Torino, 24 Novembre 2017

AGGIORNAMENTI DI PROTOCOLLI FONDAZIONE ITALIANA LINFOMI

LINFOMI A GRANDI CELLULE

Annalisa Chiappella

Ematologia

AOU Città della Salute e della Scienza di 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.

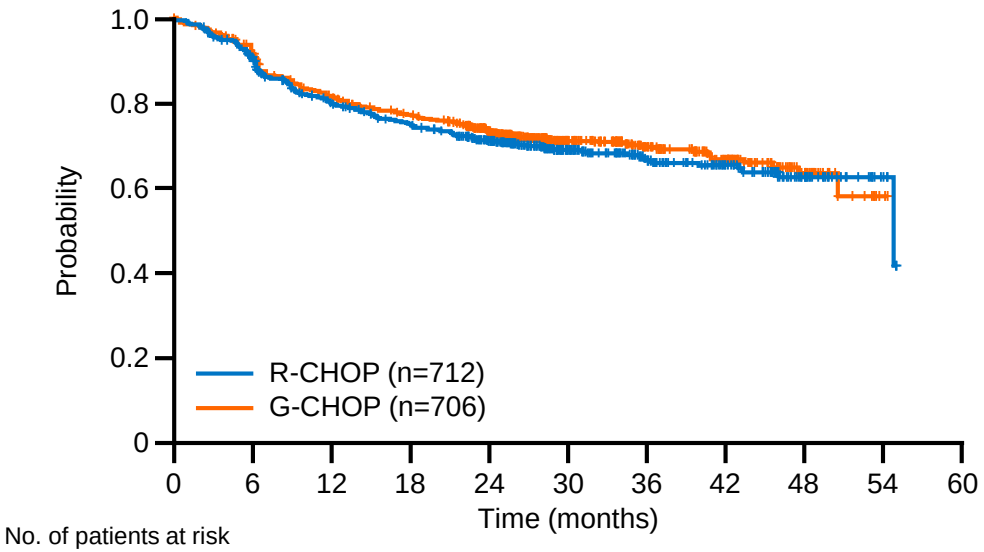
- Posizione di dipendente in aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)
- Consulenza ad aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)
- 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**

DLBCL:
First Line treatment.
RI-CHOP+I

Background and Rationale

GOYA study
Investigator-assessed PFS (primary endpoint)

Kaplan-Meier plot of investigator-assessed PFS by treatment arm



No. of patients at risk

R-CHOP	712	616	527	488	413	227	142	96	41	6
G-CHOP	706	622	540	502	425	240	158	102	39	2

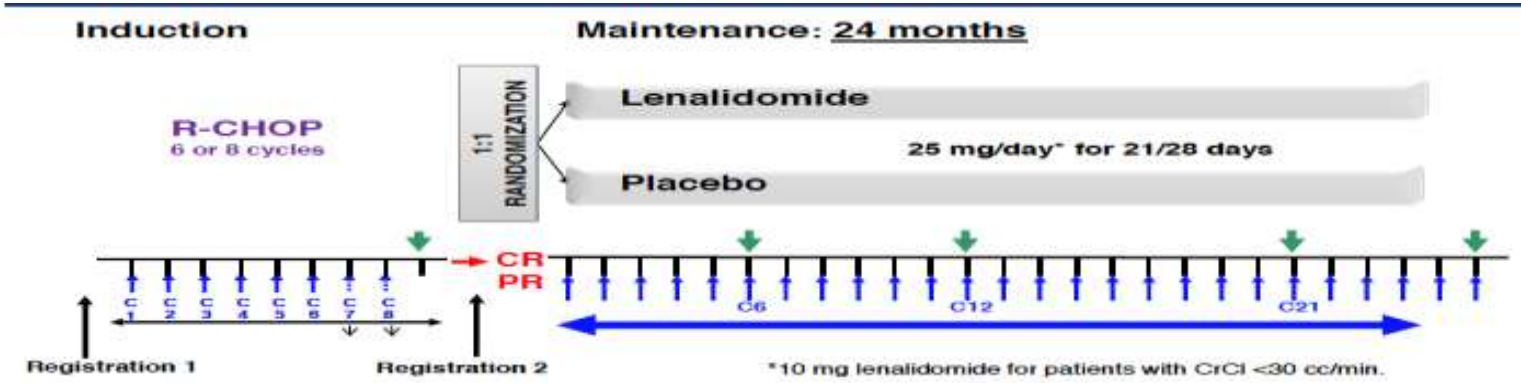
	R-CHOP, n=712	*G-CHOP, n=706*
Pts with event, n (%)	215 (30.2)	201 (28.5)
1-yr PFS, %	79.8	81.6
2-yr PFS, %	71.3	73.4
3-yr PFS, %	66.9	69.6
HR (95% CI), p-value*	0.92 (0.76, 1.11), p=0.3868	

Median follow-up: 29 months

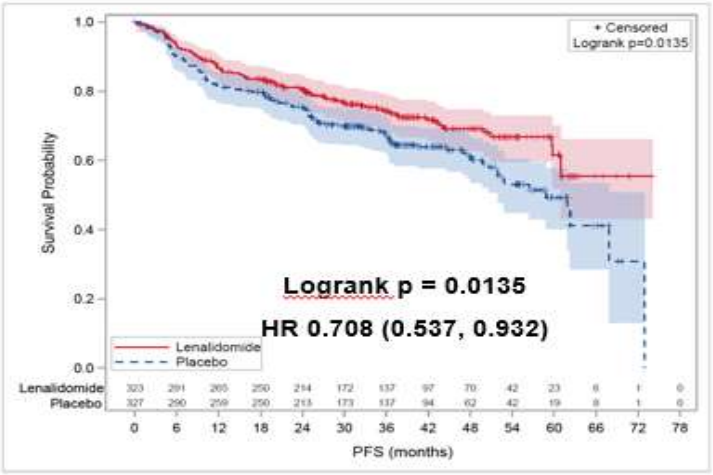
*Stratified analysis; stratification factors: IPI score, number of planned chemotherapy cycles

Vitolo U et al, J Clin Oncol 2017

Background and Rationale



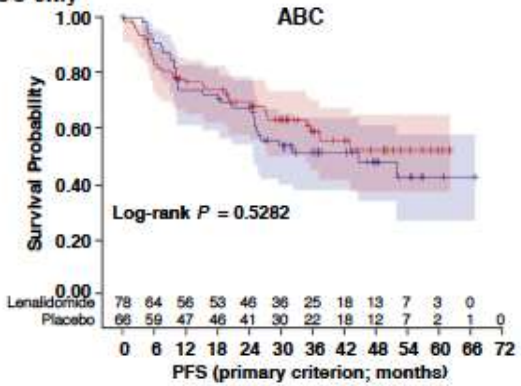
Progression-Free Survival

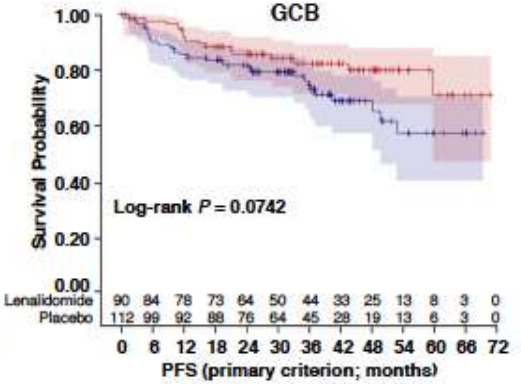


Follow-up of 40 months

REMARC PFS: GCB vs ABC (GEP)

