INCONTRO di AGGIORNAMENTO sui DISORDINI LINFOPROLIFERATIVI
e sui PROTOCOLLI della FONDAZIONE ITALIANA LINFOMI

Torino, 14 dicembre 2018

LINFOMI DIFFUSI A GRANDI CELLULE B

Alessia Castellino

Ematologia, AO Santa Croce e Carle, Cuneo

PROTOCOLLI CONCLUSI

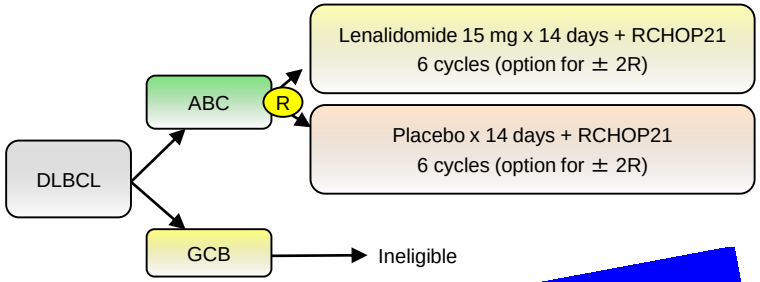
- **DLBCL Prima Linea (ABC subtype)**
  -ROBUST trial
- **RR-DLBCL**
  - VERAL trial

NUOVE PROPOSTE

- **DLBCL Prima Linea (ABC subtype)**
  -Ri-CHOP-I trial
- **RR-disease**
  - DLBCL: RB-Copa trial
  - PBL: DALYA trial

ROBUST CC5013-DLC-002

Phase 3 randomized, double-blind, placebo controlled, multicenter study to compare the efficacy and safety of lenalidomide (CC-5013) plus R-CHOP chemotherapy (R2-CHOP) versus placebo plus R-CHOP chemotherapy in subjects with previoysly untreated activated B-type diffuse large B-Cell Lymphoma



Centro Coordinatore: SC Ematologia
Città della Salute e della Scienza
Dr. Umberto Vitolo

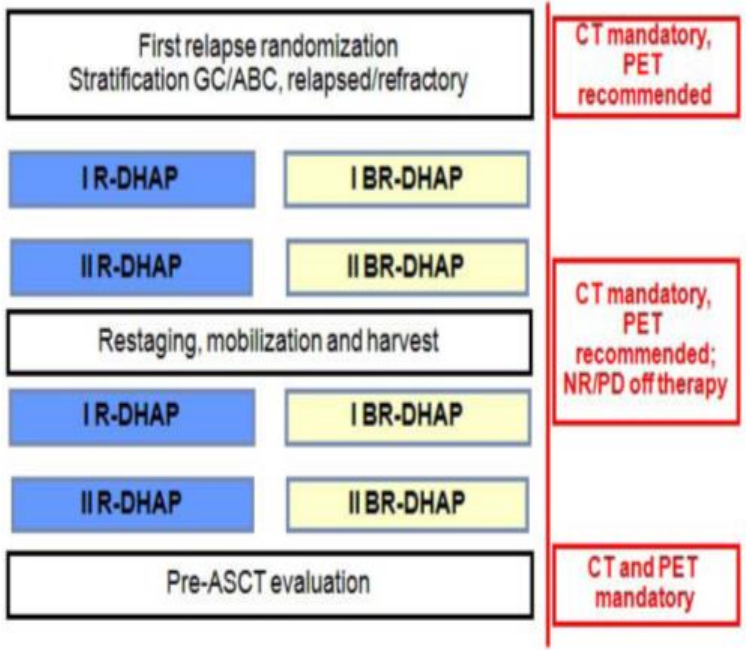
560
CC-5013-DCL-002 Enrolment Target Met

Italy
Global Top
Recruiting Country

FIL_VERAL12

Phase II randomized study with R-DHAP +/- Bortezomib as induction therapy in relapsed/refractory Diffuse Large B-cell Lymphoma (DLBCL) patients eligible to transplantation BR-DHAP versus R-DHAP

PI: Dr . U. Vitolo, Dr. M. Balzarotti, Dr.ssa A. Chiappella



- Centro Coordinatore: SC Ematologia, Città della Salute e della Scienza-Dr. Vitolo
- Data Apertura: ottobre 2012
- Centri partecipanti/Centri attivi: 32/29
- Centri arruolanti/Centri attivi: 25/29
- Pazienti arruolati: 108/108

ANALISI in CORSO

RI-CHOP-I

Phase II multicentric single arm study to evaluate the efficacy and safety of ibrutinib in combination to rituximab-CHOP followed by ibrutinib maintenance in untreated patients with Activated-B-Cell (ABC)-DLBCL, intermediate-high and high risk (IPI ≥2).

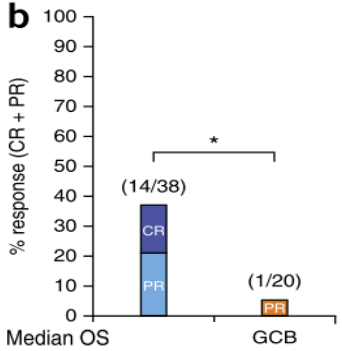
Sponsor	**Fondazione Italiana Linfomi (FIL)**
Financial support	Janssen
Primary Investigators	Maurizio Martelli
CO-PIs	Umberto Vitolo, Annalisa Chiappella, Alice Di Rocco
Writing committee	Maurizio Martelli , Umberto Vitolo, Annalisa Chiappella, Alice Di Rocco, Annalisa Arcari, Simone Ferrero, Gianluca Gaidano, Marco Ladetto, Stefano Pileri, Umberto Ricardi
Statisticians	Giovannino Ciccone, Andrea Evangelista
Pharmacovigilance	Alessandro Levis

