Response Adapted treatment of cHL using BV in first line

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From the book of ^{18}FDG-PET in BV treatment patients

1 In the beginning Seattle Genetics created SGN35.
3 And Anas said:

LET THERE BE RESPONSE ASSESSMENT TO SGN35 PERFORMED BY PET

and there was response assessment to SGN35 performed by PET.

Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed Hodgkin's lymphoma: a phase 1, open-label, dose-escalation study was launched.

Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed Hodgkin's lymphoma: a phase 1, open-label, dose-escalation study

Treatment response was assessed by CT and ^{18}F-fluorodeoxyglucose (18F-FDG) PET scans, done in accordance with institutional standards of care which also included an exploratory retrospective PET scan review by a central radiology review facility (CoreLab Partners Inc, Princeton, NJ, USA), for all patients after cycle 2.

Brentuximab vedotin: testing in first line

Phase 1 study of brentuximab vedotin combined with ABVD or AVD in patients with newly diagnosed advanced-stage HL

Eligibility

- Treatment-naïve HL
- Age ≥18 years to ≤60 years
- Stage IIa bulky disease or Stage IIb–IV disease

Treatment (n=51)*

- Brentuximab vedotin 0.6–1.2 mg/kg iv on Day 1 and Day 15 of 28-day cycles
- ABVD or AVD (standard doses) on Day 1 and 15 of 28-day cycles
- Five cohorts**
  - 0.6 mg/kg + ABVD, n=6
  - 0.9 mg/kg + ABVD, n=13
  - 1.2 mg/kg + ABVD, n=6
  - 1.2 mg/kg + AVD, n=6
  - 1.2 mg/kg + AVD (expansion cohort), n=13 of 20 planned
- Maximum 6 cycles

Objectives

- Assess safety profile of brentuximab vedotin in combination with ABVD or AVD
- Determine the MTD of brentuximab vedotin in combination with ABVD or AVD
- Assess anti-tumour activity of brentuximab vedotin in combination with ABVD or AVD