DLBCL NOS only*





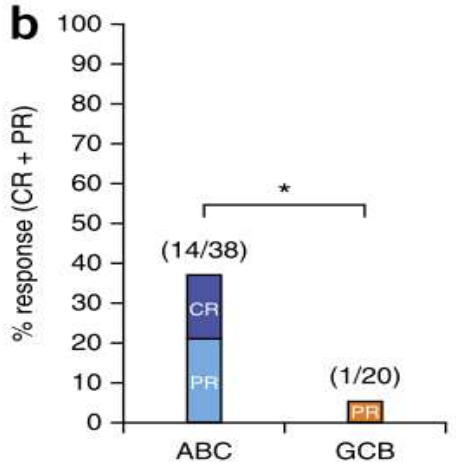
Thieblemont, J Clin Oncol 2017

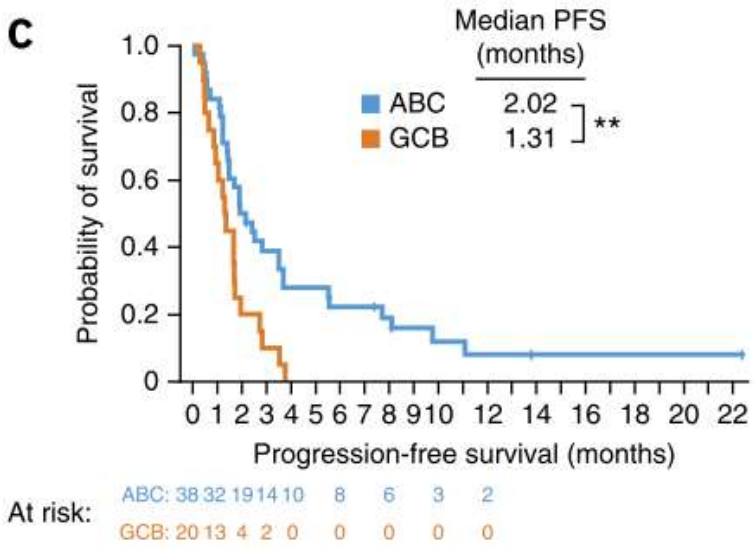
Background and Rationale

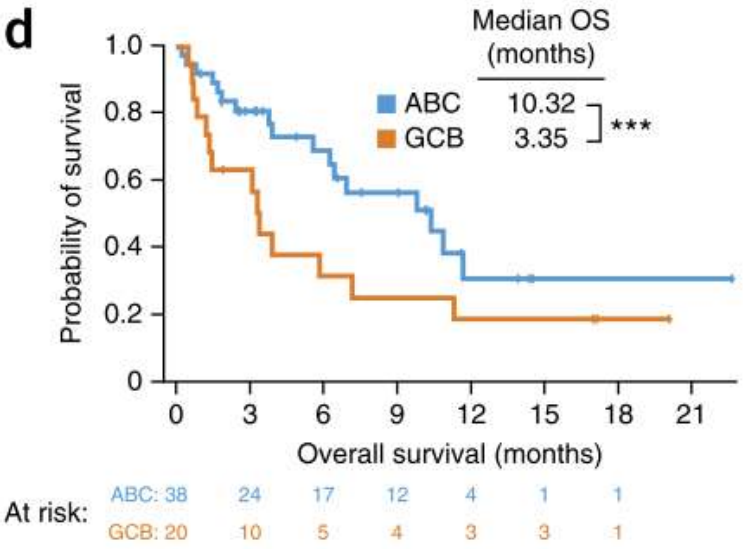
The Bruton's Tyrosine Kinase (BTK) inhibitor, ibrutinib (PCI-32765) has a preferential activity in ABC DLBCL: phase II interim results

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%





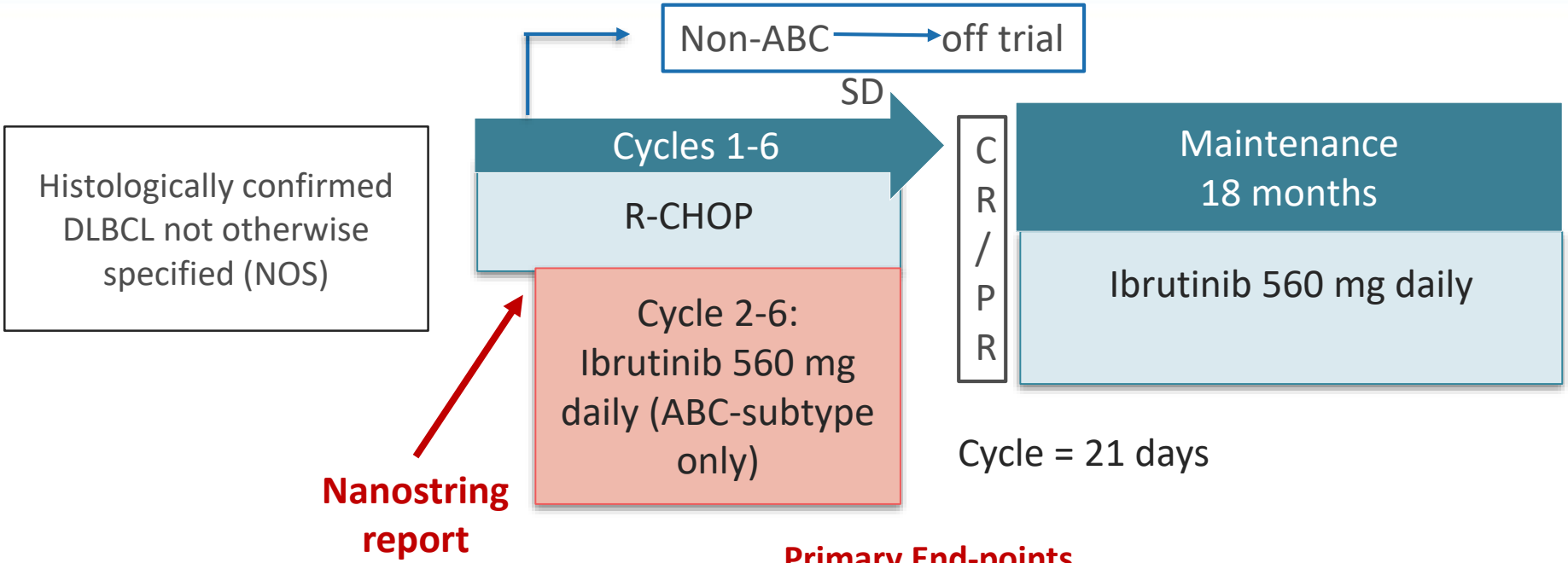


Wilson WH, Nat Med. 2015.

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, at 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

Study design



Subtype eligibility determined by GEP using the NanoString® nCounter® Analysis System.

Analysis performed by Prof S. Pileri.

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.

SAMPLE SIZE: 96 ABC patients in 36 months; roughly 280-400 DLBCL screened.

Eligibility criteria

Key Inclusion Criteria

- Previously untreated, histologically confirmed ABC-type, CD20+ DLBCL
- Measurable disease ≥1.5 cm in longest diameter and in 2 perpendicular directions by CT/MRI
- Age 18-80 years (FIT at CGA)
- International Prognostic Index score ≥2
- Ann arbor stage II-IV
- Normal organ function

Key Exclusion Criteria

- History of other malignancies, unless disease free for ≥5 years
- Evidence of transformed NHL
- Other than ABC-DLBCL
- LVEF <45%
- No CNS involvement
- HIV positivity
- Contraindication to any drug in the chemotherapy regimen

Treatment plan

Rituximab-CHOP x 6 courses every 21 days:

- rituximab 375 mg/sqm iv during the first course on day 0 or day 1 and rituximab 1400 mg sc from cycles 2 to 6 on day 1;
- cyclophosphamide 750 mg/sqm iv on day 1;
- doxorubicin 50 mg/sqm iv on day 1;
- vincristine 1.4 mg/sqm iv (capped at 2 mg) on day 1;
- prednisolone 100 mg per os (or equivalent iv) from day 1 to day 5.

