German Hodgkin Study Group
Deutsche Hodgkin Studiengruppe

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Advanced stage HL
The old and new match: *BEACOPP*

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Which answer is wrong? For patients with advanced stage HL, treatment with 6 cycles BEACOPPesc, the GHSG standard of care, results

1. In a treatment related mortality rate of 0.8%.
2. In an overall survival at 5 years of 95%.
3. In an infertility rate of about 80% in women in the age of 25 years at diagnosis.
4. In 0.3% secondary acute myeloid leukemia.

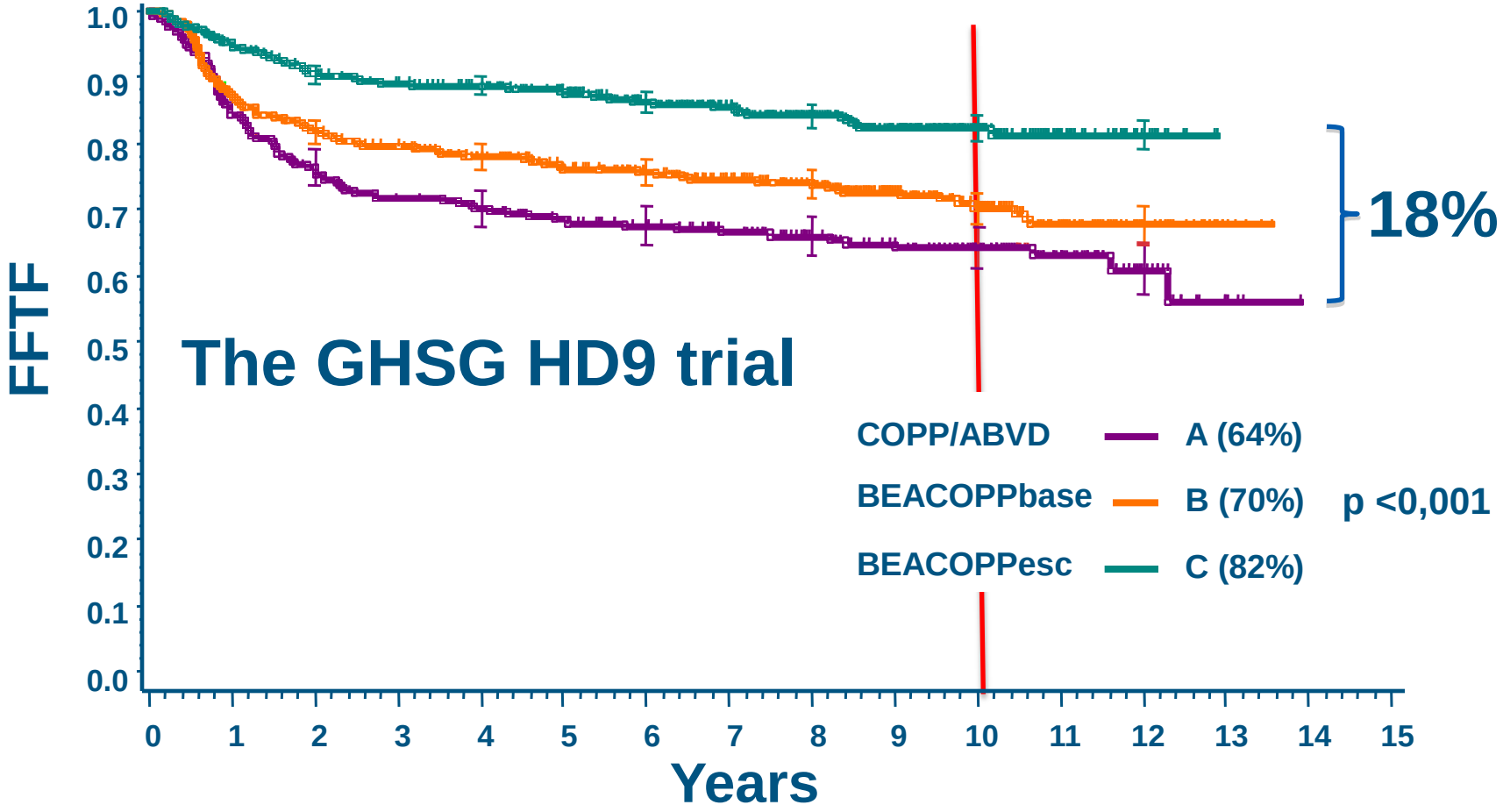
Which answer is correct? In advanced stage HL treated with BEACOPPEesc,

1. Positive early interim PET (after cycle 2) identifies a high risk group of patients
2. Residual disease is defined as any tumor > 1.5 cm at the end of chemotherapy
3. PET after the end of chemotherapy helps to identify a high risk group
4. As compared to treatment with ABVD, the superiority of BEACOPP in terms of PFS and OS is both significant and relevant in IPI low risk patients.

The old and new match: BEACOPP

1. Why do I *like* BEACOPPesc?
2. Why do I *prefer* BEACOPPesc over ABVD?
3. Can we do even better than BEACOPPesc?

I like BEACOPPesc, because it is very active.



The GHSG HD9 study, Engert et al., *J Clin Oncol, 2010, 27:4548-4554*

I like BEACOPP, because my patients ask for cure.

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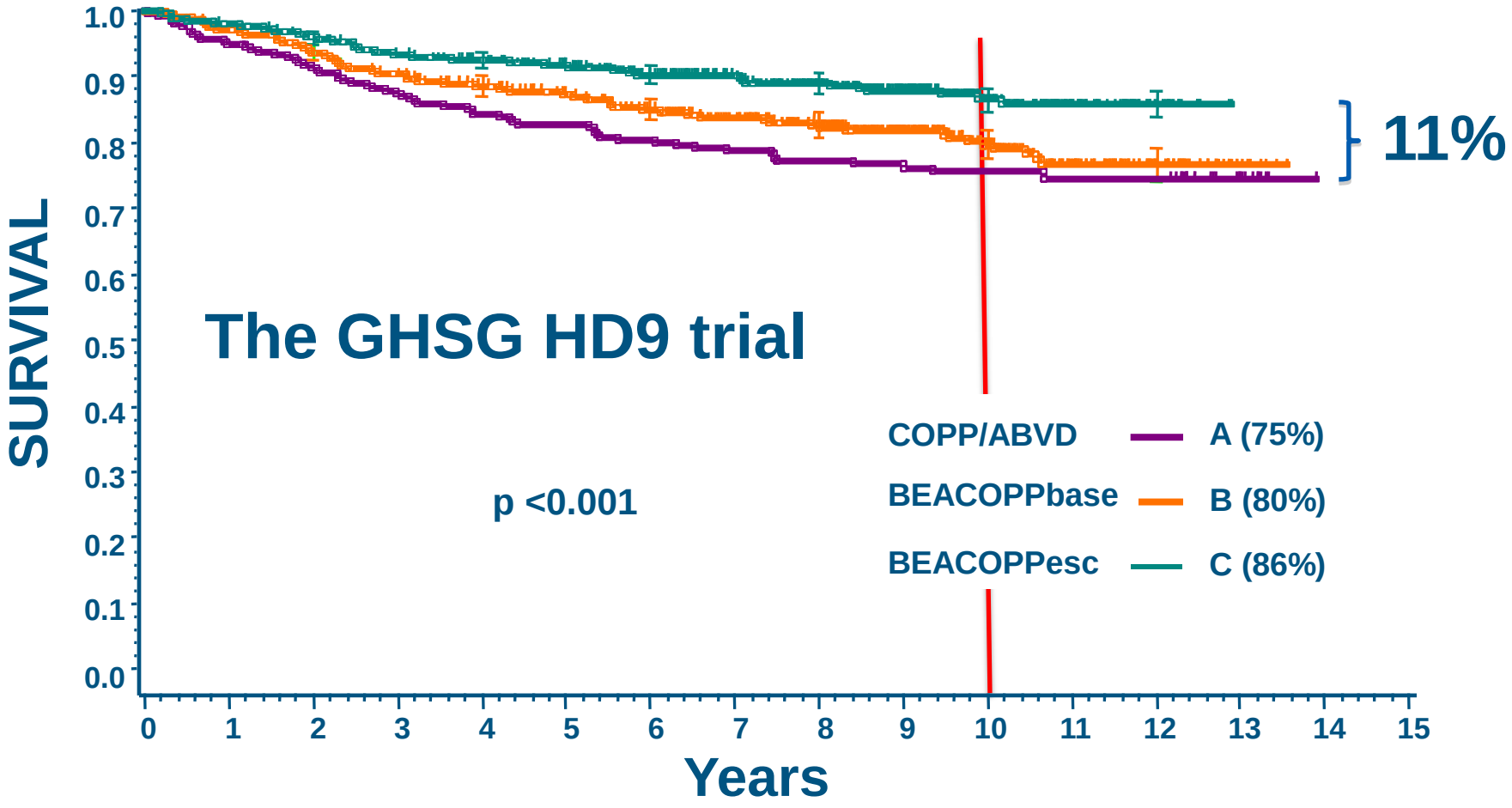
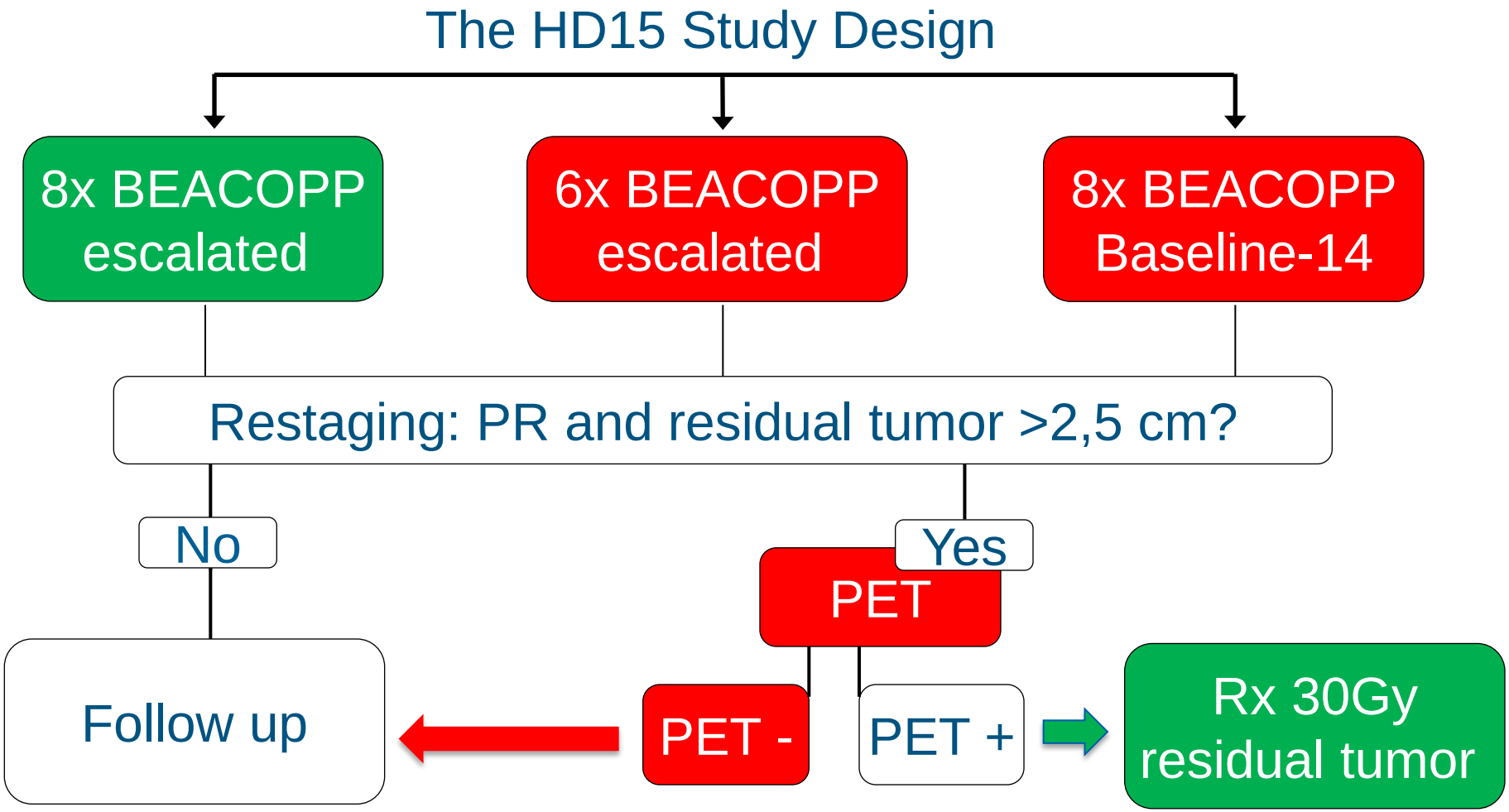


The GHSG HD9 study, Engert et al., *J Clin Oncol, 2010, 27:4548-4554*

I like BEACOPP, because it has been nicely developed: step by step, for 20 years now, including more than 5.000 patients.



