RETE ONCOEMATOLOGICA DEL PIEMONTE E VALLE D'AOSTA

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

Torino, 24 novembre 2017

Centro Congressi Torino Incontra
Via Nino Costa, 8 - Torino

Torino, 24 novembre 2017

Aggiornamento Protocolli FIL

Linfoma di Hodgkin

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FIL-Rouge

Studio randomizzato, open-label, multicentrico, di fase III a 2 bracci di confronto dell'efficacia e della tollerabilità della variante intensificata 'dose-dense/dose-intense ABVD' (ABVD DD-DI) e un programma terapeutico con ABVD a dosi standard per 2 cicli e successivamente orientato in base alla risposta PET, come trattamento di prima linea di pazienti con Linfoma di Hodgkin classico (HL) in stadio avanzato

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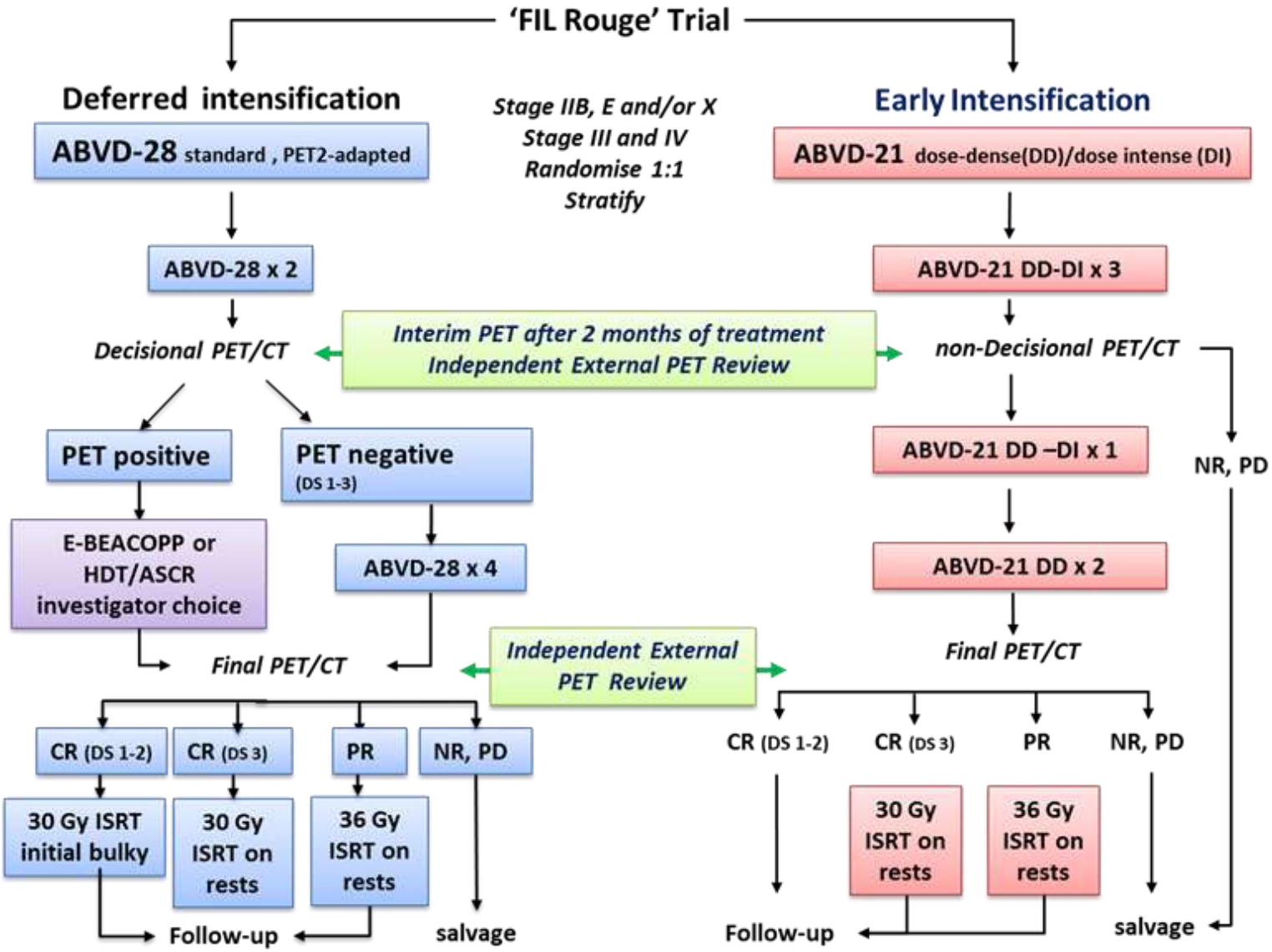
Prof. Armando Santoro (Rozzano, MI)

