Aggiornamento Protocolli FIL

Linfoma di Hodgkin

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FONDAZIONE ITALIANA LINFOMI

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FIL Rouge

A randomized, open-label, multicenter, phase III, 2-arm study comparing efficacy and tolerability of the intensified variant ‘dose dense/dose-intense ABVD’ (ABVD DD-DI) with an interim PET response- adapted ABVD program as upfront therapy in advanced stage classical HL

Prof Antonello Pinto
Prof Armando Santoro

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Objectives

- **Primary**: To demonstrate the superiority of an intensified ABVD variant (ABVD DD-DI, *Experimental arm*) over an interim PET response-adapted ABVD treatment (*Comparator arm*) in improving PFS.

- **Secondaries**:
  - To compare the anti-lymphoma activity of ABVD DD-DI and interim PET response-adapted ABVD according to Lugano 2014 Classification.
  - To compare the OS of ABVD DD-DI vs. interim PET response-adapted ABVD
  - To compare the safety of ABVD DD-DI and interim PET response-adapted ABVD
  - To compare the effect of ABVD DD-DI and interim PET response-adapted ABVD on Quality of life (QoL)
  - To compare ABVD DD-DI vs. interim PET response-adapted ABVD in term of cost-effectiveness.

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Inclusion Criteria

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- Histologically confirmed classical HL
- Previously untreated disease
- **Age 18-60 years**
- **Ann Arbor stage IIB with extranodal involvement and/or mediastinal bulk, III and IV**
- At least one target PET-avid bidimensionally assessable lesion
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2
- Adequate organ and marrow function as defined below: absolute neutrophil count >1,0 $x10^9$/L, platelets >75 $x10^9$/L
- Total bilirubin <2 mg/dl without a pattern consistent with Gilbert's syndrome
- Aspartate Transaminase and Alanine Transaminase (AST/ALT) <3 X institutional Upper Limits of Normality (ULN)
- Creatinine within normal institutional limits or creatinine clearance >50 mL/min/1.73 m^2
- Females of childbearing must have a negative pregnancy test at medical supervision even if had been using effective contraception
- Life expectancy > 6 months
- Able to adhere to the study visit schedule and other protocol requirements
- Sign (or their legally acceptable representatives must sign) an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study.
- **Access to PET-CT scans facilities qualified by FIL**

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MAIN STUDY: Amendment

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- **Duration of the study period**
- **RT administration**
- Supportive therapy
  - ✓Use of G-CSF
  - ✓Antibiotic administration
  - ✓Prophylaxis for Pneumocystis

- Bleomycin toxicity
- Minor typos
- Other sites activation

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Study Design

- **Study design:** randomized, open-label, multicenter, phase III, 2-arm study

- **Number of patients**: **500** patients (**250** patients per arm)

- **Duration of the study**: **66** months in total, **30** months for patient accrual, **6** months for treatment duration and **30** months for follow up.

AFTER AMENDAMENT:

Duration of the study: **76** months in total, **40** months for patient accrual, **6** months for treatment duration and **30** months for follow up.

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Experimental Arm: Treatment Schedule

