INCONTRO DI AGGIORNAMENTO
SUI **DISORDINI LINFOPROLIFERATIVI**
E SUI PROTOCOLLI
DELLA **FONDAZIONE ITALIANA LINFOMI**

Torino, 14 dicembre 2018

Sede:
Centro Congressi Torino Incontra
Via Nino Costa, 8 - Torino

Aggiornamenti sui protocolli FIL

Linfomi extranodali

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AZIENDA SANITARIA
LOCALE DI **BIELLA**

Aggressive lymphomas

- Primary mediastinal B-cell lymphoma

  IELSG37
- Primary central nervous system lymphoma

  IELSG43 – Matrix study

  IELSG45 – Fiorella study

Indolent lymphomas

- Marginal zone B-cell lymphomas

  IELSG47 – MALIBU study

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The role of PET in PMBCL

IELSG-26 Study patient flow

125 PMBCL enrolled

→ **6 early withdrawal**

Baseline PET
(within 14 days before R-Chemo)

→ **17 baseline PET omitted (treatment urgency)**

Full course of chemotherapy:
R-CHOP 21/14 (n=15) or
R-MACOP-B or R-VACOP-B (n=85)

→ **2 final PET omitted (major protocol violation)**

Final PET
(3-4 weeks after R-Chemo)

100 with complete PET-CT study

Consolidation RT
(according to local policy, n=93)

→ **FOLLOW UP**

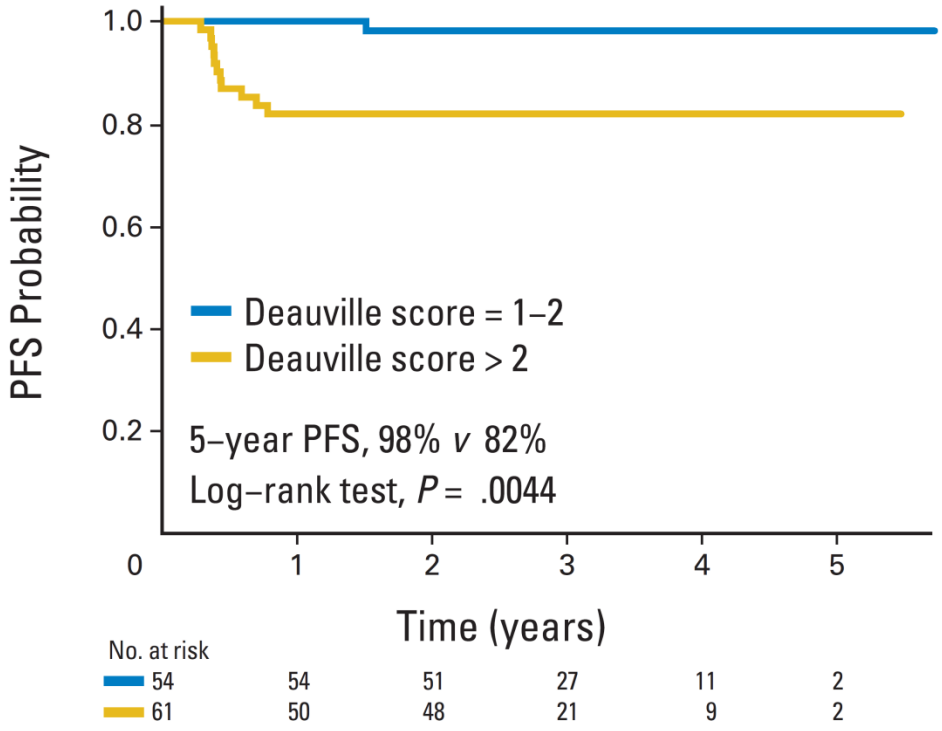
86% with initial bulk (>7.5cm)

90% with a residual lesion after R-Chemo

PFS according to the PET response after chemoimmunotherapy

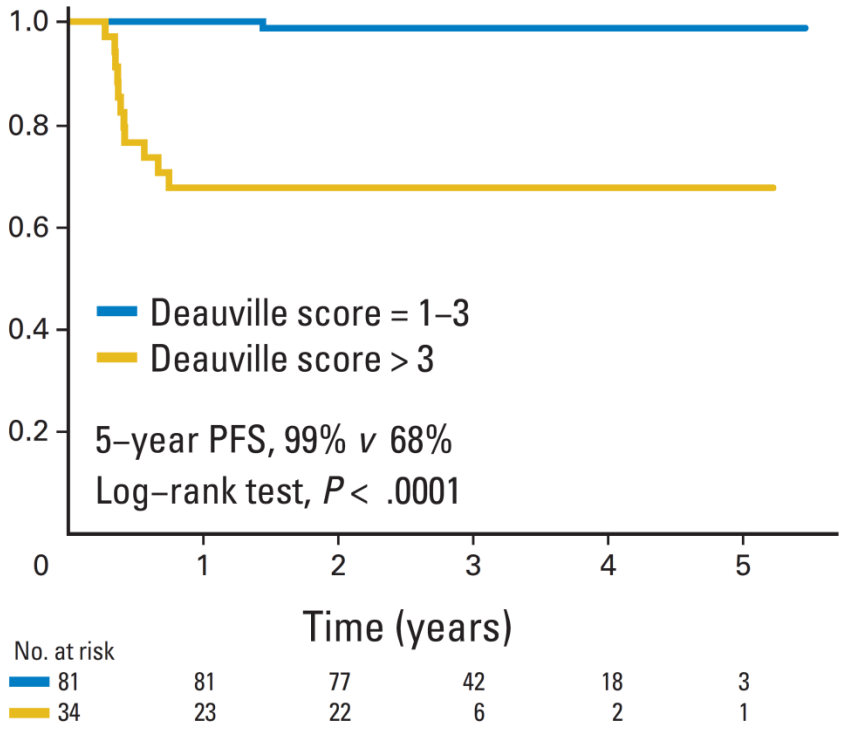
MBP cutoff

(NPV 98% and PPV 18%)