In ABC patients:

- Ibrutinib 560 mg daily per os will be started at day 1 of cycle 2 until the end of induction treatment (Provided free by Janssen-Cilag)

Responsive patients (CR and PR) after induction treatment will proceed to maintenance for 18 months.

Local radiotherapy after study chemotherapy per local practice admitted:

- for the treatment of a particular site of bulky disease (defined as ≥ 7.0 cm) or extranodal masses (bone) or focal residual uptake at final PET.

RI-CHOP+I

LN biopsy + saliva (IEO*) | **PB (Torino**)** | **PB-1** | **PB-4** | **PB-EOI** | **PB**

Maint 12
Maint 24
FU 6 months
FU 12 months
Relapse/progression

N = 97

Key eligibility

- Histologically confirmed DLBCL not otherwise specified (NOS) **ABC subtype defined by GEP nanostring**
- Previously untreated disease
- Age > 18
- IPI score >1 at high risk of relapse
- Ann Arbor stage II–IV disease

Non-ABC → off trial

SD

Cycles 1-6

R-CHOP

Cycle 2-6:
Ibrutinib 560 mg daily
(ABC-subtype only)

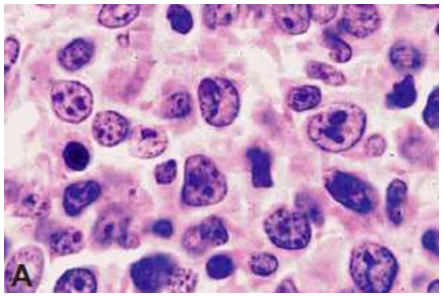
C
R
/
P
R

Maintenance
18 months

Ibrutinib 560 mg daily

Nanostring report

Cycle = 21 days



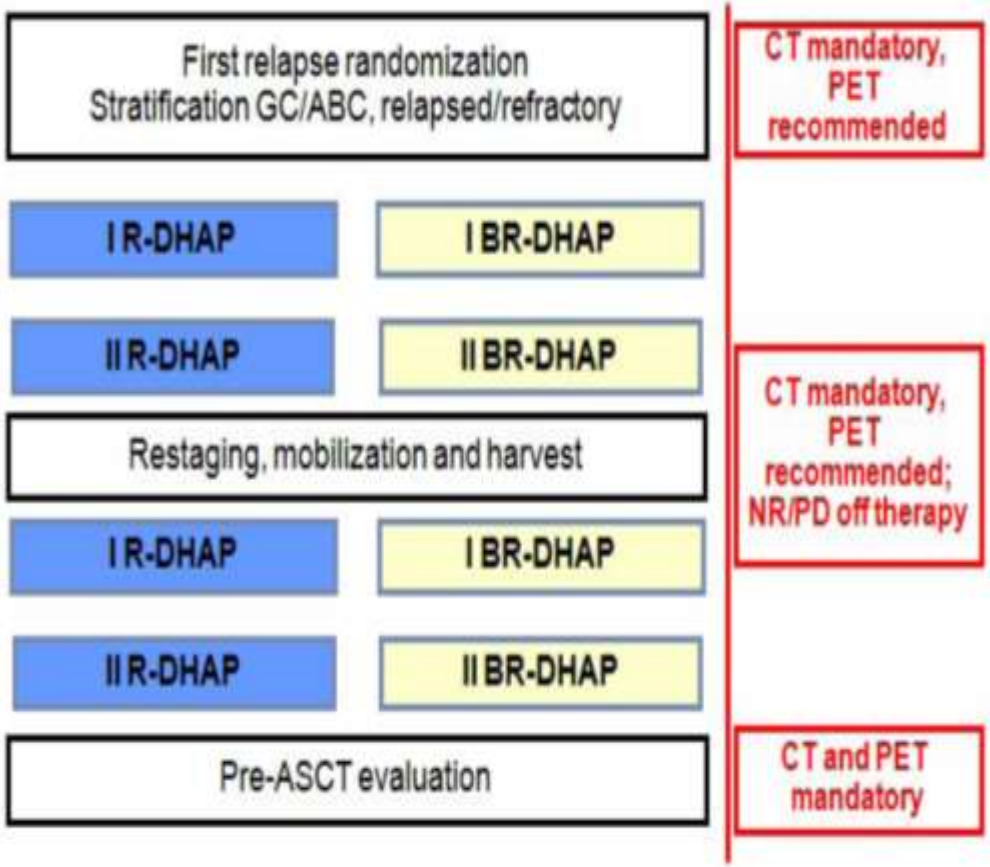
* IEO will share baseline DNA with Torino for MRD marker screening and with Novara for mutational studies
** Torino will perform MRD on plasma and will share cfDNA with Novara for mutational studies

DLBCL:
Second Line treatment.
VERAL12

Relapsed/Refractory DLBCL, 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

PIs: Dr . U. Vitolo, Dr. M. Balzarotti, Dr. A. Chiappella



- Centro Coordinatore:
  SC Ematologia, Città della Salute e della Scienza-Dr. Vitolo
- Data inizio studio: 22/10/2012
- 1. Primary endpoint: Response rate (PET CR)
  2. DLBCL r/r to R-CHOP or G-CHOP
- Ancillary studies: COO, TP53 , genetic profiles of NFkB etc

EMENDAMENTO SOSTANZIALE 2

Approvato dal CE coordinatore il 26/06/2017

Trasmesso a fine settembre per problemi tecnici con OSSC

- ✓ update nuova IB e relative modifiche ai consensi informati;
- ✓ definizione ufficiale del Responsabile delle analisi istopatologiche per la revisione istologica

FIL_VERAL-12

- 16 pazienti

Alessandria	4	Pagani	5
Ancona	4	Parma	7
Aviano	2	Piacenza	1
Brescia Emato	2	Ravenna	3
Cagliari	6	Reggio Calabria	2
Firenze	0	Reggio Emilia	2
Gallarate	2	Rimini-Cattolica	2
Genova	0	Rionero in Vulture	0
Genova San Martino	4	Roma S.Andrea	2
Lecce	0	Rozzano (Milano Humanitas)	10
Meldola	2	Siena	0
Milano INT Emato	4	Terni S.Maria	3
Milano Niguarda	1	Torino Sc Ematologia	6
Novara	3	Torino Univ Emato	8
Padova Onco 1	1	Udine	4