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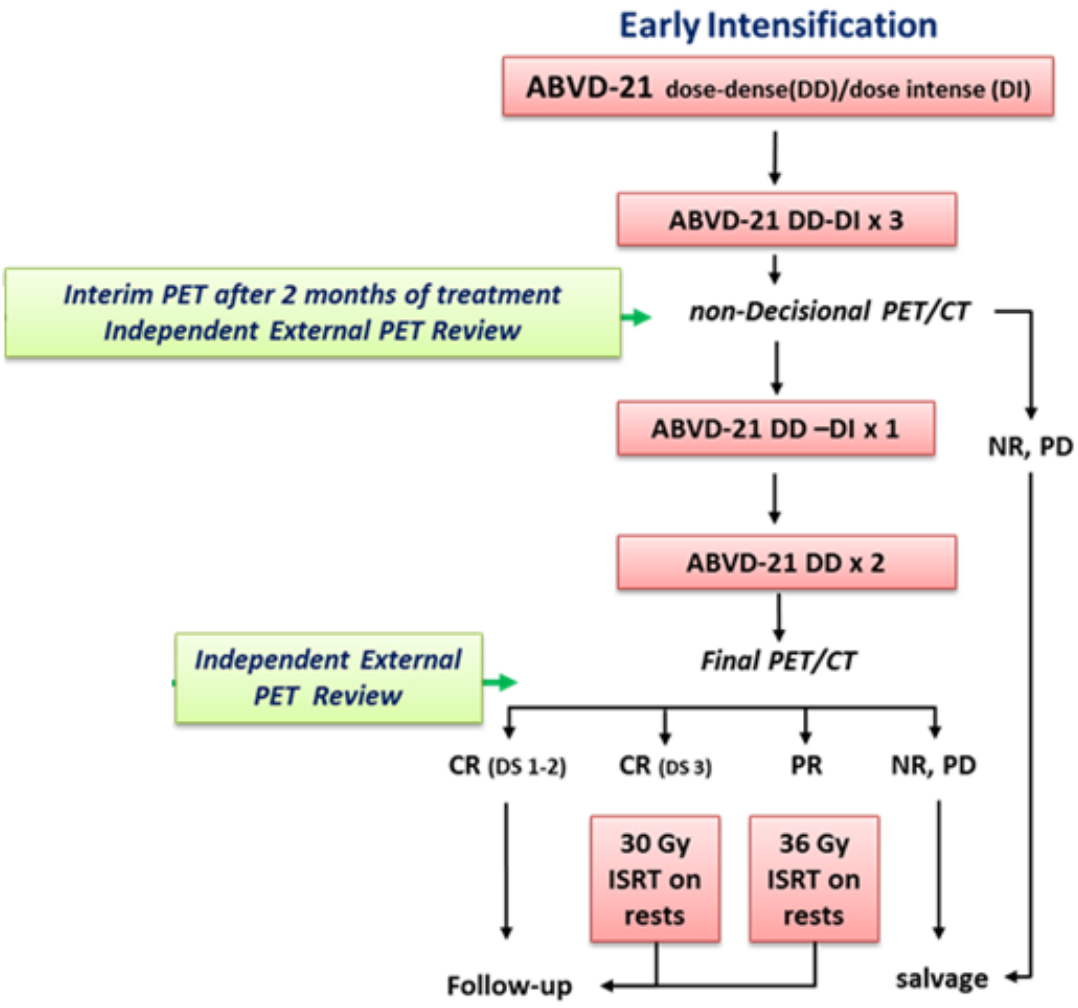
ABVD DD-DI (repeated every 21 days) - Cycles 1 to 4			
Doxorubicin	35 mg/m^2	i.v.	days 1,11
Bleomycin	10,000 units/m^2	i.v.	days 1,11
Vinblastine	6 mg/m^2	i.v.	days 1,11
Dacarbazine	375 mg/m^2	i.v.	days 1,11
G-CSF	263 µg	s.c.	days 6-8, 17-19
Reevaluate the patient's weight and recalculate the BSA at each new cycle, especially in the early cycles (to optimize the planned upfront treatment intensification) and in patients with B symptoms (since, upon treatment start, they can quickly recover the initial weight loss)			

ABVD DD (repeated every 21 days) – Cycles 5 and 6			
Doxorubicin	25 mg/m^2	i.v.	days 1,11
Bleomycin	10,000 units/m^2	i.v.	days 1,11
Vinblastine	6 mg/m^2	i.v.	days 1,11
Dacarbazine	375 mg/m^2	i.v.	days 1,11
G-CSF	263 µg	s.c.	days 6-8, 17-19



