Aggiornamenti di protocolli FIL. Linfomi T.

Annalisa Chiappella

Ematologia,

AOU Città della Salute e della Scienza, Torino

DICHIARAZIONE

Relatore: ANNALISA CHIAPPELLA

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: **CELGENE**
- 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)
- Lecture fee/attività educazionali: **AMGEN, CELGENE, JANSSEN, NANOSTRING, PFIZER, ROCHE, TEVA**

PTCL:
First Line treatment.

FIL-PTCL13. PI Prof Paolo Corradini.
Romidepsin in combination with CHOEP as first line treatment before hematopoietic stem cell transplantation in young patients with nodal peripheral T-cell lymphomas: a phase I-II study

FONDAZIONE FIL ITALIANA LINFOMI
WWW.FILINF.IT

A multicenter study including two phases:

1. A phase I study to define the maximum tolerated dose (MTD) of Romidepsin in addition to CHOEP-21 and to test the safety and feasibility of CHOEP-21 in combination with dose escalation of Romidepsin D1&8 (8, 10, 12, 14 mg). The dose level defined as MTD of Romidepsin will be used for the subsequent phase II study.

   21-24 patients (50% treated at the MTD)

   1st patient enrolled on Sept. 1

2. A phase II study to evaluate the efficacy (response rate, progression free survival and overall survival) and safety of Ro-CHOEP-21 incorporated into a treatment strategy including SCT

   110 patients (approximately 9-15 patients expected from the phase I study and treated at the MTD)

ELECTION CRITERIA

FONDAZIONE FIL ITALIANA LINFOMI
WWW.FILINF.IT

INCLUSION CRITERIA

1. **age ≥18 e ≤ 65 years**
2. **Peripheral T-cell lymphomas at diagnosis including: PTCL-NOS, AITL, ALK negative ALCL**
3. **Stage II-IV**
4. Written informed consent
5. No prior treatment for lymphoma
6. No Central Nervous System (CNS) disease (meningeal and/or brain involvement by lymphoma)
7. HIV negativity
8. Absence of active hepatitis C virus (HCV) infection
9. HBV negativity or patients with HBcAb +, HBsAg -, HBs Ab+/- with HBV-DNA negativity (in these patients Lamivudine prophylaxis is mandatory)
10. Levels of serum bilirubin, alkaline phosphatase and transaminases < 2 the upper normal limit, if not disease related
11. No psychiatric illness that precludes understanding concepts of the trial or signing informed consent
12. Ejection fraction > 50% and myocardial stroke in the last year nor QT prolongation (QTc interval < 480 msec using the Fridericia formula)
13. Clearance of creatinine > 60 ml/min if not disease related
14. Spirometry Diffusion Capacity (DLCO) > 50%
15. Absence of active, uncontrolled infection
16. For males and females of child-bearing potential, agreement upon the use of effective contraceptive methods prior to study entry, for the duration of study participation and in the following 90 days after discontinuation of study treatment
17. **Availability of histological material for central review and pathobiological studies.**