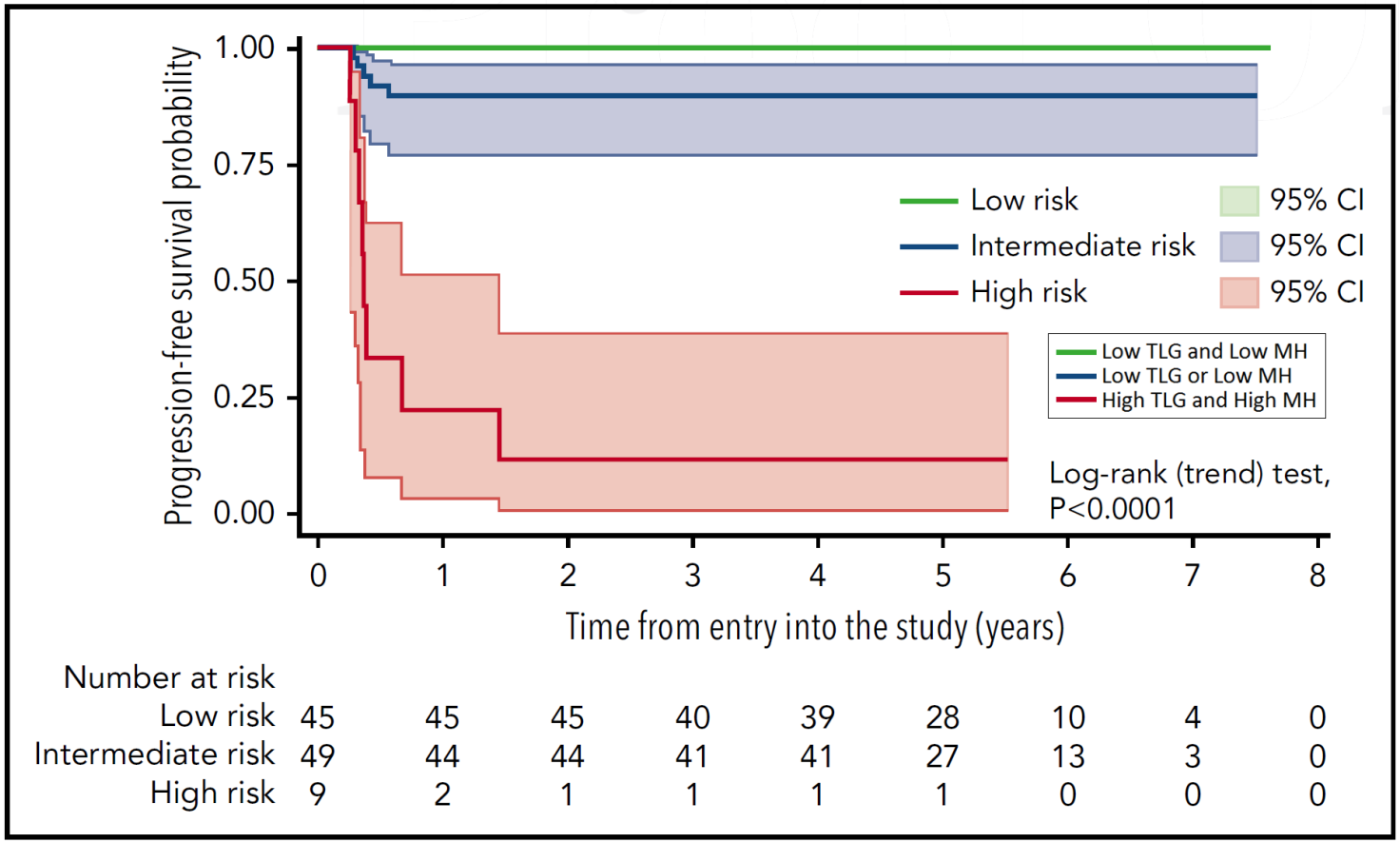
Liver cutoff

(NPV 99% and PPV 32%)



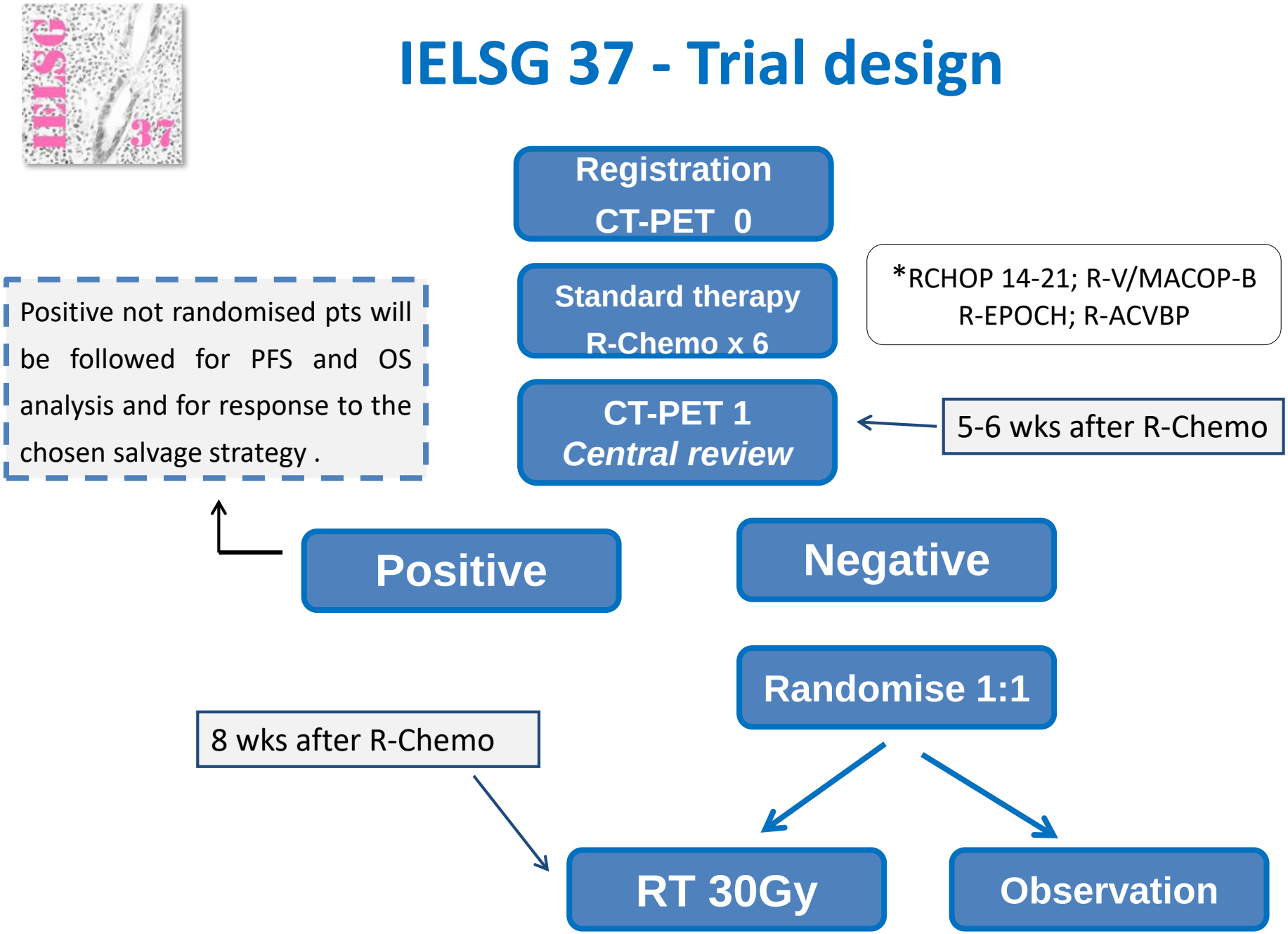
Martelli et al. J Clin Oncol 2014

Prognostic model using TLG and MH



Ceriani et al , *Blood*. 2018

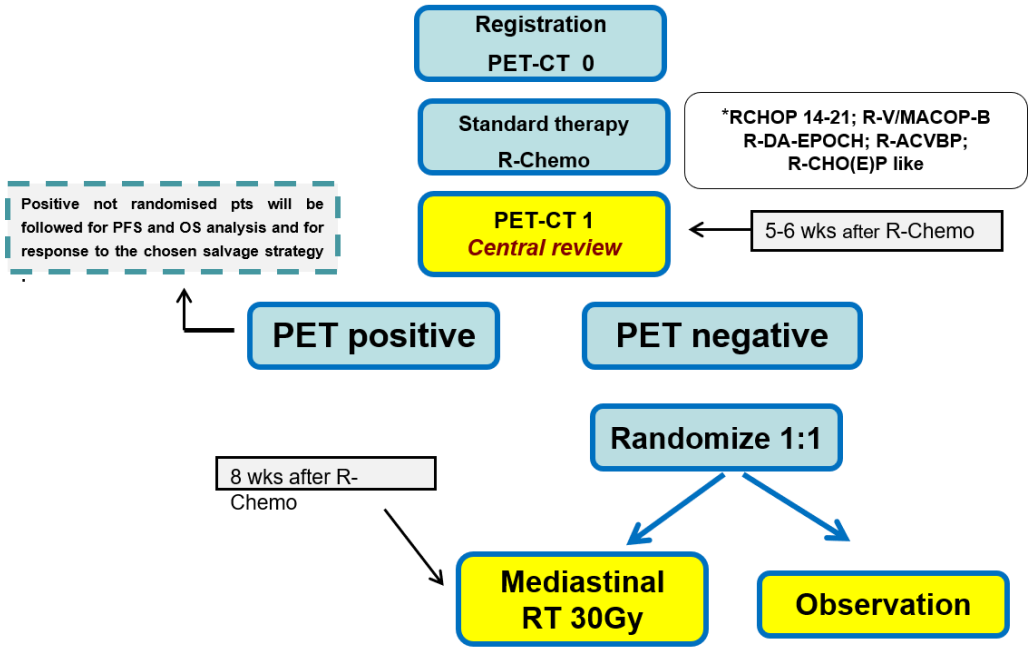
IELSG 37 - Trial design



IELSG37

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)

