	RECOMMENDATIONS: RESPONSE ASSESSMENT - VISUAL
1.	The Deauville criteria (DC) are recommended for reporting PET scans at interim and end treatment assessment when using visual assessment of response *(category 1).*
2.	If mid chemotherapy assessment is performed, PET-CT is the best imaging modality and is superior to CT alone *(category 1).*
3.	There is currently insufficient evidence to change standard treatment based solely on interim PET-CT outside clinical trials. Imaging findings on interim scans should be related to the anticipated prognosis, clinical findings and other markers of response *(category 1).*
4.	Further investigation of the significance of PET negative residual masses is warranted (*category 3*). Data should be collected prospectively in clinical trials dividing CR into two categories: Complete Metabolic Response (CMR) and Complete Metabolic Response with a residual mass (CMRr) *(category 3).* Residual mass size should be recorded on end of treatment PET-CT report.

	RECOMMENDATIONS: RESPONSE ASSESSMENT - VISUAL
1.	The Deauville criteria (DC) are recommended for reporting PET scans at interim and end treatment assessment when using visual assessment of response *(category 1).*
2.	If mid chemotherapy assessment is performed, PET-CT is the best imaging modality and is superior to CT alone *(category 1).*
3.	There is currently insufficient evidence to change standard treatment based solely on interim PET-CT outside clinical trials. Imaging findings on interim scans should be related to the anticipated prognosis, clinical findings and other markers of response *(category 1).*
4.	Further investigation of the significance of PET negative residual masses is warranted (*category 3*). Data should be collected prospectively in clinical trials dividing CR into two categories: Complete Metabolic Response (CMR) and Complete Metabolic Response with a residual mass (CMRr) *(category 3).* Residual mass size should be recorded on end of treatment PET-CT report.

Rationale

- Many centres perform *mid-chemo* imaging.
- We should be using the best method available for any assessment performed
- PET/CT shows anatomical + metabolic response. Metabolic response is evident earlier.
- Assessment of early response is better with PET/CT than CT

	RECOMMENDATIONS: RESPONSE ASSESSMENT - VISUAL
1.	The Deauville criteria (DC) are recommended for reporting PET scans at interim and end treatment assessment when using visual assessment of response *(category 1).*
2.	If mid chemotherapy assessment is performed, PET-CT is the best imaging modality and is superior to CT alone *(category 1).*
3.	There is currently insufficient evidence to change standard treatment based solely on interim PET-CT outside clinical trials. Imaging findings on interim scans should be related to the anticipated prognosis, clinical findings and other markers of response *(category 1).*
4.	Further investigation of the significance of PET negative residual masses is warranted (*category 3*). Data should be collected prospectively in clinical trials dividing CR into two categories: Complete Metabolic Response (CMR) and Complete Metabolic Response with a residual mass (CMRr) *(category 3).* Residual mass size should be recorded on end of treatment PET-CT report.

	RECOMMENDATIONS: RESPONSE ASSESSMENT - VISUAL
1.	The Deauville criteria (DC) are recommended for reporting PET scans at interim and end treatment assessment when using visual assessment of response *(category 1).*
2.	If mid chemotherapy assessment is performed, PET-CT is the best imaging modality and is superior to CT alone *(category 1).*
3.	There is currently insufficient evidence to change standard treatment based solely on interim PET-CT outside clinical trials. Imaging findings on interim scans should be related to the anticipated prognosis, clinical findings and other markers of response *(category 1).*
4.	Further investigation of the significance of PET negative residual masses is warranted (*category 3*). Data should be collected prospectively in clinical trials dividing CR into two categories: Complete Metabolic Response (CMR) and Complete Metabolic Response with a residual mass (CMRr) *(category 3).* Residual mass size should be recorded on end of treatment PET-CT report.

Consensus

- Mid-Rx PET/CT should be used in the same way as mid-Rx CT is currently used

- Rationale:
  - Early response in PET is prognostic
  - However, there is currently no level-1 evidence that a change in treatment improves outcome
  - Results of current clinical trials are awaited

Examples of PET-based trials in Hodgkin lymphoma

Early /Favourable:

- PET- >chemo: omit RT (UK-RAPID, HD16)

IM / Early unfavourable:

- PET- >2chemo: omit RT (HD17, H10, CALGB phII)
- PET+>2chemo: change ABVD to BEACOPP (H10, CALGB phII)

Advanced

- PET->2chemo:
  - AVD (RATHL)
  - less BEACOPP (HD18)
  - no RT (HD0801, GITIL)
- PET+>2chemo:
  - change ABVD to BEACOPP (RATHL)
  - add Ritux (HD18, GITIL)
  - escalate to HD+ASCT (HD0801)
- PET+>1chemo:
  - escalate to BEACOPP (H11)

Mid-Rx Imaging in Routine Practice

Why mid-Rx imaging is done:

- Is this Rx working?
- How well is it working?
  - Prognosis
  - Action (if disease progression)

Choice of action depends on:

- Prognosis: expected outcome for the specific disease & chemo
- Confidence in response assessment
- Expected outcome of change in Rx (i.e. effectiveness of consolidation or salvage)

Consensus

- Ideally, mid-Rx imaging should be discussed in multidisciplinary meeting to decide on action (if any is required).
- Rationale:
  - To discuss the significance of the imaging in the context of clinical history and findings and the overall prognosis.
  - To minimise diagnostic pitfalls
  - To build experience and enhance mutual understanding of clinicians and nuclear medicine physicians

	RECOMMENDATIONS: RESPONSE ASSESSMENT - VISUAL
1.	The Deauville criteria (DC) are recommended for reporting PET scans at interim and end treatment assessment when using visual assessment of response *(category 1).*
2.	If mid chemotherapy assessment is performed, PET-CT is the best imaging modality and is superior to CT alone *(category 1).*
3.	There is currently insufficient evidence to change standard treatment based solely on interim PET-CT outside clinical trials. Imaging findings on interim scans should be related to the anticipated prognosis, clinical findings and other markers of response *(category 1).*
4.	Further investigation of the significance of PET negative residual masses is warranted (*category 3*). Data should be collected prospectively in clinical trials dividing CR into two categories: Complete Metabolic Response (CMR) and Complete Metabolic Response with a residual mass (CMRr) *(category 3).* Residual mass size should be recorded on end of treatment PET-CT report.

Supplementary slides

The use of Interim PET in routine practice outside trials

3 Questions

- Should we do iPET outside trials?
- What should we do with iPET result?
- Which cases may benefit most?

Should we do iPET outside trials?