Younes et al. Lancet Oncol 2013

Deauville Criteria

NEGATIVE SCAN

Score 1 no uptake

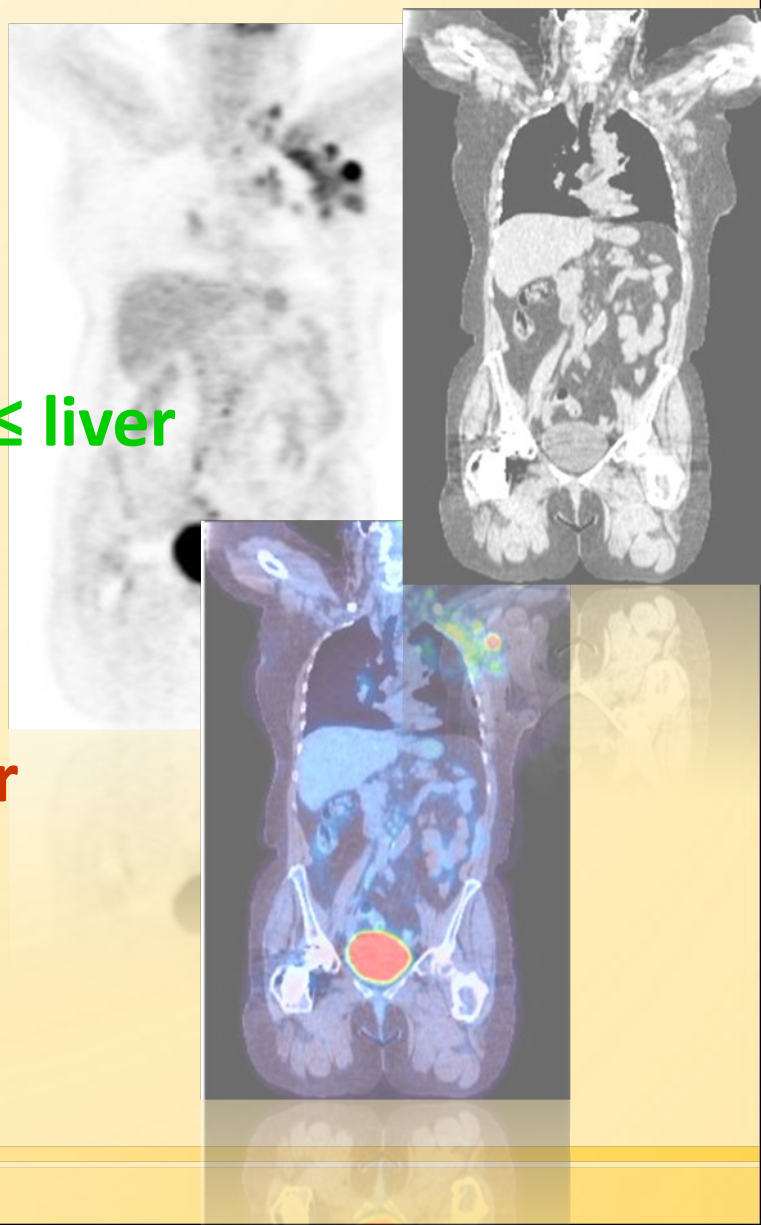
Score 2 uptake ≤ mediastinum

Score 3 uptake > mediastinum but ≤ liver

POSITIVE SCAN

Score 4: moderately ↑uptake > liver

Score 5 markedly ↑uptake > liver

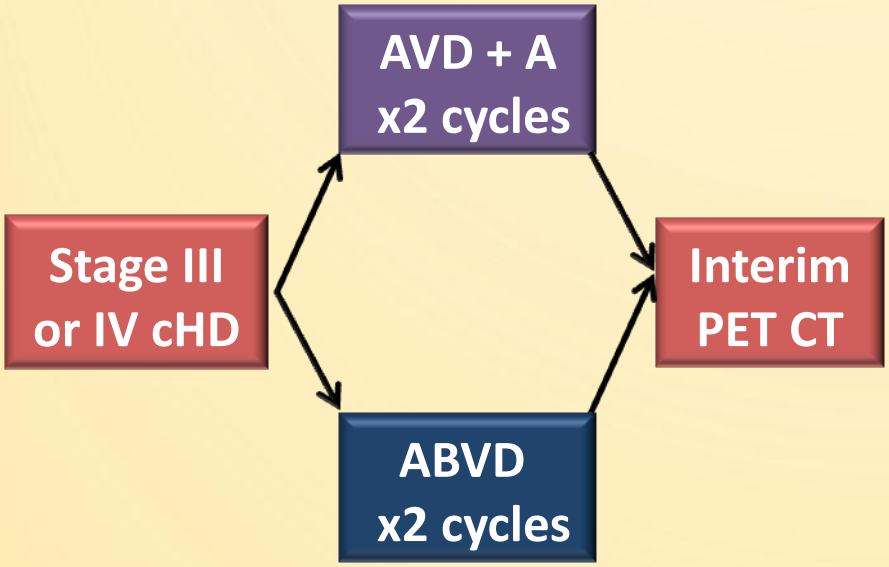


Response

		BVand ABVD group (n=25)	BVand AVD group (n=26)
Cycle 2 PET scan per IRF		22	26
	Neg	22 (100%)	24 (92%)
	Pos	0	2 (8%)
Best response at end of front-line treatment per investigator		22	25
	CR	21 (95%)	24 (96%)
	PD	0	1 (4%)
	N/E	1 (5%)	0
95% CI for CR		77·2-99·9	79.7-99·9

Younes et al. Lancet Oncol 2013

ECHELON-1 phase III study



Primary endpoint: PFS
n=1040, 2 year recruitment

PET Reviewing
(According to the Revised Response Criteria for Malignant Lymphoma)

LOCAL

Nuclear medical physician

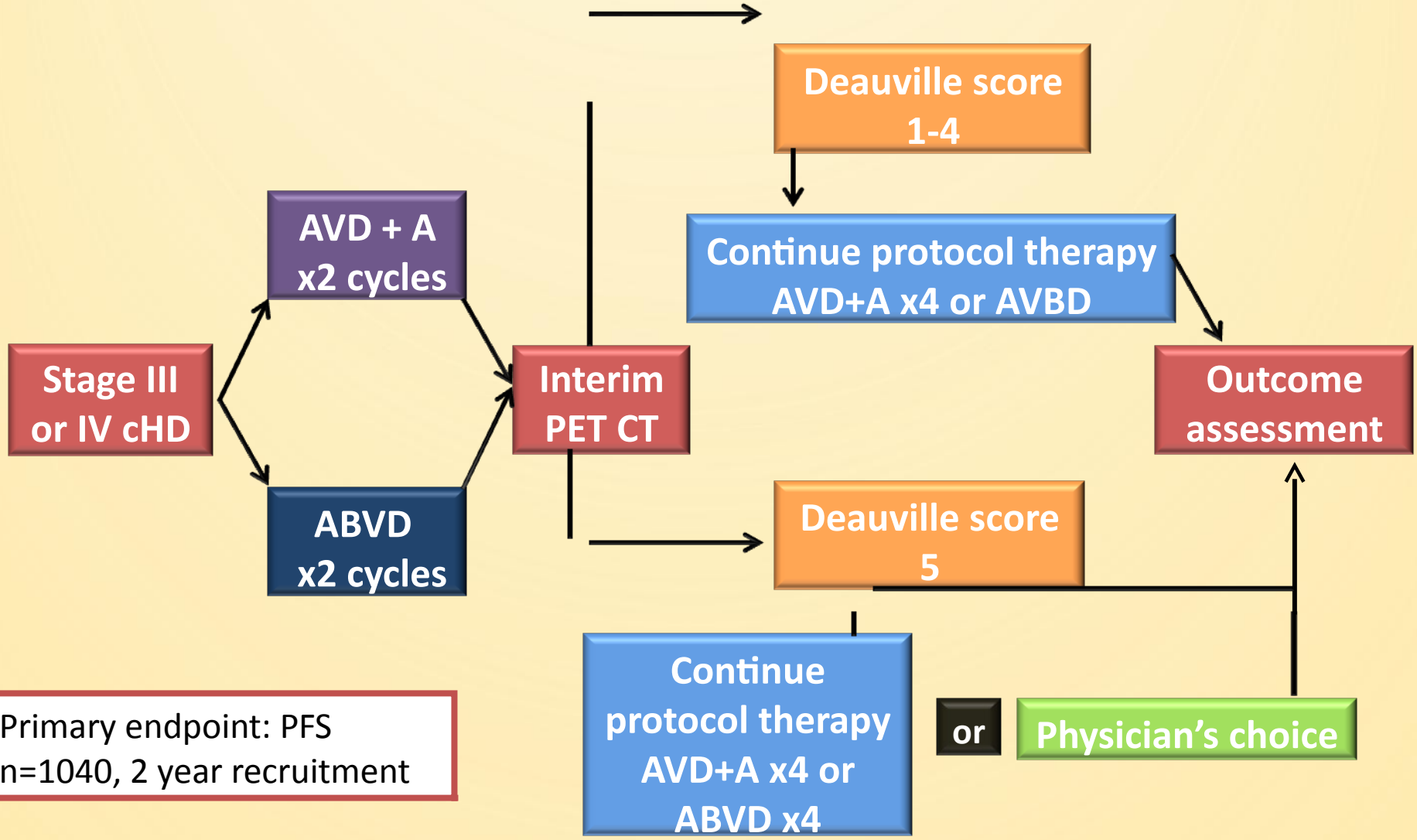
CENTRALIZED

CoreLab

PET score 1-5

Cycle 2 PET scan must be submitted to CoreLab partners via Internet Media Transfer (IMT) within 24 hours of scanning → Deauville Scoring will be used to evaluate the results of PET