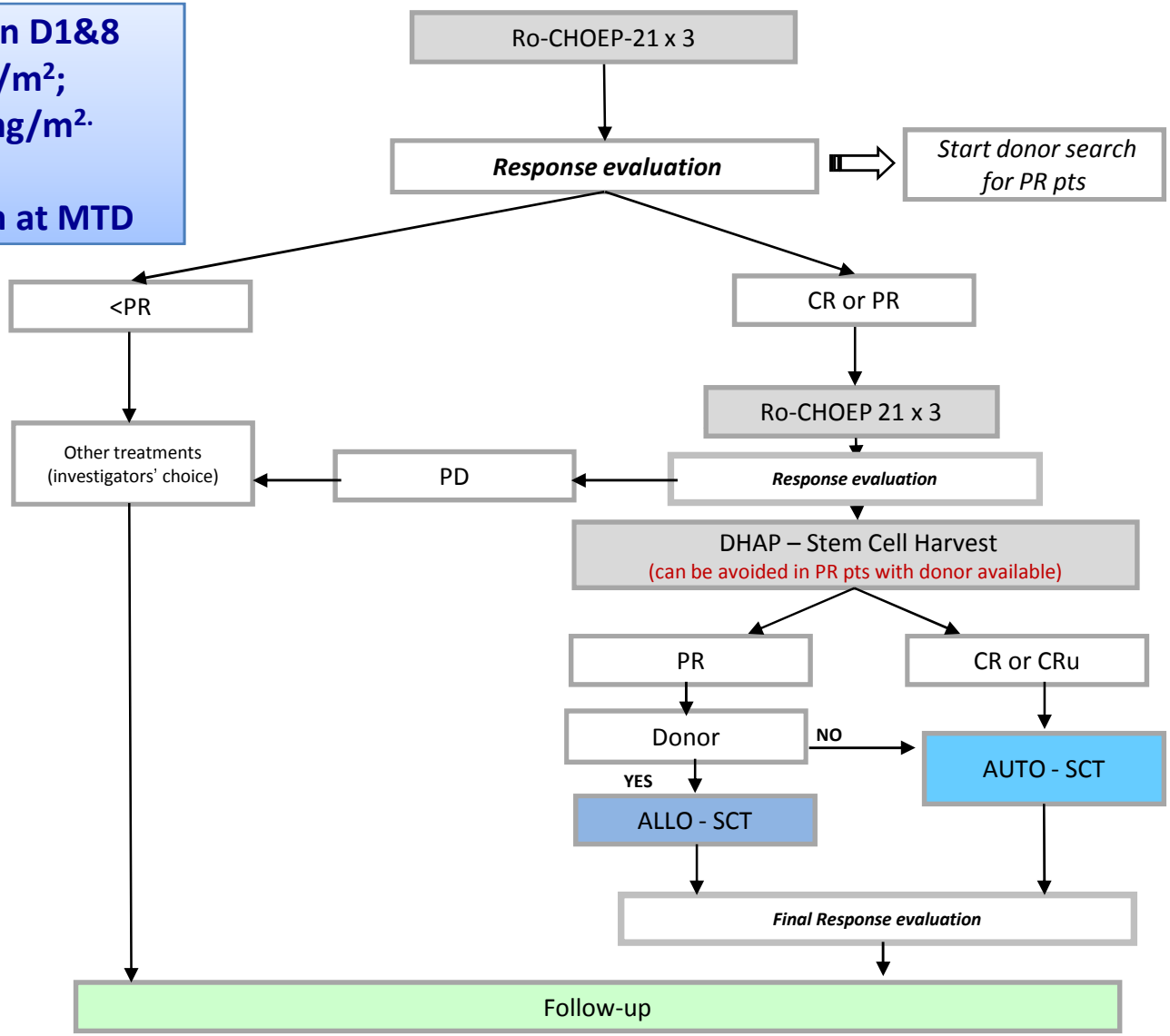
EXCLUSION CRITERIA

1. age <18 e > 65 years
2. Hystology other than: PTCL-NOS, AITL, ALK negative ALCL
3. Stage I
4. Prior treatment for lymphoma
5. Positive serologic markers for human immunodeficiency virus (HIV)
6. Active hepatitis B virus (HBV) infection
7. Active hepatitis C virus (HCV) infection
8. Levels of serum bilirubin, alkaline phosphatase and transaminases > 2 the upper normal limit, if not disease related
9. Ejection fraction < 50% and no myocardial stroke in the last year or QT prolongation (QTc interval > 480 msec using the Fridericia formula)
10. Clearance of creatinine < 60 ml/min if not disease related
11. Spirometry Diffusion Capacity (DLCO) < 50%
12. Pregnancy or lactation
13. Patient not agreeing to take adequate contraceptive measures during the study
14. Psychiatric disease that precludes understanding concepts of the trial or signing informed consent
15. Any active, uncontrolled infection
16. Prior history of malignancies other than PTCLs in the last five years (except for basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix or breast).

STUDY DESIGN

Phase I : Romidepsin D1&8
8, 10, 12, 14 mg/m^2;
starting with 12 mg/m^2.

Phase II: Romidepsin at MTD



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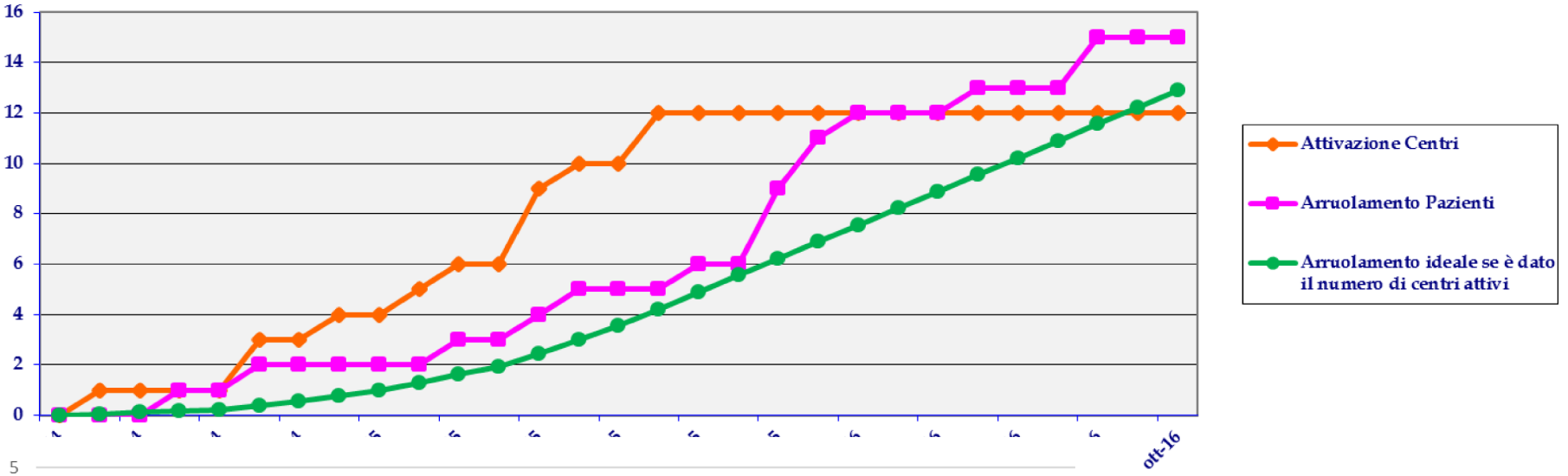
STUDY STATUS

Patients enrolled	Group	Romidepsin mg/m²	DLTs
3	I	12	0
6	II	14	1 (mucositis g3)
9	III	14	1 (FUO g3)
12	IV	14	0
15	V	14	1 (fatigue g3)
18	VI	14	SLOTS AVAILABLE