Engert et al., Lancet, 2012

I like BEACOPPesc, because only 11% of my patients will need Rx. Based on evidence, not on NCCN guidelines only ;-)

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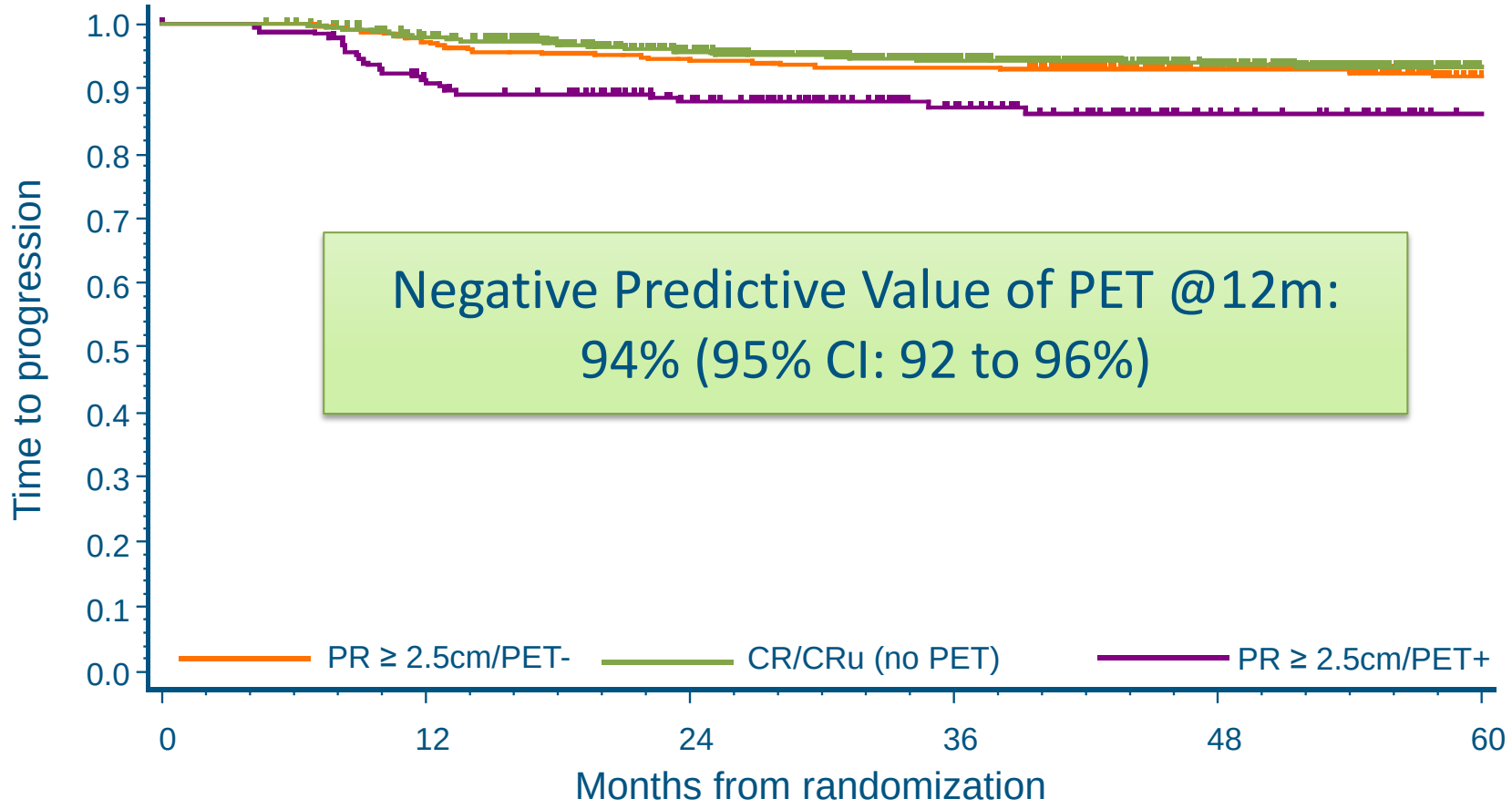
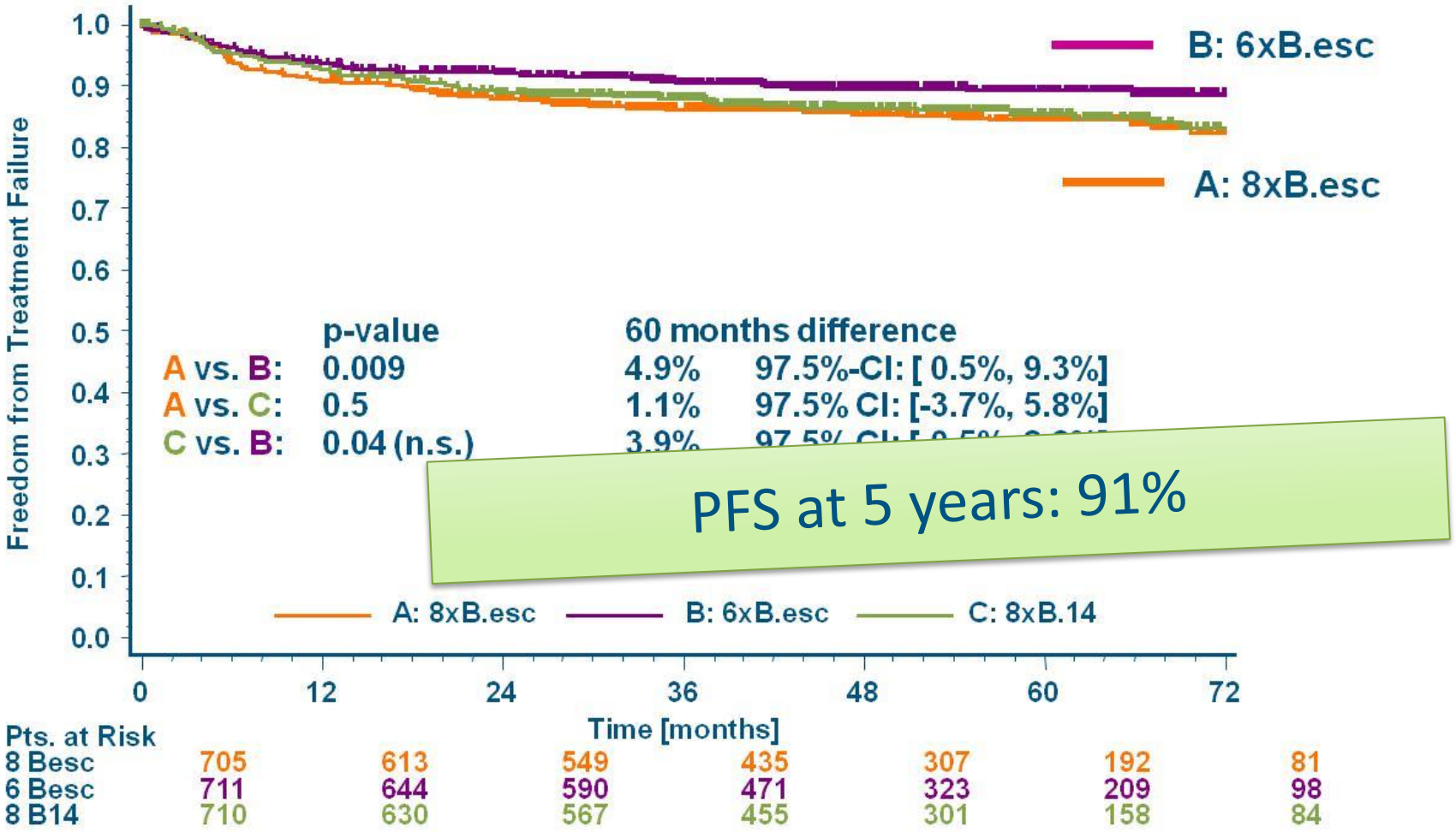


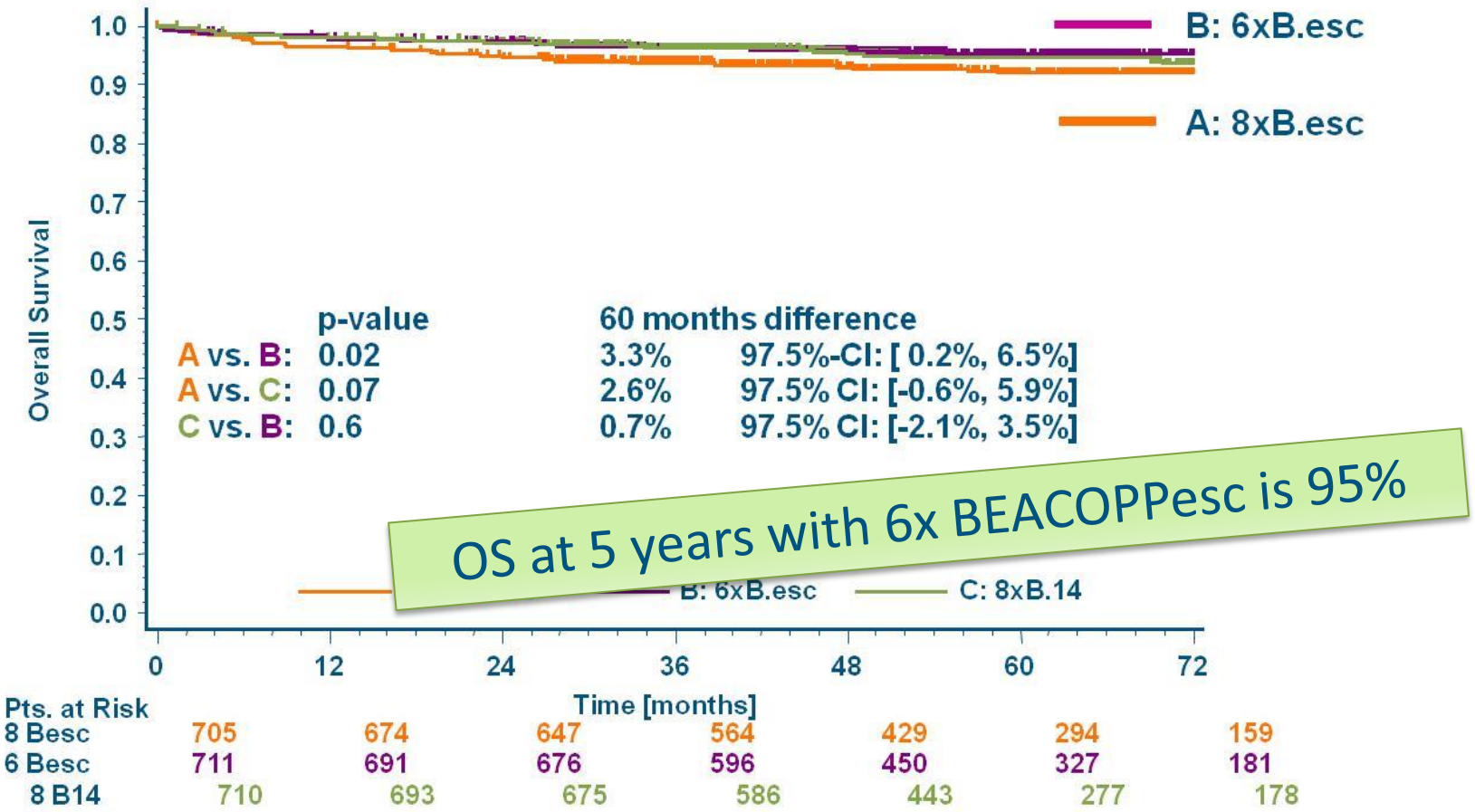
Negative Predictive Value of PET @12m:
94% (95% CI: 92 to 96%)

Pts. at Risk						
PET-	540	517	449	338	224	118
PET+	188	166	139	97	58	35
CR/CRu	854	811	690	482	303	155

I just like it, because only 6 quick courses are even better than 8



and because I don´t like funerals



OS at 5 years with 6x BEACOPPesc is 95%

The old and new match: BEACOPP

1. Why do I like BEACOPPesc?
2. Why do I prefer BEACOPPesc over A
3. C

Because my patients ask for cure first and foremost and I can offer cure using BEACOPP with the by far highest likelihood. That´s why.

