FONDAZIONE ITALIANA LINFOMI

Protocolli della FIL

Linfomi aggressivi dell'anziano

Federica Cavallo, MD, PhD

Dipartimento di Biotecnologie Molecolari e Scienze per la Salute

Divisione di Ematologia dell'Università di Torino

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

“Definition and Validation of the New Elderly Prognostic Index (EPI) for Elderly Patients with Diffuse Large B-Cell Lymphoma Integrating Geriatric and Clinical Assessment: Results of the Prospective “Elderly Project” on 1353 Patients by the Fondazione Italiana Linfomi”

M.Spina, *F.Merli, B.Puccini, F.Cavallo, M.G.Cabras, A.Fabbri, F.Angrilli, VR.Zilioli, D.Marino, M.Balzarotti, M.Ladetto, MC.Cox, L.Petrucci, A.Arcari, G.Gini, A.Chiappella, S.Hohaus, G.Musuraca, M.Merli, R.Sartori, L.Nassi, M.Tani, F.Re, L.Flenghi, AL.Molinari, S.Kovalchuk, C.Bottelli, S.Ferrero, D.Dessì, E.Cencini, E.Pennese, V.Tabanelli, L.Marcheselli, C.Mammi, S.Luminari and A.Tucci.*

61st ASH Annual Meeting and Exposition
December 7-10, 2019
Orlando, FL

Elderly Project: Methods

- Study design: prospective, multicentre, observational
- Inclusion Criteria:
  - Untreated de novo DLBCL
  - Age ≥65 years
  - sCGA performed at diagnosis
- Primary Endpoint: OS

	FIT	UNFIT	FRAIL
ADL	6	5*	≤4*
IADL	8	7- 6*	≤5*
CIRS	0 score = 3-4 < 5 score = 2	0 score = 3-4 5-8 score = 2	1 score = 3-4 > 8 score = 2
AGE		**≥ 80 fit**	**≥ 80 unfit**

* Number of residual functions

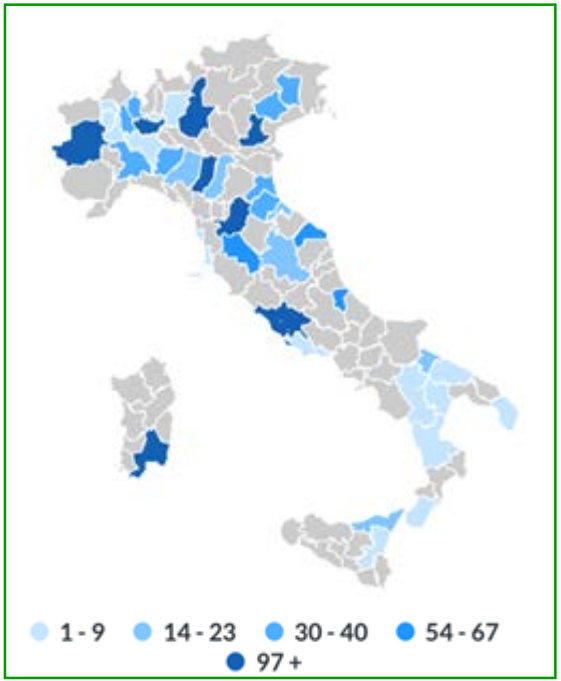
- Treatment choice was independent from sCGA results
- According to anthracycline doses, treatment was classified as:
  - full dose (≥70%)
  - intermediate (<70%)
  - no anthracycline

Spina M. et al, 15-ICML, Lugano 2019

Elderly Project: Clinical Characteristics and sCGA

Enrollment period: Dec 2013 – Dec 2017

- **37 Italian centres**
- **1353 patients (1207 eligible)**



	N. (%)
Age (median) [range]	76 [65-94]
Gender (male)	609 (50%)
IPI (3-5) [N=1102]	612 (56%)

Fitness Status by sCGA

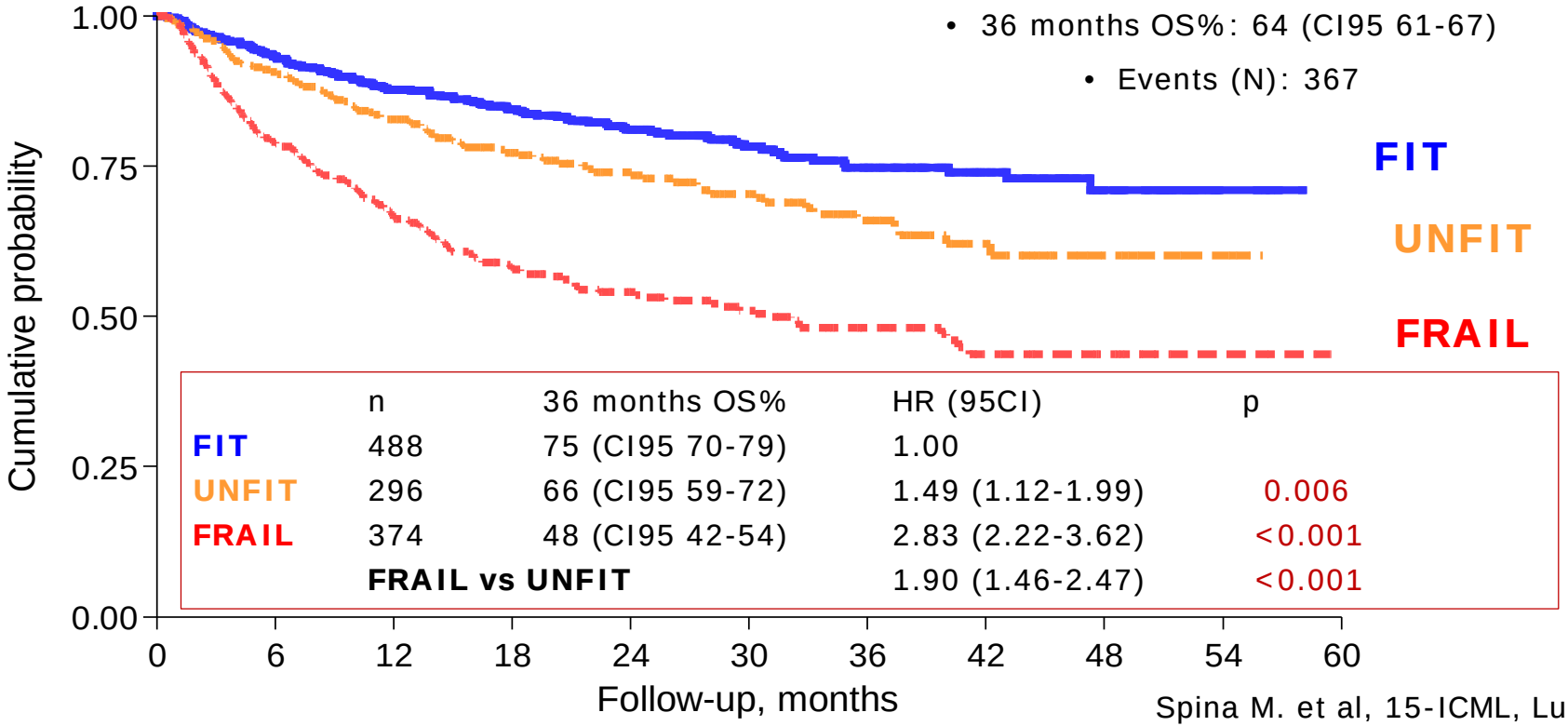
	N. (%)
FIT	520 (43%)
UNFIT	300 (25%)
FRAIL	387 (32%)
Total	1207 (100%)

