LINFOMI FOLLICOLARI

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LINFOMI FOLLICOLARI

I linea

-**Mirò** closed

-**FOLL12** closed

II linea

-**FLAZ12** on going

-**RENOIR12** on going

Osservazionale

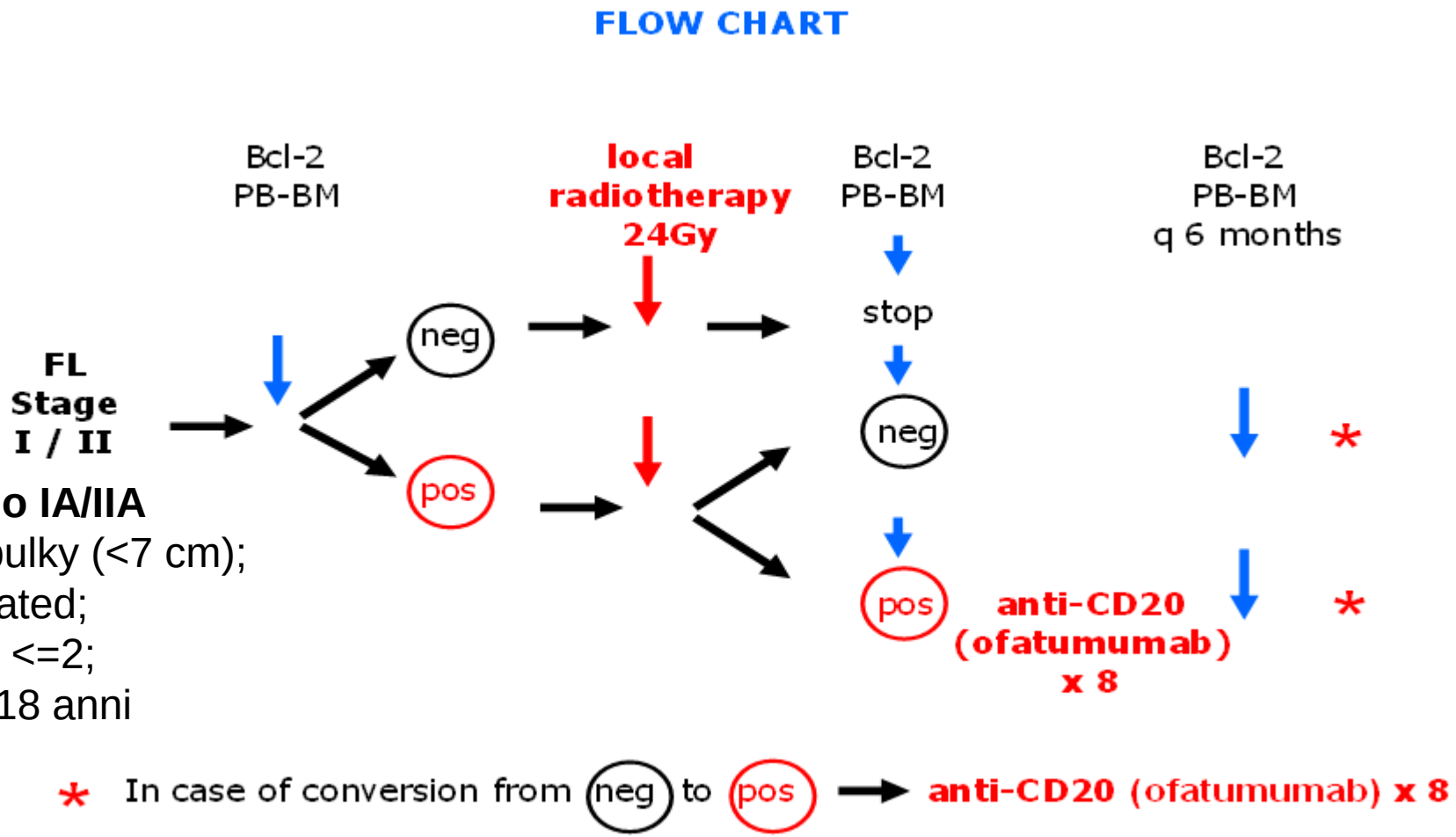
-**PETRA** on going

FIL_Mirò

Studio “MIRO’ ” (Molecularly Immuno-radio-therapy Oriented): studio multicentrico di fase II per il trattamento su base molecolare dei Linfomi Follicolari stadio I/II con radioterapia locale con/senza Ofatumumab