Flow Chart


'FIL Rouge' Trial
Deferred intensification
ABVD-28 standard , PET2-adapted
ABVD-28 x 2
Decisional PET/CT
PET positive
E-BEACOPP or HDT/ASCR investigator choice
PET negative (DS 1-3)
ABVD-28 x 4
Final PET/CT
CR (DS 1-2)
CR (DS 3)
PR
NR, PD
30 Gy ISRT initial bulky
30 Gy ISRT on rests
36 Gy ISRT on rests
Follow-up
salvage
Stage IIB, E and/or X
Stage III and IV
Randomise 1:1
Stratify
Interim PET after 2 months of treatment
Independent External PET Review
Independent External PET Review
Early Intensification
ABVD-21 dose-dense(DD)/dose intense (DI)
ABVD-21 DD-DI x 3
non-Decisional PET/CT
ABVD-21 DD –DI x 1
ABVD-21 DD x 2
Final PET/CT
NR, PD
CR (DS 1-2)
CR (DS 3)
PR
NR, PD
30 Gy ISRT on rests
36 Gy ISRT on rests
Follow-up
salvage

Objectives

- **Primary**: To demonstrate the superiority of an intensified ABVD variant (ABVD DD-DI, *Experimental arm*) over an interim PET response-adapted ABVD treatment (*Comparator arm*) in improving PFS.

- **Secondaries**:
  - To compare the anti-lymphoma activity of ABVD DD-DI and interim PET response-adapted ABVD according to Lugano 2014 Classification.
  - To compare the OS of ABVD DD-DI vs. interim PET response-adapted ABVD
  - To compare the safety of ABVD DD-DI and interim PET response-adapted ABVD
  - To compare the effect of ABVD DD-DI and interim PET response-adapted ABVD on Quality of life (QoL)
  - To compare ABVD DD-DI vs. interim PET response-adapted ABVD in term of cost-effectiveness.

bjh BRITISH JOURNAL OF HAEMATOLOGY

A phase II study of dose-dense and dose-intense ABVD ($ABVD_{DD-DI}$) without consolidation radiotherapy in patients with advanced Hodgkin lymphoma

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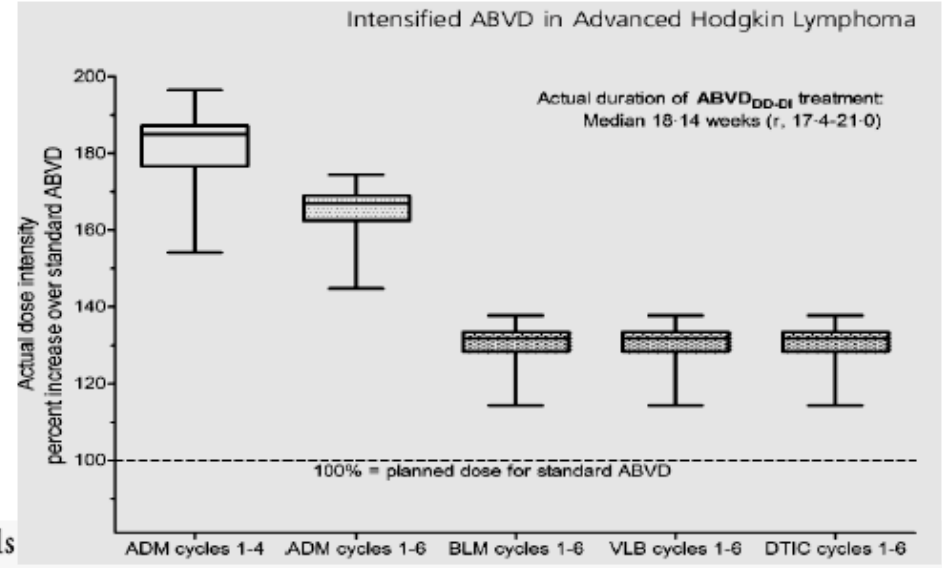