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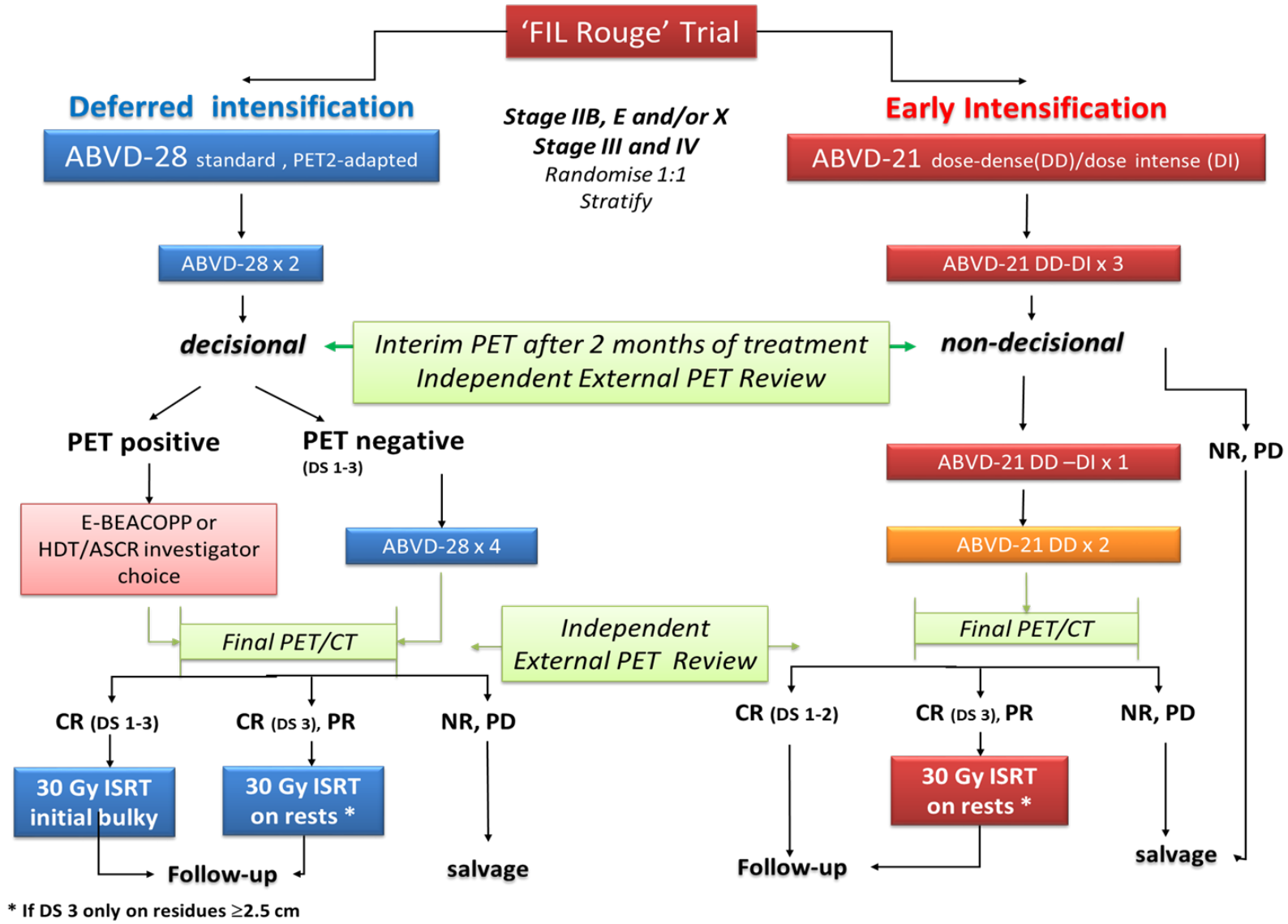
AFTER AMENDMENT: Flow chart



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Stato attivazione centri

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- ✓ **Autorizzazione AIFA:** 17/07/2017
- ✓ **Parere Unico Centro Coordinatore:** 19/04/2017
- ✓ **Centri partecipanti:** 61 (60 centri iniziali, 9 centri chiusi nel corso del tempo, 10 centri nuovi aggiunti con emendamento ad hoc in data 12/02/2019)
- ✓ **Centri attivi:** 51
- ✓ **Centri arruolanti:** 43
- ✓ **Centri in fase di attivazione (ufficio Start up FIL in attesa dei docs per formalizzare l'apertura del centro):** 4 (Benevento, Cagliari, Napoli - Cardarelli, Palermo – Giaccone)
- ✓ **Centri con iter di valutazione in atto:** 6 (Asti, Campobasso, Genova, Matera, Napoli Vanvitelli, Padova Ematologia)

