mPFS 12 m
- Phase III: R-Bendamustine + Copanlisib/placebo is safe and feasible

R/R Aggressive lymphoma:

- Single-agent (MCL+DLBCL+PTCL): ORR 27%, 1y PFS 13%
- DLBCL: ORR 25%, CR 12.5%; suggested higher efficacy in ABC (ORR 35%, CR 25%)

Dreyling et al, 2017; Patnaik et al, 2016, Gerecitano et al, 2017; Lenz et al, 2017

FONDAZIONE ITALIANA LINFOMI

Study endpoints

www.filinf.it

- **Multicentric single arm phase II trial** to investigate the efficacy (in terms of PFS) of the combination regimen Rituximab–Bendamustine in association with Copanlisib in patients affected by relapsed refractory DLBCL, not eligible to HDC and ASCT or to CART-Cell or relapsed after intensified regimens.
- **Primary objective:** To explore the improvement of PFS by adding Copanlisib to Rituximab-Bendamustine in Relapsed-Refractory Diffuse Large B-cell Lymphoma
- **Primary endpoint: Progression-free survival (PFS) at 12 months**
- **Secondary Endpoints:** Overall Survival (OS), Overall Response Rate (ORR), complete response (CR), duration of response (DOR), conversion rate from SD/PR to PR/CR with maintenance, safety of the Copa-BR combination
- **Exploratory analysis:**
  - ORR, PFS and OS by cell-of origin subtypes (GCB e ABC)
  - ORR, PFS and OS by *MYC/Bcl2/Bcl6* rearrangements
  - Other exploratory analysis (biological, imaging, QoL): TBD

FONDAZIONE ITALIANA LINFOMI

Inclusion criteria

www.filinf.it

- Age > 18 years old
- Histologically confirmed DLBCL (de-novo DLBCL or DLBCL transformed by indolent lymphoma; double hit lymphoma can be included); new biopsy at relapse time is recommended, but not mandatory.
- Relapsed (recurrence after complete response or presented progression after partial response) or progressed after at least ≥ 1 (but ≤ 3) prior lines of therapy, including rituximab-based immunochemotherapy.
- Not eligible to high-dose chemotherapy and ASCT, or relapsed after that.
- Not eligible to CAR-T therapy, or relapsed after that.
- Measurable disease.
- Acceptable organ function.
- Primary mediastinal B-cell Lymphoma (PMBCL).
- High grade B-lymphoma NOS (other morphology).
- Prior treatment with Bendamustine (subjects treated > 24 months before, with a response > 1 year to bendamustine containing regimen, will be eligible).
- Prior treatment with Copanlisib.
- Prior treatment with Idelalisib or other PI3K inhibitors (< 28 days before start of treatment, unless evidence of progression since last treatment).
- Prior allogeneic bone marrow or organ transplant.
- Uncontrolled arterial hypertension despite optimal medical management.
- HbA1c> 8.5%.

FONDAZIONE ITALIANA LINFOMI

Study design

www.filinf.it

INDUCTION PHASE

Refractory/relapsed DLBCL (local diagnosis)

Screening phase

Treatment phase

Copa-BR: 6 cycles q28 days

Copanlisib:	60 mg/day i.v. days 1,8,15
Rituximab:	375 mg/m² i.v. day 1
Bendamustine:	90 mg/m² i.v. days 1,2

Restaging after 2 cycles SD/PR/CR → cycles 3 and 4

Restaging after 4 cycles SD/PR/CR → cycles 5 and 6

Restaging after 6 cycles SD/PR/CR

PD or unacceptable toxicity → STOP

MAINTENANCE

Maintenance with copanlisib

Copanlisib

60 mg/day days 1 and 15

every 28 days

up to 12 cycles

Response assessment

Induction phase

- CT every 8 weeks (after cycle 2, 4 and 6)
- PET + CT at the end of induction (EOI)

Maintenance

- CT (+ PET if PR/SD at EOI) every 4 months
- CT + PET at the end of maintenance/treatment (EOT)

Follow-up

- CT at 6 and 12 months after EOT

Biological assessment

- To be defined

Timeline and accrual

- **Study start :** Q1 2020
- Duration of the study: ~ 3.5 years (12 months for patients screening and to complete accrual of DLBCL patients + 6 months for induction treatment completion of the last patient entered, + 12 months of maintenance completion of the last patient registered and eligible for maintenance, + a minimum follow-up for 12 months)

- **Accrual:** 81 patients
- Participants: 30 FIL centers + Mayo Clinic, Rochester, MN, US
- Data collection**:** REDCAP – www.ricercatori.filinf.it
- Drugs: Rituximab, Bendamustine and Copanlisib will be provided free by FIL

FONDAZIONE ITALIANA LINFOMI

www.filinf.it

An Open Label, Phase 2 Study to Evaluate Activity and Safety of Daratumumab in combination with Bortezomib and Dexamethasone in patients with Relapsed or Refractory Plasmablastic Lymphoma (DALYA trial)

Andrés J. M. Ferreri, Ospedale San Raffaele, Milano
Michele Bibas, Ospedale Spallanzani, Roma
Alessandro Re, Spedali Civili, Brescia
Michele Spina, Centro di Riferimento Oncologico (CRO), Aviano

Rational of bortezomib in PBL

www.filinf.it

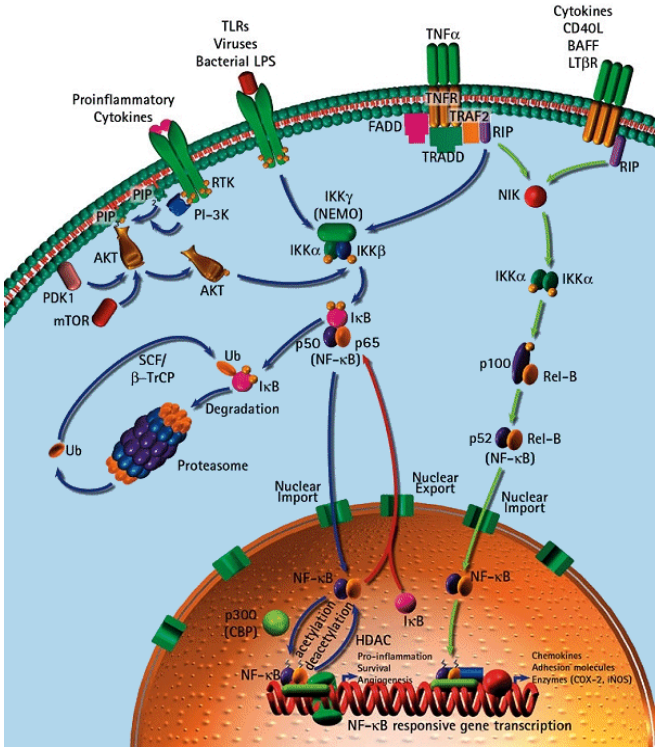
Bortezomib interferes with NF-kB, which plays a role in ABC-DLBCL

Bortezomib has been shown to be a potent activator of gamma-herpesvirus lytic cycle and lytic activation of viruses latently infecting tumors represent a strategy of antineoplastic therapy

Bortezomib is effective in MM pts. Xbp1 e Blimp1 expression is associated with the efficacy of bortezomib in MM pts

Several case reports suggest efficacy of Bortezomib in first and second line, alone or in combo, in PBL

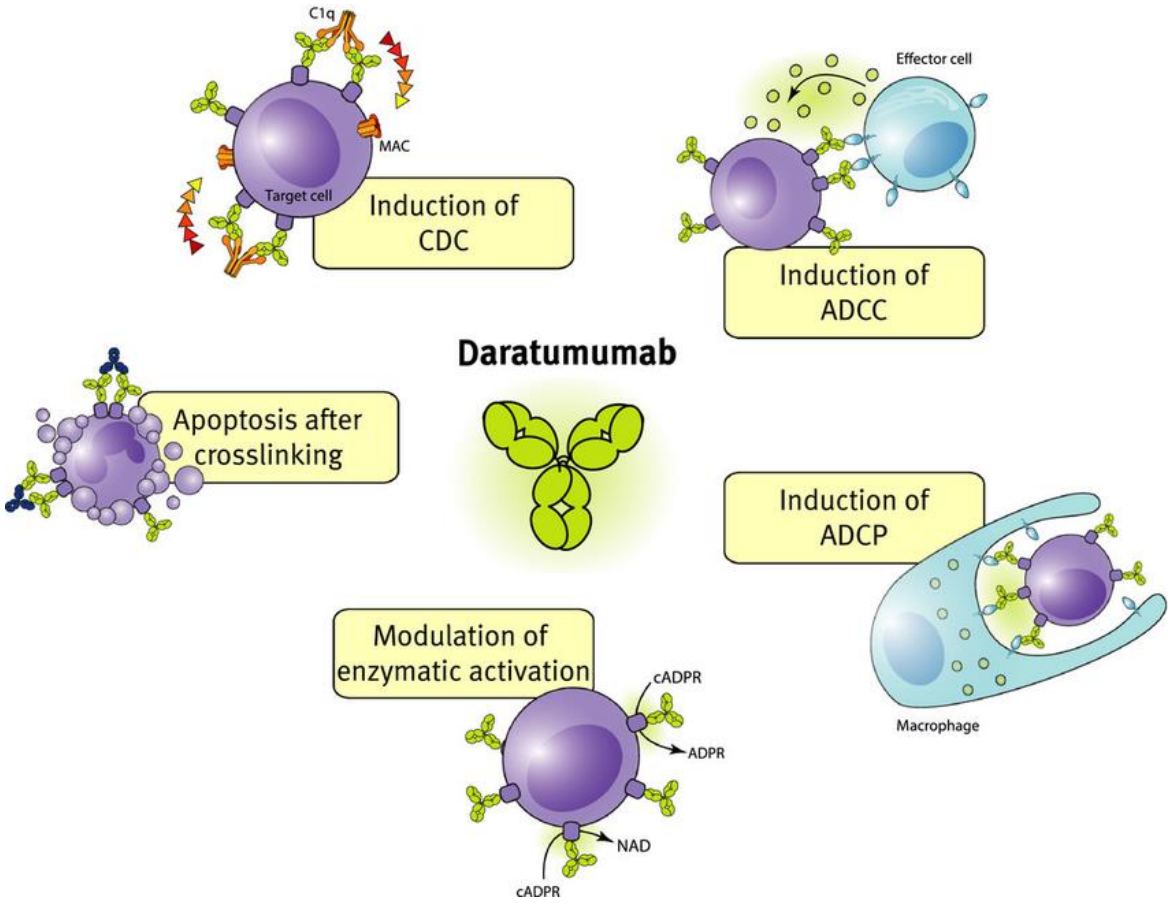
BLOOD, 9 JUNE 2011 • VOLUME 117, NUMBER 23



FONDAZIONE ITALIANA LINFOMI

Targeting CD38 (~90% PBL are CD38+)

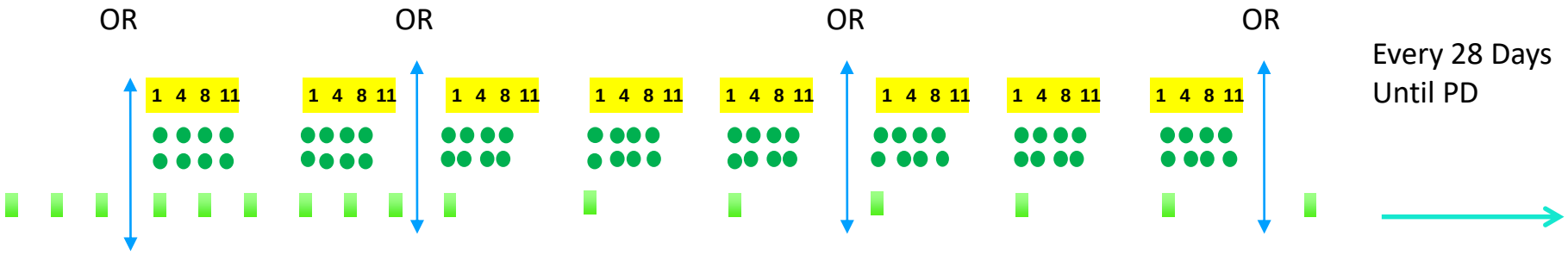
www.filinf.it



Trial design and endopoints

www.filinf.it

Daratumumab 16 mg/kg
Dexametazone 20 mg — **DVd**
1 4 8 11 **Bortezomib 1,3 mg/m² SC**