The old and new match: BEACOPP

1. Why do I like BEACOPPesc?
2. Why do I prefer BEACOPPesc over ABVD?
3. Can we do even better?

Because it is just better: as shown by 4 out of 4 (yes, all!) controlled and randomized studies

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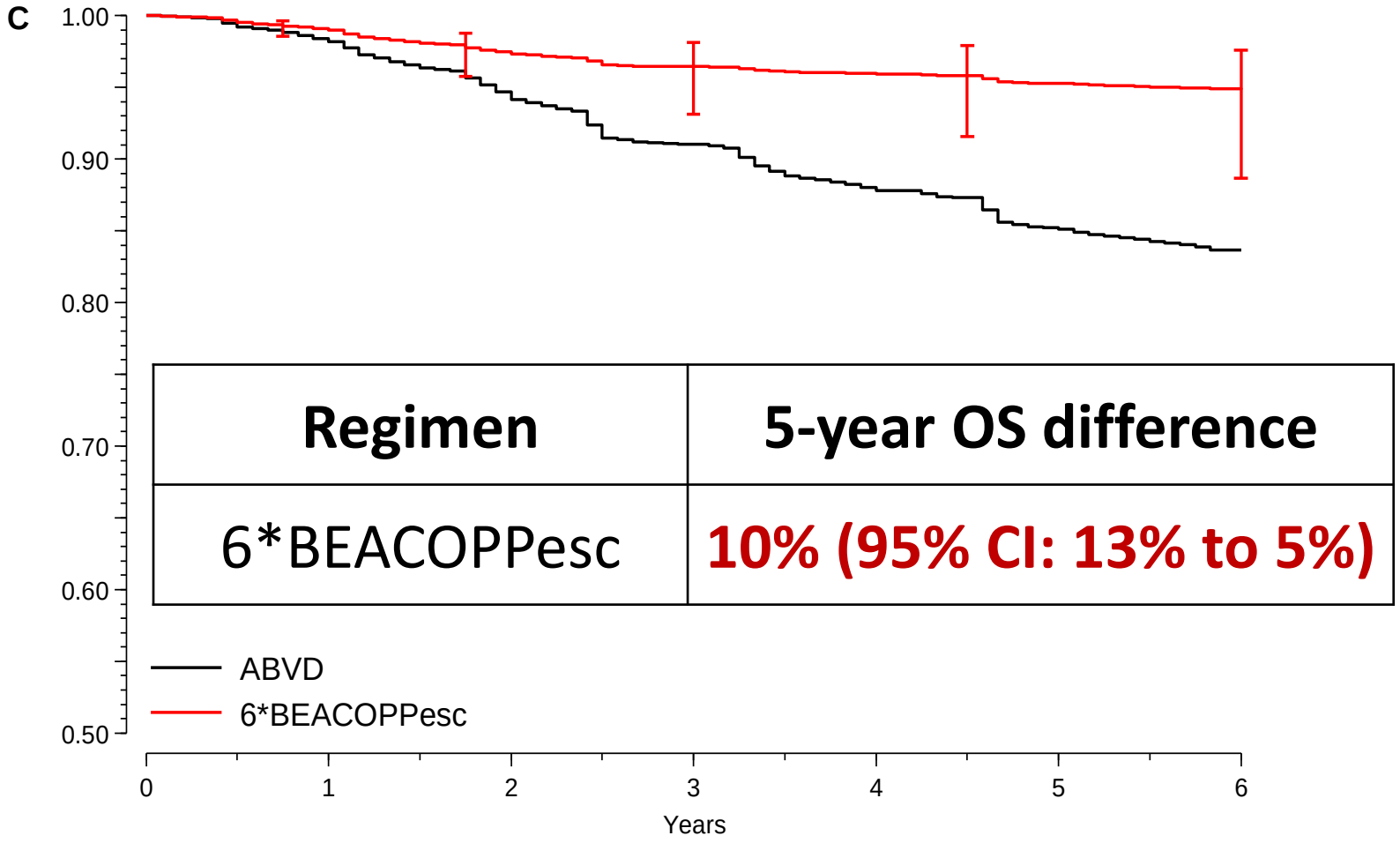
Study	Group	n	5-y PFS	Difference (%)	p	5-y OS	Difference (%)
HD 2000	ABVD	99	68	13	0.038	84	8
	BEACOPP (4 esc + 2 std)	98	81			92	
IIL †	ABVD	168	73	12	0.004	84	5
	BEACOPP (4 esc + 4 std)	163	85			89	
IG 20012 ‡ IPS 3-7	ABVD	275	69	15	0.0003	86,7	4
	BEACOPP (4 esc + 4 std)	274	84			90,3	
LYSA H34 IPS 0-2	ABVD	77	75	18	0.008	92	7
	BEACOPP (4 esc + 4 std)	68	93			99	
HD15	6 BEACOPPesc	711	91			95.3	

†7-year PFS; ‡ 4-year PFS.

You still don´t believe it? Let´s have a look the highest level of evidence: a metanalysis.

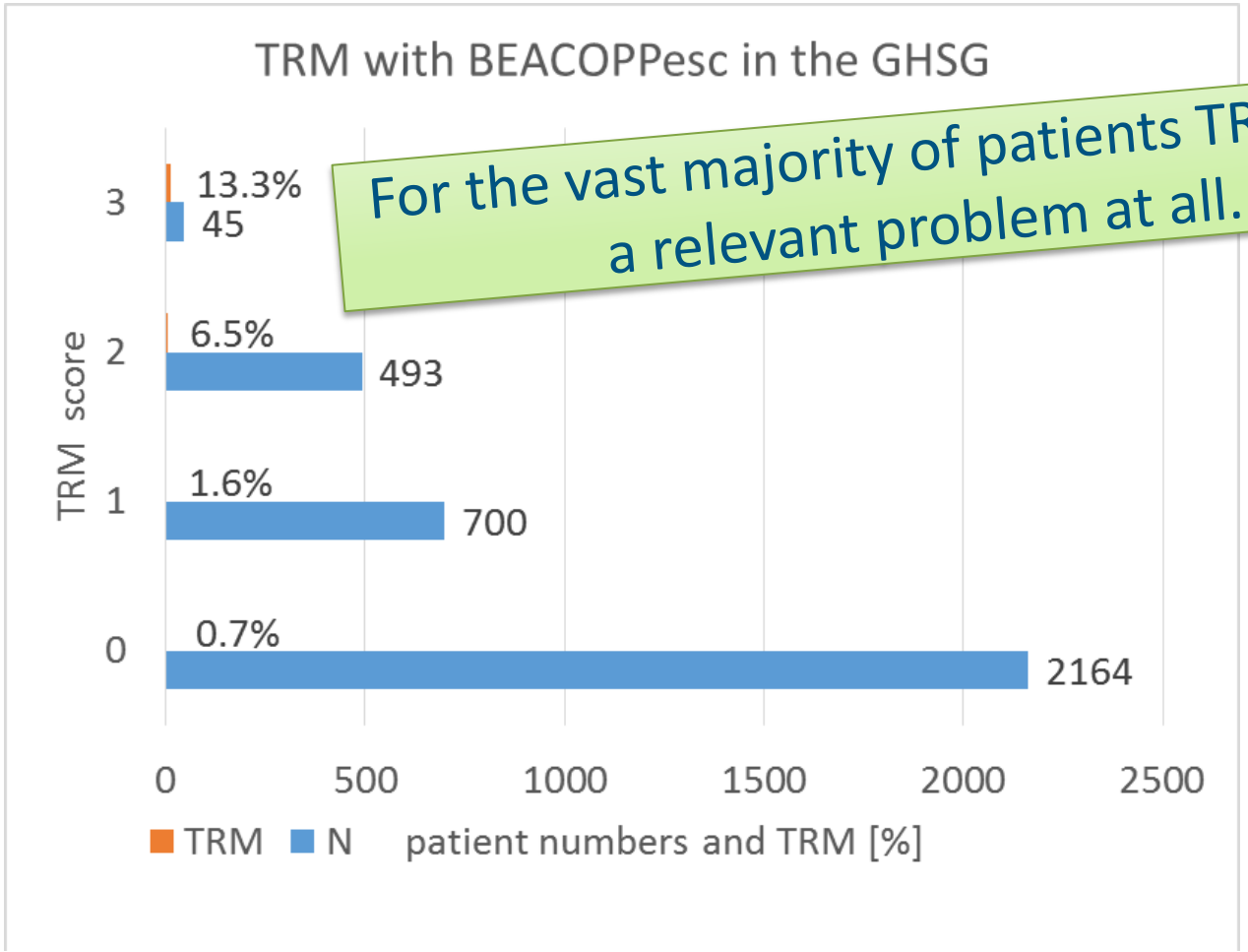
- 1,984 references were identified, referring to
- 77 publications,
- reporting 14 trials,
- evaluating 11 different regimens with a total of
- 10,011 patients and
- 47,033 patient-years of follow-up evaluable for the analyses of survival outcomes
- including 1,189 events with a
- average median follow-up 5.9 years

BEACOPPesc is not just better. It is *much* better than ABVD ;-)



Regimen	5-year OS difference
6*BEACOPPesc	**10% (95% CI: 13% to 5%)**

And BEACOPPesc is very safe!



TRM acoording individual risk score: age (>40, > 50, WHO PS 2)

Another surprise: neither more secondary neoplasia nor more sAML/MDS than with ABVD!