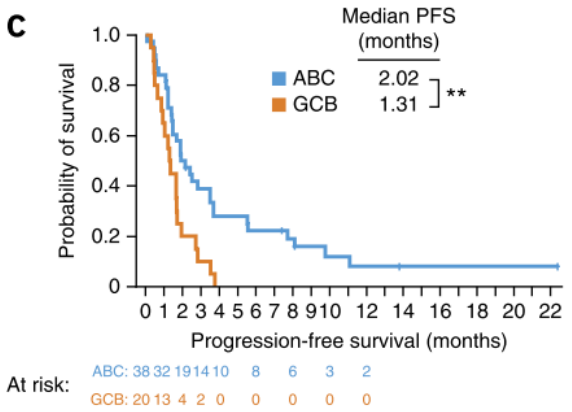
Background and Rationale

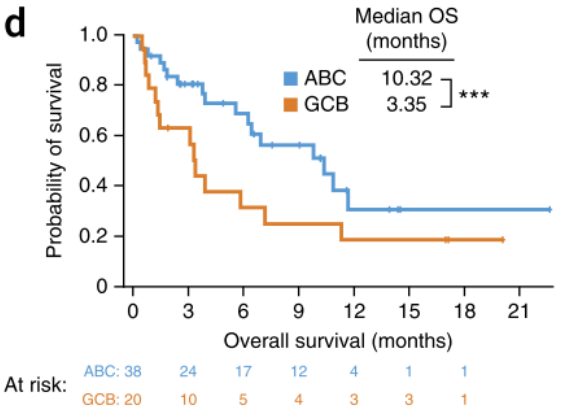
The Bruton's Tyrosine Kinase (BTK) inhibitor, ibrutinib (PCI-32765) has a preferential activity in ABC DLBCL: phase II interim results

Table 1 Baseline characteristics by DLBCL subtype

Characteristics	ABC (*N* = 38)	GCB (*N* = 20)	Unclassified (*N* = 17)	Unknown (*N* = 5)
Median age, years (range)	60 (34–89)	65 (28–92)	63 (44–85)	65 (58–78)
Sex (male)	66%	70%	82%	60%
ECOG performance score ≥ 2	5%	20%	24%	40%
RIPI (poor)	63%	59%	50%	60%
Median time from diagnosis, months (range)	19 (4–118)	17 (11–104)	21 (7–332)	19 (9–57)
Median number of prior regimens (range)	3 (1–7)	3.5 (1–7)	3 (1–4)	3 (1–3)
Prior ASCT	13%	30%	24%	40%
Chemotherapy-refractory disease	66%	65%	59%	50%

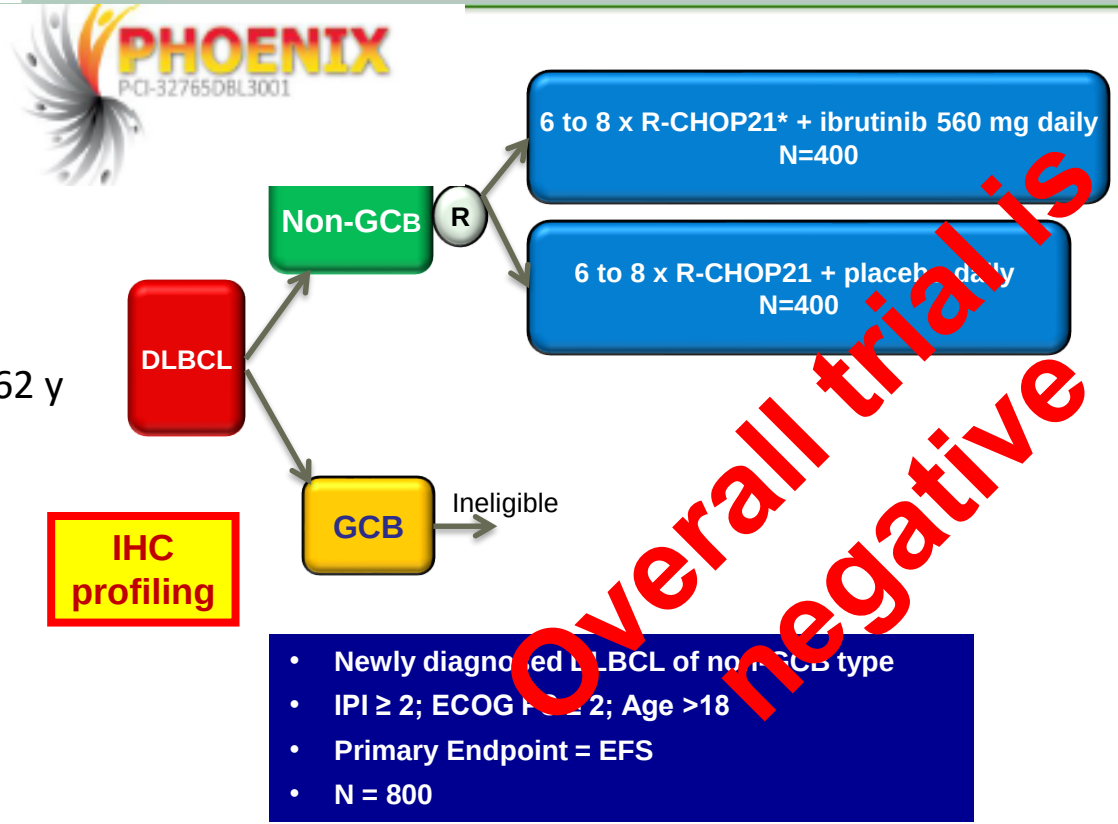






Wilson WH, Nat Med. 2015.