Table I. Drug doses, schedule and treatment administration details

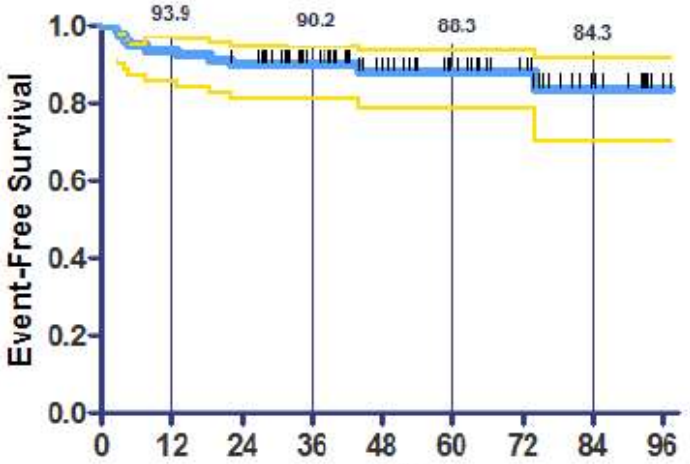
Drug	Dose (mg/m^2)	Route	Days	Cycles 1	2	3	4	5	6
Doxorubicin	35	IV	1, 11	↓	↓	↓	↓		
Doxorubicin	25	IV	1, 11					↓	↓
Bleomycin	10	IV	1, 11	↓	↓	↓	↓	↓	↓
Vinblastine	6	IV	1, 11	↓	↓	↓	↓	↓	↓
Dacarbazine	375	IV	1, 11	↓	↓	↓	↓	↓	↓
Lenograstim (G-CSF)	263 μg/d*	SC	6→8	↔	↔	↔	↔	↔	↔
Lenograstim (G-CSF)	263 μg/d*	SC	17→19	↔	↔	↔	↔	↔	↔

Russo et al. British Journal of Haematology, 2014, 166, 118–12

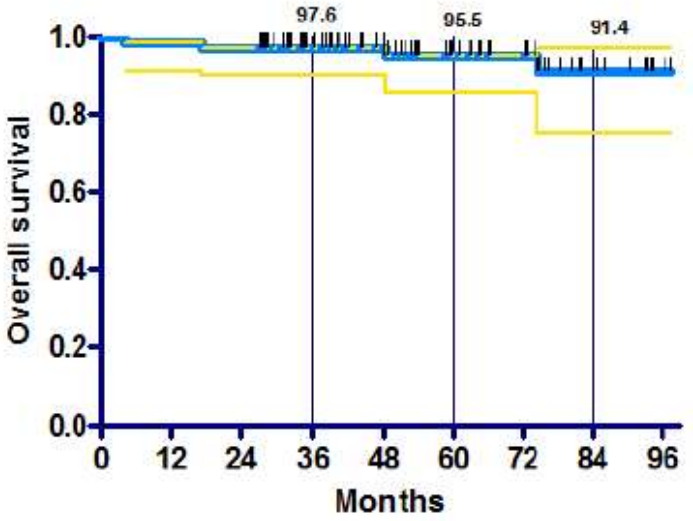
Median observation time for event-free survival was 57 months (range, 27–97 months).

Table IV. Treatment response, events and survival outcomes.

Outcome	*n*	%	95% CI
Final treatment response	82		
Complete remission	78	95·1	87·7–98·5
Partial remission	2	2·4	
Progression	1	1·2	
Unknown*	1	1·2	
Cycle 2 PET	82		
Negative	72	87·8	78·8–93·4
Positive	10	12·2	
Cycle 4 I			
Negati			
Positiv			
Cycle 6 PET	79		
Negative	78		
Positive	1		
Events	10	12·2	6·6–21·2
<Complete remission	2		
Progression	1		
Early relapse (3–12 months)	2		
Late relapse (>12 months)	2		
Secondary tumour	2		
Death from acute toxicity	1		
5-year			
Event-free survival		88·3	78·5–93·8
Disease-free survival		93·7	85·5–97·3
Overall survival		95·5	86·2–98·6