PI: Dott. Alessandro Pulsoni

FIL_MIRÒ

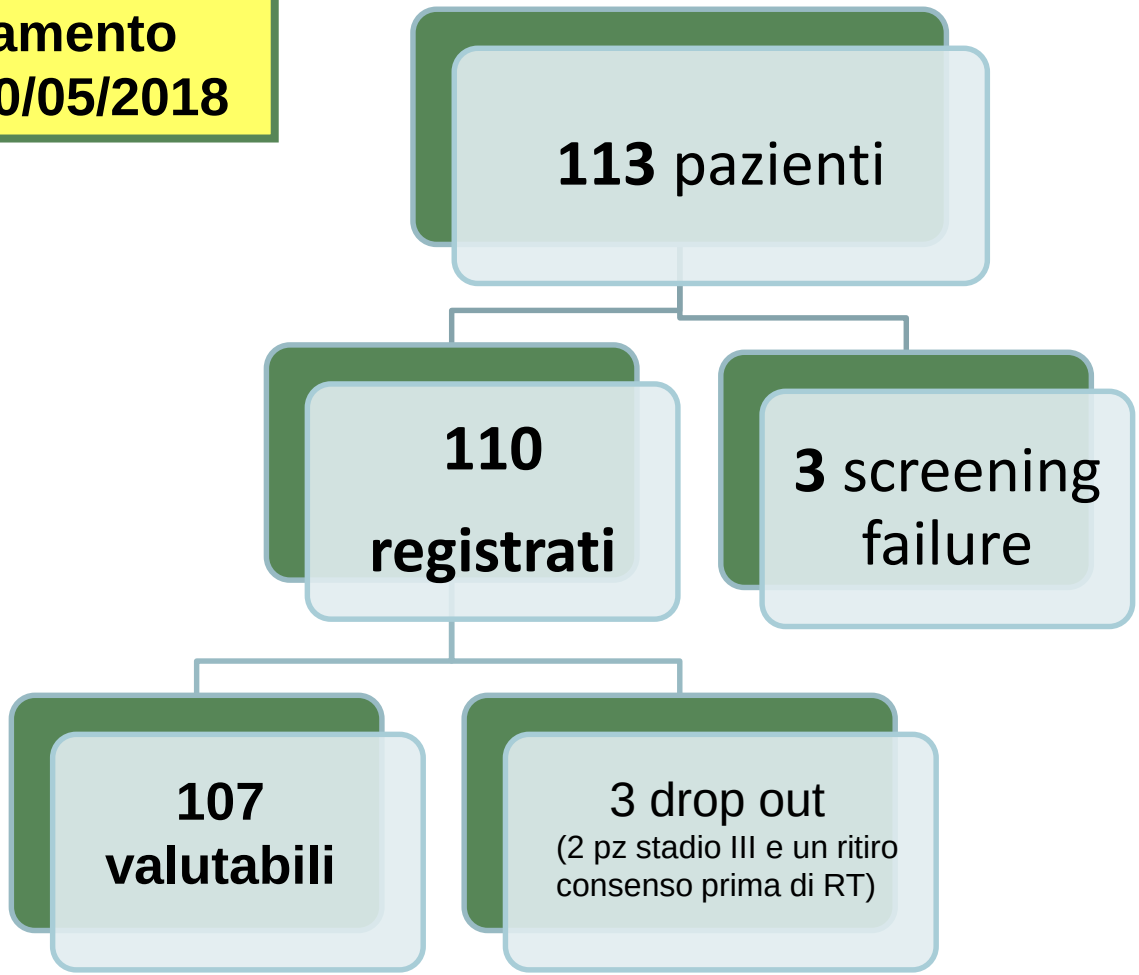


Stadio IA/IIA
non bulky (<7 cm);
untreated;
FLIPI <=2;
età >18 anni

Obiettivo primario: % di pazienti che ottiene MRD neg dopo ofatumumab

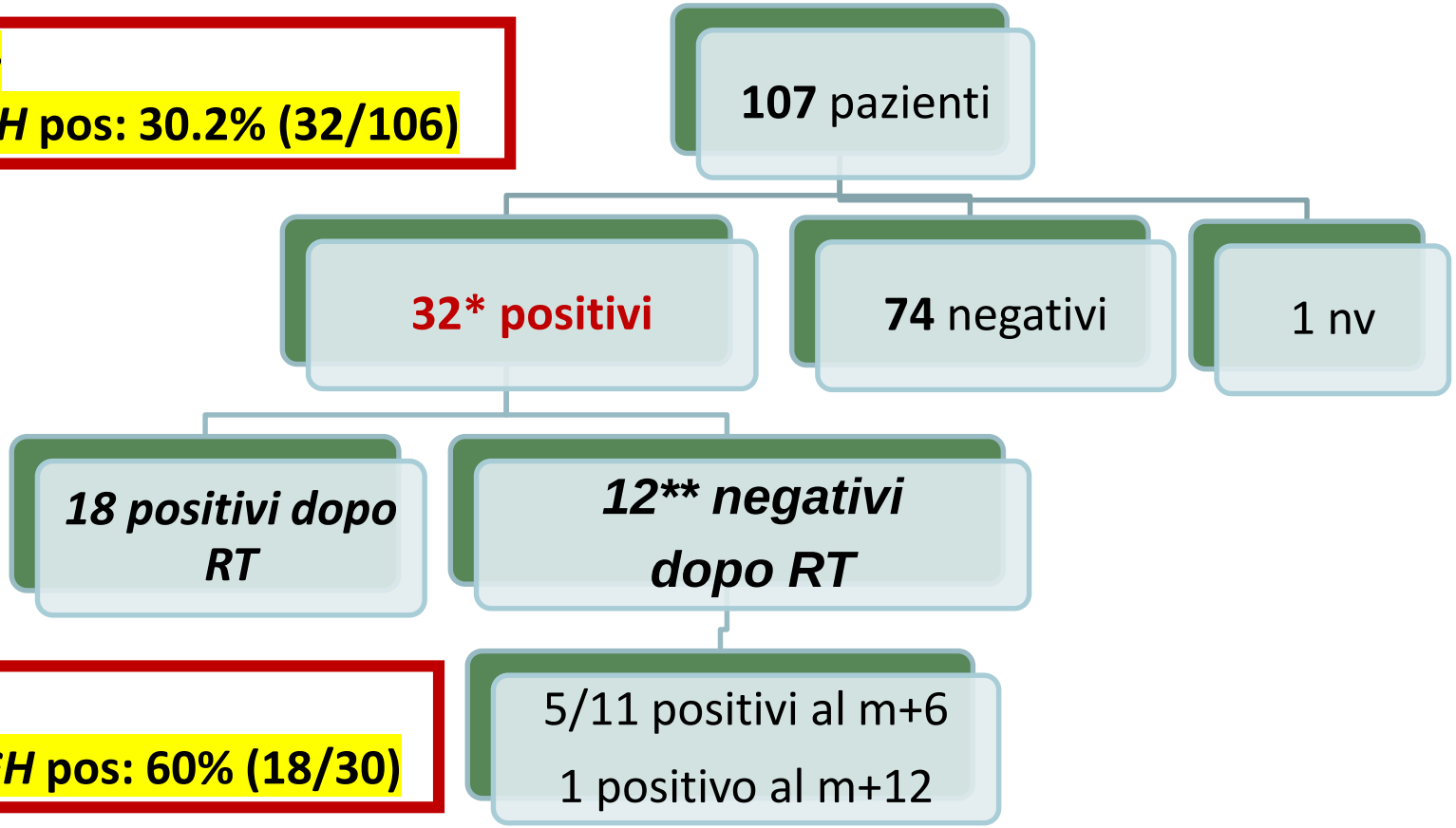
ARRUOLAMENTO PAZIENTI

Arruolamento chiuso 10/05/2018



ARRUOLAMENTO PAZIENTI

Baseline
***BCL2/IGH* pos: 30.2% (32/106)**



Post RT
***BCL2/IGH* pos: 60% (18/30)**

*pz deceduto in corso di radioterapia, 1 paziente è risultato in progressione dopo RT
** un paziente uscito per PD prima di rivalutazione mese 6

TRATTAMENTO (30/10/2018)

24 pazienti avviati al trattamento

21 hanno completato terapia

3 paz hanno interrotto prematuramente

1 pz : 1 dose di Ofa e ritira il consenso
1 pz: 4 dosi di Ofa e stop per AE
1 pz : reazione dopo prima infusione

RISPOSTA A OFATUMUMAB

MRD post Ofatumumab:
***BCL2/IGH* neg (PB&BM): 84.2% (16/19)**

2 pazienti (esclusi x trattamento incompleto) hanno ottenuto la negativizzazione, se li consideriamo: -> 85.7% (18/21)