PI: Prof. M. Martelli



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

<u>DATI PER CENTRI FIL</u>

- **Centri partecipanti/Centri attivi: 65/52**
- **Centri arruolanti/Centri attivi: 39/52**
- **Pazienti arruolati:** *336*

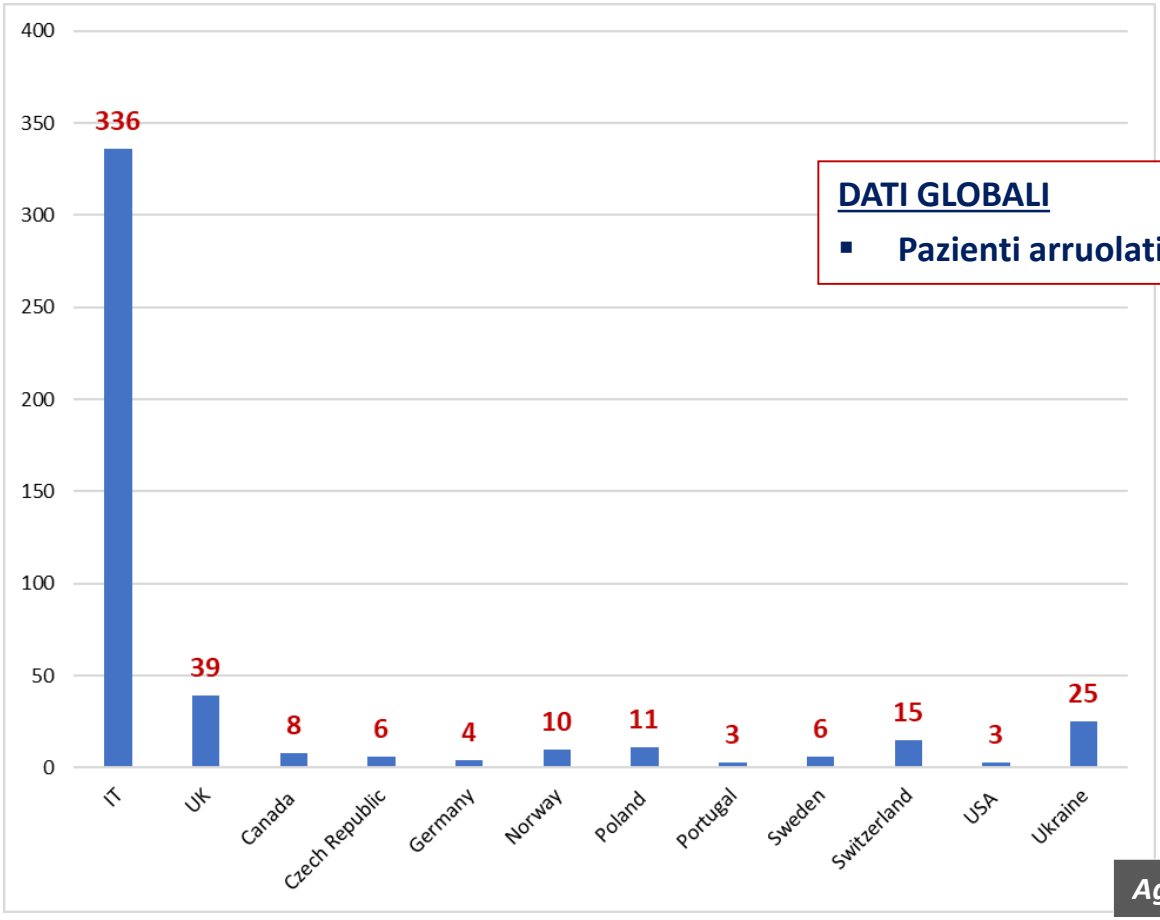
Italian Top 5 sites

Centro	n. pt
Roma Sapienza	**37**
Torino (Vitolo)	**27**
Brescia	**18**
Rozzano Humanitas	**18**
Cagliari	**16**
Milano Niguarda	**15**
Pavia	**15**

Agg. al 18 ottobre 2018

IELSG37

Total number of pt enrolled	468
Countries enrolling	***12***
Centres with at least 1 pt	***70***



DATI GLOBALI

- **Pazienti arruolati: 468/540**

Agg. al 18 ottobre 2018

Aggressive lymphomas

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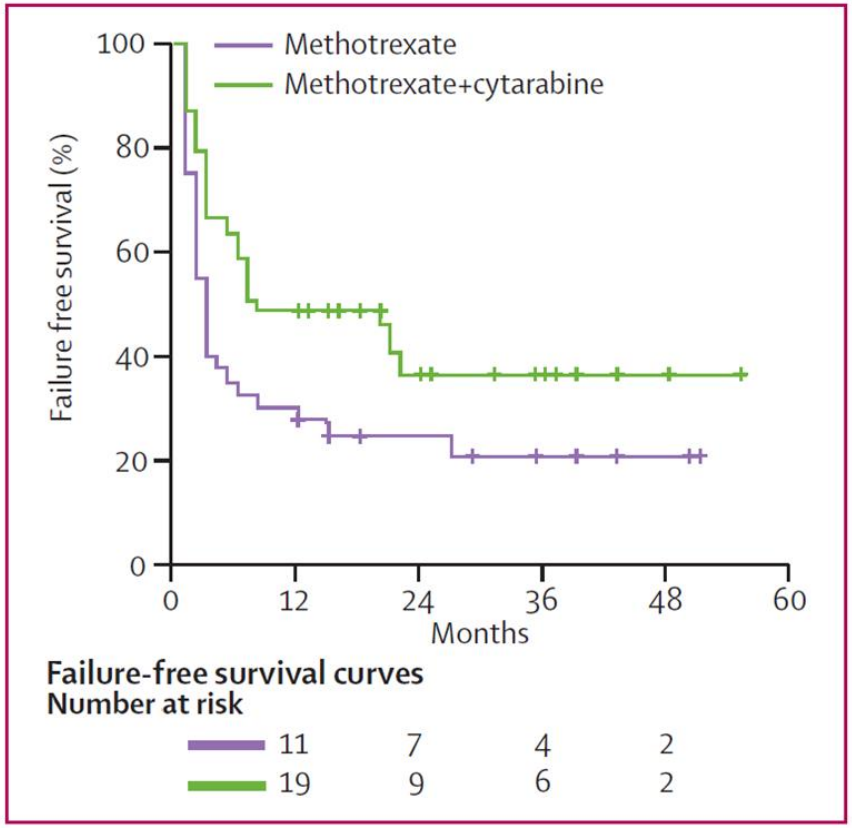
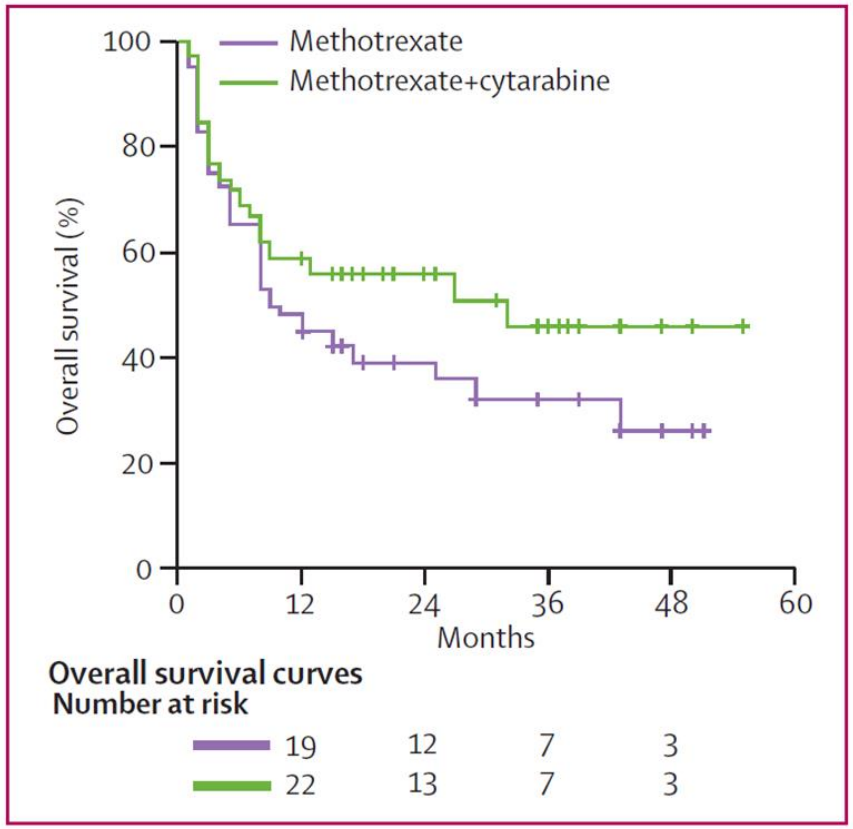
IELSG20: randomised phase-2 study

