LINFOMI INDOLENTI NON FOLLICOLARI E WALDENSTROM

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Torino

LINFOMI INDOLENTI NON-FOLLICOLARI

Interventistico

-BART

-BRB

Osservazionale

-NF10

-BIOWM

STUDIO BArT

LINFOMI INDOLENTI HCV POSITIVI

A multicenter study to evaluate the anti-viral activity of an interferon-free treatment with ledipasvir/sofosbuvir (G1 and G4) and sofosbuvir/velpatasvir (G2 and G3) for patients with hepatitis C virus-associated indolent B-cell lymphomas

INCLUSION CRITERIA (1)

1. Age > 18 years
2. **Indolent B cell lymphoma:**
    - ***Marginal Zone Lymphoma*** *(MZL):*
        - ***Nodal*** *(NMZL)*
        - ***Extranodal*** *(EMZL, MALT-type)*
        - ***Splenic*** *(SMZL)*
        - ***Disseminated***
    - ***Lymphoplasmacytic lymphoma*** *(LPL)*
    - ***Small Lymphocytic Lymphoma*** *(SLL)*
    - ***Follicular lymphoma*** *(FL)* ***grade 1-2***
    - ***CD5-negative B-cell lymphoma NOS***
3. **HCV-RNA positive** patients
4. **Assessable HCV genotype (1, 2, 3 or 4)**
5. **No previous therapy for lymphoma**

INCLUSION CRITERIA (2)

6. **Measurable disease** after diagnostic biopsy (*longest axis ≥1.5 cm for nodal and ≥1 cm for extranodal lesions*) **and/or evaluable disease** *(quantifiable BM infiltrate and >5 x10^9/L clonal B-cells in PB in case of exclusive BM/leukemic disease)*
7. **No need for immediate lymphoma treatment**, *defined by the* ***absence of all the following criteria***:
   - systemic symptoms
   - bulky (>7 cm) and symptomatic nodal or extranodal mass
   - symptomatic splenomegaly
   - progressive leukemic phase
   - serous effusions
8. Performance status < 2 according to ECOG scale
9. **Adequate haematological counts**:
   - ANC >1 x 10^9/l
   - Hb >9 g/dl (transfusion independent)
   - Plt >50 x 10^9/l (transfusion independent)

MAIN EXCLUSION CRITERIA

- Diagnosis of **cirrhosis** (histological *or* Stiffness >12 KpA at fibroscan)
- **Uncontrolled diabetes** (if under therapy subjects must be on stable dose ≥3 months)
- Concomitant therapy with **Amiodarone**
- HIV positivity
- HBV positivity (HBsAg+ or HBV-DNA+) [pts with HBcAb+, HBsAg-, HBsAb+/- and HBV-DNA-negativity are eligible]
- If female: pregnant or breast-feeding

ENDPOINTS

Primary endpoint

- Sustained virologic response at 12 weeks (**SVR12**)

Secondary endpoints

- Overall response rate (**ORR**) of lymphoma

  (Lymphoma response will be assessed *12 weeks after the end of AT*)