Primary endpoint: ORR (CR+PR)

Primary objective: to improve the ORR from 15% to 35% with the combination Dara + Velcade + Dexa (DVd)

Secondary endpoints: PFS, OS, DoR, toxicity

FONDAZIONE ITALIANA LINFOMI

Main inclusion criteria

www.filinf.it

- Histologically confirmed plasmablastic lymphoma (WHO 2016)
- CD38+ (>1% positive cells by IHC)
- Patients with plasmablastic lymphoma relapsed or refractory:
- after at least one line of conventional-dose chemotherapy +/- ASCT
- after at least one line of conventional-dose chemo and not eligible for transplantation
- ECOG Performance Status ≤ 3
- Age ≥ 18 years
- HIV-negative and HIV-positive
- HIV infection responsive to ongoing cART
- No active hepatitis B or C
- No CNS involvement
- At least one measurable disease lesion

FONDAZIONE ITALIANA LINFOMI

Ancillary biological and molecular studies

www.filinf.it

Hypotheses

- The anti-CD38 antibody may modulate CD4 and CD8 T-cell homeostasis, inflammatory environment and reduce the frequency of regulatory cells
- During HIV infection an increase of regulatory cells has been reported
- EBV or CMV may play a role in the PBL occurrence. The lack of specific immunity both in the periphery and in the tumor may contribute to the pathogenesis

Objectives

- To evaluate the effect of Daratumumab treatment on
- CD4 and CD8 T cell homeostasis
- Regulatory cells (MDSC and Treg) homeostasis
- inflammatory cytokines profile
- Evaluate the effect of Daratumumab treatment on functional properties of HIV-specific, EBV-specific and CMV-specific T cells
- To analyze the lymphocyte infiltrating the PBL

FONDAZIONE ITALIANA LINFOMI

Involved centers

www.filinf.it

1. Unità Linfomi, Ospedale San Raffaele, Milano (Andrés J.M. Ferreri) Centro Coordinatore
2. I.N.M.I. "L. Spallanzani", Roma (Michele Bibas) Centro Coordinatore
3. Ematologia, ASST Spedali Civili, Brescia (Alessandro Re)
4. Oncologia Medica A, CRO, Aviano (Michele Spina)
5. A.O. Universitaria Careggi, Firenze (Benedetta Puccini)
6. S.C. Oncologia Medica, Ospedale San Paolo, Milano (Daris Ferraris)
7. A.O. San Gerardo, Monza (Luisa Verga)
8. U.O. Ematologia 2, AOU. Città della Salute e della Scienza, Torino (Barbara Botto)
9. Ematologia, USL di Piacenza (Annalisa Arcari)
10. S.C. Oncoematologia, A.O. Santa Maria, Terni (Anna Marina Liberati)
11. Ematologia, AO di Ancona, Ancona (Guido Gini)
12. Ematologia, ASST Niguarda, Milano (Emanuele Ravano)
13. Ematologia, A.O. di Verona, Verona (Carlo Visco)
14. Ematologia, ASMN, Reggio Emilia (Francesco Merli)
15. Ematologia, Ospedale Treviso (Piero Maria Stefani)
16. UOC Oncologia, Ospedale dei Colli, Napoli (Vincenzo Montesarchio)
17. Ematologia, Policlinico Paolo Giaccone, Palermo (Salvatrice Mancuso)
18. Ematologia, San Camillo, Roma (Luigi Rigacci)
19. Ematologia, San Matteo, Pavia (Luca Arcaini

FONDAZIONE ITALIANA LINFOMI

www.filinf.it

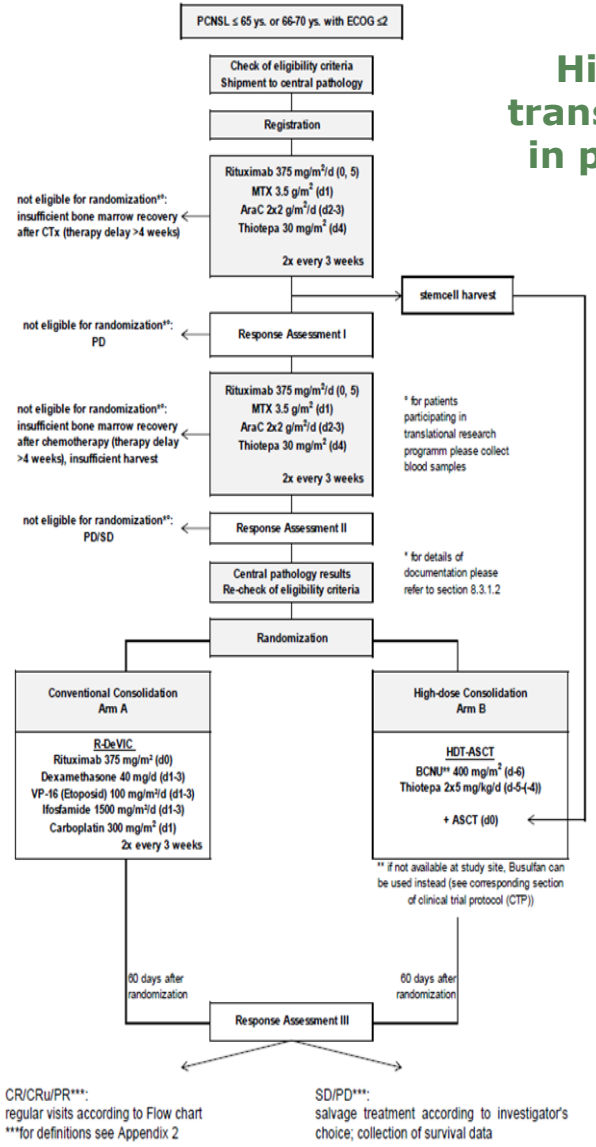
STUDI CON ARRUOLAMENTO CHIUSO

FONDAZIONE ITALIANA LINFOMI

IELSG43 MATRIX Trial

www.filinf.it

High-dose chemotherapy and autologous stem cell transplant or consolidation conventional chemotherapy in primary CNS lymphoma-randomized phase III trial



- <u>Centro Coordinatore</u>: IRCCS Ospedale San Raffaele – Prof. Andrés Ferreri
- Centri attivi/Centri partecipanti: 35/39
- Centri arruolanti/Centri attivi: 16* /35
- Pazienti arruolati: 47 (in Centri FIL)
- <u>DATI GLOBALI</u>

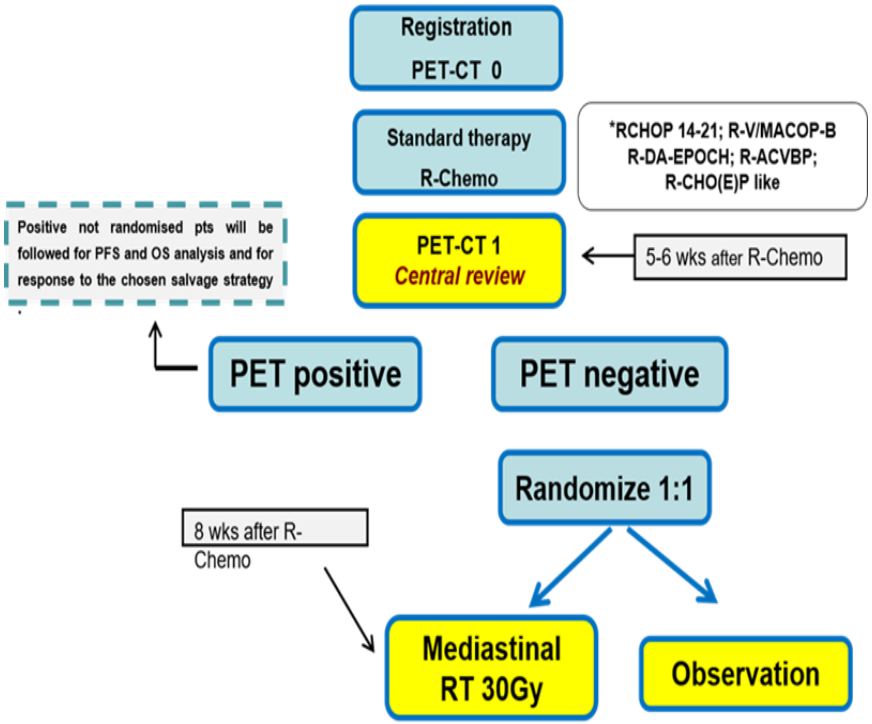
Pazienti arruolati: 347/330

FONDAZIONE ITALIANA LINFOMI

IELSG37

www.filinf.it

A randomized, open-label, multicentre, two-arm phase III comparative study assessing the role of mediastinal radiotherapy after Rituximab containing chemotherapy regimens to patients with newly diagnosed Primary Mediastinal Large B-Cell Lymphoma (PMLBCL)



<u>Centro Coordinatore</u>: Dipartimento di Biotecnologie Cellulari ed Ematologia, Università "La Sapienza" - Prof. Martelli

- **In data <u>05 agosto 2019</u>: CHIUSURA ARRUOLAMENTO**

540 pazienti arruolati

FONDAZIONE ITALIANA LINFOMI

Phase II randomized study with R-DHAP +/- Bortezomib as induction therapy in relapsed/refractory DLBCL patients eligible to transplantation BR-DHAP versus R-DHAP

www.filinf.it

PIs: Dr . U. Vitolo, Dr. M. Balzarotti, Dr. A. Chiappella

First relapse randomisation
Stratification : Relapsed/refractory

- I R-DHAP
- I BR-DHAP
- II R-DHAP
- II BR-DHAP

Stratification : Relapsed / Refractory

CT mandatory, PET recommended

Restaging, mobilization and harvest

- I R-DHAP
- I BR-DHAP
- II R-DHAP
- II BR-DHAP

CT mandatory, PET recommended

NR/PD off therapy

Pre-ASCT evaluation

CT and PET mandatory

First patient enrolled: 22/10/2012

Last patient enrolled: 21/11/2018

Primary endpoint: to demonstrate an increase of Complete Response for BR-DHAP vs R-DHAP (50% vs 30%) before ASCT

Sample size: 108 patients, 54 for each arm

Bortezomib sc 1.5 mg/sqm, day 1 and day 4.