HD Ara-C plus HD MTX vs HD MTX alone in PCNSL

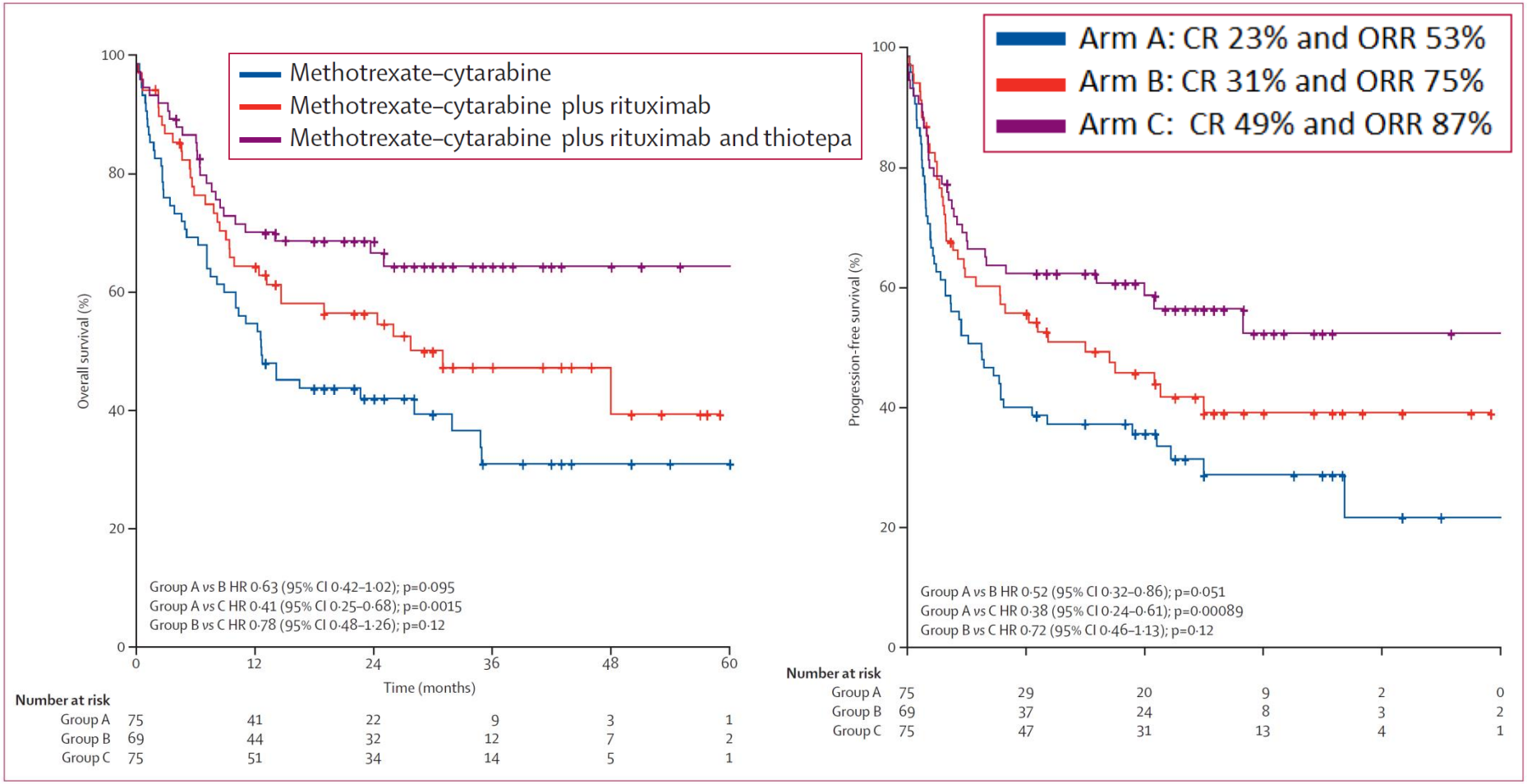




	HD MTX alone	HD Ara-C plus HD MTX	
CR	18% (95% CI 6–30)	46% (95% CI 31–61)	p=0·006
ORR	40% (95% CI 25–55)	69% (95% CI 55–83)	p=0·009

