RIUNIONE NAZIONALE FIL

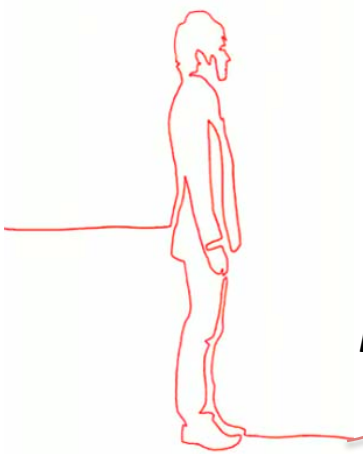
FONDAZIONE ITALIANA LINFOMI

LINFOMA DI HODGKIN

NUOVO STUDIO IN PRIMA LINEA

FIL ROUGE TRIAL

Napoli, 5-7 Novembre 2015

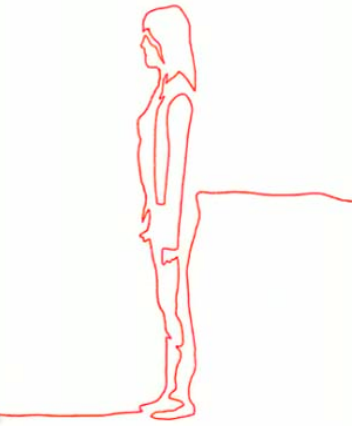


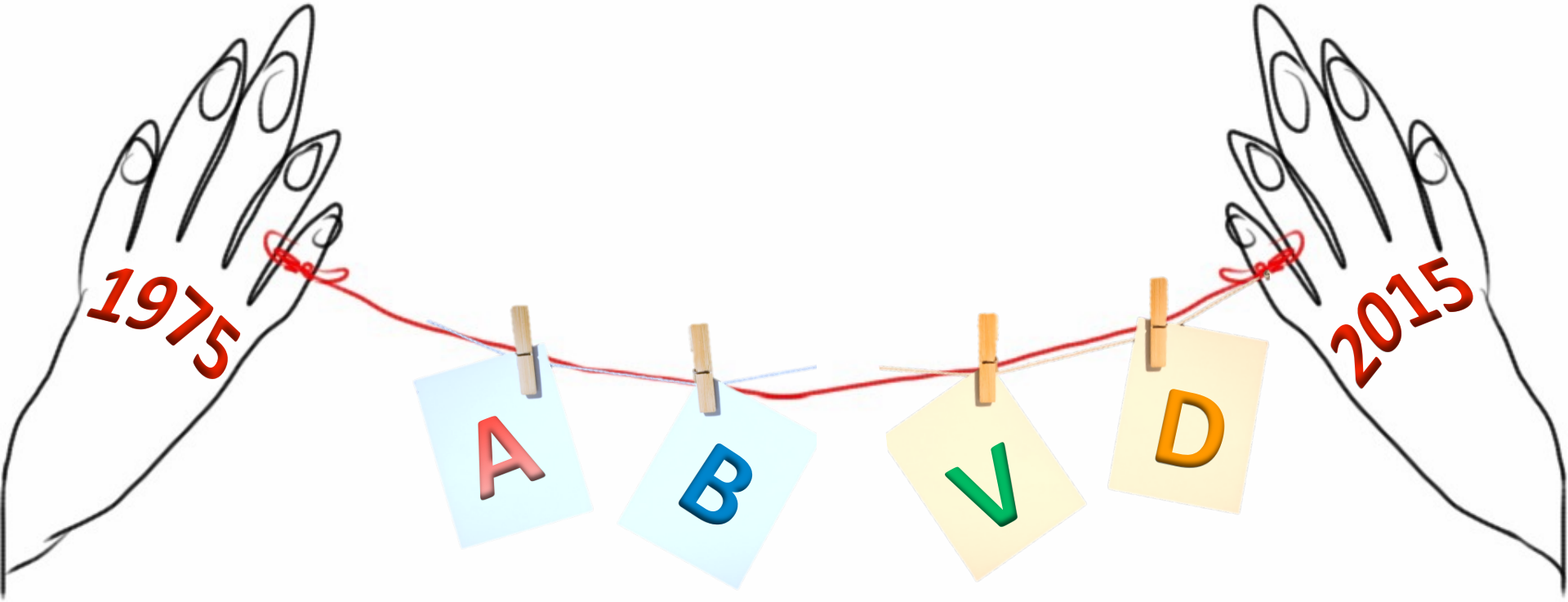
Gaetano Corazzelli

IRCCS Istituto Tumori Napoli

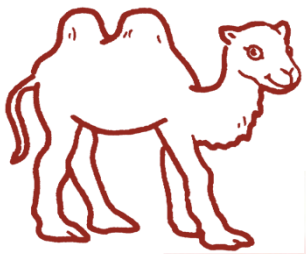
Francesca Ricci

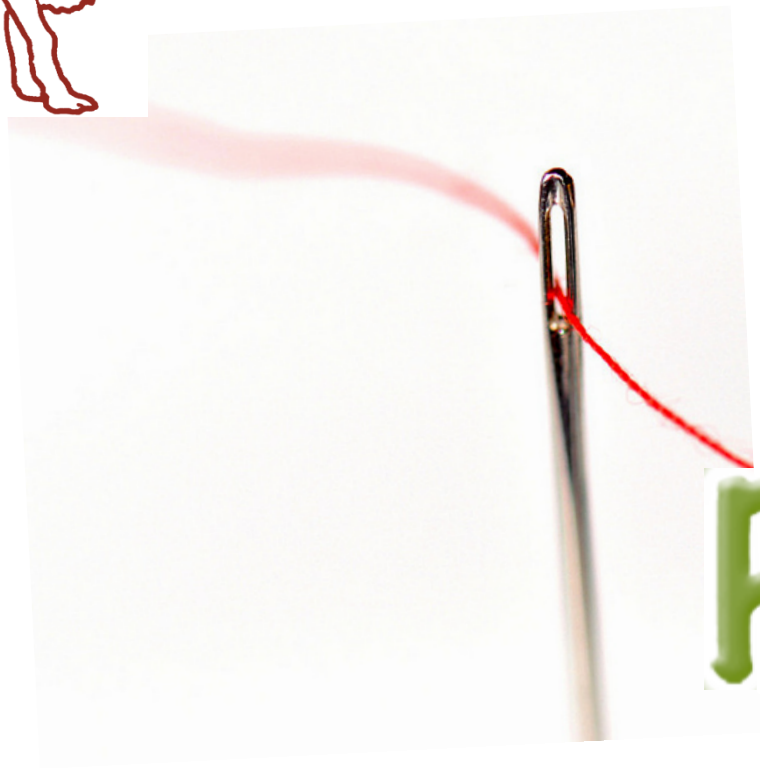
IRCCS Humanitas , Milano




1975
A
B
V
D
2015

FROM A CUMBERSOME COMPLEXITY ….