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Arruolamento

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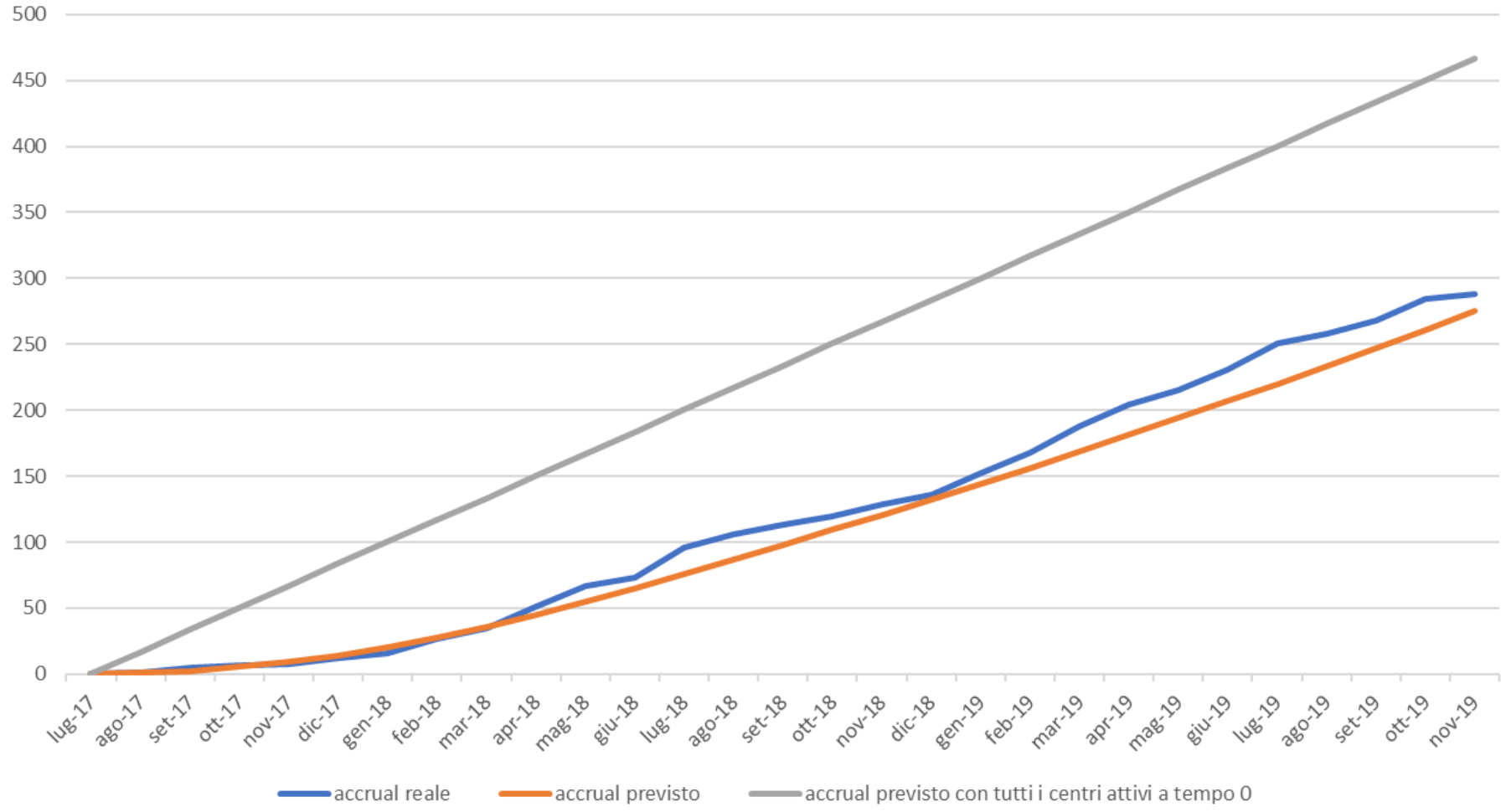
- 288 pazienti arruolati al 12/11/19