Introduction

- Outside trials, virtually all centres perform *mid-chemo* imaging.
- Many centres perform iPET outside trials.
- Centres not performing iPET use iCT (?slightly later in the course of chemo).

Why mid-chemo imaging?

- Is this Rx working?
- How well is it working?
  - Prognosis
  - action

Possible actions:

- Is it working *very well*: continue or reduce Rx? (especially if toxicity)
- Is response *suboptimal*: consolidation? (assuming there is effective consolidation)
- Is response *poor* or disease *progressing*: change treatment? (assuming there is effective salvage)

Choice of action

Depends on:

- Prognosis: expected outcome for the specific disease & chemo
- Confidence in response assessment
- Expected outcome of change in Rx (i.e. effectiveness of consolidation or salvage)

What mid-chemo imaging

- PET/CT is superior to CT alone:
  - Metabolic + anatomical response
  - Metabolic response shows earlier
- CT:
  - Cheaper
  - More available
- We should be using the best method available for any assessment performed.

Why is there a problem?

- iPET is attractive
- Many *studies* are examining role of iPET in guiding therapeutic intervention based on iPET result.
- Clinicians are starting to use iPET to change treatment before evidence is available.

Recommendations for discussion-1

- Where mid-Rx imaging is performed, it should be by PET/CT.
- Rationale:
  - We should be using the best method available for any assessment performed
  - It allows collection of data in real life
  - It allows building of local experience in multi-disciplinary teams

Recommendations for discussion-2

- Mid-Rx PET/CT should be used in the same way as mid-Rx CT is currently used (in terms of actions).
- Rationale:
  - Until evidence from clinical trials emerge, we should not change practice.
  - Enables comparisons with CT data

Recommendations for discussion-3

- Ideally, mid-Rx imaging should be discussed in multidisciplinary meeting to decide on action (if any is required).
- Rationale:
  - To discuss the significance of the imaging in the context of clinical history and findings and the overall prognosis.
  - To minimise diagnostic pitfalls
  - To build experience and enhance mutual understanding of clinicians and nuclear medicine physicians

Recommendations for discussion-4

- Any more?

What should we do with iPET result?

Current state of knowledge

HL-1

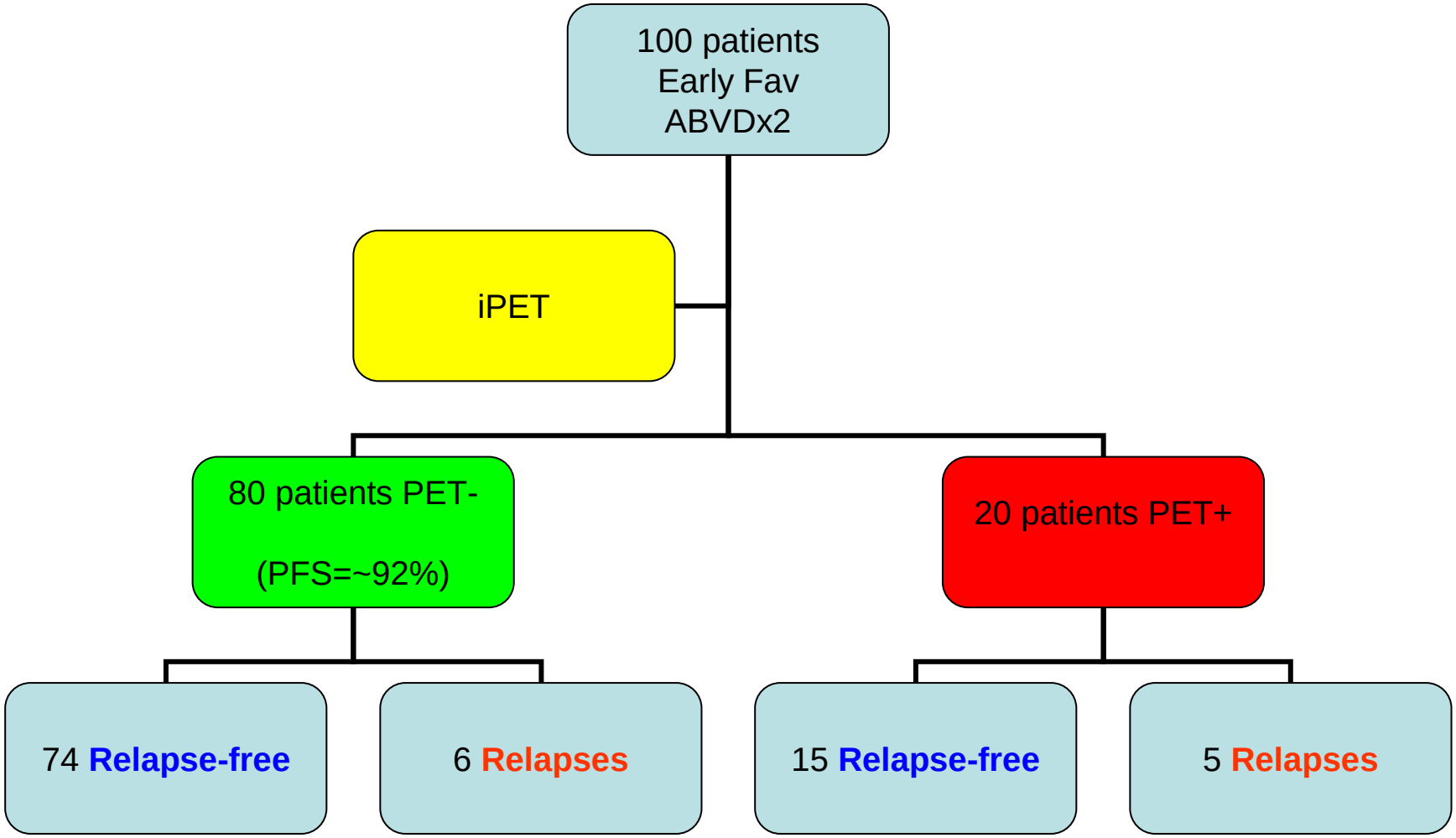
	Experimental	**Clinical Practice**
Early Favourable	PET- >chemo: omit RT (UK-RAPID, HD16)	•PMR: ?no action (excellent outcome of the gp overall) •Poor response: ?change Rx (v rare)
Early IM	PET- >2chemo: omit RT (HD17, H10, CALGB phII) PET+>2chemo: Change ABVD to BEACOPP (H10, CALGB phII)	•Good PMR: ?no action (excellent outcome of the gp overall) •little or No response: ?change Rx

PET/CT result >2-3 ABVD in limited stage HL (Cologne 2010)