Rouge Trial

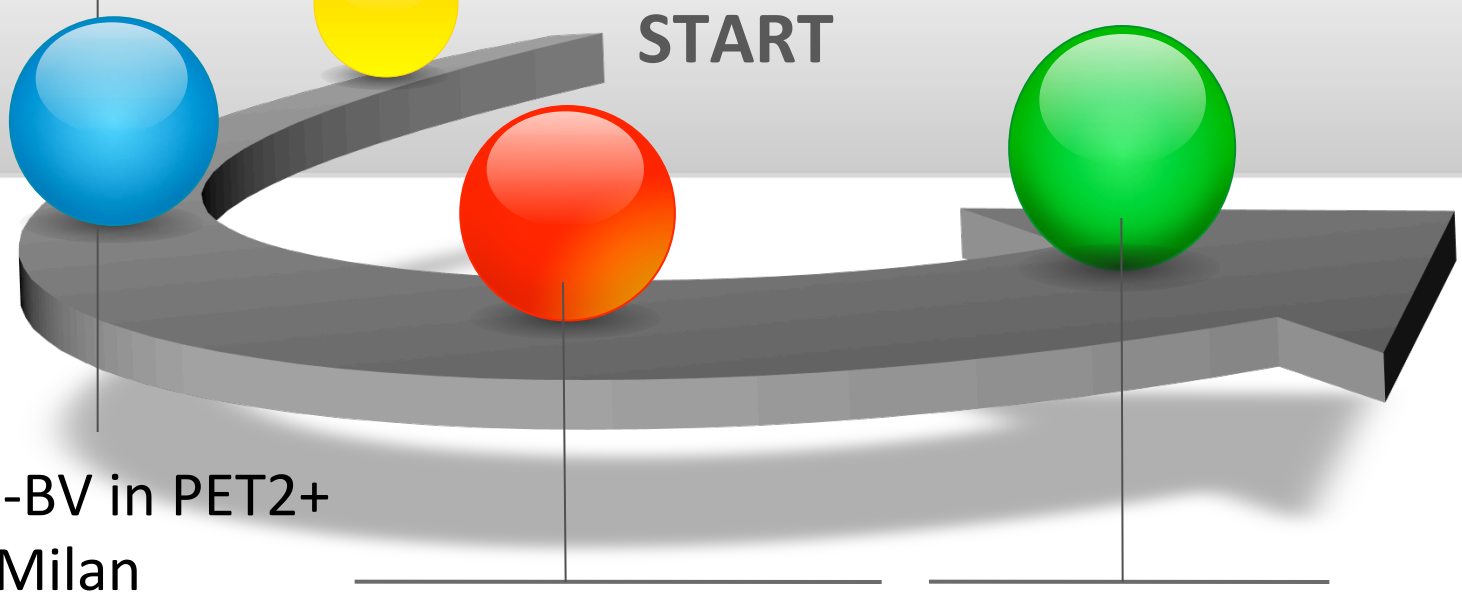
FIL-Rouge: from Genesis to Revelation

FIL ∩ UK NCRI ?
AVD+BV (Raven)

ABVD x 6-8 +RT

FIL Rouge Trial

PET2-adaptation
Vs.
Upfront intensification



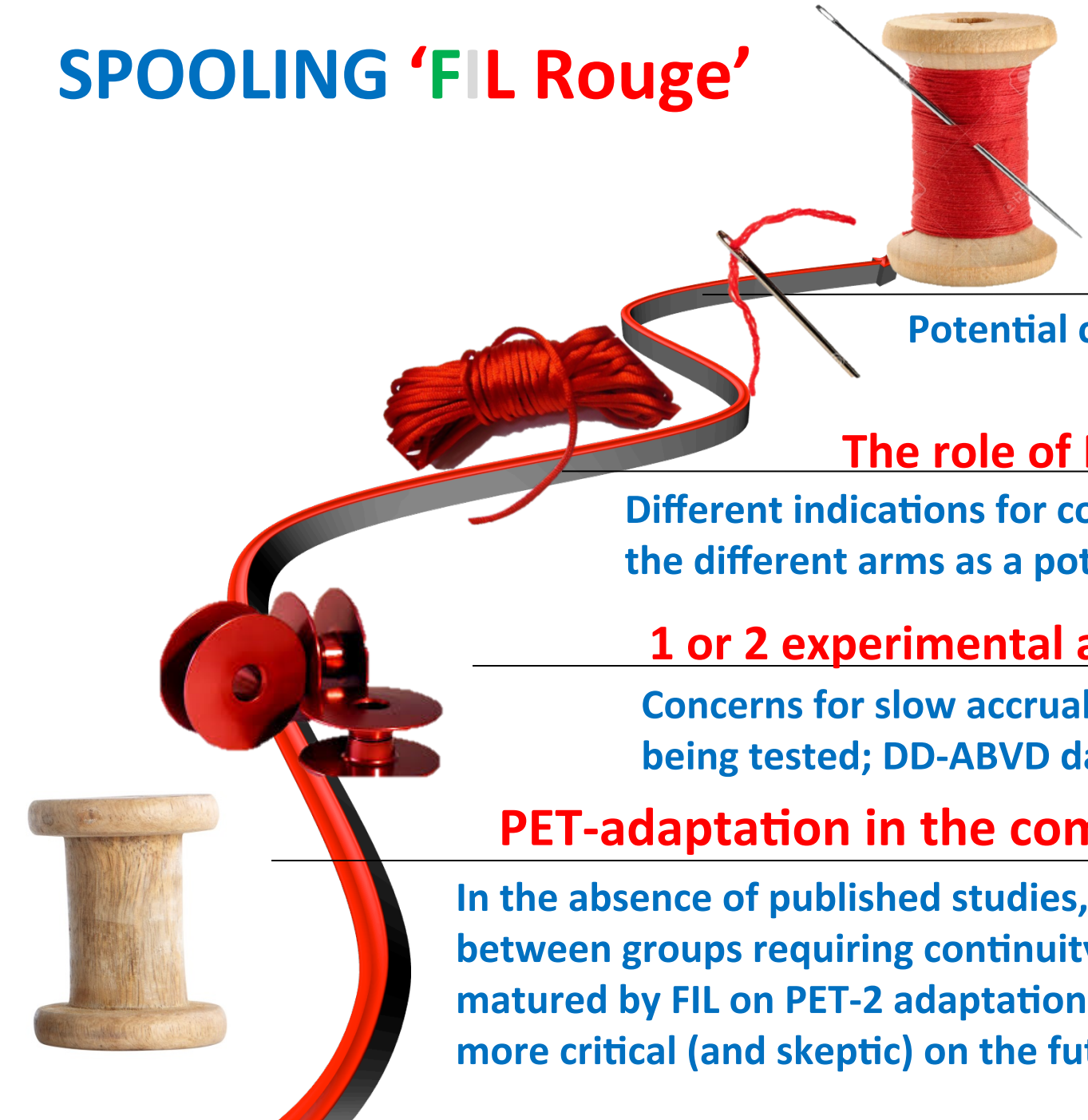
AVD-BV in PET2+
INT Milan

ABVD DD-DI, Napoli
DD-ABVD, Milano

Mature results of HD0607
Final results of HD0801

FIL 2008-2013 ⇒ 1292 pts

SPOOLING 'FIL Rouge'



Toxicity

Potential cardiopulmonary AEs

The role of Radiotherapy

Different indications for consolidation through the different arms as a potential bias

1 or 2 experimental arms?

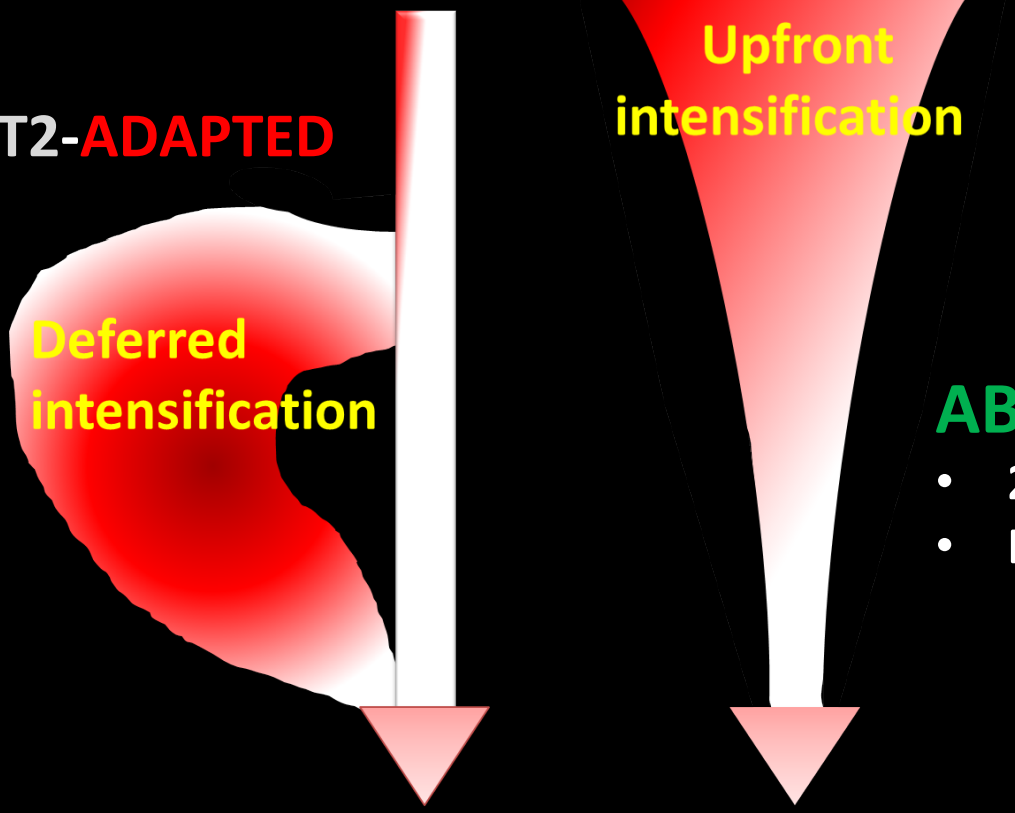
Concerns for slow accrual; similar hypotheses being tested; DD-ABVD data still unpublished

PET-adaptation in the comparator arm !