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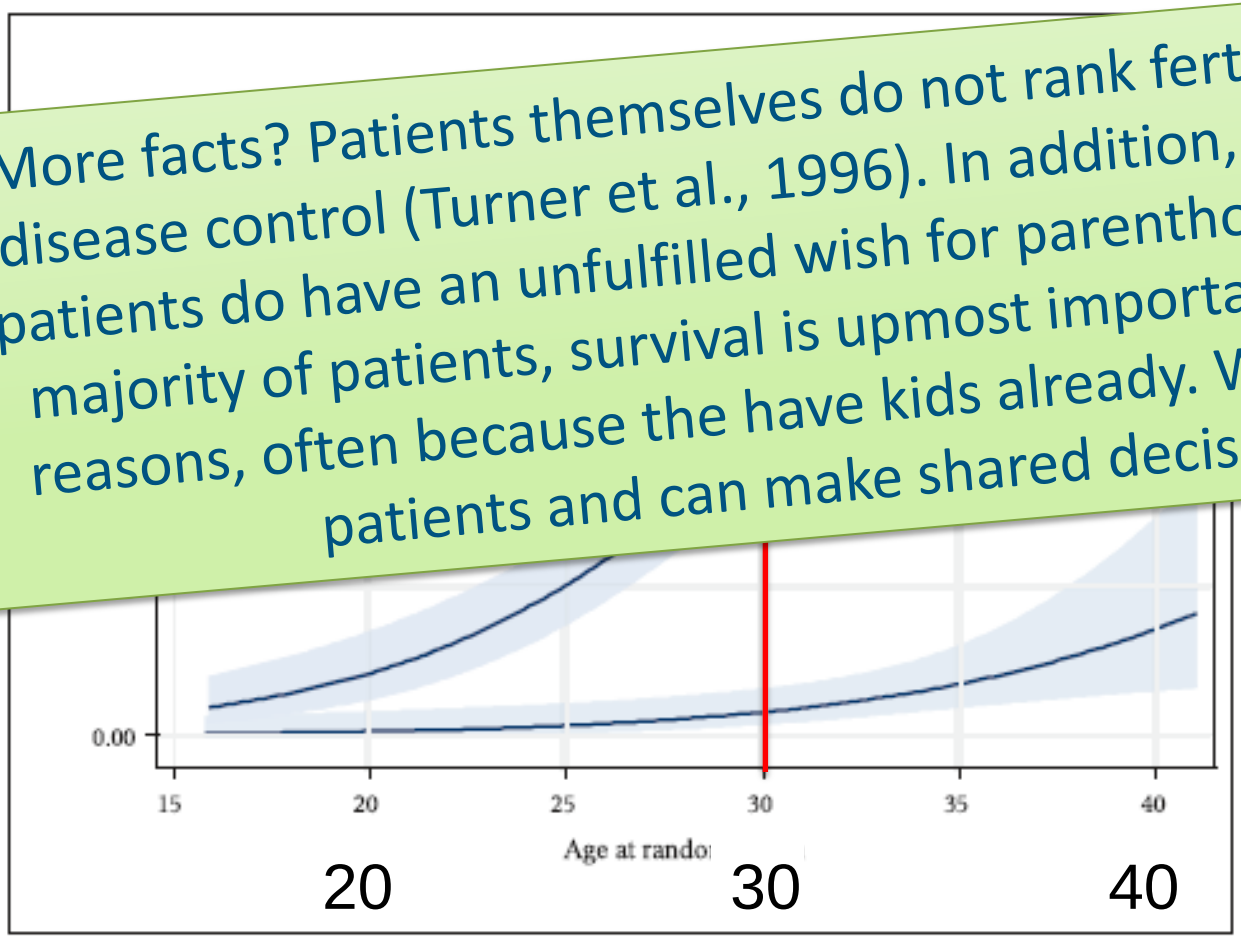
Study	Group	n	TRM (%)	sAML/MDS (%)	Second neoplasia n (%)
HD 2000	ABVD	99	n.r.	0	1 (1)
	BEACOPP (4 esc + 2 std)	98	n.r.	0	1 (1)
IIL†	ABVD	168	1	1	3 (1.8)
	BEACOPP (4 esc + 4 std)	163	3	1	1 (0.6)
IG 20012 ‡ IPS 3-7	ABVD	275	3.3	0.7	8 (2.9)
	BEACOPP (4 esc + 4 std)	274	2.2	1.5	10 (3.7)
LYSA H34 IPS 0-2	ABVD	77	0	0	5 (6.5)
	BEACOPP (4 esc + 4 std)	68	0	0	1 (1.5)
HD15	6 BEACOPPesc	711	0.8	0.3	15 (2.1)

†7-year PFS; ‡ 4-year PFS.

But: „Almost all patients become infertile after BEACOPPesc!“ True or not?
Looking at data can help, if one wants to know ;-)

More facts? Patients themselves do not rank fertility issues over disease control (Turner et al., 1996). In addition, only 1/6 of our patients do have an unfulfilled wish for parenthood. For the vast majority of patients, survival is upmost important for different reasons, often because the have kids already. We can trust our patients and can make shared decisions!



2x Besc + 2x ABVD

Behringer et al., JCO, 2013

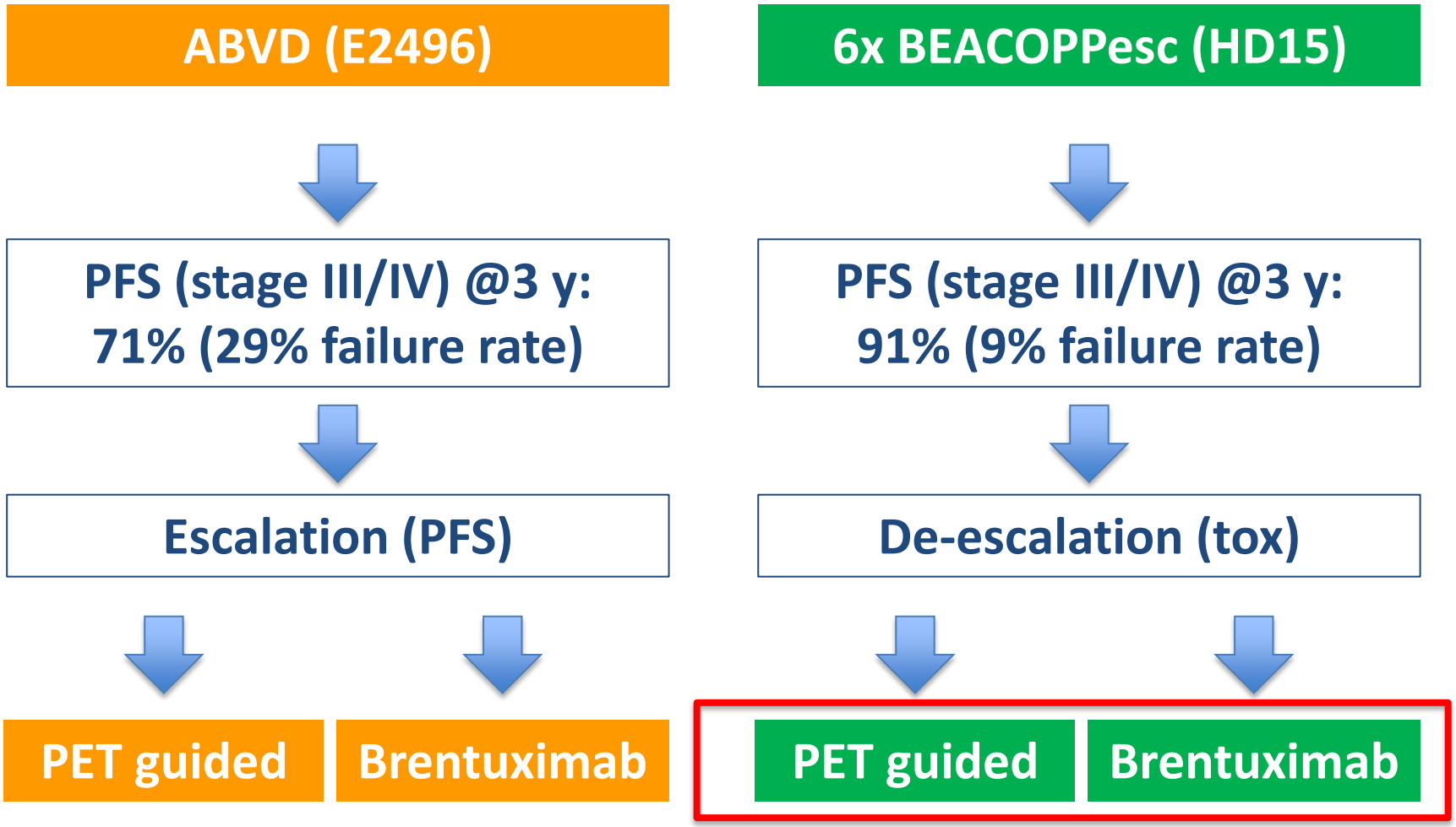
The old and new match: BEACOPP

1. Why do I like BEACOPPesc?
2. Why do I prefer BEACOPPesc over ABVD?
3. Because this is very reasonable. Much better survival, no more relevant toxicities.

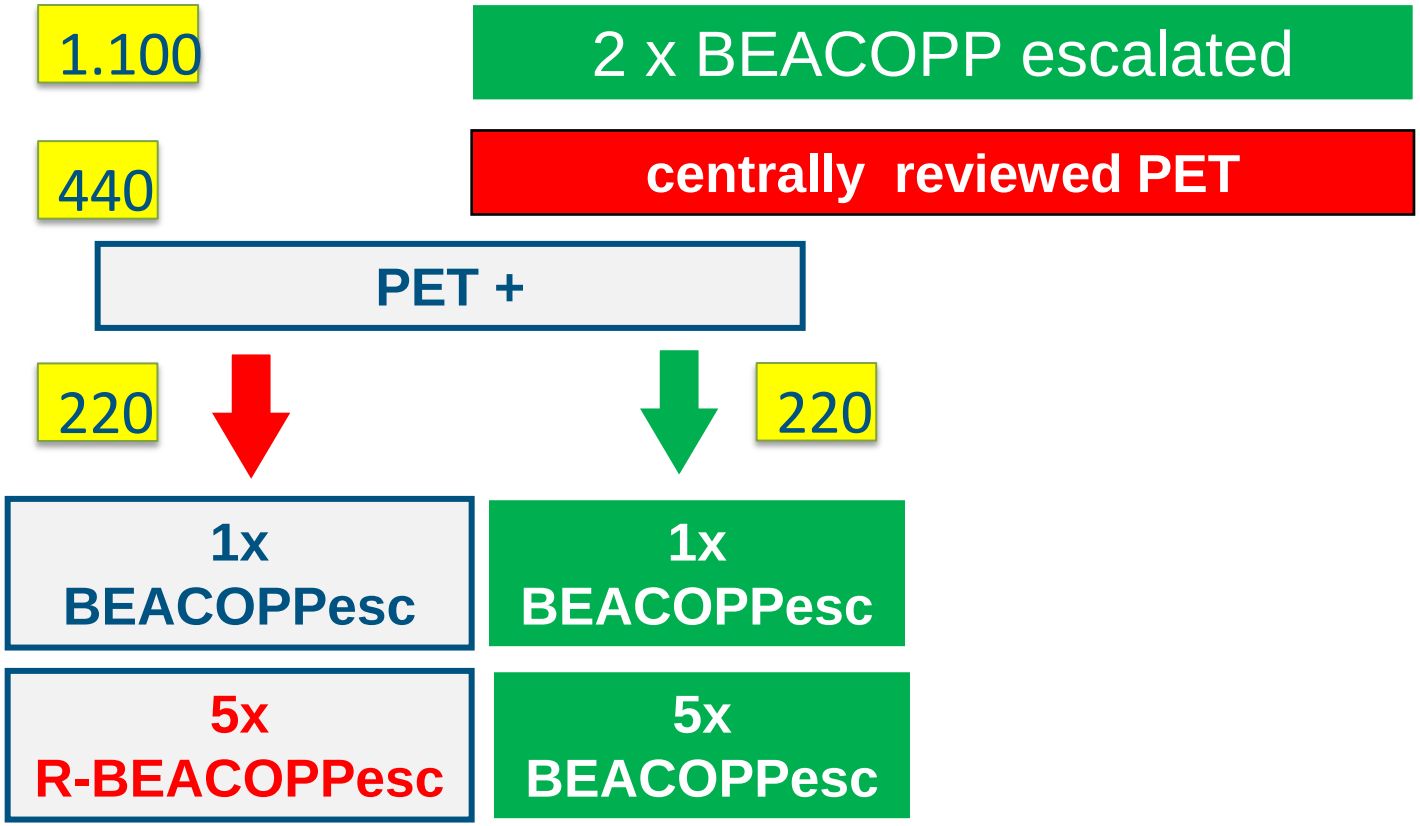
The old and new match: BEACOPP

1. Why do I like BEACOPPesc?
2. Why do I prefer BEACOPPesc over ABVD?
3. Can we do even better?

Which tools do we have to improve our regimen?