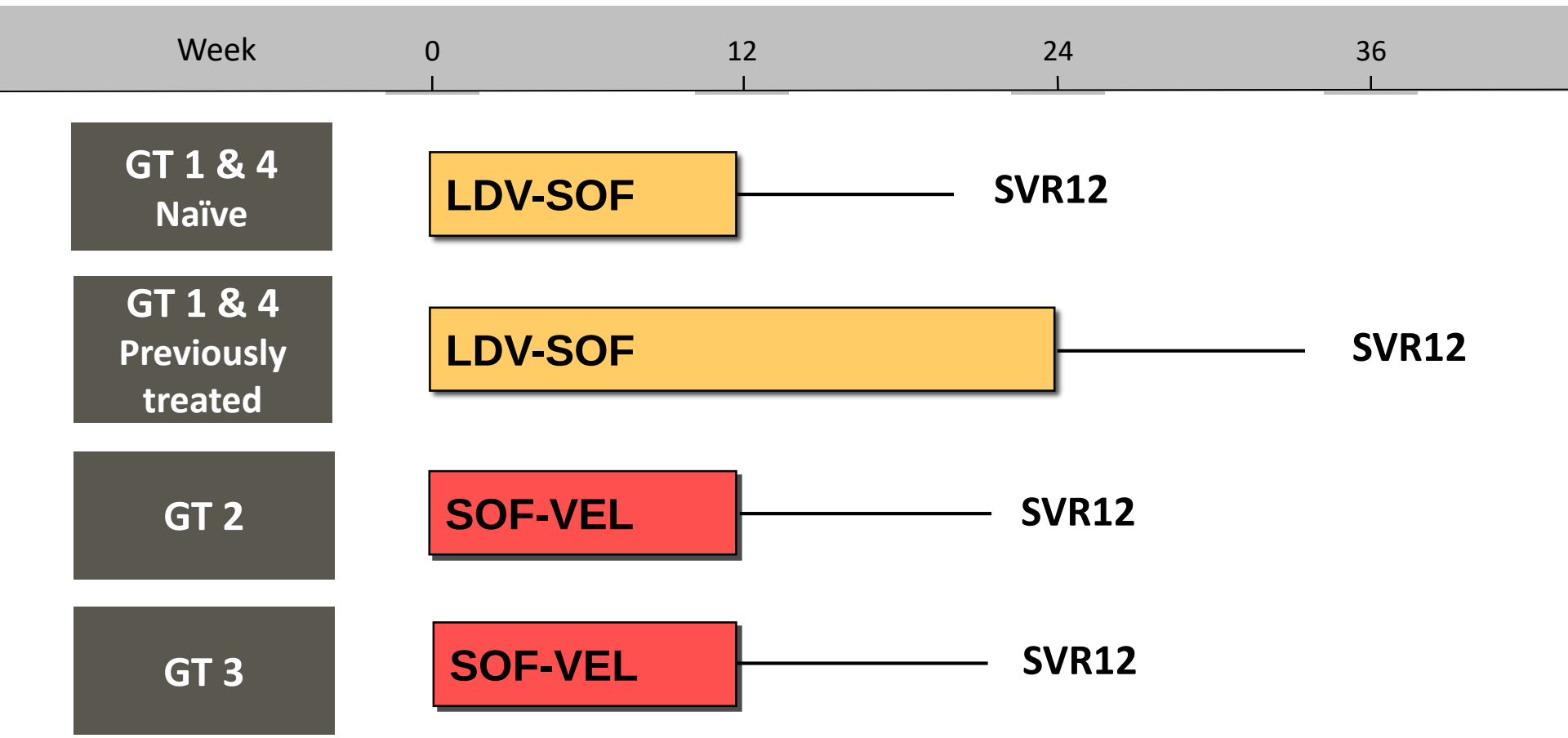
- **PFS, EFS, OS**

- Reduction of peripheral lymphocytes, lymph nodes and splenomegaly and amelioration of cytopenias during AVT (monthly evaluation)

- **Rate of virological responses**: *rapid virologic response* (RVR), *extended RVR* (eRVR), *early virologic response* (EVR), *early responders*, *partial response*, *breakthrough*, *end-of-treatment response* (ETR), *relapse*, *null-response*

- **Toxicity** (CTCAE version 4.03), evaluated by incidence of severe/life-threatening events (grade 3, 4 and 5) and/or SAE

NEWS FOR G2 E G3



LDV-SOF: Ledipasvir-Sofosbuvir (90/400 mg) one pill once daily

SOF-VEL: Sofosbuvir-Velpatasvir (400/100 mg) one pill once daily

STUDY DURATION

Sample size: 44 patients

Number of FIL centers: 21

Planned accrual time: **24 months** *(first patient May 2016)*

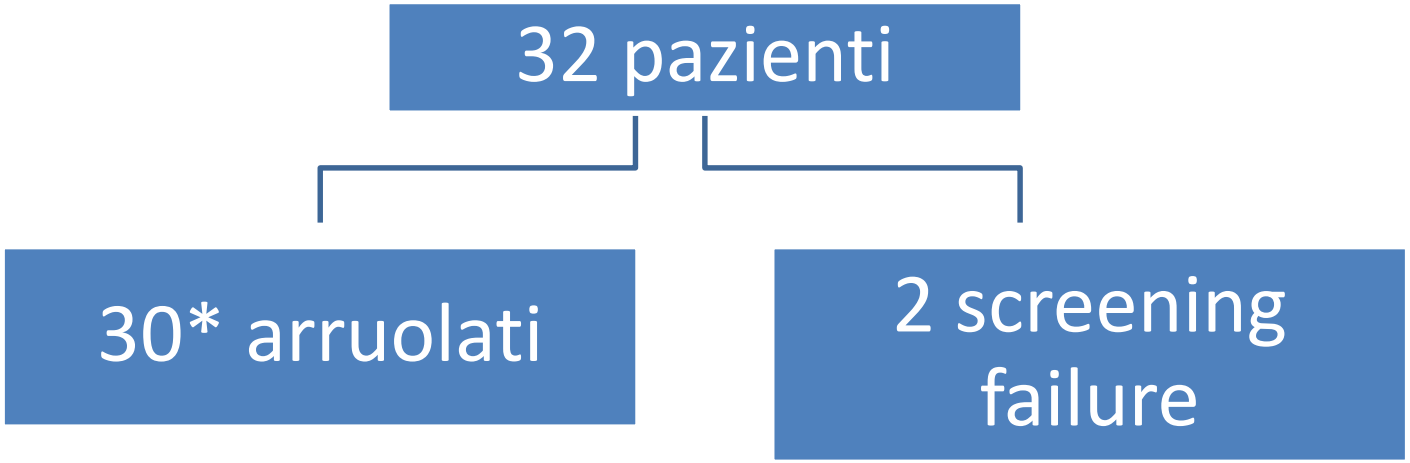
Treatment time: 12 or 24 weeks (according to genotype)