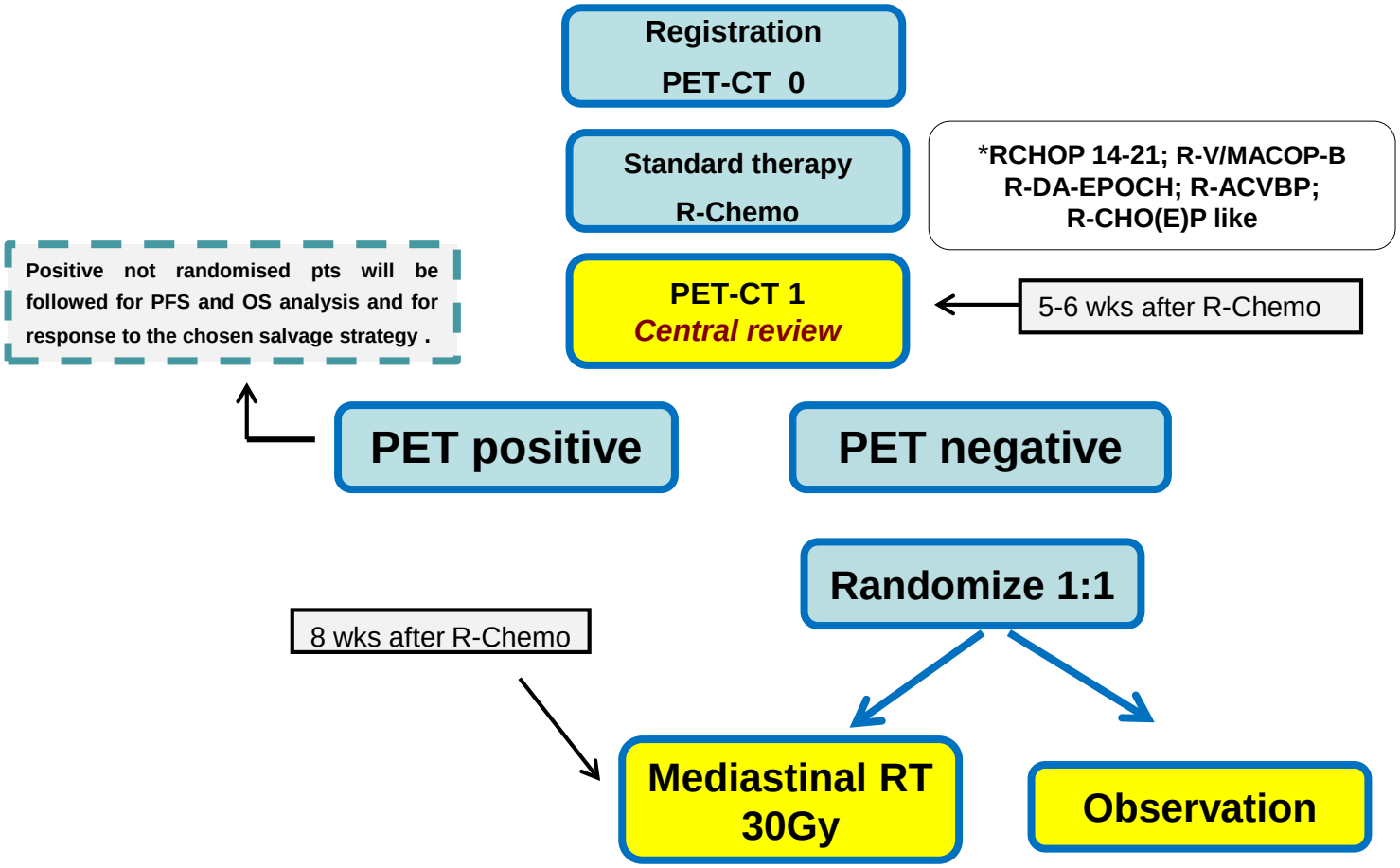
Nuova fine Arruolamento: Aprile 2018

Massimo sforzo per completare il tutto entro fine 2017

Primary Mediastinal B-Cell Lymphoma: First Line treatment. IELSG37

IELSG37

A randomized, open-label, multicentre, two-arm phase III comparative study assessing the role of mediastinal radiotherapy after Rituximab containing chemotherapy regimens to patients with newly diagnosed Primary Mediastinal Large B-Cell Lymphoma (PMLBCL)



- Centro Coordinatore: Università "Sapienza" Roma - Prof. Martelli
- Centri attivi/Centri partecipanti: 51/65
- Centri arruolanti/Centri attivi: 39/51

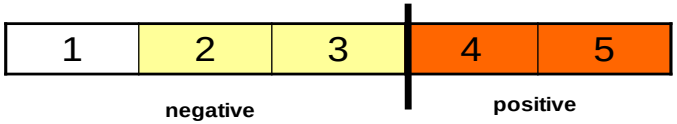
IELSG37,

CENTRAL PET REVIEW AND RANDOMIZATION RESULTS AT OCTOBER 20, 2017

PET-CT response evaluation
visual analysis (Deauville score)

Amendment April 2014
based on IELSG 26 final results

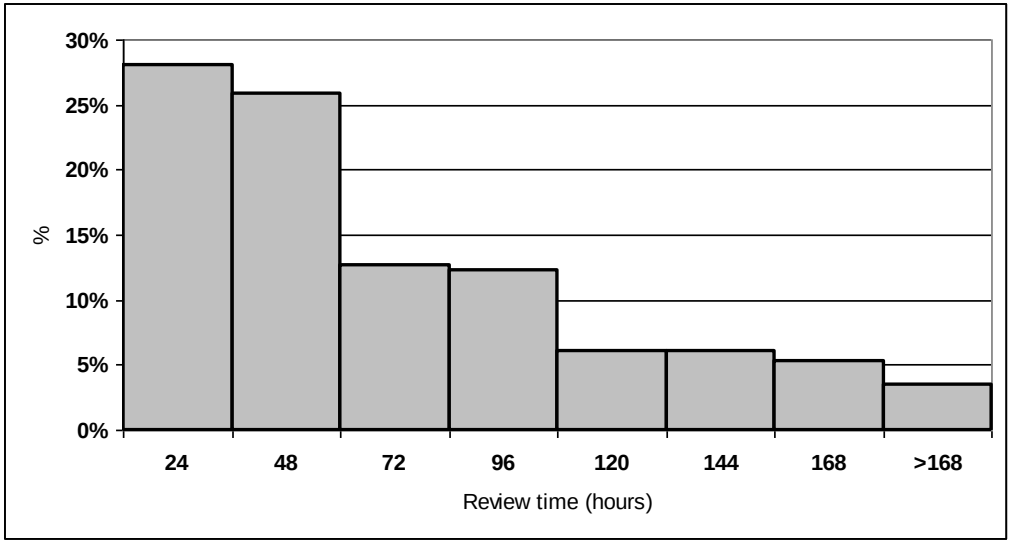
1. No uptake.
2. Uptake ≤ mediastinum.
3. Uptake > mediastinum but ≤ liver.
4. Uptake moderately more than liver uptake, at any site.
5. Markedly increased uptake at any site and new disease sites



liver cut-point

Predicted to improve consensus among PET panel

The median review time was 46 h.

