Incontro di aggiornamento sui disordini linfoproliferativi e sui protocolli FIL

TORINO 24 novembre 2014

FLAVIA Salvi
Ospedale Alessandria

DICHIARAZIONE

Relatore: Flavia Salvi

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 (NIENTE DA DICHIARARE)
- 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: (NIENTE DA DICHIARARE)

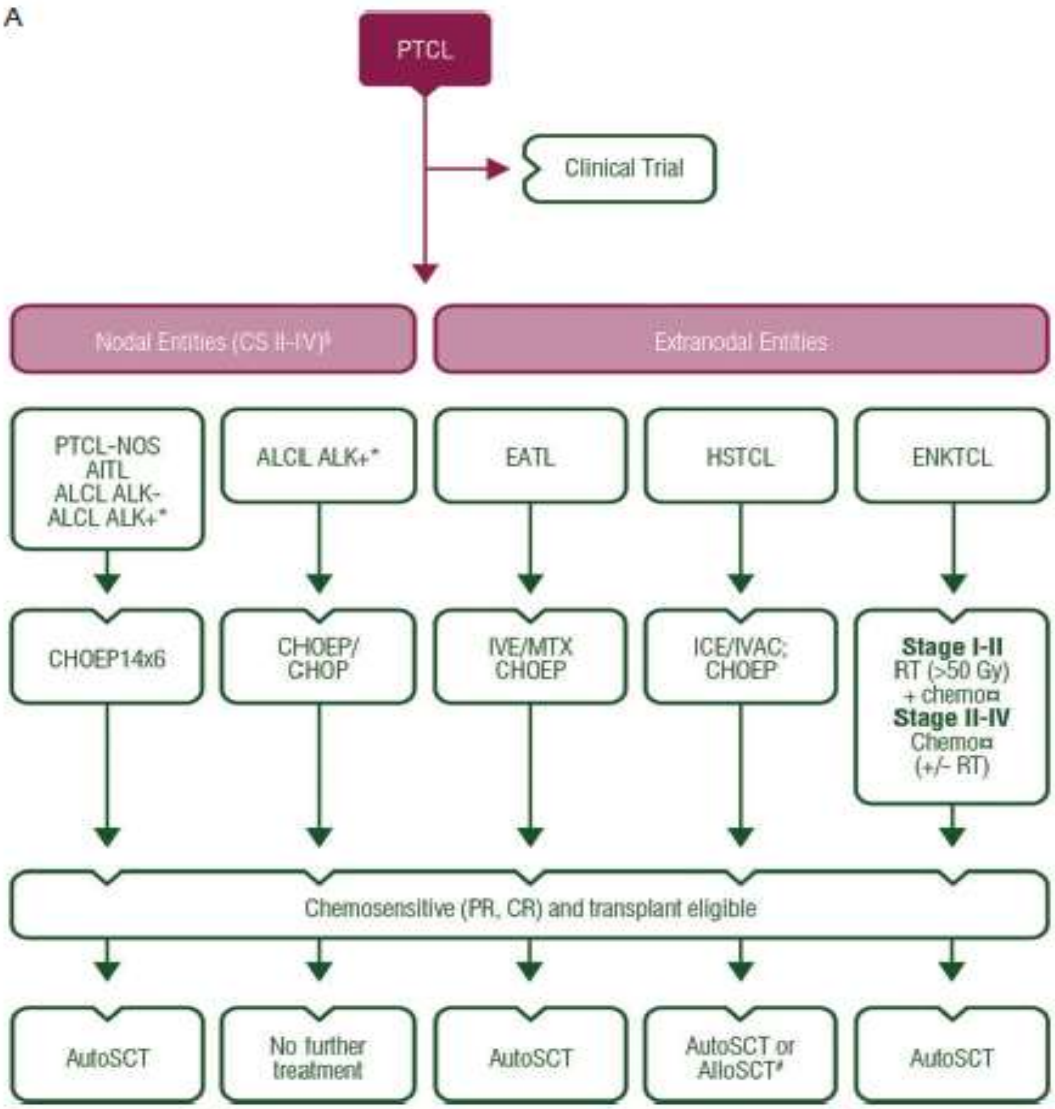
Peripheral T cell lymphoma

- CHOP or CHOP-like regimens are still considered as the standard treatment for PTCLs and are associated with a dismal outcome of a 5-year OS in ~25–35%.
- Neither intensified /escalated chemotherapeutic approaches nor the addition of monoclonal antibodies such as alemtuzumab have demonstrated a clear advantage in remission rate and OS
- Trials of up-front auto-SCT reported a favorable outcome with 3-year PFS and OS ranging from 36 to 48% and from 48 to 56%, respectively (Reimer JCO 2009; D'Amore JCO 2012)