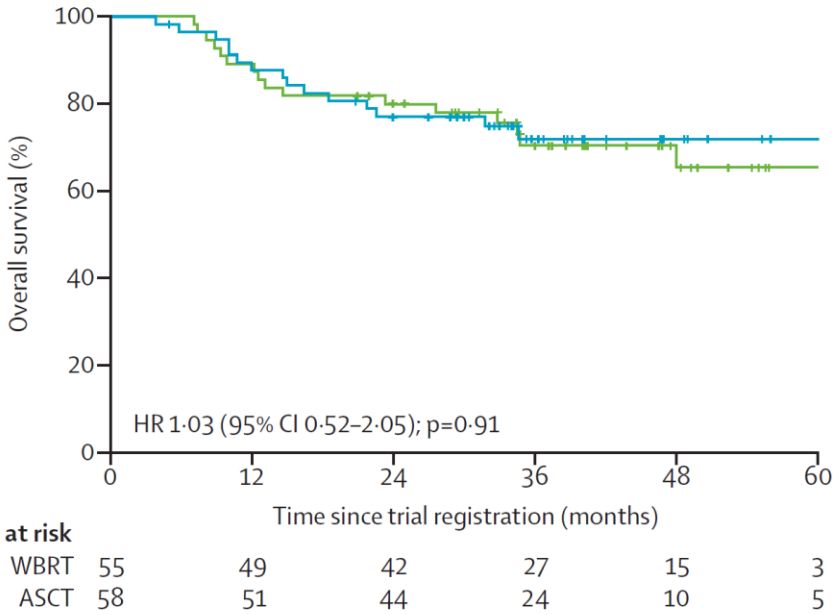
Ferreri et al, Lancet 2009

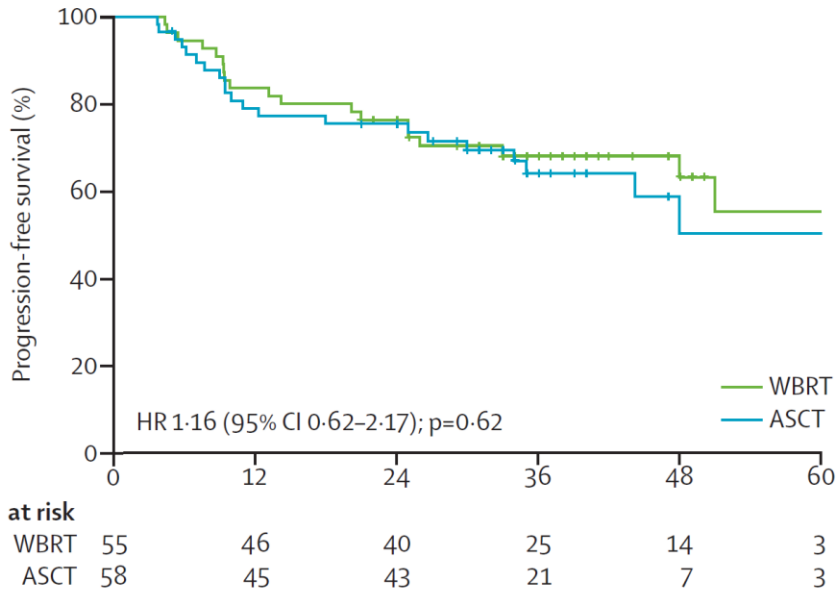
IELSG32: 1st randomisation



Ferreri et al Lancet Hematol. 2016

IELSG32: 2nd randomisation





Overall and progression-free survival curves of randomly assigned patients (per-protocol populations)

Ferreri et al Lancet Hematol. 2017

IELSG43 MATRix Randomised Study

PI: Prof. A. J. Ferreri

2x MATRix
(R-MTX/AraC/TT)

Harvest → PD: off study

2x MATRix

→ SD/PD: off study

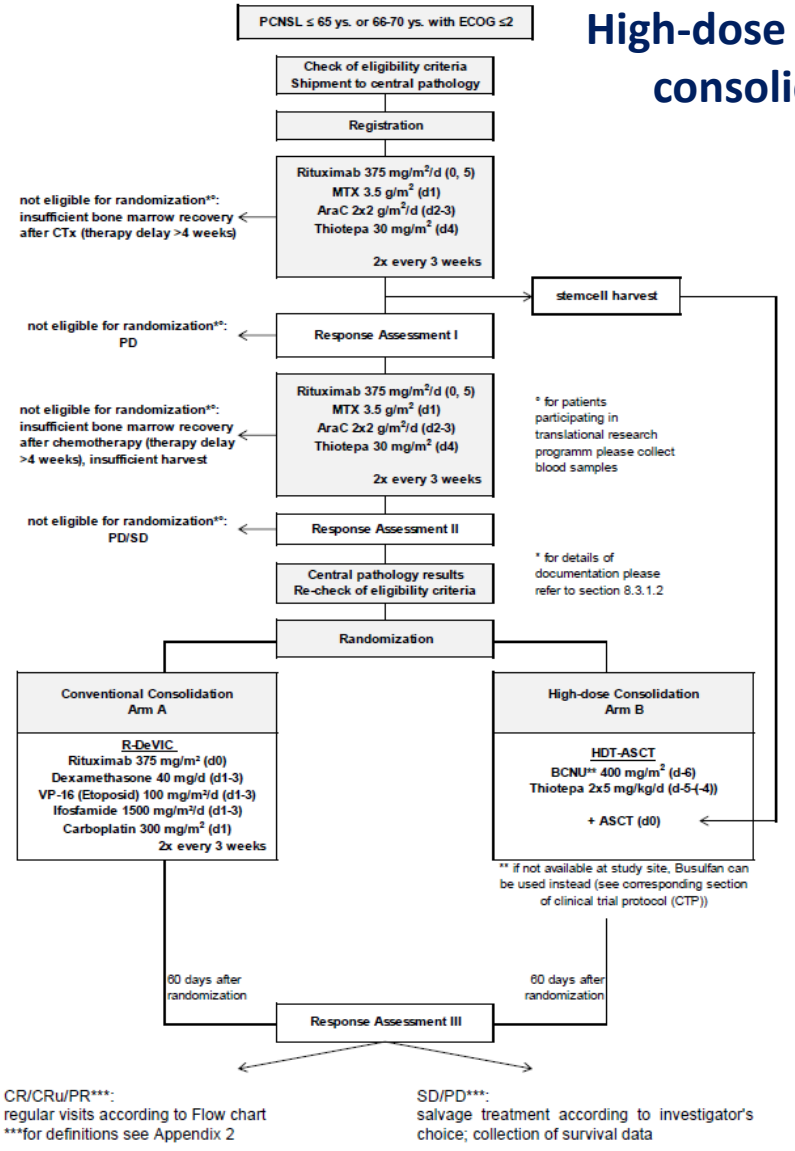
Randomisation

HDT / ASCT
(HD BCNU / TT)

2x R-DeVIC
(Rituximab/Dexa/Ifo/VP16/Carbopl.)

High-dose chemotherapy and autologous stem cell transplant or consolidating conventional chemotherapy in PCNSL

IELSG43 MATRIX Trial



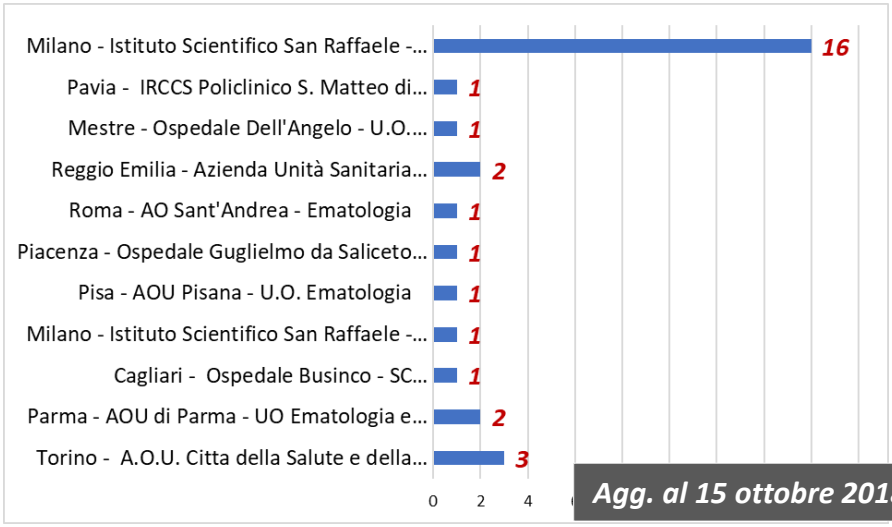
High-dose chemotherapy and autologous stem cell transplant or consolidating conventional chemotherapy in primary CNS lymphoma - randomized phase III trial