Cardiopulmonary toxicity never exceeded grade 2 and affected 14.6% of patients.
Most frequent toxicities: grade 4 neutropenia (10%) grade 3 infection (17%)



Inclusion Criteria

- Histologically confirmed classical HL
- Previously untreated disease
- **Age 18-60 years**
- **Ann Arbor stage IIB with extranodal involvement and/or mediastinal bulk, III and IV**
- At least one target PET-avid bidimensionally assessable lesion
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2
- Adequate organ and marrow function as defined below: absolute neutrophil count >1,0 $x10^9$/L, platelets >75 $x10^9$/L
- Total bilirubin <2 mg/dl without a pattern consistent with Gilbert's syndrome
- Aspartate Transaminase and Alanine Transaminase (AST/ALT) <3 X institutional Upper Limits of Normality (ULN)
- Creatinine within normal institutional limits or creatinine clearance >50 mL/min/1.73 m^2
- Females of childbearing must have a negative pregnancy test at medical supervision even if had been using effective contraception
- Life expectancy > 6 months
- Able to adhere to the study visit schedule and other protocol requirements
- Sign (or their legally acceptable representatives must sign) an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study.
- **Access to PET-CT scans facilities qualified by FIL**

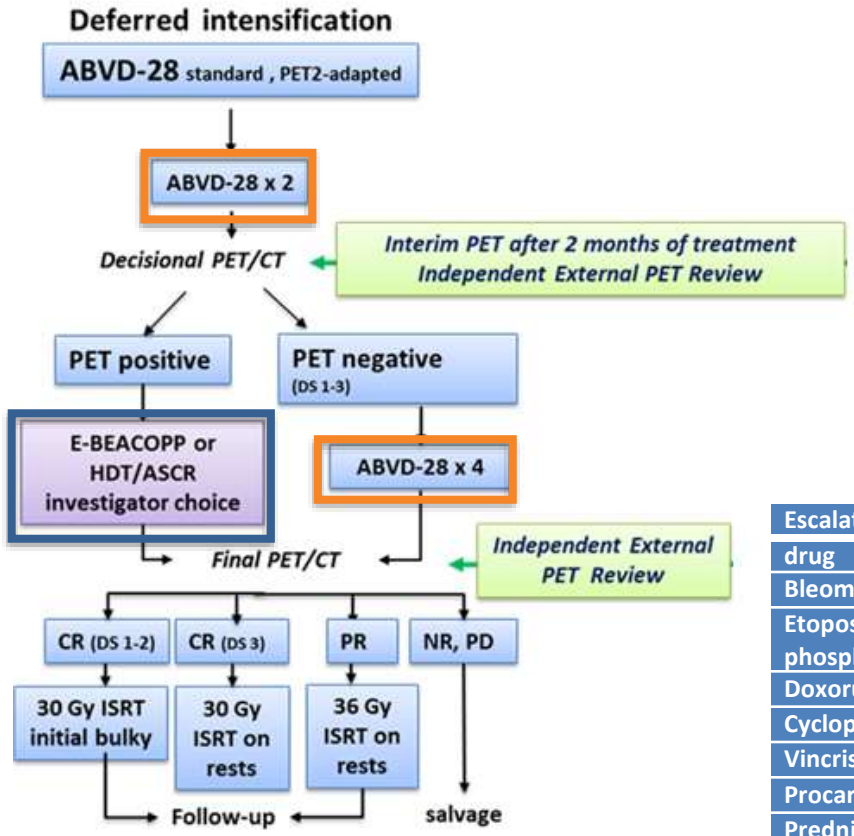
Exclusion Criteria

- Nodular Lymphocyte Predominant HL
- **Ann Arbor stage IIB without extranodal involvement and/or mediastinal bulky**
- Prior chemotherapy or radiation therapy
- Pregnant or lactating females
- Known hypertension, cardiac arrhythmia, conduction abnormalities, ischemic cardiopathy, left ventricular hypertrophy or left ventricular ejection fraction (LVEF) ≤50% at echocardiography.
- Abnormal QTc interval prolonged (>450 msec in males; >470 msec in women)
- Diffusion lung capacity for CO (DLCO) and/or forced expiratory volume in the 1st second (FEV1) tests <50% of predicted
- Known cerebral or meningeal disease (HL or any other etiology)
- Prior history of malignancies unless the patient has been free of the disease for five years. Exceptions include the following: basal cells carcinoma of the skin, squamous cell carcinoma of the skin, carcinoma in situ of the cervix, carcinoma in situ of the breast and prostate cancer with TNM stage of T1a or T1b
- Uncontrolled infectious disease
- Human immunodeficiency virus (HIV) positivity or active infectious A, B or C hepatitis. HBsAg-negative patients with anti-HBc antibody and can be enrolled provided that Hepatitis B Virus (HBV)-DNA are negative and that antiviral treatment with nucleos(t)ide analogs is provided
- Uncompensated diabetes
- Refusal of adequate contraception
- Any medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment.