Group/trial/country	N	PET2–3–negative, n (%)*	Failure-free survival after PET2–3–negative, % (y)	Reference (8th International Symposium on Hodgkin Lymphoma, Cologne, October 2010)
Rapid/UK (PET3)	500	378 (76)	>89 (2 y)	11
Italy	170	144 (85)	97 (2 y)	12
EORTC HD10	124	100 (81)	96 (4 y)	13
Vancouver	117	96 (82)	96 (4 y)	14
Boston	96	79 (82)	91 (4 y)	20
Italy-Milan	62	55 (90)	90 (3 y)	15
Italy-North	58	52 (89)	90 (3 y)	16
Totals	1127	904 (80)	~92 (3 y)	

Connors J, ASH educational book 2011

Example from Early Favourable



HL-1

	Experimental	**Clinical Practice**
Early Favourable	PET- >chemo: omit RT (UK-RAPID, HD16)	•PMR: ?no action (excellent outcome of the gp overall) •Poor response: ?change Rx (v rare)
Early IM	PET- >2chemo: omit RT (HD17, H10, CALGB phII) PET+>2chemo: Change ABVD to BEACOPP (H10, CALGB phII)	•Good PMR: ?no action (excellent outcome of the gp overall) •little or No response: ?change Rx

Outcome of ABVD in randomised trials of advanced HL

Study	N	Median age, y	% RT	% High IPS	% outcome	% OS	Median follow-up, y
US Intergroup (2003)[6]	433	35	None	NR	FFS 63	82	6
Italian Cooperative Study (2005)[15]	122	31	62	14	PFS 85	90	5
UK LY09 (2005)[5]	406	35	38	19	EFS 75	90	4.3
UK NCRI (2009)[1]	252	35	53	13	PFS 76	90	4.3
NA Intergroup (2010)[13,22]	404	33	28	33	FFS 73	88	5.25
MCG, GITIL/IIL (2008)[10*]	166	32	46	54	FFP 71	91	2.5
GISL HD2000 (2009)[9]	99	32	46	11	PFS 68	84	3.4

Advani R, ASH educational book 2011

HL-2

	Experimental	**Clinical Practice**
Advanced	PET->2chemo: •AVD (RATHL) •less BEACOPP (HD18) •no RT (HD0801, GITIL) PET+>2chemo: •Change ABVD to BEACOPP (RATHL) •add Ritux (HD18, GITIL) •escalate to HD+ASCT (HD0801) PET+>1chemo: •escalate to BEACOPP (H11)	•CMR: continue ABVD. •Good PMR: – ?no action – ?Repeat PET>4ABVD & change Rx then – ?RT consolidation – ?close surveillance •little or No response: – ?change Rx (makes sense but unproven yet)

Which cases may benefit most?

Potential uses of PET/CT to guide treatment in HL

Condition	Clinical trial recommendation	Non-clinical trial recommendation
Initial staging	Definite	Only selected cases 1. Equivocal CT scan findings 2. Difficult radiation field planning
Limited stage: response assessment after 2 cycles of chemotherapy*	Definite	Recommended if a choice between additional chemotherapy or switch to radiation is planned
Advanced-stage: mid-treatment response assessment for further treatment planning†	Definite *if* this is the question being investigated, otherwise not recommended	Not recommended
Any stage: assessment of response, evaluation of a residual mass after completion of planned chemotherapy	Definite	Recommended if additional radiation is a reasonable option
Monitoring for evidence of relapse after completion of planned treatment	Not recommended	Not recommended
Assessment of response to secondary treatment of relapsed/refractory disease prior to high-dose chemotherapy and autologous hematopoietic stem cell transplantation	Definite	Not recommended

Connors J, ASH educational book 2011

Which cases may benefit most?

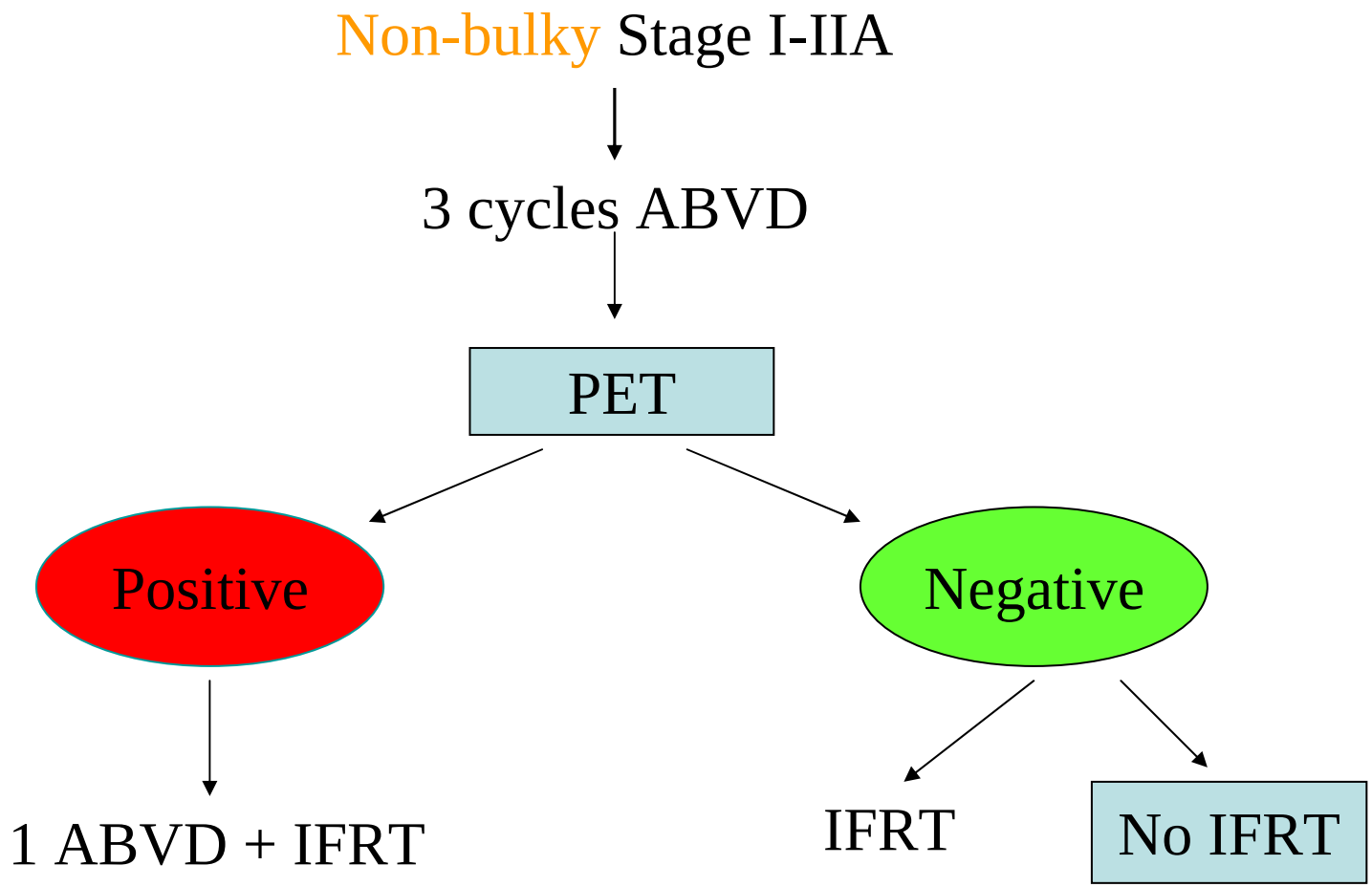
HL:

- Not early stage: v good prognosis
- Advanced stage:
  - select poor response (not any positive) for change in Rx?
  - Select suboptimal response for consolidation?

DLBCL:

- Not good prognosis stage1 non bulky (IPI= 0-1)
- All other:
  - select poor response (not any positive) for change in Rx???
  - Select suboptimal response for consolidation?

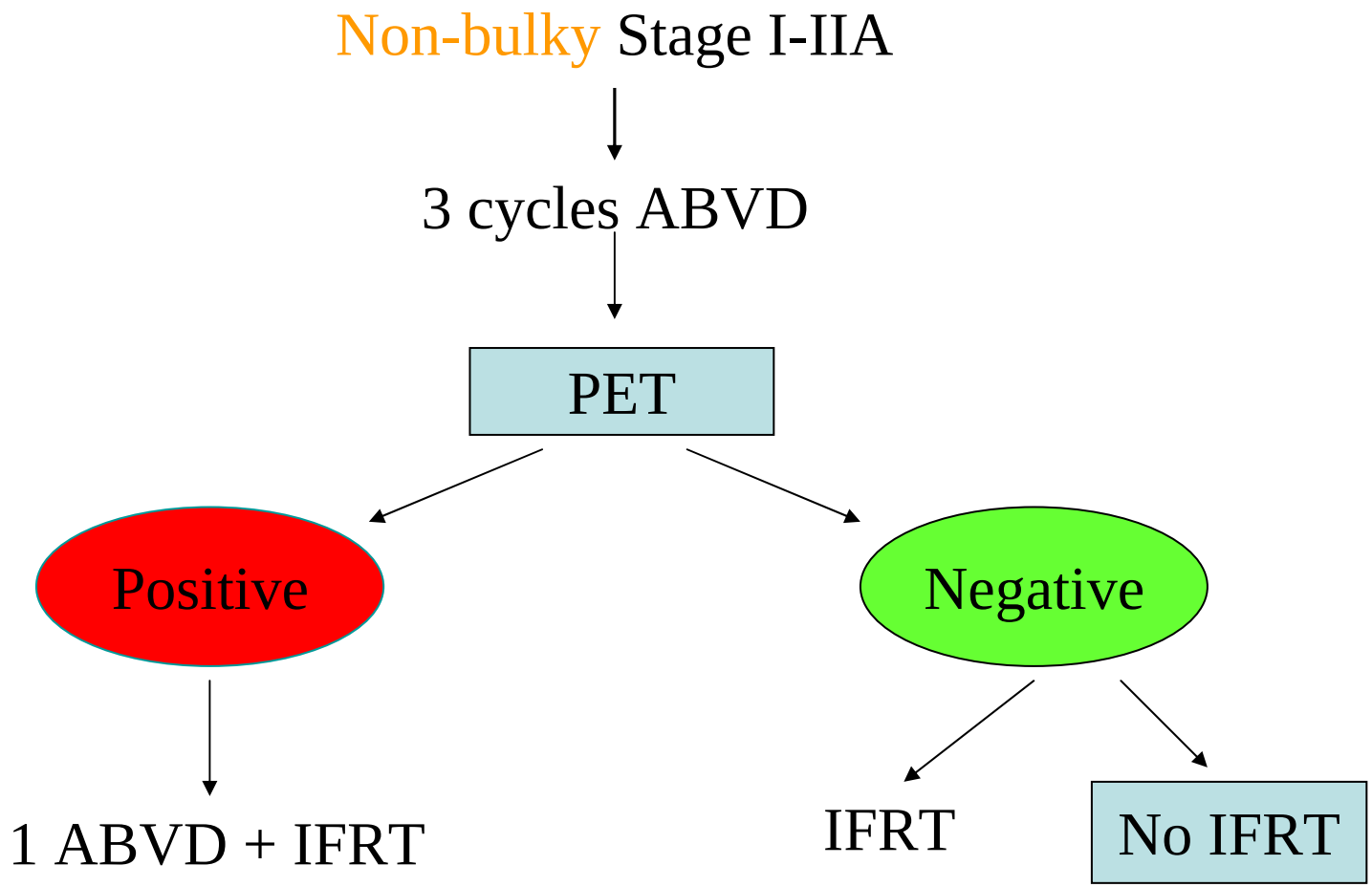
Early Hodgkin RAPID



N= 700 pts, 2003-2011