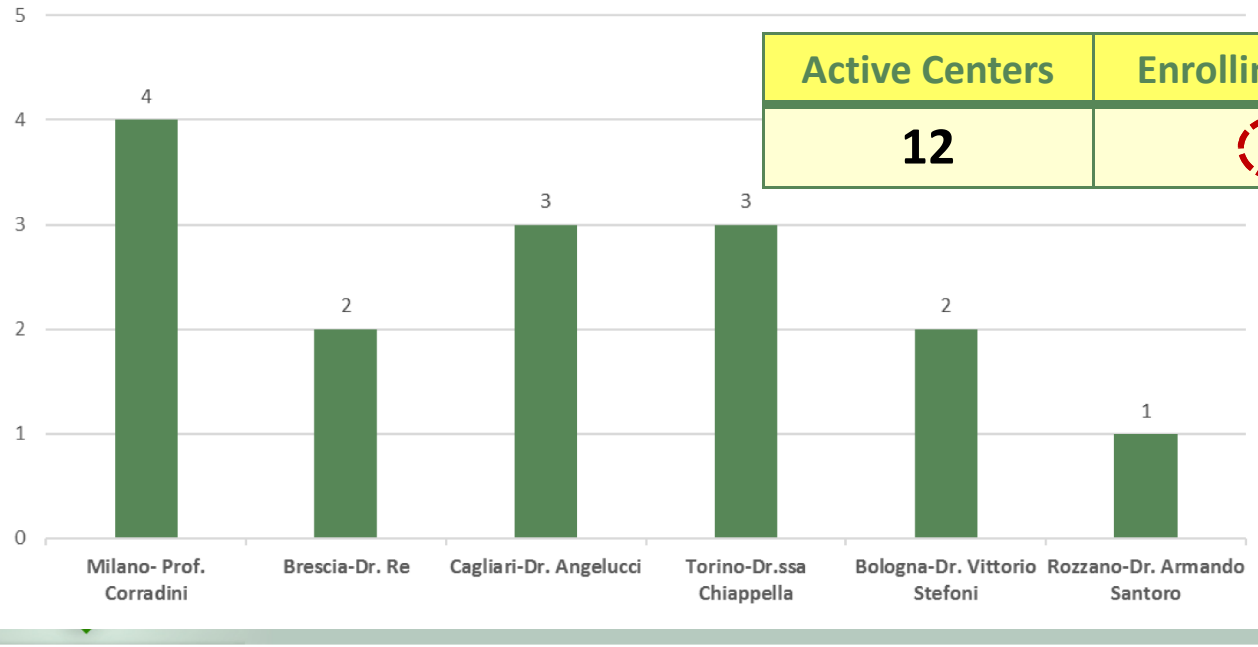
ENROLLMENT OPEN!!!

The enrollment was reopened on October 27th, 2016

STUDY STATUS



Active Centers	Enrolling Centers	Enrolled Patients
12	6	16



STUDY STATUS_Participating Centres (38)

FONDAZIONE FIL ITALIANA LINFOMI
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Participating Centers Phase I	Active Centers
12	12

Participating Centers Phase II	Active Centers
26	-

Phase I

ID	Città	Ospedale	PI
1	Alessandria	A.O. SS. Antonio e Biagio e Cesare Arrigo	Dott.ssa Flavia Salvi
2	Bologna	Policlinico S.Orsola-Malpighi	Dott. Vittorio Stefoni
3	Brescia	A.O. Spedali Civili di Brescia	Dott. Alessandro Re
4	Cagliari	Ospedale Businco	Dott. Emanuele Angelucci
5	Cuneo	A.O. S. Croce e Carle	Dott.ssa Claudia Castellino
6	Genova	IRCCS AOU S.martino - IST	Prof. Angelo Michele Carella
7	Milano	Ospedale Niguarda CA' Granda	Dott.ssa Chiara Rusconi
8	Milano	Fondazione IRCCS Istituto Nazionale dei Tumori di Milano	Prof. Paolo Corradini
9	Roma	Policlinico Umberto I - Università "La Sapienza"	Prof. Maurizio Martelli
10	Rozzano (MI)	Istituto Clinico Humanitas	Prof. Armando Santoro
11	Torino	A.O.U. Citta della Salute e della Scienza di Torino	Dott.ssa Annalisa Chiappella
12	Udine	AOU di Udine	Dott. Francesco Zaja

Phase II

ID	Città	Ospedale	PI
1	Ancona	Università Politecnica delle Marche	Prof. Attilio Olivieri
2	Aviano (PN)	Centro Riferimento Oncologico	Dott. Michele Spina
3	Bari	AOU Policlinico Consorziale	Prof.ssa Giorgina Specchia
4	Campobasso	Università Cattolica	Dott. Sergio Storti
5	Firenze	Azienda Ospedaliera universitaria Careggi	Dott. Luigi Rigacci
6	Genova	IRCCS AOU S.martino - IST	Dott. Filippo Ballerini
7	Meldola (FC)	Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (I.R.S.T.)	Dott. Gerardo Musuraca
8	Milano	Ospedale Maggiore - Policlinico - Fondazione IRCCS ca' Granda	Dott. Luca Baldini
9	Napoli	IRCCS Istituto Nazionale dei Tumori di Napoli - Pascale	Dott. Antonello Pinto
10	Novara	AOU Maggiore della Carità di Novara	Prof. Gianluca Gaidano
11	Palermo	[illegible]	[illegible]
12	Parma		
13	Pavia		
14	Perugia		
15	Pescara		
16	Piacenza		
17	Ravenna		
18	Reggio Calabria	A.O. Bianchi Melacrino Morelli	Dott.ssa Caterina Stelitano
19	Reggio Emilia	Azienda Ospedaliera Arcispedale Santa Maria Nuova - IRCCS	Dott. Francesco Merli
20	Rimini	Ospedale degli Infermi di Rimini	Dott.ssa Annalia Molinari
21	Rionero in vulture	IRCCS-Centro di riferimento oncologico	Dott. Roberto Guariglia
22	Roma	Università Cattolica S. Cuore	Dott. Stefan Hohaus
23	San Giovanni Rotondo (FO)	Casa Sollievo della Sofferenza	Dott. Nicola Cascavilla
24	Torino	A.O.U. Citta della Salute e della Scienza di Torino	Dott.ssa Federica Cavallo
25	Verona	AOU Integrata di Verona	Dott. Fabio Benedetti
26	Vicenza	Ospedale ULSS 6 di Vicenza	Dott. Carlo Visco