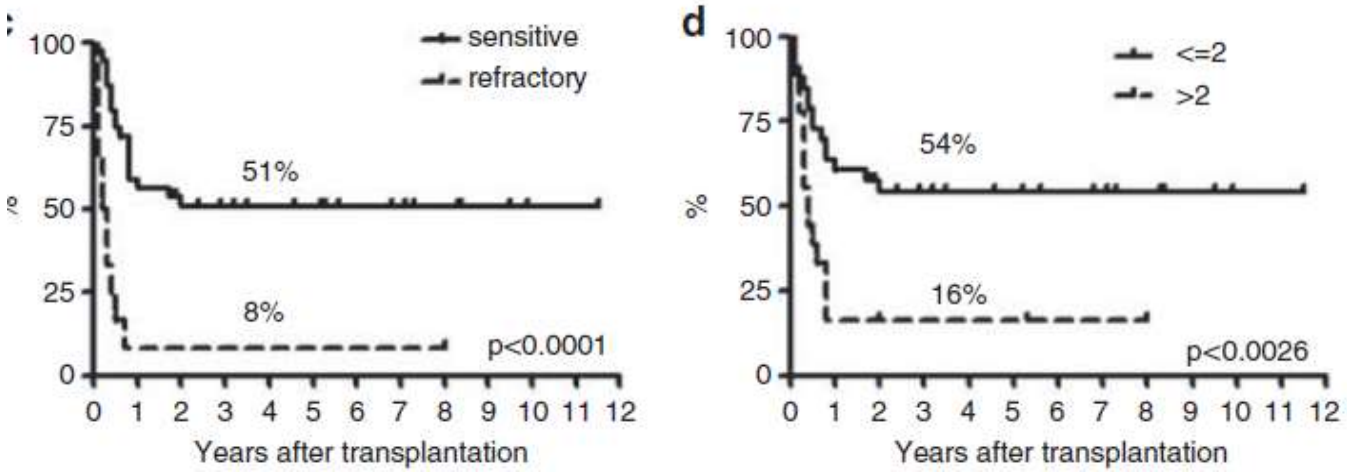
Role of front-line auto-SCT in PTCL

- The achievement of CR before ABMT is a prerequisite for long-term disease control
- Long term OS for pts with chemosensitive disease before ABMT is around 50%
- Approximately 25-30% of pts do not reach the transplant phase because of refractory or progressive disease
- The procedure is safe and feasible with a TRM <5%

ESMO Clinical Guidelines



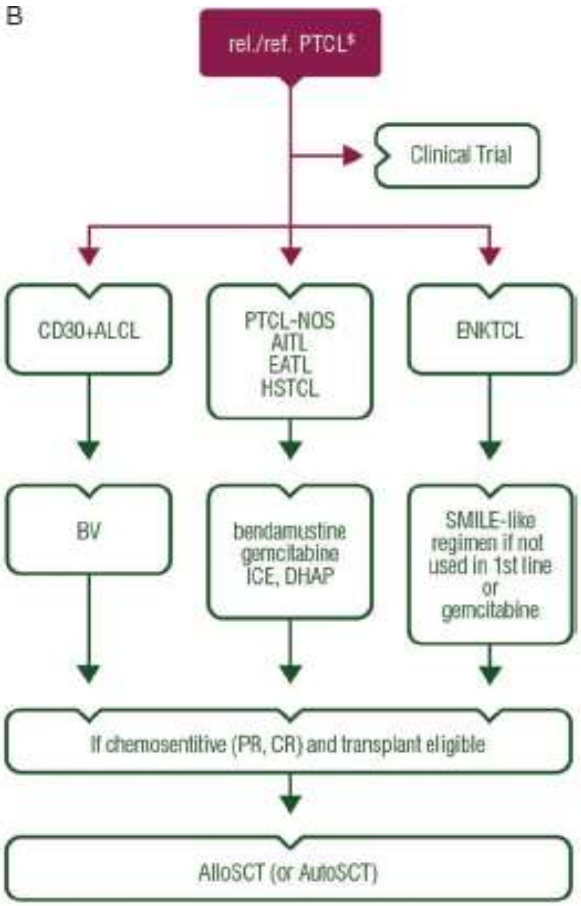
Role of allo-SCT in PTCL



- RIC allogenic SCT is an effective salvage treatment with a better outcome for younger patients with chemosensitive disease. Leukemia (2012)
- NRM is 12% at 5 years
- Long term OS for chemosensitive relapses is 50%

Dodero A , Leukemia 2012

ESMO Clinical Guidelines



PTCL: unmet clinical needs

- Overcome early treatment failure with novel drug
- Role of auto-HSCT vs allo-HSCT in up-front setting responding patients
- Improve diagnostic accurancy with molecular profiling to drive therapeutic decisions
- Identify new prognostic factor and response biomarkers

BACKGROUND (1)

Farmaco	Autore	Pz.	ORR, %	RC, %	OS mediana (mesi)	PFS mediana (mesi)
Pralatrexate	O'Connor, 2011	111	29	11	14.5	3.5
Romidepsina	Piekarz, 2011	47	38	18	NV	NV
	Coiffier, 2012	130	25	15	NV	4.0
Brentuximab vedotin	Pro, 2012	58	86	57	non raggiunta	20.0
	Horwitz, 2014	34	42	24	NV	2.6
Belinostat	O'Connor, 2015	129	23	9	7.9	1.6

O'Connor OA. *J Clin Oncol*, 2011; 29: 1182-1189
Piekarz RL. *Blood*, 2011; 117: 5827-5834
Coiffier B. *J Clin Oncol*, 2012; 30: 631-636
Pro B. *J Clin Oncol*, 2012; 30: 2190-2196
Horwitz SM. *Blood*, 2014; 123: 3095-3100
O'Connor OA. *J Clin Oncol*, 2015; 33: 2492-2499
Broccoli A. *Blood*, 2017; 129: 1103-1112
Broccoli A. *Cancer Treat Rev*, 2017; 60: 120-129

Studio FIL_PTCL13

ROMIDEPSINA IN COMBINAZIONE CON CHOEP COME TERAPIA DI PRIMA LINEA IN PREPARAZIONE AL TRAPIANTO DI CELLULE STAMINALI EMOPOIETICHE NEI PAZIENTI GIOVANI CON LINFOMA A CELLULE T PERIFERICHE A LOCALIZZAZIONE NODALE: STUDIO DI FASE I-II

Principal Investigator: Prof. Paolo Corradini
SC. Ematologia – Fondazione IRCCS "Istituto Nazionale dei Tumori" di Milano

INFO GENERALI /Schema di trattamento

Studio di Fase I finalizzato alla definizione della Massima Dose Tollerata (MTD) di Romidepsina in combinazione con CHOEP-21, e alla valutazione della tossicità e della fattibilità di CHOEP-21 in combinazione con dosi crescenti di Romidepsina. La dose di Romidepsina identificata come MTD verrà utilizzata per lo studio di fase II successivo.

ACCRUAL → **21-24 pazienti (1° paziente arruolato 01 settembre 2014)**

Studio di Fase II finalizzato alla valutazione di efficacia (response rate ; PFS ; OS) e di tossicità di Ro-CHOEP-21 incorporato in un programma terapeutico comprensivo di Trapianto di Cellule Staminali Emopoietiche (SCT).