PI: Prof. A. J. Ferreri

- **Centro Coordinatore: IRCCS Ospedale San Raffaele - Prof. Ferreri**

DATI PER CENTRI FIL

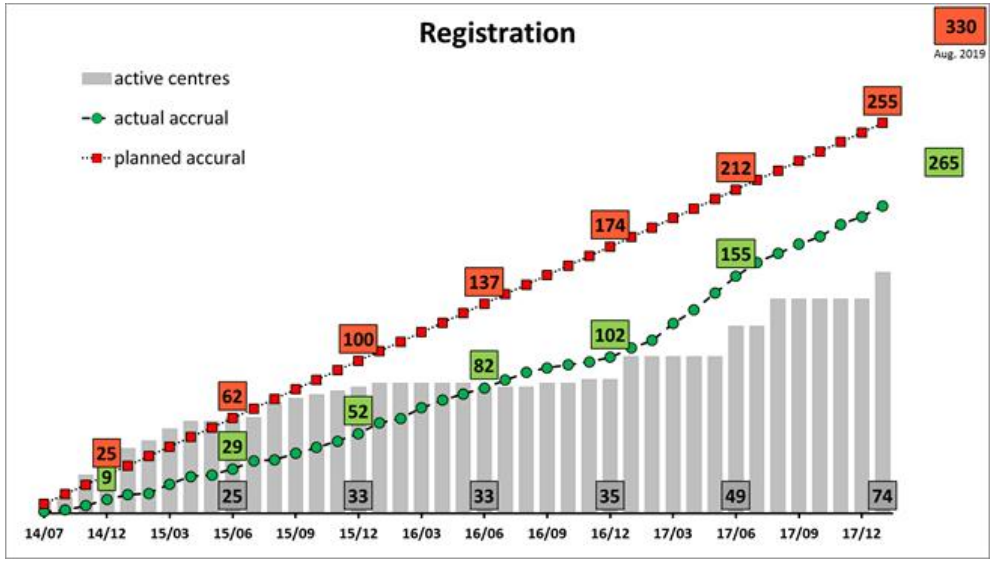
- **Data apertura: dicembre 2016**
- **Centri partecipanti/Centri attivi: 39/33**
- **Centri arruolanti/Centri attivi: 11/33**
- **Pazienti arruolati:** *30*



IELSG43 MATRIX Trial

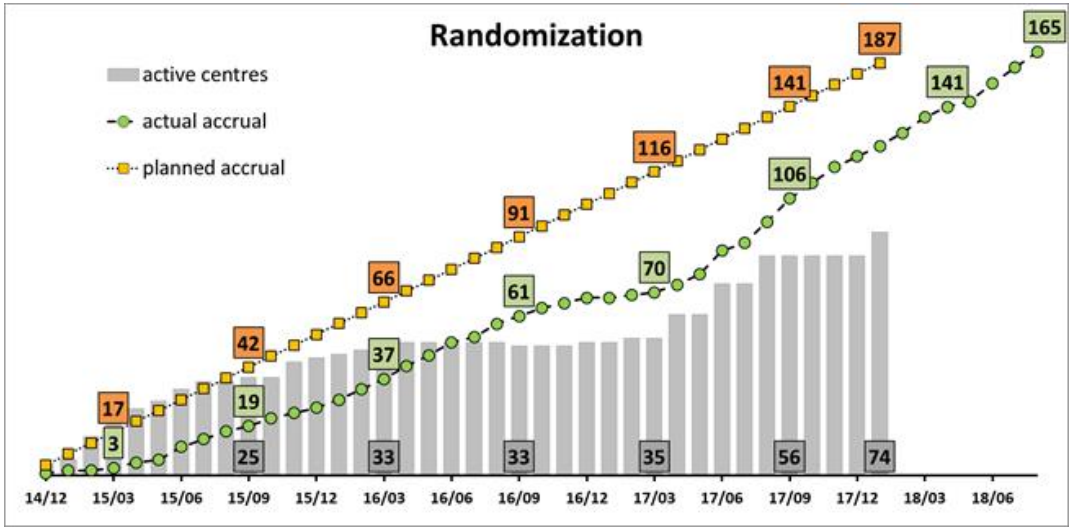
Number of participating sites and countries

	GER	IT	DEN	CZR	NOR	CH
No. of sites	35	41	4	3	2	6
initiated	35	33	3	none	1	5



DATI GLOBALI

- **Fine arruolamento prevista: 31 agosto 2019**
- **Pazienti arruolati: 245/330**



Agg. al 04 ottobre 2018

IELSG45 FIORELLA Trial

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

Agenzia Italiana del Farmaco
AIFA

PROSSIMA APERTURA

- **Coordinator Site:**
- IRCCS Ospedale San Raffaele - Prof. Ferreri
- **Inclusion Criteria (partial):**
- - Histologically or cytologically assessed diagnosis of CD20+ diffuse large B-cell lymphoma exclusively localized in the central nervous system - **Age ≥70 years**
- **- Patients not eligible for high-dose chemotherapy supported by autologous stem cell transplant**
- - ECOG PS ≤3.
- **Primary endpoint**

2-year progression-free survival (PFS)

- **Estimated enrolling pts: 208** who will be stratified according to their suitability to tolerate an induction chemo-immunotherapy regimen containing high-dose methotrexate.

IELSG45 FIORELLA Trial

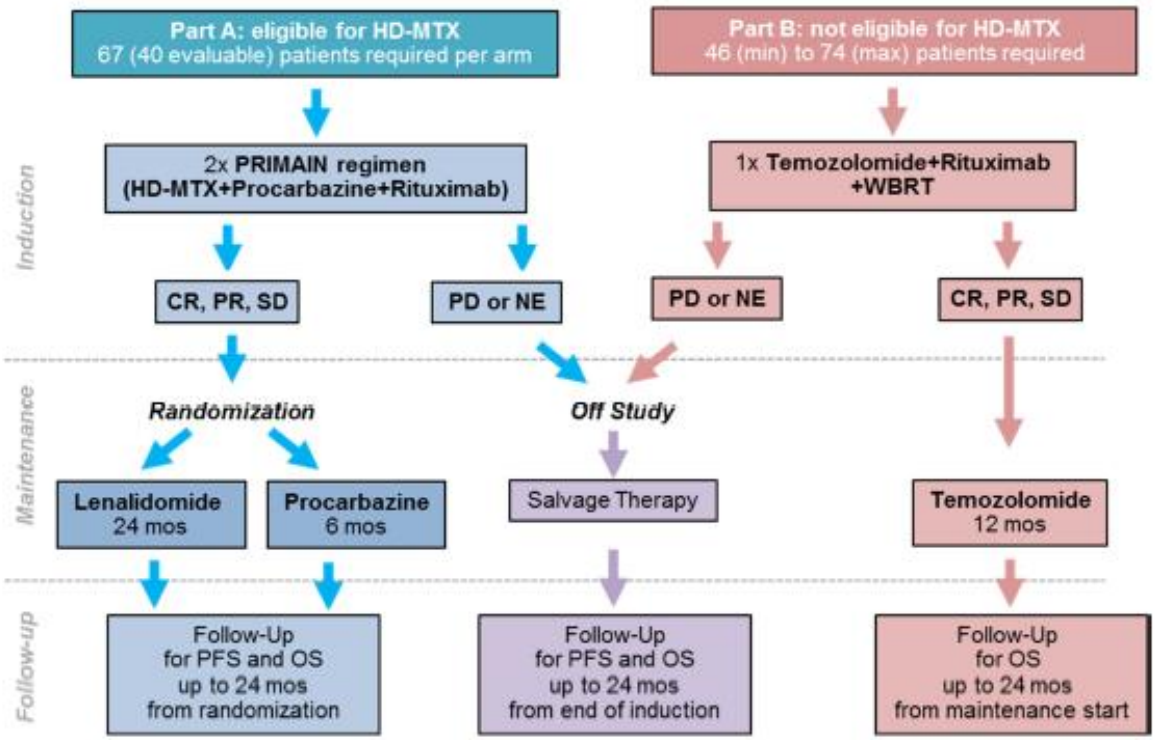
All PCNSL pts ≥ 70 years old

Trial registration

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

Ineligible for therapy

ONLY DATA COLLECTION



IELSG45 FIORELLA Trial

At registration, pt will be defined as eligible for HD-MTX based on all of the following mandated criteria:

- ✓ Adequate bone marrow function (Platelet ≥100.000/mm^3, Hb ≥8 g/dL, ANC ≥ 1.500 mm^3)
- ✓ Creatinine clearance ≥50 ml/min
- ✓ Adequate cardiac function (LVEF ≥45%)
- ✓ Absence of symptomatic coronary artery disease, cardiac arrhythmias uncontrolled with medication or myocardial infarction within the last 6 months (NYHA Class III or IV)
- ✓ Physician's preference (overall assessment other than age and comorbidities)

Part A

To establish the efficacy of two consolidation strategies: lenalidomide or procarbazine in elderly PCNSL pts (>70 ys) eligible to receive HD-MTX.