Time for virological & hematological assessment: 12 weeks

Follow-up: 36 months

Total study duration: **69 months**

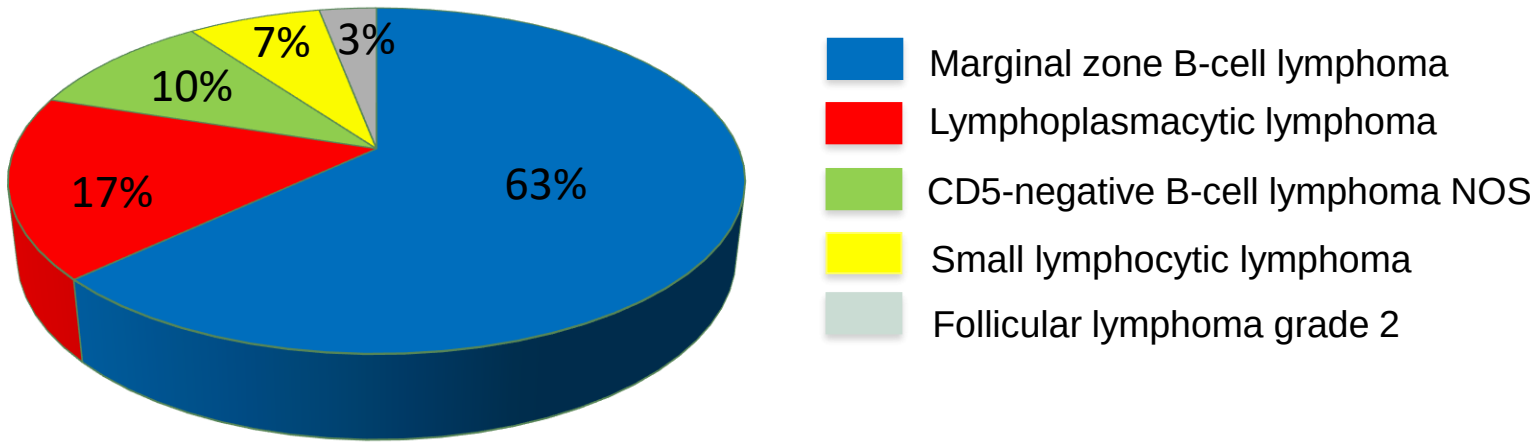
STATUS ARRUOLAMENTO (31/10/18)



*1 paziente registrato ma poi non trattato

PATIENTS' CHARACTERISTICS (N=30)

Histology	N	%
Marginal zone B-cell lymphoma	19	63
Lymphoplasmacytic lymphoma	5	17
CD5-negative B-cell lymphoma NOS	3	10
Small lymphocytic lymphoma	2	7
Follicular lymphoma grade 2	1	3



STUDIO FIL-BRB

PHASE II STUDY WITH BORTEZOMIB, RITUXIMAB AND BENDAMUSTIN –BRB- FOR NON-HODGKIN LYMPHOPLASMACYTIC LYMPHOMA/WALDENSTROM MACROGLOBULINEMIA'S PATIENTS AT FIRST RELAPSE

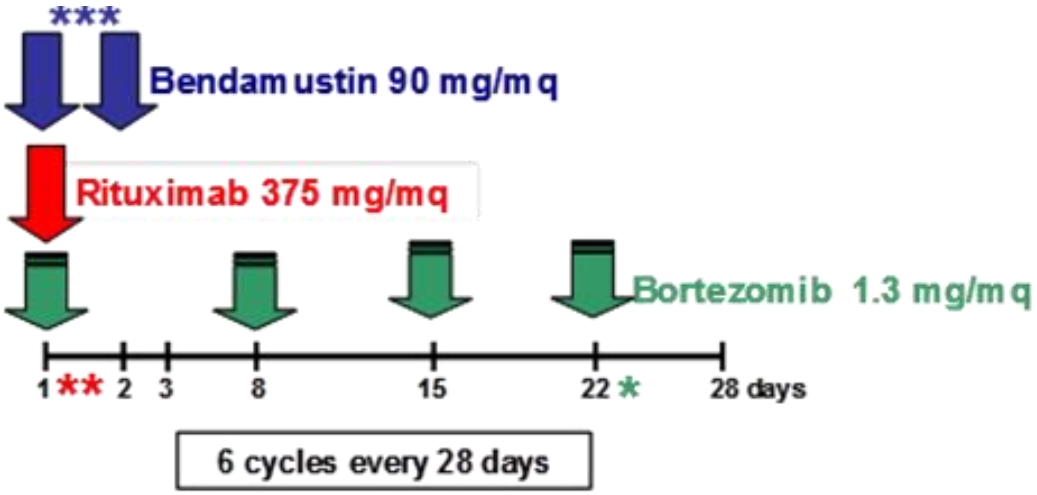
Dr Lorella Orsucci

Dr Giulia Benevolo

FIL_BRB: CARATTERISTICHE DELLO STUDIO

FASE II STUDY WITH BORTEZOMIB, RITUXIMAB AND BENDAMUSTIN -BRB- FOR NON-HODGKIN LYMPHOPLASMACYTIC LYMPHOMA/WALDENSTROM MACROGLOBULINEMIA'S PATIENTS AT FIRST RELAPSE

SPONSOR **Fondazione Italiana Linfomi (FIL)**
COORDINATORI DELLO STUDIO **Dr Lorella Orsucci, Dr Giulia Benevolo**
SC Ematologia , AOU Città della salute e della Scienza di Torino, Presidio Molinette.
ANALISI STATISTICA **Dr Giovannino Ciccone**
AOU Città della Salute e della Scienza, CPO Piemonte, Torino
FARMACOVIGILANZA **Dr Alessandro Levis/Dr Daniela Gioia**
Fondazione Italiana Linfomi



OBIETTIVO PRIMARIO

- **Valutazione della sopravvivenza libera da progressione di malattia**.