ACCRUAL → **110 pazienti** (inclusi i pazienti trattati con Romidepsina alla dose identificata come MTD nello studio di Fase I)

ENDPOINTS

PHASE I

Primary endpoint

- **Incidence of dose-limiting toxicity (DLT) of Ro-CHOEP-21**, considering as maximum dose the one causing induction of any grade ≥ 3 non hematologic toxicity or a delay >15 days of planned cycle date observed during the first two cycles according to the definitions of NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (2009)

Secondary endpoints

- Proportion of patients reaching SCT.
- Overall response rate (ORR, defined according to the Lugano Classification 2014 response criteria) of the combination of Ro-CHOEP-21.

PHASE II

Primary endpoint

- **PFS on intention to treatment (ITT) evaluated at 18 months.** PFS will be defined as the time between the date of enrolment and the date of disease progression, relapse or death from any cause.

Secondary endpoints

- ORR and CR (defined according to the Lugano Classification 2014 response criteria), after induction treatment and after SCT.
- Event free survival (EFS) defined as the time between the date of enrollment and the date of discontinuation of treatment for any reason
- Overall survival (OS) defined as the time between the date of enrolment and the date of death from any cause in the ITT population enrolled in the study
- PFS and OS in patients not responding to the first 3 courses of Ro-CHOEP-21
- Any grade III or higher toxicities, recorded and classified according to the definitions of NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (2009)
- Evaluation during the interim analyses of any grade III or higher toxicities, recorded and classified according to the definitions of NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (2009)
- Evaluation during all the pretransplant phase of any grade III or higher toxicities, recorded and classified according to the definitions of NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (2009)
- Treatment-related mortality defined as any death that was not attributable to the lymphoma.
- Incidence of acute and chronic GVHD in allografted patients

Exploratory endpoint

- Evaluation of response biomarkers (eg TET2 mutations)

ELECTION CRITERIA

INCLUSION CRITERIA

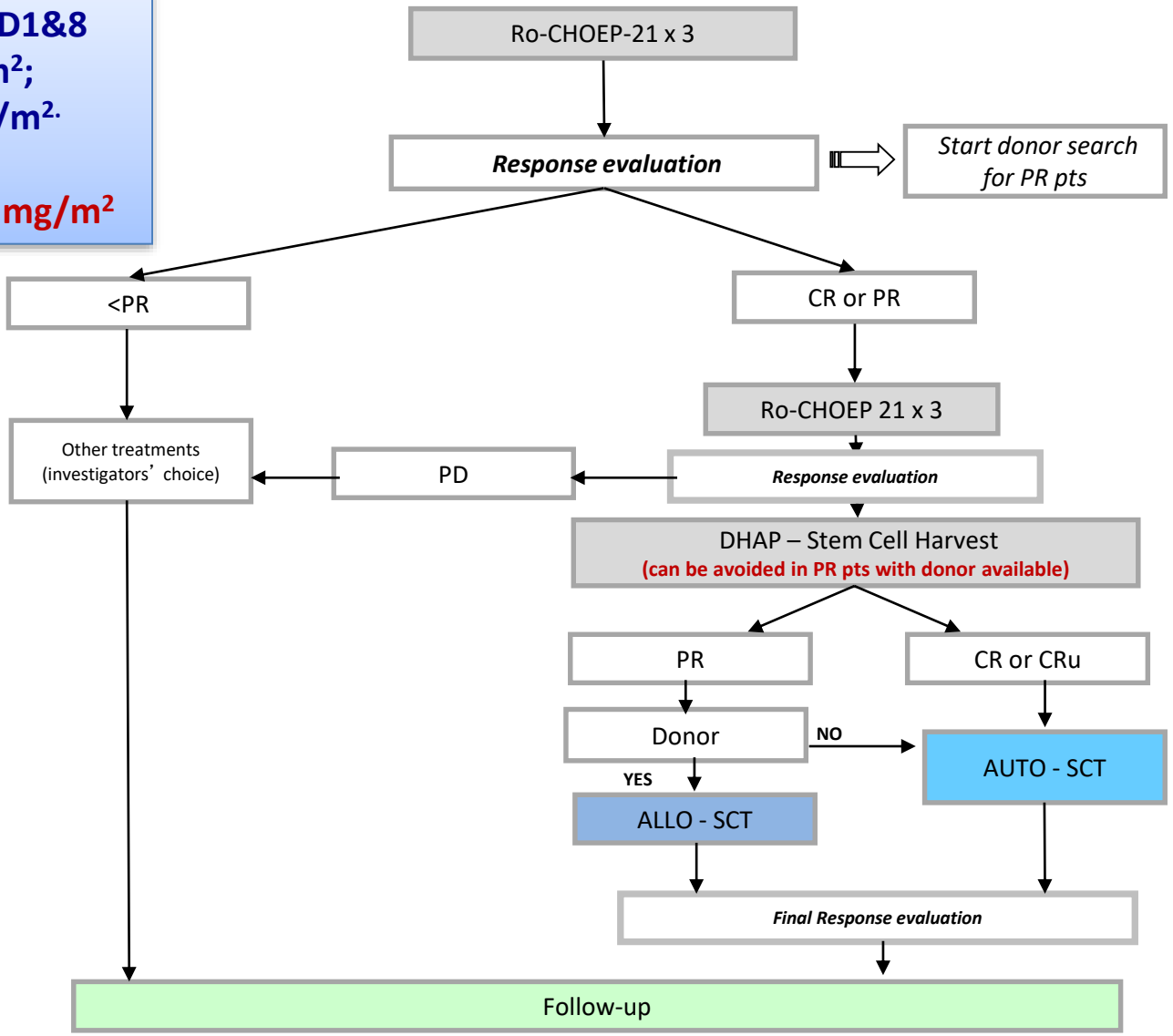
1. **age ≥18 e ≤ 65 years**
2. **Peripheral T-cell lymphomas at diagnosis including: PTCL-NOS, AITL, ALK negative ALCL**
3. **Stage II-IV**
4. Written informed consent
5. No prior treatment for lymphoma
6. No Central Nervous System (CNS) disease (meningeal and/or brain involvement by lymphoma)
7. HIV 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 14 mg/m^2