FONDAZIONE ITALIANA LINFOMI

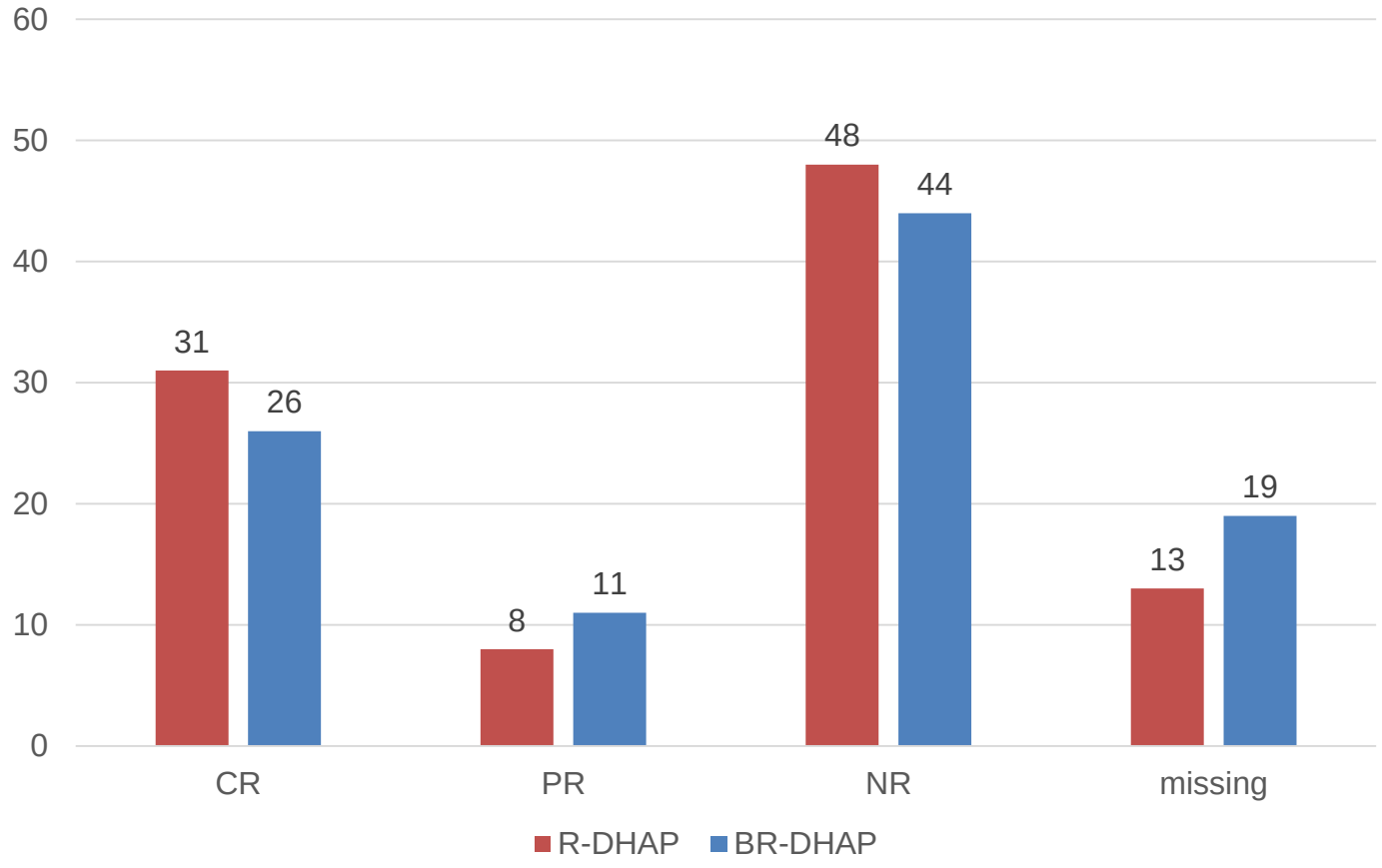
Clinical characteristics

www.filinf.it

	R-DHAP (54)	BR-DHAP (54)	TOTAL (108)
Median age (IQR)	57.6 (49-62.1)	55 (45.5-62)	56.6 (47.9-62.1)
Stage III/IV	42 (78%)	40 (74%)	82 (76%)
LDH UNL	28 (51.9%)	21(38.9%)	49(45.4%)
BM +	4 (7.4%)	4 (7.4%)	8 (7.4%)
Refractory	25 (46%)	21 (39%)	46 (43%)
Median time to relapse (IQR) months	2.6 (1-9.1)	3.9 (0.9-14.5)	2.9 (0.9-12.6)

Clinical response after 4 cycles

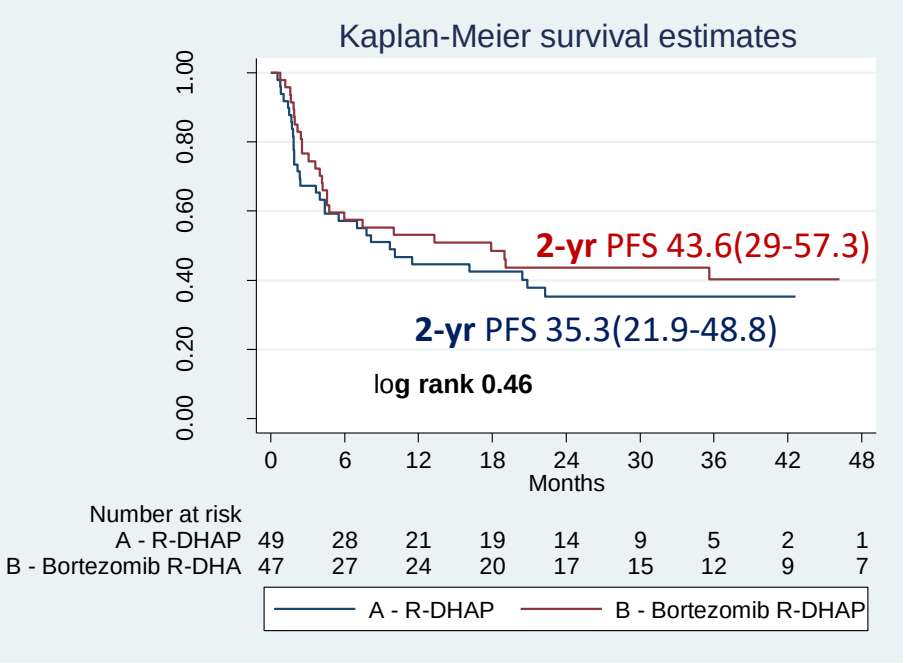
Final response



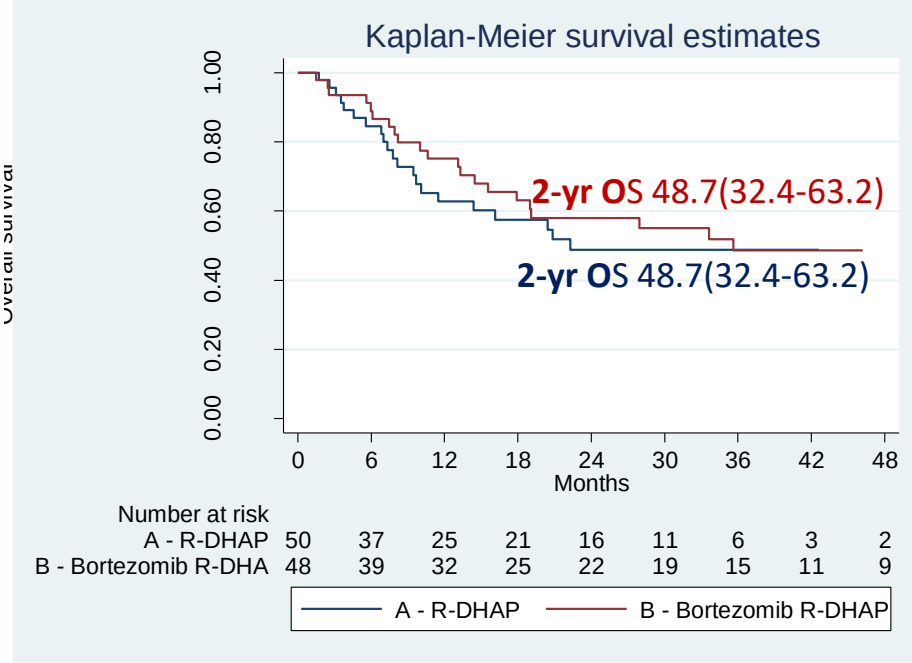
Outcome, median FU 29 months (8-41)

www.filinf.it

PFS



OS

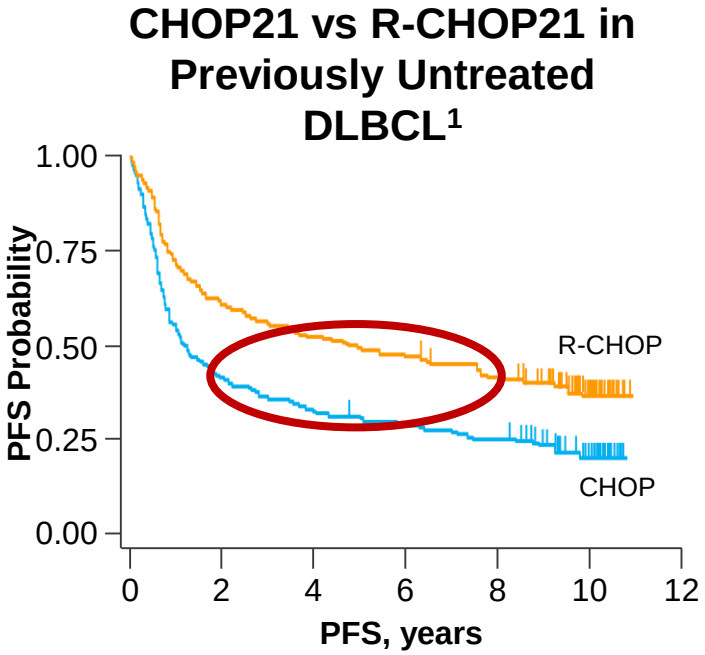


ROBUST: First Report of Phase III Randomized Study of Lenalidomide/R-CHOP (R^2-CHOP) vs Placebo/R-CHOP in Previously Untreated ABC-Type Diffuse Large B-Cell Lymphoma

Umberto Vitolo, MD;[1] Thomas E. Witzig, MD;[2] Randy D. Gascoyne, MD;[3] David W. Scott, MBChB, PhD;[3] Qingyuan Zhang, MD;[4] Wojciech Jurczak, MD, PhD;[5] Muhit Özcan, Prof Dr;[6] Xiaonan Hong, MD;[7] Jun Zhu, MD;[8] Jie Jin, MD;[9] David Belada, MD;[10] Juan Miguel Bergua, MD;[11] Francesco Piazza, MD;[12] Heidi Mócikova, MD;[13] Anna Lia Molinari, MD;[14] Dok Hyun Yoon;[15] Federica Cavallo, MD;[16] Monica Tani, MD;[17] Koji Izutsu, MD;[18] Koji Kato, MD;[19] Myron Czuczman, MD;[20] Sarah Hersey;[20] Adrian Kilcoyne, MD;[20] Jacqueline Russo;[20] Krista Hudak, PharmD;[20] Jingshan Zhang, PhD;[20] Annalisa Chiappella, MD;[1] and Grzegorz S. Nowakowski, MD;[2] on behalf of the ROBUST study investigators

atology, A.O.U. Città della Salute e della Scienza Hospital and University, Torino, Italy; [2]Division of Hematology, Mayo Clinic, Rochester, MN, USA; [3]Centre for Lymphoid Cancer, British Columbia Cancer, Vancouver, British Columbia, niversity Cancer Hospital, Harbin, Heilongjiang, China; [5]Department of Hematology, Jagiellonian University, Krakow, Poland; [6]Department of Hematology, Ankara University, Ankara, Turkey; [7]Cancer Hospital, Fudan University, Shang ospital, Beijing, China; [9]The First Affiliated Hospital of Medical School of Zhejiang University, First Hospital of Zhejiang Province, Hangzhou, Zhejiang, China; [10]Fourth Department of Internal Medicine-Hematology, Charles University H icine, Hradec Králové, Czech Republic; [11]Servicio de Hematologia, Hospital Universitario San Pedro de Alcántara, Cáceres, Spain; [12]Division of Hematology, Department of Medicine, University of Padova and Azienda Ospedaliera di P [13]Department of Internal Medicine and Haematology, Faculty Hospital Kralovske Vinohrady, Prague, Czech Republic; [14]UO Ematologia, Ospedale Degli Infermi, Rimini, Italy; [15]Department of Oncology, Asan Medical Center, University e, Seoul, South Korea; [16]AOU Città della Salute e della Scienza di Torino, Turin, Italy; [17]U.O. Ematologia, Dipartimento Oncologia e Ematologia, Ospedale Santa Maria delle Croci, Ravenna, Italy; [18]National Cancer Center Hospital, To [19]Department of Medicine and Biosystemic Science, Kyushu University Faculty of Medicine, Fukuoka City, Japan; and [20]Clinical Research & Development and Precision Medicine/CDx, Celgene Corporation, Summit, NJ, USA