In the absence of published studies, a contest raised between groups requiring continuity with the experience matured by FIL on PET-2 adaptation and groups who were more critical (and skeptic) on the future role of interim PET

FIL Rouge Trial

Randomizes



ABVD PET2-ADAPTED

ABVD DD-DI

- 21 days intervals
- DOX 35 mg/m2 cycles 1-4

To offer a less toxic alternative to Esc BEACOPP

To devise a cheaper option to BV *'for all'*

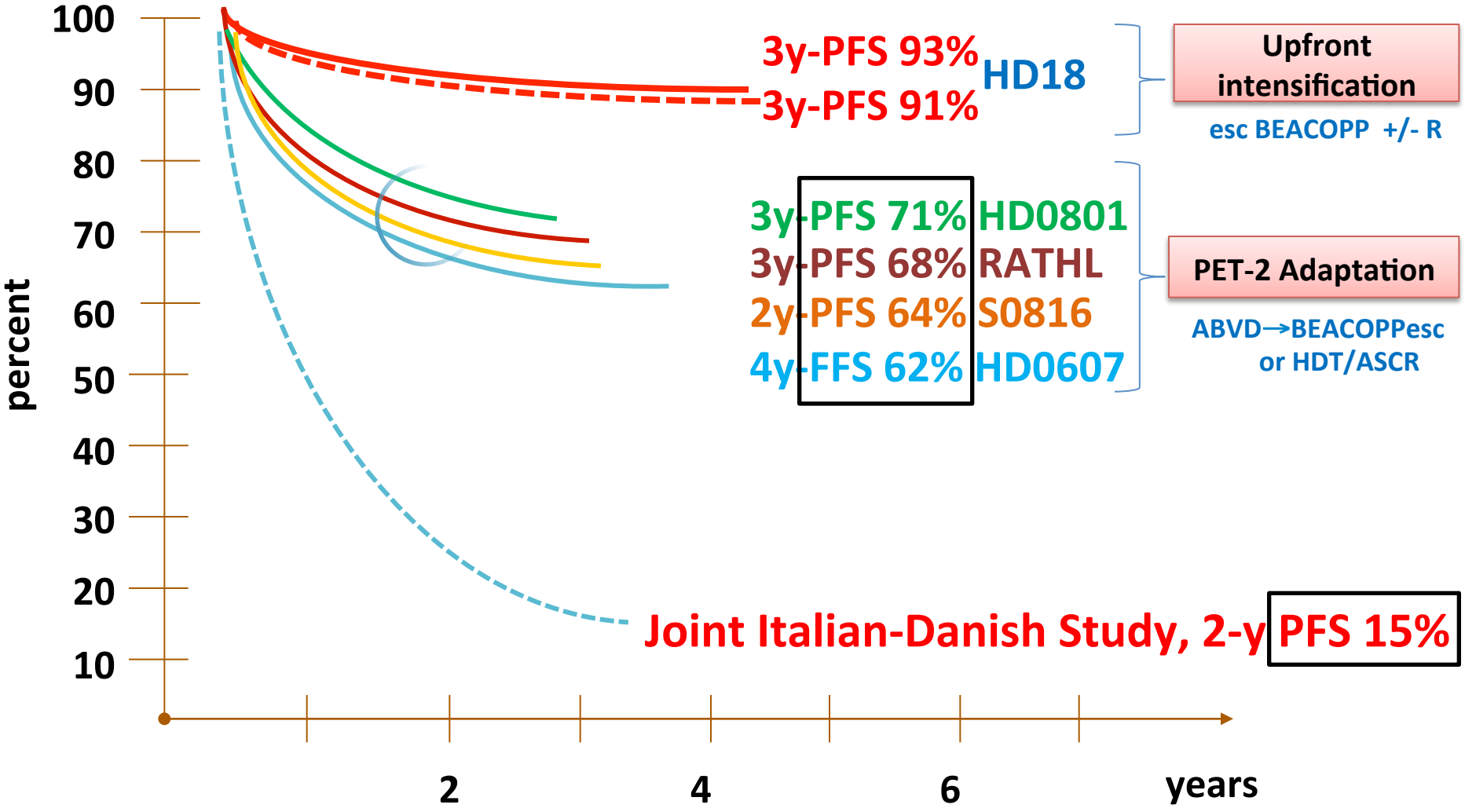
PET2-ADAPTATION – ABVD-BASED STUDIES

Study	Status	N. Enroll/ Eval	IPS ≥3	Stage II	PFS (%)		
					overall	PET-	PET+
UK RATHL	Interim data	1214/1137	37%	41%*	82.5 (3y)	85	68
GITIL/FIL HD 0607	Interim data	773/500	39%	34%	81 (4y)	85	62
US SWOG S0816	Closed Paper under review	371/356	51%	0	79 (2y)	82	64
FIL HD0801	Closed Paper under review	519/512	46%	19%	76 (3y)	78	71

