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

Torino, 14 dicembre 2018

Sede
Sala Giolitti - Centro Congressi Torino Incontra
Via Nino Costa, 8 - Torino

Protocolli FIL: linfomi T

Luca Nassi

SCDU Ematologia

AOU Maggiore della Carità

Novara

DICHIARAZIONE

Relatore: Luca Nassi

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 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: **MSD, TAKEDA, JANSSEN**
- 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: **MOLMED**
- Lecture fee/attività educazionali (NIENTE DA DICHIARARE)

FIL_PTCL13 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.

PI Prof Paolo Corradini

FIL_PTCL13 ROMIDEPSIN IN COMBINATION WITH CHOEP AS FIRST LINE TREATMENT BEFORE SCT IN YOUNG PATIENTS WITH NODAL PERIPHERAL T-CELL LYMPHOMAS: A PHASE I-II STUDY.

A multicenter study including two phases:

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)

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)

INCLUSION AND EXCLUSION CRITERIA

INCLUSION CRITERIA

- **age ≥18 e ≤ 65 years**
- **Peripheral T-cell lymphomas at diagnosis including: PTCL-NOS, AITL, ALK negative ALCL**
- Stage II-IV
- Written informed consent
- No CNS disease
- HIV negativity
- Absence of active HCV infection
- HBV negativity or patients with HBcAb +, HBsAg -, HBs Ab+/- with HBV-DNA negativity (in these patients Lamivudine prophylaxis is mandatory)
- Levels of serum bilirubin, alkaline phosphatase and transaminases < 2 the upper normal limit, if not disease related
- Ejection fraction > 50% and myocardial stroke in the last year nor QT prolongation (QTc interval < 480 msec using the Fridericia formula)
- Normal organ function
- **Availability of histological material for central review and pathobiological studies**

EXCLUSION CRITERIA

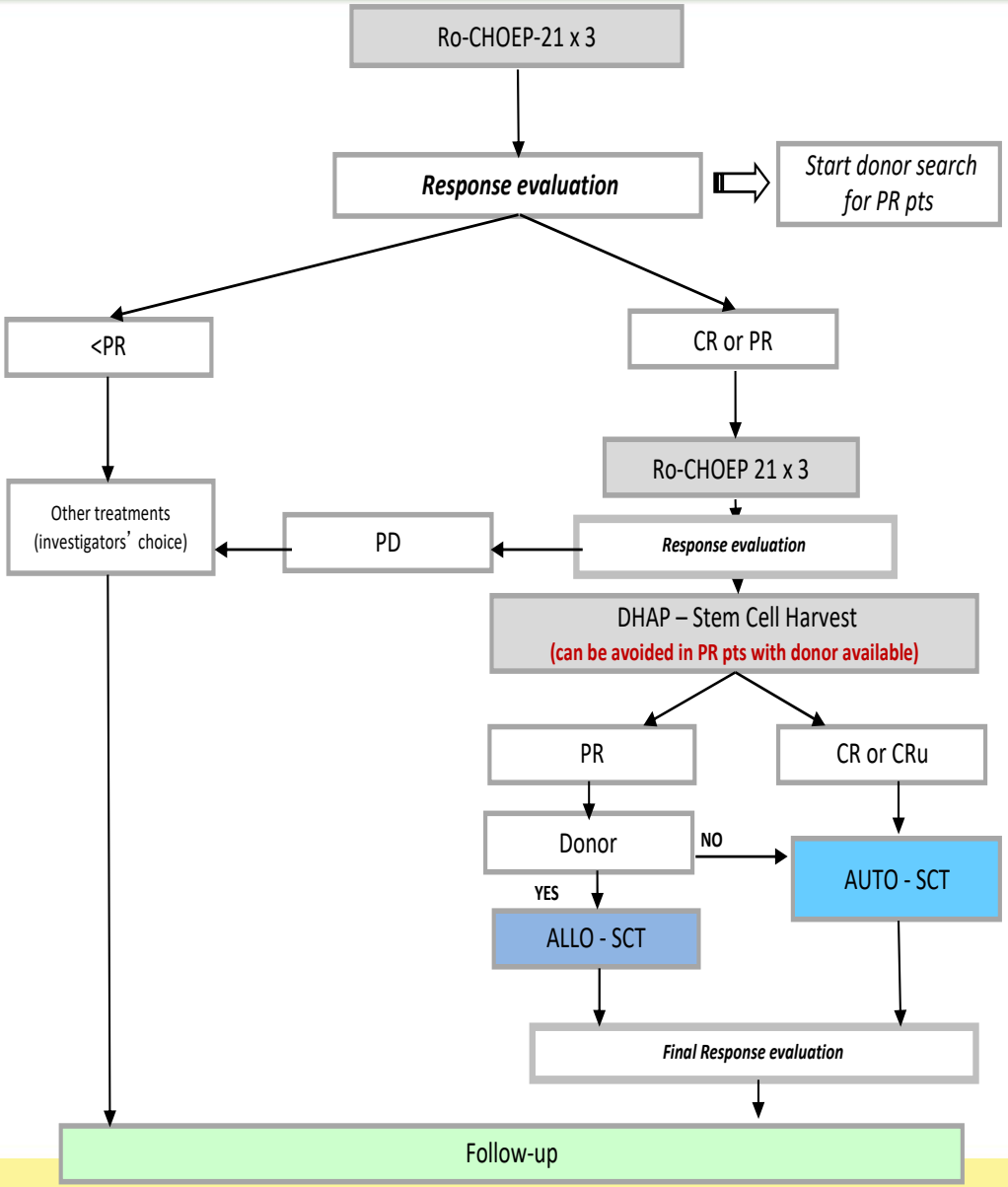
- age <18 e > 65 years
- Hystology other than: PTCL-NOS, AITL, ALK NEG ALCL
- Stage I
- Prior treatment for lymphoma
- Positive serologic markers for HIV
- Active HBV infection
- Active HCV infection
- Levels of serum bilirubin, alkaline phosphatase and transaminases > 2 the upper normal limit, if not disease related
- Ejection fraction < 50% and no myocardial stroke in the last year or QT prolongation (QTc interval > 480 msec using the Fridericia formula)
- Abnormal organ functions
- Pregnancy or lactation
- Any active, uncontrolled infection
- 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&D8
8, 10, 12, 14 mg/m²;
starting with 12 mg/m².
Phase II:
Romidepsin at MTD 14 mg/m²