De-escalation

Early Hodgkin RAPID



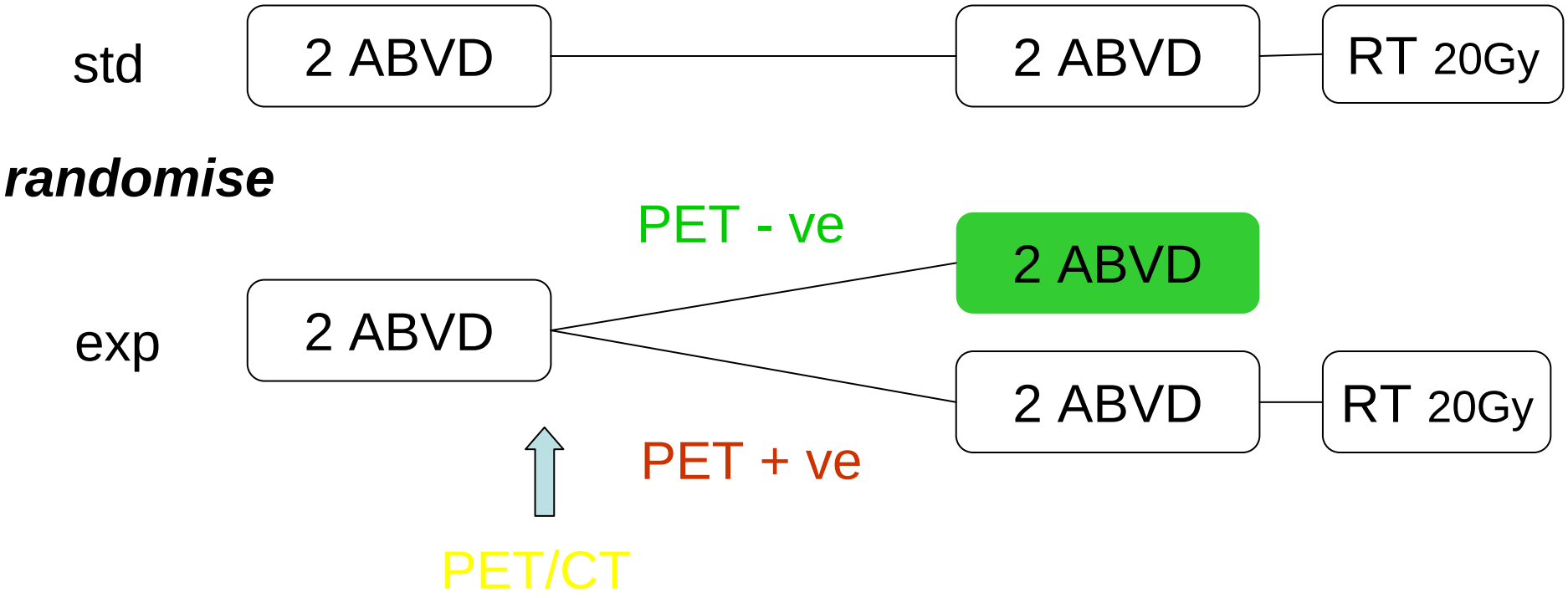
N= 700 pts, 2003-2011

De-escalation

HD16 GHSG n = 1100

Early stage

started 2009

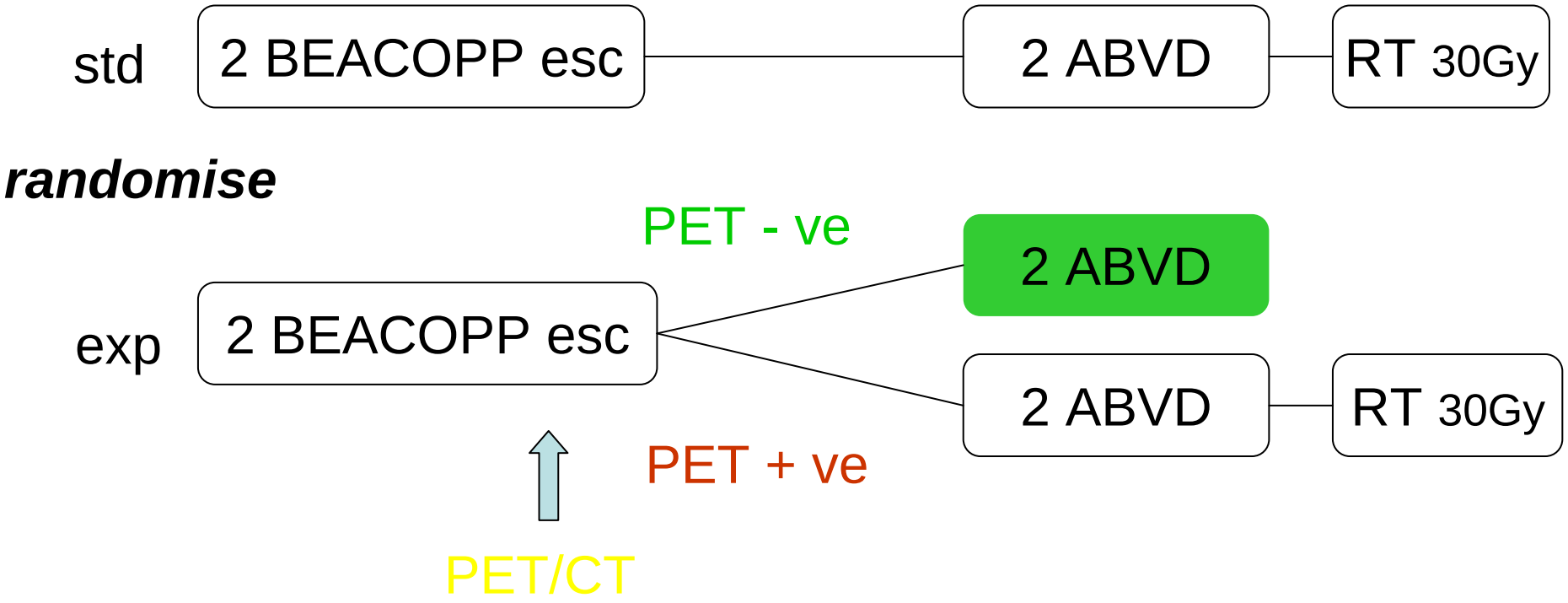


PI Prof A Engert, Univ of Cologne

HD17 GHSG n = 1100

IM stage

In preparation

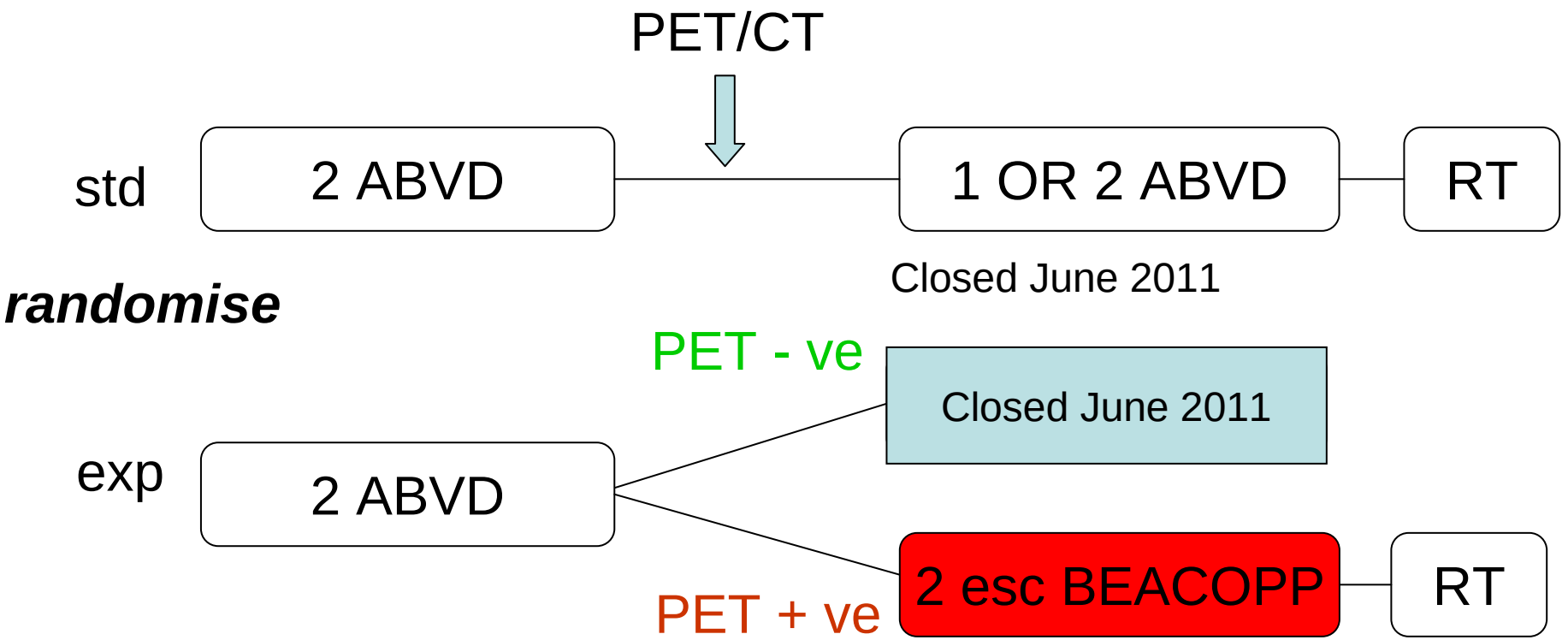


PI Prof A Engert, Univ of Cologne

H10 EORTC/GELA/IIL

n = 1600

started 2006



Study chairs:

Dr John Raemaekers, Universitair Medisch Centrum St. Radboud - Nijmegen

Marc Andre, MD Centre Hospitalier Notre Dame

Massimo Federico University of Modena and Reggio Emilia

St Thomas' 5 point Scoring System

- Score 0 (CR): no uptake

- Score 1 (MRU1): uptake ≤ mediastinum
- Score 2 (MRU2): uptake > mediast. but ≤ liver

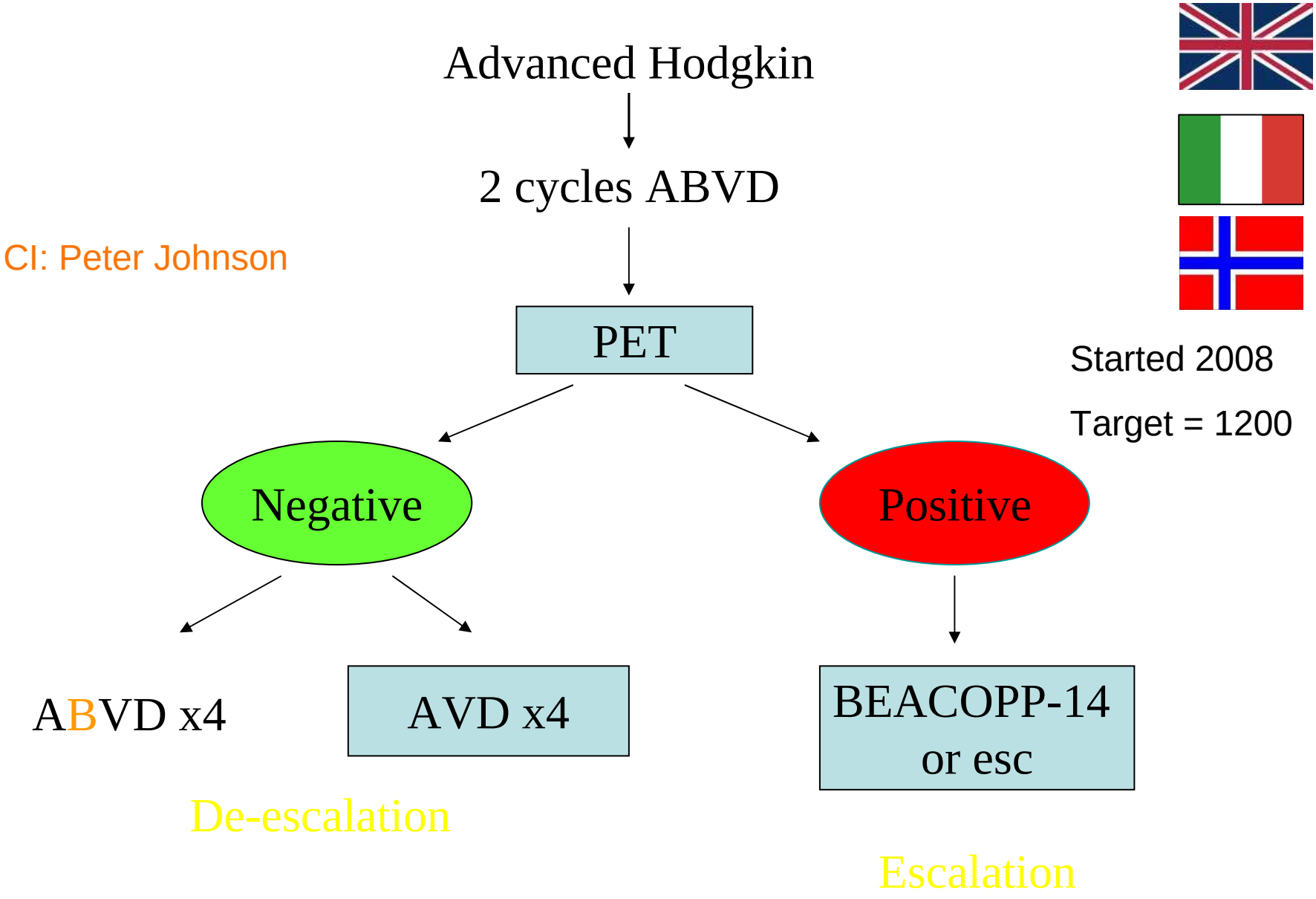
- Score 3: uptake > liver
  (residual lymphoma)
- Score 4 (PD): new lesion(s) likely to be lymphoma