* Include Stage IIA with bulky (mediastinal or nodal) or >2 sites

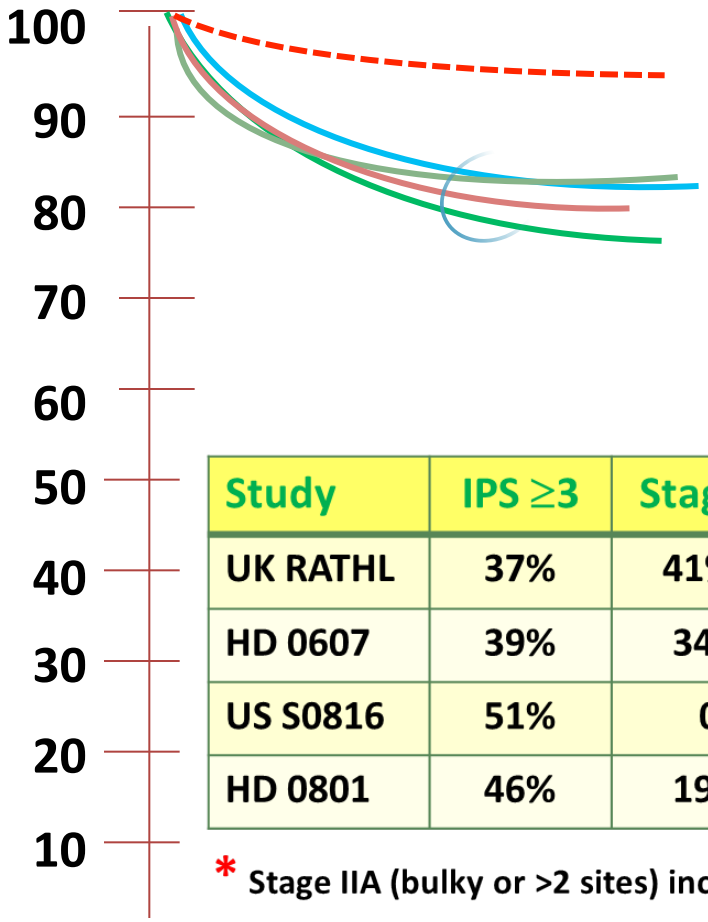
PET2 ADAPTED TRIALS

PFS FOR PET2 POSITIVE PATIENTS



PET2 ADAPTED TRIALS

PFS FOR PET2 NEGATIVE (5PS 1-3) PATIENTS



Joint Italian-Danish Study, 2-y PFS 95%

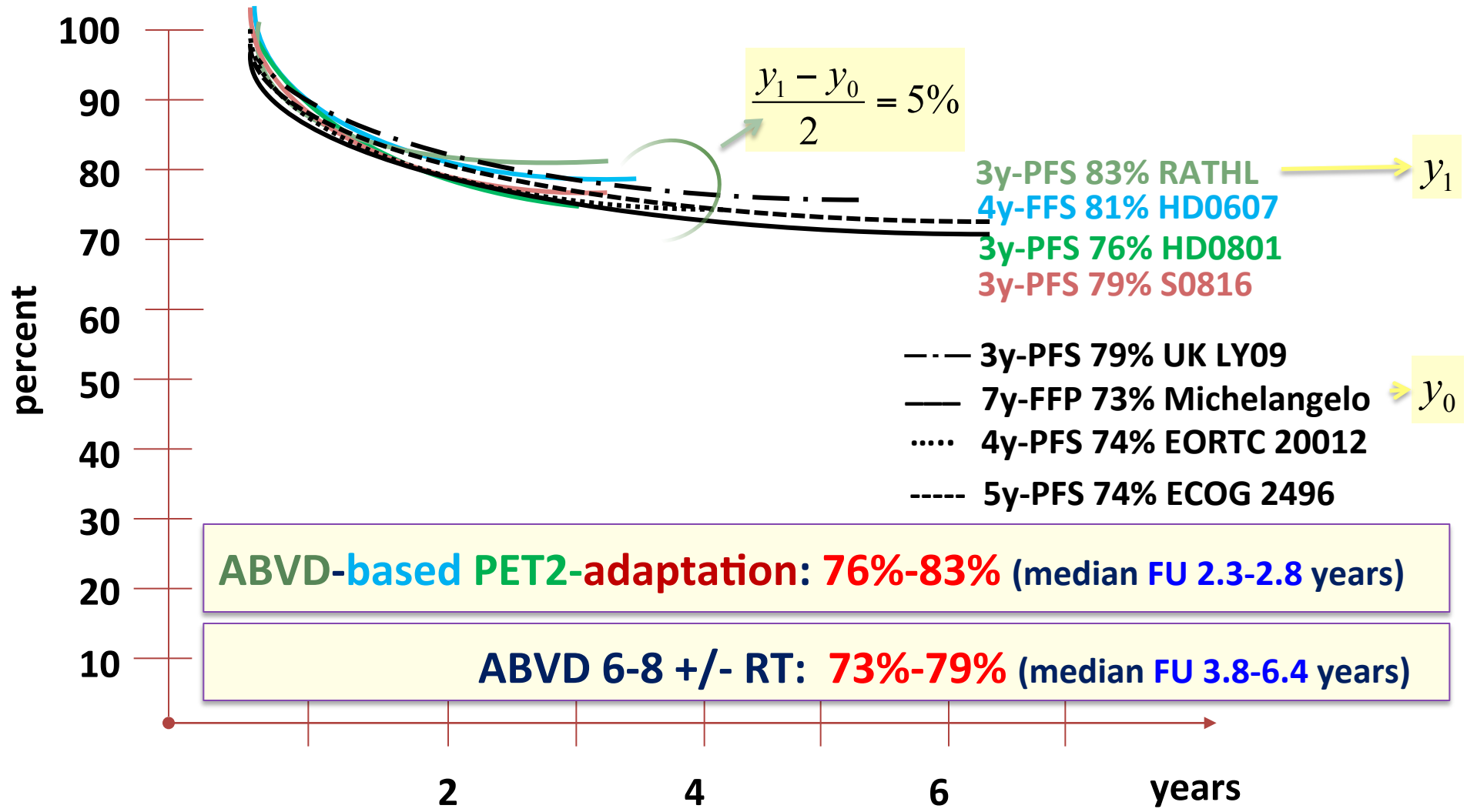
3y-PFS 85% RATHL
4y-FFS 85% HD0607
3y-PFS 82% S0816
3y-PFS 78% HD0801

$10\% < \Delta < 17\%$

Study	IPS ≥3	Stage II
UK RATHL	37%	41%*
HD 0607	39%	34%
US S0816	51%	0
HD 0801	46%	19%

* Stage IIA (bulky or >2 sites) included

PET2 ADAPTED TRIALS – OVERALL PFS



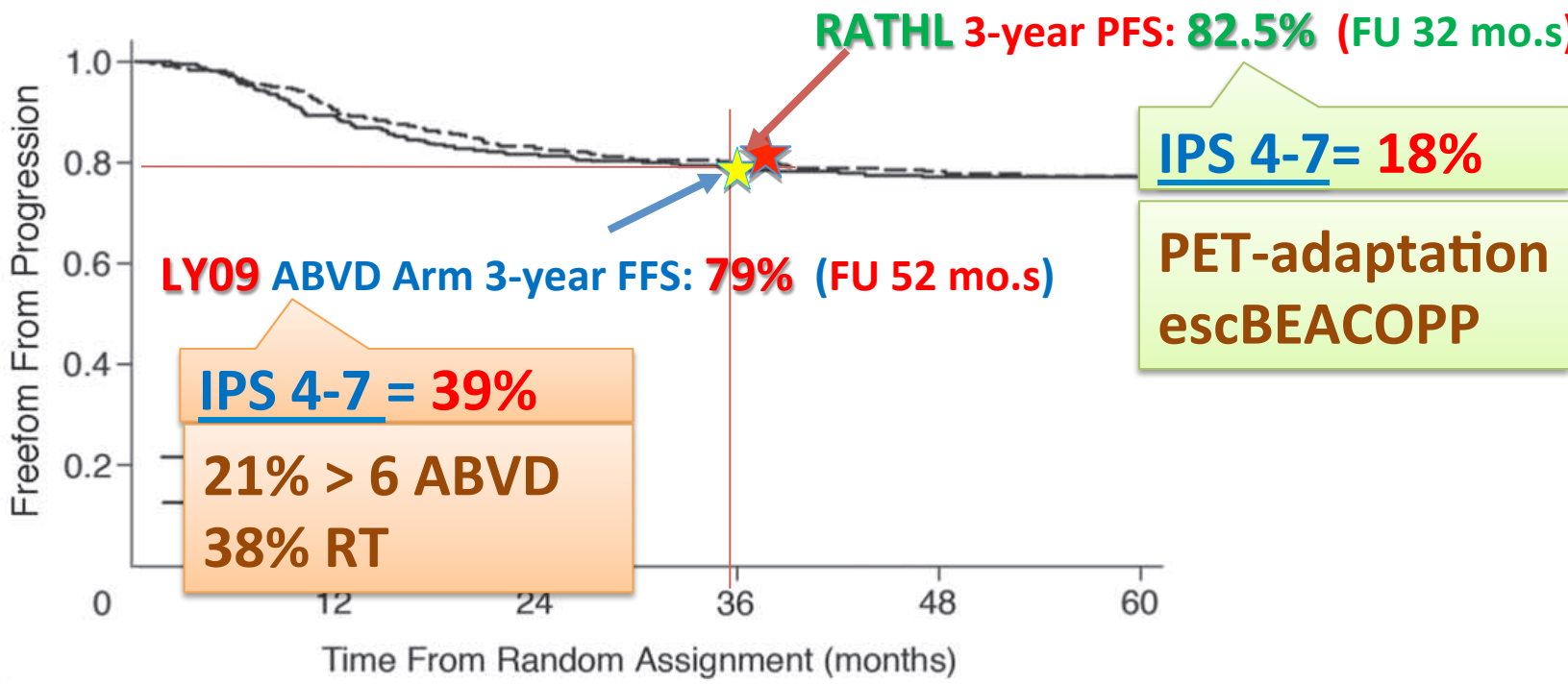
VOLUME 23 · NUMBER 36 · DECEMBER 20 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Comparison of ABVD and Alternating or Hybrid Multidrug Regimens for the Treatment of Advanced Hodgkin's Lymphoma: Results of the United Kingdom Lymphoma Group LY09 Trial (ISRCTN97144519)