Spina M. et al, 15-ICML, Lugano 2019

Aim 1: sCGA Validation

Overall Survival by Fitness Status (N=1163/1207)

- Median follow-up: 30 months (95CI 29-31) [range 1-59 months]
- 36 months OS%: 64 (CI95 61-67)
- Events (N): 367

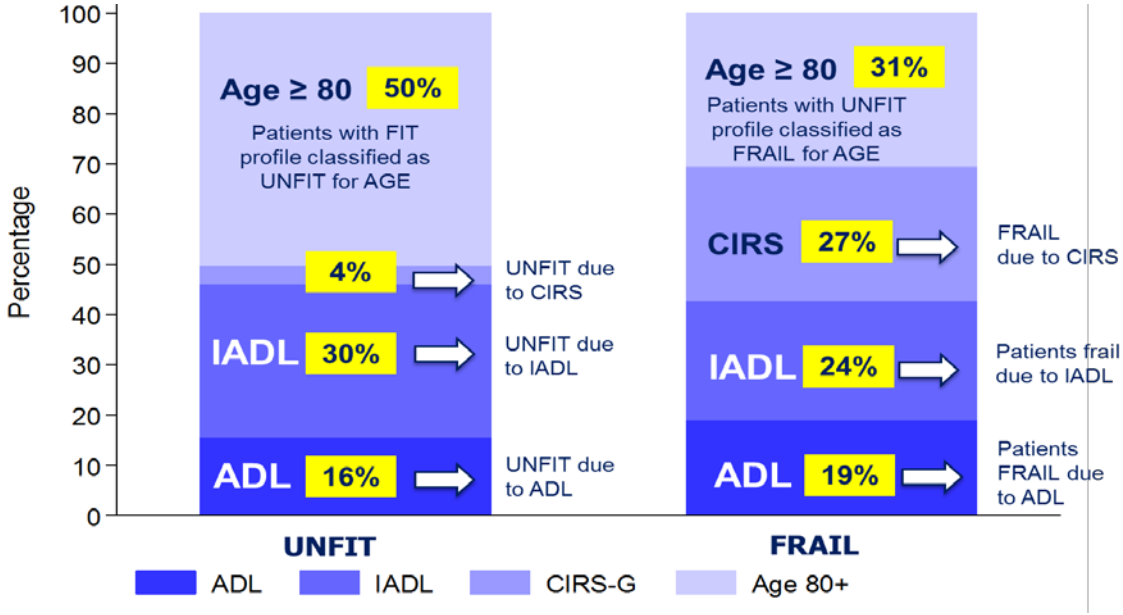


	n	36 months OS%	HR (95CI)	p
FIT	488	75 (CI95 70-79)	1.00	
UNFIT	296	66 (CI95 59-72)	1.49 (1.12-1.99)	0.006
FRAIL	374	48 (CI95 42-54)	2.83 (2.22-3.62)	<0.001
	FRAIL vs UNFIT		1.90 (1.46-2.47)	<0.001

Spina M. et al, 15-ICML, Lugano 2019

Aim 2: Prognostic Assessment

- In our study age ≥ 80 was a cut off to define non-fit patients
- However in our “real life” study a significant proportion of 80yo+ did not have a limitation in ADL/IADL or comorbidities



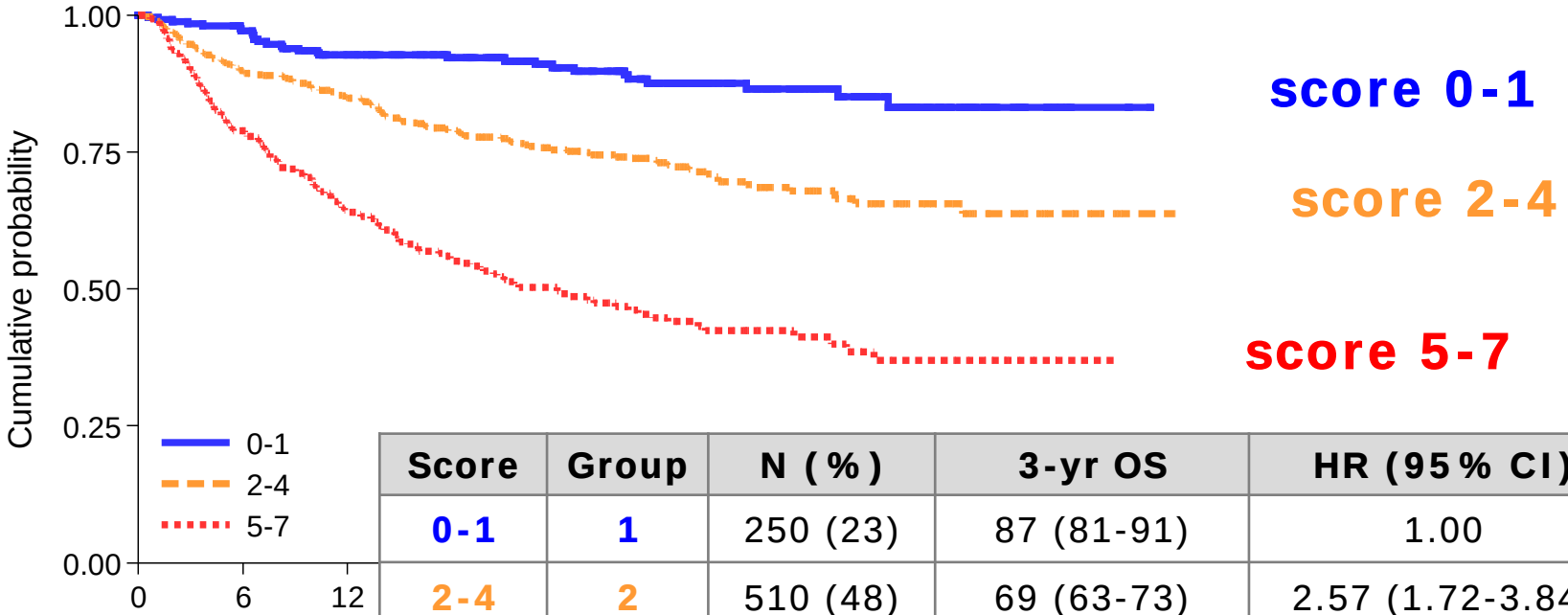
Overall Survival – Multivariable Cox PH model

		HR	95CI	p
sCGA Group1 [FIT – UNFIT<80]		1.00		
sCGA Group2 [UNFIT >80-FRAIL<80]		1.93	1.49-2.50	<0.001
sCGA Group3 [FRAIL, age 80+]		2.74	2.07-3.62	<0.001
IPI 1		1.00		
IPI 2		1.55	0.99-2.44	0.055
IPI 3-5		2.90	1.93-4.35	<0.001
Hb < 12 g/dL		1.28	1.02-1.60	0.033