Lo studio ha come obiettivo l'ottenimento di una migliore PFS a 18 mesi, almeno pari al 65%, rispetto al 50% ottenibile con altre terapie riportate in letteratura.

OBIETTIVI SECONDARI

- tasso di risposta globale
- sopravvivenza globale
- profilo di tossicità

FIL_BRB: STATUS SPERIMENTAZIONE

ARRUOLAMENTO CONCLUSO

DIMENSIONE DEL CAMPIONE

- **38** pazienti arruolati (**22** pazienti inseriti nello studio biologico

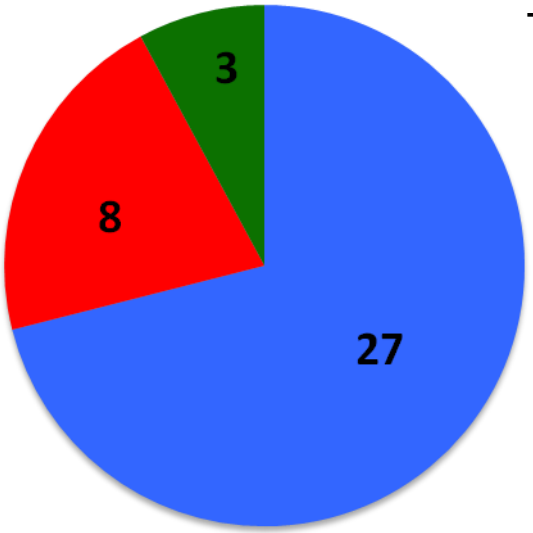
Terapia conclusa → 27

Interruzioni premature → 8

Terminato il trattamento ma non valutabili → 3

DETTAGLIO CENTRI

- Centri attivi → 23
- Centri arruolanti → 18



Tossicità di grado 1-2: ematologica (neutropenia e plt-penia)
Tossicità di grado 3-4: gastrointestinale e neurologica

RISULTATI **ORR was 82.9%:**

3 (9%) CR
13 (37%) VGPR,
12 (34%) PR and
1 (3%) MR

Follow up mediano di 12 mesi

4 progressioni, 2 morti (una ischemia cerebrovascolare ed una embolia polmonare)