Peter W.M. Johnson, John A. Radford, Michael H. Cullen, Matthew R. Sydes, Jan Walewski, Andrew S. Jack, Kenneth A. MacLennan, Sally P. Stenning, Simon Clawson, Paul Smith, David Ryder, and Barry W. Hancock

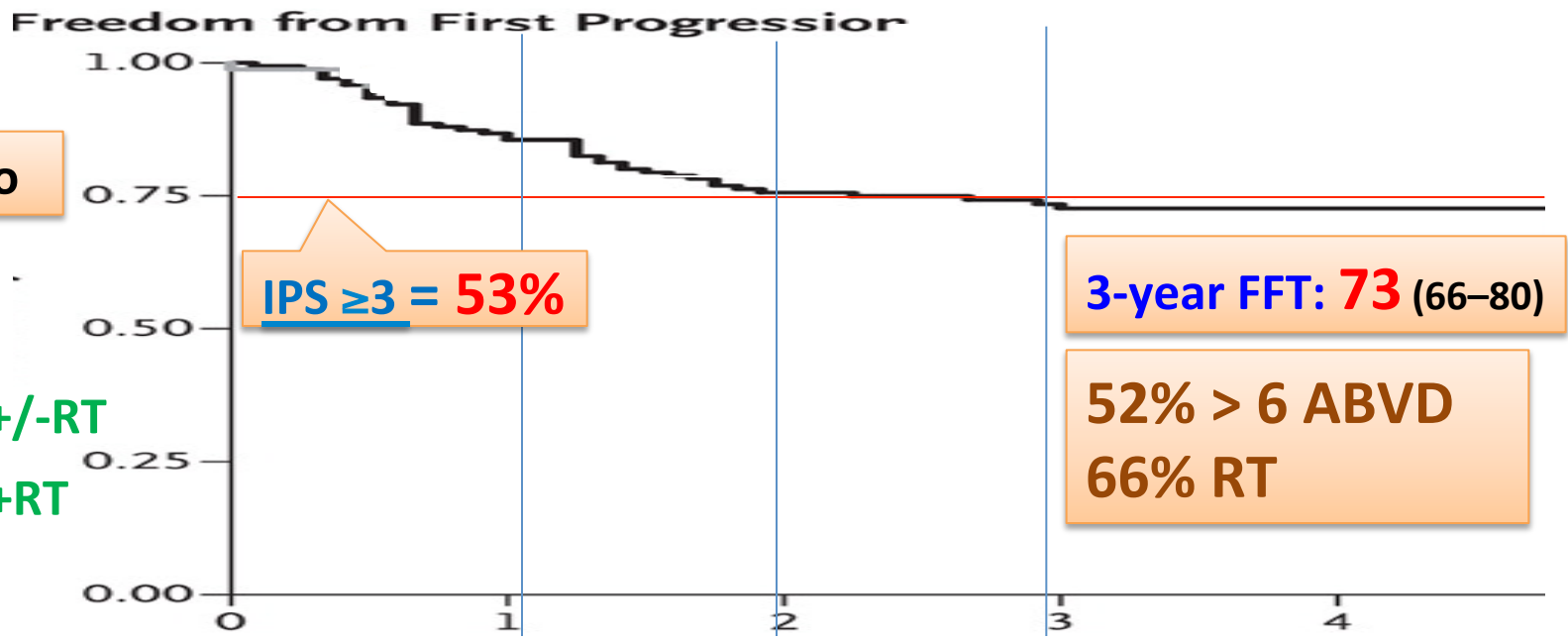


CT Response-adapted vs PET2-adapted ABVD program

Michelangelo

ABVD x4 + 2 +/-RT

ABVD x4 + 4 +RT



IPS ≥3 = 53%

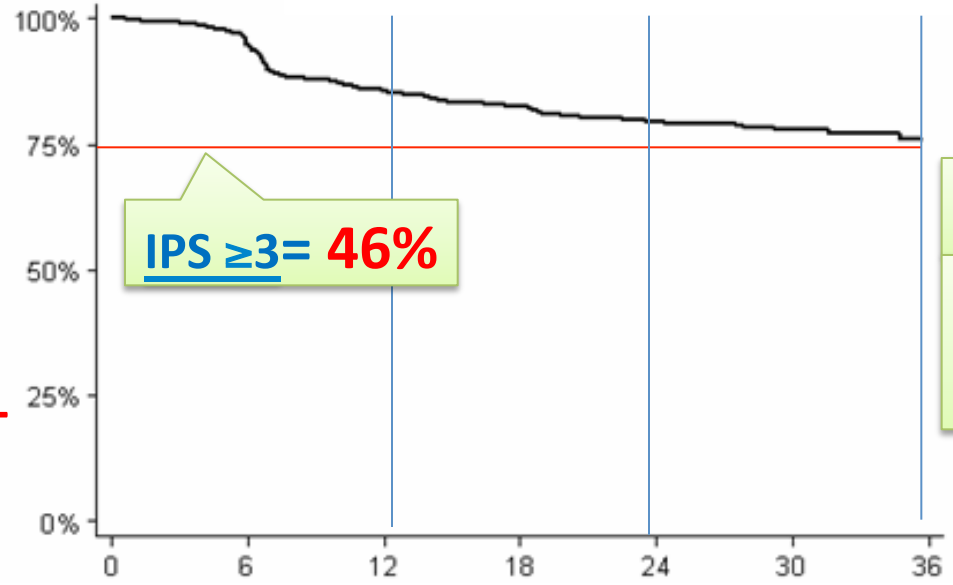
3-year FFT: 73 (66–80)

52% > 6 ABVD
66% RT

FIL HD0801

ABVD x2 + 4 +/- RT

ABVD x2 + HDT/SCT



IPS ≥3= 46%

3-year FFT: 76 (71–80)