EC submission:
Dec 2016- Jan 2017

NEW Substancial Amendment 2

- ✓ Apertura centri fase II
- ✓ Revisione istologica
  - Prof Pileri, IEO
- ✓ Implementazione studi biologici:
  - Prof Corradini, Drsa Carniti, INT
- ✓ Aggiornamento IB Romidepsin (v.15, 22 Apr 2016)

Ro-CHOP STUDY

PHASE 3 MULTI-CENTER RANDOMIZED STUDY TO COMPARE EFFICACY AND SAFETY OF ROMIDEPSIN-CHOP (Ro-CHOP) *VERSUS* CHOP IN PATIENTS WITH PREVIOUSLY UNTREATED PERIPHERAL T-CELL LYMPHOMA

LYSARC

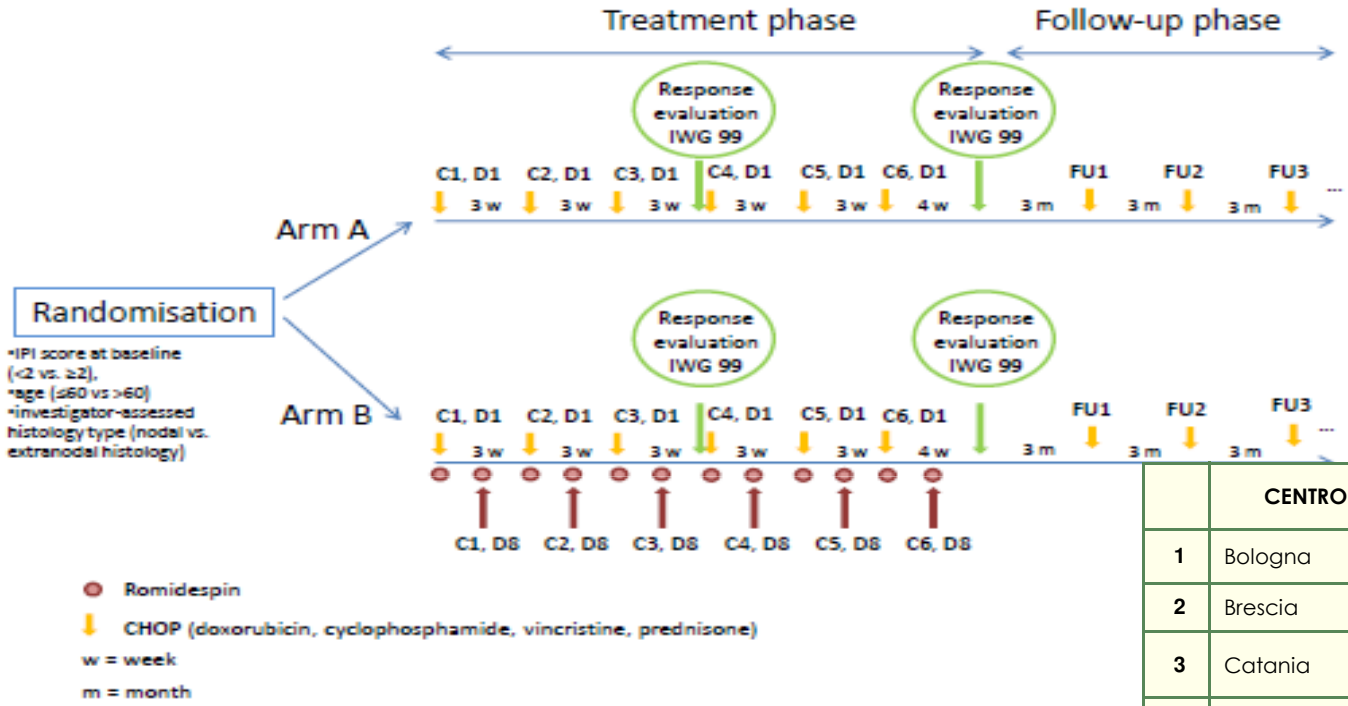
Main inclusion criteria

- ≥18 and ≤ 80 years
- PTCL-NOS, AILT, ALCL ALK neg
- EATL, HS
- Panniculitis, cutaneous T-delta, cutaneous CD8, cutaneous CD4
- No previous threapy
- ECOG performance status score of ≤ 1 at study entry

Main exclusion criteria

- ATLL, NK/T nasal type, ALCL-ALK pos, MF/SS, CD30 pos LD
- CNS involvement
- HIV, HBV, HCV
- QT > 480msec
- IMA 6 months before treatment
- EF < 45%

CHOP vs RO-CHOP



Sample size: 420 patients

November 2016: 288/420 patients enrolled

	CENTRO	PI	Codice centro	Pz Arruolati
1	Bologna	Dr. Vittorio Stefoni	21201	5
2	Brescia	Dr. Giuseppe Rossi	21207	3
3	Catania	Dr. Francesco Di Raimondo	21209	2
4	Cuneo	Dr.ssa Claudia Castellino	21202	2
5	Firenze	Dr. Luigi Rigacci	21210	2
6	Napoli	Dr. Antonello Pinto	21212	
7	Reggio Calabria	Dr.ssa Caterina Stelitano	21208	
8	Roma	Dr. Maurizio Martelli	21206	
9	Torino	Dr. Umberto Vitolo	21205	2
10	Udine	Dr. Francesco Zaja	21204	2
TOT.				18

PTCL:
Relapse treatment.