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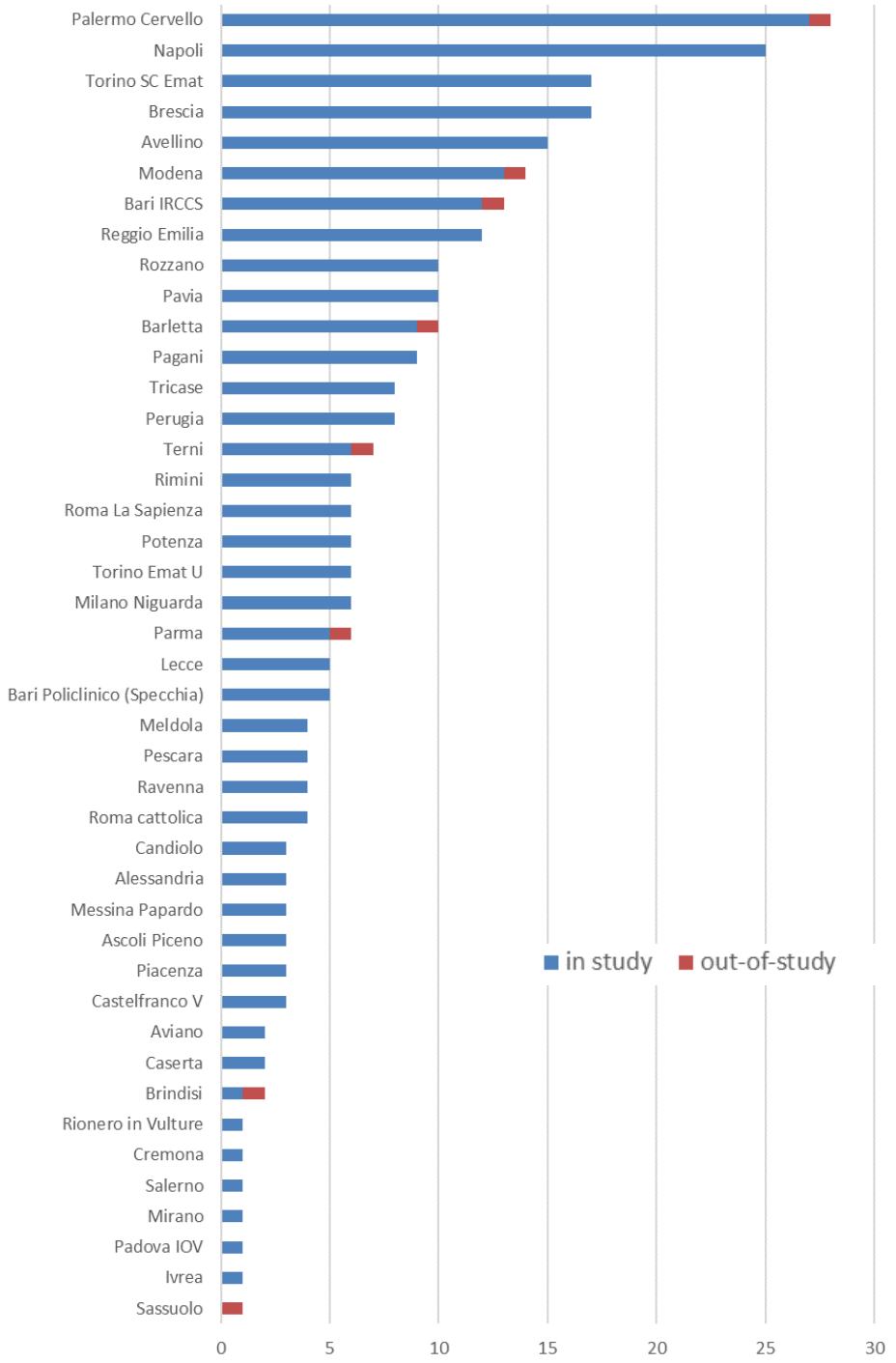
Enrollment by site

Authorized Sites not Enrolling
Biella
Udine
Roma Campus Bio
Messina (Dott.ssa Penna)
Arezzo
Firenze
Ancona
Taranto



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Farmacovigilanza

INDEPENDENT DATA SAFETY MONITORING COMMITTEE (DSMC).

This trial will be monitored and scrutinized by DSMC.

A confidential interim analysis will be performed every 6 months and submitted to the IDMC that will make appropriate recommendations to the Steering Committee for the sequel of the trial.

Stopping rules for toxicity

Interim analyses to evaluate safety will be performed by an independent Data Safety Monitoring Committee (DSMC) without pre-specified statistical restraints. Safety will be strictly monitored, both during the ABVD cycles and the salvage treatments. Decisions about the early stopping of the trial will be based on both frequency and severity of AE rates.