Accrual Phase I
Sep 2014 – Sep 2017:
21 patients

Accrual Phase II
20 Sep 2017 - ongoing

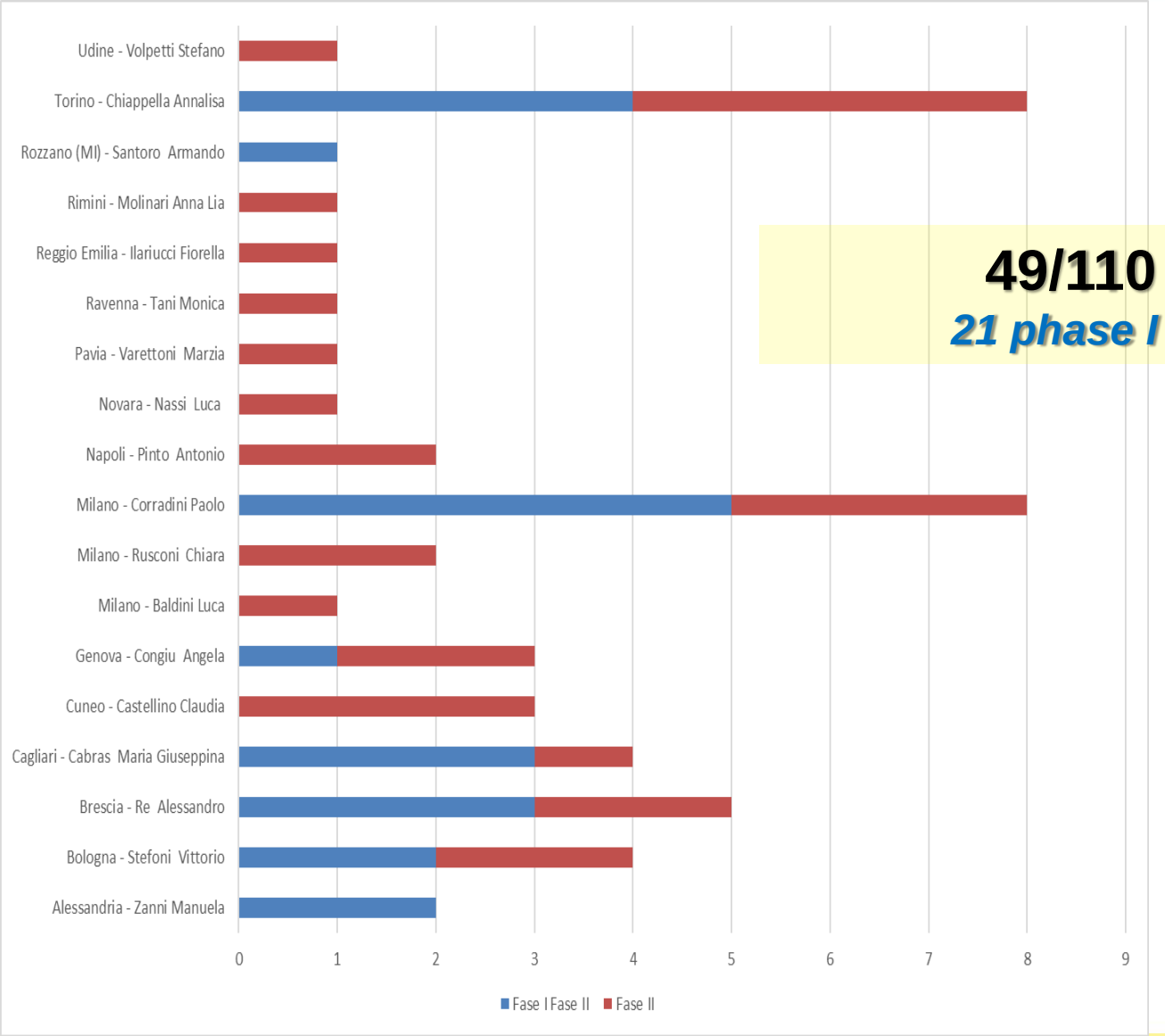


CENTRI PARTECIPANTI /CENTRI ATTIVI → 37/27

CENTRI ATTIVI/ CENTRI ARRUOLANTI → 27/18

Localita	Struttura	PI
Alessandria	A.O. SS. Antonio e Biagio e Cesare Arrigo - S.C. Ematologia	Zanni Manuela
Ancona	Università Politecnica delle Marche - Clinica di Ematologia	Olivieri Attilio
Aviano	Aviano - Centro Riferimento Oncologico - S.O.C. Oncologia Medica A	Ciancia Rosanna
Bologna	Policlinico S.Orsola-Malpighi - Istituto di Ematologia "Seragnoli"	Stefoni Vittorio
Brescia	ASST Spedali Civili di Brescia - Ematologia	Re Alessandro
Cagliari	Ospedale Businco - SC Ematologia e CTMO	Cabras Maria Giuseppina
Cuneo	A.O. S. Croce e Carle - S.C. di Ematologia e Trapianto di Midollo Osseo	Castellino Claudia
Genova	Ospedale Policlinico San Martino S.S.R.L. - IRCCS per l'Oncologia - Ematologia	Congiu Angela
Meldola	Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (I.R.S.T.) - Ematologia	Musuraca Gerardo
Milano	Ospedale Maggiore Policlinico - Fondazione IRCCS Ca' Granda - Ematologia	Baldini Luca
Milano	ASST Grande Ospedale Metropolitano Niguarda - SC Ematologia	Rusconi Chiara
Milano	Fondazione IRCCS Istituto Nazionale dei Tumori di Milano - Ematologia	Corradini Paolo
Napoli	Istituto Nazionale Tumori - IRCCS Fondazione G. Pascale - UOC Ematologia Oncologica	Pinto Antonio
Novara	AOU Maggiore della Carità di Novara - SCDU Ematologia	Nassi Luca
Parma	AOU di Parma - UO Ematologia e CTMO	Re Francesca
Pavia	IRCCS Policlinico S. Matteo di Pavia - Div. di Ematologia	Varettoni Marzia
Perugia	Ospedale S. Maria della Misericordia - Ematologia	Flenghi Leonardo
Pescara	P.O. Spirito Santo di Pescara - UOS Dipartimentale - Centro di diagnosi e Terapia dei linfomi	Angrilli Francesco
Piacenza	Ospedale Guglielmo da Saliceto - U.O.Ematologia	Arcari Annalisa
Ravenna	Ospedale delle Croci - Ematologia	Tani Monica
Reggio Emilia	Azienda Unità Sanitaria Locale-IRCCS - Arcispedale Santa Maria Nuova - Ematologia	Ilariucci Fiorella
Rimini	Ospedale degli Infermi di Rimini - U.O. di Ematologia	Molinari Anna Lia
Roma	Policlinico Umberto I - Università "La Sapienza" - Istituto Ematologia -Dipartimento di Biotecnologie Cellulari ed Ematologia	Martelli Maurizio
Rozzano *	Istituto Clinico Humanitas - U.O. Ematologia	Santoro Armando
Torino	A.O.U. Citta della Salute e della Scienza di Torino - S.C.Ematologia	Chiappella Annalisa
Torino	A.O.U. Citta della Salute e della Scienza di Torino - Ematologia Universitaria	Cavallo Federica
Udine	Azienda Sanitaria Universitaria Integrata di Udine (A.S.U.I. Udine) - SOC Clinica Ematologica	Volpetti Stefano
Verona	AOU Integrata di Verona - U.O. Ematologia	Benedetti Fabio

ACCRUAL BY CENTERS, CUT-OFF 31 OCT 2018



49/110 patients

21 phase I + 28 phase II

Accrual Phase I:
0.5 patient/month

Accrual Phase II:
2.3 patients/month

STOCKHOLM 23RD CONGRESS JUNE 14 - 17 | 2018
European Hematology Association

THE ADDITION OF ROMIDEPSIN TO CHOEP FOLLOWED BY HIGH-DOSE CHEMOTHERAPY AND TRANSPLANTATION IS FEASIBLE IN UNTREATED PERIPHERAL T-CELL LYMPHOMAS: RESULTS OF PHASE IB FIL-PTCL13

Chiappella A1, Carniti C2, Evangelista A3, Cabras MG4, Re A5, Salvi F6, Stefoni V7, Santoro A8, Congiu AG9, Dodero A2, Gioia D10, Pileri SA11, Ciccone G3, Corradini P2 On behalf of Fondazione Italiana Linfomi. 1. Hematology, Città della Salute e della Scienza di Torino Hospital and University, Torino, 2 Division of Hematology and Bone Marrow Transplant, Fondazione IRCCS Istituto Nazionale dei Tumori; Department of Oncology and Hemato-oncology, University of Milan, Milano, 3 Unit of Clinical Epidemiology and CPO, Città della Salute Hospital and University, Torino, 4 Hematology, Ospedale A. Businco Cagliari, Haematology & Transplant Centre Wilma Deplano, Cagliari, 5 Hematology, ASST Spedali Civili di Brescia, Brescia, 6 Hematology, Azienda Ospedaliera SS Antonio e Biagio e Cesare Arrigo, Alessandria, 7 Hematology, Istituto L e A Seragnoli, Policlinico S.Orsola-Malpighi, Bologna, 8 Hematology, Istituto Clinico Humanitas and IRCCS, Rozzano, 9 Division of Hematology and Bone Marrow Transplantation, Ematologia Ospedale Policlinico San Martino, Genova, 10 Pharmacovigilance, Secretary Fondazione Italiana Linfomi, Alessandria, 11 Haematopathology Unit, Istituto Europeo di Oncologia, Milano, Italy.

Clinical Characteristics

Median age	57 (37-65)	Stage III/IV	18 (86%)
Sex	9 F, 12 M	PS ≥ 2	3 (15%)
IPI III/IV	8 (38%)	BM+	6 (29%)
PIT score ≥2	8 (38%)	LDH increased	10 (50%)
		N extranodal sites >1	7 (35%)

DLTs:

3 patients Ro at 12mg/ms: no DLTs

18 patients Ro at 14mg/ms: 9 DLTs

9 DLTs were reported in 7/21 patients:

3 events of g3 mucositis

1 event of g3 maculopapular rash

1 event g3 fatigue

1 event g3 fever

1 event g3 respiratory failure

1 event g3 typhlitis

1 event g4 neutropenic fever

Observed toxicity was 35.2% (95% CI: 17.1%>56.5%) --> 14 mg/ms recommended dose of Ro + CHOEP.

No unexpected toxicities and no toxic deaths were reported into the phase I part of the trial.

Median of 4.3 × 10 (IQR 3.4-5.71) peripheral blood CD34-positive cells/Kg collected.