FONDAZIONE FIL ITALIANA LINFOMI
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"Phase II study on the role of brentuximab vedotin as single agent in the treatment of relapsed/refractory CD30 positive peripheral T cell lymphoma (PTCL) patients"

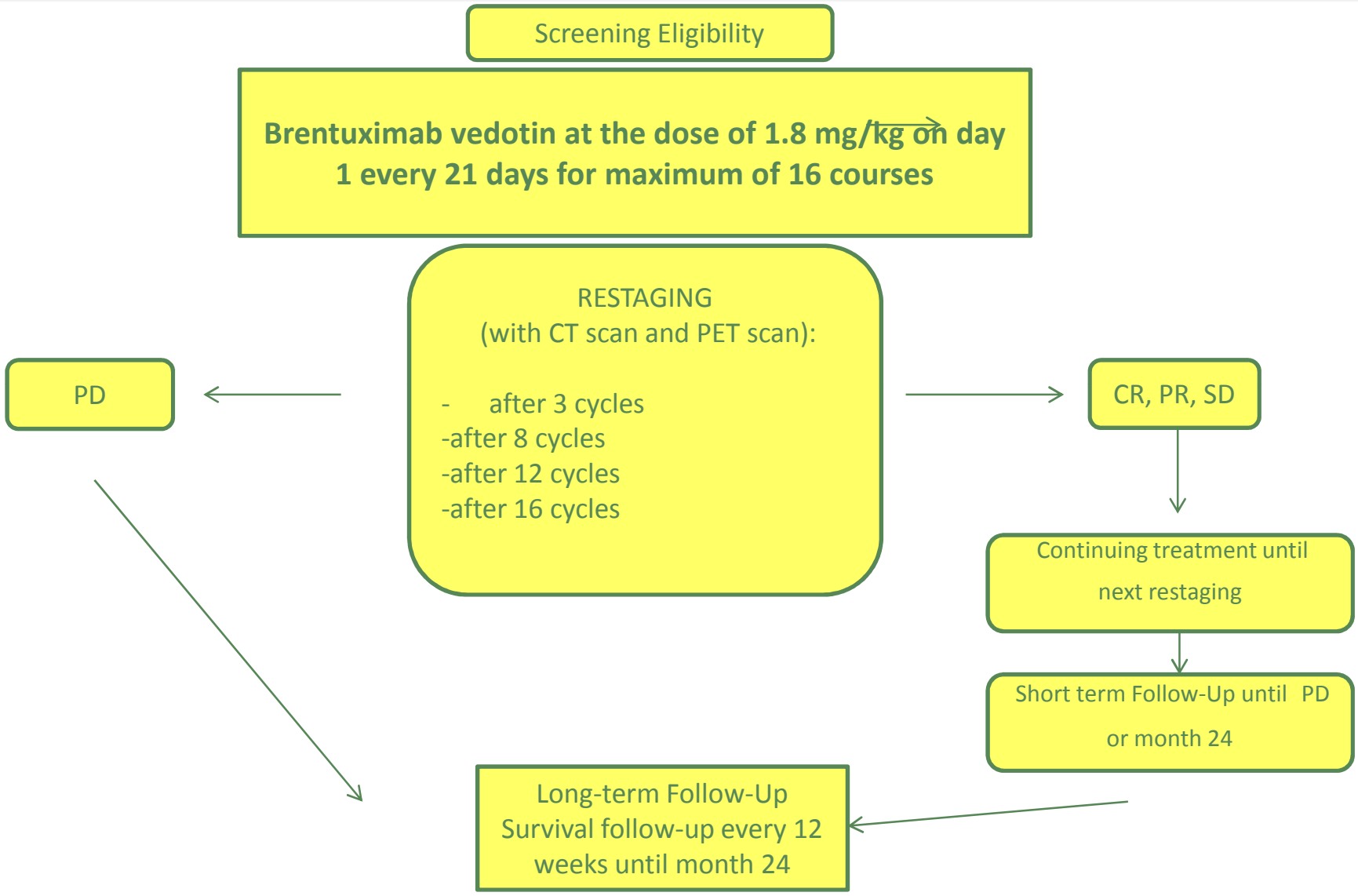
FIL_PTCL_BV

PIs: Dr Vittorio Stefoni, Prof Pierluigi Zinzani

PRINCIPALI CRITERI DI INCLUSIONE:
- Diagnosi confermata istologicamente di PTCL (PTCL nos, non altrimenti specificato, linfoma T angioimmunoblastico e micosi fungoide trasformata) in accordo con la classificazione WHO 2008
- PTCL confermato istologicamente come CD30 positivo
- Età ≥ 18 e ≤ 75 anni
- PS ECOG ≤ 1 all'arruolamento