The toxic death rate will be evaluated every six months in patients in whom at least four cycles have been documented (or who died of toxicity before the 4th cycle could be given). If the lower limit of the 95% confidence interval is >3% in one of the arms, the results will be submitted to the Data Safety Monitoring Committee (DSMC) that may recommend the closure of the trial.

Sono state condotte due analisi in itinere dalle quali non sono emerse particolari problematiche relative alla safety. Una terza analisi di safety è al momento on going.

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FIL_ROUGE_BIO

Circulating tumor DNA genotyping for biological monitoring of patients with advanced-stage classical HL receiving upfront ABVD-based chemotherapy. An ancillary study to the FIL_ROUGE Phase III trial

A prospective, observational, multicentric, non-interventional study

Fondazione Italiana Linfomi
Hematology Oncology Institute of Southern Switzerland
Ospedale San Giovanni, Bellinzona

Antonello Pinto
Davide Rossi

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FIL_ROUGE_BIO: Rationale

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- **Background:**
  - **Detection of cancer gene mutations in circulating tumor DNA (ctDNA) may provide a tumor fingerprint**
  - **ctDNA genotyping/quantitation (CAPP-seq targeted ultra-deep-NGS) can be used as a tool for measuring residual disease at the systemic level in lymphomas**
  - ***Preliminary evidence:***
    - **A drop of 100-fold or 2-log drop in ctDNA after 2 chemotherapy courses associated with an eventual complete response and cure. Conversely, a drop of less than 2-log in ctDNA after 2 ABVD courses associated with an eventual progression**
  - **Serum levels of TARC, IL6, sCD30, and sCD163 early post-treatment are associated with an increased risk for disease progression**

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Biological study

Prospective validation of the concept of the liquid biopsy as a biomarker for disease response assessment in cHL. Impact of the study will be the incorporation of the liquid biopsy in the next international consensus on treatment response criteria for cHL.

- PB samples (20 ml of peripheral blood in Cell-Free DNA BCT tubes) will be collected at the following timepoints:
  - ✓ before treatment start
  - ✓ interim PET/CT assessment
  - ✓ end of treatment PET/CT assessment
  - ✓ disease progression/end of study

- Centralized to FIL designated laboratory

Research laboratory of the Hematology-Oncology and Stem Cell Transplantation Unit, at the Fondazione Pascale IRCCS: parallel cytokine/chemokine correlative analyses

Oncology Institute of Southern Switzerland (OISS, Dott. Davide Rossi): ctDNA and gDNA genotyping analyses

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Cardiologic assessment

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cTnI level will be assessed before every treatment infusion in the two arms (*Comparator* and *Experimental*).
Troponin level will be considered above normal if present an elevation > 0.08 ng/mL from baseline assessed at local checks.

Standard transthoracic 2D echocardiography must be done at baseline, at the end of chemotherapy (3-4 weeks), at the end of eventual radiotherapy (3-4 weeks) and during follow-up (every six months in the first year and then annually) in both two arms (*Comparator* and *Experimental*).

GLS should be assessed with a 2D speckle tracking echocardiography using three apical views.

A relative percentage GLS reduction >15% from baseline will be considered to be abnormal according to ESC Guidelines.

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BANDO AIFA

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- Finanziati **40**/343 studi

- I criteri identificati per la valutazione (linee guida del Ministero della Salute):
  - rilevanza scientifica
  - metodologia/disegno di studio/bibliografia di riferimento
  - livello di innovatività
  - organizzazione/centro sperimentale
  - sperimentatore principale

- FIL_ROUGE è alla posizione n. **16**

"Merito e trasparenza sono i principi che hanno ispirato l'intero percorso di valutazione. Sono stati premiati progetti di qualità eccellente dai quali ci attendiamo un contributo importante sia in termini di arricchimento delle conoscenze cliniche e terapeutiche in aree di minore interesse per la ricerca profit, sia in termini di ricadute regolatorie e razionalizzazione dei costi per il Servizio Sanitario Nazionale.."