Statistical plan

- The primary objective is to show the superiority of the intensified ABVD regimen over a PET-adapted ABVD treatment on the primary efficacy endpoint of PFS.
- A stratified randomization will allocate patients with a 1:1 ratio in the two arms.
- With 30 months of uniform accrual and a minimum follow-up of 30 months, 3-years PFS rate of about 75% for the *comparator* PET-2-adapted ABVD arm and a minimum expected absolute improvement of 10% in the *experimental arm*.
- Statistical power of 85%, type I alpha error of 0.05 and drop out of no more than 5% of pts, a **minimum of 250 pts per arm are required (N=500, with a cumulative number of failures of 110).**
- One interim efficacy analysis is planned when 33% (N=37) of the total expected events will be recorded.
- **Interim analyses to evaluate safety will be performed by an independent DSMC without pre-specified statistical restraints.**

Comparator Arm: Treatment Schedule



ABVD standard (repeat every 28 days)			
drug	one-day dose	route	schedule (days)
Doxorubicin	25 mg/m^2	i.v.	days 1,15
Bleomycin	10,000 units/m^2	i.v.	days 1,15
Vinblastine	6 mg/m^2	i.v	days 1,15
Dacarbazine	375 mg/m^2	i.v.	days 1,15

Escalated BEACOPP (repeated every 21 days)			
drug	one-day dose	route	schedule (days)
Bleomycin	10,000 units/m^2	i.v.	day 8
Etoposide or etoposide phosphate*	200 mg/m^2	i.v.	days 1-3
Doxorubicin	35 mg/m^2	i.v.	day 1
Cyclophosphamide**	1250 mg/m^2	i.v.	day 1
Vincristine	1.4 mg/m^2 (max 2 mg)	i.v	day 8
Procarbazine	100 mg/m^2	PO	days 1-7
Prednisone***	40 mg/m^2	PO	days 1-14 cycle 1 days-1-7 cycles 2-4
G-CSF/pegylated G-CSF	150 µg/m^2/6 mg	s.c.	from day 9/on day 4

* Etoposide phosphate as etoposide-equivalent dose: 113 mg etoposide phosphate is equivalent to 100 mg etoposide.

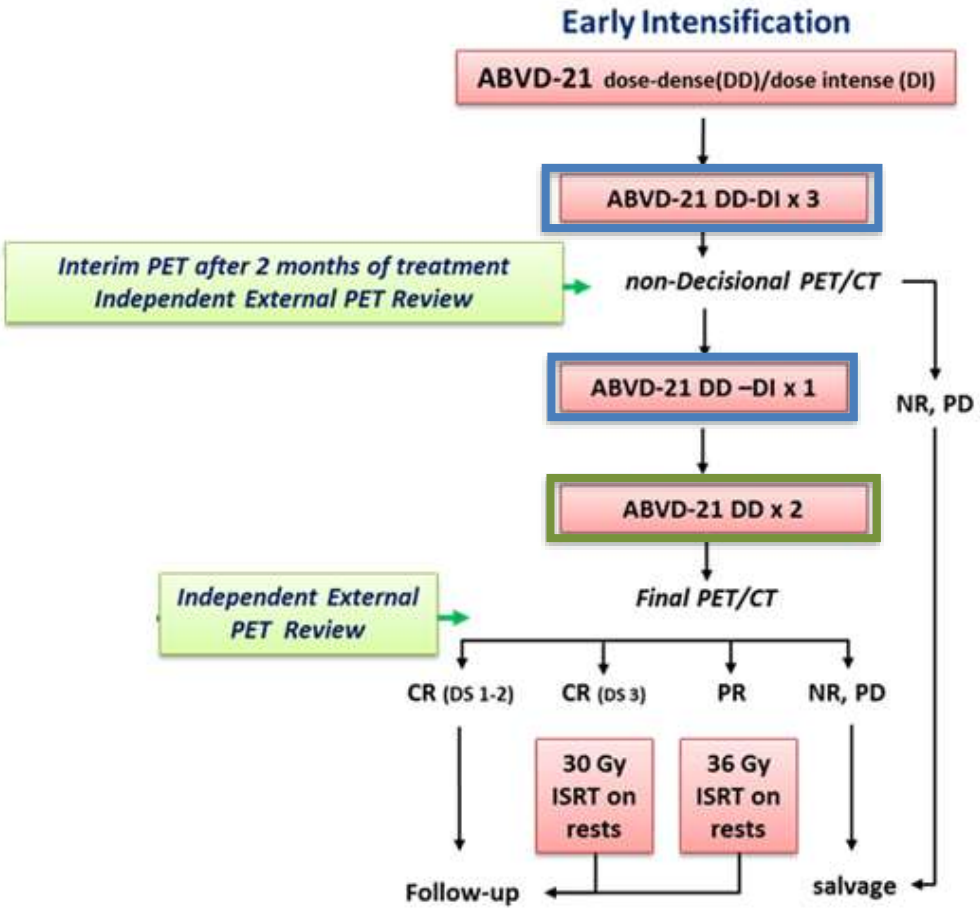
** Uromitexan is obligatory. The patient should ingest 2.5 liters of fluid on the day of administration.