Part B

To establish the efficacy of concomitant chemo-immuno-radiotherapy followed by temozolomide maintenance in elderly PCNSL pts (>70 ys) not eligible to receive HD-MTX.

Primary endpoint: 2-year PFS

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Indolent lymphomas

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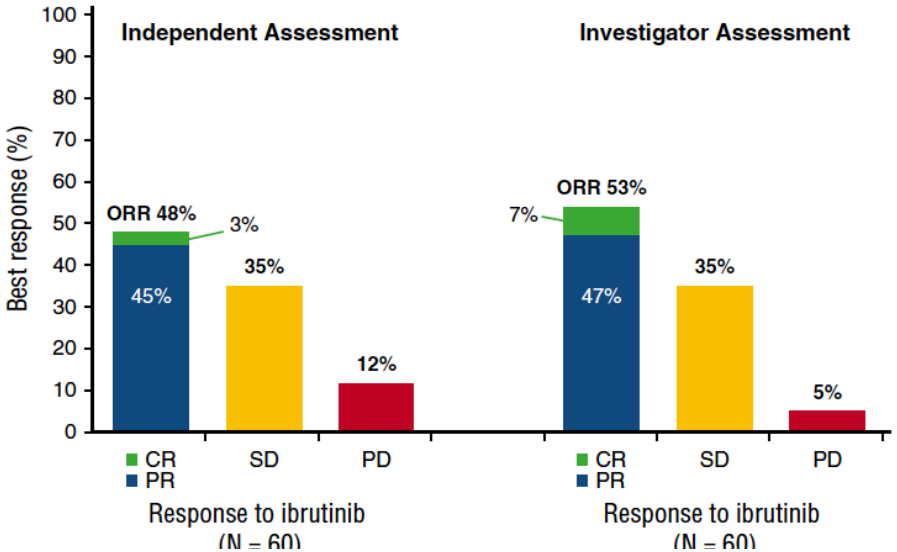
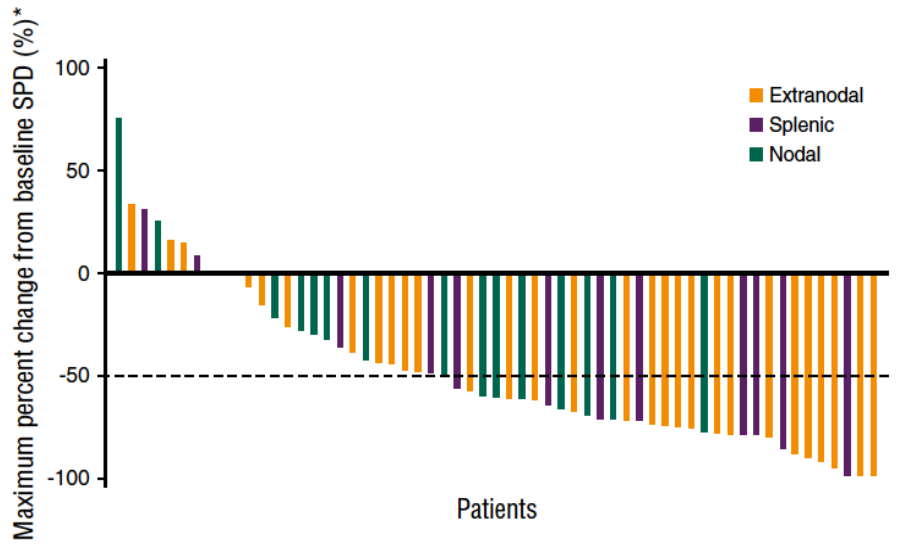
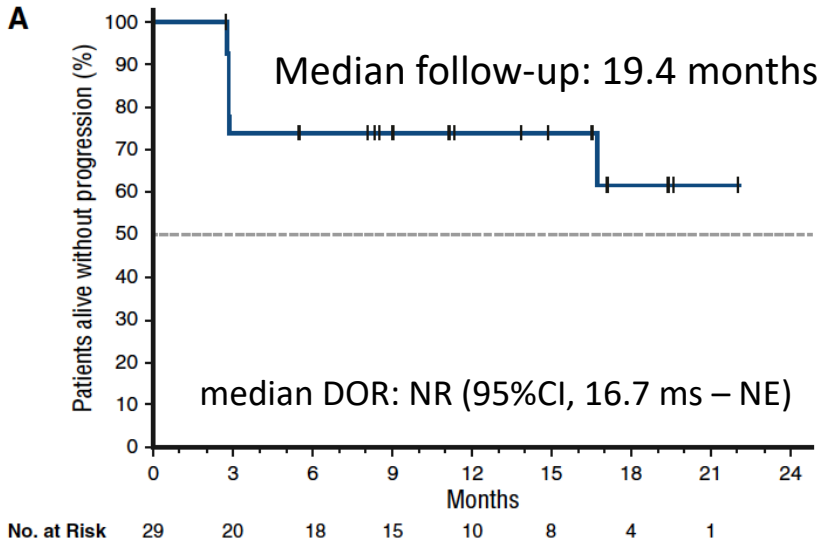
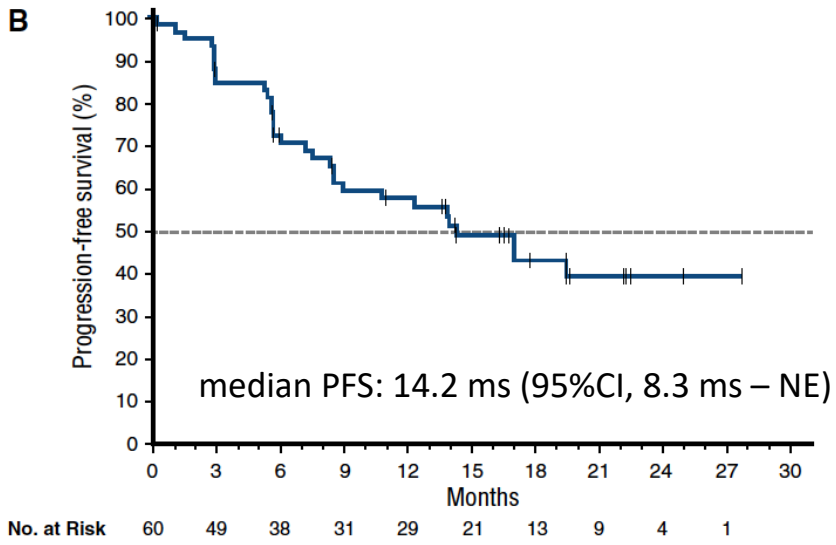
  IELSG47 – MALIBU study

IBRUTINIB IN R/R MZL: PHASE II STUDY









Noy *et al*. Blood 2017

MALIBU TRIAL – IELSG47 STUDY

Phase II study of combination
ibrutinib and rituximab
in untreated marginal zone lymphomas (MZL)

MALIBU TRIAL: study design

- **Single-arm, phase II clinical trial of patients with EMZL (N=130)**

  The study primary endpoints will be analysed on the EMZL population

- Additional patients, with SMZL (up to 15) and NMZL (up to 15), with exploratory purposes

Primary objectives

- assess the safety and efficacy of the combination of rituximab and ibrutinib in EMZL patients
- explore its activity in SMZL and NMZL

Primary endpoints

- Complete Response (CR) rate at 12 months
- Progression-Free Survival (PFS) at 5 years

MALIBU TRIAL: inclusion criteria (*i*)

Systemic therapy-naïve patients, symptomatic and in need of treatment, with histologically proven CD20+ MZL not eligible for local therapy

MALT Lymphoma patients with MALT- IPI score ≥1

- either de novo or relapsed following local therapy (including surgery, radiotherapy and antibiotics for *HP*-positive gastric lymphoma) arisen at any extranodal site

1.1. The following patients with gastric MALT Lymphoma can be entered:

a) H. pylori-negative cases, either de novo (non pretreated) or at relapse following local therapy (i.e., surgery, radiotherapy or antibiotics).