ECHELON-1 phase III study



Primary endpoint: PFS
n=1040, 2 year recruitment

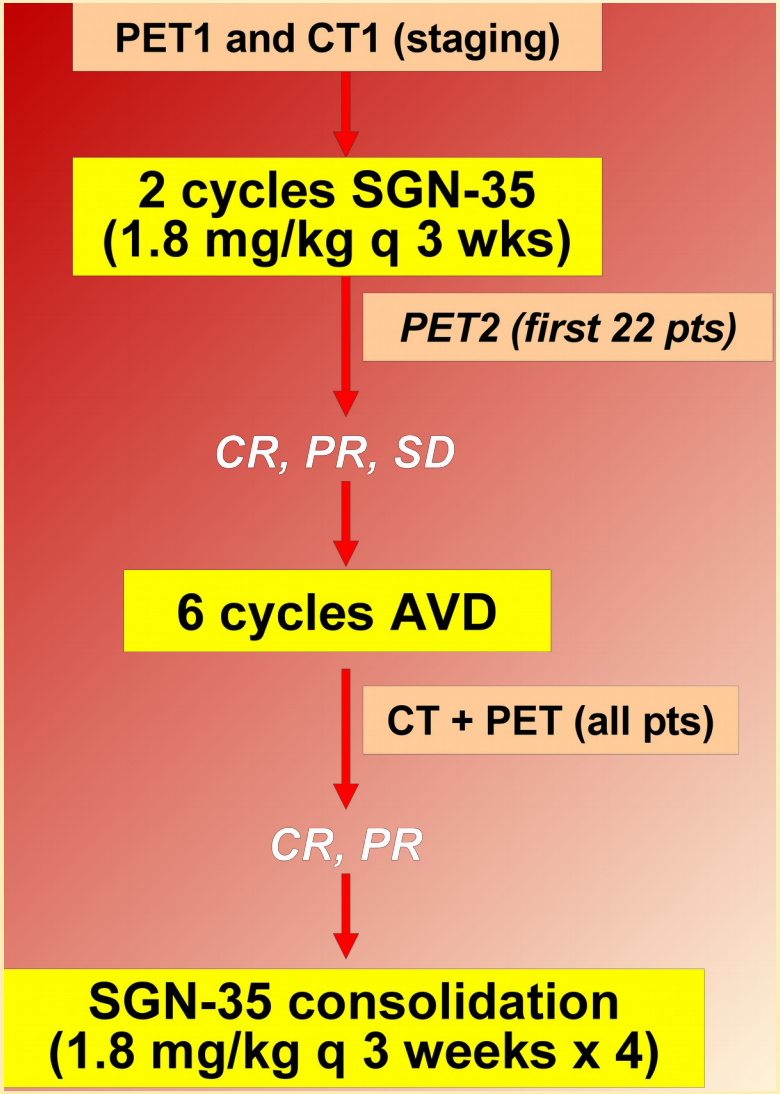
Sequential Brentuximab Vedotin (BV) With Adriamycin, Vinblastine, and Dacarbazine (AVD) for Older Patients with Untreated Hodgkin Lymphoma: Preliminary Toxicity Findings from a Phase II Window Study

Andrew Evens (1), Paul Hamlin (2), Ranjana Advani (3), Michelle Fanale (4), Sonali M. Smith (5), Gregory Bociek (6), Timothy Fenske (7), Adam Petrich (8), Jane Winter (8), Leo Gordon (8)

(1)Tufts Medical Center, Boston, MA; (2) Memorial Sloan Kettering Cancer Center, New York, NY; (3) MD Anderson Cancer Center, Houston, TX; (4) Stanford University, Stanford, CA; (5) University of Chicago, Chicago, IL; (6) University of Nebraska, Omaha, NE; (7) Medical College of Wisconsin, Milwaukee, WI; (8) Northwestern University, Chicago, IL

9th ISHL, Cologne 2013, Abstract #77

Incorporation of Brentuximab Vedotin (BV) into Frontline Therapy



- Phase II investigator-initiated study
- Untreated advanced-stage elderly HD (=/> 60 yrs)
- PS 0-2, no limit ADLs, etc
- Sites: Northwestern, Ohio State, UMass, Nebraska, Univ. of Chicago, MSKCC, MDACC, Stanford, Tufts
- Window (lead in) w/ SGN-35
- Prim objective: CR rate (goal n=45 evaluable)
- Tissue based studies
- CGA (CIRS-G) and HRQL
- Study of “early” FDG-PET