Background and Rationale



838 pts
Median age 62 y

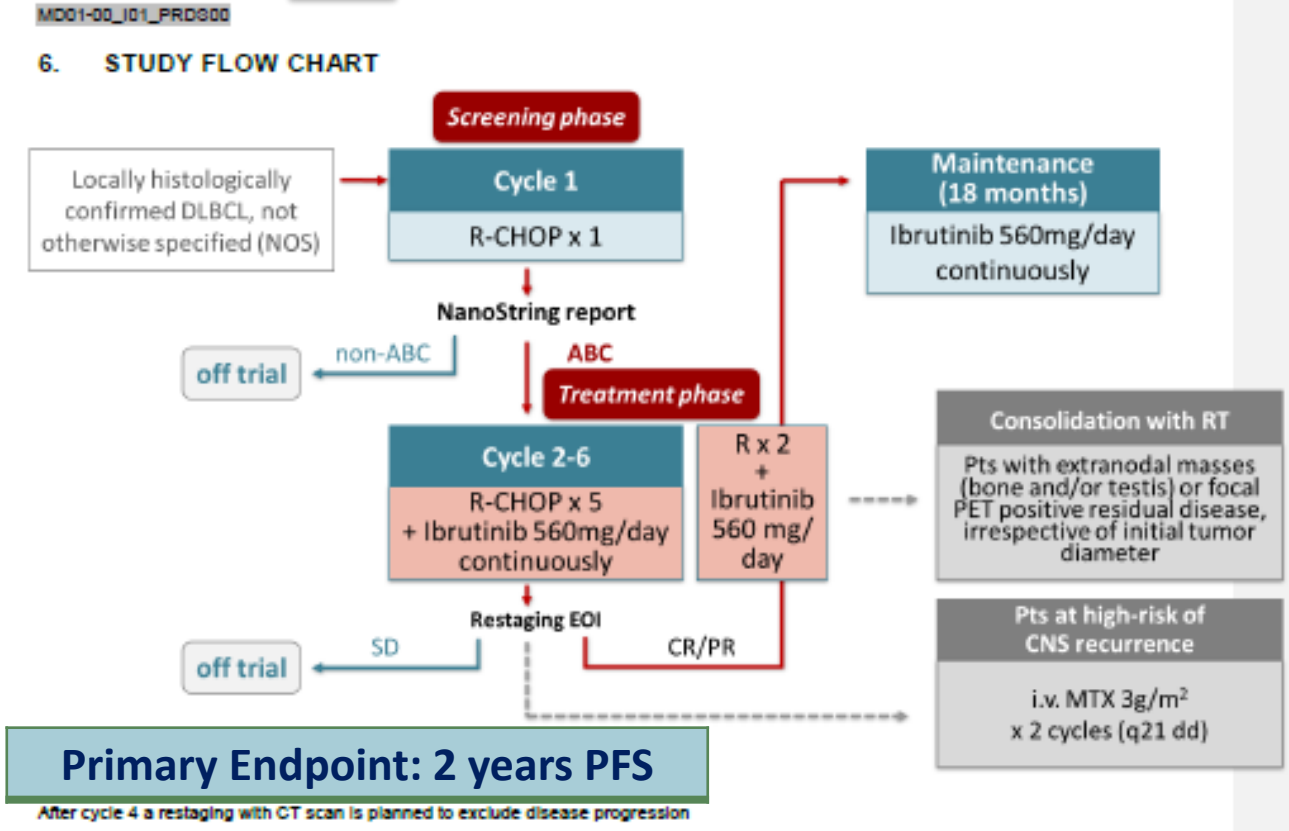
Overall trial is negative

Ibr + R-CHOP did not improve EFS (HR 0.934)
In all pts

EFS significantly higher in pts < 65y
Risk reduction
EFS (30%), OS (43%)

ClinicalTrials.gov Identifier: NCT02285062.ASH 2018
Press release available from: https://www.jnj.com/janssen-provides-update-on-imbruvica-ibrutinib-phase-3-phoenix-trial-in-newly-diagnosed-

RI-CHOP-I study



Primary Endpoint: 2 years PFS

After cycle 4 a restaging with CT scan is planned to exclude disease progression

INCLUSION CRITERIA:

- Previously untreated disease
- Age ≥ 18 and < 65 years
- IPI score ≥ 2
- DLBCL NOS, ABC nanostring

ESCLUSION CRITERIA:

- DLBCL, NOS GC-type
- HGBL, DHL and NOS
- Composite or transformed disease,
- FL IIIB
- DLBCL with IRF4 rearr
- PMBCL
- CNS involvement
- Primary testicular lymphoma

PI : Maurizio Martelli

RI-CHOP-I study

RADIOTHERAPY– consolidation

To whom:

-to focal PET positive residual disease, or
-to bone extranodal lesions
- to scrotum (involved and contralateral testis) in case of testicular involvement, irrespective of initial tumor diameter.

When:

- At the end of R-chemotherapy as per institution clinical practice

CNS phrophylaxis with IV MTX

To whom:

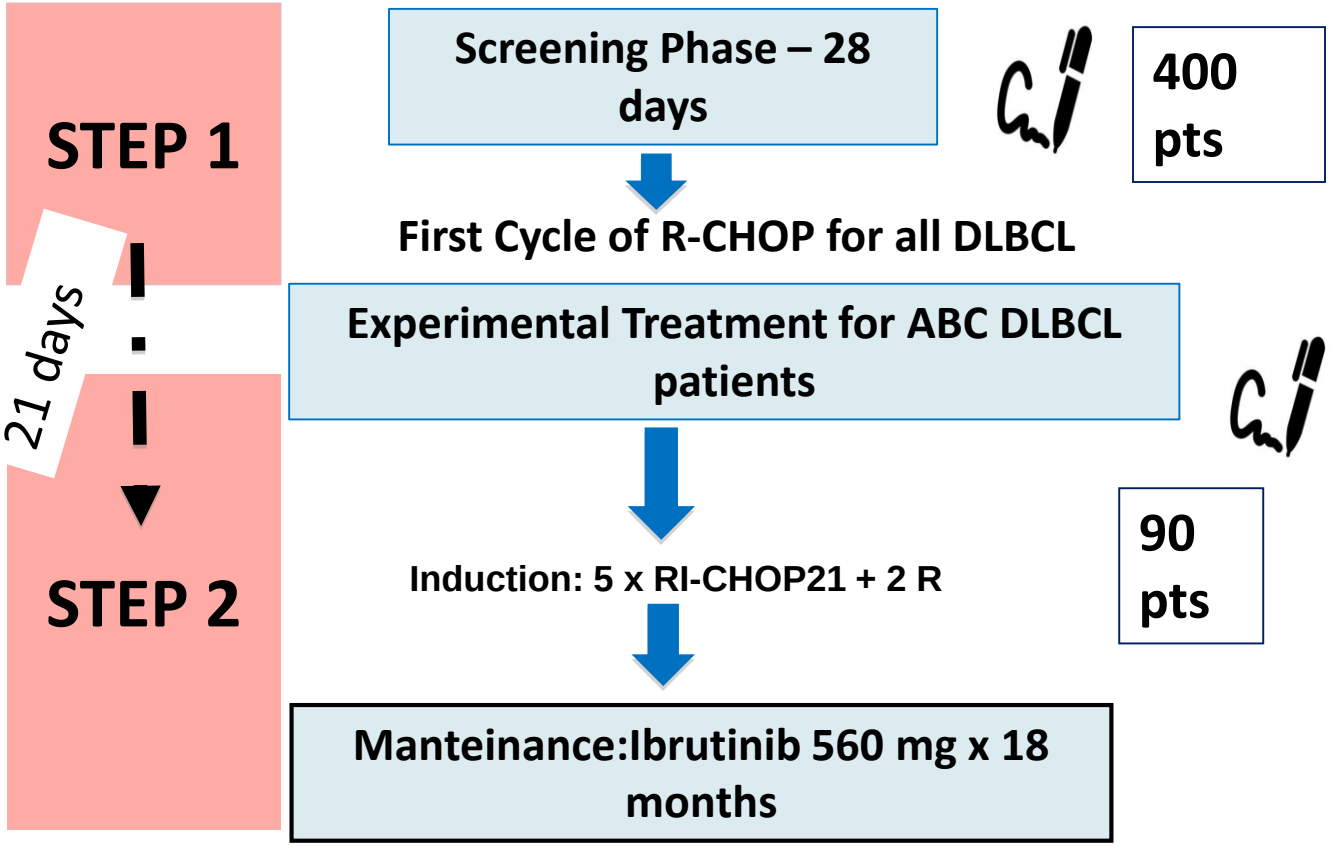
1)high risk CNS-IPI (Shmitz et al);
2)testis or a para-meningeal site involvement that are considered to have a high risk of developing CNS recurrence.