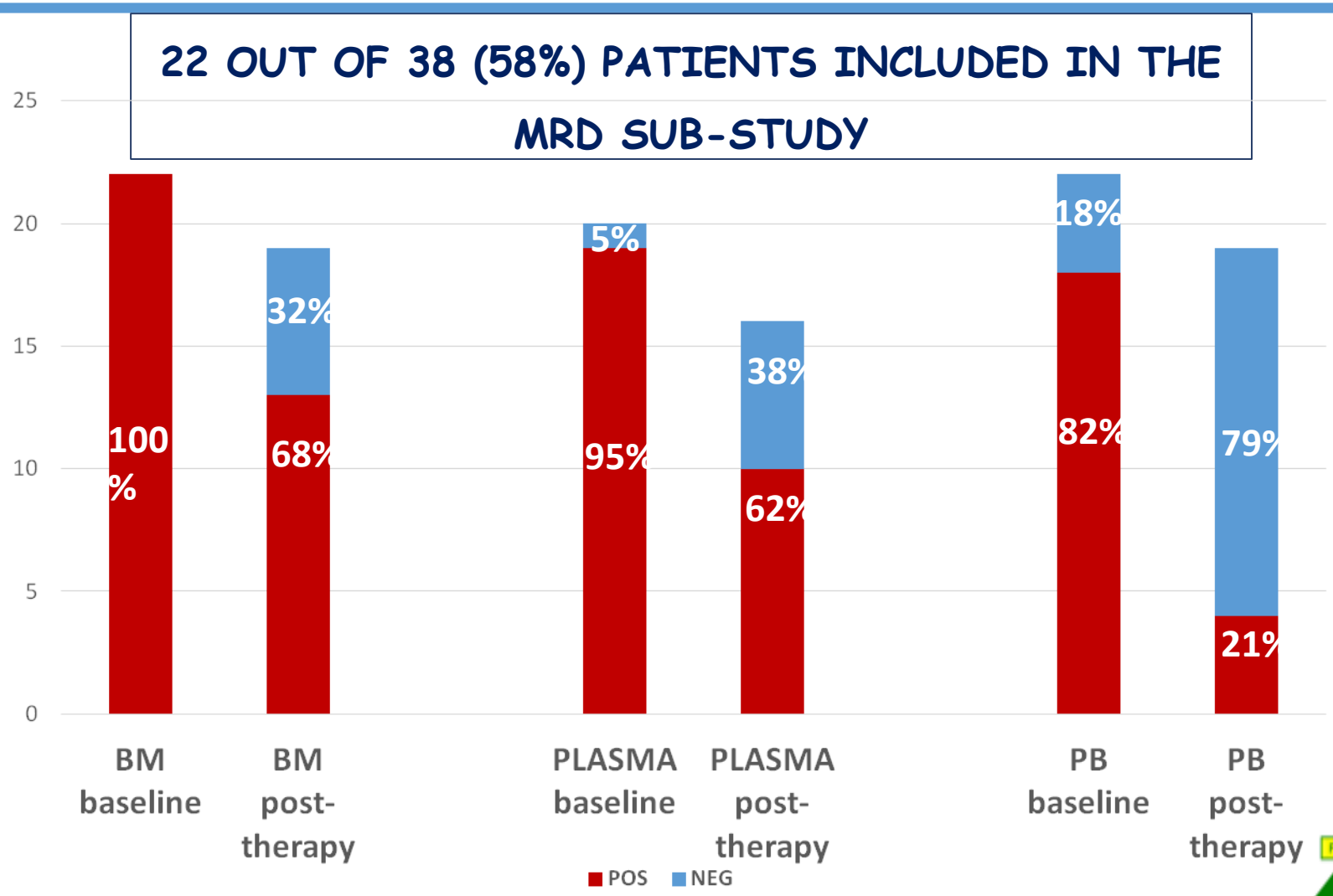
BIO – BRB STUDY

Mutational characterization of Waldenström Macroglobulinemia and minimal residual disease monitoring in the context of BRB phase II trial by Fondazione Italiana Linfomi (FIL)

Referente per lo studio biologico: Simone Ferrero Ematologia Univ. Torino

SPECIFIC AIMS

- **Mutational screening** of baseline samples for the most frequently mutated genes in WM: MYD88, CXCR4 and ARID1A
- **MRD quantitative evaluation** on $MYD88^{L265P}$ by the sensitive ddPCR approach at baseline and after BRB treatment on BM and PB
- Development of a sensitive, **plasma-based ddPCR tool** to detect $MYD88L^{265P}$ on circulating tumor DNA



MYD88^{L265P} detection rate before and after therapy (MRD)

FIL_BRB: PUBBLICAZIONI

Comunicazione orale

10th International Workshop on Waldenström's Macroglobulinemia
IWWM2018
New York, October11-13, 2018

International Workshops on WALDENSTRÖM'S MACROGLOBULINEMIA

Poster

60th ASH Annual Meeting
San Diego, December1-4, 2018

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Grazie ai Centri che hanno partecipato allo studio

Uffici Studi FIL segreteria@filinf.it
Dott.ssa Claudia Peracchio

STUDIO BIO_WM

Da: IWMF Office [mailto:office@iwmf.com]
Inviato: giovedì 29 giugno 2017 22:31
A: segreteria@filinf.it
Oggetto: IWMF-LLS Research Roadmap Notification

Dear Dr. Varettoni,
The Board of Trustees of the International Waldenstrom's Macroglobulinemia Foundation (IWMF) is very pleased to inform you that you are the recipient of a two-year **$400,000 grant award under the 2016 IWMF-LLS Strategic Research Roadmap RFP for your project**

Guy Sherwood, MD, CCFP, FAAFP
IWMF Vice President for Research

Study Protocol

Non-invasive diagnostics and monitoring of minimal residual disease and clonal evolution in Waldenström's Macroglobulinemia and in IgM monoclonal gammopathy of undetermined significance

ID Study: FIL_BIOWM

INVESTIGATOR SPONSOR

Fondazione Italiana Linfomi ONLUS (FIL)

COORDINATING INVESTIGATOR (PI) CO-INVESTIGATOR	Marzia Varettoni, Pavia (Italy) Ramon Garcia-Sanz, Salamanca (Spain)
WRITING COMMITTEE AND SCIENTIFIC SUPPORT	Marzia Varettoni, Pavia (Italy) Simone Ferrero, Torino (Italy) Marco Ladetto, Alessandria (Italy) Ramon Garcia-Sanz, Salamanca (Spain)

REGISTRATION (SEE SECTION 12)	www.filinf.it

Version 1, February 15, 2018

Study objectives

Primary objective

- demonstrate that the rate of mutation of MYD88 (L265P) and CXCR4 (S338X) detected with dd-PCR in peripheral blood (PB), plasma or urine show a negligible difference with the rate of mutations detected in bone marrow samples (gold standard)

Secondary objectives

- assess whether WM may be differentiated from IgM MGUS based on results of mutation analysis and/or flow cytometry
- assess the rate of MRD negativity after treatment and its correlation with progression-free survival
- evaluate the clonal evolution on sequential samples using NGS
- evaluate progression free and overall survival

Population and inclusion/exclusion criteria

Sample size

- 300 pts: 150 retrospective (learning cohort) + 150 prospective (validation cohort)