Pz retreated with 2° course of Ofatumumab -> none

FONDAZIONE ITALIANA LINFOMI
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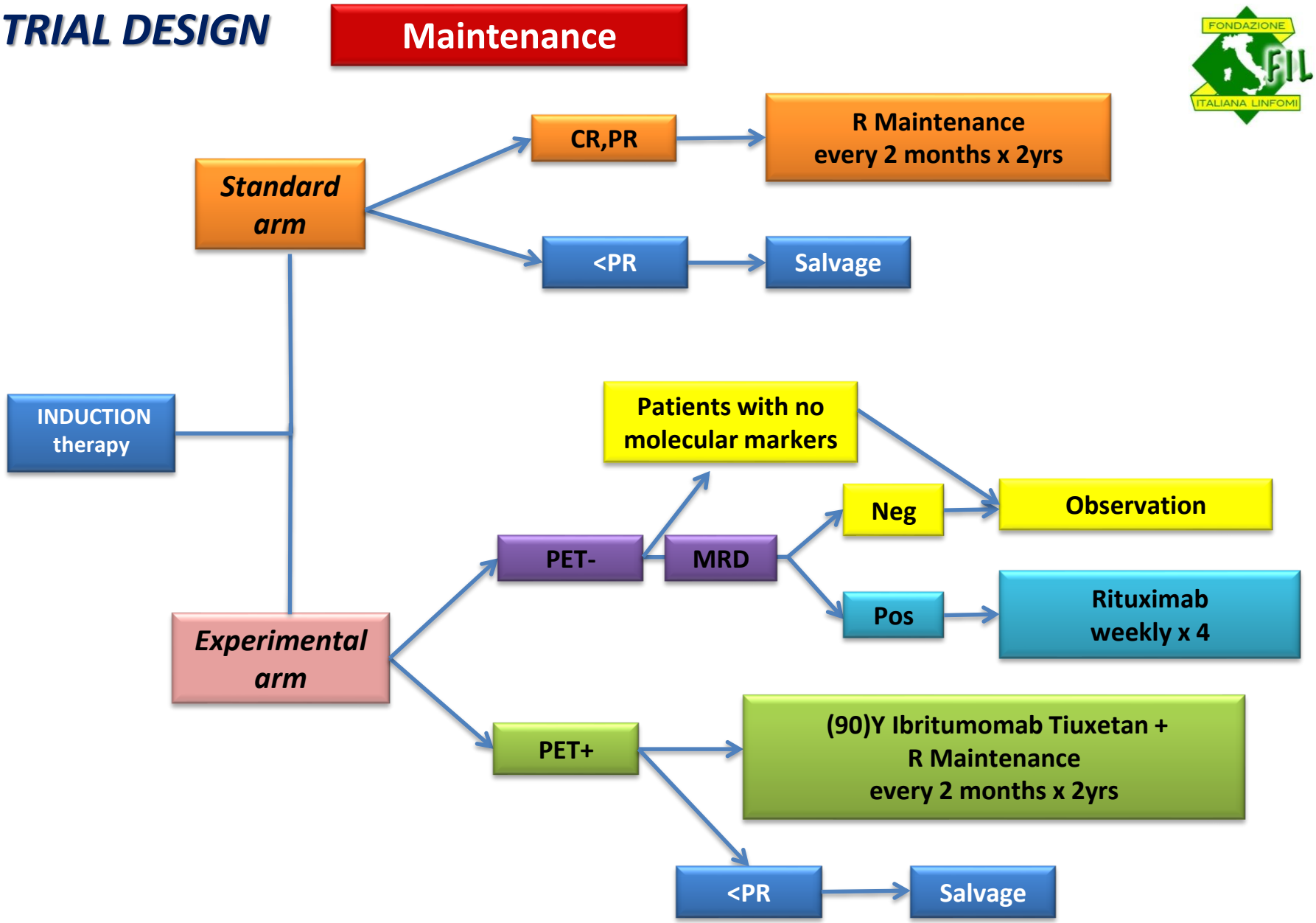
FOLL12

A multicenter, phase III, randomized study to evaluate the efficacy of a response-adapted strategy to define maintenance after standard chemoimmunotherapy in patients with advanced-stage Follicular Lymphoma

EUDRACT NUMBER 2012-003170-60

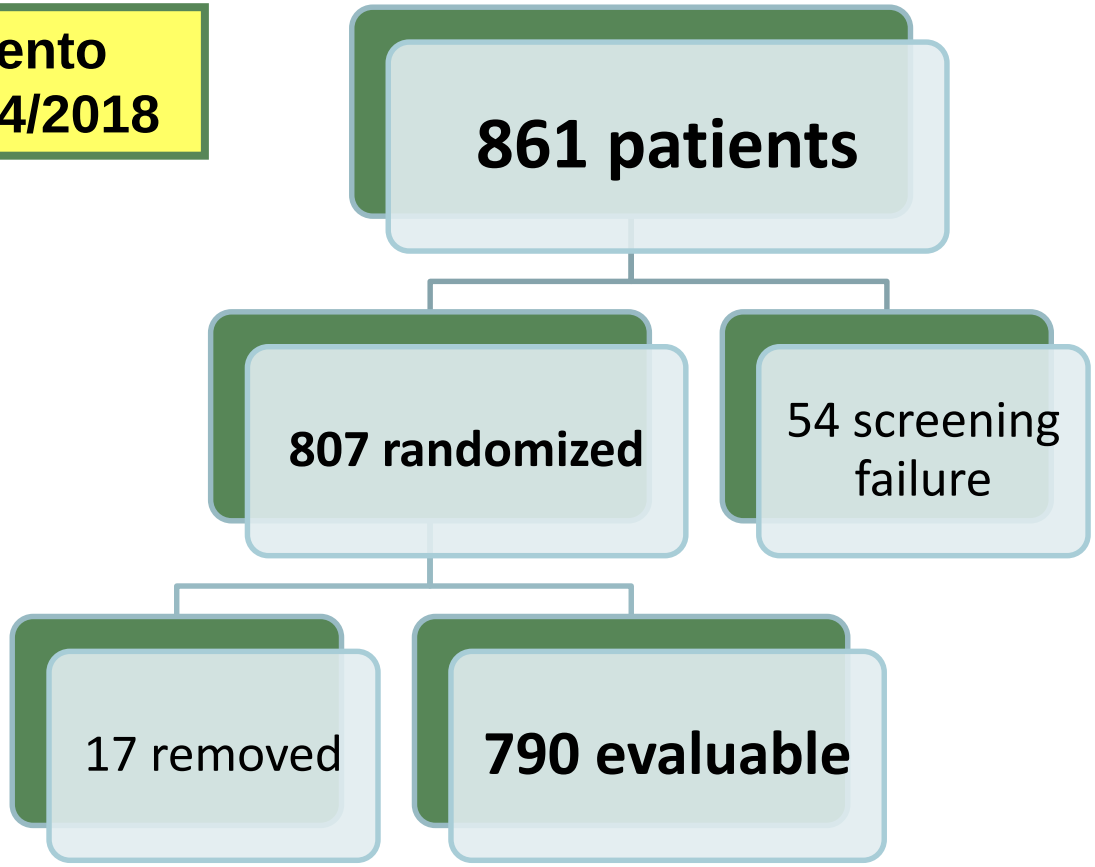
STUDY COORDINATORS Massimo Federico
Donato Mannina