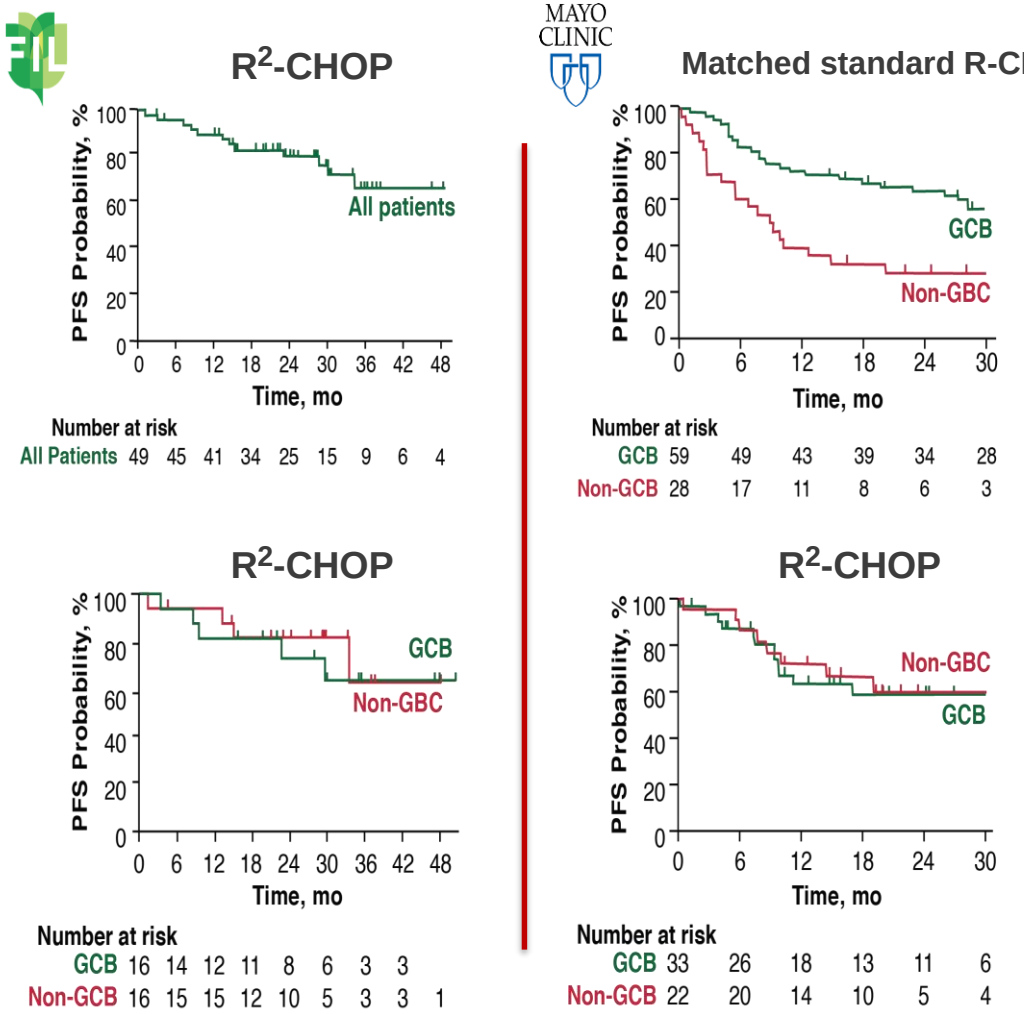
Evolving Induction Treatment With R-CHOP + Novel Drugs



Target	Randomized Phase II/III Studies	n	R-CHOP ±	Primary Endpoint Outcome
NF-κB	PYRAMID[2]	399	Bortezomib	No PFS improvement in non-GCB DLBCL
NF-κB	REMoDL-B[3]	201	Bortezomib	No PFS improvement in GCB/ABC DLBCL
CD20	GOYA[4]	1418	GA101-CHOP vs R-CHOP	No PFS improvement
BTK	PHOENIX[5]	838	Ibrutinib	No EFS improvement in non-GCB DLBCL
Cereblon	*ROBUST*	*570*	*Lenalidomide*	*Current study*

1. Coiffier et al, *Blood.* 2010;116:2040-2045. 2. Leonard et al. *J Clin Oncol*. 2017;35:3538-3546. 3. Davies et al. *Lancet Oncol* 2019;20:649-662.
4. Vitolo et al. *J Clin Oncol.* 2017;35:3529-3537. 5. Younes et al. *J Clin Oncol.* 2019;37:1285-1295.

Rationale for lenalidomide+R-CHOP (R^2-CHOP) in DLBCL



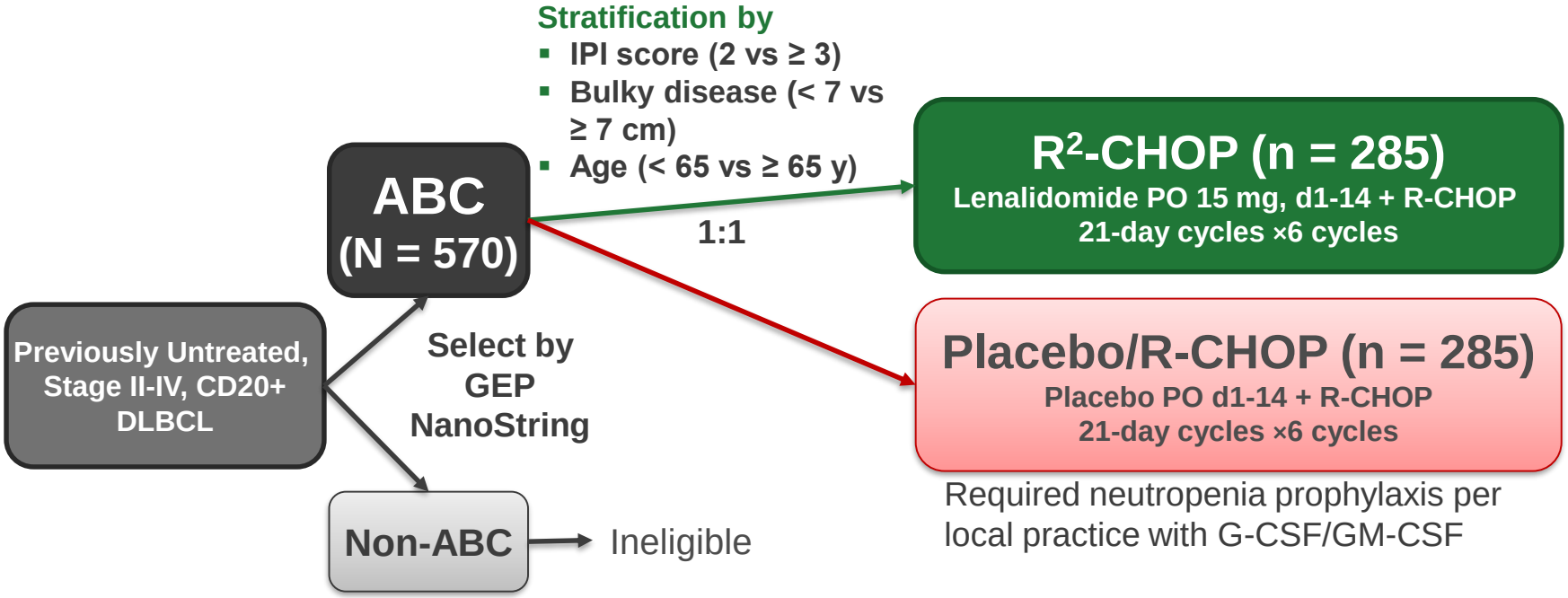
- Single-agent lenalidomide was clinically active in patients with R/R DLBCL, especially non-GCB type[1,2]
- Lenalidomide + R-CHOP (R^2-CHOP) proof of concept studies in previously untreated DLBCL patients (FIL REAL07 and Mayo Clinic MC078E)[3,4]
  - Cell-of-origin was evaluated by IHC
- Lenalidomide dosing differences (+ R-CHOP21)
  - REAL07: 15 mg/d, d1-14 (total dose/cycle 210 mg)
  - MC078E: 25 mg/d, d1-10 (total dose/cycle 240 mg)

Lenalidomide 15 mg/d, d1-14 dose was selected for ROBUST based on benefit:risk considerations

1. Hernandez-Ilizaliturri et al. *Cancer*. 2011;117:5058-5066. 2. Czuczman et al. *Clin Cancer Res*. 2017;23:4127-4137.
3. Nowakowski et al. *J Clin Oncol.* 2015;33:251-257. 4. Vitolo et al. *Lancet Oncol.* 2014;15:730-737.