Cycle 7-8 – Only ABC (patients candidate to CNS prophylaxis), Q21 days		
Rituximab	375 mg/m^2, IV ***or*** 1400 mg SC	day 1
Ibrutinib	560 mg/day, PO	days 5-21
MTX	3 g/m^2, IV	day 2

When:

- After Restaging at EOI

Study Design



Statistical Analysis

The study sample size has been calculated according to primary efficacy endpoint. An **absolute improvement of 0.15 of the 2 years PFS (from 0.50 to 0.65)** is considered clinically promising the experimental treatment. According to one arm non-parametric survival method [65] provided by SWOG group (NCI), with 18 months of enrollment and 2 years of minimum follow-up, **a total of 90 ABC-DLBCL** patients are required to detect an increase in the 2 years PFS from 0.50 to 0.65 assessed with a one-sided alpha error of 5% and a high statistical power of 90%.

✓ **SAFETY MONITORING AND STOPPING RULES**

Monitoring of toxicity to ensure that the proportion of patients with relevant toxicity (**non-hematological toxicity ≥ grade 3 or treatment interruption for safety reasons or any toxic death**) during the induction therapy was not higher than an acceptable level of 25%.
The prior probability of toxicity (25%) is modeled by a beta distribution [Beta (0.5,1.5)]. Patients will be monitored, without suspending the enrollment, in cohorts of 15 patients.

Patients assessed for toxicity	Stop the enrollment in the cohort if the relevant toxicities are greater or equal to:
15	7
30	12
45	17
60	21
75	26

END-POINTS

Primary End-points

- The 2-years PFS of R-CHOP21 in combination with ibrutinib followed by maintenance in untreated with ABC-DLBCL, at IPI ≥2.
- The safety of R-CHOP21 in combination with Ibrutinib (extra-hematologic toxicity ≥ grade 3 or treatment interruption for safety reasons or any toxic death during the 6 cycles of treatment) and safety during Ibrutinib maintenance.

Secondary End-points

- To evaluate the efficacy in terms of OS;
- To evaluate the Complete Response (CR) rate and Overall Response Rate (ORR) (Lugano 2014);
- To evaluate the duration of response (DOR) after the end of treatment.
- To evaluate the rate of conversion to CR with ibrutinib maintenance for patients in PR at EoT.

EXPLORATIVE ANALYSIS

To assess the prognostic impact on 2-yrs PFS of:

- MYC, BCL2, double expressors in IHC;
- other biomarkers (additional Nanostring panels);
- mutations of selected genes (both on FFPE lymph nodes and on ctDNA – “liquid biopsy”);
- predictive value of different threshold of the quantitative PET indexes (QPI) at baseline (PET-0), i.e. metabolic tumour volume (MTV) and total lesion glycolysis (TLG);
- the role of the minimal residual disease (MRD) as an early predictor of clinical outcome (2-yrs PFS) and relapse, targeting ctDNA on plasma samples.

To explore the role of:

- predictive value of QPI on treatment response at EoT;
- predictive value of QPI variation between baseline (PET0) and EoT-PET on 2-yrs PFS;
- predictive value of SUV_{max} variation between baseline (PET0) and EoT-PET on 2-yrs PFS;
- the efficacy of the present therapeutic schedule in inducing deep responses in DLBCL, in terms of molecular remission;
- to correlate the MRD results with the clinical outcome and the classical radiologic monitoring already planned.

RB-COPA

Copanlisib in combination with Rituximab-Bendamustine versus Rituximab-Bendamustine alone in patients with Relapsed-Refractory DLBCL: a multicentric randomized Phase III trial.

Principal Investigators: Grzegorz S. Nowakowski, Umberto Vitolo.

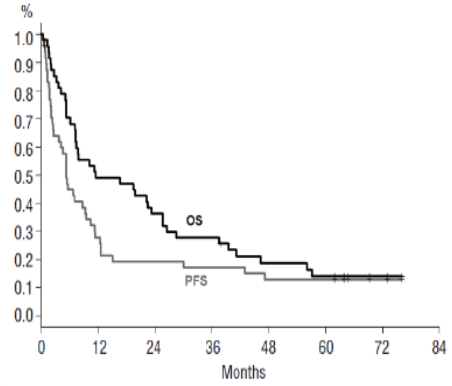
Writing committee:

GS. Nowakowski, U. Vitolo, A. Chiappella, A. Castellino, B. LaPlant, P. Mei-Yin, R. King, T.E. Witzig, T.M. Habermann, G. Ciccone, M. Spina, M. Balzarotti.