*weight considering the z-value of Cox PH model

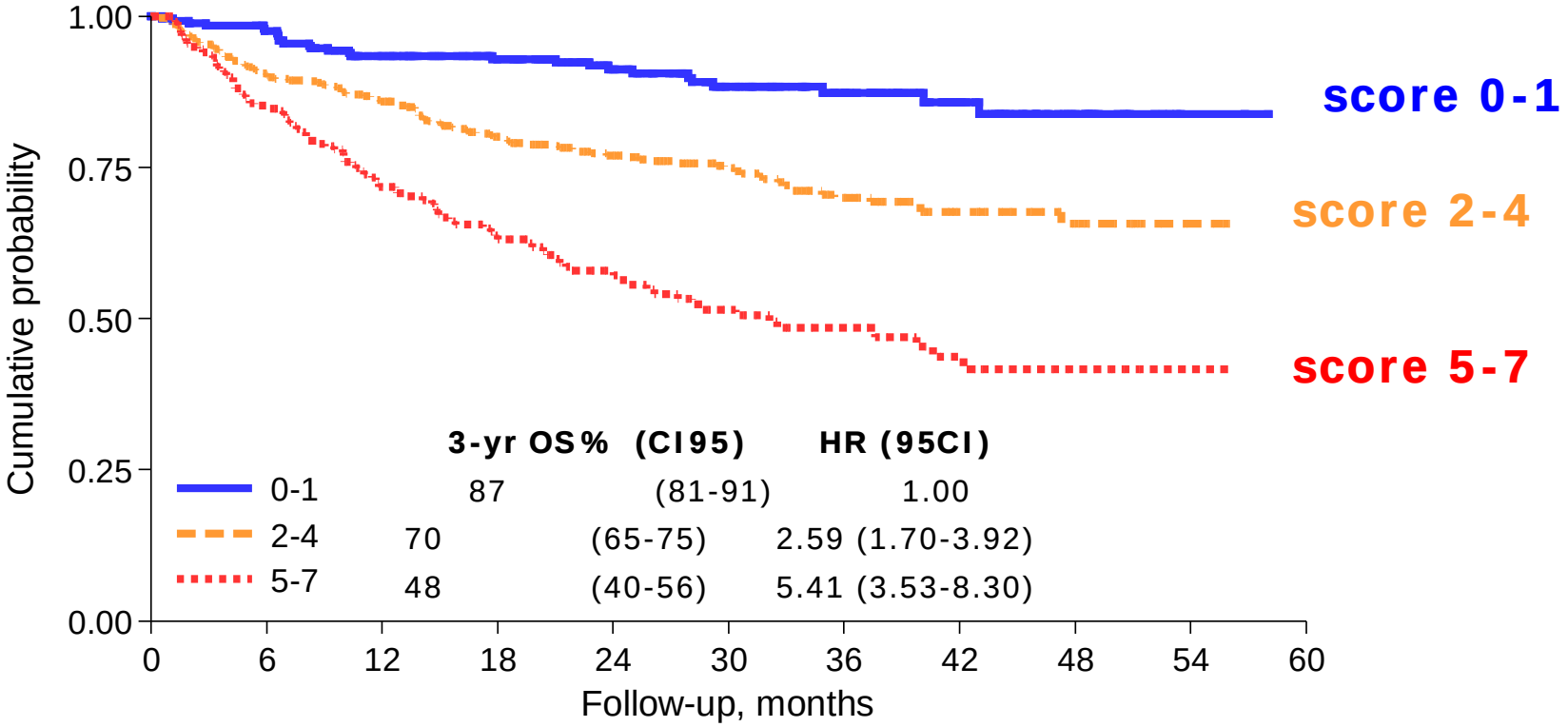
OS by Elderly Prognostic Index - EPI

Median FU: 30 months (range 1-59)
Events (N): 317



Score	Group	N (%)	3-yr OS	HR (95% CI)
0-1	1	250 (23)	87 (81-91)	1.00
2-4	2	510 (48)	69 (63-73)	2.57 (1.72-3.84)
5-7	3	305 (29)	42 (36-49)	6.21 (4.17-9.25)
		1065	Group 3 vs 2	2.41 (1.91-3.05)

OS by EPI in patients treated with anthracycline containing regimen (1016 patients)



Conclusions

- sCGA is a validated tool to predict overall survival of elderly patients with DLBCL (also for patients treated with anthracycline containing regimens)
- EPI is the first index that integrates geriatric assessment with clinical features identifying 3 risk groups with significant differences in terms of OS
- EPI could contribute to improve the management and clinical research in elderly patients with DLBCL

Protocolli Linfomi aggressivi dell’anziano

ReRi

DEVEC

Rec_Anz

FIL_ReRi

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 Lymphoma. A phase II study of the Fondazione Italiana Linfomi.

PI: Guido Gini (Ancona)
Stefano Luminari (Reggio Emilia)

Objectives

scale	FIT	UNFIT	FRAIL
ADL	6	5*	≤ 4
IADL	8	7-6*	≤ 5
CIRS	0 score=3-4 ≤ 5 score=2	0 score=3-4 5-8 score=2	1 score=3-4 > 8 score=2
Age		≥ 80 fit	≥ 80 unfit

*number of residual functions

Mancanza di valide alternative terapeutiche nei pz anziani fragili con DLBCL non candidabili a terapia standard con R CHOP

Dimostrata attività di Lenalidomide ± Rituximab in DLBCL R/R

Objectives

- **Primary**: To evaluate the efficacy and the safety of the R2 (Lenalidomide + Rituximab) combination in first line DLBCL patients not candidate for the standard R-CHOP (or R-CHOP like) treatments due to frail status.

  The efficacy will be measured as overall response rate.

  The safety will be measured as rate of the extra-hematologic AEs of WHO grade 3-4.

- **Secondaries**:
  - Complete Response Rate (CRR)
  - Progression-Free Survival (PFS)
  - Overall Survival (OS)
  - Event-Free Survival (EFS)
  - Drop-out rate
  - Rate of treatment discontinuation due to AE or treatment intolerance
  - QoL (baseline, 4, 6, 12 months by EORTC-QLQ-C30 and FACT-Lym questionnaires)
  - Hematologic adverse events of any WHO grade.