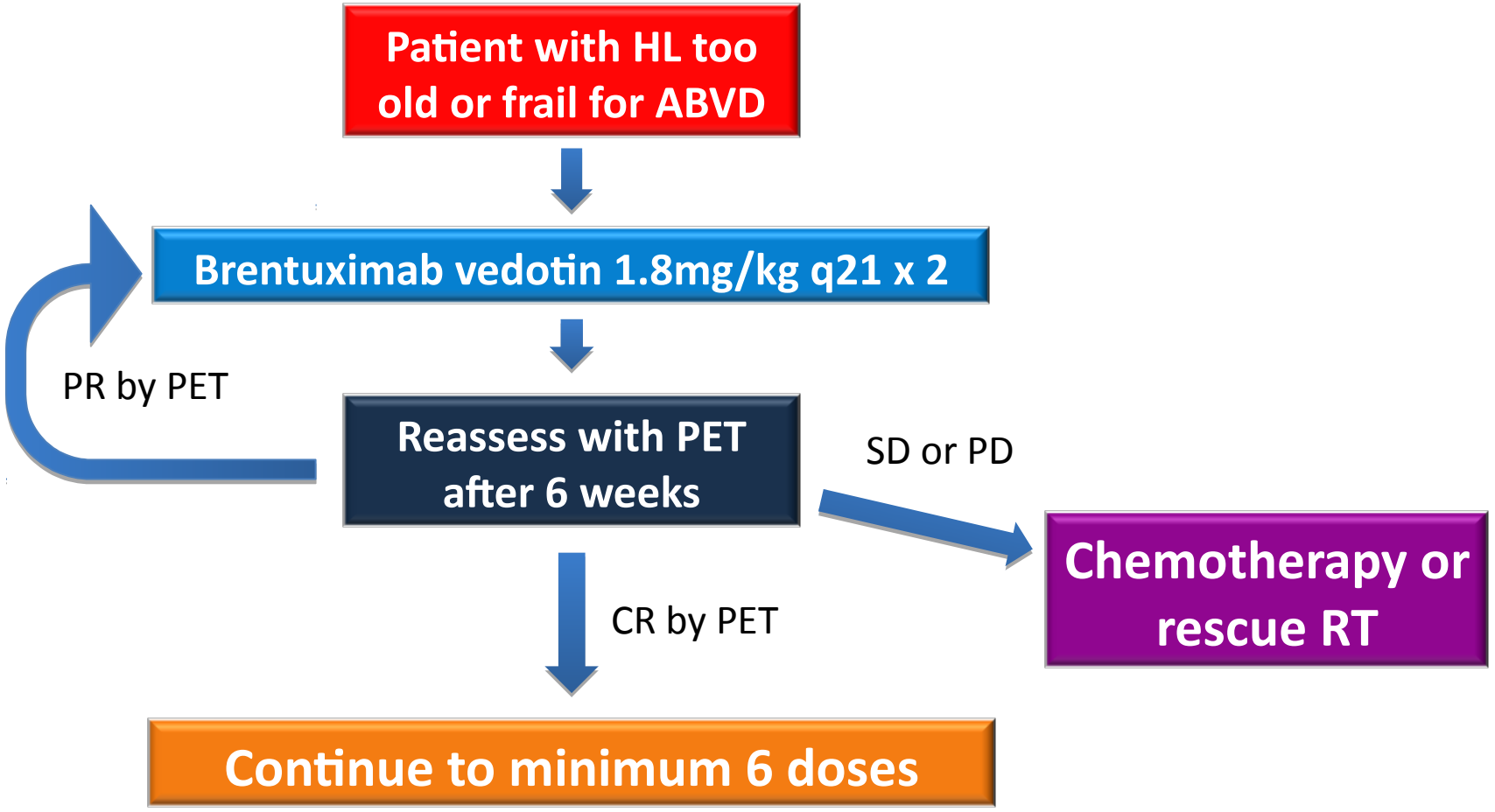
Patient Characteristics

Characteristic	Data
Age	Median 73 years (61-88)
Gender	5F and 2M
Histology	NSHD (n=4) and MC (n=3)
ECOG PS	0 (n=3), 1 (n=2), and 2 (n=2)
Stage	II (n=2), III (n=2), and IV (n=3)
IPS	Median 4 (range, 2-7)
Functional status	57% grade 3-4 co-morbidity (CIRS), 29% “not fit”, 14% geriatric syndrome, and 14% loss ADLs