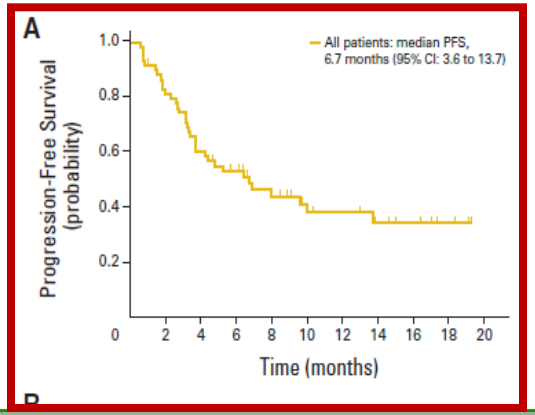
BACKGROUND AND RATIONALE

REGIMEN	N	Median age	ORR%	CR %	PFS	Reference
R-GEMOX	49	69	46	38	5-yrs 12.8%	Mounier N, Haematol 2013
R-Bendamustine	59	67	63	37	Median 6.7 mo	Ohmachi K, L Clin Oncol 2013
	55	76	50	28	Median 8.8 mo	Arcari A, Leuk Lymphoma 2015
	39	71	33	20	Median 2 mo	Sehn L, ASH 2017 (arm standard, Polarix)
Pixantrone	70	60	37	20	Median 5.3 mo	Pettengel R, Lancet Oncol 2012

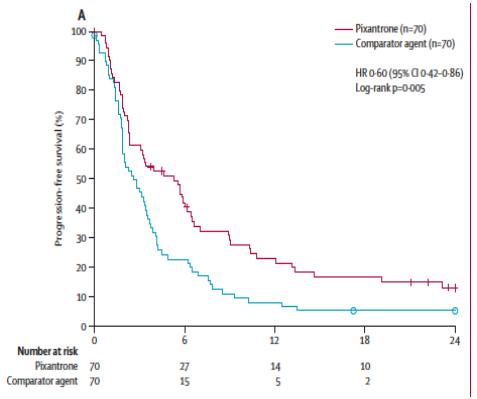
R-GEMOX



R-BENDAMUSTINE

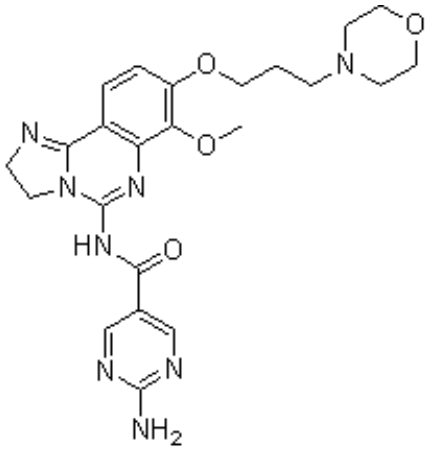


PIXANTRONE



BACKGROUND AND RATIONALE

Copanlisib (BAY 80-6946)



- pan-Class PI3K inhibitor, predominant activity against the α and δ isoforms
- PI3Kδ isoform: B-cell signaling, development and survival
- PI3Kα isoform upregulation may contribute to resistance mechanism in lymphoma cells
- metabolized by the cytochrome P450 (CYP) 3A4 and CYP1A1: lower risk for clinical drug-drug interactions in combination regimens

- **R/R Indolent lymphoma:**
  - Single-agent: ORR of 59%, mPFS 12 mo
  - Phase III: R-bendamustine + Copanlisib/placebo is safe and feasible
- **R/R Aggressive lymphoma:**
  - Single-agent (MCL+DLBCL+PTCL): ORR 27%, 1-yr PFS 13%
  - DLBCL: ORR 25%, CR 12.5%; suggested higher efficacy in ABC (ORR 35%, CR 25%)

Dreyling et al, 2017; Patnaik et al, 2016, Gerecitano et al, 2017; Lenz et al, 2017

BACKGROUND AND RATIONALE

COPANLISIB IN R/R DLBCL: ORR BY DLBCL COO SUBTYPE

	Overall FAS (*n*=67)	Overall PPS (*n*=40)	DLBCL COO subgroup (PPS, *n*=40)		
			ABC DLBCL (*n*=16)	GCB DLBCL (*n*=22)	Unclassifiable (*n*=2)
Best overall response, *n* (%)					
Complete response	**5 (7.5)**	**5 (12.5)**	**4 (25.0)**	**1 (4.5)**	**0**
Partial response	8 (11.9)	5 (12.5)	2 (12.5)	2 (9.1)	1 (50.0)
Stable disease	14 (20.9)	12 (30.0)	4 (25.0)	8 (36.4)	0
Disease progression	30 (44.8)	16 (40.0)	5 (31.3)	10 (45.5)	1 (50.0)
ORR	**13 (19.4)**	**10 (25.0)**	**6 (37.5)**	**3 (13.6)**	**1 (50.0)**

Grade 3-4 AEs: Hypertension 33%; Hyperglycemia 31%.

Lenz et al, ICML 2017

BACKGROUND AND RATIONALE

www.FILINF.IT

SAFETY RUN-IN OF COPANLISIB IN COMBINATION WITH RITUXIMAB PLUS BENDAMUSTINE IN PATIENTS WITH RELAPSED INDOLENT NON-HODGKIN'S LYMPHOMA

J. Gerecitano[1*] | A. Santoro[2] | S. Leppä[3] | T. Kim[4] | W. Kim[5] | A. Janssens[6] | M. Pedersen[7] | D. Reis[8] | C. Granvil[9] | J. Shen[10] | H. Zheng[11] | B.H. Childs[11] | P. Zinzani[12]

10 patients: 7 FL, 1 MZL, and 2 LPL-WM.
6 courses R-Benda-Copanlisib
R 375 mg/mq; Bendamustine 90 mg/mq dd1-2
Copanlisib 45 mg in 3, 60 mg in 7 patients.

- No DLTs.
- Most common grade ≥ 3 TEAEs:
  - Neutropenia 50%; Hyperglycemia 50%; Hypertension 20%
- Two pts had serious TEAE: lung infection grade 4 and hypereosinophilia grade 3.

- Response in 7 evaluable pts: 2 CR and 5 PR.