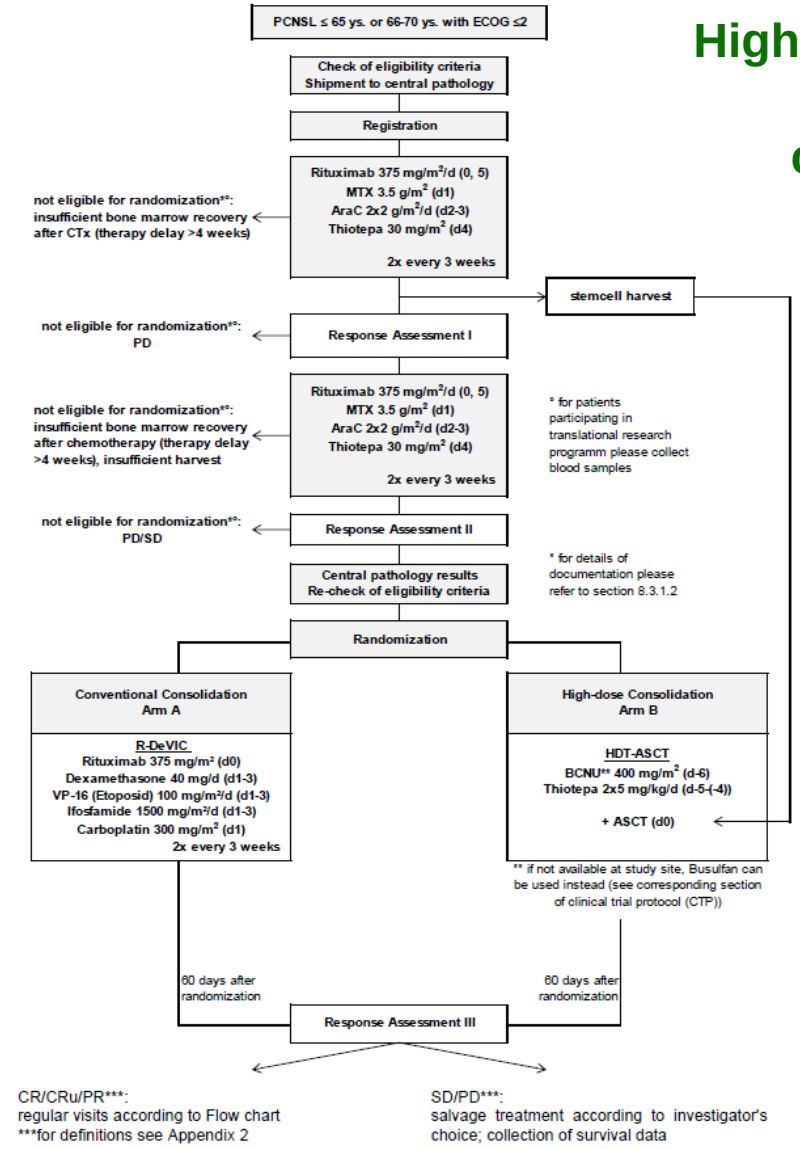


PET NEGATIVE	PET POSITIVE	PET REVIEWED
165 (49.8%)	167 (50.2%)	331

RANDOMIZED Patients	ARM A (Radiotherapy)	ARM B (Observation)
165	82	83

Primary CNS Lymphoma: First Line treatment. IELSG43 - Matrix

IELSG43 MATRIX TRIAL



High-dose chemotherapy and autologous stem cell transplant or consolidating conventional chemotherapy in primary CNS lymphoma - randomized phase III trial

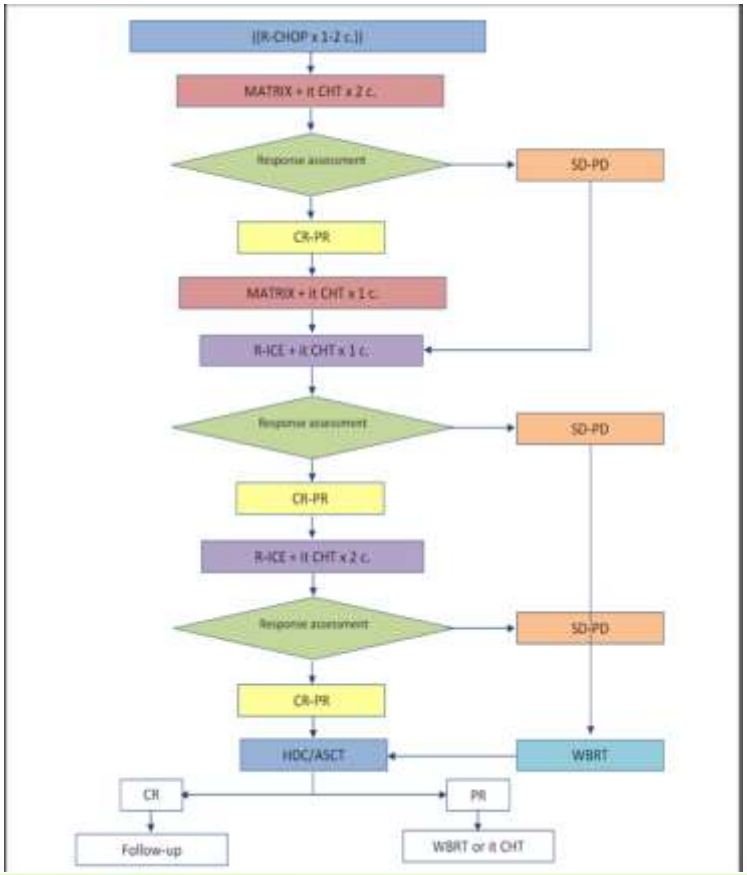
- **PI:** Dr. Andrés Ferreri
- Centri attivi/Centri partecipanti: **14/41**
- Attivazione del primo centro in Italia: **20/12/16**
- **Pareri Favorevoli: 28**
- **Delibere aziendali: 24** (5 centri - Pisa, Roma S. Eugenio, San Giovanni Rotondo, Siena e Tricase (Le) – in via di attivazione, 1 in attesa della firma del contratto)
- **Centri Attivi: 18**
- **Pazienti arruolati: 177/330**

DLBCL with CNS involvement: First or Second Line treatment. IELSG42 - Marietta

IELSG-42 (MARIETTA)

An international phase II trial assessing tolerability and efficacy of sequential Methotrexate-Aracytin-based combination and R-ICE combination, followed by high-dose chemotherapy supported by autologous stem cell transplant, in patients with systemic B-cell lymphoma with central nervous system involvement at diagnosis or relapse (MARIETTA regimen)

PI: Prof. A. J. Ferreri



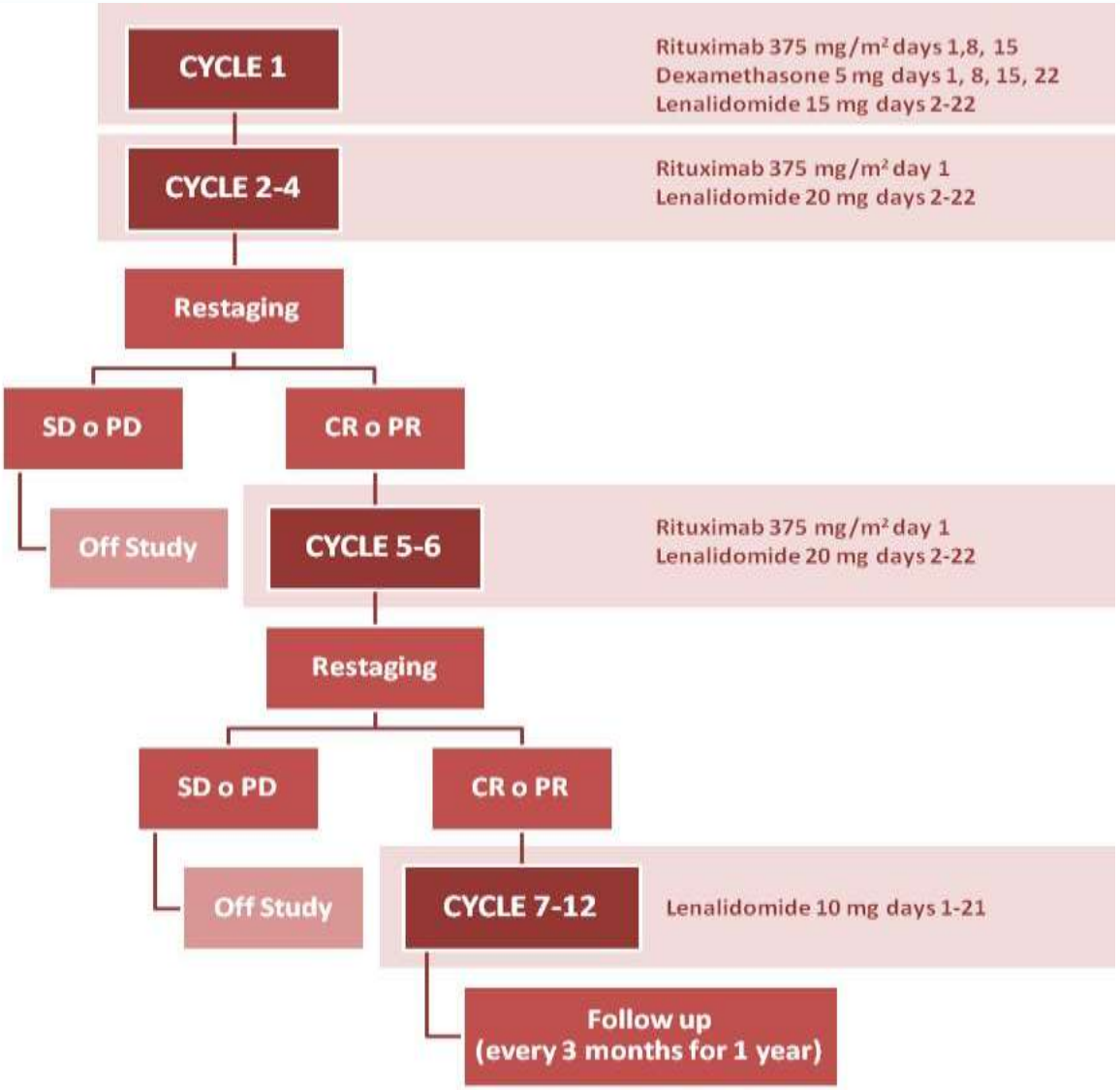
- ***PI: Prof. A. J. Ferreri***
- **Coordinator Site:**
- IRCCS Ospedale San Raffaele - Prof. Ferreri
- **Data Apertura:** Gennaio 2015