PHASE 1 DLTs

01/Sep/2014 - 26/Jul/2017

Patients enrolled	Group	Romidepsin mg/m²	DLTs
3	I	12	0
	II	14	1 (mucositis g3)
			2 (1 patient, FUO g3)
15	V		
18	VI	14	1 (mu
21	VII	14	2 (1 patient, mucositis g3 and macupapular erithema g3)

Target toxicity fixed by protocol: 33%.
Toxicity for recommended dose of 14 mg/m²:
26.1% (95% Credibility Interval: 10.1%-46.3%).
→ ENROLLMENT PHASE II OPEN ON SEPTEMBER 19, 2017
→ DOSAGE Romidepsin 14 mg/m²

Substancial Amendment 2

EC submission amendment 2: Aug2017

- ✓ Apertura centri fase II
- ✓ Estensione periodo di arruolamento a 5 anni (previsione conclusione arruolamento settembre 2019
- ✓ Revisione istologica
  - Prof Pileri, IEO
- ✓ Implementazione studi biologici
  - Prof Corradini, Drssa Carniti, INT
    - numero di invii di materiale biologico che saranno effettuati anche al 3 e 6 ciclo di terapia e dopo la rivalutazione post-trapianto;
    - raccolta della saliva (in apposito kit);
    - utilizzo delle provette BCT per la raccolta del sangue periferico.
- ✓ Aggiornamento IB Romidepsina.

STUDY STATUS_Participating Centres (38)

Participating Centers Phase I	Active Centers
12	12

Participating Centers Phase II	Active Centers
26	-

PHASE I → *in rosso centri attivi per l'emend sost 2*

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	A.O.	
12	Parma	AO	
13	Pavia	IRC	
14	Perugia	AO di Perugia	
15	Pescara	P.O. Spirito Santo	Dott. Francesco Angrilli
16	Piacenza	Ospedale Guglielmo da Saliceto	Dott.ssa Annalisa Arcari
17	Ravenna	Ospedale delle Croci	Dott.ssa Monica Tani
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: Aug2017

Nuove PROCEDURE OPERATIVE STUDI BIOLOGICI

Biological studies

- Tissue microarrays analysis (TMA)
- Next generation sequencing

SAMPLES

- 6 ml of PB collected in standard EDTA tubes
- 10 ml of PB collected in Cell-Free DNA BCT
- 10 ml Bone Marrow aspirate collected in a polypropylene tube plasma
- a brushing of oral mucosa and a buccal swab collected in Kit Orangene DNA OG-500
- formalin-fixed paraffin-embedded (FFPE) tissue block ***(the preparation of an extra-block would be desirable to be centralised and devoted to the planned bio-pathological studies)***
- If the FFPE block is not available, at least 10 unstained slides (10 micron)

TIMEPOINTS

- Baseline
- After Cycle 3
- After Cycle 6
- Final response (after auto/allo)
- PD/relapse

Pathobiological review

- Gene Expression Profiling (GEP)-based molecular classifiers (MCs)

SAMPLES

- formalin-fixed paraffin-embedded (FFPE) tissue block
- If the FFPE block is not available, at least 20 unstained slides (3 micron)

TIME POINTS

- Baseline
- PD/relapse

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

Study ID: FIL_PTCL_BV

EudraCT n. 2013-003946-17

BACKGROUND (1)

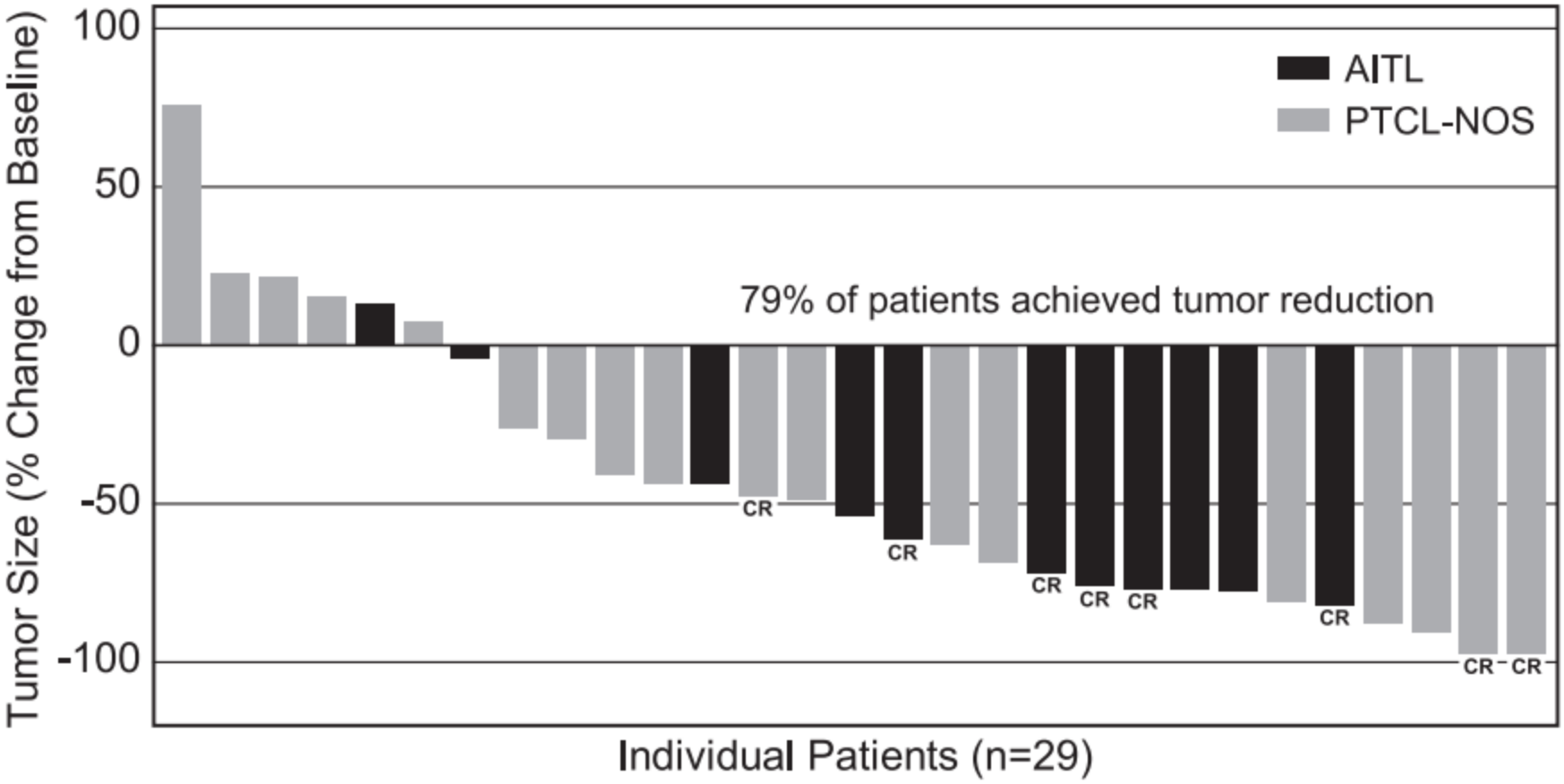
Objective responses in relapsed T-cell lymphomas with single-agent brentuximab vedotin