HD18: testing a PET guided treatment strategy



End of therapy AND residual nodes > 2.5 cm : PET positiv: Rx

Borchmann et al., ASH, 2014, abs 500

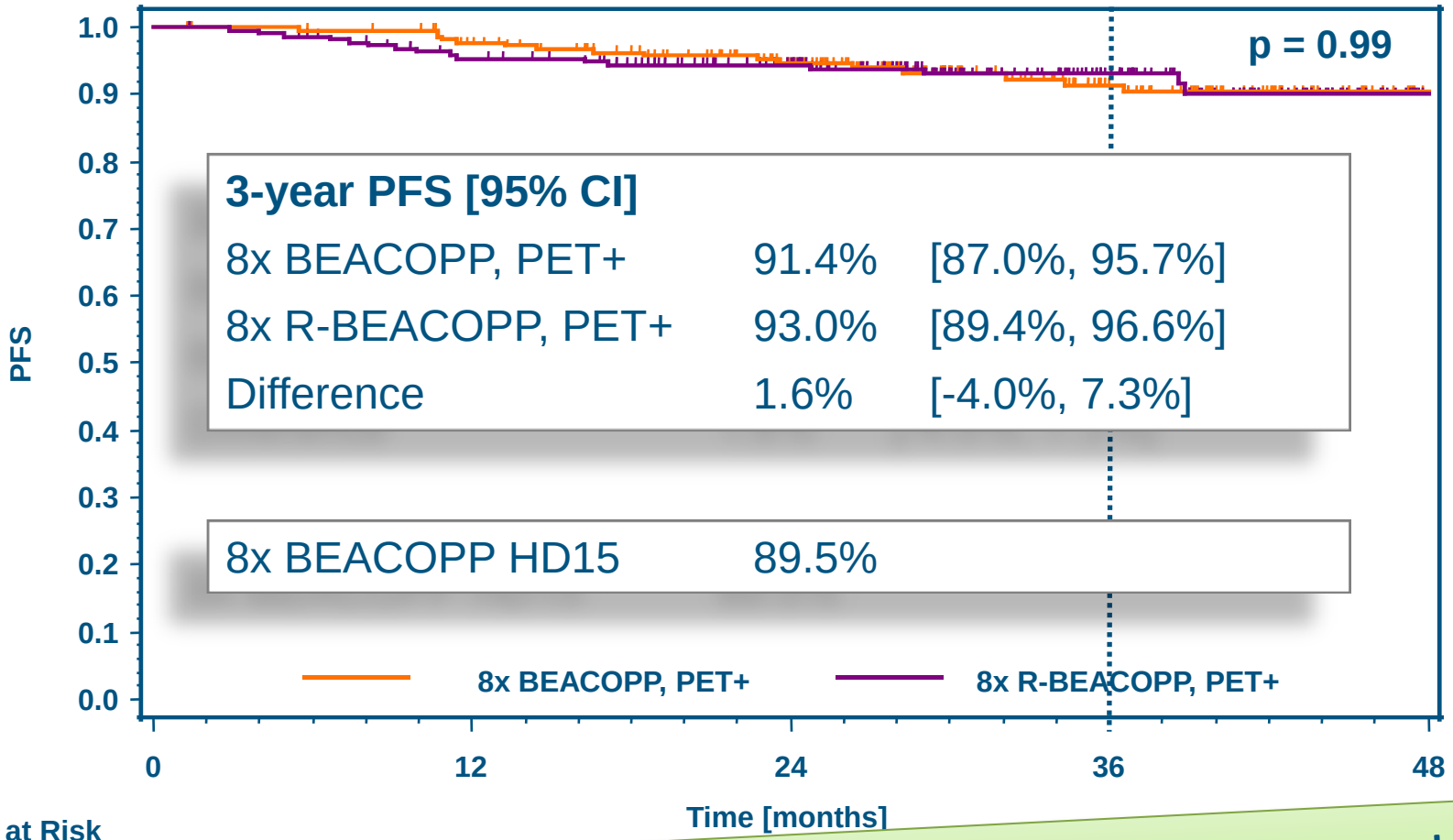
Assumptions and primary objective

1. Total 5-year PFS with 8x BEACOPPesc. is 86.3% (HD9/12)
2. 30% of patients will be PET positive after 2 courses (SUV uptake above mediastinal bloodpool)
3. 70% of all events will occur in PET-2 positive patients, resulting in a **five year PFS of 68%** for these patients

➢ **Show that the addition of rituximab to our standard chemotherapy BEACOPPesc (R-BEACOPP) improves 5-year PFS to 83%** (hazard ratio 0.483, i.e. rituximab more than halves the hazard)

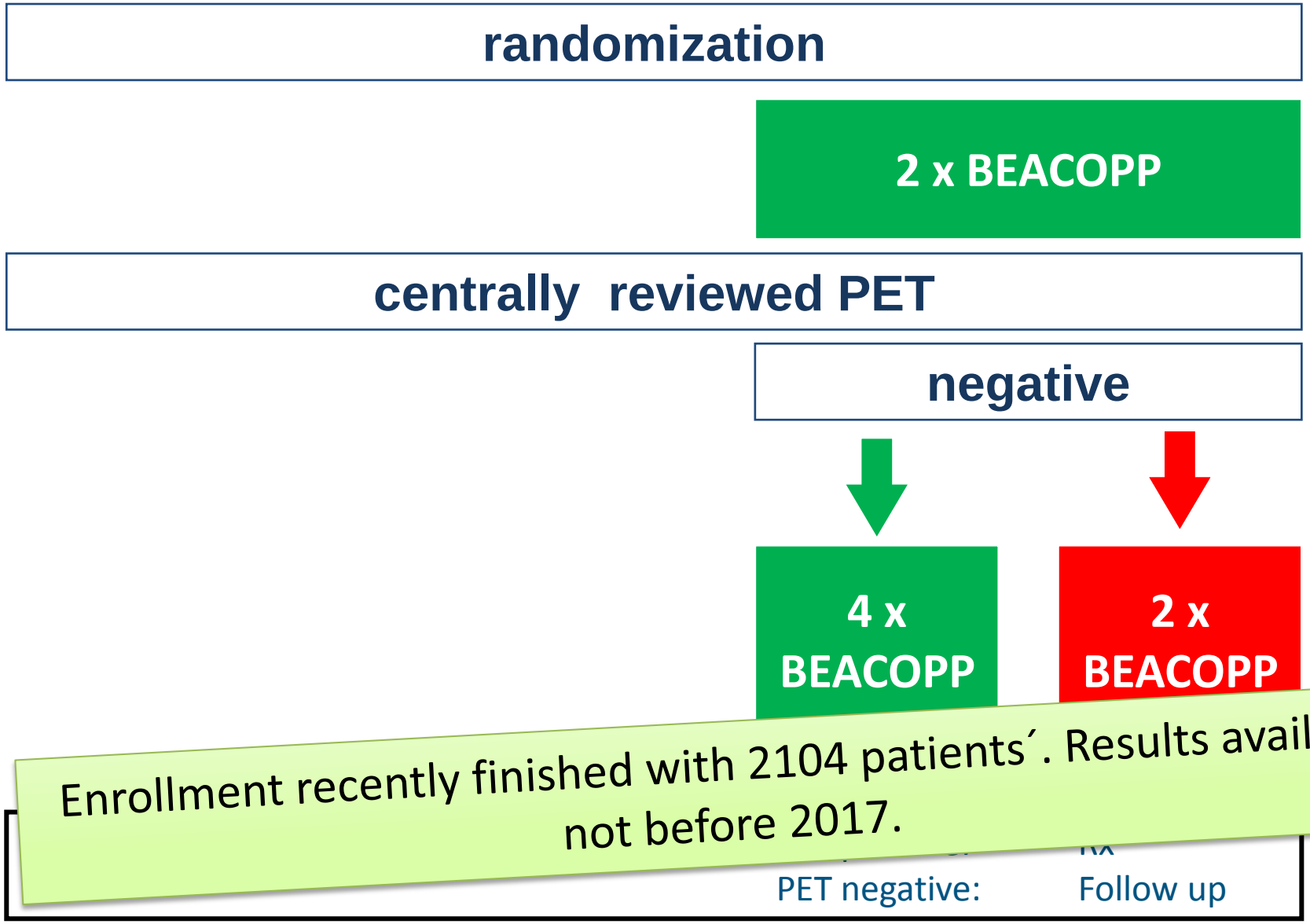
PFS of iPET positive patients in HD18

Borchmann et al., ASH, 2014, abs 500



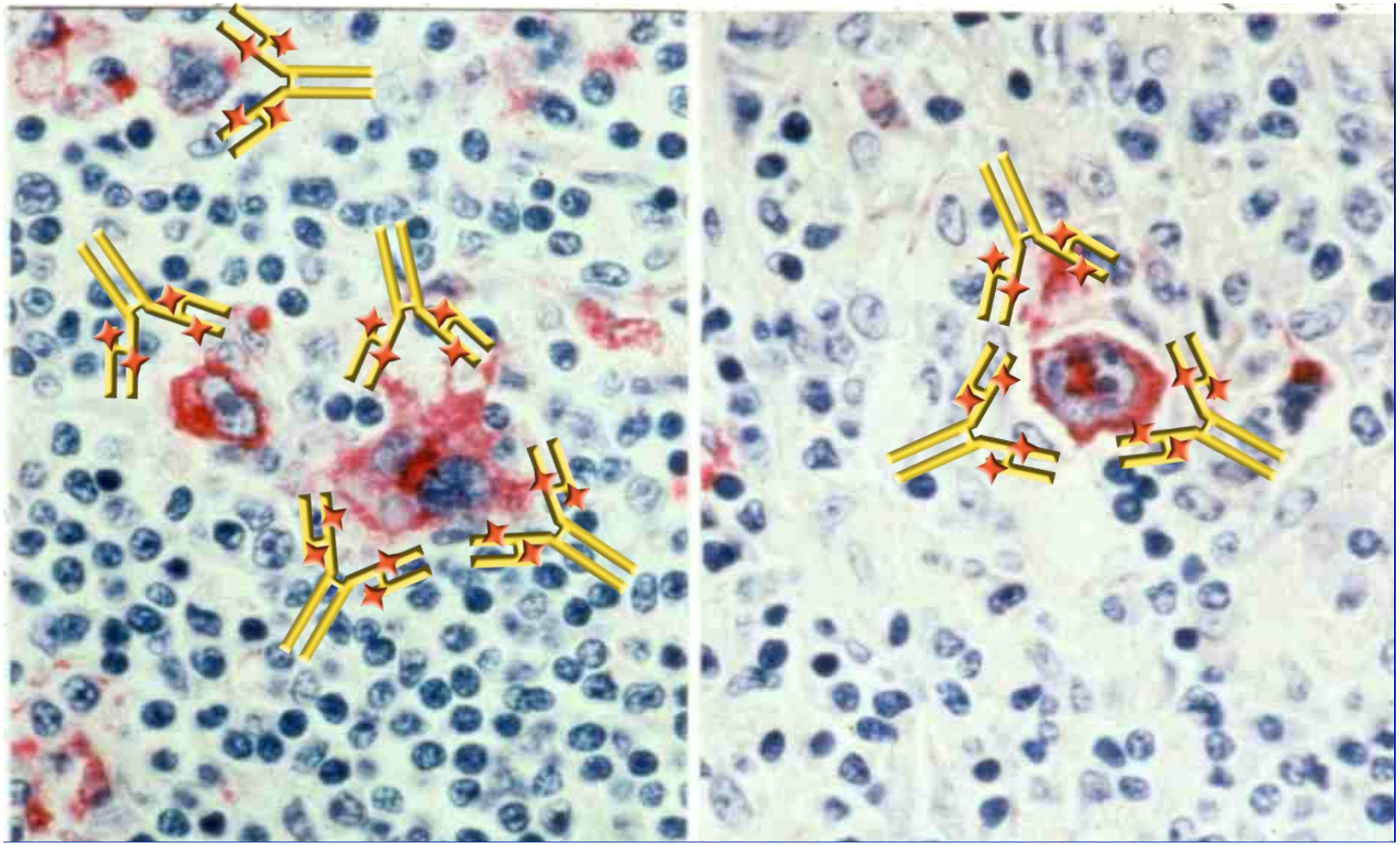
Interim PET positivity does not define a high risk cohort!

GHSG HD 18 trial



Enrollment recently finished with 2104 patients´. Results available not before 2017.