FONDAZIONE FIL ITALIANA LINFOMI
WWW.FILINF.IT

ASH Annual Meeting

2902 Romidepsin-CHOEP Plus Intensification with up-Front Stem-Cell Transplantation in Peripheral T-Cell Lymphoma: Final Results of Phase Ib PTCL13 Study of the Fondazione Italiana Linfomi

Program: Oral and Poster Abstracts
Session: 624. Hodgkin Lymphoma and T/NK Cell Lymphoma—Clinical Studies: Poster II
Hematology Disease Topics & Pathways:
Biological, Diseases, Adult, Therapies, Biological Processes, Technology and Procedures, T-Cell Lymphoma, Study Population, immunotherapy, Clinically relevant, Lymphoid Malignancies

Sunday, December 2, 2018, 6:00 PM-8:00 PM
Hall GH (San Diego Convention Center)

Annalisa Chiappella, MD[1], *Cristiana Carniti*[2*], *Andrea Evangelista, PhD*[3*], *Maria Giuseppina Cabras, MD*[4*], *Alessandro Re, MD*[5*], *Manuela Zanni, MD*[6*], *Vittorio Stefoni*[7*], *Armando Santoro, MD*[8*], *Angela Giovanna Congiu*[9*], *Anna Dodero, MD*[10*], *Stefano A. Pileri, MD, PhD*[11], *Giovannino Ciccone, MD*[3*] *and Paolo Corradini, MD*[12,13]

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.

PI DR VITTORIO STEFONI

CRITERI DI INCLUSIONE

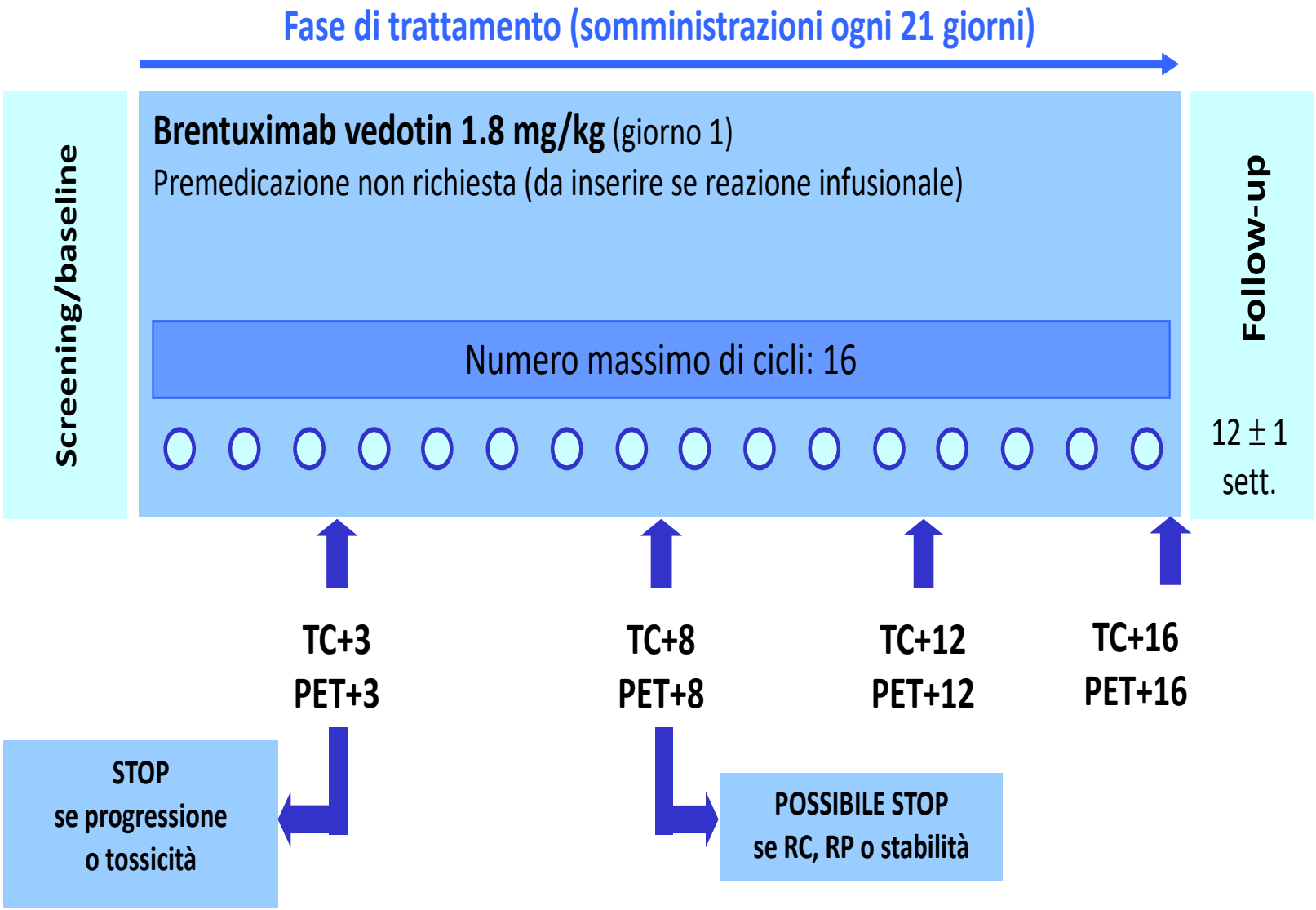
- Diagnosi confermata istologicamente di linfoma a cellule T periferiche (PTCL-NOS, AITL, MF trasformata), in accordo con la classificazione WHO 2008.

- Malattia CD30+ > 10% secondo i criteri di immunoistochimica.

- Ricaduta o refrattarietà ad almeno una precedente linea di trattamento antilinfoma.

- Età $\geq$ 18 anni e $\leq$ 75 anni.
- Laboratorio: neutrofili $\geq$ 1.000/mmc, piastrine $\geq$ 75.000/mmc (o 50.000 in presenza di coinvolgimento midollare), emoglobina > 8 g/dL.
- Adeguata funzionalità epato-renale.
- Assetto sierologico permissivo per HBV, HCV e HIV.

PROTOCOLLO DI TRATTAMENTO



STATUS ARRUOLAMENTO

- **Data inizio studio**: settembre 2015
- **Data inizio arruolamento**: settembre 2015
- **Durata studio**: 18 mesi per arruolamento (**esteso**) + 2 anni di *follow-up*

Centro	Attivazione	Pazienti arruolati
Bologna*	Sì	7
Brescia	Sì	0
Milano (INT)*	Sì	7
Torino	Sì	4
Udine	Sì	1
TOTALE		**19**
Previsti		**25**

(*) Screening failure in due pazienti (non riportati)

A PHASE II STUDY ON WITH BENDAMUSTINE PLUS BRENTUXIMAB VEDOTIN IN HODGKIN'S LYMPHOMA AND CD30 POSITIVE PERIPHERAL T CELL LYMPHOMA (PTCL) IN SALVAGE SETTING: THE BBV REGIMEN.

CD30+ PTCL PART.

PI DR VITTORIO STEFONI

CRITERI DI INCLUSIONE

- Diagnosi di linfoma a cellule T periferiche (PTCL-NOS, AITL, MF trasformata), in ricaduta o refrattario, indipendentemente dal numero di precedenti linee di trattamento **(*)**.
- Malattia $CD30^{+}$.
- Età compresa tra 18 e 60 anni **(**)**.
- Malattia misurabile in TC (linfonodi: Ø massimo > 1,5 cm oppure asse lungo compreso tra 1,1 e 1,5 cm e asse corto > 1 cm) e FDG-PET-positiva.
- ECOG ≤ 1.
- Laboratorio: neutrofili $\geq$ 1.500/mmc, piastrine $\geq$ 75.000/mmc, bilirubina e creatinina sieriche $\leq 1{,}5 \times$ ULN, AST/ALT $\leq 2{,}5 \times$ ULN, albumina ≥ 3 g/dL.
- Adeguate misure contraccettive.