	AITL, n = 13	PTCL-NOS, n = 21	Total, N = 34
Best clinical response, n (%)*			
CR	5 (38)	3 (14)	8 (24)
PR	2 (15)	4 (19)	6 (18)
SD	3 (23)	3 (14)	6 (18)
PD	3 (23)	11 (52)	14 (41)
Objective response rate, n (%)	7 (54)	7 (33)	14 (41)
95% CI for objective response rate†	25.1, 80.8	14.6, 57	24.6, 59.3
Disease control rate, n (%)‡	10 (77)	10 (48)	20 (59)

*Per Cheson, as assessed by the investigator.
†Two-sided 95% exact confidence interval.
‡CR + PR + SD.

Horwitz SM. *Blood*, 2014; 123: 3095-3100

BACKGROUND (3)



Horwitz SM. *Blood*, 2014; 123: 3095-3100

OBIETTIVI DELLO STUDIO

- **Obiettivo primario**: effetto antitumorale di brentuximab vedotin (1,8 mg/kg ogni 21 giorni) quando somministrato come terapia di salvataggio in pazienti con linfomi a cellule T periferiche ricaduti o refrattari.

- **Obiettivi secondari**: durata di risposta, sopravvivenza, profilo di sicurezza e tollerabilità di brentuximab vedotin.

- ***Endpoint* primario**: tasso globale di risposta (*overall response rate*, ORR) .

- ***Endpoints* secondari**: durata di risposta (DOR), tasso di risposta completa (CR rate), sopravvivenza globale (*overall survival*, OS) e sopravvivenza libera da progressione (*progression-free survival*, PFS) a 1 anno.

- ***Endpoint* addizionale**: studio delle possibili correlazioni tra espressione dell'antigene CD30 e la risposta osservata.