*** Prednisone should be rounded to nearest 5 mg; it can be substituted by a corresponding dosage of Dexamethasone (e.g., 5 mg/m2/day).

Experimental Arm: Treatment Schedule

ABVD DD-DI (repeated every 21 days) - Cycles 1 to 4			
Doxorubicin	35 mg/m^2	i.v.	days 1,11
Bleomycin	10,000 units/m^2	i.v.	days 1,11
Vinblastine	6 mg/m^2	i.v.	days 1,11
Dacarbazine	375 mg/m^2	i.v.	days 1,11
G-CSF	263 µg	s.c.	days 6-8, 17-19
Reevaluate the patient's weight and recalculate the BSA at each new cycle, especially in the early cycles (to optimize the planned upfront treatment intensification) and in patients with B symptoms (since, upon treatment start, they can quickly recover the initial weight loss)			

ABVD DD (repeated every 21 days) – Cycles 5 and 6			
Doxorubicin	25 mg/m^2	i.v.	days 1,11
Bleomycin	10,000 units/m^2	i.v.	days 1,11
Vinblastine	6 mg/m^2	i.v.	days 1,11
Dacarbazine	375 mg/m^2	i.v.	days 1,11
G-CSF	263 µg	s.c.	days 6-8, 17-19



THE IMPLEMENTATION OF ABVD PLATFORM

TIME AND DOSE INTENSIFICATION

Chemotherapy	Cumulative dose		Dose density per week		
	ABVD	ABVD DD-DI	ABVD	ABVD DD-DI	Increase in dose intensity
Doxorubicin mg/mq	300	380	12.5	21.1	69%
Bleomycin units/mq	120	120	5	6.6	33%
Vinblastine mg/mq	72	72	3	4	33%
Dacarbazine mg/mq	4500	4500	188	250	33%

Cardiologic assessment

cTnI level will be assessed before every treatment infusion in the two arms (*Comparator* and *Experimental*).
Troponin level will be considered above normal if present an elevation > 0.08 ng/mL from baseline assessed at local checks.

Standard transthoracic 2D echocardiography must be done at baseline, at the end of chemotherapy (3-4 weeks), at the end of eventual radiotherapy (3-4 weeks) and during follow-up (every six months in the first year and then annually) in both two arms (*Comparator* and *Experimental*).

GLS should be assessed with a 2D speckle tracking echocardiography using three apical views.

A relative percentage GLS reduction >15% from baseline will be considered to be abnormal according to ESC Guidelines.