(*) Emendamento 2, v. 12/12/2016

(**) Emendamento 1, v. 05/01/2016

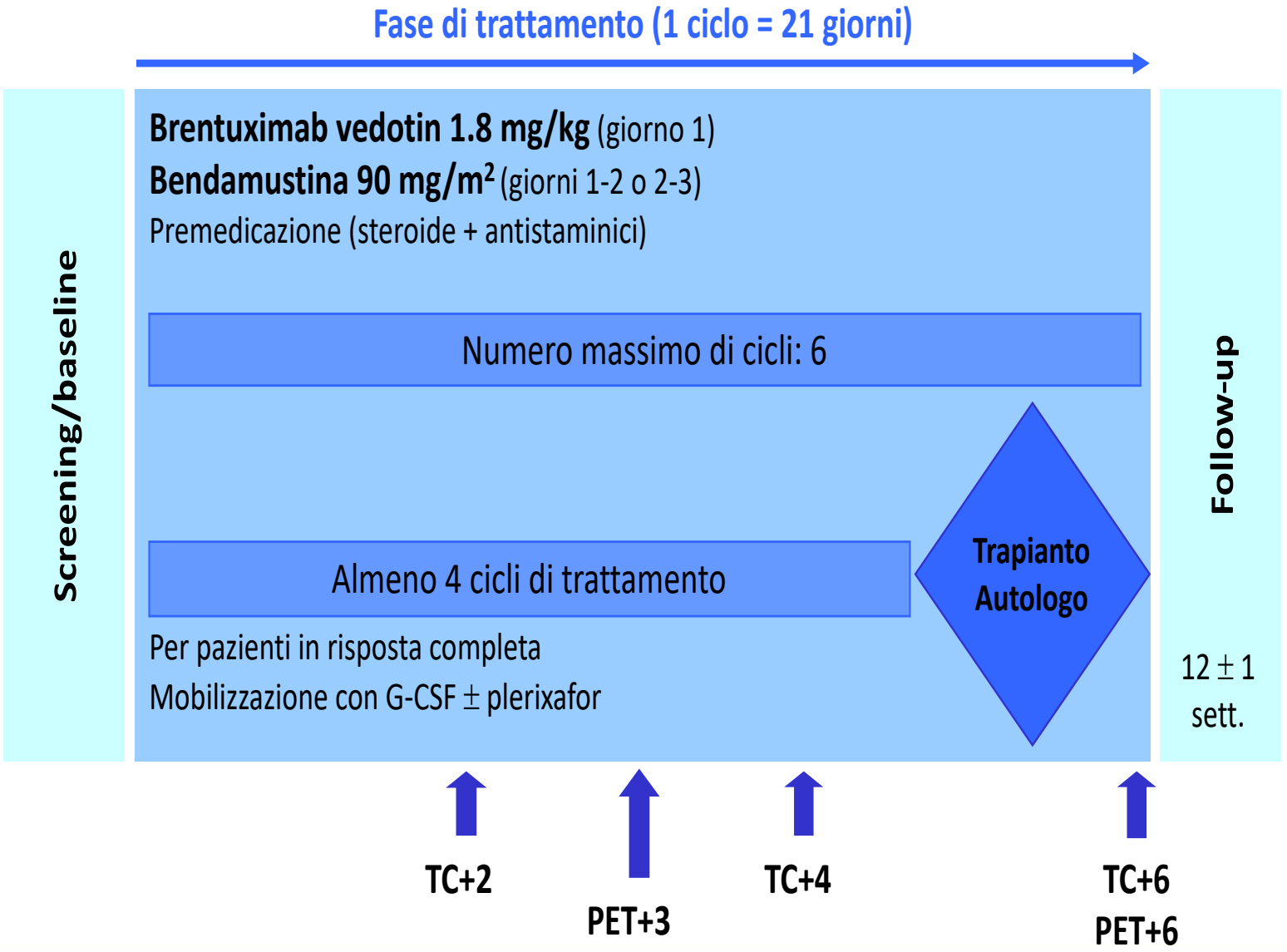
CRITERI DI ESCLUSIONE

- Diagnosi di linfoma a cellule T della cute, linfoma T-anaplastico (ALCL), micosi fungoide o sindrome di Sézary.
- Pregresso trattamento con brentuximab vedotin e/o bendamustina.
- Età superiore a 60 anni **(**)**
- ~~Pregresso trapianto autologo di cellule staminali emopoietiche.~~ **(***)**
- Comorbilità cardiologiche, tra cui: infarto miocardico (entro 2 anni), scompenso cardiaco (NYHA III-IV), angina, aritmia o alterazioni della conduzione, frazione di eiezione < 50%.
- Anamnesi oncologica (precedenti 3 anni), escludendo: neoplasie cutanee non-melanomatose, neoplasia prostatica sottoposta a trattamento radicale, neoplasia cervicale *in situ*.
- Segni o sintomi di encefalopatia multifocale progressiva.
- Neuropatia periferica preesistente di grado ≥ 2.
- Terapia steroidea (≥ 20 mg/die di prednisone o equivalente) fino ad una settimana prima dell'arruolamento.
- HIV e HCV-positività; HBsAg-positività.

(**) Emendamento 1, v. 05/01/2016

(***) Emendamento sostanziale 3, v. 29/06/2018 (autorizzazione AIFA 08/08/2018)

PROTOCOLLO DI TRATTAMENTO



STATUS ARRUOLAMENTO

- **Data inizio studio**: dicembre 2015
- **Data inizio arruolamento**: dicembre 2015
- **Durata studio**: 2 anni per arruolamento **(esteso fino ad aprile 2019)*** + 2 anni di *follow-up*

Centro	Linfomi cellule T
Bologna	1
Brescia	0
Milano (INT)	1
Napoli (Pascale)	1
Torino	0
Milano (Niguarda)	0
Rozzano	0
TOTALE/Previsti	**3/25**

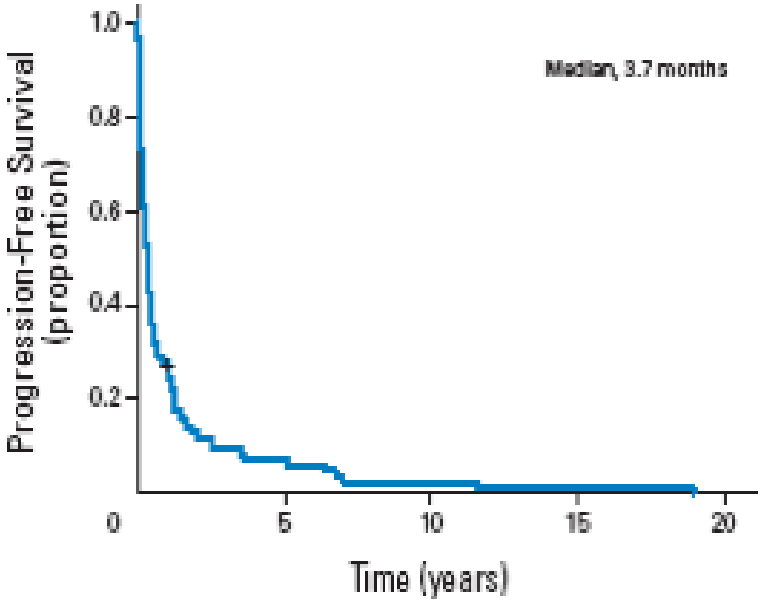
(*) Emendamento sostanziale 3, v. 29/06/2018 (autorizzazione AIFA 08/08/2018)

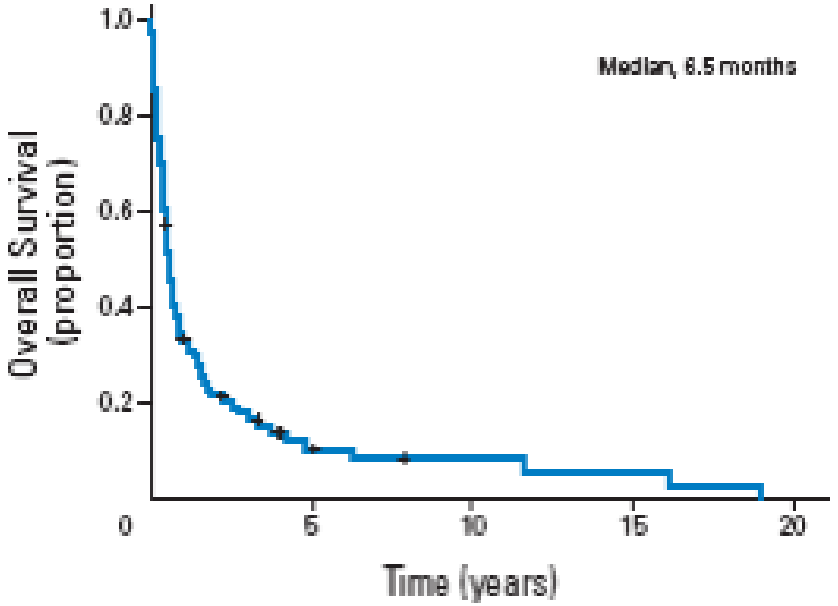
FIL_VERT A phase 2, open label, multicenter trial of venetoclax single agent in patients with relapsed/refractory BCL-2 positive PTCL_NOS, AITL and TFH.