***Score X**: new areas of uptake unlikely to be related to lymphoma*

Advanced HL

	PET driven intervention
RATHL ABVD	ABVD vs. AVD esc BEACOPP or BEACOPP 14
HD18 esc BEACOPP	4 vs. 8 esc BEACOPP esc BEACOPP vs esc BEACOPP-R
HD0801 ABVD	RT vs. no RT HDCT and ASCT
GITIL ABVD PI: Prof A Gallamini Cuneo Italy	bulky disease: RT vs no RT esc BEACOPP vs esc BEACOPP-R
SWOG ABVD PI: Dr Oliver Press, Fred Hutchinson Ca Research Centre	esc BEACOPP vs std BEACOPP

Advanced Hodgkin (RATHL)



HD18 GHSG n = 1500
started 2009

2 esc BEACOPP → PET/CT

PET negative

randomise

6 esc BEACOPP

2 esc BEACOPP

PET positive

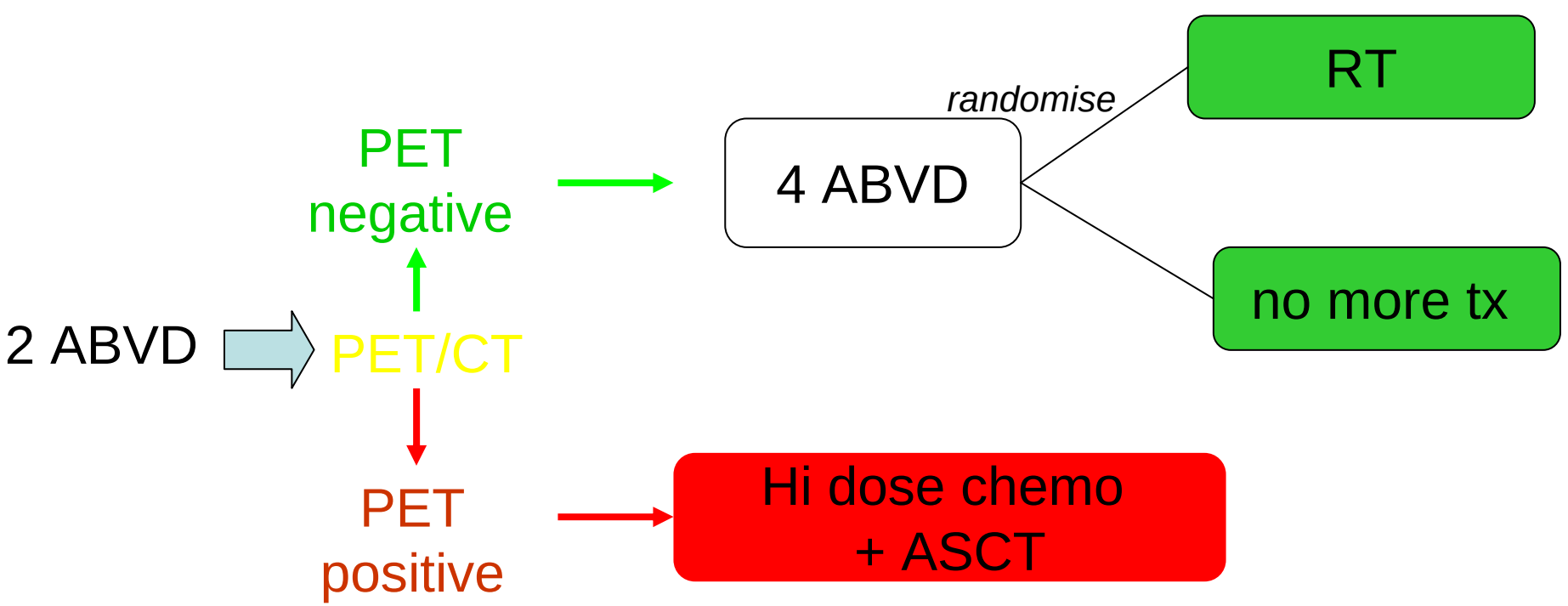
randomise

6 esc BEACOPP

6 esc BEACOPP
+ Rituximab

PI Prof A Engert, Univ of Cologne

HD0801 IIL n = 300
started 2008



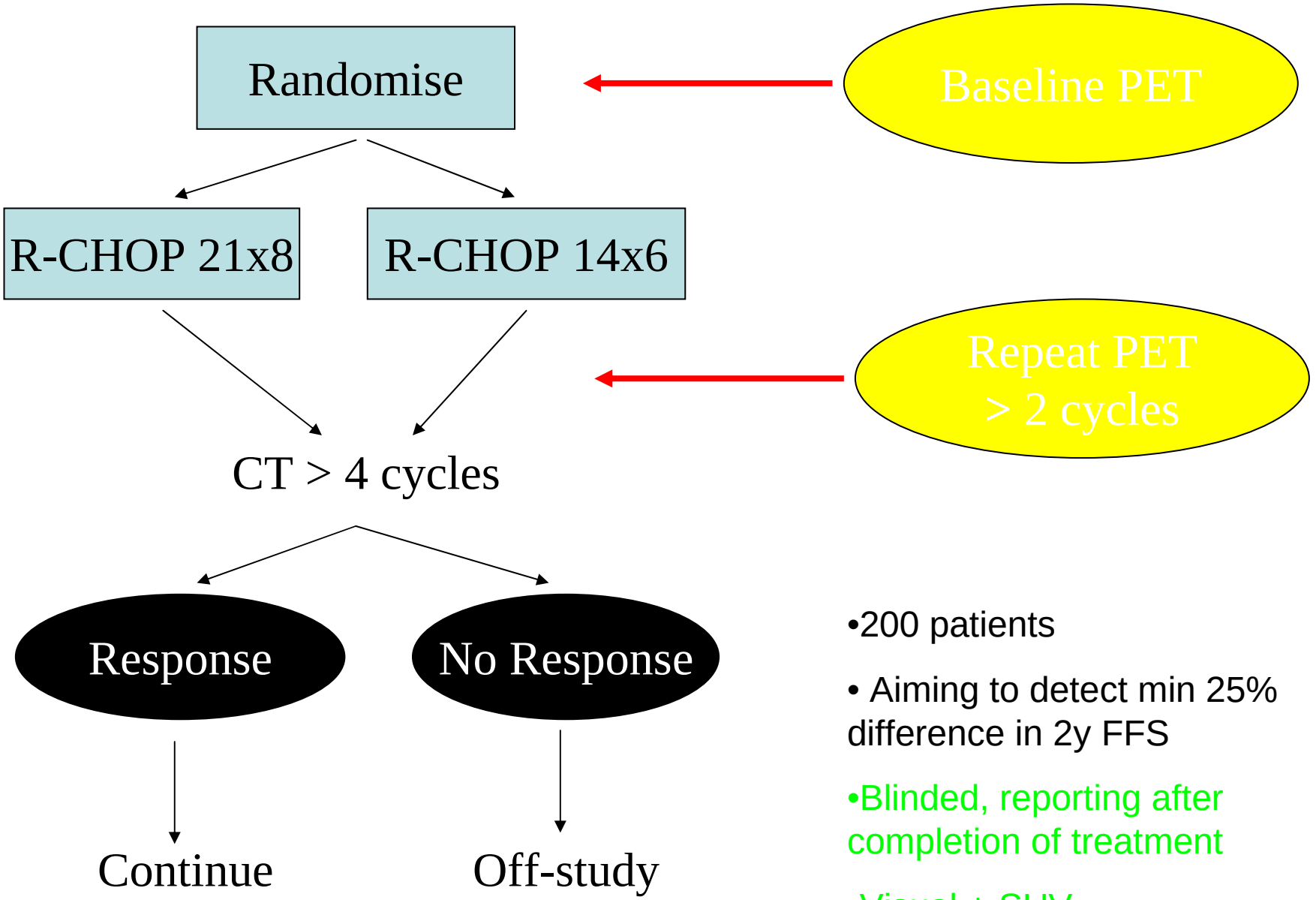
PI: Dr A Levis, Ospedale SS. Antonio, Biagio e Cesare Arrigo