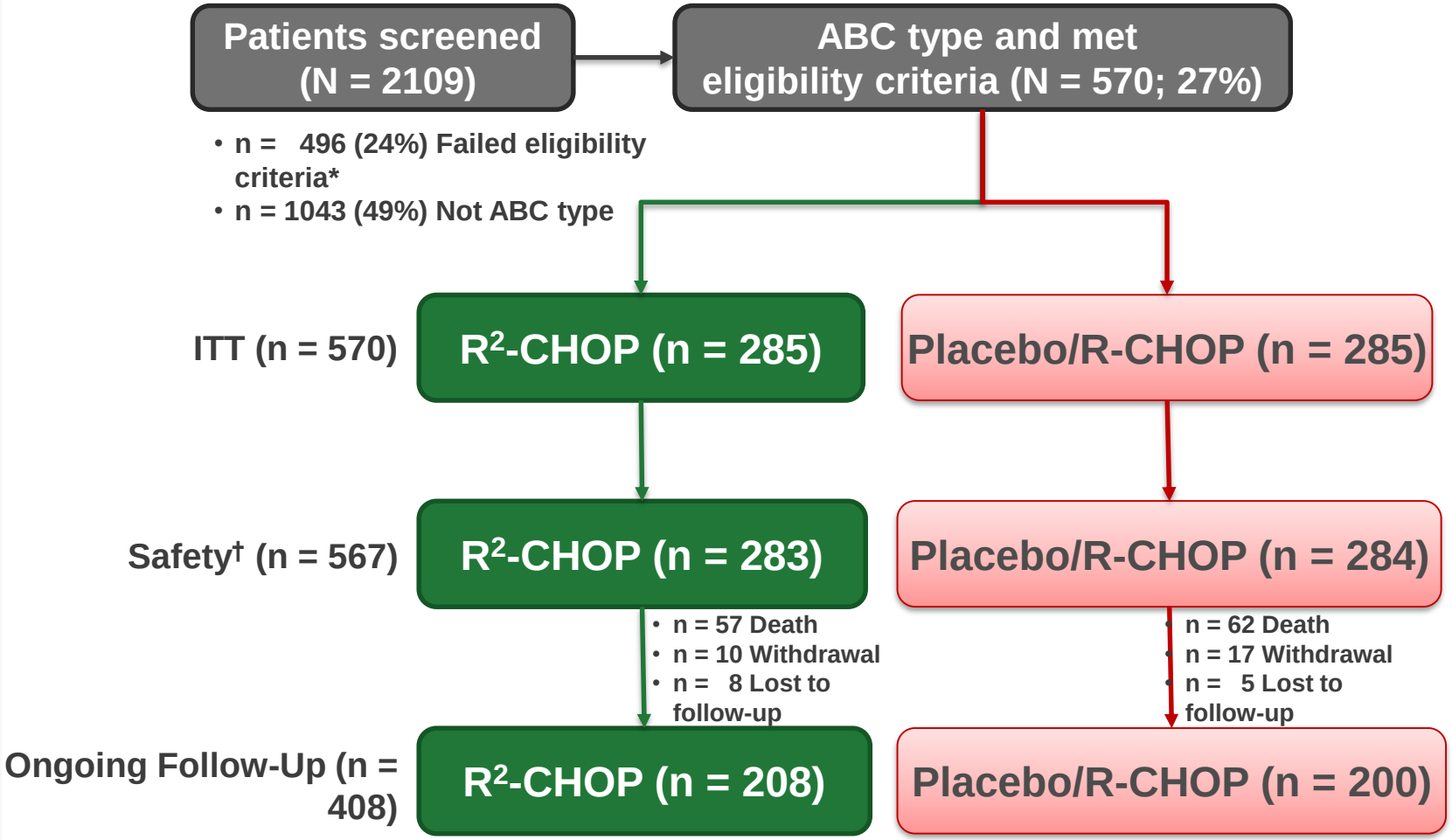
ROBUST Phase III Study Design

- Multicenter, international, randomized, double-blind, placebo-controlled, phase III study in 257 global sites
- Primary endpoint: PFS by central review (per 2014 IWG)[1]
  - Median PFS improved from 24 mo with R-CHOP to 38 mo with R^2-CHOP in ABC-DLBCL (192 events with 90% power; HR = 0.625)
- Secondary endpoints: EFS (key secondary), OS, ORR, CR rate, DOR, and safety



NCT02285062; EudraCT 2013-004054-21. 1. Cheson et al. *J Clin Oncol.* 2014;32:3059-3068.

Patient Disposition



*Main reasons for failing eligibility criteria: 8% inadequate lymph node/biopsy specimen available, 5% not Ann Arbor stage II-IV, 4% not IPI ≥ 2, and 3% unable to adhere to protocol requirements.

†2 R^2-CHOP and 1 Placebo/R-CHOP patients were randomized, but never received lenalidomide/placebo or R-CHOP.

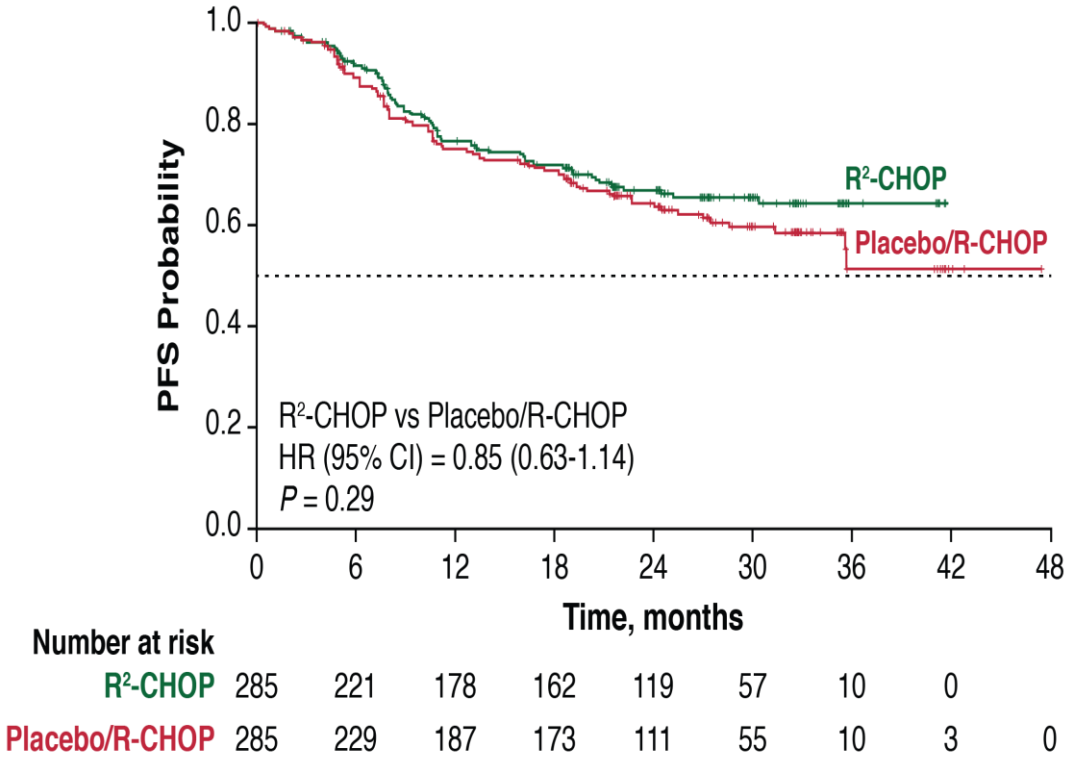
Patient Demographics and Baseline Characteristics (ITT)

n (%)		R²-CHOP (n = 285)	Placebo/R-CHOP (n = 285)
IPI score*	2	121 (42)	120 (42)
	≥ 3	164 (58)	165 (58)
Bulky disease (≥ 7 cm)*		97 (34)	99 (35)
Median age, y (range)		65 (21-82)	65 (28-83)
≥ 65 y*		147 (52)	148 (52)
Male/female		164 (58)/121 (42)	143 (50)/142 (50)
ECOG PS	0	129 (45)	111 (39)
	1	104 (36)	118 (41)
	2	52 (18)	56 (20)
Ann Arbor disease stage	II	37 (13)	33 (12)†
	III	80 (28)	98 (34)
	IV	168 (59)	154 (54)
Elevated LDH (> 234 U/L)		177 (62)	176 (62)
Geographic distribution	Europe	124 (44)	150 (53)
	Asia-Pacific	111 (39)	92 (33)
	North America	24 (8)	23 (8)
	Other	26 (9)	20 (7)

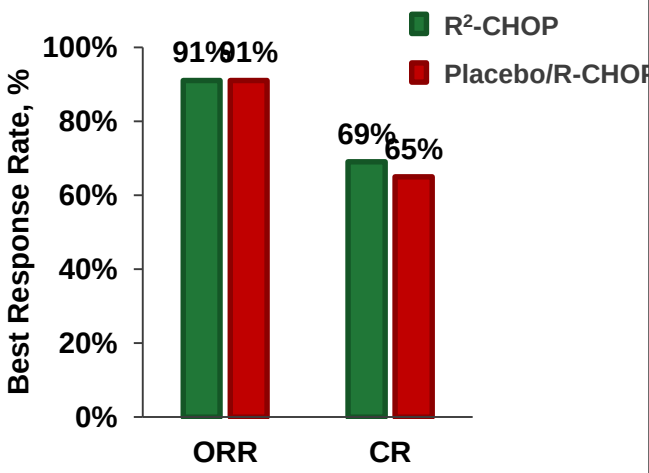
- Baseline demographics were similar between arms
- Stratification factors were balanced
  - 42% IPI score of 2
  - 34% Bulky disease
  - Median age overall was 65 y (52% ≥ 65 y; 2% ≥ 80 y)
- 88% Had stage III/IV disease

Data cut-off 15Mar2019.
*Stratification factors. †Includes 1 patient with ineligible stage I disease.

Primary Endpoint: Progression-Free Survival (ITT, IRAC)



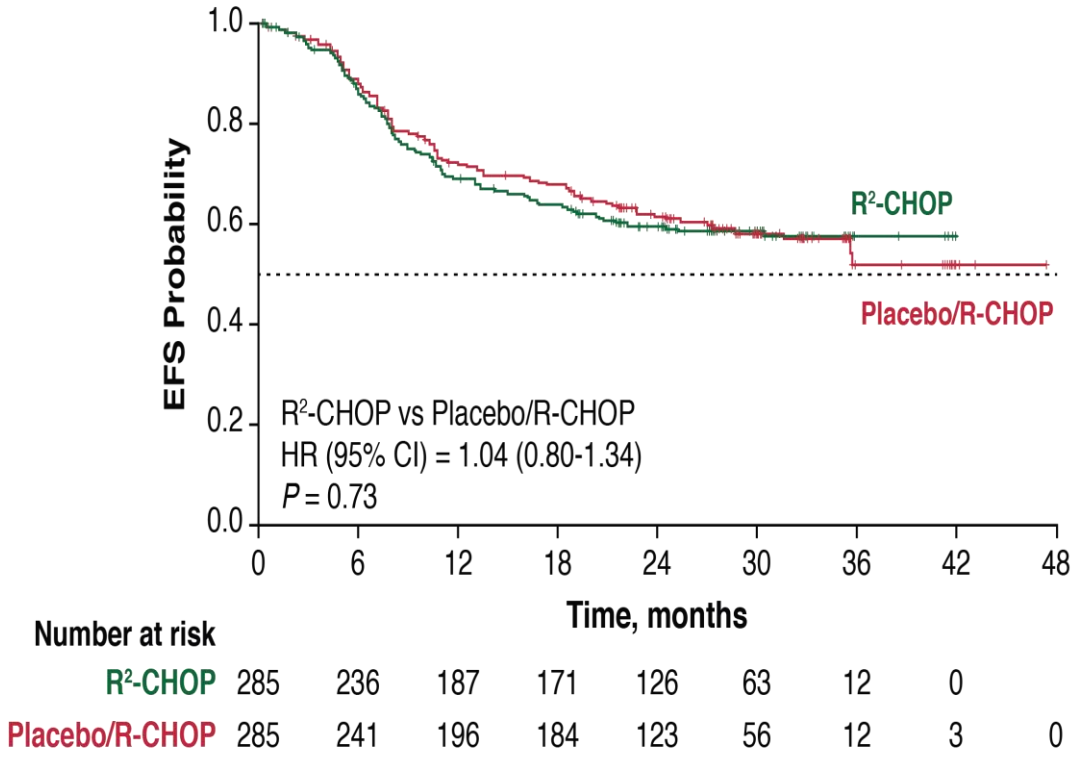
PFS Rates	R²-CHOP (n = 285)	Placebo/R-CHOP (n = 285)
1-y	77%	75%
2-y	67%	64%



- At a median follow-up of 27.1 mo (range, 0-47), the primary endpoint of PFS was not met (medians not reached)
- ORR and CR rates were high in both arms
- **Median time from diagnosis to treatment was 31 days for each arm**

Data cut-off 15Mar2019.
Complete response (CR) was assessed by 2014 IWG criteria with CT-PET (Cheson et al. *J Clin Oncol.* 2014;32:3059-3068).