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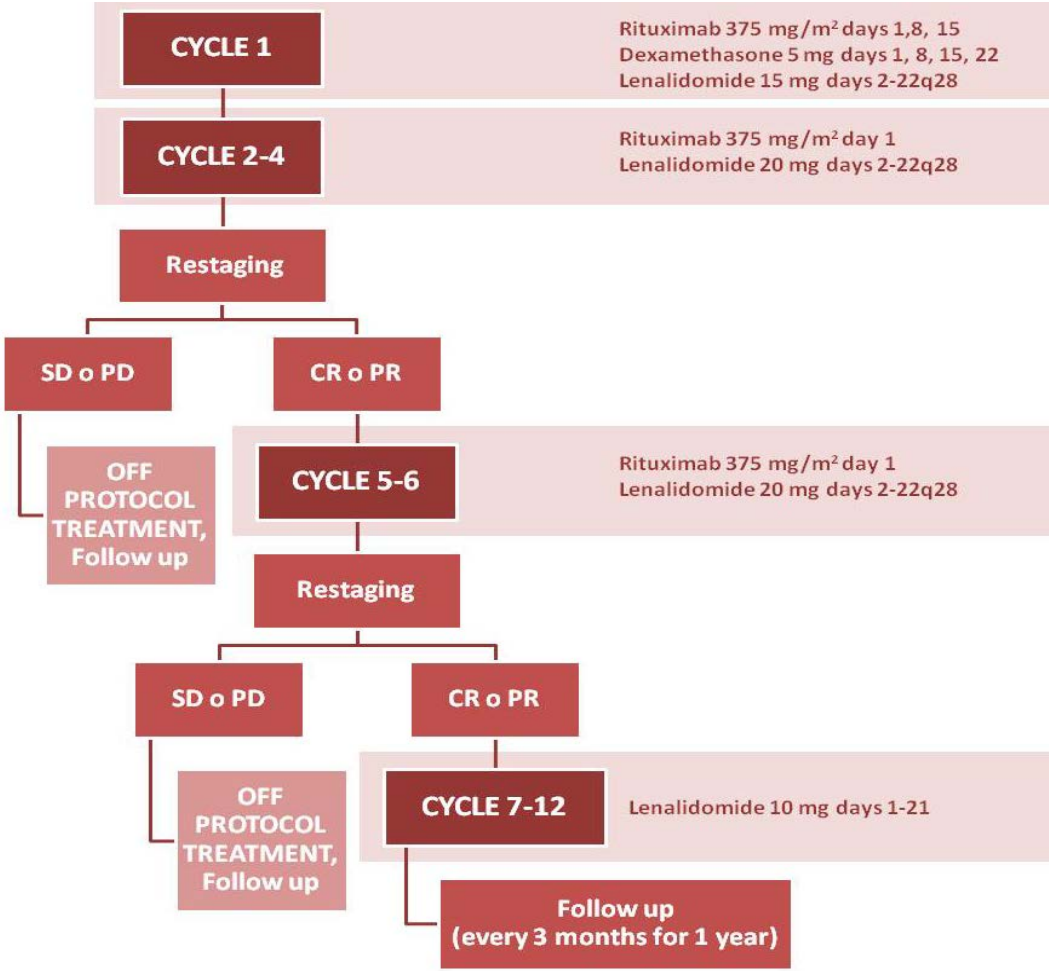

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Criteri di arruolamento

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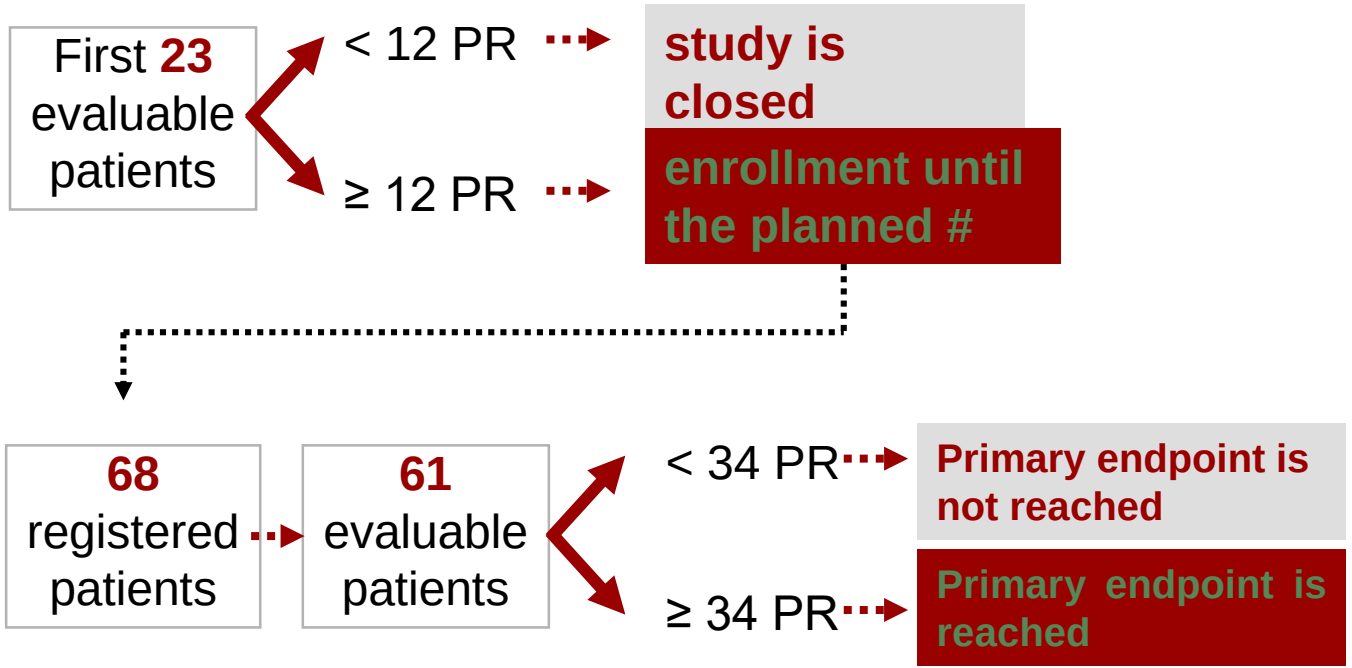
- **DLBCL CD20+**
- **Età ≥ 70 anni**
- **No precedenti trattamenti**
- **FRAIL secondo CGA**
- **Stadio I-IV**
- ECOG 0-3
- Hb > 10 g/dl, GB > 2000/mmc con GN> 1000, PLT > 75000/mmc
- Clearance crea ≥ 10 ml/min
- Aspettativa di vita > 6 mesi

- **HBsAg +** (OK antiHBc+ profilassati)
- **Infezione attiva da HZV**
- **HIV+**
- **HCV RNA+**
- **Assenza di caregiver per pz non autonomi**
- Coinvolgimento SNC
- Neoplasie maligne nei 5 anni precedenti
- Cardiopatia severa (NYHA III-IV)
- AST/ALT > 2 x UNL
- Bilirubina > 2 mg/dl
- Clearance Crea < 10 ml/min