PET-adaptation
HDT / ASCT

Viviani et al, NEJM 2011, 365;3
Zinzani et al, 2015 - under review

Love in the Time of … PET

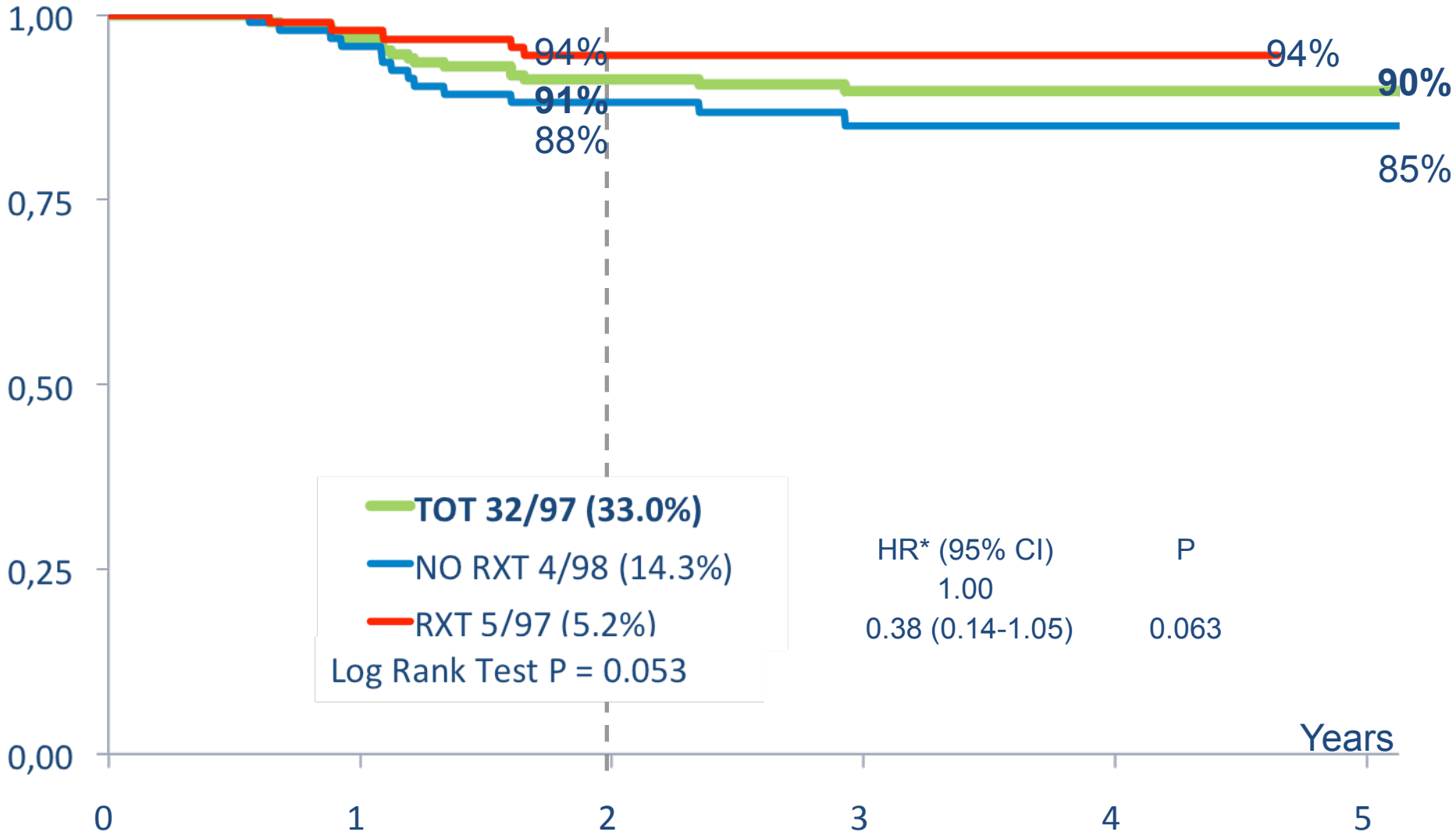
ABVD and Radiotherapy

in advanced stage HL

MAGRITTE : "Les amants"

(1928, olio su tela, New York, RS.Zeisler Collection)

HD0607: FFS in PET2 NEG +/- Radiotherapy (N=195)



Patients at risk (Events)

TOT	**195**	**(6)**	**180**	**(10)**	**151**	**(2)**	**93**	**(0)**	**19**	**(0)**	**1**	**(1)**
NO RXT	98	(4)	90	(7)	75	(2)	41	(0)	6	(0)	1	(1)
RXT	97	(2)	90	(3)	76	(0)	52	(0)	13	(0)	-	(-)

*Unadjusted

Courtesy of Prof Gallamini

SCORE 3: FUNCTIONAL OR ABSOLUTE ?

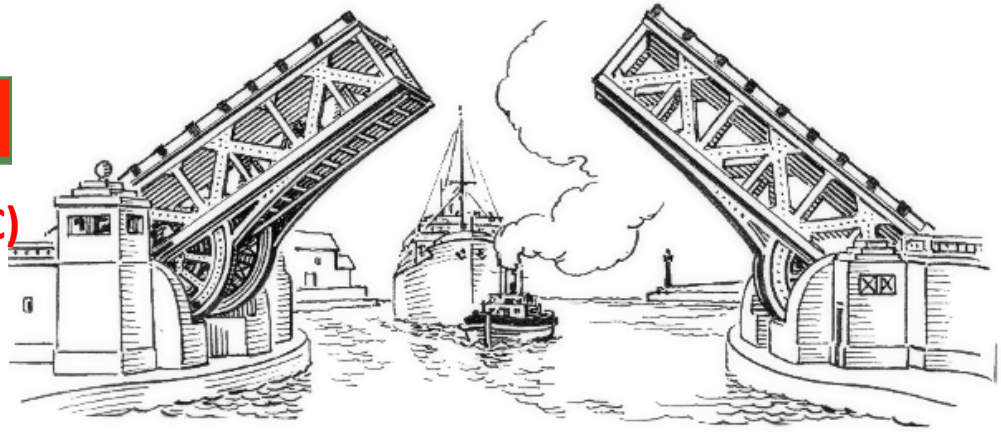
DEAUVILLE Scale

- Score 1 no uptake
- Score 2 uptake ≤ mediastinum
- Score 3 uptake > mediastinum but ≤ liver
- Score 4: moderately ↑uptake > liver
- Score 5 markedly ↑uptake > liver and/or new sites of disease

CR

1 2 3 4 5

Juweid criteria (IHC)
GHSG HD18
UK RAPID
LYSA/FIL HD10



CR

1 2 3 4 5

UK RATHL
HD0606
HD0801
S0816

a ‘bascule bridge’ fitting clinical trials but possibly treacherous in daily clinical practice

A study to investigate dose escalation of doxorubicin in ABVD chemotherapy for Hodgkin lymphoma incorporating biomarkers of response and toxicity

A Gibb[1,7], A Greystoke[1,2,3,7], M Ranson[1,2,3], K Linton[1,2], S Neeson[1], G Hampson[2,3], T Illidge[1,2,3], E Smith[1], C Dive[2,3], A Pettitt[4], A Lister[5], P Johnson[6] and J Radford[*,1,2]

Table 1. Planned doses of Dox by cohort delivered in the phase 1 study of dose-escalated Dox in cycles 1–3 ABVD

Cohort	Dose of Dox in mg m^{-2} in cycles: 1–3	4	5	6	Total dose Dox (% of standard ABVD)	Dose intensity Dox cycles 1–3 as % of standard ABVD
1	35	25	25	0	310 mg m^{-2} (103)	140
2	45	25	0	0	330 mg m^{-2} (110)	180
3	55	0	0	0	330 mg m^{-2} (110)	220
4	65	0	0	0	390 mg m^{-2} (130)	260

Escalated ABVD incorporating doxorubicin at 45 mg m^{-2} in cycles 1–3 can be delivered safely

"…in terms of next steps ***a randomized trial addressing the hypothesis that a strategy of escalated ABVD*** *with early biomarker driven adjustments of dose* ***is more effective than standard ABVD is currently under consideration by the UK NCRI*** *Lymphoma Clinical Studies Group.»*

www.bjcancer.com | DOI:10.1038/bjc.2013.605

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

Filippo Russo,[1]* Gaetano Corazzelli,[1]* Ferdinando Frigeri,[1] Gaetana Capobianco,[1] Luigi Aloj,[2] Francesco Volzone,[1] Annarosaria De Chiara,[3] Annamaria Bonelli,[4] Tindaro Gatani,[5] Gianpaolo Marcacci,[1] Daniela Donnarumma,[1] Cristina Becchimanzi,[1] Elisabetta de Lutio,[6] Franco Ionna,[7] Rosaria De Filippi,[8] Secondo Lastoria[2] and Antonello Pinto[1]