- **Inclusion Criteria (partial):**
- Histologically confirmed diagnosis of DLBCL
- CNS involvement at diagnosis (concomitant to extra-CNS disease) or relapse after conventional chemoimmunotherapy
- Diagnosis of CNS involvement either by brain biopsy or CSF cytology examination
- Age 18-70 yrs
- **Primary endpoint**
- 1-year progression-free survival (PFS)
- **Enrolling sites /active sites: 14/27**

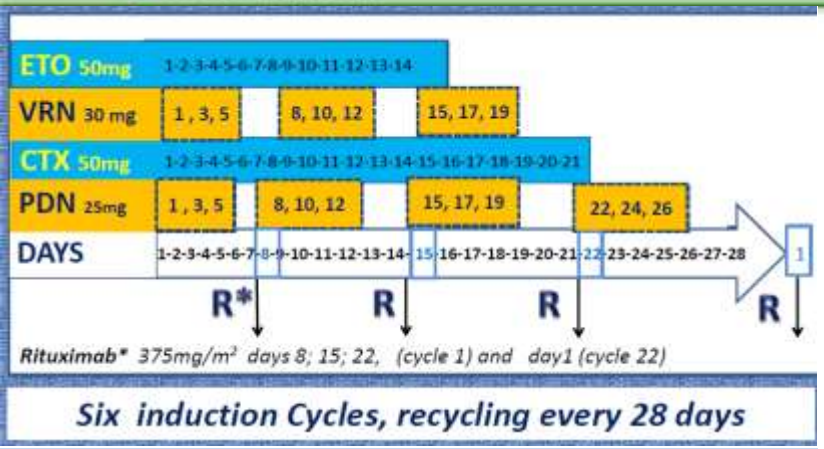
DLBCL:
Elderly Patients

ELDERLY DLBCL

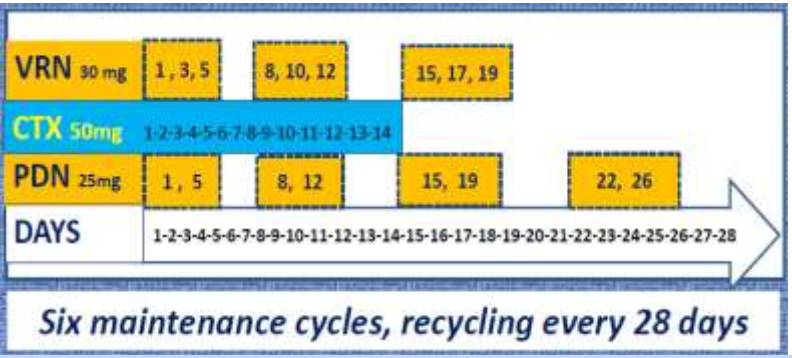
A combination of Lenalidomide and Rituximab as front line therapy for the treatment of elderly frail patients evaluated in CGA with diffuse large B-cells non-Hodgkin's lymphoma. PIs: Guido Gini, Stefano Luminari



A Phase II study of Metronomic Chemotherapy in Elderly Non-FIT patients ≥ 65 years with Aggressive B-Cell Lymphomas (DEVEC). PI: Maria Cristina Cox



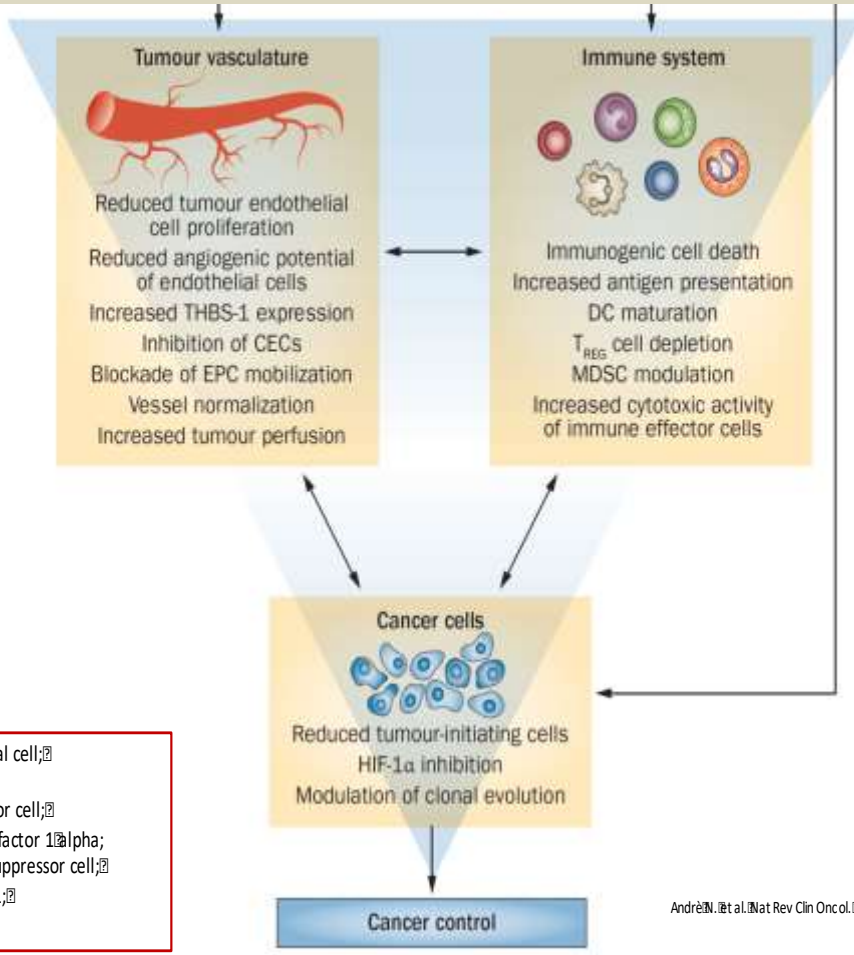
INDUZIONE
- ETOPOSIDE, CICLOFOSFAMIDE, VINORELBINA
- PREDNISONE
- +/-RITUXIMAB



MANTENIMENTO
- CICLOFOSFAMIDE, VINORELBINA, PREDNISONE

CEC, circulating endothelial cell;
DC, dendritic cell;
EPC, endothelial progenitor cell;
HIF-1α, hypoxia inducible factor 1 alpha;
MDSC, myeloid-derived suppressor cell;
THBS-1, thrombospondin 1;
T^{REG}, regulatory T cell.