Statistical considerations - efficacy

according to Simon Optimal 2-stage design



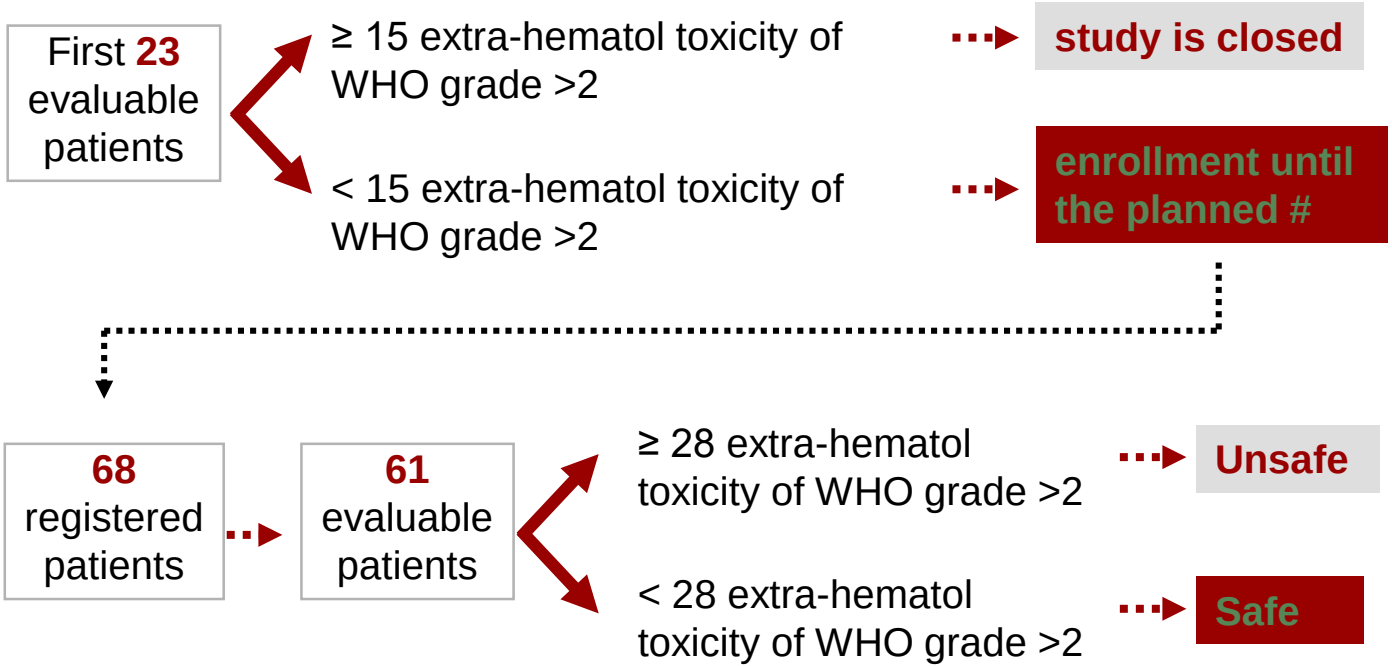
Efficacy evaluation:

Table 3. Response attained in the 24 patients after treatment with ReRi

Response	N	%	95% CI
CR	4	17	5-37
PR	8	33	16-55
ORR	12	50	29-71
SD	2	8	1-27
PD	3	12	3-32
AE/Dead	7	29	13-51

Statistical considerations - safety

according to Ray and Rai method

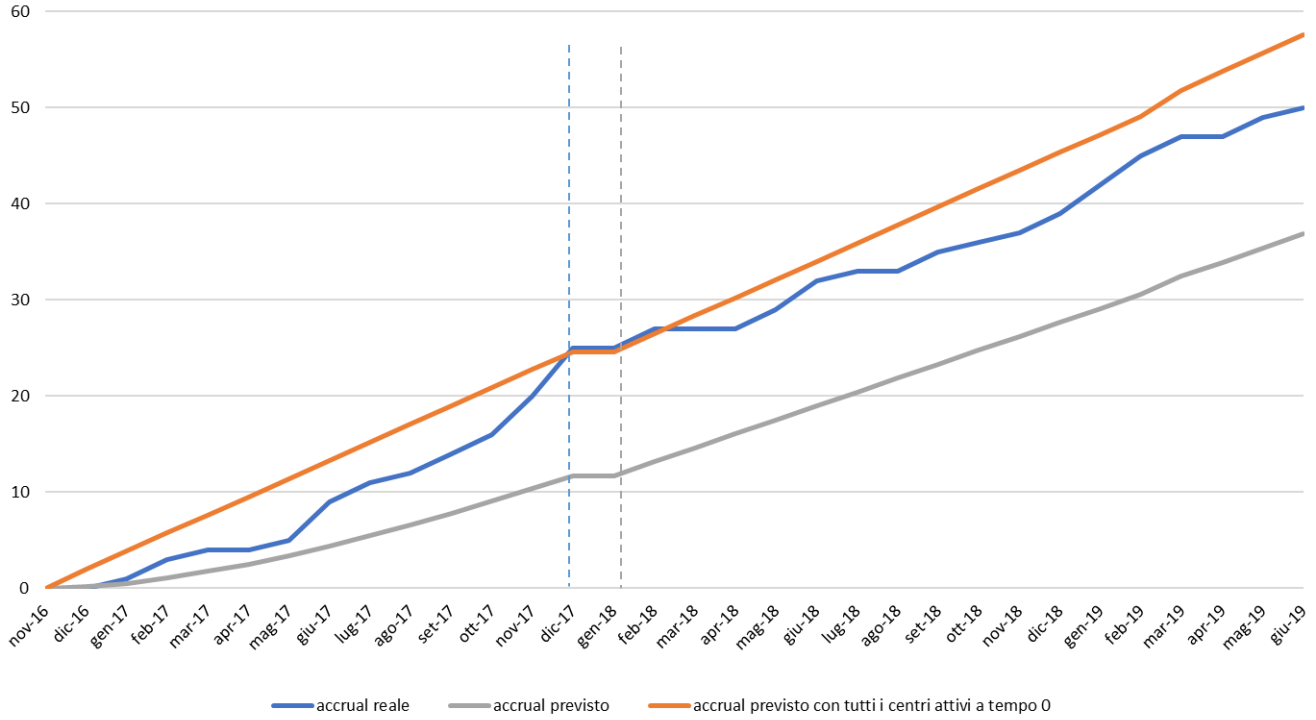


ID	Cause of death	Month from registration
0001	Progression	1.6
0003	Progression	0.9
0009	Progression	6.8
0011	Lung metastasis from renal carcinoma	4.1
0014	Progression	2.7
0017	Visceral arteria ischemia	4.4
0034	Viral infection	2.4
0035	Bowel infarction	2.7
0026	Pulmonary embolism	8.0

Lo studio ha superato l'analisi ad interim (ORR>11 e CTCAE>2 extranodali<15).

Arruolamento

- **50** pazienti arruolati al 12/11/2019



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FIL_DEVEC

A phase II study of metronomic chemotherapy in elderly non-FIT patients (>65 years) with aggressive B-cell lymphomas

PI: Maria Christina Cox (Roma)
Francesco Merli (Reggio Emilia)

Caratteristiche dei pazienti

- Età > 65 anni
- Linfoma aggressivo a cellule B
- Pazienti UNFIT/FRAIL in (prima o seconda) recidiva o progressione
- Pazienti SUPERFRAIL in prima linea

Obiettivi primari

- Attività e Sicurezza della combinazione DEVEC

Sample Size: 55 [21 pazienti (stadio 1) + 34 pazienti (stadio 2)]