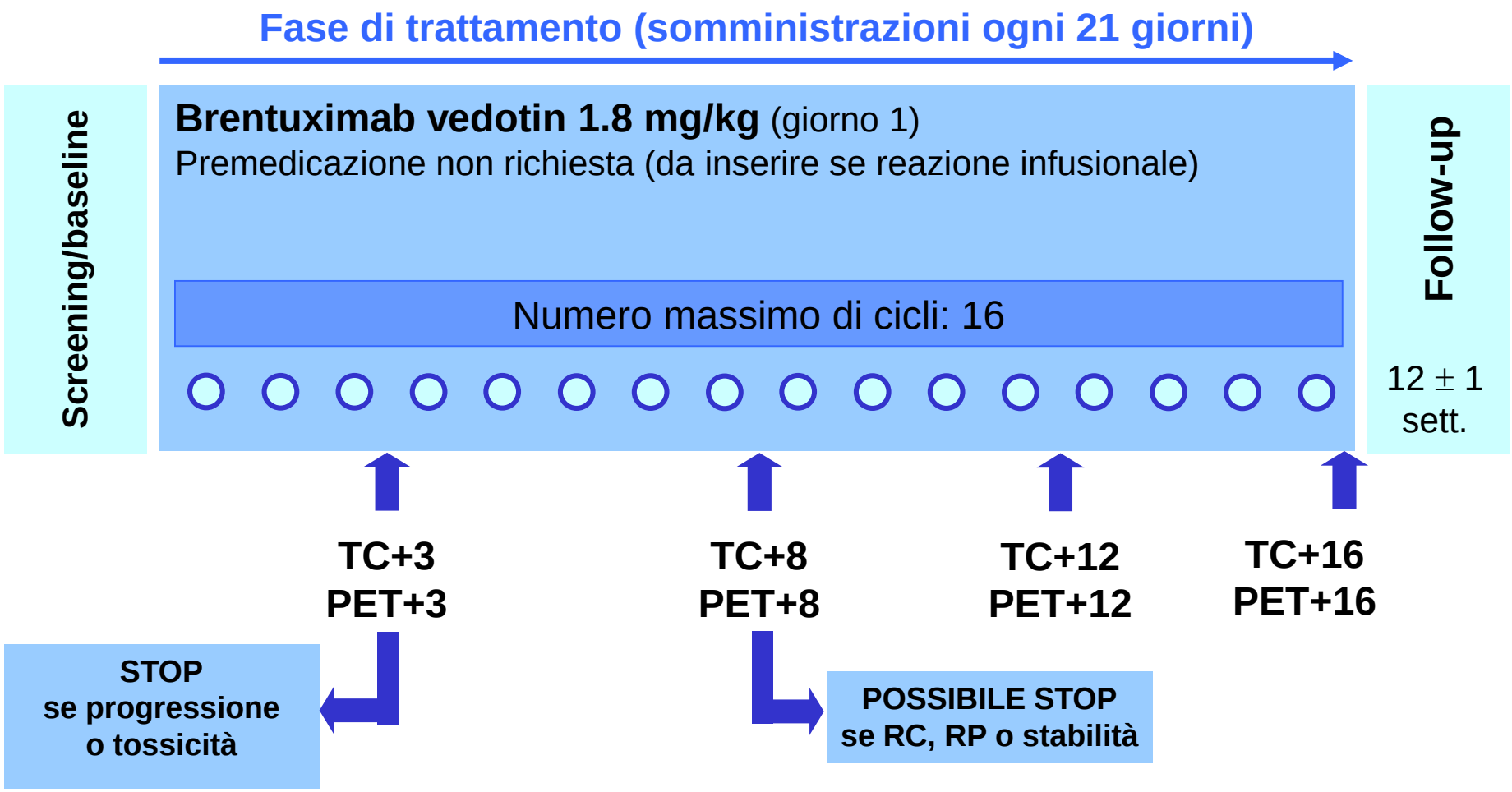
CRITERI DI INCLUSIONE

- Diagnosi confermata istologicamente di linfoma a cellule T periferiche **(PTCL-NOS, AITL, MF trasformata**), in accordo con la classificazione WHO 2008.
- **Malattia CD30 + (espressione di CD30 > al 10% valutata in IHC)**
- **Ricaduta o refrattarietà** ad <u>almeno una</u> precedente linea di trattamento antilinfoma.
- Età ≥ 18 anni e ≤ **75 anni**.
- Laboratorio: neutrofili ≥ 1.000/mmc, piastrine ≥ 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.

CRITERI DI ESCLUSIONE

- Diagnosi di linfoma a cellule T della cute, linfoma T-anaplastico (ALCL), micosi fungoide o sindrome di Sézary.
- **Espressione dell'antigene CD30 < 10%** valutata in immunoistochimica.
- **Neuropatia periferica preesistente** di grado 3-4 (o di grado 2 non responsiva a terapia).
- Comorbilità cardiologiche, tra cui: infarto miocardico (entro 2 anni), scompenso cardiaco (NYHA III-IV), aritmia non controllata, evidenza ECG di ischemia miocardica o alterazioni della conduzione, recente riscontro (< 6 mesi) di frazione di eiezione < 50%.
- **Malattia cerebrale, meningea o testicolare.**
- Segni o sintomi di encefalopatia multifocale progressiva.
- **Precedente trapianto allogenico** di cellule staminali emopoietiche.

PROTOCOLLO DI TRATTAMENTO



STATUS ARRUOLAMENTO (1)

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

Centro	Attivazione	Pazienti arruolati
Bologna	Sì	5
Brescia	Sì	0
Milano (INT)	Sì	6 (*)
Torino	Sì	4
Udine	No	0
TOTALE		**15 (**)**
Previsti		**25**

(*) Screening failure in due pazienti (non riportati)
(**) Da aggiungere un paziente in screening al 13/10/2017

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

BACKGROUND (1)

Characteristic	No.	%
Patients	60	
Age, years		
Median	66	
Range	43-87	
> 75	14	23
Sex		
Male	38	
Female	22	
Histology		
AILT	32	53
PTCLu	23	38
ALCL	2	3.5
EATL	1	2
MF	2	3.5
Disease stage		
II	6	10
III/IV	52	87
IIB/IVA	2	3
ECOG performance score		
1	40	67
2	17	28
3-4	3	5
IPI	58	100
1-2	20	34
3-5	38	66
PIT	58	100
0-1	8	14
2-4	46	79
Missing	4	7
Bulky disease ≥ 5 cm	12	20
Extranodal site involvement	36	60

Results From a Prospective, Open-Label, Phase II Trial of Bendamustine in Refractory or Relapsed T-Cell Lymphomas: The BENTLY Trial

	By Local Investigator	
Response	No.	%
Overall response rate after three cycles		
CR + CRu + PR	30	50
CR + CRu	17	28
PR	13	22
SD	3	5
PD	27	45
DOR, months		
Median	3.5	
Range	1-20.7	

Damaj G. *J Clin Oncol*, 2012; 31: 104-110

OBIETTIVI DELLO STUDIO

- **Obiettivo primario**: effetto antitumorale della combinazione bendamustina + brentuximab vedotin (BBV) in termini di risposta globale, quando applicata come terapia di salvataggio nei pazienti con linfoma a cellule T periferiche, $CD30^{+}$.

- **Obiettivi secondari**: sicurezza e tollerabilità del regime BBV; sopravvivenza e miglioramento clinico (riduzione della sintomatologia linfoma-correlata)

- ***Endpoint* primario**: tasso globale di risposta (*overall response rate*, ORR) .

- ***Endpoints* secondari**: durata di risposta (DOR), tasso di risposta completa (CR rate), sopravvivenza globale (*overall survival*, OS) e sopravvivenza libera da progressione (*progression-free survival*, PFS) a 1 anno.

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 $\leq$ 1.
- Laboratorio: neutrofili $\geq$ 1.500/mmc, piastrine $\geq$ 75.000/mmc, bilirubina e creatinina sieriche $\leq$ 1,5 × ULN, AST/ALT $\leq$ 2,5 × ULN, albumina $\geq$ 3 g/dL.
- Adeguate misure contraccettive.