PI Prof francesco zaja

Outcome of patients with relapsed/refractory PTCL not eligible to transplant

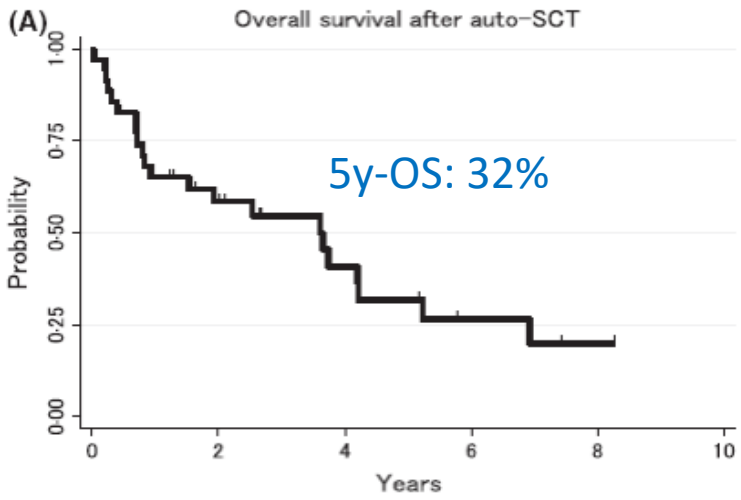
- N=153 (79 PTCL NOS, 38 AITL, 27 ALK-neg ALCL, 11 ALK-pos ALCL)
- Relapsed or progressed after primary therapy
- Not eligible to transplant

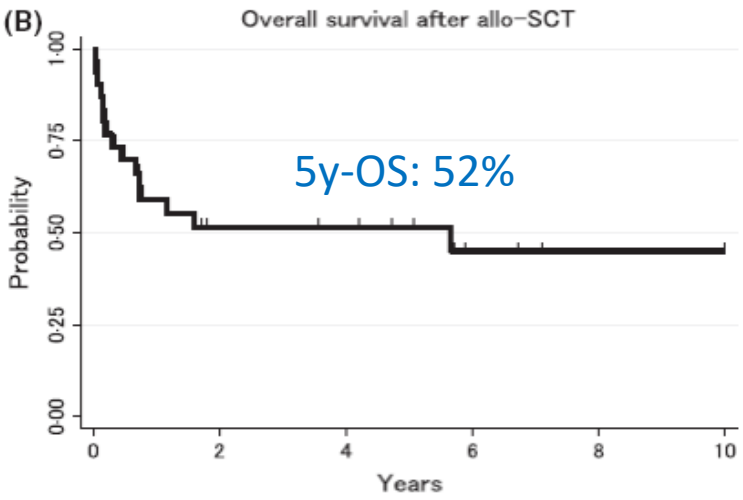


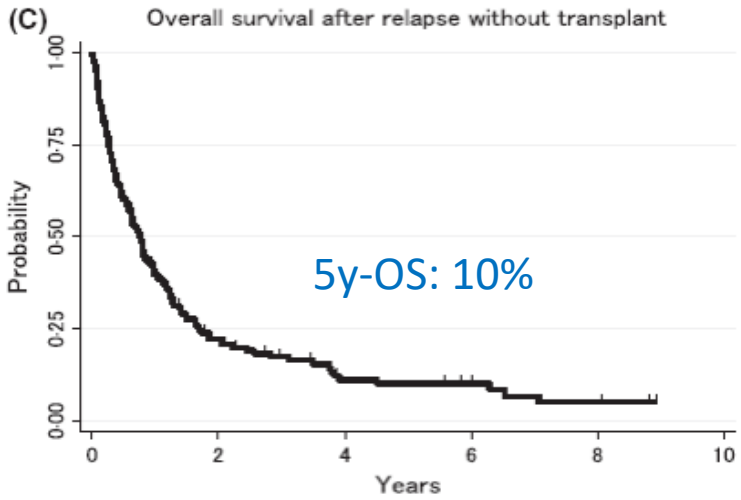


Mak V et al, JCO 2013

OS of patients with relapsed/refractory PTCL-NOS or AITL according to salvage treatment







Period of observation 1999-2015

PTCL NOS n=180

AITL n=141

Median follow-up 52 months

Chihara D et al, Br J Haematol 2017

A phase II, open label, multicenter trial of Venetoclax single agent in patients with relapsed/refractory BCL-2 positive PTCL-NOS, AITL and TFH

- **Sponsor:**
  FIL
- **Principal Investigator:**
  Prof. Francesco Zaja
- **Writing committee:**
  Prof. Francesco Zaja
  Prof. Pier Luigi Zinzani
  Dr. Marzia Varettoni
  Dr. Annalisa Chiappella
- **Coordinating Pathologist:**
  Prof. Stefano Pileri
- **Coordinating Statistician:**
  Dr. Gianni Ciccone
- **Pharmacovigilance:**
  Dr. Alessandro Levis
  Dr. Daniela Gioia
- **Study Coordinator:**
  Dr. Emanuela Pesce

Bcl-2 expression in nodal PTCL

	Cases	Positive	75-100%	50-74%	25-49%	5-24%
ALCL ALK negative	35	19 (55%)	14 (40%)	2 (6%)	3 (9%)	0
ALCL ALK positive	12	4 (32%)	1 (8%)	1 (8%)	1 (8%)	1 (8%)
PTCL NOS	43	35 (82%)	22 (51%)	5 (12%)	5 (12%)	3 (7%)
AITL	26	23 (88%)	10 (38%)	3 (12%)	4 (15%)	6 (23%)

Zaja F. et al, Am J Hematol 2017

Venetoclax in BCL-2 positive PTCL: study design

- Interventional prospective multi-center, open-label, single arm, phase 2 trial
- Pre-screening evaluation of immunohistochemical positivity of BCL-2 in the relapse biopsy, if available, or otherwise in the initial biopsy (centralized to Prof. Pileri, IEO Milan)
- Only patients with a percentage of BCL-2 positive tumor cells ≥ 25% will be included
- Patients will receive ABT-199 800 mg once daily on 28-day cycles until disease progression, unacceptable toxicity, withdrawal of consent or the investigator determines that further therapy is not in the patient's interest

Venetoclax in BCL-2 positive PTCLs: study objectives

- **Primary objective**

  ORR after 3 cycles

- **Secondary objectives**

  CR, PR, SD rate

  OS

  Time to response

  Duration of response (DoR)

  PFS

  Duration of treatment

  Relevant toxicity

  Overall toxicity

- **Explorative objective**

  Relationship between response and levels of BCL-2 expression

Venetoclax in BCL-2 positive PTCLs: sample size and duration of the study

- According to a Simon two-stage optimal design, with alpha=0.05 (one sided) and beta=0.10, the required **sample size is 18 for the first stage and 35 for the completion of the study**
- To proceed to the second stage, the minimum number of patients with an ORR required at the first stage is **3/18**; at the end of the study the treatment will be considered promising if the number of patient reaching an ORR is at least **7/35**
- Total study duration**: 30 months** (accrual: 18 months, follow-up: 12 months from the enrollment of the last patient)
- Patients will be recruited in **21 FIL centers**