M-CHT is a Multitarget Therapy



André N. et al. Nat Rev Clin Oncol. 2014

AKNOWLEDGMENTS

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Aggressive Lymphoma Committee

Uffici Studi FIL

Data Manager Office Torino

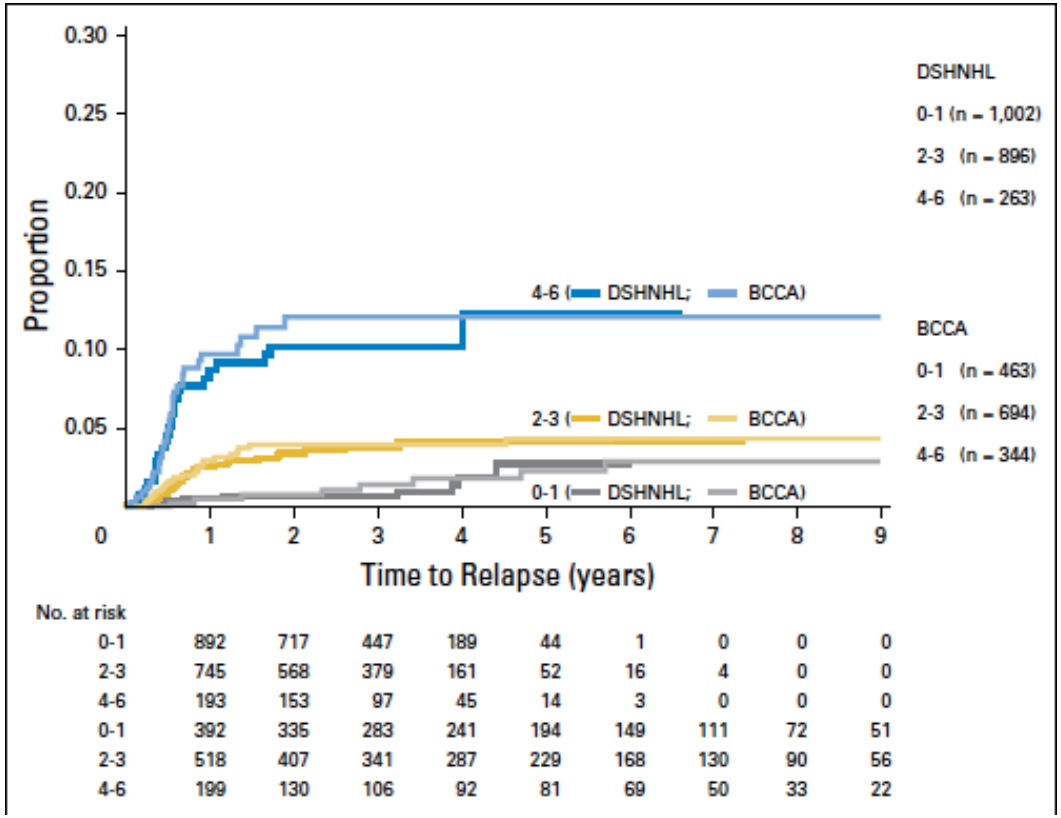
Pathological and Biological Team

FIL Biostatistics

BACK-UP

DLBCL: CNS-IPI

CNS-IPI



CNS-IPI

1 point for:

Age, y > 60

LDH > normal

ECOG Performance status >1

Ann Arbor stage III -IV

Extranodal disease >1

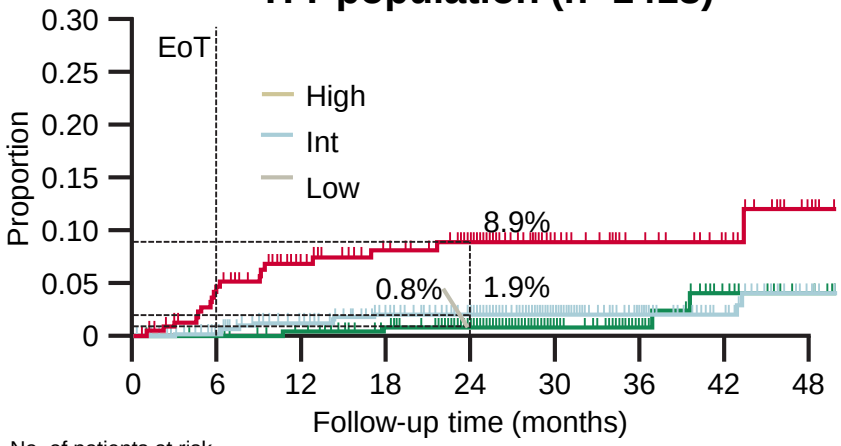
Kidney and/or adrenal gland involvement

Three distinct risk groups: low (L, 0-1 pt), intermediate (I, 2-3 pts), high (H, 4-5-6 pts).

Schmitz N et al, J Clin Oncol 2016

RISK OF CNS RELAPSE BY CNS IPI

Risk of CNS relapse by CNS IPI, ITT population (n=1418)



No. of patients at risk

High	245	192	150	132	113	65	45	35	14
Int	894	783	668	623	529	299	186	118	48
Low	279	263	249	235	196	104	69	46	18

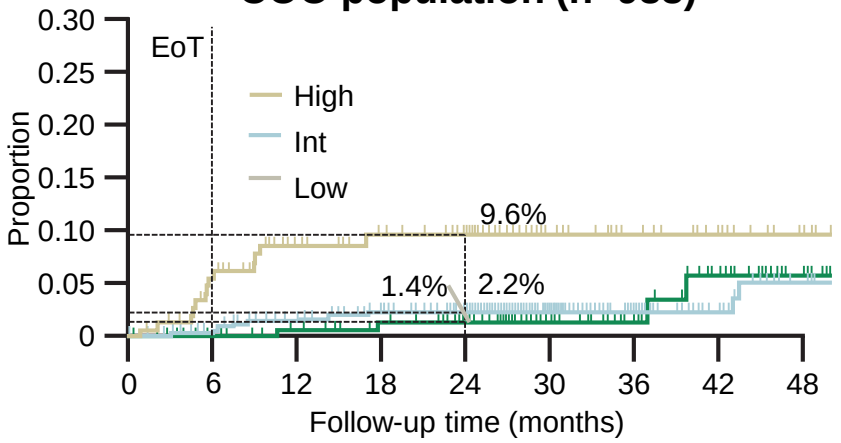
2-year CNS relapse rates:

H-R (n=245, 17.3%): **8.9%** (95% CI: 4.7–12.9)

I-R (n=894, 63.0%): **1.9%** (95% CI: 0.9–2.9)

L-R (n=279, 19.7%): **0.8%** (95% CI: 0.0–1.9)

Risk of CNS relapse by CNS IPI, COO population (n=933)



No. of patients at risk

High	165	130	100	91	78	48	36	28	13
Int	596	527	454	430	374	223	145	90	38
Low	172	160	148	141	122	78	52	36	12

2-year CNS relapse rates:

H-R (n=165, 17.7%): **9.6%** (95% CI: 4.5–14.5)

I-R (n=596, 63.9%): **2.2%** (95% CI: 0.9–3.5)