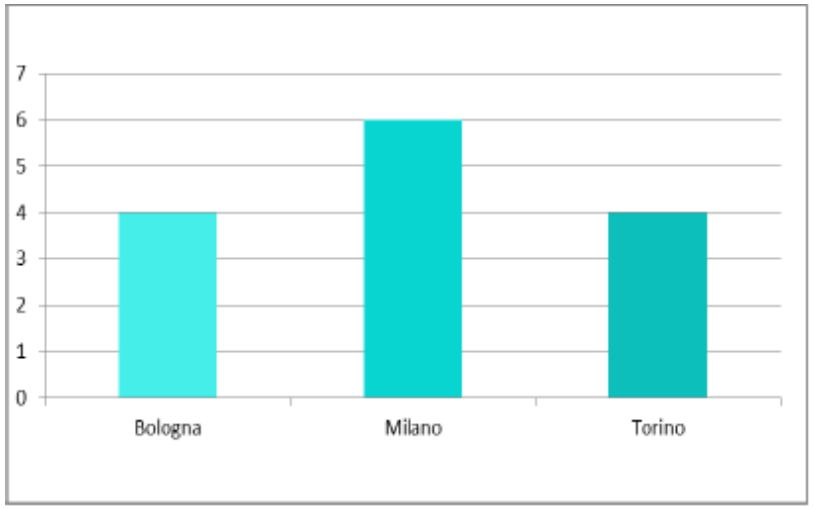
PRINCIPALI CRITERI DI ESCLUSIONE:
- Diagnosi di CTCL, ALCL, micosi fungoide o sindrome di Sezary
- Espressione di CD30 <10% misurati secondo i criteri IHC
- Pazienti con neuropatia periferica di grado 3-4 (anche di grado 2 con persistenza di dolore non rispondente al trattamento)

Study Flow Chart

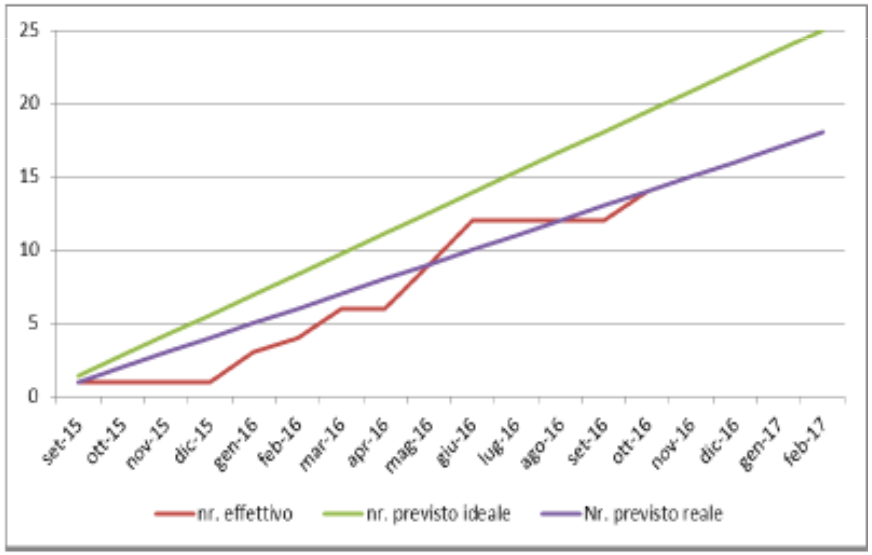


Enrolment status

STATUS	CENTRO		PI
	Bologna	Ematologia "L. & A. Seragnoli" Policlinico S. Orsola Malpighi	Dott. Vittorio Stefoni
	Brescia	Ematologia Spedali Civili	Dott. Giuseppe Rossi
	Milano INT	SC Ematologia - Fondazione IRCCS "Istituto Nazionale dei Tumori"	Prof. Paolo Corradini
	Torino	SC Ematologia - AO Città della Salute e della Scienza	Dott. Umberto Vitolo
	Udine	Clinica Ematologica Centro Trapianti e Terapie Cellulari "Carlo Melzi" AOU "Santa Maria della Misericordia"	Dott. Francesco Zaja



- ✓ ACCRUAL PREVISTO: 25 pazienti
- ✓ ACCRUAL ATTUALE: **14** pazienti



A phase II study with bendamustine plus brentuximab vedotin in Hodgkin's lymphoma and CD30^{+} peripheral T-cell lymphoma in first salvage setting: the BBV regimen.