Gerecitano et al, Hematol Oncol 2017

STUDY END POINTS

- **Primary objectives: PFS and OS as co-primary end-points**
  - to evaluate the superiority in terms of PFS of Copanlisib in combination with Rituximab-Bendamustine regimen compared to Rituximab-Bendamustine alone in relapsed/refractory DLBCL not eligible or relapsed after HDC+ASCT
  - if superiority in PFS will be achieved: to evaluate the superiority in OS
  - subgroup analysis according to COO (by IHC and by Nanostring)
- **Secondary objectives:**
  - ORR, CR
  - Duration of response (median DOR)
  - TTR
  - Safety and tolerability of Rituximab-Bendamustine-Copanlisib
  - QoL

SAMPLE SIZE CALCULATION

- **Sample size calculation:**
  - based on the primary efficacy endpoint, PFS and OS coprimary end point Hierarchic al testing PFS→ OS

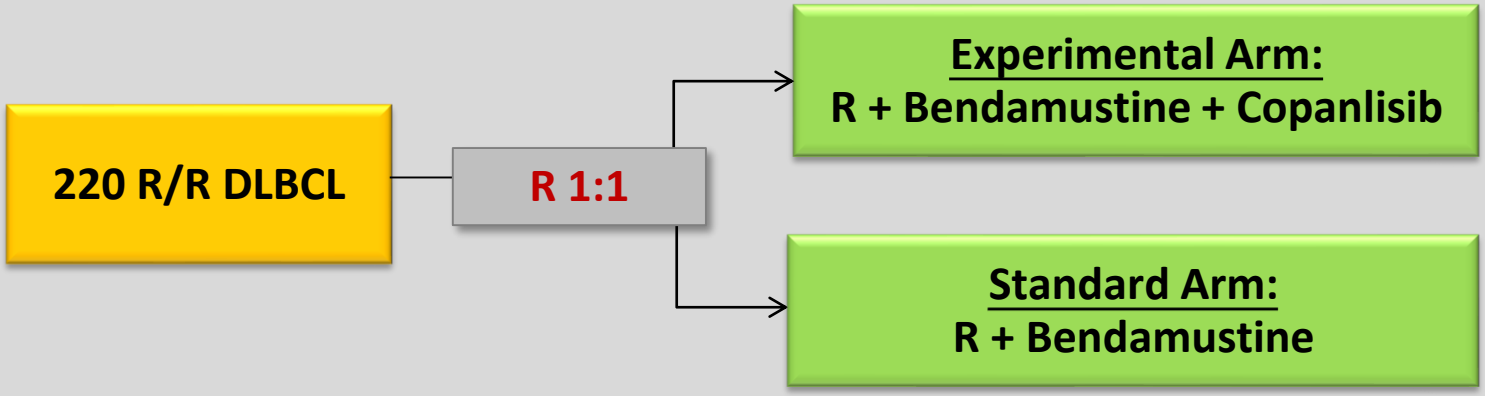
- **Targeted improvement:**
  - median PFS from 4 to 7 months (HR = 0.57);
  - median OS from 6 to 10 months (HR = 0.59).
  - Test PFS first at 2-sided 0.05 level. If significant, test PFS at 2-sided 0.05 level; otherwise, OS is not formally compared

- **Accrual period:**
  - 220 patients in 22 months (~10 patients/month).

INCLUSION CRITERIA

- **Inclusion criteria:**
  - Age ≥ 18 years old
  - Histologically confirmed DLBCL (de-novo DLBCL or DLBCL transformed by indolent lymphoma; high grade and double hit lymphoma can be included); new biopsy at relapse time is recommended, but not mandatory.
  - Relapsed (recurrence after complete response or presented progression after partial response) or progressed after at least > 1 (but < 4) prior lines of therapy, including rituximab-based immunochemotherapy.
  - Not eligible to high-dose chemotherapy and ASCT, or relapsed after that.
  - Not eligible to CAR-T therapy
  - Measurable disease
  - Normal organ function

Study Design and Scheme of Treatment



Experimental Arm:
R + Bendamustine + Copanlisib

Copanlisib IV 60 mg/day D1, D8, D15 of each 28-days-cycle: cycle 1-6
Rituximab IV 375 mg/sqm D1 of each 28-days-cycle: cycle 1-6
Bendamustine IV 90 mg/sqm D 1-2 of each 28-days-cycle: cycle 1-6
Copanlisib Maintenance 60 mg/day D1 of each 21-days-cycle: 1 year

Standard Arm:
R + Bendamustine

Rituximab IV 375 mg/sqm D1 of each 28-days-cycle: cycle 1-6
Bendamustine IV 90 mg/sqm D1-2 of each 28-days-cycle: cycle 1-6

DALYA

An Open Label, Phase 2 Study to Evaluate Activity and Safety of Daratumumab in combination with Bortezomib and Dexamethasone in patients with Relapsed or Refractory Plasmablastic Lymphoma (DALYA trial)

Andrés J. M. Ferreri, Ospedale San Raffaele, Milano
Michele Bibas, Ospedale Spallanzani, Roma
Alessandro Re, Spedali Civili, Brescia
Michele Spina, Centro di Riferimento Oncologico (CRO), Aviano

BACKGROUND AND RATIONALE

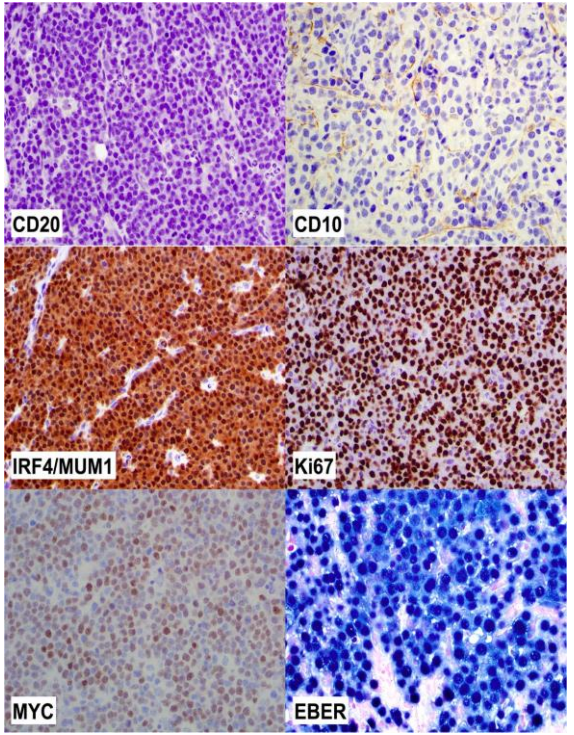
PBL is an aggressive B-cell lymphoma with features overlapping between MM and lymphomas with plasmablastic morphology.