TRIAL DESIGN

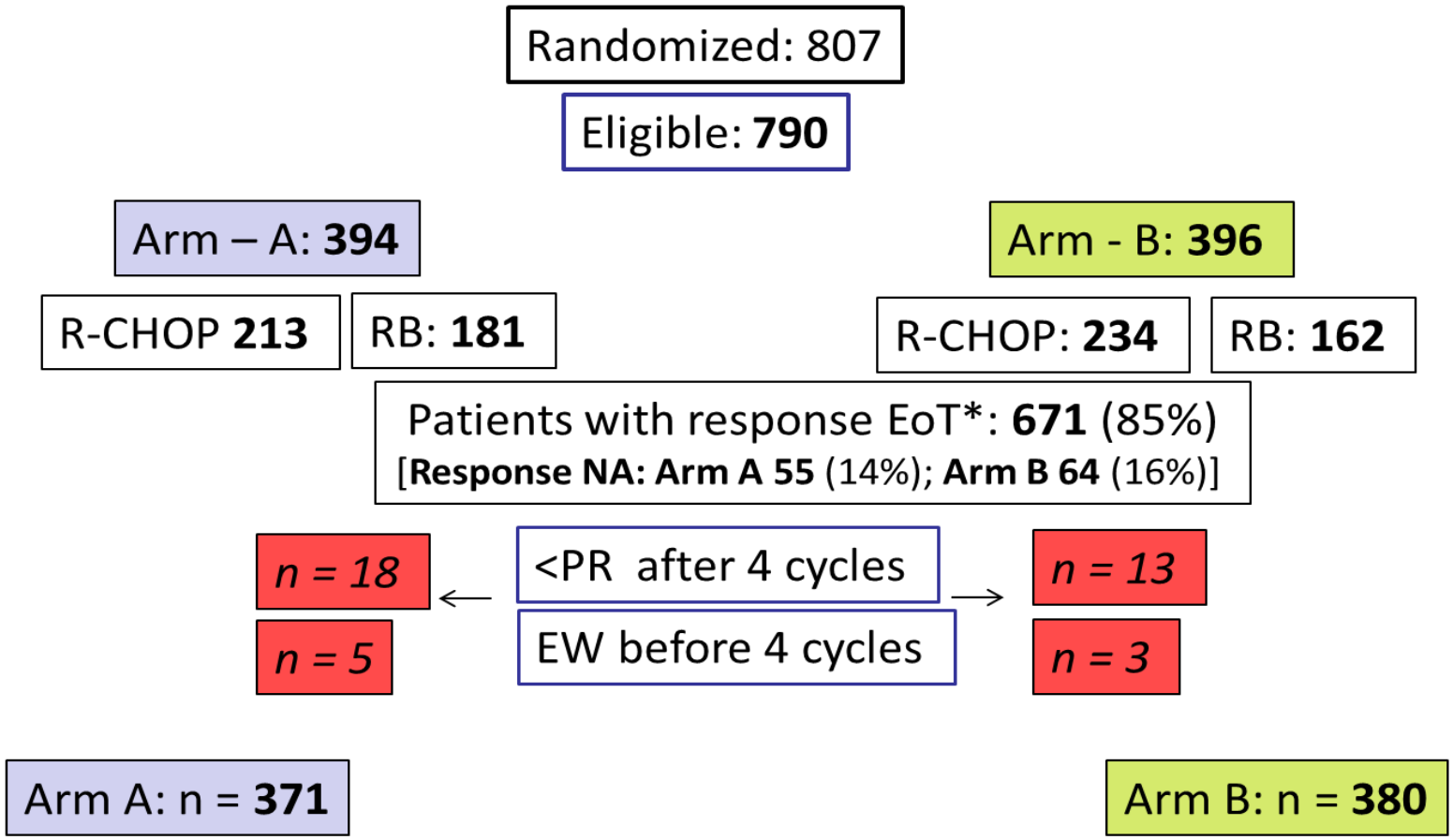


FIL_FOLL12 ACCRUAL

Arruolamento chiuso 26/04/2018



FIL_FOLL12 ACCRUAL



FIL_FLAZ-12 STUDY

A PHASE III MULTICENTER, RANDOMIZED STUDY COMPARING CONSOLIDATION WITH ^{90}YTTRIUM-LABELED IBRITUMOMAB TIUXETAN (ZEVALIN®) RADIOIMMUNOTHERAPY VS AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) IN PATIENTS WITH RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA (FL) AGED 18-65 YEARS