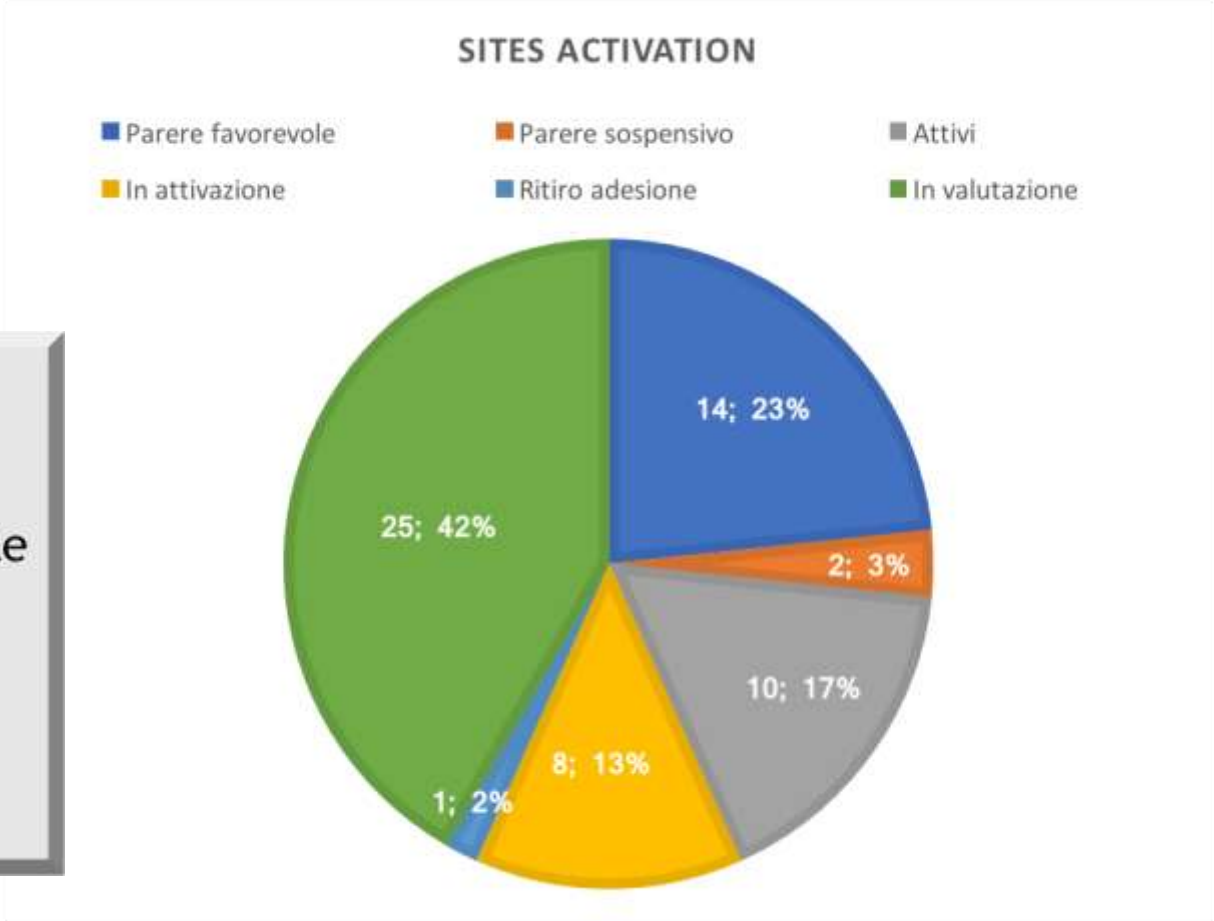
Sites activation (31/10/17)

- First active site: **July 2017**
- **7** patient randomized

59 FIL Centers

Centri in Piemonte:

- SC Città della Salute
- SCDU Città della Salute
- Ivrea
- Alessandria
- Biella
- Candiolo



PO Revisione PET (1)

- Per consentire una misurazione accurata delle lesioni nodali in vista della pianificazione della eventuale RT di consolidamento, la **PET/CT basale** deve essere:

  - ✓ PET/CT (with contrast-enhanced CT) **OPPURE**
  - ✓ Conventional PET/CT (w/o contrast-enhanced CT)+ contrast enhanced CT

- Successivamente al basale, **l'esame convenzionale PET/CT** sarà sufficiente per la valutazione della risposta terapeutica a meno che la contrast-enhanced CT basale non abbia messo in evidenza elementi aggiuntivi di rilievo.