The CD30 antigen: targeting the H-RS cell in HL with antibodies



Remodeling BEACOPPesc with Brentuximab vedotin

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Drug	Day	6x BEACOPP	6x BrECADD
Bleomycin	8	10	
Etoposide	**1-3**	**200**	**150**
Adriamycin	**1**	**35**	**40**
Cyclophosphamide	**2**	**1250**	**1250**
Vincristine	8	1.4	
Brentuximab vedotin	1		**1.8**
Procarbazine	1-7	100	
Prednisone	1-14	40	
Dacarbazine	**2-3**		**250**
Dexamethasone	**1-4**		**40**

Interim analysis of the BEACOPP variant BrECADD indicate

1. an efficacy comparable to BEACOPPesc (BrECADD, n=37, CR n=35 (95%), PR n= 2 (5%))
2. a safety profile superior to BEACOPPesc (grade 3 or 4 non-hematological toxicity 3% with
3. only 30% grade 1 or 2 neurotoxicity

6x BEACOPPesc will be challenged by 6x BrECADD in the international GHSG HD21 study starting soon.

How can we do better? Co-primary objectives in HD21

Primary objectives: to show

- Non-inferiority of BrECADD in terms of **PFS (observed in HD15: 91% stage II/IV at 3 years)**
- Superiority of BrECADD regarding **treatment-related morbidity (TRM) at end of treatment**

What do you think: how does this endpoint compare to the primary endpoint of ECHELON I, which is: improving the PFS at 3 years from 75% for ABVD to 82,5% for AVD-A? Honestly: how relevant is this objective taking into account some more relevant toxicities as neuropathy (roughly 75%!)?

The old and new match: BEACOPP

1. We should always try to improve our treatment strategies, of course. However, any new strategy must be better in terms of overall survival than BEACOPPesc: Patients want to be cured!
2.
3. Can we do even better than BEACOPPesc?

We, the GHSG, thank you for your attention!

Which answer is correct? In advanced stage HL treated with BEACOPPEesc,

1. Positive early interim PET (after cycle 2) identifies a high risk group of patients
2. Residual disease is defined as any tumor > 1.5 cm at the end of chemotherapy
3. PET after the end of chemotherapy helps to identify a high risk group
4. As compared to treatment with ABVD, the superiority of BEACOPP in terms of PFS and OS is both significant and relevant in IPI low risk patients.

Which answer is wrong? For patients with advanced stage HL, treatment with 6 cycles BEACOPPesc, the GHSG standard of care, results

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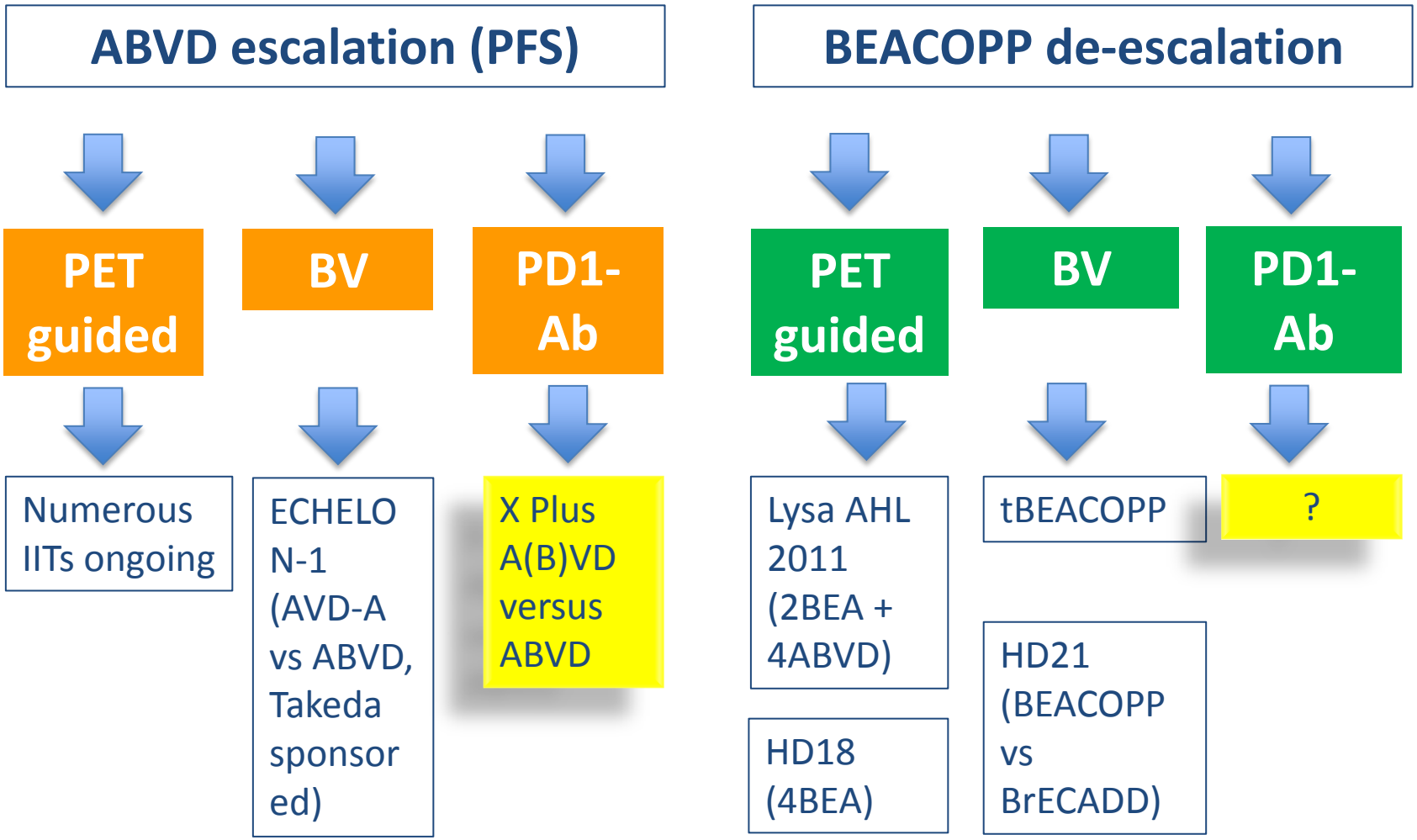
1. In a treatment related mortality rate of 0.8%.
2. In an overall survival at 5 years of 95%.
3. In an infertility rate of about 80% in women in the age of 25 years at diagnosis.
4. In 0.3% secondary acute myeloid leukemia.

Future developments?



Current international developments

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ABVD escalation (PFS)

PET guided

- Numerous IITs ongoing

Brentuximab

- ECHELON-1 (AVD-A vs ABVD, Takeda sponsored)

BEACOPP de-escalation

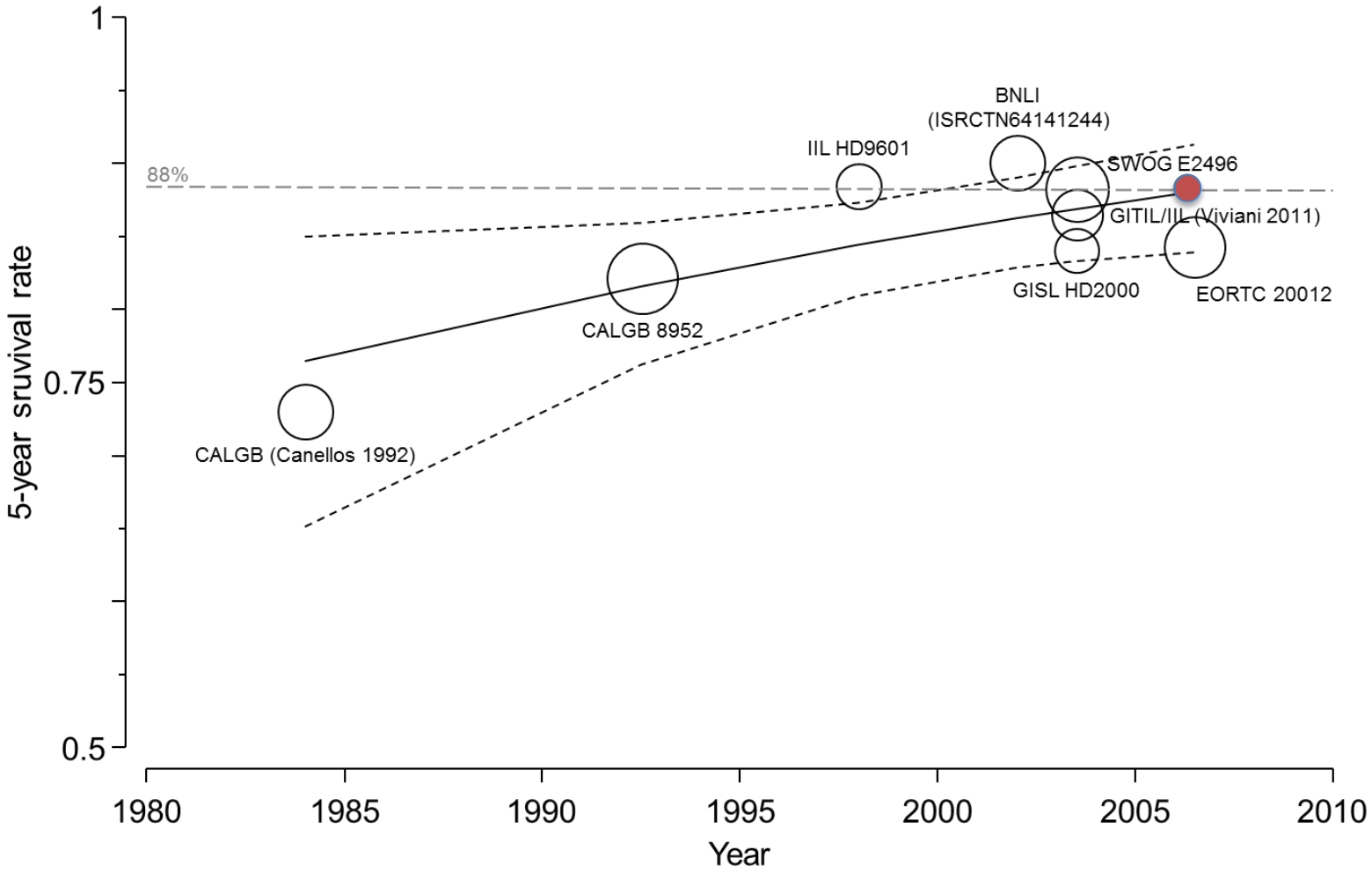
PET guided

- Lysa AHL 2011 (2BEA + 4ABVD)
- HD18 (4BEA)

Brentuximab

- tBEACOPP
- HD21 (BEACOPP vs BrECADD)