PI: Dott. Marco Ladetto

FLAZ-12: STUDY OBJECTIVES

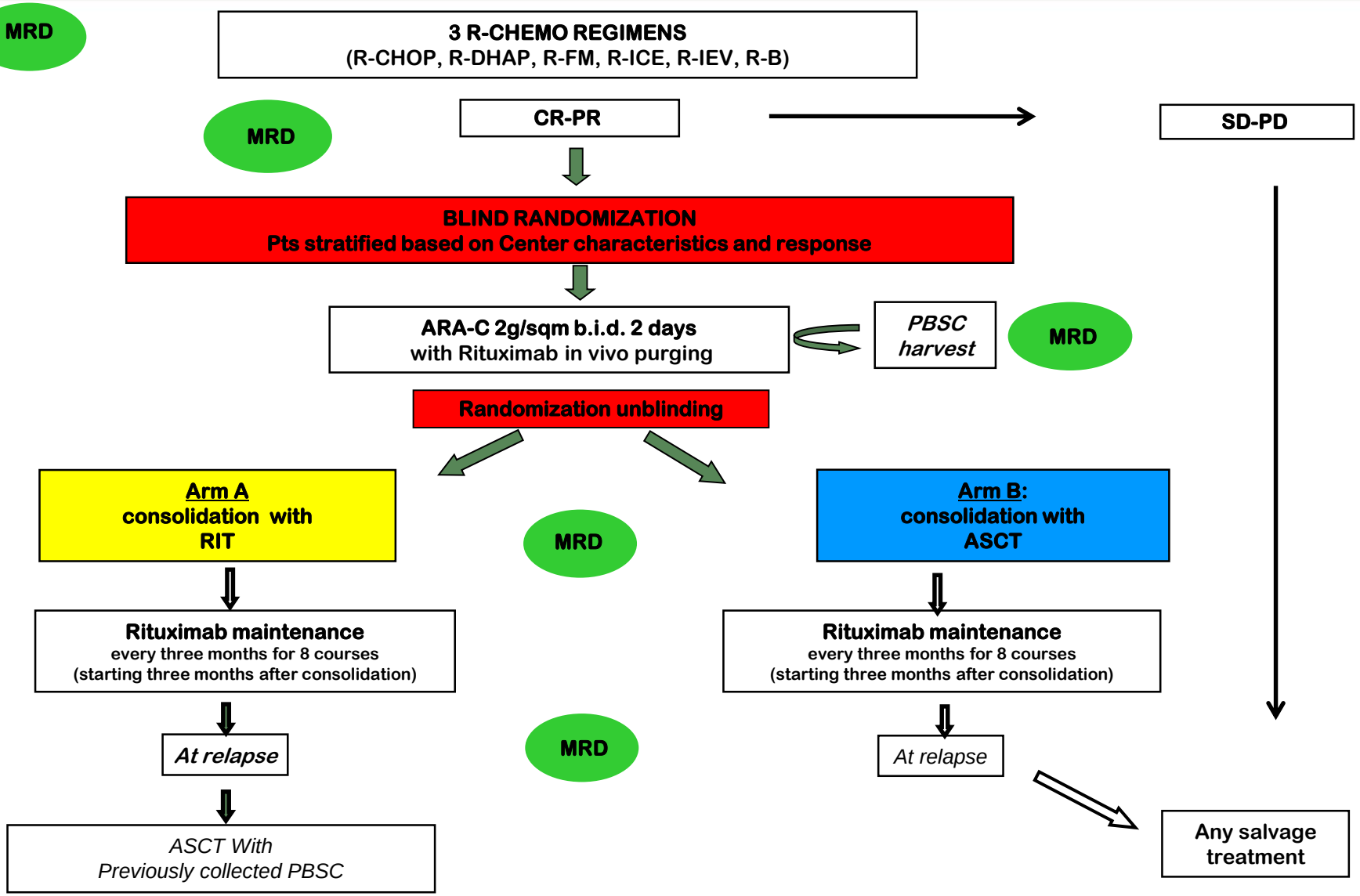
PRIMARY

- Compare 2 different consolidation regimes: ***RIT (Zevalin) vs. ASCT*** in terms of **progression free survival (PFS)** in ***relapsed/refractory FL patients aged 18-65.***

SECONDARY

- Complete Remission **(CR)** and Overall Response Rate **(ORR)**
- Events-free Survival **(EFS)**, Treatment-free survival **(TFS)** from randomization and Overall Survival **(OS)**
- Effect of ASCT vs RIT on **minimal residual disease (MRD)** in terms of: molecular response rate, molecular relapse rate, kinetics of disease assessed by real-time PCR on bone marrow and peripheral blood
- Prognostic impact of **molecular disease persistence** on PFS and OS
- Assess feasibility, toxicity and efficacy (ORR, PFS and OS) **of ASCT after RIT faillure**
- Assess **toxicity** in both arms during induction, consolidation and maintenance
- Compare **cost-effectiveness** of both treatment regimens **(verrà eliminato nell'emend. sottomesso)**
- Check the impact of the two treatment on **quality of life** in the short and long term **(verrà eliminato nell'emend. sottomesso)**

FLAZ-12: STUDY DESIGN



FLAZ-12: Em. Sost. N. 3

È stato sottomesso l'emendamento sostanziale n.3 ai Comitati Etici e ad AIFA:

Le modifiche più rilevanti sono:

- ✓ Formalizzazione dell'emendamento urgente del 18/08/2017, trasmesso a seguito della ricezione della nota AIFA relativa al farmaco Bendamustina integrando nel protocollo le misure di sicurezza intraprese con l'emendamento urgente.
- ✓ Aumento del periodo di arruolamento a **8 anni**
- ✓ Introduzione dell'uso del Rituximab sc nella terapia di mantenimento
- ✓ Questionari sulla qualità della vita (EORTC QLQ-C30 questionnaire; Euro-Qol (EQ-5D) e sulla valutazione costo-efficacia non mandatori

FLAZ-12: MAIN INCLUSION/EXCLUSION CRITERIA

INCLUSION

- Age 18-65 years
- Histologically documented diagnosis of grade I-IIIa
- ECOG performance status 0-2 (unless disease –related)
- Relapsed or refractory disease after ≤ 2 chemotherapy lines
- Clinical indication for treatment (according to SIE and GELF criteria)
- Adequate cardiac function : LVEF > 50% by echocardiography or MUGA scan

EXCLUSION

- Grade IIIb FL, transformed FL or histologies different from FL
- Previous treatment with > 2 lines of chemotherapy (Rituximab maint. is not considered a treatment line)
- Previous ASCT or RIT treatment
- CNS involvement by lymphoma
- Treatment with an experimental agent within 30 days prior to study entry
- Myelosuppressive chemotherapy or biological therapy within three weeks before study

FLAZ-12: FIL CENTERS

- ✓ **First patient: September 2012**
- ✓ **Sample size: 210 randomized (265 total)**
- ✓ **Study duration: 8 yrs accrual + 2 yrs FU (emendamento sottomesso)**
- ✓ **ACTIVE CENTERS: 48**
- ✓ **ENROLLED PATIENTS: 150 !!!!!!!!!!!!!!! -115**

FLAZ-12: RANDOMIZATION

ARM	N. Of Patients
A (RIT)	65
B (ASCT)	60
To be randomized	10
ND WITHDRAWAL BEFORE RANDOMIZATION	15

FLAZ-12: CURRENT SITUATION

- ✓ Regular administration of zevalin
- ✓ Enrollment remains low although slightly improving
- ✓ STOP AIFA support
- ✓ Ongoing CRF monitoring
- ✓ Planned Interim Analysis

ADVERSE EVENTS

ACTUALLY NO MAJOR PROBLEMS HAVE BEEN OBSERVED FOR ENROLLED PATIENTS

SAE	SUSAR
26	1

FONDAZIONE ITALIANA LINFOMI
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FIL_RENOIR12

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-chemotherapy (R-CHT) for relapsed/refractory FL patients not eligible for autologous transplantation (ASCT)

STUDY COORDINATORS Umberto Vitolo
Stefano Sacchi
Barbara Botto

RENOIR12

Aim of the study

To verify whether, in patients responsive to Rituximab-*chemotherapy (R-CHT)* induction, a maintenance program based on Rituximab associated with Lenalidomide is superior to the standard maintenance program (R-MANT) where Rituximab is delivered as single agent.

Study design

This is a multicenter phase III trial with one randomization step that will compare two maintenance regimens (in patients responsive to induction):

R2-MANT program versus standard R-MANT

- Random will be done in 1:1 ratio and stratified by clinical response (PR or CR) after induction
- Lenalidomide supplied by Celgene
- PET not mandatory but reccomended

RENOIR12: OBJECTIVES

Primary

- To evaluate in patients responsive to induction whether the R2-MANT program may improve **progression-free survival (PFS**) compared to patients treated with R-MANT

Secondary

- To compare in patients respondents to induction the R2-MANT vs the R-MANT program for: **safety** (grade III-IV adverse events) and **efficacy (OS)**
- To evaluate the activity of maintenance program on minimal residual disease **(MRD)** in the bone marrow (BM) and peripheral blood (PB).
- To assess the **prognostic impact of molecular persistence and molecular relapse** on PFS and OS.
- To assess **quality of life (QoL)** at study entry and at 6, 12 and 24 months of maintenance , using the EORTC QLQ-C30C questionnaire
- To compare the **cost-effectiveness** of treatment arms with an analysis of direct medical costs with the evaluation of total healthcare costs and Quality AdjustedLife Years (QALYs) using Euro-Qol (EQ-5D) questionnaire.