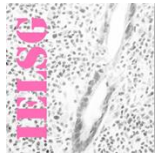
b) H. pylori-positive cases at diagnosis, who had either first line antibiotics or further local treatment (surgery or radiotherapy), including patients with:

− clinical (endoscopic) and histological evidence of disease progression at any time post HP eradication

− clinical (endoscopic) and histological relapse (without HP re-infection), after a remission

− persistent (stable) lymphoma at ≥ 1 year post HP eradication

1.2. Similar consideration for patients with ocular adnexal lymphoma treated with antibiotics.



MALIBU TRIAL: inclusion criteria (*ii*)

Systemic therapy-naïve patients, symptomatic and in need of treatment, with histologically proven CD20+ MZL not eligible for local therapy

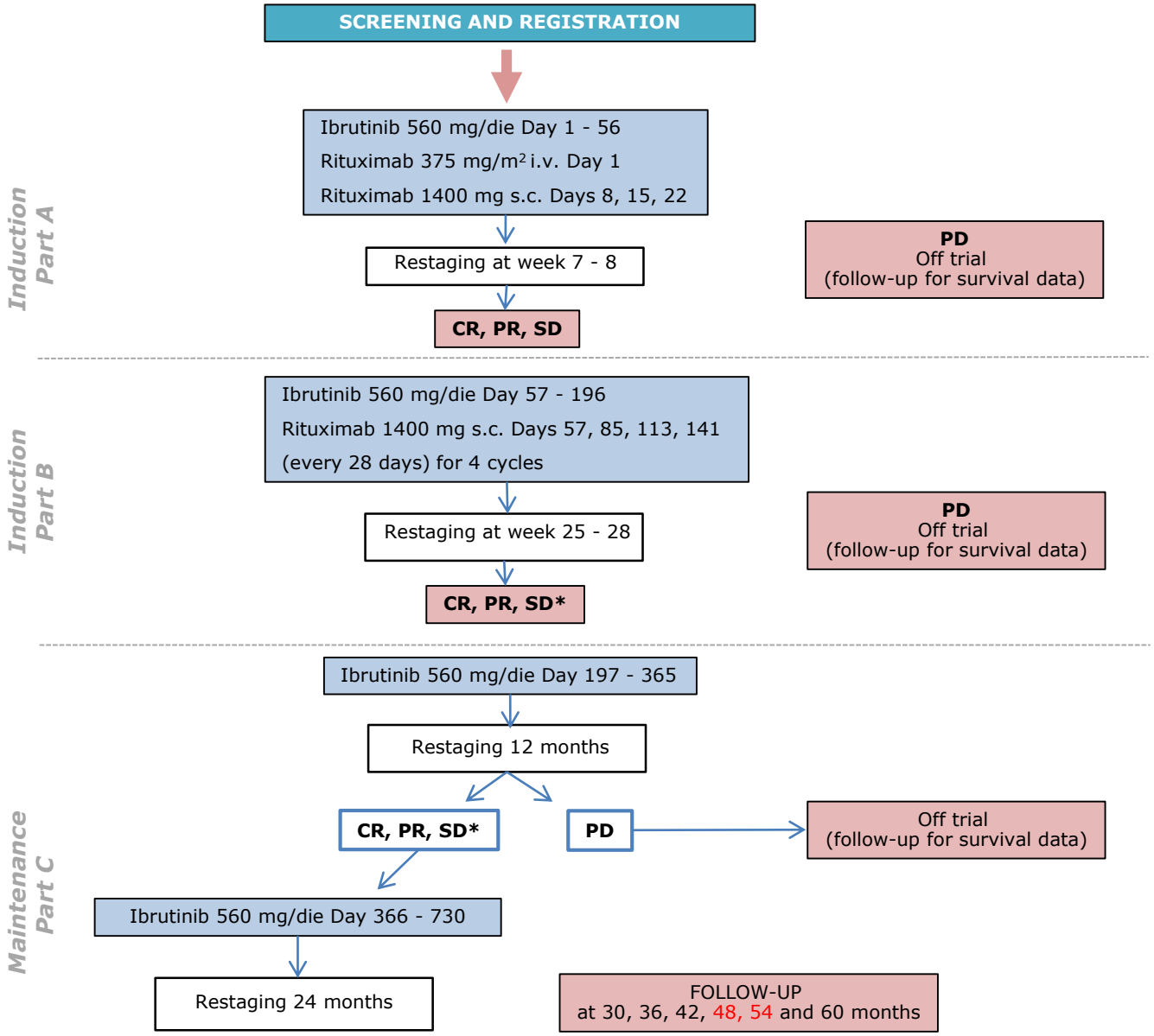
SMZL patients in need of therapy

- either de novo or relapsed following local therapy (including surgery and antiviral therapy for Hepatitis C virus)
- patient must have a symptomatic disease requiring treatment and be not eligible for splenectomy or not willing to undergo splenectomy

NMZL patients in need of therapy

- either, de novo presenting with disseminated disease or relapsed after local radiotherapy or following antiviral therapy for Hepatitis C virus

MALIBU trial flow



*patients in SD will continue study treatment at discretion of the investigator, if of clinical benefit

MALIBU TRIAL: sample size

Primary endpoint. The statistical hypothesis is based on an improvement of the **CR rate at 12 months from 72.9 %** (as observed with the combination of Rituximab and Chlorambucil in the IELSG19 study in patients with MALTIPI>0) **to 85%**

Ho: p = 0.7290 and alternative p = 0.8500
alpha = 0.0250 (one-sided)
power = 0.9000
n = 120

Taking into account exclusion of cases after central histology review and non-evaluable patients, **130 patients with EZML will be enrolled**

Co-primary endpoint. The statistical hypothesis is based on a **15% improvement of the 5-yrs PFS rate from 61.4 %** (as observed with the combination of Rituximab and Chlorambucil in the IELSG19 study in patients with MALT-IPI>0)

Ho: p = 0.614 and alternative p = 0.7640
alpha = 0.025 (two-sided)
power = 0.9000
n = 100

In the case of statistically significant result on CR,
the study will yield a type 1 error rate = 0.05 and power = 0.95.

MALIBU ANCILLARY STUDIES

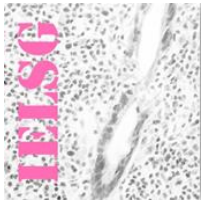
PET study

With centralisation of the studies

Biological studies

With collection of different kind of samples

MALIBU TRIAL-CENTERS



Sponsor: IELSG

• Italy	16 centers
• France	13 centers
• United Kingdom	12 centers
• Switzerland	2 centers
• Belgium	1 center
• Portugal	1 center


Acknowledgements

- The FIL Central Office staff
- The IELSG Central Office staff
- F. Cavalli, E. Zucca, U Vitolo, M. Martelli, A.Ferreri, L. Ceriani , P. Johnson, A. Lopez Guillermo, C. Thieblemont and all the many other IELSG investigators
- The study nurses and data managers