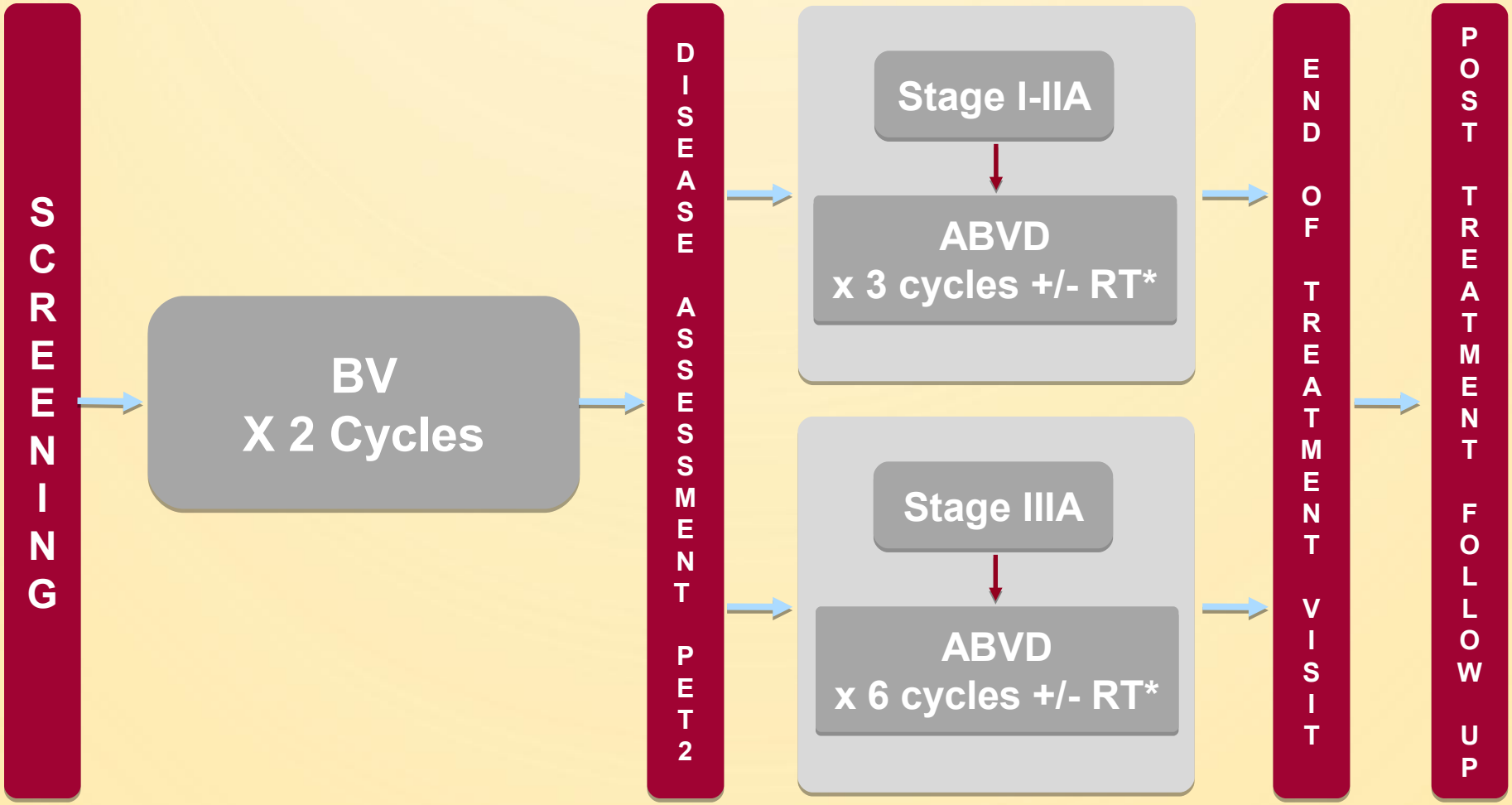
Preliminary Efficacy

- **Response to "lead in" BV Rx (by PET Deauville)**
  - **PET negative in 4/6 and n=1 pathologic CR (71%)**
- **Survival: 5/7 alive (1 death due to PD [pt #1] and 1 due to toxicity)**

Testing in older patients: BREVITY study



BV followed by ABVD in patients with previously untreated Hodgkin lymphoma



M. Federico et al: EUDRACT 2012-002012-46

Aims of the Study

- Primary objective:

To determine the efficacy and safety of 2 courses of BV before the start of a standard program with ABVD +/- RT in patients with limited/intermediate stage HL.

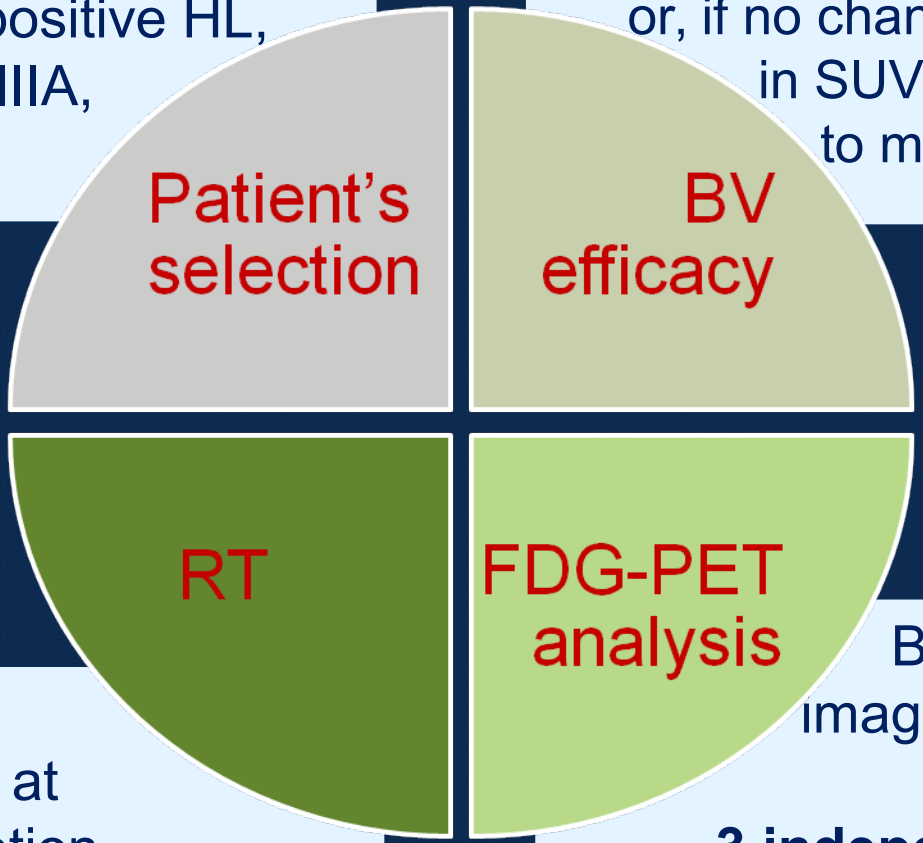
- Secondary objectives:

Estimate the clinical benefit to the full treatment program with BV followed by ABVD +/- RT in terms of response and progression free survival.

Methods

Patients with previously untreated CD30-positive HL, stage IA or IIA or IIIA, no bulky disease.

Reduction of **Deauville Score (DS)** or, if no change in DS, reduction in SUV intensity compared to maximum basal SUV.



Decision on radiotherapy was at physician's discretion.