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FIL ELHL

Prospective study on elderly (≥ 65 years) patients affected with cHL undergoing CGA at diagnosis

Dr Vittorio Zilioli

Study Design: prospective, observational, nonrandomized study

Objectives

Primary Objective: to develop a prognostic index for elderly patients with newly diagnosed cHL starting from a prospective observational study of consecutive cases registered after the completion of the Comprehensive Geriatric Assessment (CGA)

Secondary Objectives:

MAIN

- to describe **clinical features** of elderly cHL cases
- to describe **pattern of care** of elderly cHL cases
- to analyze outcome of elderly cHL cases
- to evaluate CGA results and assess **impact of CGA groups** on tx choice, response and survival

OPTIONAL SUBGROUPS

- to validate the prognostic role of **PET2** in the setting of elderly cHL population
- to evaluate the role of biomarkers through **TMAs**
- to assess the role of **immune senescence** in elderly cHL population

Inclusion Criteria

- Diagnosis of classical Hodgkin Lymphoma
- Age ≥ 65 year-old
- Evaluation of CGA at baseline
- Signed informed consent
- Previously untreated patients
- All pts, regardless if addressed to curative-intent or palliative tx or not planned to be treated

Exclusion Criteria

- None

Sample Size: 400 patients

Study Duration: 7 years

5 years recruitment + 2 years of follow up from the enrolment of the last patients

Status Attivazione Centri e Arruolamento Pazienti (12/11/2019)