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Flow chart

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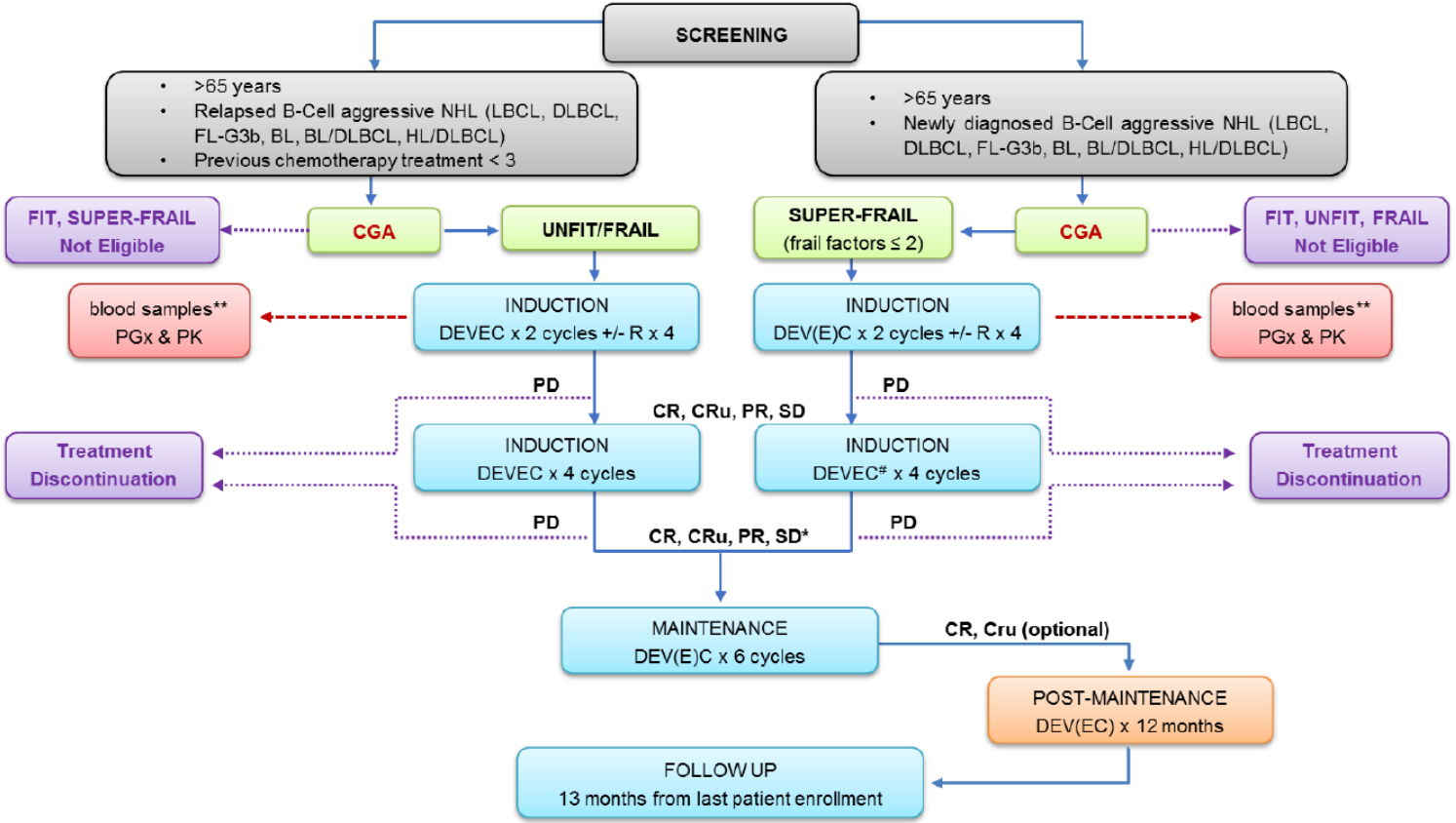

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Fig. 1. Induction Schedule.

Days		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
ETO	50 mg	x	x	x	x	x	x	x	x	x	x	x	x	x	x														
VRN	30 mg	x		x		x			x		x		x			x		x		x									
CTX	50 mg	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x							
PDN**	25 mg	x		x		x			x		x		x			x		x		x			x		x		x		

Abbreviations: ETO, Etoposide; VRN, Vinorelbine; CTX, Cyclophosphamide; PDN, Prednisone.

Rituximab: 375 mg/m^2 will be administered by IV infusion up to four infusions on days 8, 15, 22, 29, only in patients CD20+ suitable for infusion treatment and relapsed after >6 months from last R-chemotherapy. Refractory patients who received at least 5 doses of Rituximab will not repeat it during the metronomic therapy.

****Only in cycle 1 PDN will be administered continuously from day 1 to day 28. From cycle 2 to 6 reduce to three times a week.***

Fig. 2. Maintenance Schedule.

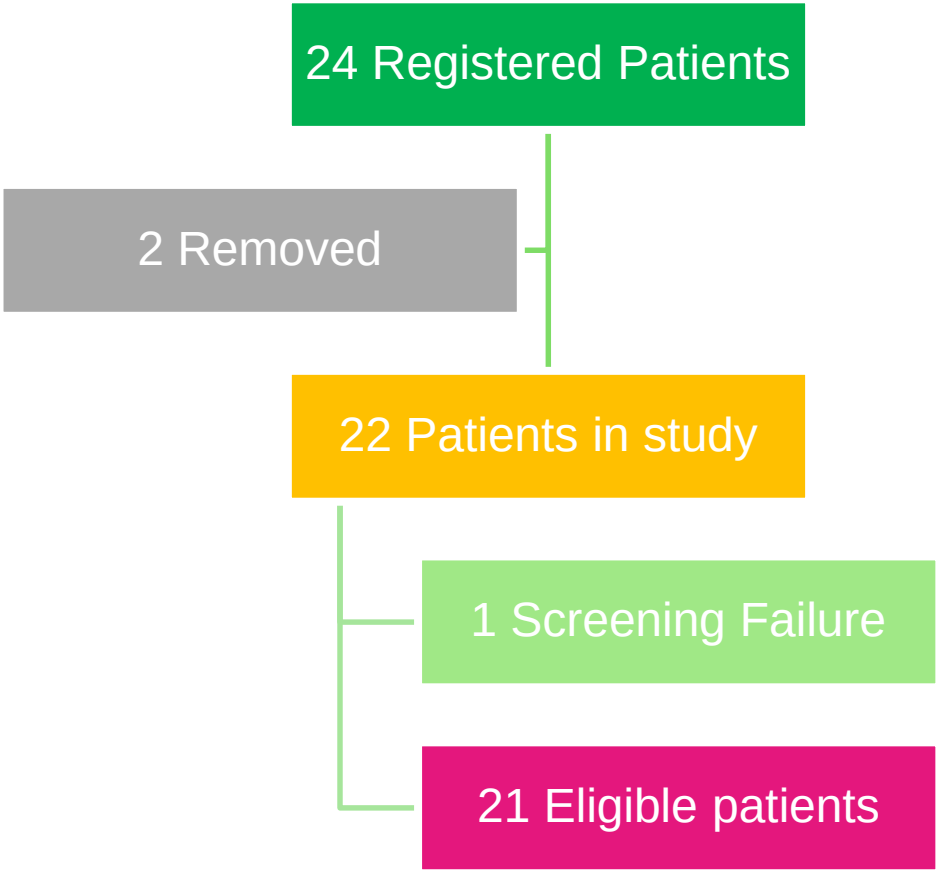
Days		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
VRN	30 mg	x		x		x			x		x		x			x		x		x									
CTX	50 mg	x	x	x	x	x	x	x	x	x	x	x	x	x	x														
PDN	25 mg	x				x			x				x			x				x			x				x		

Abbreviations: VRN, Vinorelbine; CTX, Cyclophosphamide; PDN, Prednisone.

Fig. 3. Post-Maintenance Schedule.