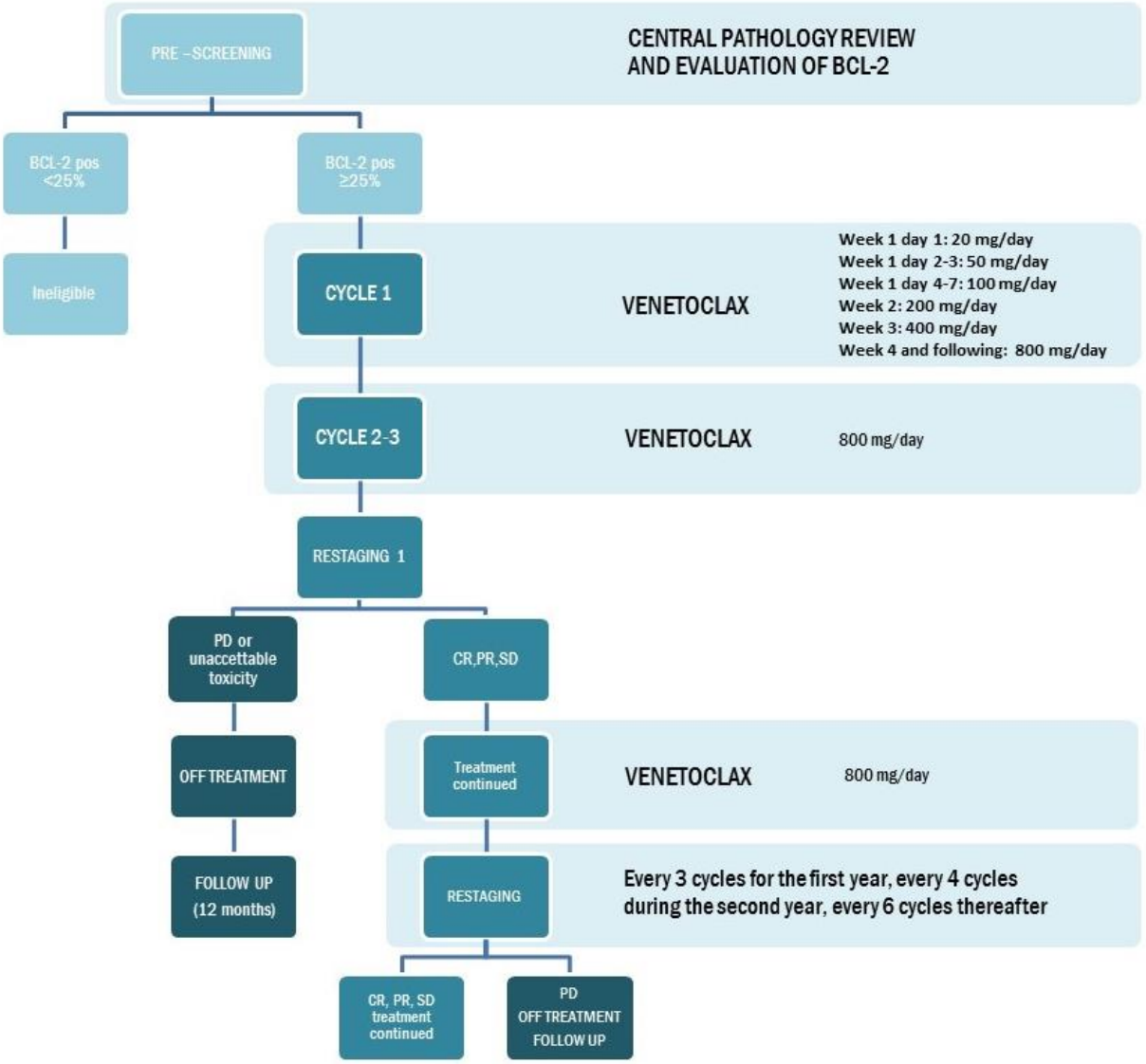
Venetoclax in BCL-2 positive PTCLs: main inclusion criteria

- Histological diagnosis of **BCL-2 positive (≥ 25%)** PTCL-NOS, AITL, TFH
- Age ≥ 18 years
- **Relapsed or refractory to at least one previous standard line of treatment**
- Patients **not eligible for high dose chemotherapy and ASCT**
- **ECOG performance status ≤ 2**
- **Measurable nodal disease** (at least one lymph node ≥2 cm in the longest transverse diameter by CT scan)
- **Adequate blood cell counts:** ANC ≥1.0 x 10^9/L, PLT ≥50.000/mmc (unless due to BM involvement by lymphoma)
- Adequate liver and renal function

Venetoclax in BCL-2 positive PTCLs: main exclusion criteria

- **Allo- or auto- stem cell transplant within 6 months** prior to study entry
- **CNS involvement by lymphoma**
- Previous treatment with a BCL-2 family protein inhibitor
- Anti-cancer therapy within 14 days prior to the first study drug administration
- Active HBV or HCV hepatitis, HIV infection
- Other malignancies within 3 years prior to study entry (with exception of *in situ* carcinoma of the uterine cervix, basal cell carcinoma or localized squamous cell carcinoma of the skin)
- Malabsorption syndrome or conditions precluding enteral route of administration

Venetoclax in BCL-2 positive PTCLs: treatment and response evaluation



Prophylasis of tumor lysis syndrome

- Hospitalization and monitoring of the subject for a minimum of 72 hours after the initial dose
- IV hydration started upon admission and continued at least for 72 hours after the initial dose of ABT199 with monitoring of urine output
- Anti-hyperuricemic drugs
- Chemistry will be monitored according to the following schedule:

	Week 1							Week 2-3-4						
Day	1	2*	3	4	5	6	7	1	2*	3	4	5	6	7
Timepoint (hours)	-4 +6-8	+24	+48	+72	+96			-4 +6-8	+24					

Venetoclax in BCL-2 positive PTCLs: safety

- The safety of Venetoclax will be monitored on a patient-by-patient basis using the Bayesian approach of Thall, Simon, Estey as extended by Thall and Sung for monitoring toxicity in single-arm clinical trials

- Enrollment will be stopped if the posterior probability of the experimental treatment being more toxic is greater than 95%

Stopping boundaries for toxicity

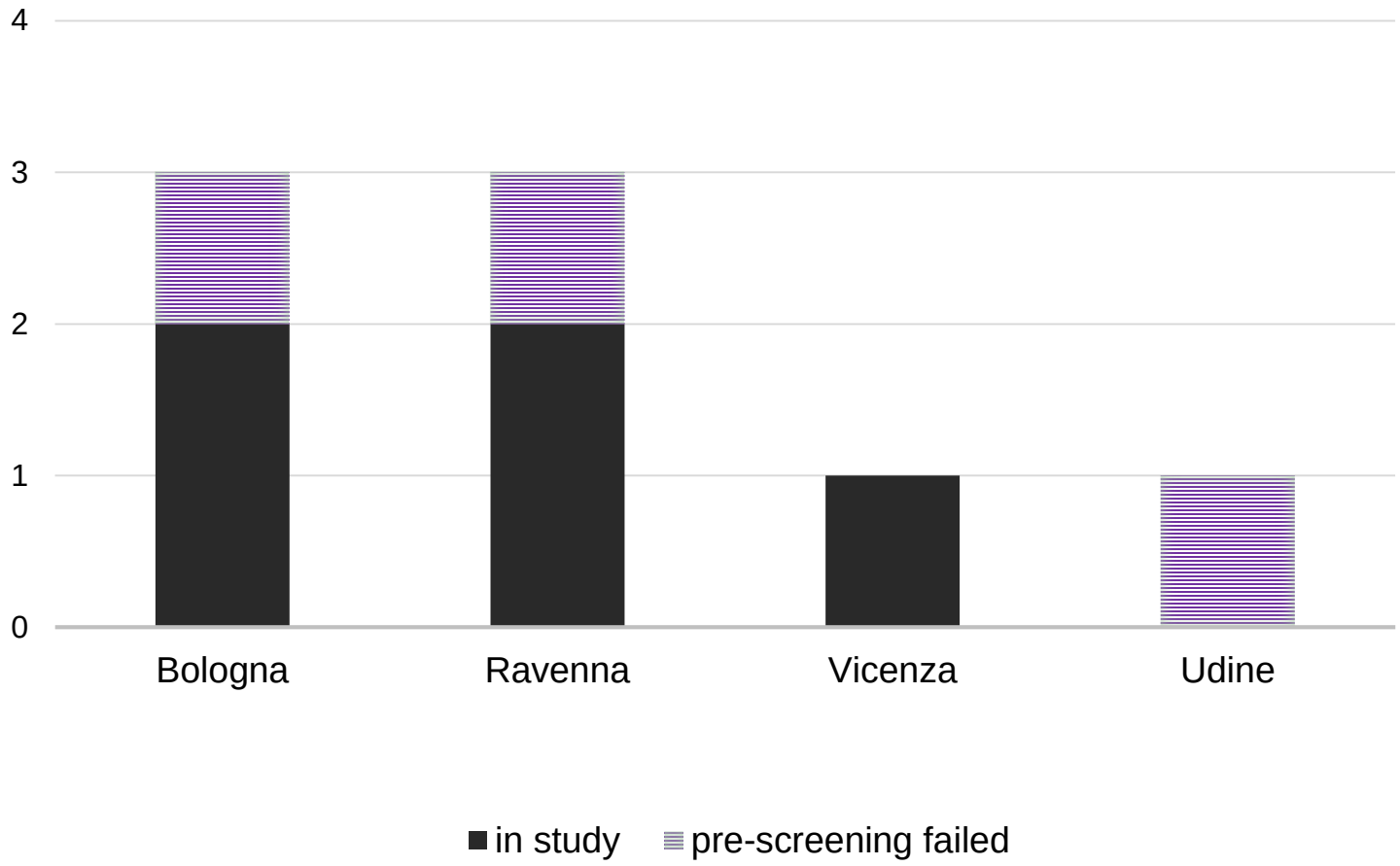
Patients Enrolled* (the range is inclusive)	Stop the trial if the toxicities are greater than or equal to:
1-2	Never stop
3	3
4-5	4
6-7	5
8-9	6
10-11	7
12-13	8
14-15	9
16-17	10
18-19	11
20-21	12
22-23	13
24-26	14
27-28	15
29-30	16
31-32	17
33-34	18