HIV+ 63%
HIV- 28%
post-transplant 6%

The immunophenotype is similar to that in plasma cell neoplasms,
Positive for CD79a, MUM-1, BLIMP-1, CD38, CD138.
Negative for CD19, CD20, and PAX-5
EBV+ (EBER+ > 90% cases)

OS significantly lower than DLBCL

90% PBL are CD38+ → Ab Anti CD38: **Daratumumab** (90% ORR in MM)

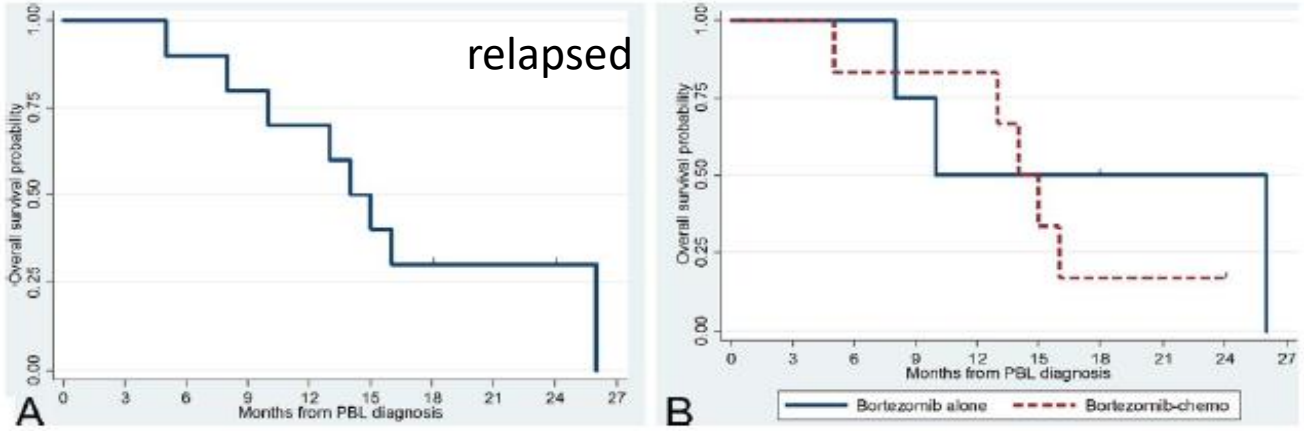


Qunaj L, et al. *Leuk Lymphoma* 2017; Shirley et al, Blod 2009.

BACKGROUND AND RATIONALE

Several case reports suggest efficacy of **bortezomib** in first and second line, alone or in combo, in PBL.

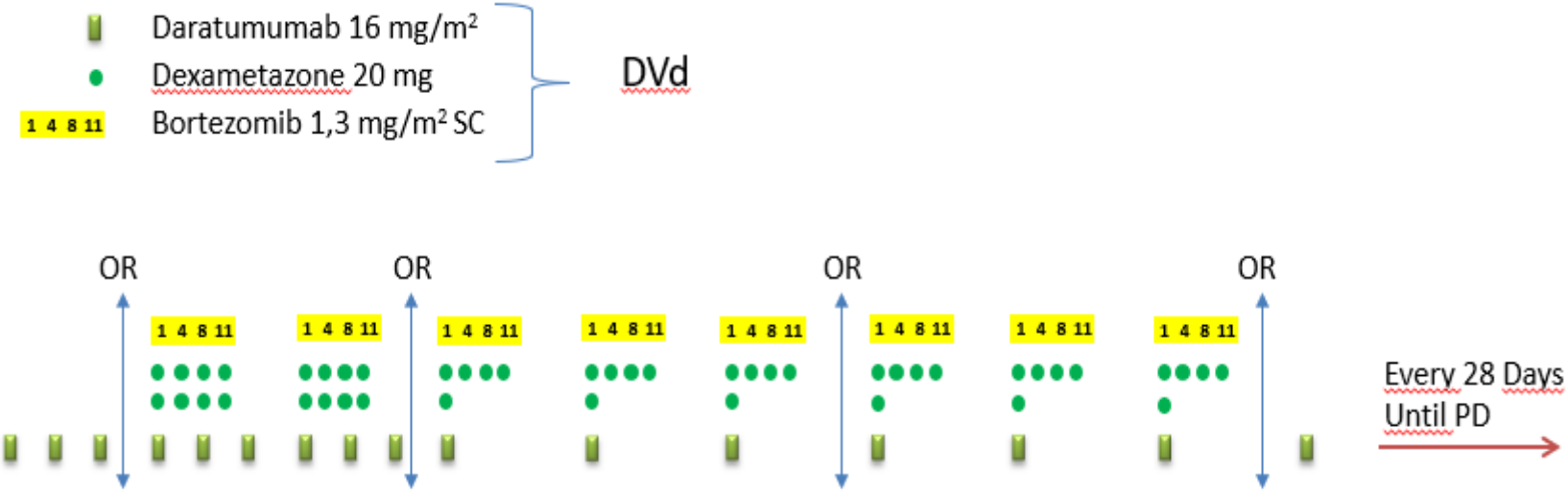
21 PBL pts (11 frontline; 10 relapsed): 11 pts were HIV-pos and 10 HIV-neg.
ORR to bortezomib-containing regimens:
100% in frontline
90% in relapsed



High rate ORR and PFS in PBL patients treated with Bortezomib + R-DaEPOCH.

Shirley et al, Blod 2009; Guerrero-Grancia et al, Leukemia Research 2017; Castillo JJ, *et al.* BJH 2018; Dittus C, *et al.* L&L 2018.

STUDY DESIGN AND END POINTS



- Primary endpoint: ORR (CR+PR)
  → Primary objective: to improve the ORR from 15% to 35% with the combination Dara + Velcade + Dexa (DVd)

- Secondary endpoints: PFS, OS, DoR, toxicity.

Inclusion Criteria

- Histologically confirmed plasmablastic lymphoma (WHO 2016)
- CD38+ (>1% positive cells by IHC)
- Patients with plasmablastic lymphoma relapsed or refractory:
  - after at least one line of conventional-dose chemotherapy +/- ASCT
  - after at least one line of conventional-dose chemo and not eligible for transplantation
- ECOG Performance Status ≤ 3
- Age ≥ 18 years
- HIV-negative and HIV-positive
- HIV infection responsive to ongoing cART
- At least one measureable disease lesion

STATISTICAL ANALYSIS

- A Simon's two-stage minimax design will be used
- The null hypothesis that the true ORR is 15% will be tested against a one-sided alternative.
- Sample size= 28 pts (First Step: >2 / 15).
- The null hypothesis will be rejected if ≥8 CR+PR will be reported.
- This design yields a type I error rate of 0.04610 and power of 0.8027 when the true ORR is 35%.