Centers

20 FIL centers + 5 centers in Spain

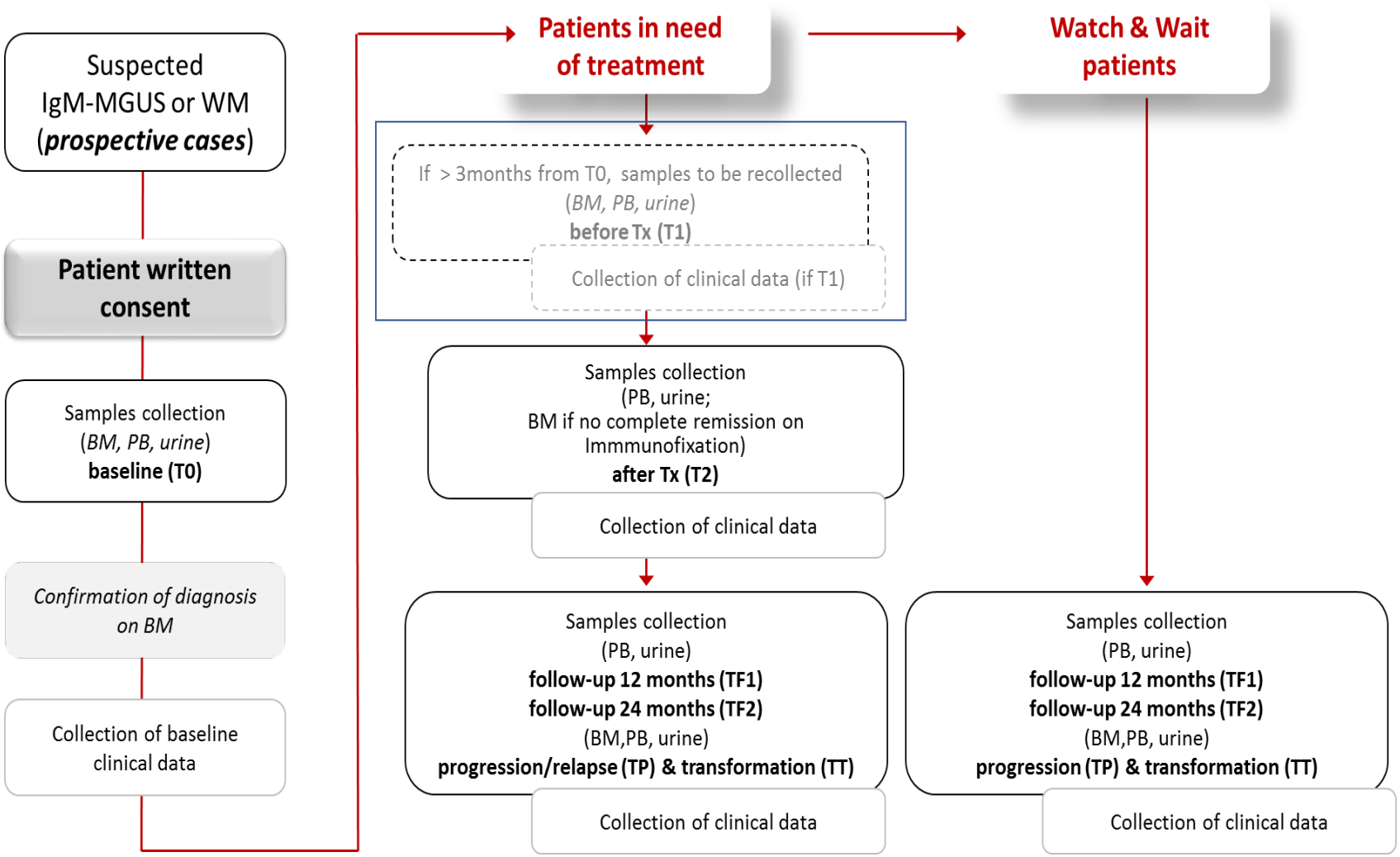
Inclusion criteria

- Diagnosis of Waldenstrom's Macroglobulinemia (symptomatic or asymptomatic) or IgM MGUS according to criteria established during the second IWWM
- No prior treatment for WM
- Age ≥ 18 years
- Informed consent

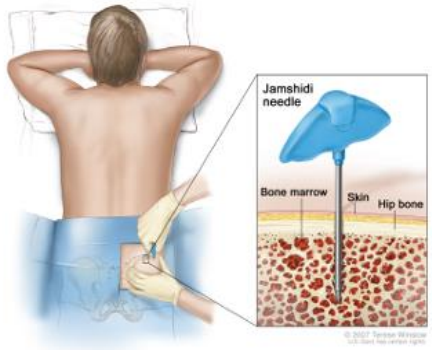
Exclusion criteria

- Prior treatment with immunotherapy and/or chemotherapy and/or novel agents
- Active HBV, HCV, HIV infection

Study flow-chart



Biological studies and timepoints



BM CD19+ MNCs

PB MNCs

Plasma

genomic DNA

cell-free DNA

Multiparameter flow citometry
(Pavia, Salamanca, Torino)