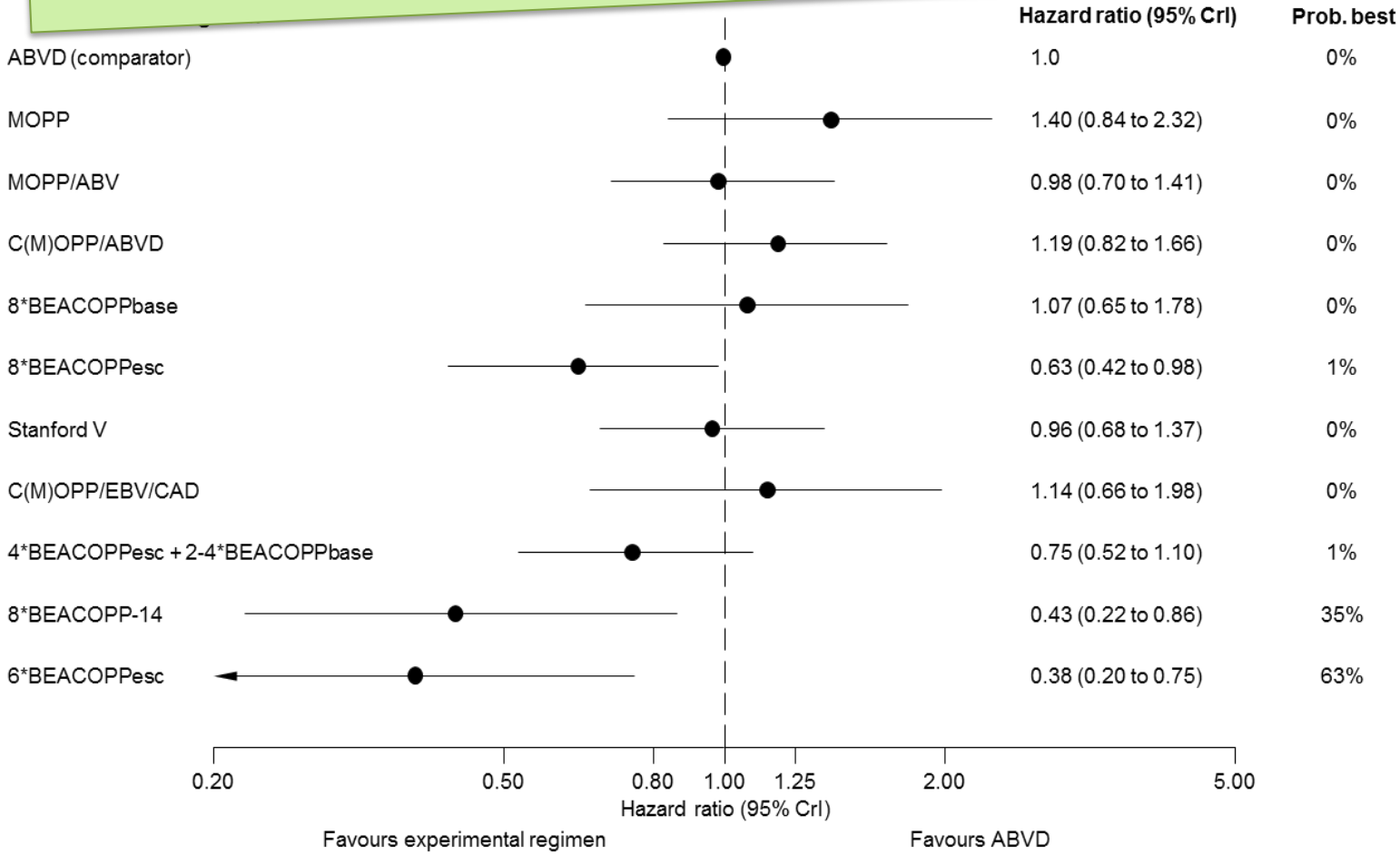
OS for ABVD (reference regimen)



5y-OS of 88% (84-91%) is the estimate for ABVD for this analysis (reference value)

Forest plot for OS

Probability for superiority of a BEACOPP containing over ABVD regimen is 100%



Treatment outcome after chemotherapy (primary endpoint)

Treatment Outcome	BrECAPP N = 33	BrECADD N = 37	Total N = 70	HD18 (6 cycles)
CR or PET negative PR	28 (85%)	35 (95%)	**63 (90%)** (97.5%-CI 80%-96%)	**91,9%**
Less than PR or PET positive (above liver)	5 (15%)	2 (5%)	**7 (10%)** (97.5%-CI 4%–20%)	**7 %**

The lower limit of the one-sided 95% confidence interval for the number of treatment successes is 80.5%.

Acute Toxicities
6x BRECADD (n=38)

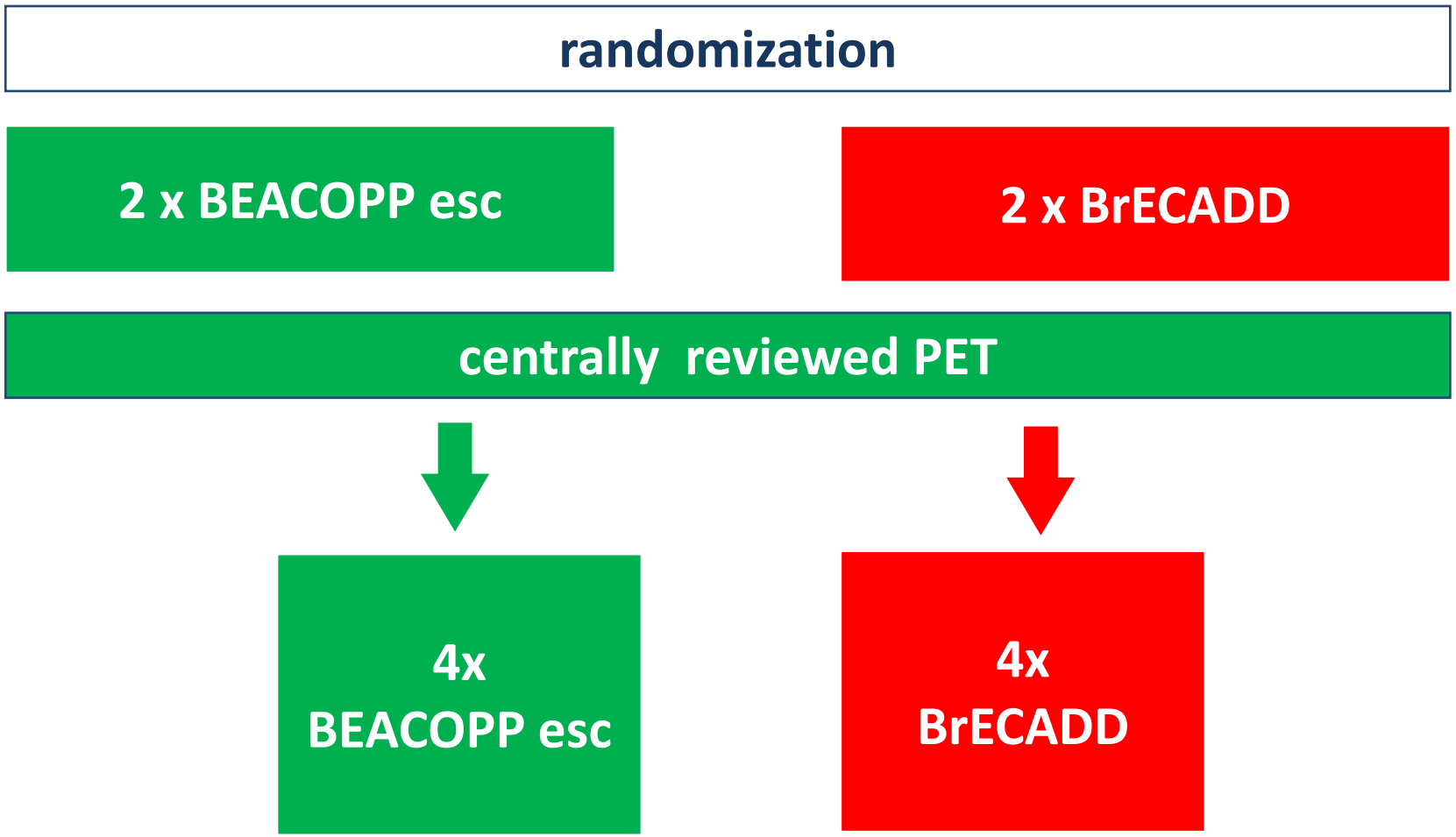
Type of Toxicity	NCIC-CTC Grade						*HD18* III/IV (n=447)*
	none	I	II	III	IV	III/IV	III/IV
Hematological		1 (3%)	1 (3%)	4 (11%)	32 (84%)	36 (95%)	*404 (90.4%)*
Organs	16 (42%)	14 (37%)	7 (18%)	1 (3%)		1 (3%)	*64 (14.3%)*

Neurotoxicity with tBEACOPP (n=71, all patients after 6 cycles)

Type of Toxicity	NCIC-CTC Grade						*HD18* III/IV (n=447)*
	none	I	II	III	IV	III/IV	
Nervous system (sensory)	49 69%	14 20%	7 10%	1 1%		1 1%	*38* *5%*
Nervous system (mot.)	70 99%	1 1%					

In the entire study cohort, 22/71 patients showed grade 1 or 2 neurotoxicity, i.e. 30% (73% with AVD-A)

The GHSG perspective: HD21



End of therapy AND residual nodes > 2.5 cm:	PET positiv:	Rx
	PET negative:	Follow up

Can we further improve the efficacy of BEACOPPesc?

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Standard treatment defining study result:

Study	Group	Median FU	n	PFS (%)	OS (%)
HD15 Engert et al Lancet 2012	**6x BEACOPPesc**	60	711	**90**	**95**
IIL Viviani et al NEJM 2011	**6-8 x ABVD**	61	168	73	84

BEACOPP is obviously highly active with a very high progression free and overall survival rate.