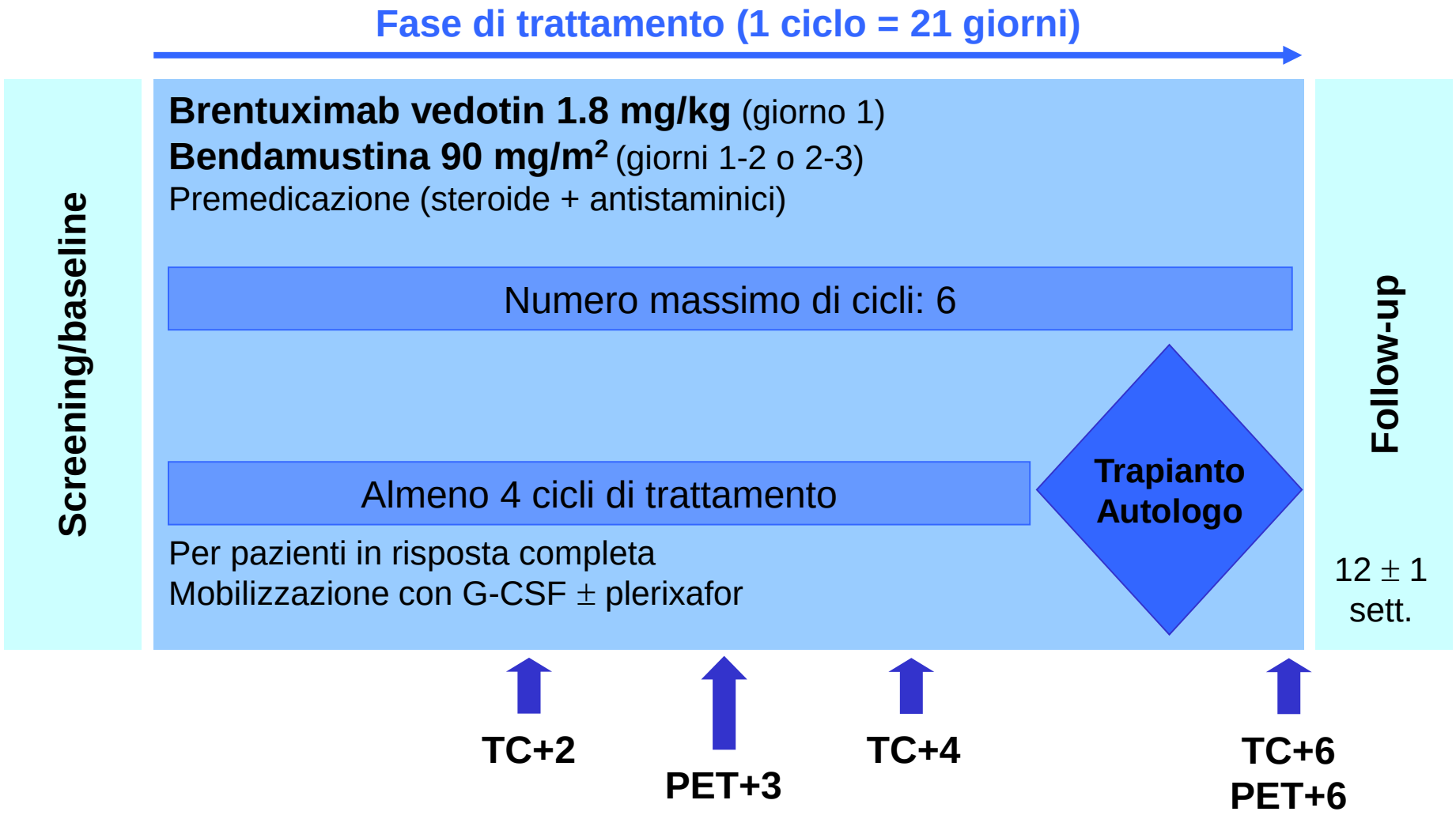
(*) Emendamento n° 2, v. 12/12/2016

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

PROTOCOLLO DI TRATTAMENTO



STATUS ARRUOLAMENTO

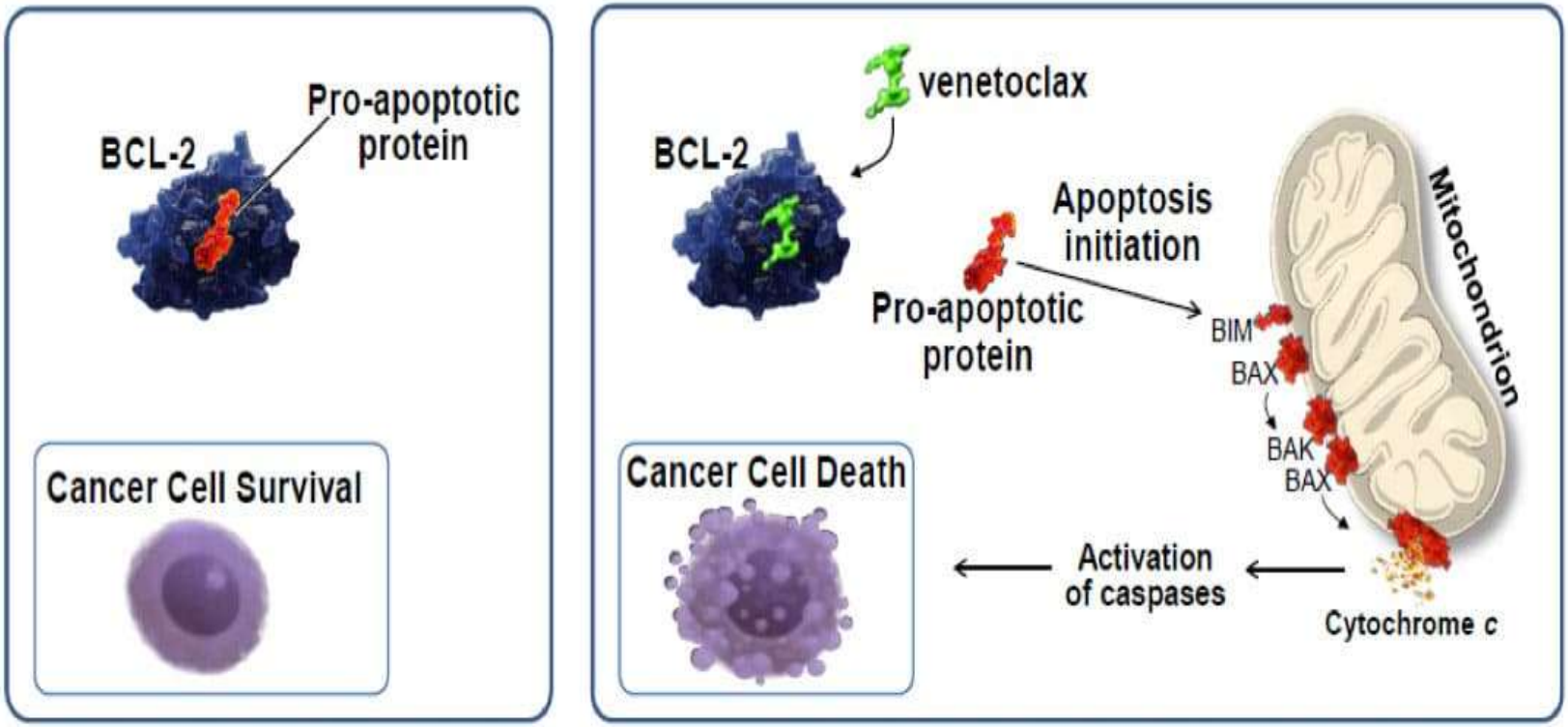
- **Data inizio studio**: dicembre 2015
- **Data inizio arruolamento**: dicembre 2015
- **Durata studio**: 2 anni per arruolamento + 2 anni di *follow-up*