NHL Trials

Blinded evaluation of prognostic value of FDG-PET after 2 cycles of chemotherapy in Diffuse Large B-cell Non-Hodgkin's Lymphoma

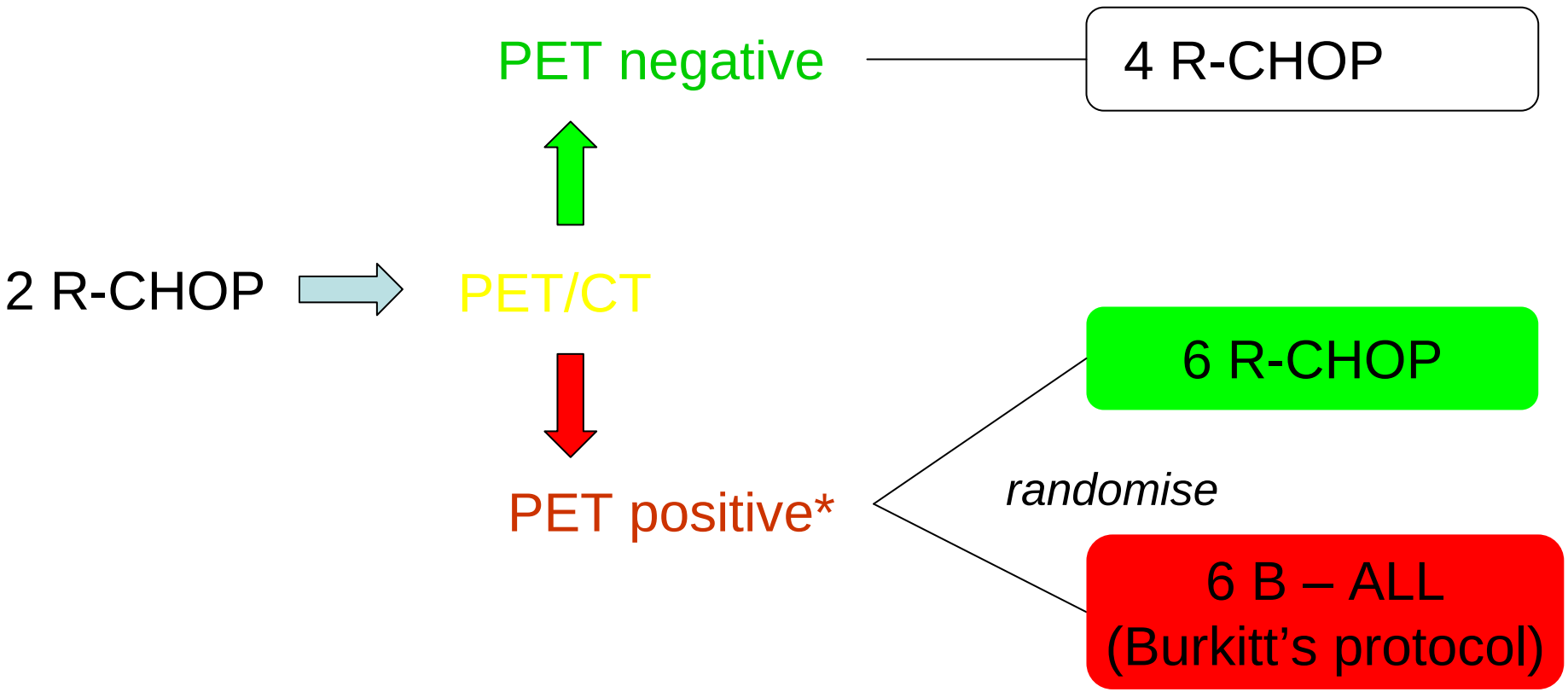
Short title: PET after 2 cycles

Chief Investigator: George Mikhaeel



- 200 patients
- Aiming to detect min 25% difference in 2y FFS
- Blinded, reporting after completion of treatment
- Visual + SUV

PETAL Univ of Essen n = 696
Aggressive NHL
Started 2007



(*) +ve = <66% reduction in SUV max

PI: Prof Ulrich Duehrsen, University Hospital Essen

What questions will be answered?

Early HL

Can RT be safely avoided in PET –ve patients, without detriment to PFS?

Can PFS be improved in PET+ by esc BEACOPP?

Advanced HL

Can treatment be safely de-escalated in PET –ve patients:

- By omitting bleomycin after 2 ABVD (RATHL)
- By reducing the number of cycles of esc BEACOPP from 8 to 4 (HD 18)
- By avoiding RT (HD0801, GITIL)

Can PFS be improved in PET+ patients

- By switching from ABVD to a BEACOPP regime (RATHL, SWOG)
- By addition of rituximab to BEACOPP (HD 18, GITIL)
- By switching to high dose chemo + early ASCT (HD 0801)

NHL

- What is the best way to separate different prognostic groups by PET (in RCHOP era)?
- Does switching to a more intensive chemotx or high dose chemo ± ASCT in PET +ve patients improve survival?