Days		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
VRN	30 mg	x		x		x			x		x		x			x		x		x									
PDN	25 mg	x				x			x				x			x				x			x				x		

Abbreviations: VRN, Vinorelbine; CTX, Cyclophosphamide; PDN, Prednisone.


24 Registered Patients
2 Removed
22 Patients in study
1 Screening Failure
21 Eligible patients

STUDY DETAILS
Start Date: July 2017
First enrollment: September 2017
Duration of the study: approximately 35 months

ACTIVATION STATUS
Partecipanting Sites: 33
Authorized Sites: 15
Active Sites: 10 (with at least 1 enrolled patient)

ENROLLMENT
Planned accrual: 21 patients (study stage 1) – 34 patients (study stage 2)
Current accrual: 21 patients

ENROLLMENT IS CLOSED!!

FIL_RecAnz

Studio prospettico di fase II di terapia mieloablativa ad alte dosi, con supporto di cellule staminali periferiche, in pazienti Anziani (>65 e <76 anni) affetti da linfoma non Hodgkin aggressivo recidivato o resistente alla terapia di prima linea

PI: Maria Christina Cox (Roma)
Luca Castagna (Rozzano)
Alessandra Tucci (Brescia)

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Caratteristiche dei pazienti

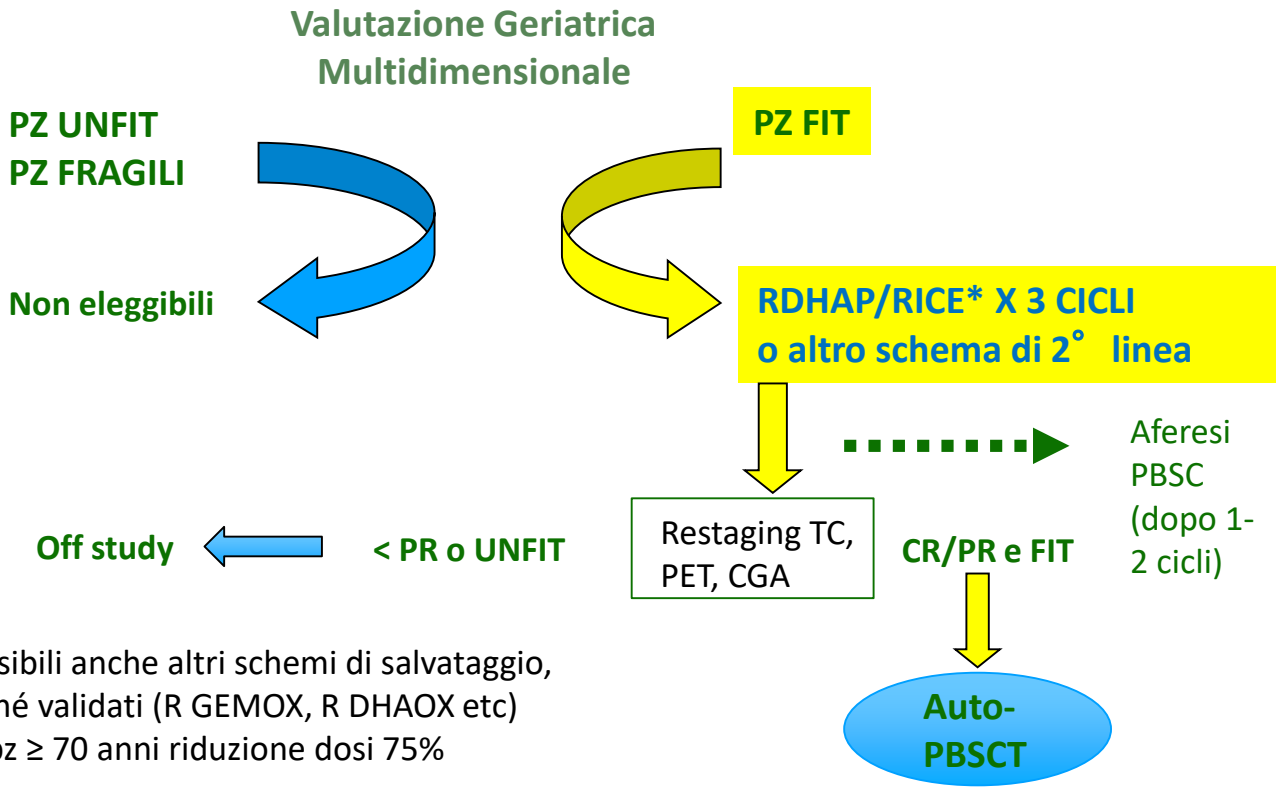
- Età 65-75 anni
- Linfoma aggressivo a cellule B (DLBCL, FL3b, tFL, MCL, BL)
- Pazienti FIT in recidiva o progressione

Obiettivi primari

- Attività e Fattibilità della CT ad alte dosi con autoPBSC

Sample Size: **81** [30 pazienti (stadio 1) + 51 pazienti (stadio 2)]

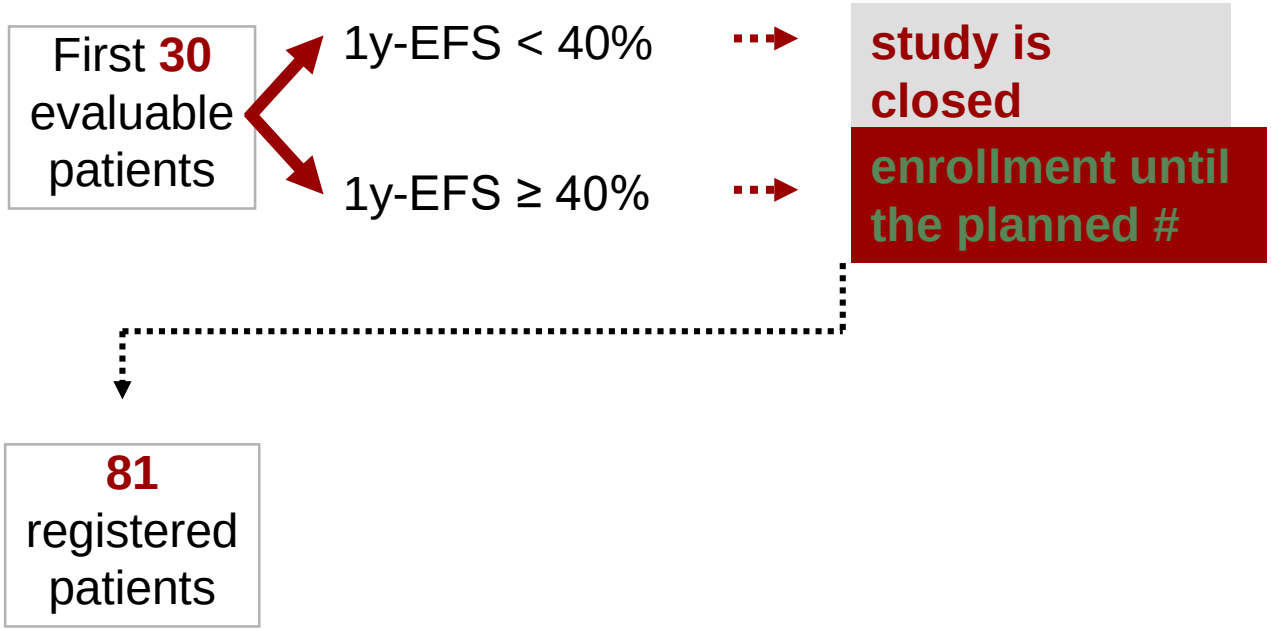
LNH B aggressivi 65-75 anni



*Possibili anche altri schemi di salvataggio, purché validati (R GEMOX, R DHAOX etc)
Nei pz ≥ 70 anni riduzione dosi 75%