RENOIR12: INCLUSION/EXCLUSION CRITERIA

Inclusion

- Follicular lymphoma grade I, II and IIIa according to the WHO classification.
- Re-biopsy mandatory only in case of suspected transformation.
- **First or second relapse or progression** following R-chemotherapy (maintenance and RT not considered treatment lines)
- Patients not eligible for high dose chemotherapy and ASCT
- **Enrollment possible if previous treatment with Bendamustine more than 2 years or prevoius ASCT**
- Age >18 years.
- Need of treatment according to SIE-SIES-GITMO guidelines

Exclusion

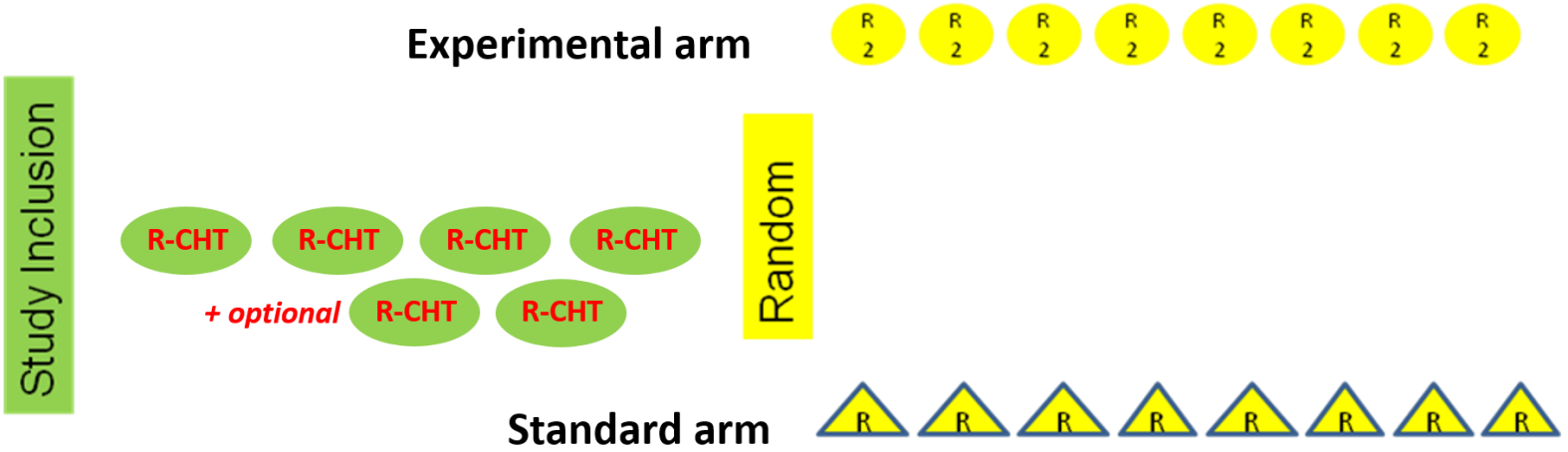
- Any lymphoma subtype other than FL ,grade 3b follicular lymphoma.
- Prior history of malignancies, other than follicular lymphoma, unless the subject has been free of the disease for > 3 years
- Prior use of Lenalidomide
- Neuropathy > Grade 1
- Presence or history of CNS involvement by lymphoma.

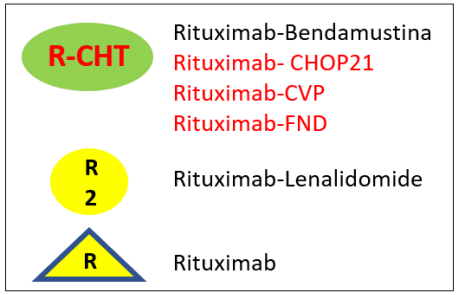
RENOIR12: SAMPLE SIZE EMENDAMENTO

- The expected PFS at 2 years from the end of the treatment is about 60%.
- In the arm randomized to R2-MANT an absolute improvement of PFS of at least 18% at 2 years is considered clinically relevant.
- **Accrual time 54 months, follow up 30 months**
- According to O'Brien and Fleming group sequential design, allowing for a 5% of losses to follow-up, a total of **128 responders** (**64 per group**) need to be randomized to detect an increase in the 2-yr PFS from 60% to 78% (corresponding to a HR=0.5), assessed with a two-sided log-rank test with alpha of 5% and a **power of 80%.**

160 patients (128/0.80) should be enrolled and treated with the induction regimen to assure 128 patients available for the randomization

RENOIR12: TREATMENT DESIGN EMENDAMENTO





- Terapia di induzione: oltre a R- bendamustina è possibile utilizzare anche i seguenti schemi terapeutici: *R-CHOP, R-CVP, R-FND*.
- Possibilità di effettuare fino a *6 cicli* di R-CHT in caso di SD/PR al fine di ottenere la migliore risposta possibile prima della randomizzazione.
- È autorizzato l'utilizzo del *Rituximab sottocute* e *biosimilare anti-CD20* sia nella terapia di induzione che nel mantenimento, in accordo con le disposizioni locali.

RENOIR12: STATUS REGOLATORIO

DATA INIZIO STUDIO → 23/04/2014

1° PAZIENTE ARRUOLATO → 01/09/2014

DURATA STUDIO → 98 mesi (68 mesi per l'arruolamento + 30 mesi di follow up)

CONCLUSIONE ARRUOLAMENTO → *settembre 2019*

- Centri partecipanti/Centri attivi: 53/44 (→ *36/33*)*
- Centri Attivi/Centri arruolanti: 44/24 (→ *33/24*)*