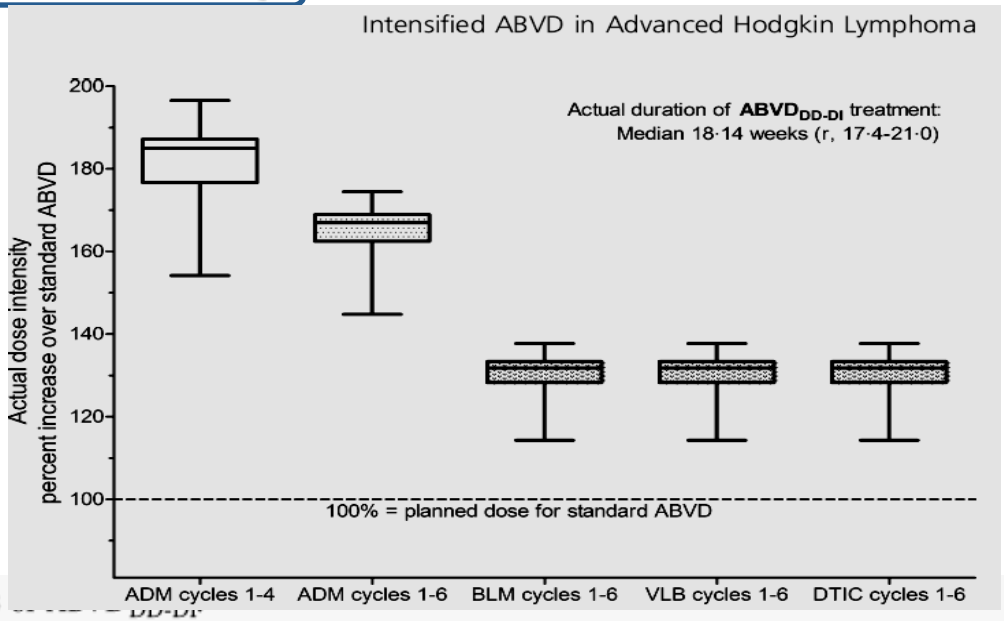


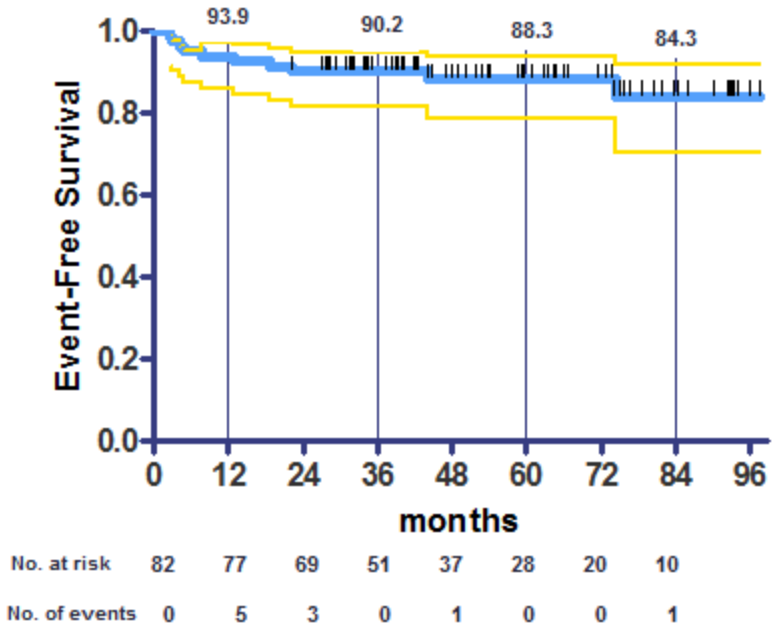
Table I. Drug doses, schedule and treatment administration details

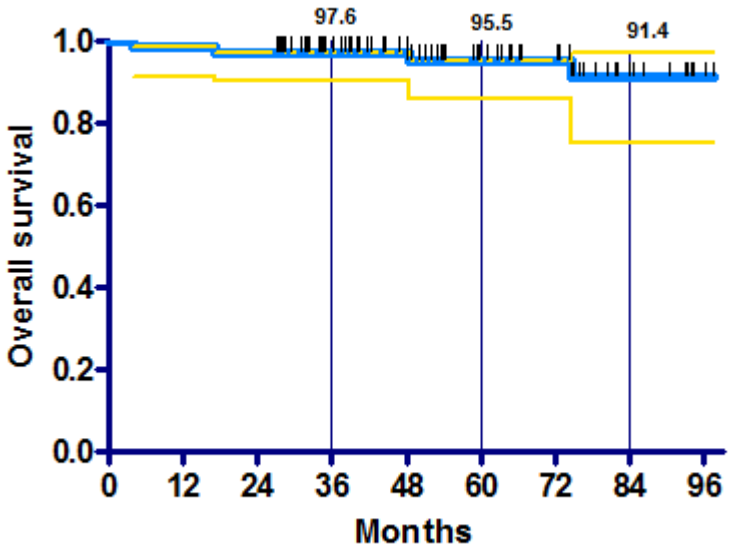
Drug	Dose (mg/m^2)	Route	Days	Cycles 1	2	3	4	5	6
Doxorubicin	35	IV	1, 11	↓	↓	↓	↓		
Doxorubicin	25	IV	1, 11					↓	↓
Bleomycin	10	IV	1, 11	↓	↓	↓	↓	↓	↓
Vinblastine	6	IV	1, 11	↓	↓	↓	↓	↓	↓
Dacarbazine	375	IV	1, 11	↓	↓	↓	↓	↓	↓
Lenograstim (G-CSF)	263 μg/d*	SC	6→8	↔	↔	↔	↔	↔	↔
Lenograstim (G-CSF)	263 μg/d*	SC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

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 PET	10		
Negative	8		
Positive	2		
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



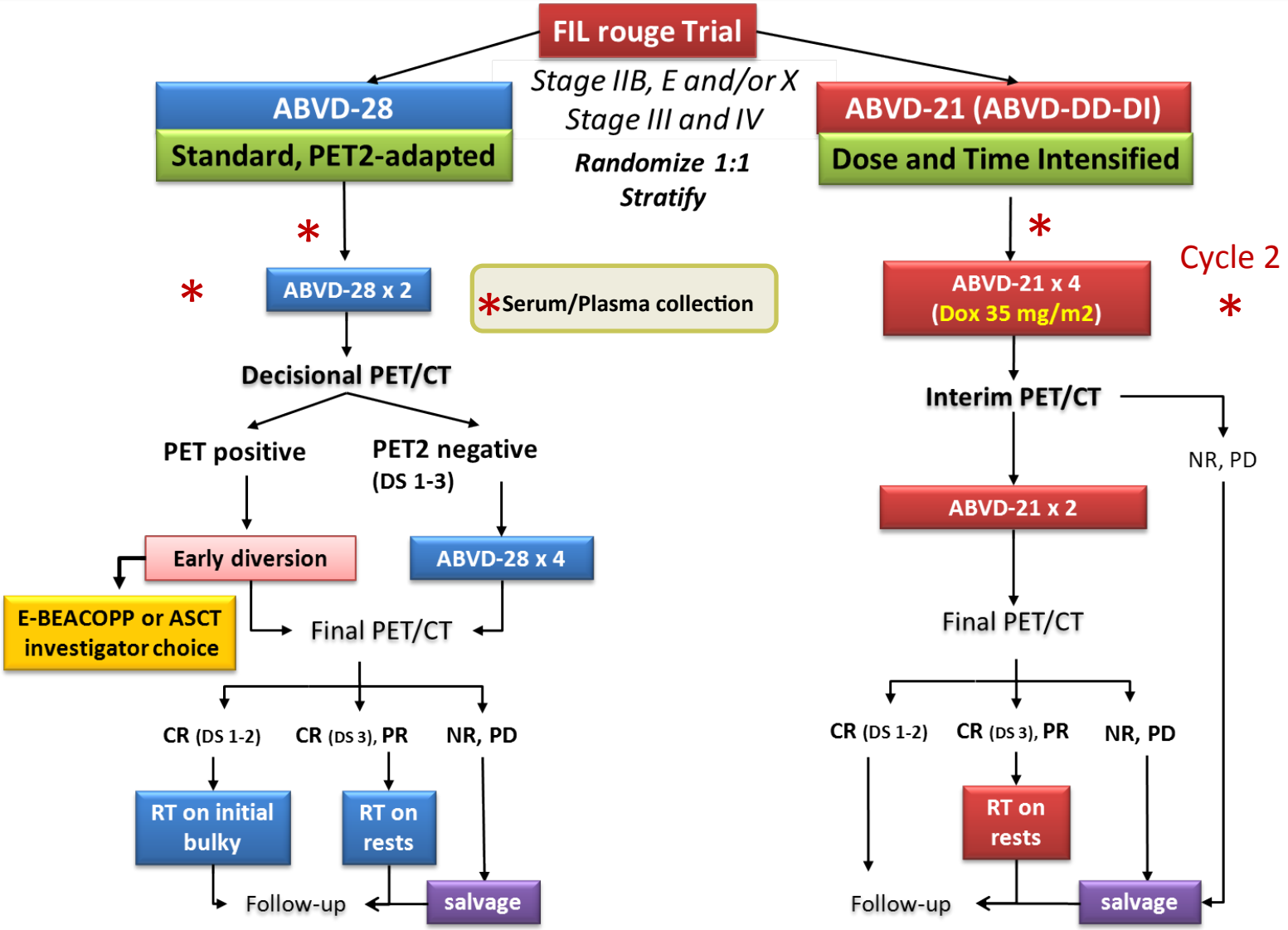


UPFRONT DOXORUBICIN INTENSIFICATION (FIRST 3 TO 5 COURSES)

intensified	DOXO single dose	days	Cycle intervals	DOXO DI mg/m2/w	Increase over standard ABVD	
ABVD						
UK NCRI	45 mg	1, 15	28	22.5	+80%	BJC, 2013
INT Napoli	35 mg	1, 11	21	23.3	+86%	BJH, 2014
ABVE-PC						
US COG P9425	30	1, 2	21	20	+60%	Blood,2009
US COG AHOD0031						JCO, 2014
conventional						
ABVD	25	1, 15	28	12.5	0	