Parere Favorevole Centro Coordinatore: 25/05/2018

Centri Partecipanti: 44

Centri Attivi: 24

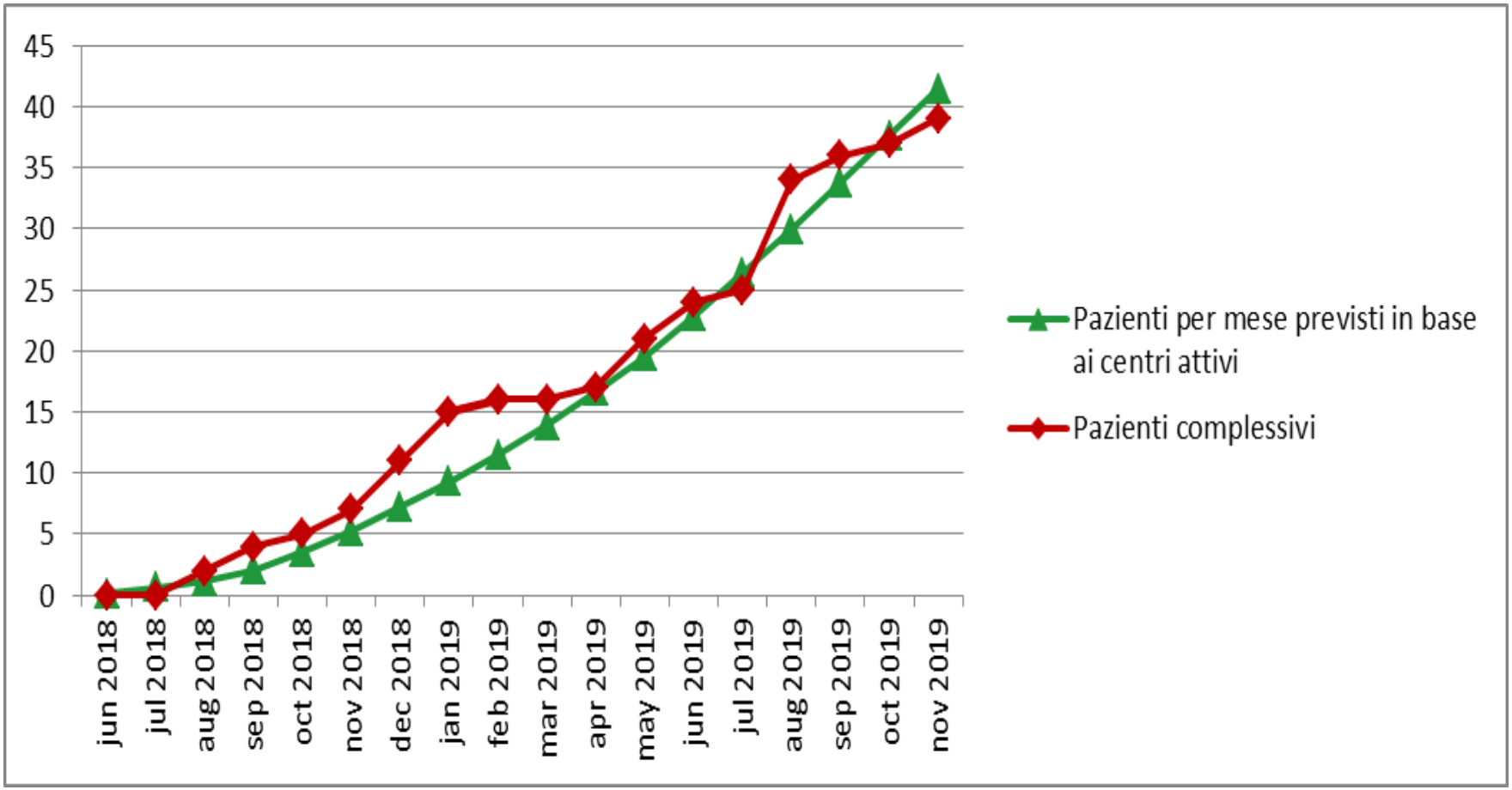
Centri Arruolanti: 13

Pazienti Registrati: 39

Alessandria M.Zanni		
Ancona G. Gini	★	3
Avellino G.R.Nunziata		
Aviano M.Spina	★	
Bari F.Gaudio	★	
Barletta G.Tarantini		
Brescia A.Tucci	★	12
Cagliari M.G.Cabras	parere negativo	
Campobasso S.Storti		
Castelfranco V.R.Sartori		
Cosenza M.Gentile		
Firenze B.Puccini	★	3
Frosinone A.Andriani		
Ivrea R.Freilone		
Matera C.Mannarella		
Meldola G.Musuraca	★	
Milano HSR A.Ferreri	★	
Milano Pol. F.G.Rossi	★	
Milano Niguarda V.R.Zilioli	★	7
Napoli A.Sica		
Novara L.Nassi	★	3
Padova IOV D.Marino	★	1

Padova L.Trentin		
Palermo S.Mancuso	★	2
Parma F.Re		
Perugia L.Flenghi	★	1
Piacenza A.Arcari	★	1
Ravenna M.Tani		
Reggio Emilia F.Merli	★	2
Rimini A.L.Molinari		
Roma S.Camillo R.Battistini	★	
Roma T.Vergata M.Cantonetti		
Roma Sapienza A.Pulsoni		
Roma S.Andrea A.Tafuri		
Roma Cattolica S.Hohaus	★	
Rozzano F.Ricci	★	1
Sassuolo S.Bigliardi	★	1
Siena A.Fabbri		
Sondrio A.M.Soccodato	★	
Terni A.M.Liberati		
Torino Molinette B.Botto	★	
Torino Università F.Cavallo	★	
Treviso P.M.Stefani	★	
Tricase V.Pavone	★	2

Arruolamento (12-11-2019)



Central Review of Diagnosis

Prof. Stefano Pileri – dott.ssa Valentina Tabanelli, Unità Diagnosi Emolinfopatologica, IEO Milano

All patients registered in the study

material to be send: **diagnostic biopsy (paraffin block)**

sample centralized (12-11-2019): **25**

PET/CT Central Review – WIDEN Platform

Coordinating Nuclearists: dott.ssa Federica Elisei, Monza – dott. Carlo Villano, Pescara

Patients treated with ABVD- ABVD like

centralization of digitalized and anonymous PET scans in DICOM format on electronic WIDEN web platform

PET centralized (12-11-2019): **18 baseline, 10 interim**

Optional Studies

- **Tissue Micro Array (TMA)**

Prof. Stefano Pileri – dott.ssa Valentina Tabanelli, Unità Diagnosi Emolinfopatologica, IEO Milano

material for TMA analysis: **paraffin block** (the same used for revision of diagnosis)

[no slides!!!!!!!!!!]

- **Immune senescence and Frailty**

Dott.ssa Luisa Imberti – dott.ssa Alessandra Tucci, Laboratorio CREA, Spedali Civili, Brescia

➡ peripheral blood sample on swab tip at baseline

- **Immune senescence and TTV**

Prof. Fabrizio Maggi, UOC Virologia Universitaria, AOU Pisana, Pisa

➡ peripheral blood sample on swab tip at baseline

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