Centro	Attivazione	Linfomi cellule T	Approvaz. emend. 2
Bologna	Sì	1	16/05/2017
Brescia	Sì	0	26/04/2017
Milano (INT)	Sì	1	26/04/2017
Napoli (Pascale)	Sì	1	17/05/2017
Torino	Sì	0	24/07/2017
Niguarda	Sì	0	
Rozzano	Sì	0	
TOTALE		**3**	
Previsti		**25**	

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

Principal Investigator prof Francesco Zaja

Venetoclax: mechanism of action



BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins[1-3]

Venetoclax binds selectively to **BCL-2**, freeing pro-apoptotic proteins that initiate programmed cell death (apoptosis)[4-6]

1. Leverson JD, et al. *Sci Transl Med* 2015;7(279):279ra40. 2. Czabotar PE, et al. *Nat Rev Mol Cell Biol*. 2014;15(1):49-63. 3. Plati J, et al. *Integr Biol (Camb)*. 2011;3(4):279-296. 4. Certo M, et al. *Cancer Cell*. 2006;9(5):351-365. 5. Souers AJ, et al. *Nat Med*. 2013;19(2):202-208. 6. Del Gaizo Moore V, et al. *J Clin Invest*. 2007;117(1):112-121.

Bcl-2 expression in nodal PTCL

	Cases	Positive	75-100%	50-74%	25-49%	5-24%
PTCL NOS	43	35 (82%)	22 (51%)	5 (12%)	5 (12%)	3 (7%)
AITL	26	23 (88%)	10 (38.5%)	3 (11.5%)	4 (15%)	6 (23%)
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%)

Zaja F. et al, Am J Hematol 2016

Venetoclax in BCL-2 positive PTCLs: study objectives

Primary objective

- ORR after 3 cycles

Secondary objectives

- CR, PR, SD
- OS
- Time to response
- Duration of response (DoR)
- PFS
- Duration of treatment
- Relevant toxicity
- Overall toxicity

Explorative objective

- Relationship between response and level of BCL-2 expression

Venetoclax in BCL-2 positive PTCLs: main inclusion criteria

- Histological diagnosis of **BCL-2 positive PTCL-NOS, AITL, TFH (percentage of BCL-2 positive tumor cells ≥ 25%)** as defined in the 2016 edition of the WHO classification
- **Relapsed or refractory** to at least one previous standard line of treatment
- Patients **not eligible for high dose chemotherapy and ASCT**
- Measurable nodal disease (at least one lymph node ≥2 cm in the longest transverse diameter by CT scan)
- Age ≥ 18 years
- ECOG performance status ≤ 2
- 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

- **Allogeneic or autologous stem cell transplant within 6 months prior to study entry**
- **CNS involvement by lymphoma**
- Anti-cancer therapy (including chemotherapy, radiotherapy, immunotherapy or investigational therapy) within 14 days prior to the first study drug administration
- Previous treatment with a BCL-2 family protein inhibitor
- 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)

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

Principal Investigator prof Zaja Francesco

CD38 expression in nodal PTCL

	Cases	Positive	75-100%	50-75%	25-50%	5-24%
PTCL NOS	42	23 (55%)	9 (21.4%)	3 (7.1%)	2 (4.8%)	9 (21.4%)
AITL	25	20 (80%)	2 (8%)	5 (20%)	4 (16%)	9 (36%)
ALCL ALK negative	34	6 (17.6%)	3 (8.8%)	1 (2.9%)	0	2 (5.9%)
ALCL ALK positive	9	0	0	0	0	0

Zaja F. et al, Am Journal Hematol 2016

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

Primary objective

- Complete Response Rate (CR) after 4 cycles of D-GDP

Secondary objectives

- Relevant toxicity during the first 2 cycles defined as:
  - -grade 4 neutropenia lasting for more than 7 days despite adequate G-CSF primary prophylasis
  - -grade 4 thrombocytopenia lasting for more than 7 days
  - -delay > 15 days in the next course
  - -febrile neutropenia lasting for more than 4 consecutive days
  - -any relevant (no alopecia & laboratoristic, IRR) grade 3-4 non-hematologic drug-related toxicity
- ORR
- OS
- Overall toxicity
- Role of Daratumumab maintenance

Exploratory objective

- Relationship between intensity of CD38 expression and response

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

- Diagnosis of CD38 positive PTCL-NOS, AITL, THF
- **CD38 immunohistochemical expression ≥ 5%** on the relapse biopsy
- **Relapsed or refractory** after at least one previous line of therapy
- Age 18-75 years
- ECOG performance status ≤ 2
- Measurable nodal disease (at least one lymph node ≥2 cm in the longest transverse diameter by CT scan)

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
- HIV seropositivity
- Active HBV or HCV hepatitis

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

Screening phase

Steroids and/or vincristine allowed during the screening phase

D-GDP x 4-6 cycles every 21 days

Daratumumab: Cycle 1: 8 mg/kg day 2 and 9
Cycle 2 to 4/6: 16 mg/kg day 2 and 9

Gemcitabine 1000 mg/m^2 day 1 and 8

Dexamethasone 40 mg day 1, 2, 3, 4, 9

Cisplatin 75 mg/m^{2}day 1

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

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

CR, PR, SD

Maintenance with Daratumumab

16 mg/kg every 4 weeks starting 28 days after the beginning of cycle 4-6 and up to 24 cycles (from start of D-GDP)

Patients in CR/PR eligible to allo-SCT can exit the study after induction


NHL B
PTCL