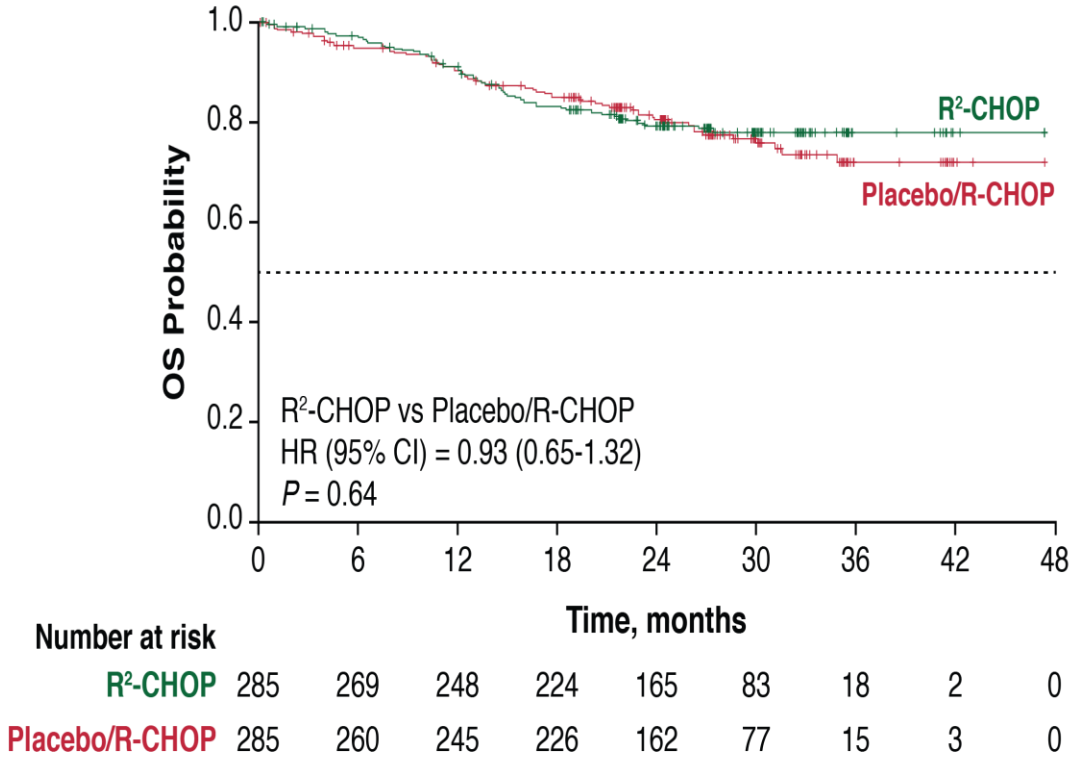
Key Secondary Endpoint: Event-Free Survival (ITT, IRAC)



EFS Rate	R²-CHOP (n = 285)	Placebo/R-CHOP (n = 285)
1-y	68%	71%
2-y	59%	61%

- Median EFS was not reached for either arm
  - EFS included the first occurrence of PD, death, relapse from CR, or initiation of subsequent antilymphoma therapy
- 10 R²-CHOP and 8 Placebo/R-CHOP patients with SD or PET-positive PR initiated new therapy

Overall Survival (ITT)

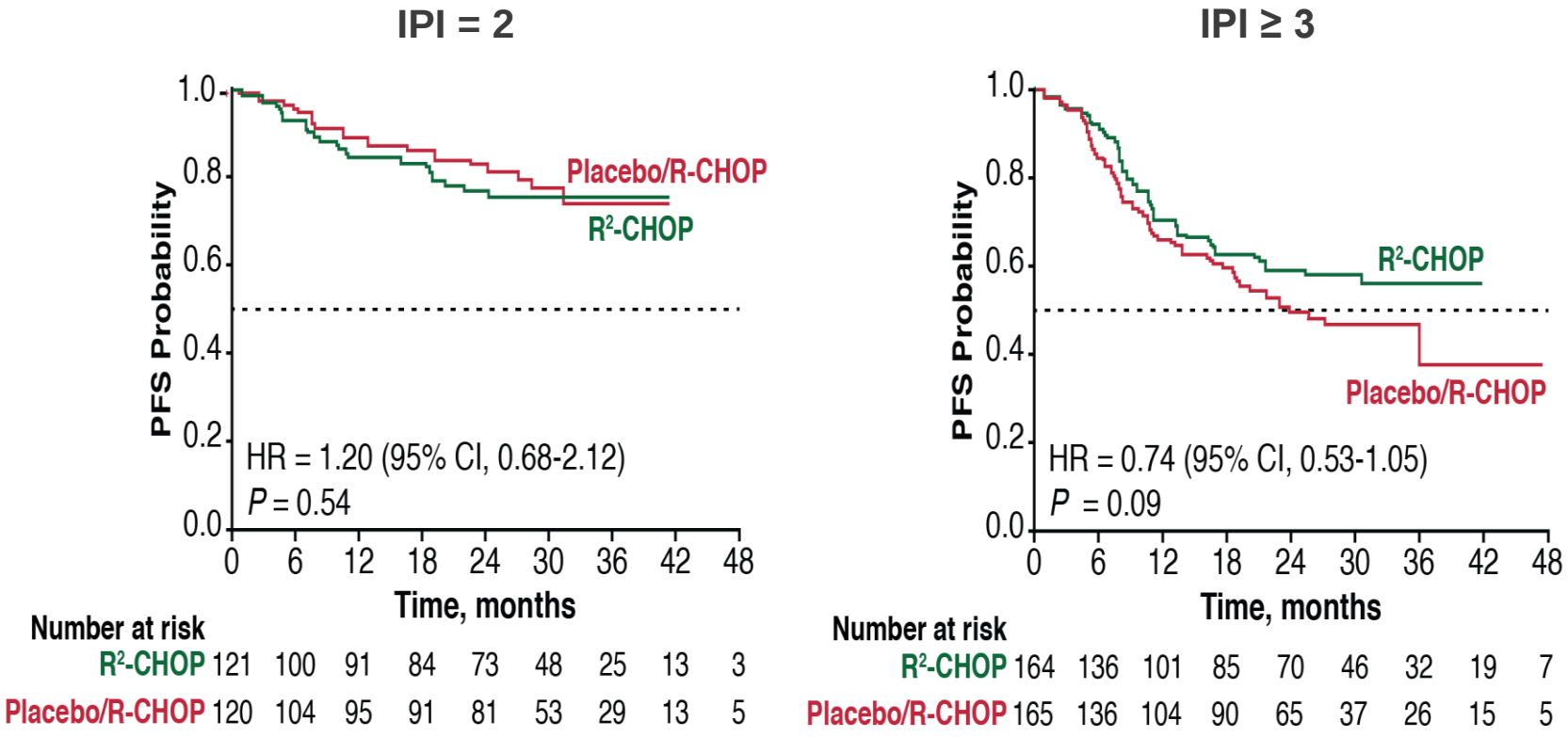


	R²-CHOP (n = 283)	Placebo/R-CHOP (n = 284)
No. of Patient Deaths (safety)		
	57	62
OS Rates (ITT)	**(n = 285)**	**(n = 285)**
1-y	91%	90%
2-y	79%	80%

- Median OS was not reached for either arm
- 93 of 119 (78%) patient deaths were due to PD

Data cut-off 15Mar2019.

PFS Based on International Prognostic Index Score (ITT)



- **Positive trend for PFS favoring R²-CHOP was observed in patients with IPI score ≥ 3**

Data cut-off 15Mar2019.

Conclusions

- ROBUST did not meet the PFS primary or key secondary endpoint for R^2-CHOP vs placebo/R-CHOP in previously untreated patients with ABC-DLBCL
- Positive trend for PFS favoring R^2-CHOP was observed in patients with higher risk IPI ≥ 3
- The safety profile of R^2-CHOP was consistent with those of the individual medicines, and no new safety signals were identified for lenalidomide or with the combination
- Ongoing and future ROBUST analyses are underway, including evaluation of pharmacokinetics/dosing, molecular classification, and mutational status
- Future direction: Promising preclinical data with next generation immunomodulatory agents (CELMoDs) will be evaluated in future DLBCL clinical trials

Sequential MATRIX-RICE Therapy Followed by Autologous Stem Cell Transplant In Patients with DLBCL and Secondary Central Nervous System Involvement: The International Extranodal Lymphoma Study Group (IELSG)-42 Phase II (MARIETTA) Trial

Andrés J. M. Ferreri[1], Jeanette Doorduijn[2], Chiara Cattaneo[3], Maria Giuseppina Cabras[4], Jeffery Smith[5], Fiorella Ilariucci[6], Franco Narni[7], Teresa Calimeri[1], Alessandro Re[3], Jahanzaib Khwaja[8], Barbara Botto[9], Claudia Cellini[10], Luca Nassi[11], Kim Linton[12], Pam McKay[13], Jacopo Olivieri[14], Caterina Patti[15], Francesca Re[16], Alessandro Fanni[4], Vikram Singh[5], Jacoline Bromberg[2], Kelly Cozens[17], Elisabetta Gastaldi[18], Nicola Cascavilla[19], Andrew Davies[20], Christopher P. Fox[21], Maurizio Frezzato[22], Wendy Osborne[23], Anna Marina Liberati[24], Urban Novak[25], Renato Zambello[26], Emanuele Zucca[18,27], Kate Cwynarski[8]

IELSG

FONDAZIONE ITALIANA LINFOMI

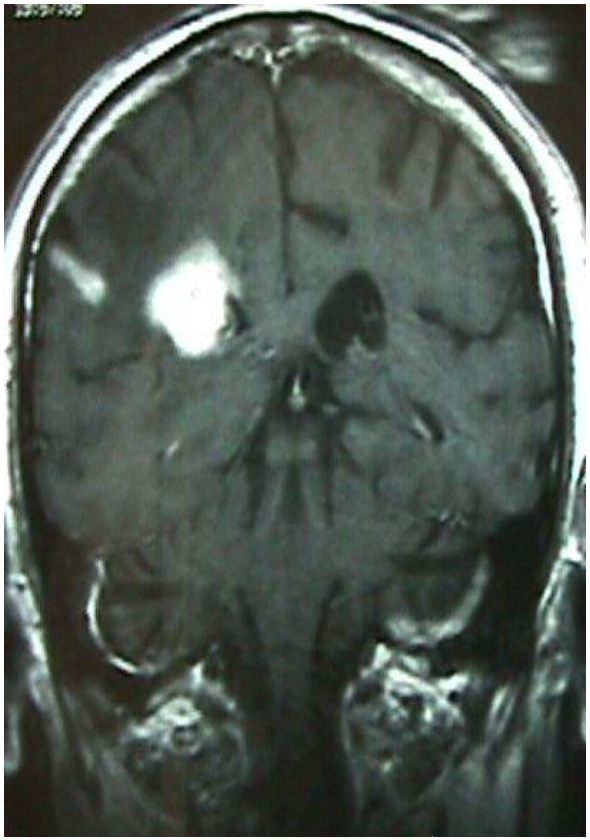
SOUTHAMPTON CLINICAL TRIALS UNIT

HOVON

SAKK
WE BRING PROGRESS TO CANCER CARE

Secondary CNS Lymphoma

The term “SCNSL” defines the involvement of the CNS at presentation, in association with systemic disease, or at relapse, during or after primary therapy, in patients with systemic lymphoma.