Baseline and PET-2 images were assessed by a panel of **3 independent reviewers**.

Review methodology

- Central panel review:
  - Independent reviewers:

  - Deauville criteria with 5 point-scale
  - Widen for image exchange

www.widen.it

- PET procedure harmonization:
  - real time analysis of violation with Widen
- PET scanner equalization in Cuneo Core Lab

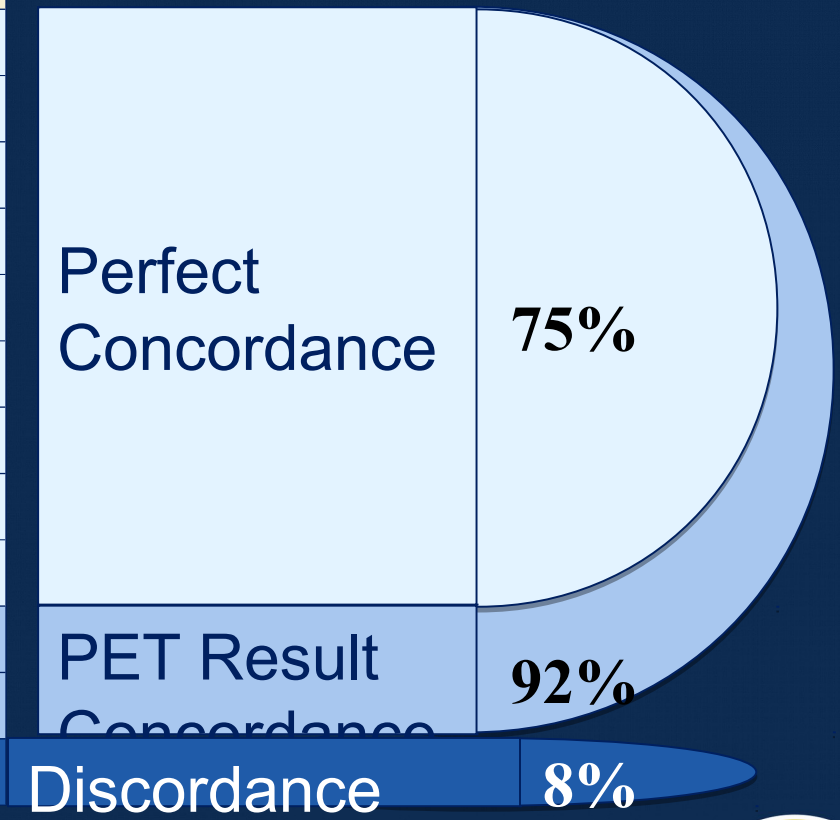
Metabolic Response by CENTRAL REVIEW

Objective Response*	N	%
Complete Metabolic Response	10	83
Partial Metabolic Response	1	8
Disease Progression	1	8

92% responding patients

PET results: LOCAL vs CENTRAL

Case ID	Local Score	Reviewed Score
001BV-ABVD	1	1
011BV-ABVD	1	1
005BV-ABVD	2	2
009BV-ABVD	2	2
010BV-ABVD	2	2
003BV-ABVD	3	3
007BV-ABVD	3	3
002BV-ABVD	4	4
006BV-ABVD	5	5
004BV-ABVD	1	2
008BV-ABVD	2	1
012BV-ABVD	4	2

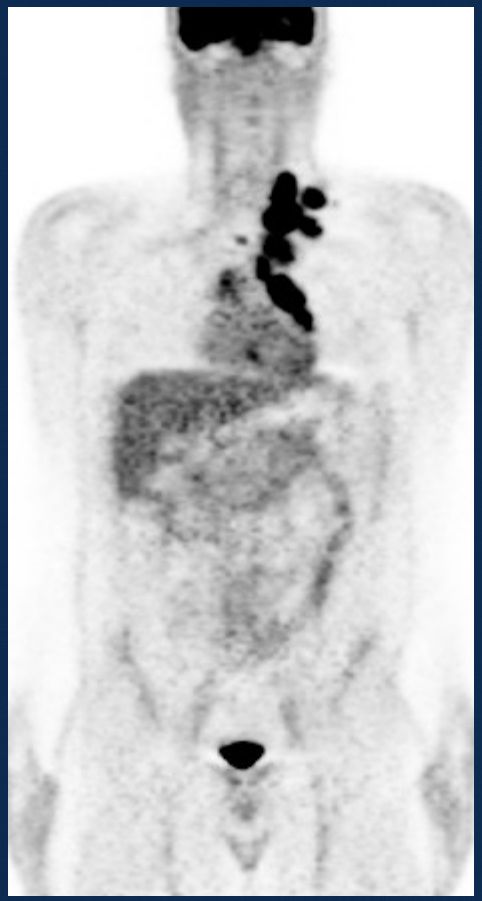


PET Response by Risk Stratification
(EORTC criteria)