SITE ACTIVATION

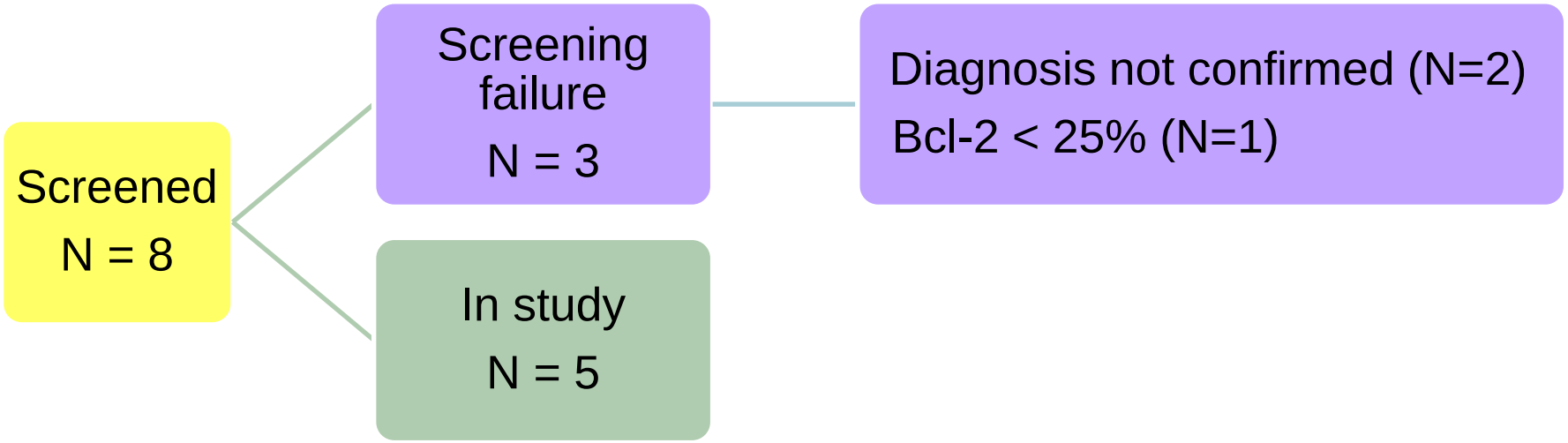
#	Site	Principal Investigator	Open
1	Alessandria - A.O. SS. Antonio e Biagio e Cesare Arrigo - S.C. Ematologia	Zanni Manuela	
2	Ancona - Università Politecnica delle Marche - Clinica di Ematologia	Olivieri Attilio	
3	**Aviano** - Centro Riferimento Oncologico - S.O.C. Oncologia Medica A	Spina Michele	X
4	**Bologna** - Policlinico S.Orsola-Malpighi - Istituto di Ematologia "Seragnoli"	Zinzani Pier Luigi	X
5	Brescia - ASST Spedali Civili di Brescia – Ematologia	Re Alessandro	
6	Firenze - Azienda Ospedaliera Universitaria Careggi - Unità funzionale di Ematologia	Rigacci Luigi	
7	Genova - Ospedale Policlinico San Martino S.S.R.L. - IRCCS per l'Oncologia – Ematologia	Congiu Angela	
8	Milano - Fondazione IRCCS Istituto Nazionale dei Tumori di Milano – Ematologia	Corradini Paolo	
9	Milano - Istituto Scientifico San Raffaele - Unità Linfomi - Dipartimento Oncoematologia	Ferreri Andrés	
10	**Novara** - AOU Maggiore della Carità di Novara - SCDU Ematologia		X
11	Palermo - A.O. Ospedali Riuniti Villa Sofia-Cervello - Divisione di Emat		
12	Pavia - IRCCS Policlinico S. Matteo di Pavia - Div. di Ematologia		
13	**Ravenna** - Ospedale delle Croci – Ematologia		X
14	Reggio Emilia - Azienda Unità Sanitaria Locale-IRCCS - Arcispedale S		
15	Roma - Policlinico Umberto I - Università "La Sapienza"		
16	Torino - A.O.U. Citta della Salute e della Scienza di Torino - S.C.Emato		
17	**Tricase** - A.O. C. Panico - U.O.C Ematologia e Trapianto		X
18	Trieste - Azienda sanitaria-universitaria integrata Trieste (ASUITS) - SC		
19	**Udine** - Azienda Sanitaria Universitaria Integrata di Udine (A.S.U.I. Udi		X
20	Varese - Ospedale di Circolo - U.O.C Ematologia	Merli Michele	
21	**Vicenza** - ULSS 8 Berica - Ospedale S. Bortolo - Ematologia	Visco Carlo	X

Planned	21
Approved by EC	16
Open	7
Active	4

ENROLMENT BY SITE



PATIENT DISPOSITION



2 SAE: acute renal failure during ramp-up (dose 400 mg/day)
fever (prolonged hospitalization)

FIL_DARA-GDP A phase II, open label, multicenter trial of daratumumab in combination with GDP (D-GDP) in patients with relapsed or refractory CD38 positive PTCL-NOS, AITL and TFH.

PI Prof francesco zaja

A phase II, open label, multicenter trial of Daratumumab in combination with GDP (D-GDP) in patients with relapsed or refractory CD38 positive PTCL-NOS, AITL and TFH

Sponsor:

- FIL

P.I.:

- Prof. Francesco Zaja

Writing committee:

- Prof. Francesco Zaja
- Prof. Stefano Pileri
- Dr.ssa Annalisa Chiappella
- Dr.ssa Marzia Varettoni

Pathology:

- Prof. Stefano A. Pileri

Statisticians:

- Dr. Gianni Ciccone
- Dr. Andrea Evangelista

Pharmacovigilance

- Dr. Alessandro Levis
- Dr. Daniela Gioia

Efficacy and toxicity of Gemcitabine containing regimens in PTCL

								Grade 3 or 4 toxicity			
Reference	**Diagnosis**	**Scheme**	**Pts**	**Age**	**ORR**	**CR**	**mPFS (months)**	**Neutropenia**	**Febrile neutropenia**	**Thrombocytopenia**	**Anemia**
Zinzani 2000[1]	PTCLU	G[1]	20	54 (32-78)	55%	30%	RD 7-60	0%	0%	0%	0%
Arkenau 2007[2]	PTCL	GEM-P[2]	16	55 (18-71)	69%	19%	4	62%	NA	NA	12%
Yao 2013[3]	NOS/AITL/ ALCL	GEMOD[3]	24	66 (60-75)	38%	13%	10	51%**	13%**	33%**	16%**
Park 2015[4]	NOS/AITL/ …	GDP[4]	25	54 (20-74)	64%*	32% *	9.4	16%	3.5%	13%	2%
Qi 2017[5]	NOS	GDP[5]	25	50 (14-72)	64%	20%	5.4	32%	0	20%	16%

*after 2 cycles; ** toxicity of 102 evaluable courses

1: G 1200 mg/mq 1,8,15 q28 days

2: G 1000 mg/mq 1,8,15; cisplatinum 100 mg/mq day 15; PDN 1g day 1-5 q28 days

3: G 1000 mg/mq 1; oxaliplatinum 100 mg/mq day 1; Dexa 20 mg day 1-4 q28 days

4**: G 1000 mg/mq 1,8; cisplatinum 75 mg/mq day 1; Dexa 40 mg day 1-4 q21 days**

5: G 1000 mg/mq 1,8; cisplatinum 25 mg/mq day 1-3; Dexa 20 mg day 1-4, 11-14 q21 days

CD38 expression in nodal PTCL

	Cases	Positive	75-100%	50-75%	25-50%	5-24%
ALCL ALK negative	34	6 (18%)	3 (9%)	1 (3%)	0	2 (6%)
ALCL ALK positive	9	0	0	0	0	0
PTCL NOS	42	23 (55%)	9 (21%)	3 (7%)	2 (5%)	9 (21%)
AITL	25	20 (80%)	2 (8%)	5 (20%)	4 (16%)	9 (36%)