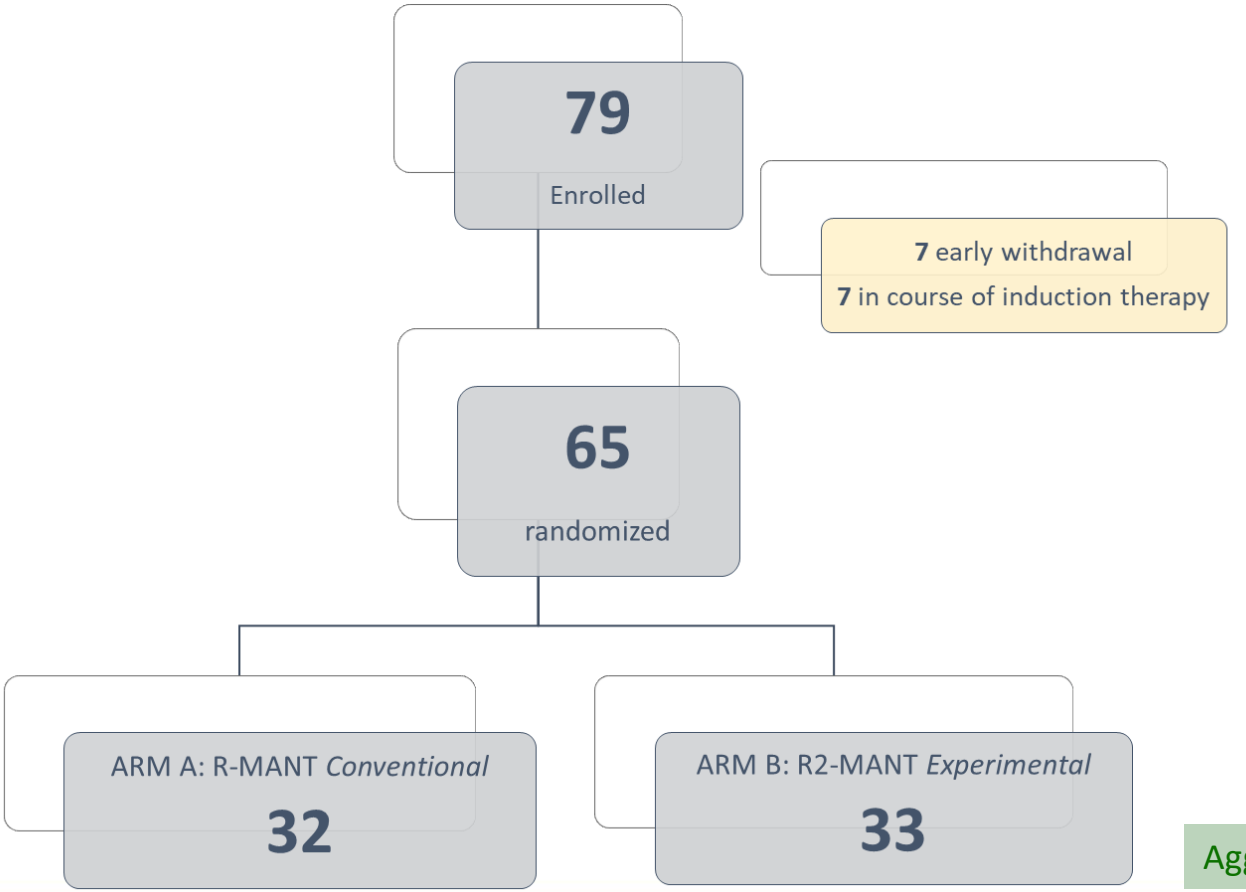
** È in corso la chiusura formale di alcuni centri non attivi e/o attivi ma non arruolanti che non hanno rinnovato l'interesse per la sperimentazione.*

Tra parentesi il numero di centri partecipanti e attivi al netto dei centri in chiusura.

RENOIR12: ARRUOLAMENTI

Accrual: 160 subjects (to randomize 128 patients)

PAZIENTI ARRUOLATI	79 (49% TOTALE)
PAZIENTI RANDOMIZZATI	65 (51% TOTALE)



Agg. al 17 ottobre 2018

FONDAZIONE FIL ITALIANA LINFOMI
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PETRA

Study on the role of FDG-PET in patients with follicular lymphoma at time of RelApse/progression

STUDY COORDINATORS ***Stefano Luminari***
Giuseppe Rossi
Annibale Versari

BACKGROUND AND RATIONALE

FOLLICULAR LYMPHOMA

- Histological transformation: 15-20% of cases; Consensus rate: 3% per year; Mean survival post-transformation: less than two years [1].

- To date there are still not useful tools for the early identification of trasformation event.

- There is evidence that FDG-PET has utility as a biomarker of transformation: the highest SUVmax is significantly higher for transformed follicular lymphoma (tFL) than FL [2].

[1] Montoto S, Fitzgibbon J, et al. Transformation of indolent B-cell lymphomas. J Clin Oncol. 2011 May 10;29(14): 1827-34.

[2] Wondergem MJ, Rizvi SN, Jauw Y, Hoekstra OS, Hoetjes N, van de Ven PM, et al. 18F-FDG or 3'-deoxy-3'-18F-fluorothymidine to detect transformation of follicular lymphoma. J Nucl Med. 2015 Feb;56(2): 216-21.

OBJECTIVES AND ENDPOINTS

OBJECTIVES

Primary objective

•To evaluate whether metabolic activity measured by FDG-PET (SUV max) at time of relapse is predictive of patient's outcome.

Secondary objectives

•To correlate metabolic activity measured by FDG-PET (SUV and SUV max) at time of relapse with the frequency of histological transformation.

•To correlate metabolic activity measured by FDG-PET and histological data with clinical and laboratory parameters.

ENDPOINTS

Primary endpoint

•Progression free survival from time of relapse/progression

Secondary endpoints

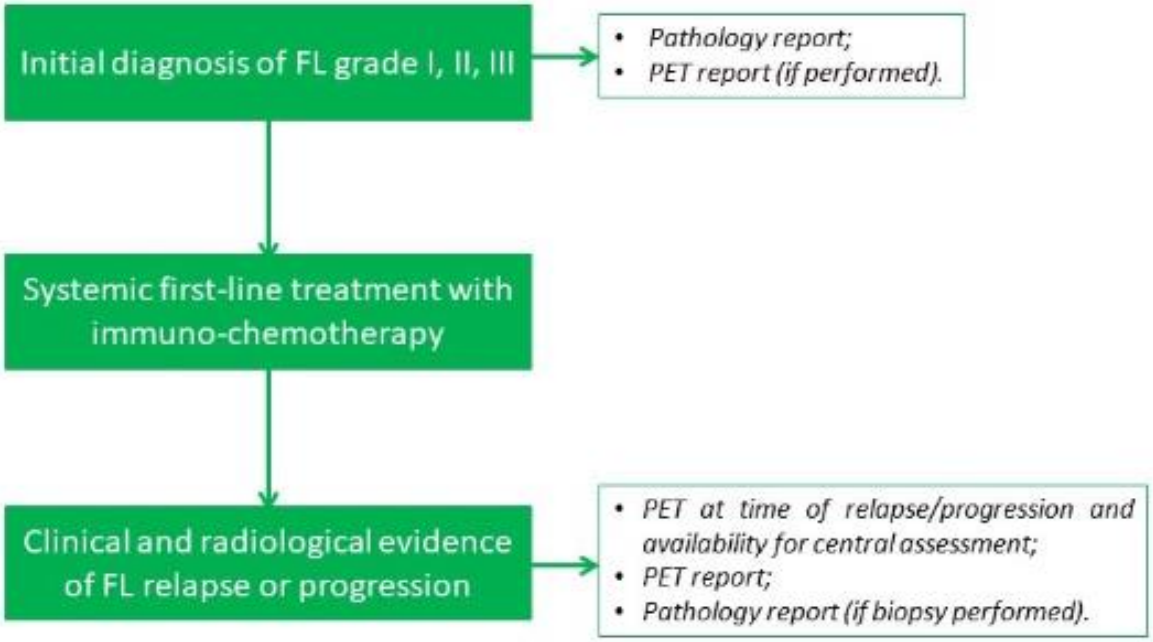
•Overall survival (OS)