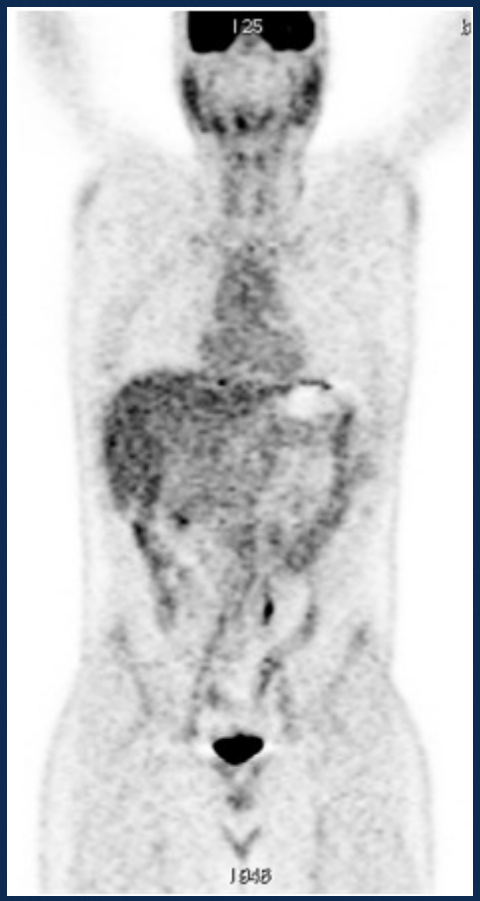
	Early favorable	Early unfavorable	Advanced
No Response	-	-	1
Partial Metabolic Response	-	1	-
Complete Metabolic Response	7	3	-
CR Rate	100%	75%	

Case 009

Baseline



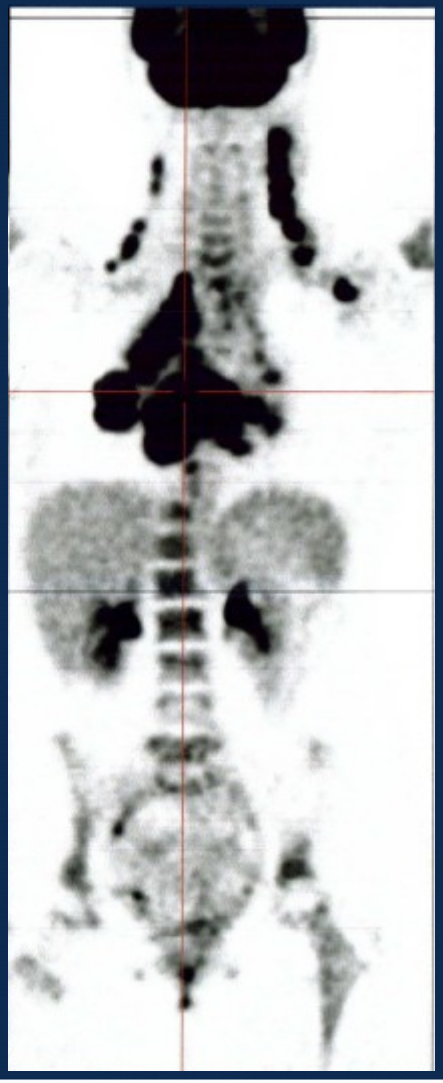
PET 2



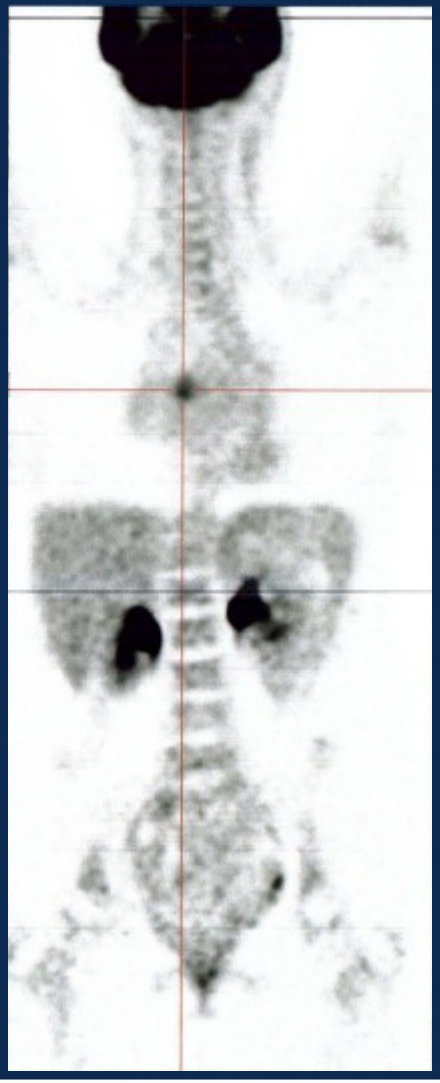
- 28-year-old male;
- Treatment:
  - 2 x Brentuximab vedotin 1.8 mg/kg, Q3wk → CR (DS2 pictured)
  - 3 x ABVD → CR
    - Remission duration = 3+ mo

Case 002

Baseline



PET 2



- 19-year-old female;
- Early unfavorable HL
- Treatment:
  - 2 x Brentuximab vedotin 1.8 mg/kg, Q3wk → PR (DS4 pictured)
  - 4 x ABVD → CR
  - RT IF 30 Gy → CR
    - Remission duration = 4+ mo

Final Response to BV + ABVD +/- RT

Case ID	PET2 results	ABVD (N° of cycles)	RT	Final Response*	Follow up (months after completing treatment)	Current Disease Status*
001BV-ABVD	CR	3	Yes	CR	7+	CR
002BV-ABVD	PR	4	Yes	CR	4+	CR
003BV-ABVD	CMR	3	Yes	CR	6+	CR
004BV-ABVD	CMR	3	Yes	CR	4+	CR
005BV-ABVD	CMR	3	Yes	CR	5+	CR
006BV-ABVD	PD	6	No	PR	5	PD
007BV-ABVD	CMR	3	No	CR	5+	CR
008BV-ABVD	CMR	3	No	CR	5+	CR
009BV-ABVD	CMR	3	No	CR	3+	CR
010BV-ABVD	CMR	3	No	CR	4+	CR
011BV-ABVD	CMR	3	No	CR	4+	CR
012BV-ABVD	CMR	3	No	CR	1+	CR