Zaja F. et al, Am Journal Hematol 2017

D-GDP in CD38 positive R/R PTCL: study design

- Interventional prospective, multi-center, open-label, single arm, phase 2 trial
- Pre-screening evaluation of immunohistochemical positivity of CD38 in the relapse biopsy (centralized to Prof. Pileri, IEO Milan). CD38 can be evaluated in bone marrow sections in those patients with bone marrow lymphoma infiltration
- Patients will receive an induction immunochemotherapy with 4-6 cycles of D-GDP (every 21 days) followed by maintenance therapy with Daratumumab up to 24 cycles

D-GDP in CD38 positive R/R PTCL: study objectives

Primary objective

- Complete remission (CR) rate after 4 cycles of D-GDP

Secondary objectives

- Overall Response Rate (ORR);
- Progression-free survival (PFS);
- Overall survival (OS);
- Safety of D-GDP

Exploratory objectives

- Role of Daratumumab maintenance
- Relationship between response and levels of CD38 expression

D-GDP in CD38 positive R/R PTCL: sample size and statistical considerations

- **Sample Size**

Sample size has been calculated according to the primary efficacy endpoint, using a 'Hern's Single-Stage Phase II design

- H0: CR after 4 cycles of GDP 20%
- H1: CR after 4 cycles of D-GDP 40%, with an absolute improvement of 20%

This design yields a type I error rate of 5% and power of 80%

Toxicity rate is maintained at 30%

Overall, **35 patients** will be accrued and the null hypothesis will be rejected if **12** or more CR are observed after 4 cycles of D-GDP

- **Centers:** 20 FIL centers

- **Duration of the study:** 42 months (accrual: 18 months; end of study: 24 months after start of therapy for the last patient enrolled)

D-GDP in CD38 positive R/R PTCL: safety and activity monitoring

- The Bayesian approach of Thall, Simon, Estey (1995), as extended by Thall and Sung (1998) will be used to monitor safety and activity
- Relevant toxicity will be assessed after D-GDP 2 cycles to ensure that it is not higher than an acceptable toxicity of 30%. Activity will be monitored to ensure that CR proportion after 4 courses of D-GDP is not lower than 35%
- Enrollment will be stopped if the posterior probability of the treatment being more toxic or less active than expected is greater than 95%.

Stopping boundaries

Number of patients enrolled:	Stop the enrollment if the cumulative relevant toxicities are greater or equal to:	Stop the enrollment if the number of cumulative CR are lower or equal to:
5	4	0
10	6	1
15	9	2
20	11	4
25	13	5
30	15	7
35	17	8

- Stop of enrollment after the first 5 patients for safety and efficacy analysis

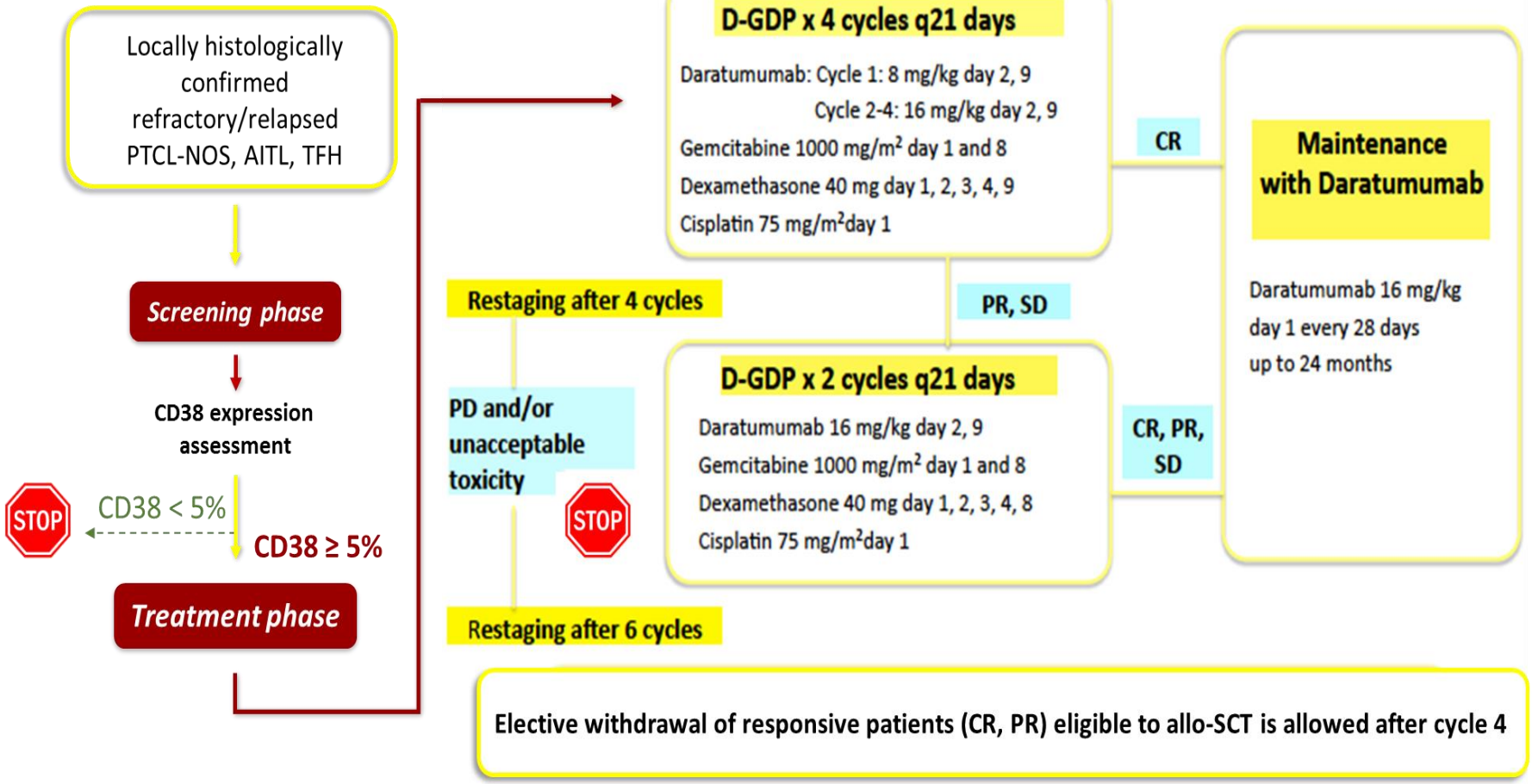
D-GDP in CD38 positive R/R PTCL: main inclusion criteria

- Diagnosis of CD38 positive PTCL-NOS, AITL, THF
- Age 18-75 years
- **CD38 positivity ≥ 5%**
- **Relapsed or refractory after at least one previous line of therapy**
- **ECOG performance status ≤ 2**
- **Measurable nodal disease** (at least one lymph node ≥2 cm in the longest transverse diameter by CT scan)
- Adequate blood cells counts: ANC ≥1.0 x 10^9/L, PLT ≥50.000/mmc (unless due to BM involvement by lymphoma)
- Adequate renal and hepatic function

D-GDP in CD38 positive R/R PTCL: main exclusion criteria

- **More than two prior systemic lines of treatment**
- **CNS involvement with lymphoma**
- **Previous treatment with Gemcitabine or Platinum containing regimens** (patients who received a single course of Platinum based course -e.g. DHAP- are not excluded)
- **Relapse after allogeneic stem cell transplantation**
- Cardiovascular disease (NYHA class ≥2)
- Creatinine Clearance < 40 mL/min (Cockcroft–Gault formula)
- HIV seropositivity, active HBV or HCV Hepatitis
- Other malignancies within 3 years (with the exception of adequately treated in situ carcinoma of the cervix uterine, basal cell carcinoma or localized squamous cell carcinoma of the skin)

D-GDP in CD38 positive R/R PTCL: treatment schedule



G-CSF support from day 3 to 6 and from day 10 to 13 (and further if needed)

Gemcitabine at day 8 should be skipped in case of hematologic grade 3 or 4 toxicity

Centri D-GDP

	Centro	Responsabile
1	Trieste	Zaja
2	Torino Univ.	Cavalli
3	Cuneo	Massaia
4	Roma	Rigacci
5	Piacenza	Vallisa
6	Meldola	Musuraca
7	Siena	Fabbri
8	Milano Niguarda	Rusconi
9	Catania	Di Raimondo
10	Roma	Cantonetti

	Centro	Responsabile
11	Padova	Semenzato
12	Bari	Guarini
13	Napoli	Pane
14	Pescara	Di Bartolomeo
15	Biella	Conconi
16	Napoli	Pinto
17	Pisa	Petrini
18	Treviso	Gherlinzoni
19	S. Giovanni Rotondo	Cascavilla
20	Milano Humanitas	Santoro

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