PO Revisione PET (2)

- I centri PET partecipanti allo studio devono avere effettuato preventivamente il Clinical Trial Qualification (CTQ) tramite il Core Lab.

- Cosa inviare?
  - ✓ **Baseline (PET-0)**
  - ✓ **Interim (PET-2)**: dopo 2 cicli per *Comparator Arm* e dopo 3 cicli per *Experimental Arm*
  - ✓ **End of treatment (PET-end)**: 3-4 settimane dopo il termine della somministrazione della terapia o nel momento in cui il trattamento viene interrotto per qualsiasi ragione (per i pazienti arruolati nel *Comparator Arm* che vengono sottoposti al trapianto si intende la PET/CT eseguita alla fine della terapia di salvataggio prima che vengano sottoposti al trapianto)
  - ✓ **After consolidation radiotherapy**: la centralizzazione di questa PET/CT non è mandatoria

PO Revisione PET (3)

- Le immagini PET anonimizzate, in formato DICOM, complete di peso e altezza del paziente, e raccolte in una cartella compressa, sono caricate sulla piattaforma web **WIDEN:**

https://trials.widen.it/filrouge

- Comunicazione dei risultati: invio mail automatica dall'indirizzo no-reply@widen.it agli Uffici Studi FIL e ai Centri.

- Giudizio PET (Lugano 2014):
  - ✓ DS score (1-3 negativo, 4-5 positivo)
  - ✓ Dettagli uptake (Reduced, No significant change, Increase and/or new lesion)

Contacts

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Per la **farmacovigilanza**: ***Daniela Gioia*** **UFFICI STUDI FIL** Tel. 0131.206066 Fax. 0131.263455 E-mail. drugvigilance@filinf.it	Per questioni riguardanti il funzionamento delle **eCRF**: ***Anna Fedina*** **UFFICI STUDI FIL** Tel. 059.4225734 Fax. 059.4223602 E-mail. afedina@filinf.it

BANDO AIFA

- Finanziati **40**/343 studi

- I criteri identificati per la valutazione (linee guida del Ministero della Salute):
  - rilevanza scientifica
  - metodologia/disegno di studio/bibliografia di riferimento
  - livello di innovatività
  - organizzazione/centro sperimentale
  - sperimentatore principale

- FIL_ROUGE è alla posizione n. **16**

"Merito e trasparenza sono i principi che hanno ispirato l'intero percorso di valutazione. Sono stati premiati progetti di qualità eccellente dai quali ci attendiamo un contributo importante sia in termini di arricchimento delle conoscenze cliniche e terapeutiche in aree di minore interesse per la ricerca profit, sia in termini di ricadute regolatorie e razionalizzazione dei costi per il Servizio Sanitario Nazionale.."

A Phase III, Randomized, Open-Label, Clinical Trial to compare Pembrolizumab (MK-3475) with Brentuximab Vedotin in Subjects with Relapsed or Refractory Classical Hodgkin's Lymphoma (KEYNOTE 204)

Have relapsed or refractory (failure to achieve CR [illegible] st recent therapy) classical HL *and meet **one of the follo***

a.Have failed to achieve a response or [illegible] auto-SCT. Subjects must not have had previous treat[illegible]tuximab vedotin.

b. Are not auto-SCT c[illegible] chemo-resistant disease (unable to achieve CR or [illegible] chemotherapy), advanced age, or comorbiditi[illegible] have received at least 2 prior multi-agent chemothe[illegible] that did not include brentuximab vedotin.

Prossimo emendamento:
Relapsed/refractory HL not BV naive

Subjects who have had a transplant greater than 5 years ago are eligible as long as no symptoms of graft-versus-host disease (GVHD).

A Phase III, Randomized, Open-Label, Clinical Trial to compare Pembrolizumab (MK-3475) with Brentuximab Vedotin in Subjects with Relapsed or Refractory Classical Hodgkin's Lymphoma (KEYNOTE 204)

Drugs	Dose/Potency	Dose Frequency	Route of Administration	Treatment Period
Pembrolizumab	200 mg	1 dose on Day 1 of every 3 weeks = 1 cycle	Intravenous infusion	Up to 35 cycles per subject
Brentuximab vedotin	1.8 mg/kg (maximum 180 mg per dose)	1 dose on Day 1 of every 3 weeks = 1 cycle	Intravenous infusion	Up to 35 cycles per subject