*According to Cheson 2007 criteria

BREACH

Brentuximab vedotin (SGN-35) associated with chemotherapy in untreated patients with stage I/II Unfavourable Hodgkin's lymphoma

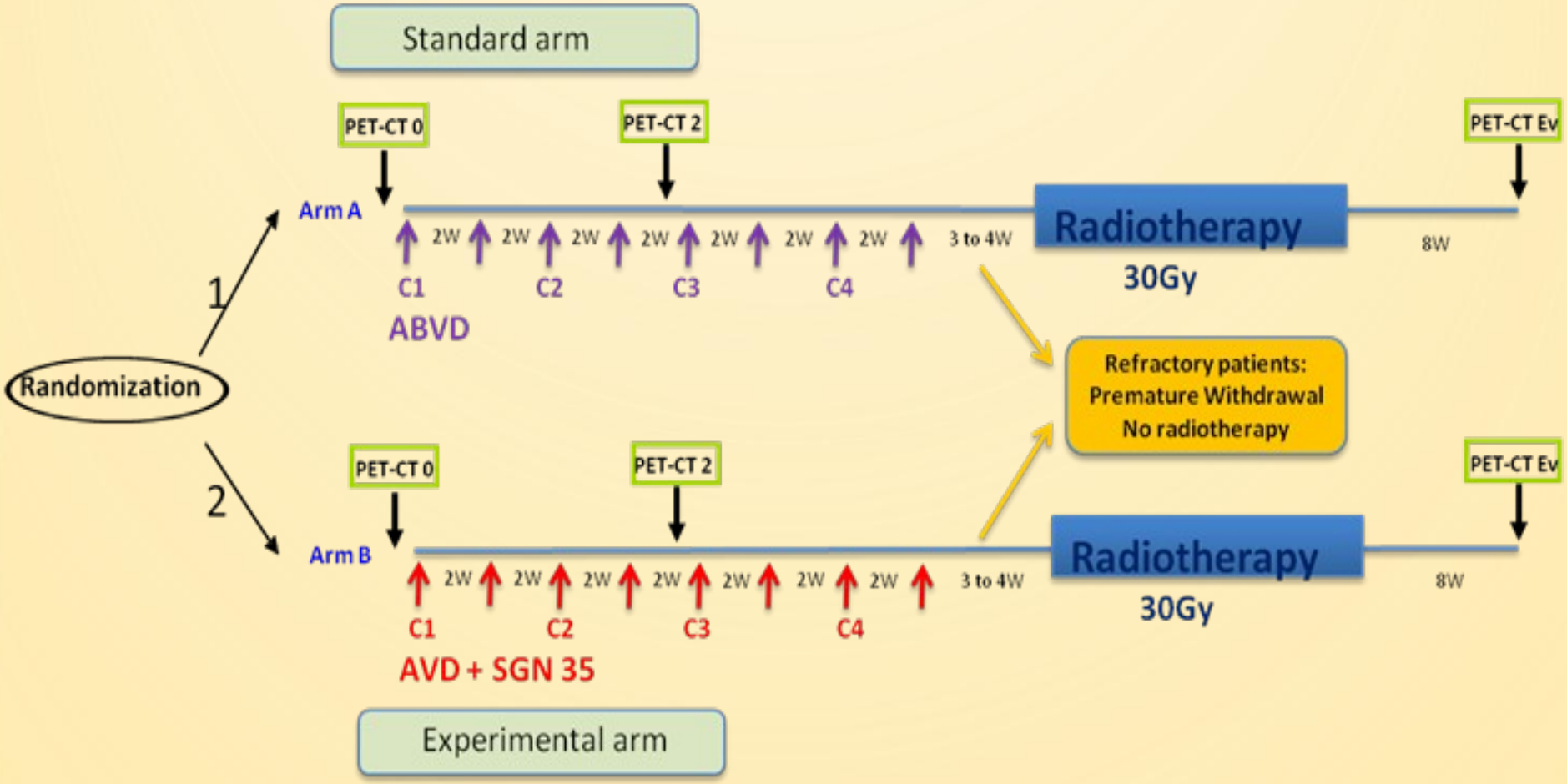
A RANDOMIZED PHASE II LySA-FIL-EORTC INTERGROUP STUDY

Study chairman : **Marc André (Lysa)**

Coordinators : ***Massimo Federico (FIL)***
Igor Aurer (EORTC)

Study design

RND ratio St/Exp 1:2



BREACH

OBJECTIVE

Primary efficacy endpoint:

PET 2 assessment according to the five-point scale Deauville criteria (Negative = 1, 2, 3 and Positive = 4, 5), based on central review.

PET Review LOGISTICS

- **Local FDG-PET reports**

Local nuclear medicine physician upload PET on the Images platform: http://lysarc.imagys.com.

- **PET central review Board**

The reviewer panel is composed by 3 nuclear physicians for review the PETs according to the following rules:
3 reviewers will analyze the PET scans independently and blinded to clinical data.

From the book of 18FDG-PET in BV treatment patients

- **2009:** BV combined with ABVD or AVD for patients with newly diagnosed Hodgkin's lymphoma: a phase 1, open-label, dose-escalation study **(A.Younes)**
- **2011 :** Millennium C25003 Study (ECHELON 1 FASE III STUDY)
- **2012:** BV followed by ABVD (EudraCT 2012-002012-46)
- **2012:** Sequential BV with AVD for older patients. **(A.M. Evens)**
- **2014:** BREACH (EudraCT 2013-000182-37)

- **2014:** Role of Imaging in the Staging and Response Assessment of Lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group. **(Sally F. Barrington at al.)**
- **2014:** Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. **(B.D. Cheson)**

How long Dauville criteria will be valid?

- 2015: The seventh day we would like to rest.