Study ID: FIL-BBV

EudraCT n. 2014-005382-79

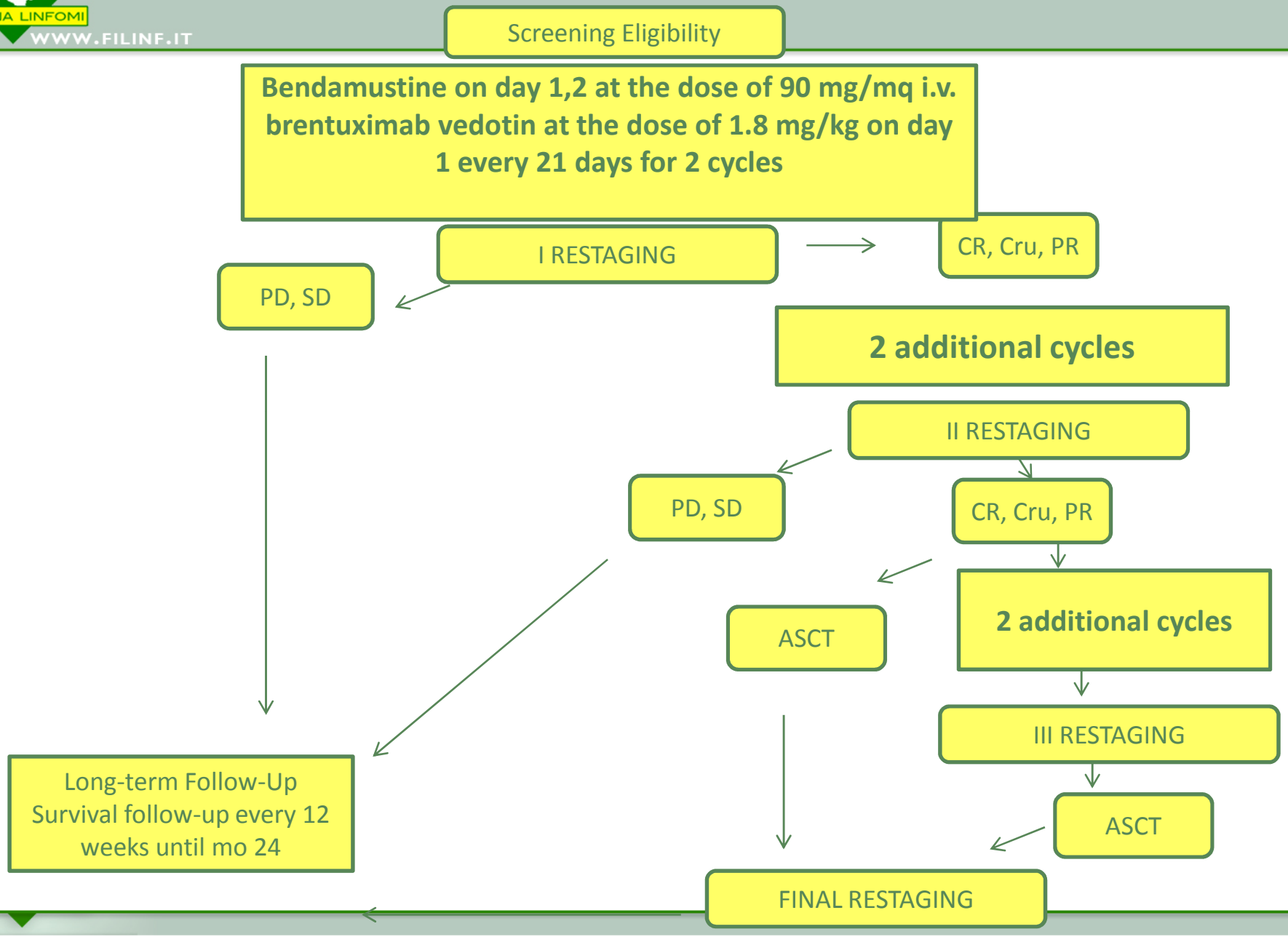
PI: Prof Pierluigi Zinzani

- Single-arm, open-label, multicenter, phase 2 clinical trial aimed at evaluating the efficacy and safety of the combination of Bendamustine and Brentuximab vedotin as a first salvage therapy in patients with relapsed or refractory Hodgkin's lymphoma or PTCL.
- A total **of 25 patients with PTCL**, and 40 with Hodgkin's lymphoma are expected to be treated according to this treatment protocol.

INCLUSION CRITERIA HD/PTCL

-Patients at first relapse or with primary refractory disease (i.e. patients who have previously received only **1 line of treatment**)
-Histologically-confirmed CD30^{+} disease (IHC BerH2 antibody)
-Age > 18 years and < 60 years.

Study Flow Chart



New perspectives

CD38, BCL-2, PD-1, and PD-1L expression in nodal peripheral T-cell lymphoma: Possible biomarkers for novel targeted therapies?

Francesco Zaja[1,4], Valentina Tabanelli[2], Claudio Agostinelli[3,4], Angelica Calleri[2], Annalisa Chiappella[5], Marzia Varettoni[6], Pier Luigi Zinzani[7], Stefano Volpetti[1], Elena Sabattini[3], Renato Fanin[1] Stefano A. Pileri[2,4]

Am J Hematol 2016, in press

	ALCL-ALK$^-$	ALCL-ALK$^+$	PTCL-NOS	AITL
Total cases	**48**	**25**	**73**	**27**
CD38				
N. of evaluable cases	36	10	42	25
CD38 positive cases	6 (17%)	0	24 (57%)	20 (80%)
Positivity score:				
4	3		9	2
3	1		3	5
2	0		2	4
1	2		10	9
0	30		18	5
BCL-2				
N. of evaluable cases	37	13	44	26
BCL-2 positive cases	21 (58%)	4 (31%)	35 (79.5%)	23 (88%)
Positivity score:				
4	13	2	22	10
3	3	0	5	3
2	3	1	5	4
1	2	1	3	6
0	16	9	9	3
PD-1				
N. of evaluable cases	36	18	46	27
PD-1 positive cases	0	2 (11%)	28 (61%)	19 (70%)
Positivity score:				
4		2	9	5
3		0	9	9
2		0	5	1
1		0	5	4
0		16	18	8
PD-1L				
N. of evaluable cases	35	11	44	27
PD1-L positive cases	16 (46%)	8 (72%)	0	0
Positivity score:				
4	9	4		
3	2	1		
2	2	2		
1	3	1		
0	19	3		

Positivity score: 4 = >75% stained cells; 3 = 75–50%; 2 = 25–49%; 1 = 5–24%; 0 = <5%.