Mutational studies
dd-PCR (Torino, Salamanca)
NGS (Pavia, Salamanca)

Clinical data
eCRF

FIL-NF10

INDOLENT NON-FOLLICULAR

LYMPHOMAS PROGNOSTIC PROJECT

Luca Arcaini

Stefano Luminari

STUDY DESIGN

- The study is aimed to verify whether a prognostic collection of data would allow the development of a more accurate prognostic assessment for non-follicular low grade B-cell lymphomas

- Enrollment: **8** years
- Follow up: **5** years

} amendament submitted

- **1500** indolent non follicular lymphoma to obtain **300** SMZL (amendament submitted)

INCLUSION AND EXCLUSION CRITERIA

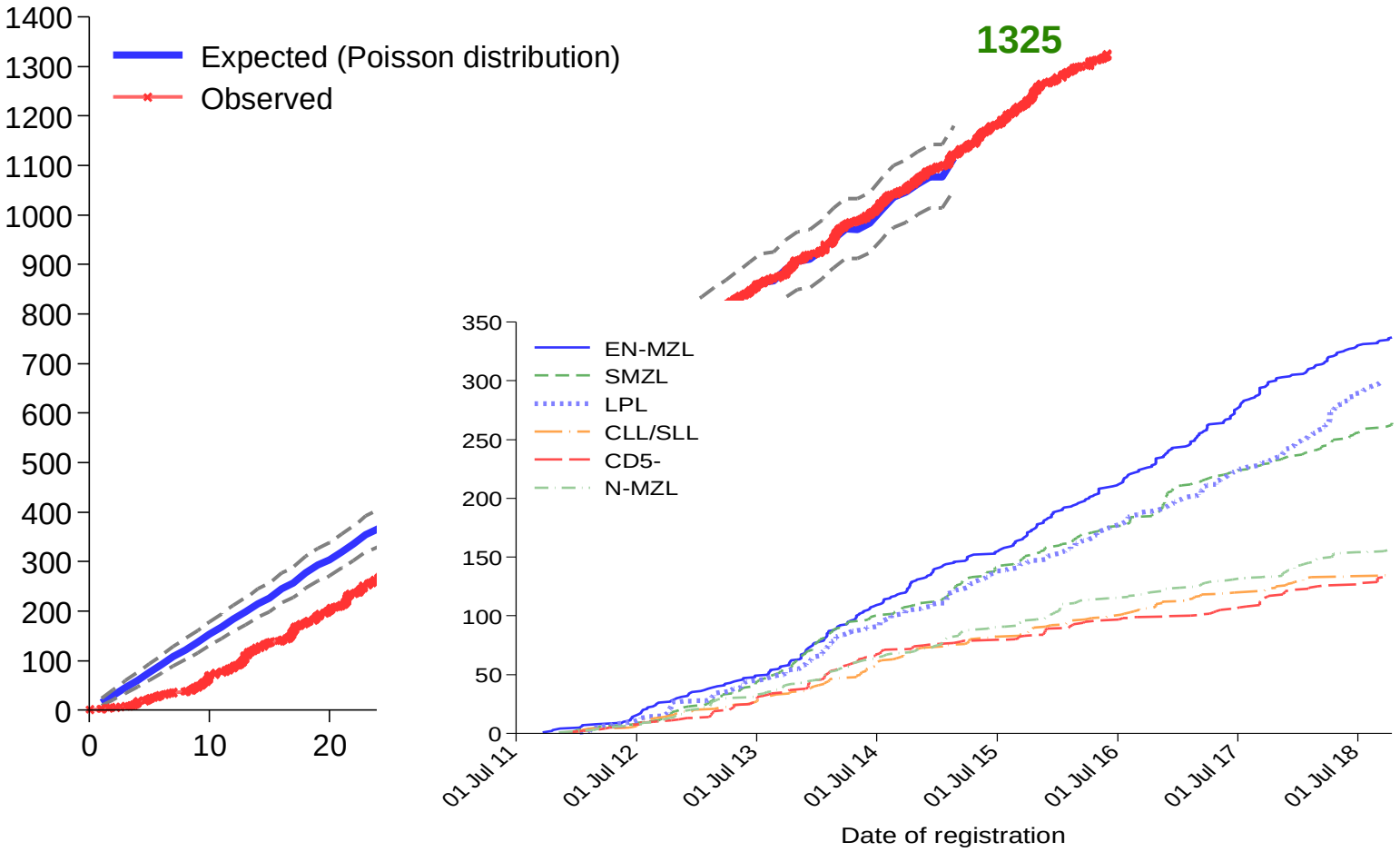
INCLUSION CRITERIA

- Patients with histologically confirmed diagnosis of non-follicular low grade B-cell lymphoma
  - Splenic MZL (bone marrow histology and/or spleen tissue)
  - Extranodal MZL of MALT (tissue biopsy)
  - Nodal MZL (lymph node biopsy)
  - Lymphocytic lymphoma (lymph node biopsy)
  - Lymphoplasmacytic lymphoma (bone marrow histology or lymph node biopsy)
  - CD5-negative low grade B-cell lymphoma (bone marrow histology)
- Age over 18
- Written informed consent