EARLY AND DELAYED INTENSIFICATION IN ADVANCED HL		PET-BASED ESCALATION (RATHL, S0816, HD0607,HD0801)	UPFRONT INTENSIFICATION (GHSG HD15, HD18, ABVE-PC, ABVD DD-DI)
Early interim PET	Predictive value	High	Low; no 'high risk ' subset
	interpretation	Deauville score 3 lingering over real negatives and true positives	Dichotomization between +ve and -ve pts unnecessary
	application	Technical expertize required	Not mandatory
Outcome	CR	PET2 negativity > 80% but only 2/3 of patients finally confirmed as CR	Reduced risk for primary refractoriness
	RT on initial bulk	Role of RT not yet clarified High PET+ve rate in case of bulk	Unnecessary or omissible
	3-y PFS	Some percent points higher than historical results; 2/3 of PET2+ve pts rescued upon escalation; unsatisfactory results in PET2-ve (<80% at 2 years)	Substantial PFS approaching or exceeding 90%
Toxicity		Unnecessary escalation for 20-40% of PET+ve pts accounted to achieve a durable CR by just continuing ABVD	Potential overtreatment of a sizeable fraction of patients Less RT-related sequelae
		BEACOPP or ASCT related sequelae	

STUDY DESIGN



Deauville Score (DS), as harmonized into IWG definitions by The Lugano Classification 2014 (Cheson et al. 2014)

EXPERIMENTAL ARM: TREATMENT SCHEDULE

Course n°	1		2		3		4		5		6	
Day	1	11	1	11	1	11	1	11	1	11	1	11
ABVD DD-DI	dose densification →											
	dose intensification →											
ADM 35 mg/m²	✓	✓	✓	✓	✓	✓	✓	✓				
ADM 25 mg/m²									✓	✓	✓	✓
BLM 10 mg /m²	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
VLB 6 mg/m²	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
DTIC 375 mg/m²	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Lenograstim dd 6 →8	☒		☒		☒		☒		☒		☒	
Lenograstim dd 17→19		☒		☒		☒		☒		☒		☒

Single course duration: 3 weeks ; total treatment lenght : 18 weeks (4.2 mo.s)

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%

RADIOTHERAPY

Treatment Arm A (PET-adaptation arm – standard ABVD):
Radiotherapy of 30 Gy (ISRT)
➔ to residual disease ≥2.5 cm in CR (5PS 3)* or PR (according to Lugano 2014)
➔ to initial bulky site in CR patients (with 5PS 1-2)

Treatment Arm B (Experimental – ABVD DD-DI):
Radiotherapy of 30 Gy (ISRT)
➔ to residual disease ≥2.5 cm in CR (5PS 3)* or PR (according to Lugano 2014)

*central review panel decision after chemotherapy.

THE IMPLEMENTATION OF ABVD PLATFORM

	HD0607 ABVD	HD0801 ABVD	AHOD0031 ABVE-PC	HD12 BEACOPPesc
Radiotherapy on intial bulky diseas	94% (4y PFS)	Not available	87.9% (4y EFS)	93%(5y FFTF)
No radiotherapy on initial bulky disease	85% (4y PFS)	Not available	84.3% (4y EFS)	92% (5y FFTF)

ENDPOINTS

PRIMARY

Progression-Free-Survival (PFS)defined as the time from randomization until lymphoma progression or death as a result of any cause (with at least 3 years of follow-up).

SECONDARY

- **CR** rate
- **disease-free survival** (DFS)
- **event-free survival** (EFS)
- **overall survival** (OS)
- acute and delayed pulmonary and cardiac **toxicity**
- **Late toxicities, second malignancies**
- quality of Life (**QoL**)
- **Cost**-effectiveness

STATISTICAL ANALYSIS

Randomization will allocate patients with a 1:1 ratio in the two arms.

We assumed a 3-year PFS rate of 75% for the comparator PET-2-adapted ABVD arm according to the recently closed study FIL HD0801 and a minimum expected absolute improvement of 10% in the experimental arm.

Absolute 3 years PFS difference Δ	α error (two-tails)	β error	Drop out	Patients x arm and total
10%	0.05	0.10	5%	250x2 =500

Duration of enrollment: 36 months

Safety will be strictly monitored, both during the ABVD cycles and the salvage treatments

This sample size will also ensure to detect similar differences between arms for most of the secondary objectives with acceptable statistical power

Prof. G. Ciccone, A.O.U. Torino
Coordinator for Statistical Design and Evaluation

WEB-BASED ALLOCATION PROCEDURE

It will be completely concealed to researchers and stratified according to:

- sex,
- participating center,
- tumor stage (IIB or IIIA vs. IIIB or IV), bulky disease
- age (<45 years vs. ≥45 years)
- International Prognostic Score (IPS, <3 vs ≥3)

- type of preferred salvage treatment by the Center (intensified conventional chemotherapy vs. HDT/ASCR)

Prof. G. Ciccone, A.O.U. Torino
Coordinator for Statistical Design and Evaluation

STUDY POPULATION

INCLUSION CRITERIA

- Must have histologically confirmed classical HL.
- Age 18-60 years
- Clinical stage IIB with extranodal involvement and/or mediastinal bulk, III and IV
- No previous chemotherapy, radiotherapy or another investigational drug for HL
- ECOG performance status ≤2
- Must have adequate organ and marrow function
- No cardiac arrhythmia, conduction abnormalities, ischemic cardiopathy, left ventricular hypertrophy or left ventricular ejection fraction (LVEF) ≤50% at echocardiography or gated blood pool scan (MUGA) with an ejection fraction > or = to 50%
- Carbon monoxide diffusion capacity (DLCO) tests and/or forced expiratory volume (FEV1) >25% lower than normal predicted value
- No known human immunodeficiency virus (HIV) positivity or active infectious hepatitis, type A, B, or C
- If patients have a history of malignancy other than cutaneous basal cell or squamous cell carcinoma, they must be disease-free for ~ five years at the time of enrollment

STUDY POPULATION

EXCLUSION CRITERIA

- Nodular Lymphocyte Predominant HL
- cardiac arrhythmia, conduction abnormalities, left ventricular hypertrophy or left ventricular ejection fraction (LVEF) ≤50% at echocardiography, ischaemic cardiopathy
- Abnormal QTcF interval prolonged (> 459 msec)
- Carbon monoxide diffusion capacity (DLCO) tests and/or forced expiratory volume (FEV1) <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 ≥ 5 years. Exceptions include the following: Basal cell carcinoma of the skin
- Squamous cell carcinoma of the skin; Carcinoma in situ of the cervix; Carcinoma in situ of the breast)
- Incidental histological finding of prostate cancer (TNM stage of T1a or T1b)
- Uncontrolled infectious disease
- Impaired renal function (creatinine clear.<60 ml/min or serum creatinine >2 mg/dL)
- Known HIV infection or active infectious hepatitis, type A, B or C
- Uncompensated diabetes

'FIL rouge' trial:

- To exploit, also through the ABVD platform, the 'first hit' principle that has been pivotal to the development of BEACOPP strategies
- To keep within an ABVD strategy those 20% to 40% of patients with a positive PET2 accounted of chance to reach a durable CR by just proceeding with ABVD, and are actually switched (and overtreated) into BEACOPP according to current PET2-based escalation strategies
- To reduce the rate of primary treatment failures, avoid the treatment mortality (4%) associated to PET-based escalation to intensified BEACOPP or HDT followed by ASCT and possibly reduce the load of consolidation radiotherapy