•Rate of histological transformation

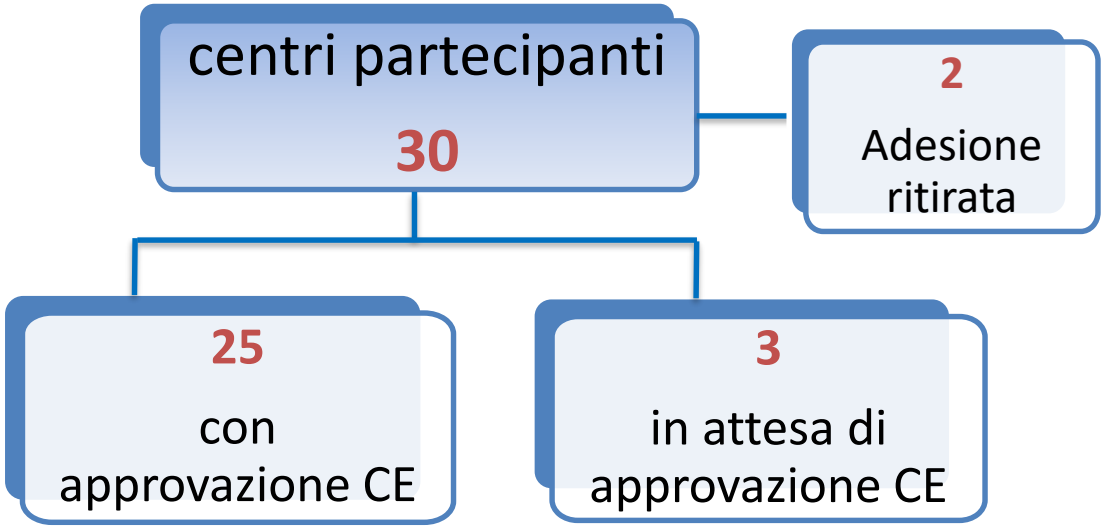
MAIN INCLUSION CRITERIA

- Patients with initial diagnosis of follicular lymphoma since 2001
- Histological confirmation of follicular lymphoma, grade I, II, III according to WHO 2008 classification, at time of initial diagnosis
- **Systemic first-line treatment with immuno-chemotherapy**
- Clinical and radiological evidence of FL relapse or progression
- Histological confirmation of relapse (strongly recommended)
- **Availability of PET at time of relapse/progression and its images available for central assessment**
- Availability of clinical, laboratory and therapeutic treatment data at time of initial diagnosis and relapse/progression
- Follow up at least of 12 months after relapse/progression

PETRA


Initial diagnosis of FL grade I, II, III
• Pathology report;
• PET report (if performed).
Systemic first-line treatment with immuno-chemotherapy
Clinical and radiological evidence of FL relapse or progression
• PET at time of relapse/progression and availability for central assessment;
• PET report;
• Pathology report (if biopsy performed).

ACTIVATION AND RECRUITMENT STATUS



Target: 200 pts meeting inclusion criteria

Actual accrual: 158 patients

A RETROSPECTIVE STUDY TO ASSESS THE ROLE FDG PET- CT IN PATIENTS WITH FOLLICULAR LYMPHOMA AT TIME OF RELAPSE/PROGRESSION.

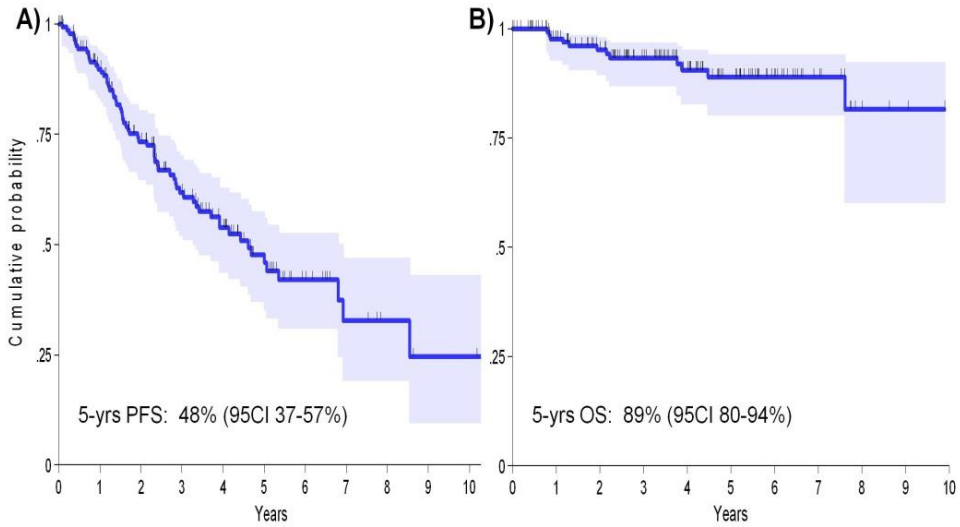


Figure 1. **A)** PFS and **B)** OS after a median follow-up of 45 months (n=147).

Variable	HR (95CI)	P-value
Age at relapse	1.01 (0.99-1.04)	0.291
Gender, F	0.66 (0.40-1.08)	0.100
Stage IV rel.	1.13 (0.69-1.87)	0.621
Treat after relapse	1.77 (0.85-3.74)	0.129
Time to rel > 2yrs	0.39 (0.24-0.64)	*<0.001*
Maint. 1 line	1.76 (1.06-2.92)	*0.029*
Maint. 2 line	0.55 (0.33-0.92)	*0.022*
LDH > ULN rel.	1.02 (0.57-1.83)	0.941
log(SUV max)	1.45 (0.73-2.87)	0.286
SUV max >10	1.26 (0.58-2.72)	0.559

Table 1. Univariate analysis for PFS from relapse.

In this preliminary analysis, metabolic features (SUVmax) assessed at time of relapse were not able to identify patients at higher risk of progression or transformation. Duration of response after first line immunochemotherapy and the use of maintenance rituximab were the only confirmed prognostic factors for rPFS. More mature results of this study will be provided when the ongoing centralized review of PET scans will be completed.

Luminari et al.

7th international workshop on PET in lymphoma and myeloma
Palais de l'Europe, Menton, France, October 4th-6th, 2018

Grazie!