EXCLUSION CRITERIA

- None

ENROLLMENT STATUS (15/10/18)



NF10 STUDY WORK IN PROGRESS

- Large repository of INFL cases
- Subtype frequency and characteristics different from what expected
- Need work: path. review, CRF validation, update
- Excellent basis for:
  - ✓ descriptive analysis
  - ✓ Prognostic studies: planned
  - ✓ Biomarker study: in development (bioNF10)

Early Progression As a Predictor of Survival in Marginal Zone Lymphomas: An Analysis from the Prospective International NF10 Study By Fondazione Italiana Linfomi

Stefano Luminari, Luigi Marcheselli, Irene Defrancesco, Sara Rattotti, Marina Cesaretti, Marco Frigeni, Roberta Sciarra, Federica Cavallo, Marina Deodato, Maria Giuseppina Cabras, Michele Merli, Angela Ferrari, Francesca Re, Michele Spina, Emanuele Cencini, Ombretta Annibali, Alessandro Pulsoni, Marcia Torresan Delamain, Donato Mannina, Gianluca Gaidano, Caterina Stelitano, Daris Ferrari, Carlo Visco, Francesco Angrilli, Vittoria Tarantino, and Luca Arcaini

- The ability of PFS24 to predict subsequent OS in a large, multinational MZL cohort as part of the NF10 observational multicentric international study promoted by FIL
- PFS24 was calculated only for pts requiring immediate therapy
- 1253 cases from 65 centres in Europe and South America: **400 pts with MZL needing immediate therapy**
- Median follow-up 38 months
- 3-yrs PFS 79% and 3-yrs OS 90%; progressive disease was the cause of death in 47% of all cases

Early Progression As a Predictor of Survival in Marginal Zone Lymphomas: An Analysis from the Prospective International NF10 Study By Fondazione Italiana Linfomi

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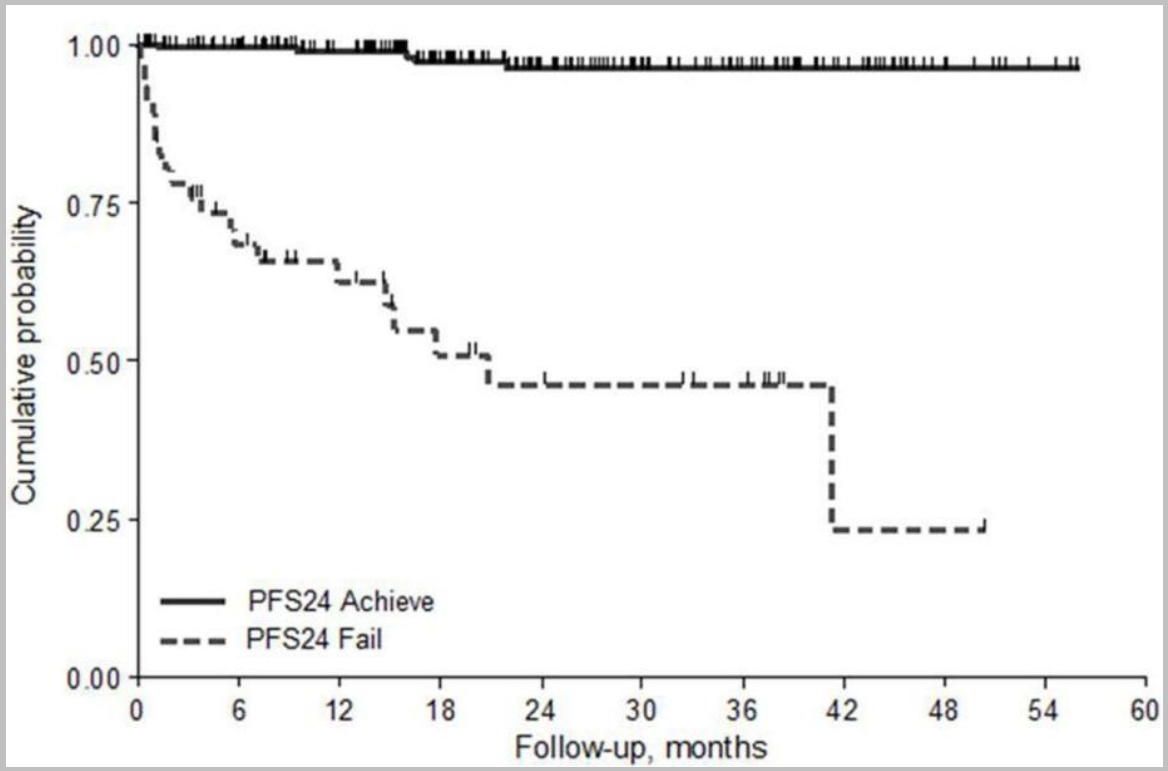
- Assessment of PFS24 predicts subsequent outcome in MZL (expecially for ENMZL, SMZL and Diss-MZL)



Grazie per l'attenzione