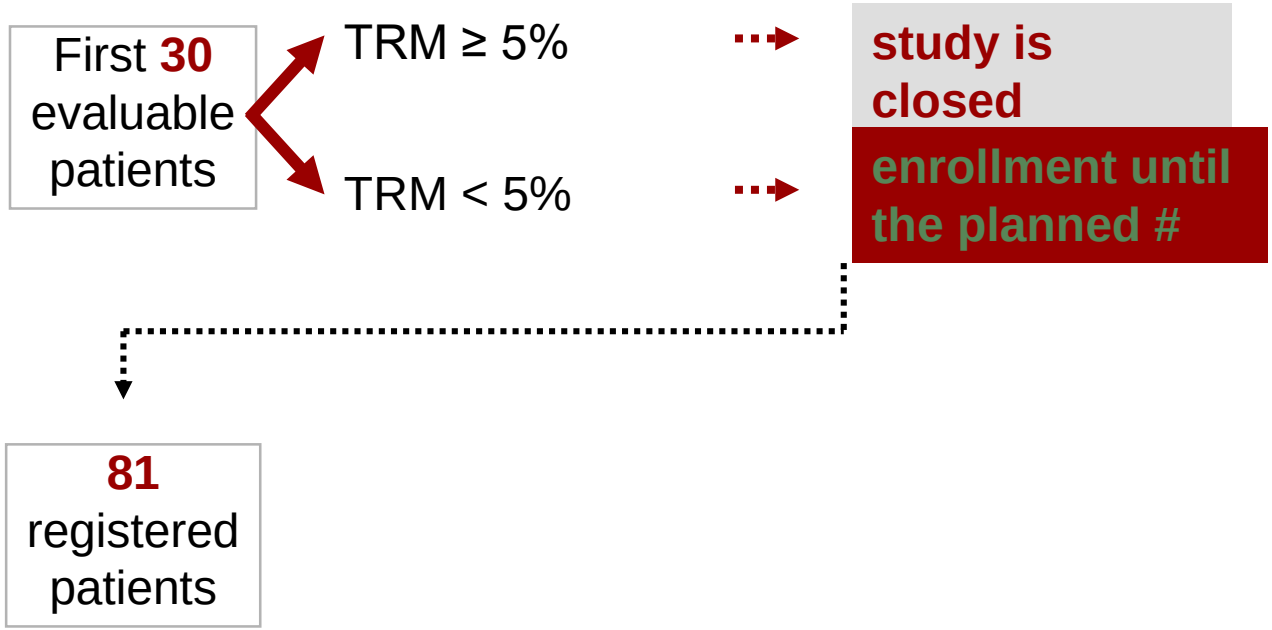
Statistical considerations - efficacy

2-stage design



Statistical considerations - safety

2-stage design



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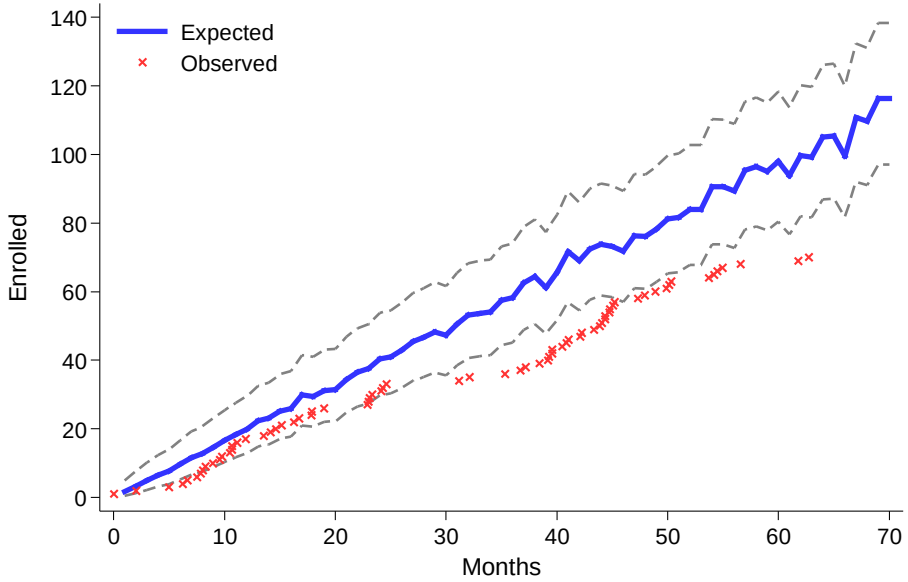
Report Studio RecAnz

Estrazione dati: 21/10/2019



Emendamento:

Aumento del periodo di arruolamento da 4 a 6 anni

Primo arruolamento
30/05/2014

ultimo arruolamento
21/8/2019

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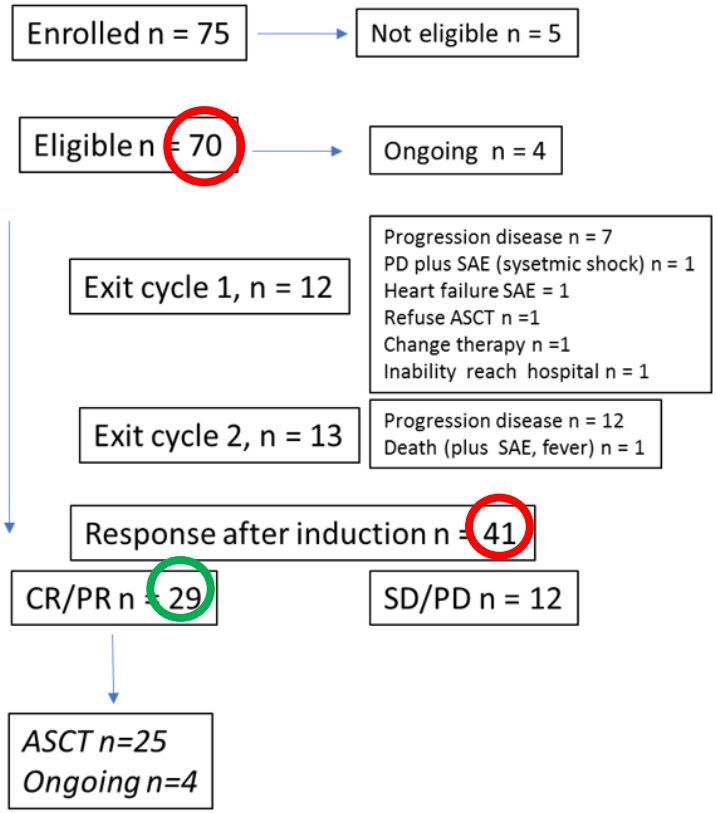

THE STUDY IS CLOSED!!

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Chi *ricerca* *ama*

Insieme contro i linfomi

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