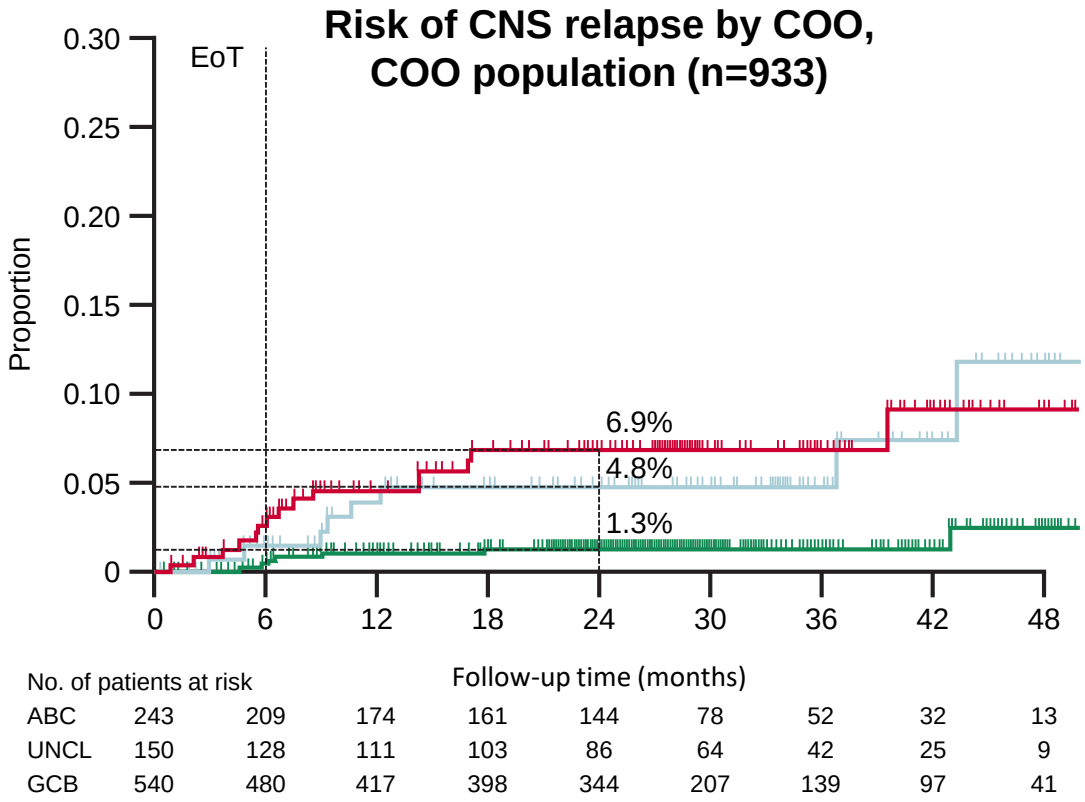
L-R (n=172, 18.4%): **1.4%** (95% CI: 0.0–3.2)

Patients with high CNS IPI had a significantly higher risk of CNS relapse compared with those with intermediate/low CNS IPI

EoT, end of treatment; H-R, high risk; I-R, intermediate risk; L-R, low risk

Sehn et al, ICML 2017

RISK OF CNS RELAPSE BY COO



2-year CNS relapse rates:

ABC (n=243, 26.0%): **6.9%**

UNCL (n=150, 16.1%): **4.8%**

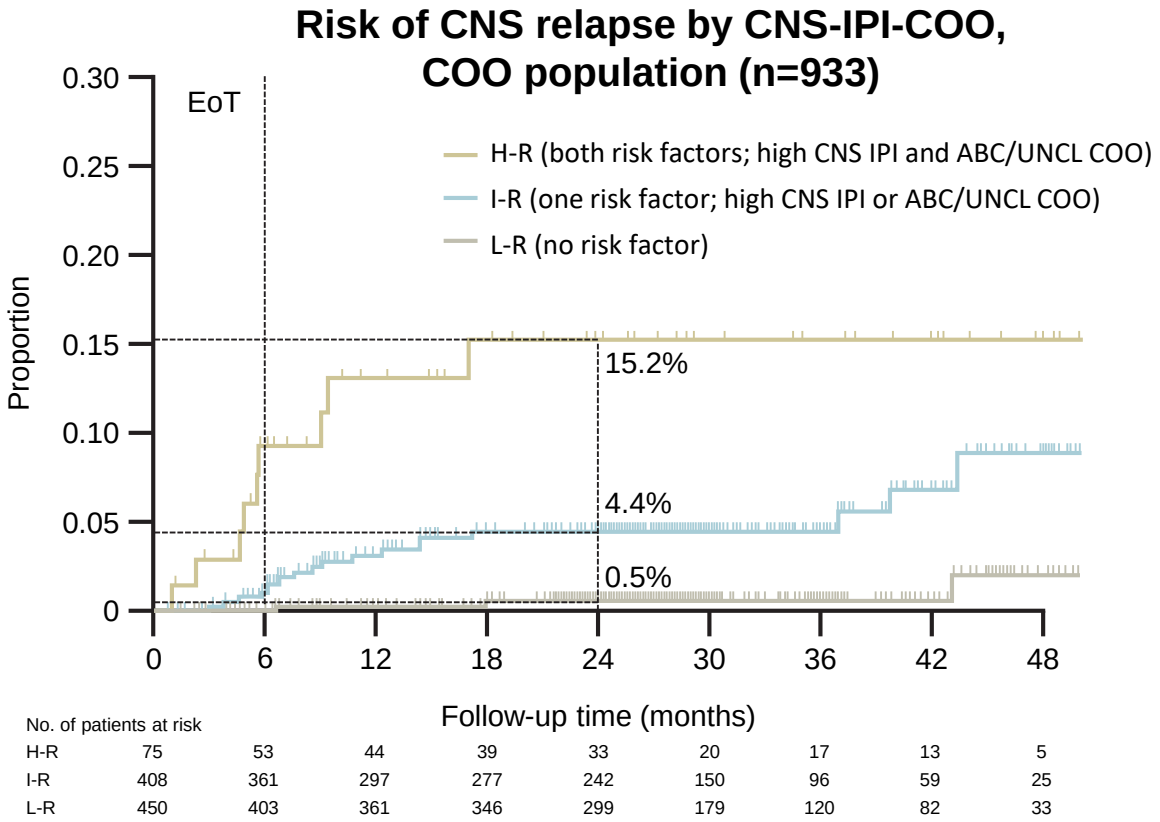
GCB (n=540, 57.9%): **1.3%**

Patients with ABC and unclassified subtypes had a significantly higher risk of CNS relapse compared with GCB DLBCL

ABC, activated B-cell; GCB, germinal centre B-cell; UNCL, unclassified

Sehn et al, ICML 2017

COO COMBINED WITH CNS IPI (CNS-IPI-COO) IMPROVES IDENTIFICATION OF DLBCL PATIENTS WITH HIGH CNS RELAPSE RISK



CNS IPI	n (%)	2-year relapse rate	n (%)	2-year relapse rate
	CNS IPI		*CNS-IPI-COO*	
H-R	165 (17.7%)	**9.6%**	75 (8.0%)	**15.2%**
I-R	596 (63.9%)	**2.2%**	408 (43.7%)	**4.4%**
L-R	172 (18.4%)	**1.4%**	450 (48.2%)	**0.5%**

Sehn et al, ICML 2017

IELSG45 FIORELLA TRIAL

Randomized Phase II Trial on Fitness- and Comorbidity- Tailored Treatment in Elderly Patients with Newly Diagnosed Primary CNS Lymphoma (FIORELLA Trial)

PROSSIMA APERTURA

- **Coordinator Site:**
- IRCCS Ospedale San Raffaele - Prof. Ferreri
- **Inclusion Criteria (partial):**

•- Histologically or cytologically assessed diagnosis of CD20+ diffuse large B-cell lymphoma exclusively localized in the central nervous system - **Age ≥70 years**

•- **Patients not eligible for high-dose chemotherapy supported by autologous stem cell transplant**

•- ECOG PS ≤3.

- **Primary endpoint**

2-year progression-free survival (PFS

- **Estimated enrolling pts: 208** who will be stratified according to their suitability to tolerate an induction chemo-immunotherapy regimen containing high-dose methotrexate.