ANCILLARY STUDY

Hypotheses

- The anti-CD38 antibody may modulate CD4 and CD8 T-cell homeostasis, inflammatory environment and reduce the frequency of regulatory cells.
- EBV or CMV may play a role in the PBL occurrence. The lack of specific immunity both in the periphery and in the tumor may contribute to the pathogenesis.

Objectives:

- To evaluate the effect of Daratumumab treatment on
  - CD4 and CD8 T cell homeostasis
  - regulatory cells (MDSC and Treg) homeostasis
  - inflammatory cytokines profile
- To evaluate the effect of Daratumumab treatment on functional properties of HIV-specific, EBV-specific and CMV-specific T cells
- To analyze the lymphocyte infiltrating the PBL

ACKNOWLEDGEMENTS

Aggressive Lymphoma Committee

Pathological and Biological Team

FIL Biostatistics

FIL Trial Office

All FIL Centers

DVd Safety

Event	Daratumumab Group (N=243)		Control Group (N=237)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Common hematologic adverse event				
Thrombocytopenia	143 (58.8)	110 (45.3)	104 (43.9)	78 (32.9)
Anemia	64 (26.3)	35 (14.4)	74 (31.2)	38 (16.0)
Neutropenia	43 (17.7)	31 (12.8)	22 (9.3)	10 (4.2)
Lymphopenia	32 (13.2)	23 (9.5)	9 (3.8)	6 (2.5)
Common nonhematologic adverse events				
Peripheral sensory neuropathy	115 (47.3)	11 (4.5)	89 (37.6)	16 (6.8)
Diarrhea	77 (31.7)	9 (3.7)	53 (22.4)	3 (1.3)
Upper respiratory tract infection	60 (24.7)	4 (1.6)	43 (18.1)	2 (0.8)
Fatigue	52 (21.4)	11 (4.5)	58 (24.5)	8 (3.4)
Cough	58 (23.9)	0	30 (12.7)	0
Constipation	48 (19.8)	0	37 (15.6)	2 (0.8)
Dyspnea	45 (18.5)	9 (3.7)	21 (8.9)	2 (0.8)
Insomnia	41 (16.9)	0	35 (14.8)	3 (1.3)
Peripheral edema	40 (16.5)	1 (0.4)	19 (8.0)	0
Asthenia	21 (8.6)	2 (0.8)	37 (15.6)	5 (2.1)
Pyrexia	38 (15.6)	3 (1.2)	27 (11.4)	3 (1.3)
Pneumonia	29 (11.9)	20 (8.2)	28 (11.8)	23 (9.7)
Hypertension	21 (8.6)	16 (6.6)	8 (3.4)	2 (0.8)
Secondary primary cancer†	6 (2.5)	NA	1 (0.4)	NA

Palumbo et al, N Engl J Med 2016

Comparator

- Most studies on pts with rrPBL treated with salvage chemo and ineligible for ASCT do not report outcome of salvage therapy separately. However, …
- … clinical responses to salvage treatment are uncommon in everyday practice (Cattaneo, et al. 2015).
- … the median OS of HIV+ PBL pts is only 3 months, which confirms the substantial inefficacy of salvage therapies (Castillo, et al. 2010).
- …. 67% of PBL pts die of lymphoma progression (Tchernonog, et al. 2017).
- On these assumptions, we estimated that unselected salvage treatment is associated with a 15% ORR.

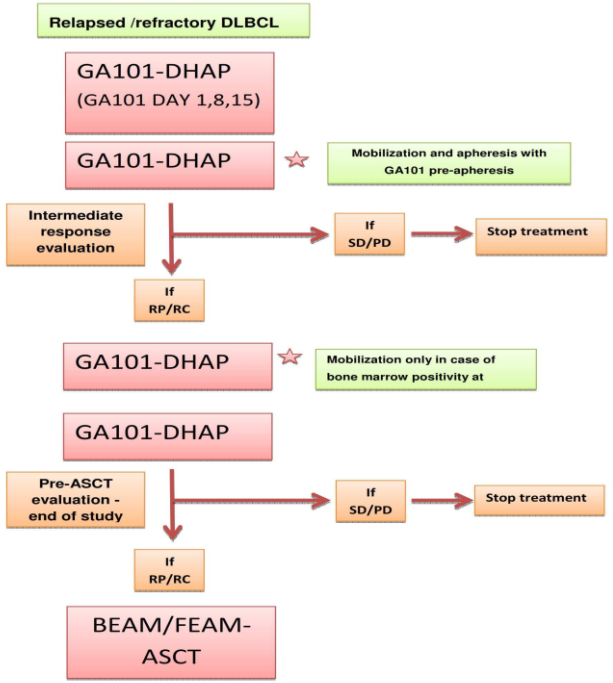
Time Frame

- Expected accrual start: Q2 2019
- Expected accrual time: 24 months
- Potential FIL recruitment= 2 pts/month
- Duration of treatment: 12 months
- Duration of follow-up: 12 months
- Expected final report: 36 months

L_GA101-DHAP (GIOTTO)

Phase II study with Ga101-DHAP as induction therapy in relapsed/refractory Diffuse Large B-cell Lymphoma (DLBCL) patients before High-Dose chemotherapy BEAM with autologous stem cell transplantation (ASCT)

PI: Prof. M. Martelli – Dr. L. Rigacci



- Centro Coordinatore: Dipartimento di Biotecnologie Cellulari ed Ematologia, Università "La Sapienza" – Prof. Martelli
- Data Apertura: Settembre 2014
- Centri arruolanti/Centri attivi: 10/20
- Pazienti arruolati: **30/78**
- In data 06 febbraio 2018 si comunica l'esito dell'analisi ad interim: lo studio non sarà riaperto a nuovi arruolamenti.

«L'analisi degli eventi avversi e delle tossicità non ha evidenziato segnali di safety diversi dall'atteso e gli eventi occorsi sono ampiamente nei limiti di quanto previsto dal protocollo.
Tuttavia, non essendo stato raggiunto l'obiettivo primario di attività dello studio non sussistono le condizioni per riaprirne l'arruolamento.
Pur essendosi dimostrata un'attività della terapia GA101-DHAP, non è prevedibile, continuando lo studio che questa si possa dimostrare più promettente della tradizionale terapia R-DHAP come era stato ipotizzato….»

- Data Chiusura (LPLV): giugno 2020