Rare event: 5% of all the DLBCLs

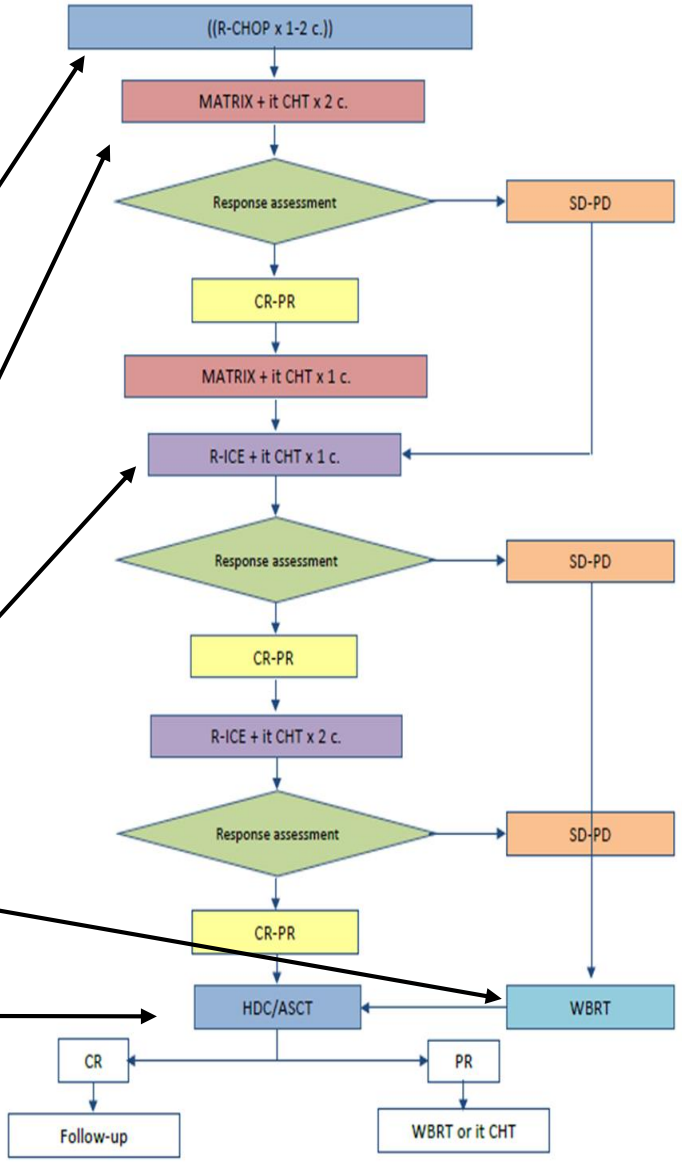
Early event: 92% of events during the first year

Lethal event: median SAR <12 months

MARIETTA: Trial Design

Rationale: Dose intensity; active drugs with good CNS bioavailability.

- To start with R-CHOP in the case of life-threatening systemic disease.
- Positive experiences on PCNSL with HD-MTX, HD-ARAC and thiotepa (MATRIX).
- R-ICE is standard in pts with rrDLBCL, and active in rrPCNSL.
- To deliver WBRT in pts with PD during induction and pts with residual CNS disease after ASCT.
- BCNU/thiotepa is safe and active in PCNSL pts.



Ferreri et al. Lancet 2009; Gisselbrecht et al. JCO 2010; Kasenda et al. Ann Oncol 2012; Mappa et al. HemOnc 2012; Ferreri et al. Lancet Haematol 2016; Ferreri et al. Lancet Haematol 2017; Schorb et al. Br J Haematol 2020

MARIETTA: Selection Criteria

- Histologically confirmed CD20+ DLBCL
- CNS (brain, meninges, cranial nerves, eyes, spinal cord) involvement
  - at presentation (concomitant systemic lymphoma)
  - at relapse (isolated or concurrent systemic)
- Diagnosis by CNS biopsy, CSF cytology (or neuroimaging if biopsy contraindicated or previous/present histology systemic DLBCL)
- No prior HD-MTX or brain RT or ASCT
- Age 18 - 70 years
- ECOG PS 0 – 3
- Seronegative HCV, seronegative HIV, no active HBV infection
- No concurrent malignancy (> 3-year follow-up)

MARIETTA: Statistics

The primary endpoint was 1-year PFS.

The Fleming design was used.

The maximum 1-year PFS considered of low interest was 50% (P0).

The minimum 1-year PFS considered of interest was 65% (P1).

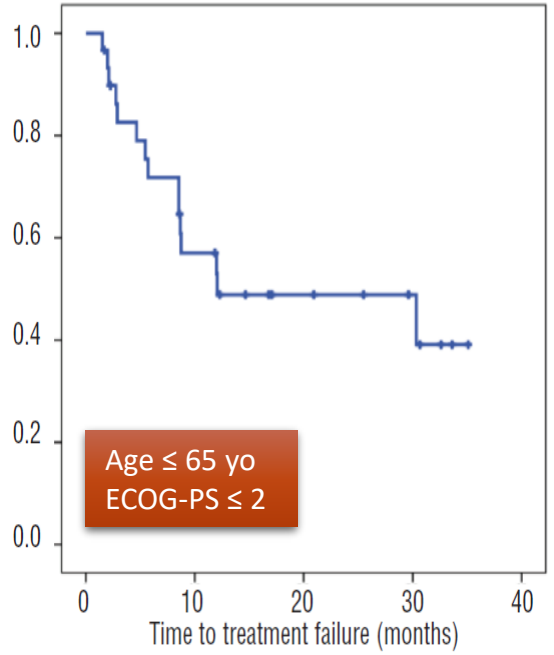
Estimated sample size: 69 patients (one-sided test, type I error 5% and power 80%).

76 patients were needed (drop-out: 10%).

Predetermined efficacy threshold: ≥41 progression-free survivors at 1 year.

Intention to treat.

CRR before ASCT, OS and safety were the secondary end-points.



Korfel et al. Haematologica 2013

Patient Characteristics (n= 75)

79 patients were enrolled at 24 centers in four countries (March 2015 to August 2018).
Four pts were excluded: unrelated exams abnormalities (2), disease only at flow cytometry of the CSF, death at registration.

		Number (%)
Age, median (range)		58 (23-70)
Gender	Male	38 (51%)
IPI variables	Age >60 yo	32 (43%)
	ECOG - PS >1	28 (37%)
	extranodal >1 (other than CNS)	23 (31%)
	high LDH serum level	37 (49%)
	advanced stage	60 (80%)
IPI risk	Low	14 (19%)
	Low-intermediate	18 (24%)
	High-intermediate	26 (35%)
	High	17 (23%)

Patient Characteristics (n= 75)

		Number (%)
Disease site at registration	CNS involvement at presentation	32 (43%)
	Isolated CNS relapse	15 (20%)
	Concomitant CNS/systemic relapse	28 (37%)
CNS sites of disease	Brain parenchyma	34 (45%)
	CSF/meninges	8 (11%)
	Spinal cord	2 (3%)
	Eyes	2 (3%)
	Brain and CSF/meninges	13 (17%)
	Brain and eyes	10 (13%)
	Brain, CSF and eyes	6 (8%)
Extra-CNS sites at registration (n= 60)	Nodal disease	22 (37%)
	Extranodal disease (other than CNS)	18 (30%)
	Nodal + Extranodal disease	20 (33%)

Prior Treatment (n= 43)

R-CHOP	40 (93%)
R-DA-EPOCH/R-VACOP	2 (5%)
R-Bendamustine	1 (2%)
Prior CNS prophylaxis (IT)	7 (17%)
Refractory to prior treatment	20 (47%)
Median time to CNS involvement	5 months (range 1-61)

Feasibility

Feature	Denominator	Events	Notes
Upfront R-CHOP	32 pts at presentation	9 (28%)	Expected toxicity
Delivered courses	450 planned courses	317 (70%)	
Intrathecal chemo	75	64 (85%)	
No cross to RICE after MATRIX	-	20 (27%)	untreatable PD (10), toxicity (5), cognitive decline (1), poor mobilizer (1), physician's choice, (1), LTF (2)
SAEs	-	78 in 42 pts	FN and infections (64), bleeding (5), bowel perforation (2), renal failure (2), neurotoxicity (2), PTE, atrial fibrillation, vomiting + diarrhoea
Recovery from SAE	78	74 (95%)	

APBSC Collection	N° pts	>2 x 10^6 CD34/kg	Median (range)
Leukapheresis	48	42 (88%)	6.75 (2.4-44.9)
MATRix #2	25	22 (88%)	
MATRix #3	16	15 (94%)	
After R-ICE	7	5 (72%)	

MARIETTA: Activity

	Response	2nd MATRIX	MATRIX-RICE	whole
CNS disease (n= 75)	CR	26 (35%)	37 (49%)	44 (59%)
	PR	31 (41%)	14 (19%)	2 (3%)
	OR	57 (76%)	51 (68%)	46 (62%)
	SD	6 (8%)	0 (0%)	0 (0%)
	PD	8 (11%)	20 (27%)	25 (33%)
Systemic disease (n= 60)	CR	26 (43%)	33 (55%)	40 (67%)
	PR	19 (32%)	12 (20%)	4 (7%)
	OR	45 (75%)	45 (75%)	44 (74%)
	SD	3 (5%)	0 (0%)	0 (0%)
	PD	10 (17%)	13 (22%)	14 (23%)
Whole series (n=75)	CR	20 (27%)	29 (39%)	40 (53%)
	PR	35 (47%)	20 (27%)	5 (7%)
	OR	55 (73%)	49 (65%)	45 (60%)
	SD	3 (3%)	0 (0%)	0 (0%)
	PD	13 (17%)	22 (29%)	26 (35%)

MARIETTA: Activity

Response after MATRIX 1 & 2	RICE	Response after MATRIX-RICE	ASCT	after whole treatment	Failure-free
CR: 20 (27%)	YES: 17 pts	CR: 16 (94%)	14 (82%)	CR: 15 (88%)	11 pts
	NO: 3 pts	CR: 3 (100%)	1	CR: 3	2 pts
PR: 35 (47%)	YES: 31 pts	CR: 9 (29%) PR: 15 (50%)	7 (23%) 12 (39%)	CR: 9 (29%) CR: 11 (35%) PR: 2 (6%)	7 pts 8 pts
	NO: 4 pts	PR: 3	0	PR: 3	1 ltf
SD: 3 (4%)	YES: 2 pts	CR: 1 PR: 1	1 1	CR: 2	2 pts
	NO: 1 pt	PD: 1	0	PD: 1	
PD: 13 (17%)	YES: 5 pts	PD: 5	0	PD: 5	
	NO: 8 pts	PD: 8	0	PD: 8	

Primary Endpoint

At one year from registration, 41 patients were progression free (predetermined efficacy threshold ≥41).

At a median follow-up of 25 months (range 12 - 47), there were 44 events:

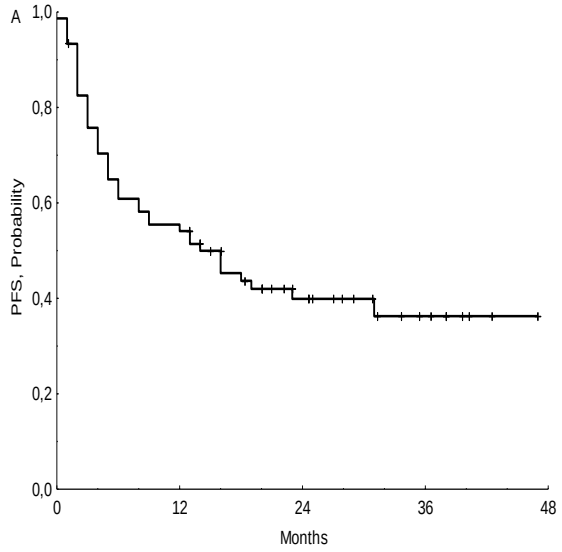
- ✓ 4 deaths due to toxicity
- ✓ 26 patients with chemo-refractory disease
- ✓ 11 responders experienced tumor relapse

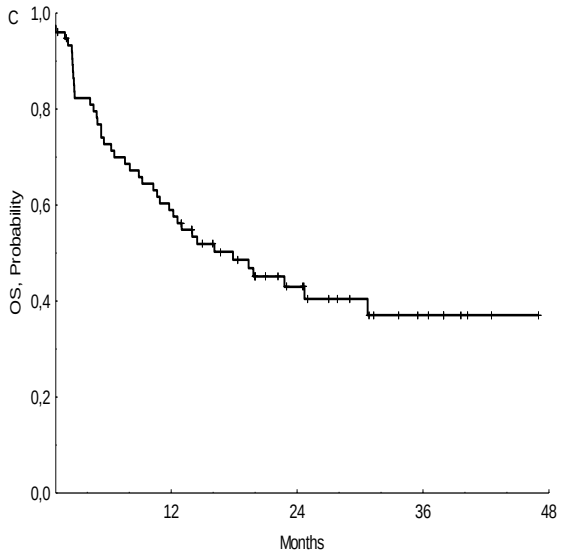
Sites: 11 CNS; 6 systemic; 20 both.