Venetoclax in BCL-2 positive PTCLs: VERT Trial

Venetoclax single agent in R/R BCL-2 positive peripheral T-cell lymphoma not otherwise specified, angioimmunoblastic T-cell lymphoma and other nodal T-cell lymphomas of T-follicular helper origin

Sponsor:

- FIL

Principal Investigator:

- Prof. Francesco Zaja

Writing committee:

- Prof. Francesco Zaja
- Prof. Pier Luigi Zinzani
- Dr. Marzia Varettoni
- Dr. Annalisa Chiappella

Pathology:

- Prof. Stefano A. Pileri

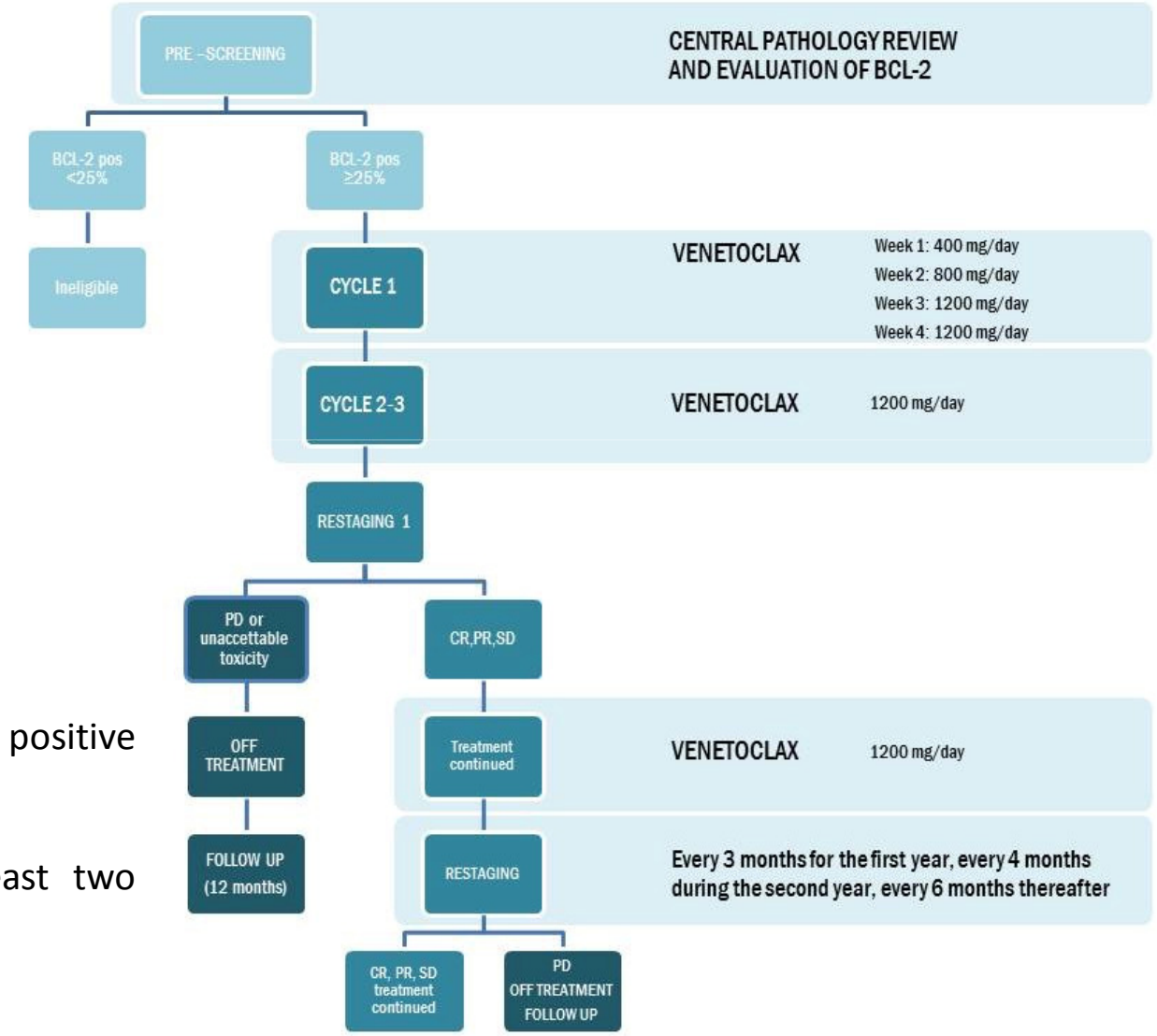
Statisticians:

- Prof. Gianni Ciccone
- Dr. Manuela Ceccarelli

Pharmacovigilance

- Dr. Alessandro Levis
- Dr. Daniela Gioia

VERT Trial: study flow-chart



INCLUSION CRITERIA

- Age ≥ 18 years
- Histological diagnosis of BCL-2 positive PTCL-NOS, AITL, TFH
- Relapsed or refractory to at least two previous lines of treatment
- BCL-2 positive tumor cells ≥ 25%

AKNOWLEDGMENTS

- Prof Paolo Corradini, INT
- Prof Stefano Pileri, IEO
- Prof Francesco Zaja, Udine
- Co-investigators
- Patients, families, and caregivers who are participating in the studies

Lymphoma T Committee

All FIL Centers

FIL Central Office Alessandria
FIL Trial Office Modena
FIL Biostatistics University of Torino