- ✓ 3 patients died without evidence of relapse (progressive neurological decline, suspected massive PTE and sudden death).

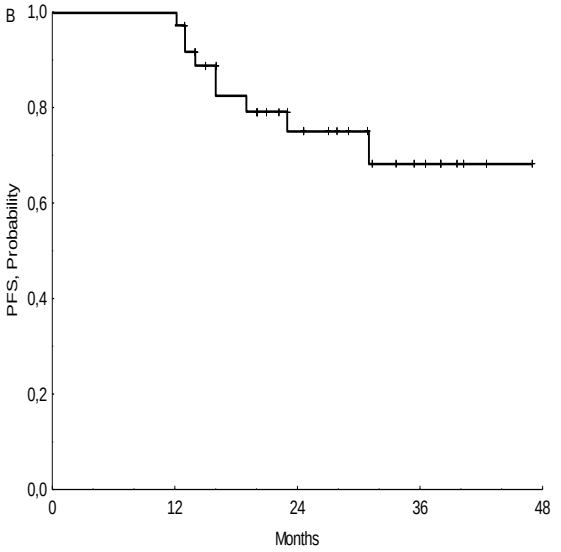
Efficacy

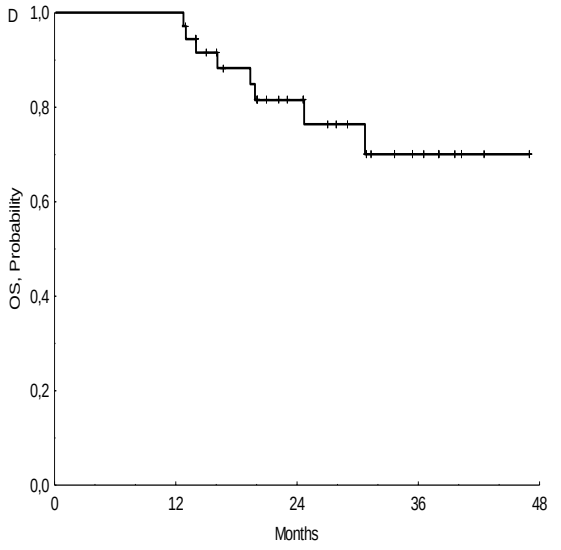
Whole series





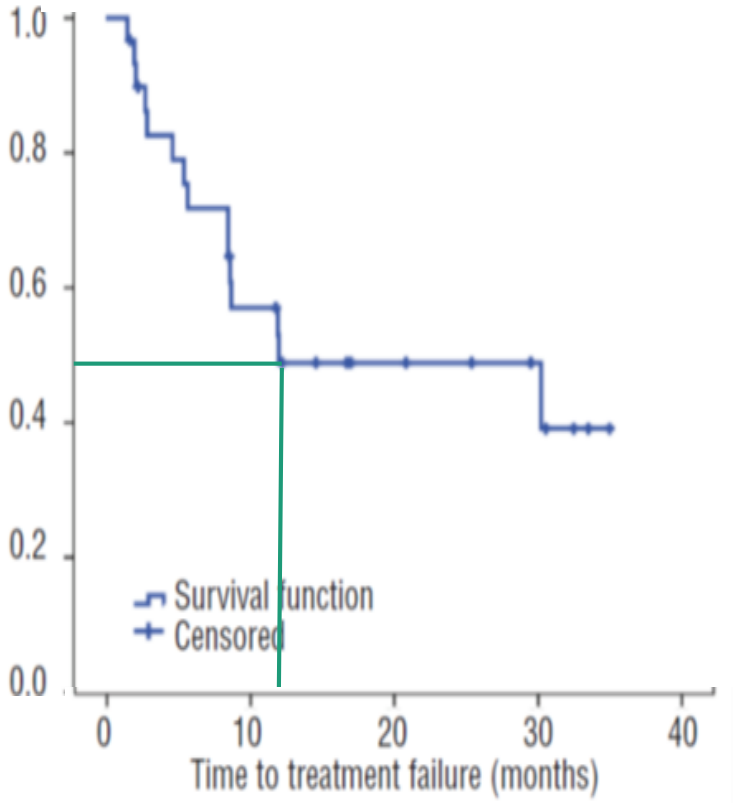
Transplanted patients





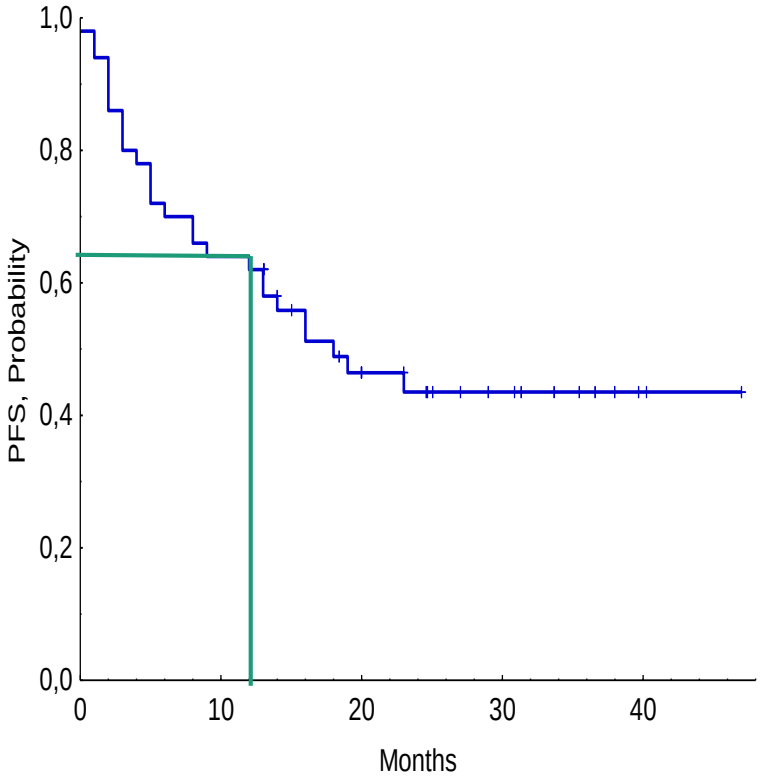
MARIETTA vs. Comparator

Korfel et al. Haematologica 2013 (edited)



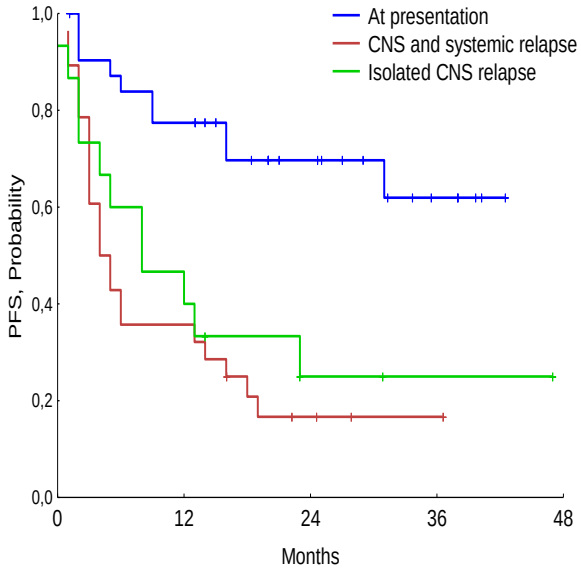
30 patients ≤ 65 yo and ECOG-PS ≤ 2
median follow up of 21 months (95%CI: 10-32)

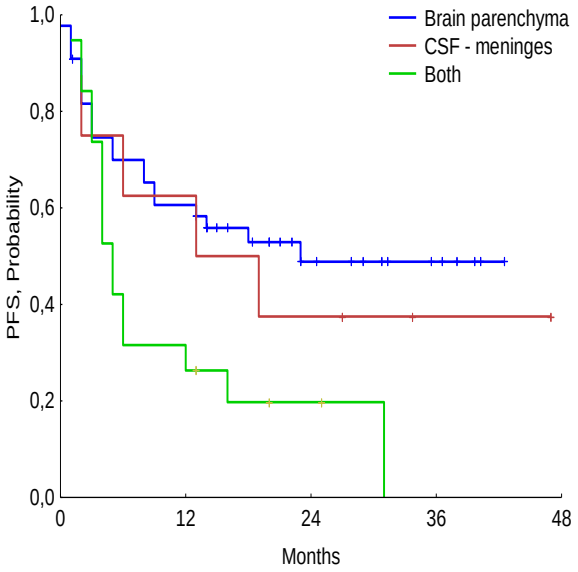
MARIETTA trial

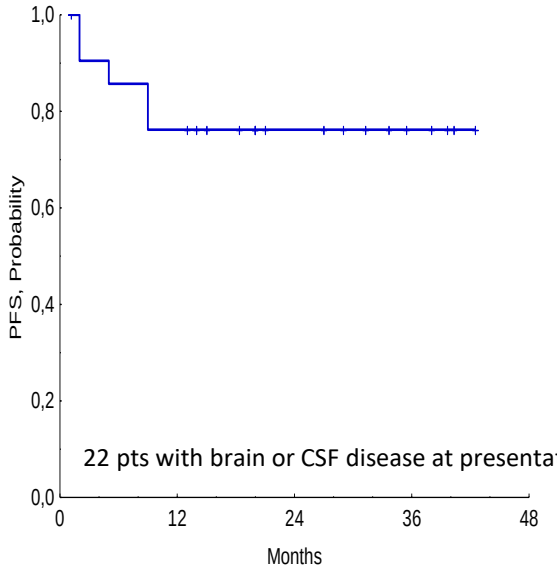


50 patients ≤ 65 yo and ECOG-PS ≤ 2
median follow-up of 25 months (range 12 - 47)

Subgroup Analyses







Variable	Subgroups	Assessed patients	1-year PFS	HR (95%IC)	p value
IPI	score 0 - 2	32	45 ± 8%	1	
	score 3 - 5	43	35 ± 8%	1.92 (0.35 – 2.31)	0.66
CNS disease	At presentation	32	77 ± 7%	1	
	Isolated relapse	15	47 ±13%	3.11 (1.25 – 7.71)	0.014
	Concomitant relapse	28	36 ± 9%	3.09 (1.44 – 6.61)	0.003
CNS site	Brain parenchyma	44	61 ± 7%	1	
	CSF/meninges	8	62 ±17%	0.57 (0.21 – 1.61)	0.293
	Both brain and CSF	19	32 ±11%	1.91 (0.91 – 3.97)	0.083

Conclusions

- MATRIX-RICE followed by ASCT achieved the primary endpoint in this very-poor-prognosis population, without major safety concerns.
- Response to MATRIX was a strong prognostic factor.
- CRR after MATRIX was improved with RICE + ASCT.
- Patients with lymphoma refractory to MATRIX did not benefit from RICE + ASCT.
- Survival figures of transplanted patients seems better than reported in prior trials.
- The best survival figures were recorded in chemo-naïve patients and in patients with disease limited to a single CNS compartment (brain or CSF/meninges).

FONDAZIONE ITALIANA LINFOMI

www.filinf.it

Grazie

- **Giuseppina Cabras**
- **Andrés J Ferreri**
- **Alice Di Rocco**
- **Mattia Novo**
- **Alessandro Re**
- **Umberto Vitolo**