ABVD: PET guided escalation strategy

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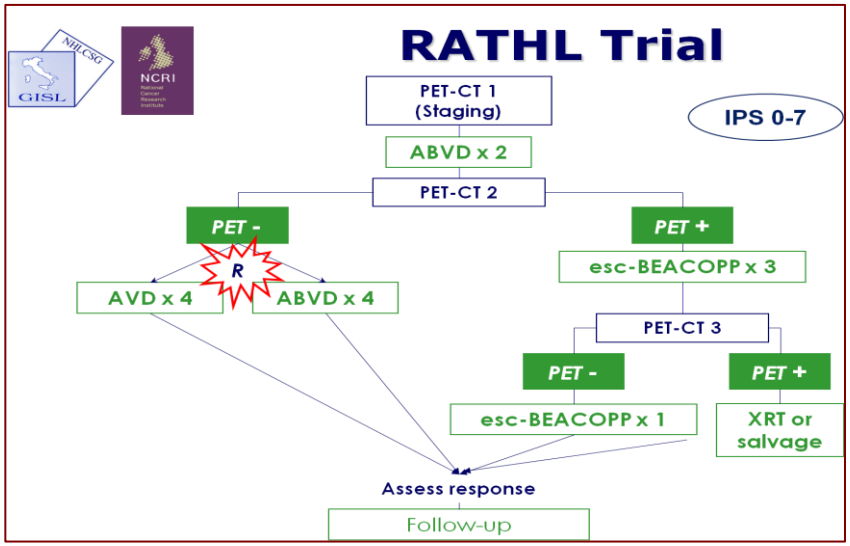
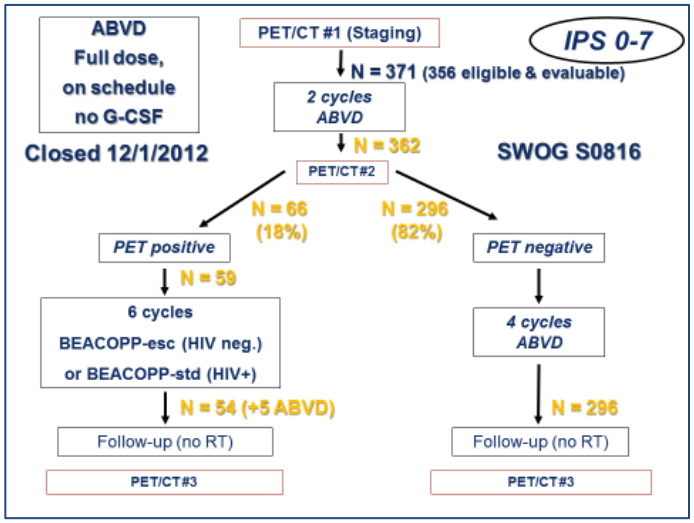
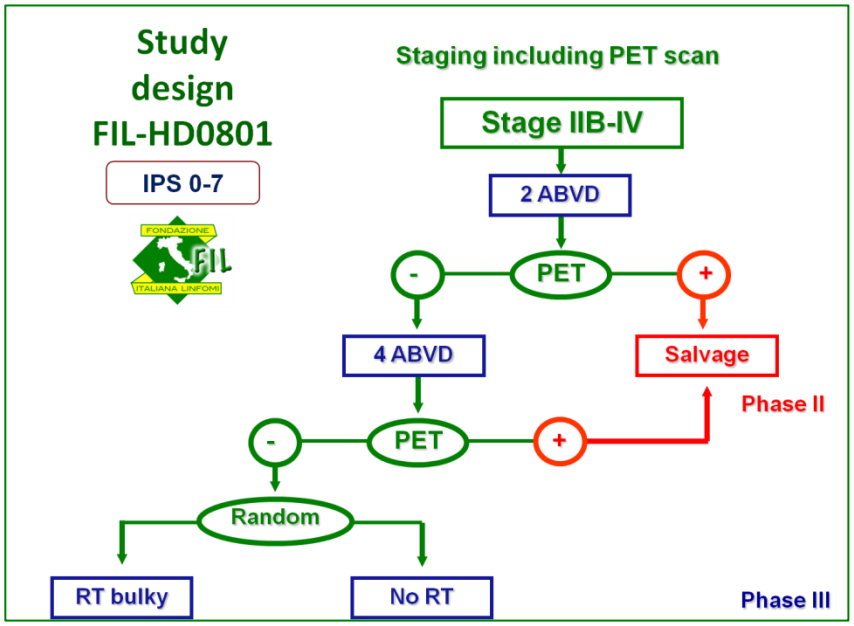
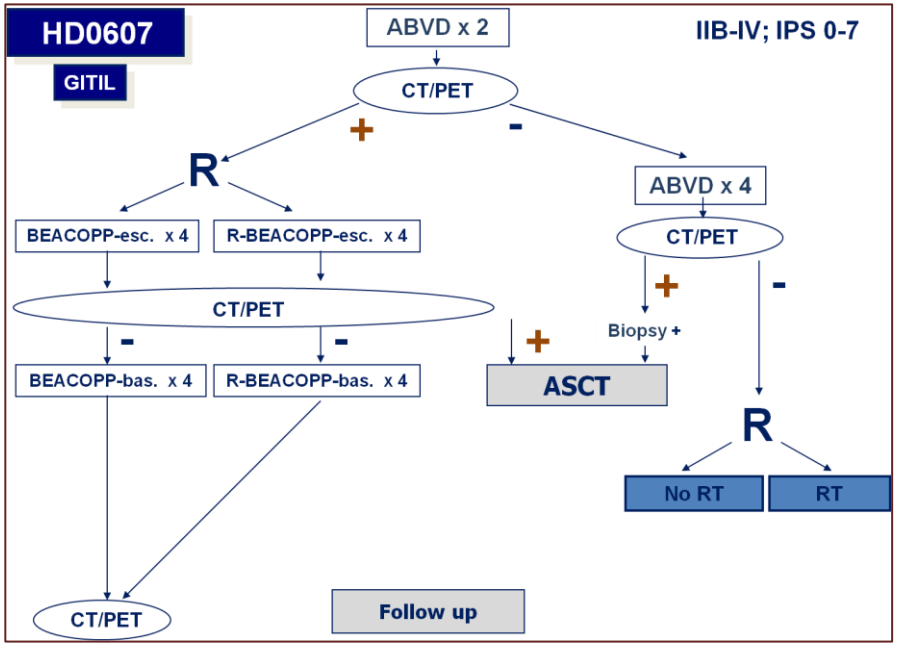
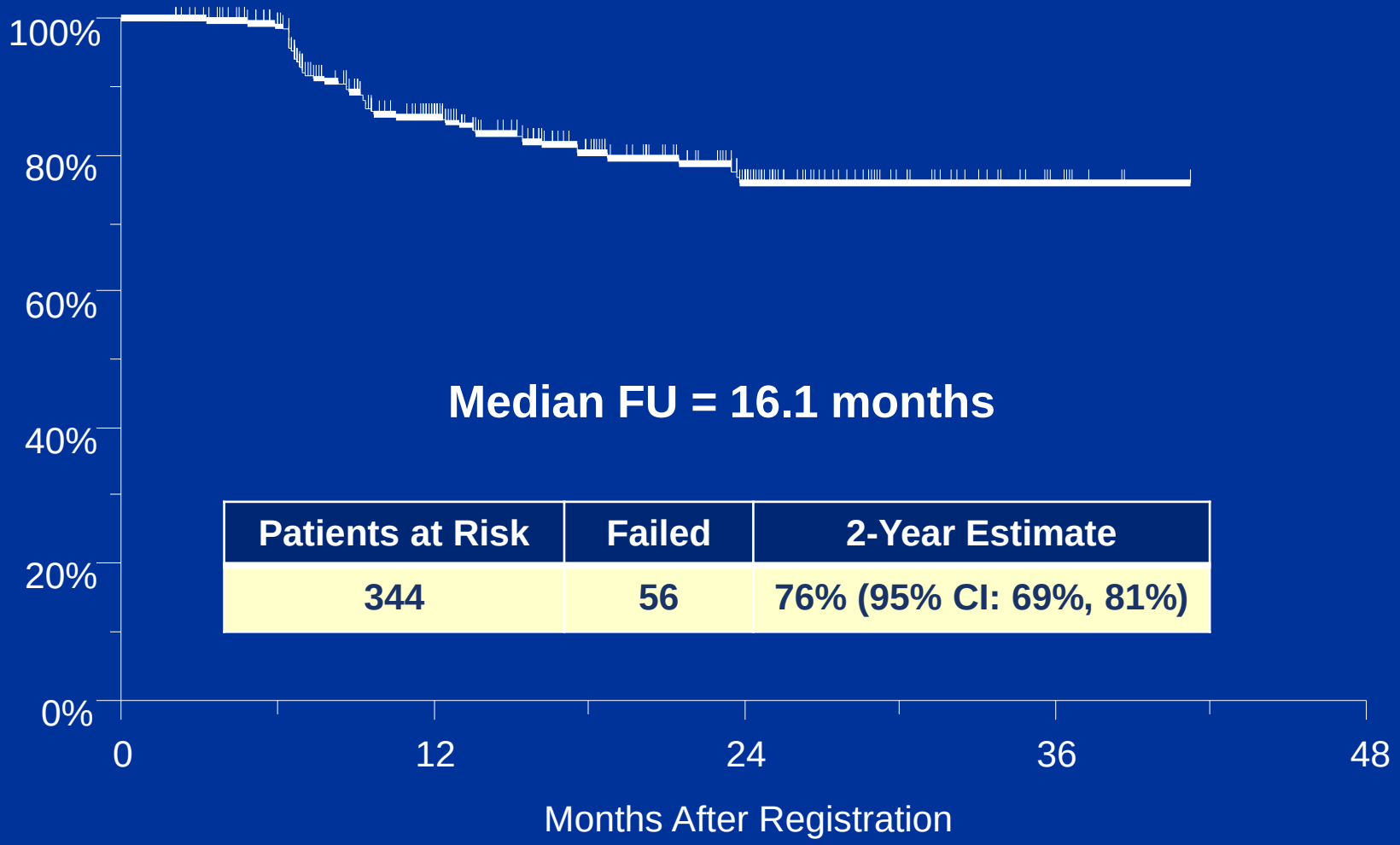








S0816: Progression-Free Survival (HIV-negative)

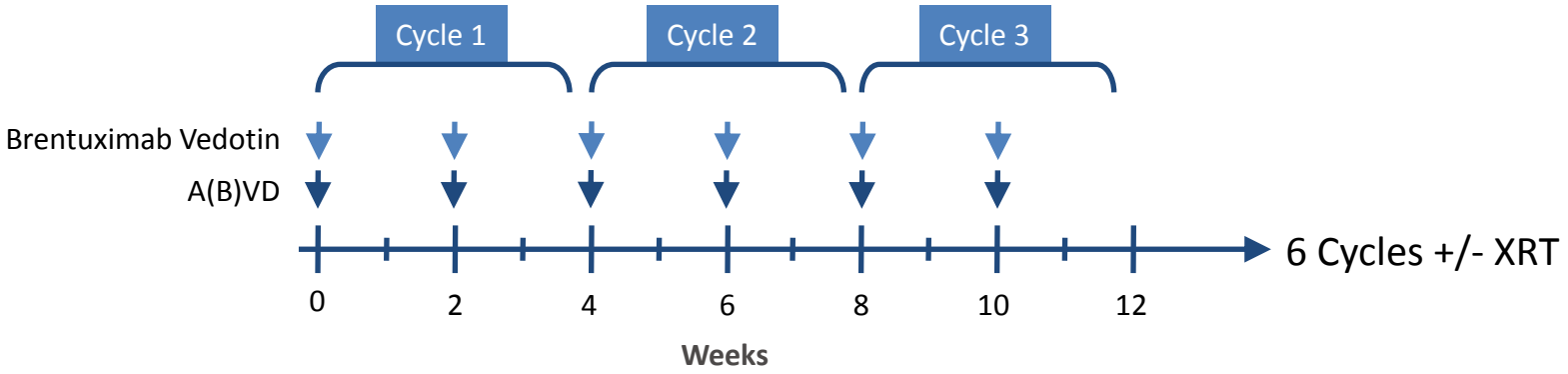


Median FU = 16.1 months

Patients at Risk	Failed	2-Year Estimate
344	56	76% (95% CI: 69%, 81%)

Combination with ABVD: Overview

- Key objectives: safety, MTD, antitumor activity
- Patients: 51 previously untreated HL patients (median age 33 years [range, 18–59]); disease stage: IIA bulky, n=3; IIB, n=8; IIIA, n=8; IIIB, n=9; IV, n=23; bulky disease, n=17; IPS ≥4, n=13
- Treatment: Up to six 28-day cycles
  - **Brentuximab vedotin 0.6 (n=6), 0.9 (n=13), or 1.2 (n=6) mg/kg, days 1 and 15 (weeks 1 and 3), plus ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine)**
  - **Brentuximab vedotin 1.2 mg/kg (n=26) plus AVD (without bleomycin)**



Ansell SM, et al. ASH 2012, Atlanta, GA, USA (Abstract 798)

Pulmonary toxicity in combination with A(B)VD

Preferred term, n (%)	ABVD with brentuximab vedotin (n=25)	AVD with brentuximab vedotin (n=26)
Any event	11 (44)	0
Pulmonary toxicity	9 (36)	0
Interstitial lung disease	1 (4)	0
Pneumonitis	1 (4)	0

- Safety: pulmonary toxicity
  - **Events generally occurred during Cycles 3-4**
  - **Two patient deaths were associated with pulmonary toxicity**
  - **Events resolved in 9 of 11 patients (82%)**
    - Median time to resolution was 2.6 weeks (range, 1.6–5 weeks)
  - **8 of 11 patients with events discontinued bleomycin and were able to complete treatment with AVD combined with brentuximab vedotin**
  - **Concomitant administration of brentuximab vedotin and bleomycin is contraindicated due to pulmonary toxicity**

Ansell SM, et al. ASH 2012, Atlanta, GA, USA (Abstract 798)

Peripheral neuropathy

Preferred term*	ABVD with brentuximab vedotin N=25	AVD with brentuximab vedotin N=26
Any event	18 (72)	20 (77)
Peripheral sensory neuropathy	18 (72)	19 (73)
Peripheral motor neuropathy	3 (12)	3 (12)
Muscular weakness	1 (4)	2 (8)
Paraesthesia	1 (4)	0

* Summary of events using a standard MedDRA query (SMQ), regardless of relationship or severity

- Events were managed with dose modifications
- Most events were Grade 1 or 2 and no events were Grade 4 or 5
- One patient experienced Grade 3 events of peripheral sensory neuropathy (fingers and toes) and peripheral motor neuropathy (hands and feet)
- Overall, 6 of 51 patients discontinued brentuximab vedotin due to peripheral neuropathy; these discontinuations occurred in Cycles 5 or 6

Ansell SM, et al. ASH 2012, Atlanta, GA, USA (Abstract 798)

Anti-tumour activity

- **DLT:** No protocol-defined DLTs observed with either ABVD or AVD in combination with brentuximab vedotin (up to the maximum planned dose of 1.2 mg/kg)
- **Antitumor activity:**

Response at end of frontline therapy, n (%)*	ABVD with brentuximab vedotin (n=22)	AVD with brentuximab vedotin (n=25)
Complete remission	21 (95)	24 (96)
Progressive disease	0	1 (4)
Not evaluable due to AE	1 (5)**	0

- Prior to completion of frontline therapy
  - 1 patient withdrew consent
  - 3 patients lost to follow-up
- Phase 3 study ongoing to assess treatment with brentuximab vedotin in combination with AVD compared to ABVD alone in treatment-naive patients

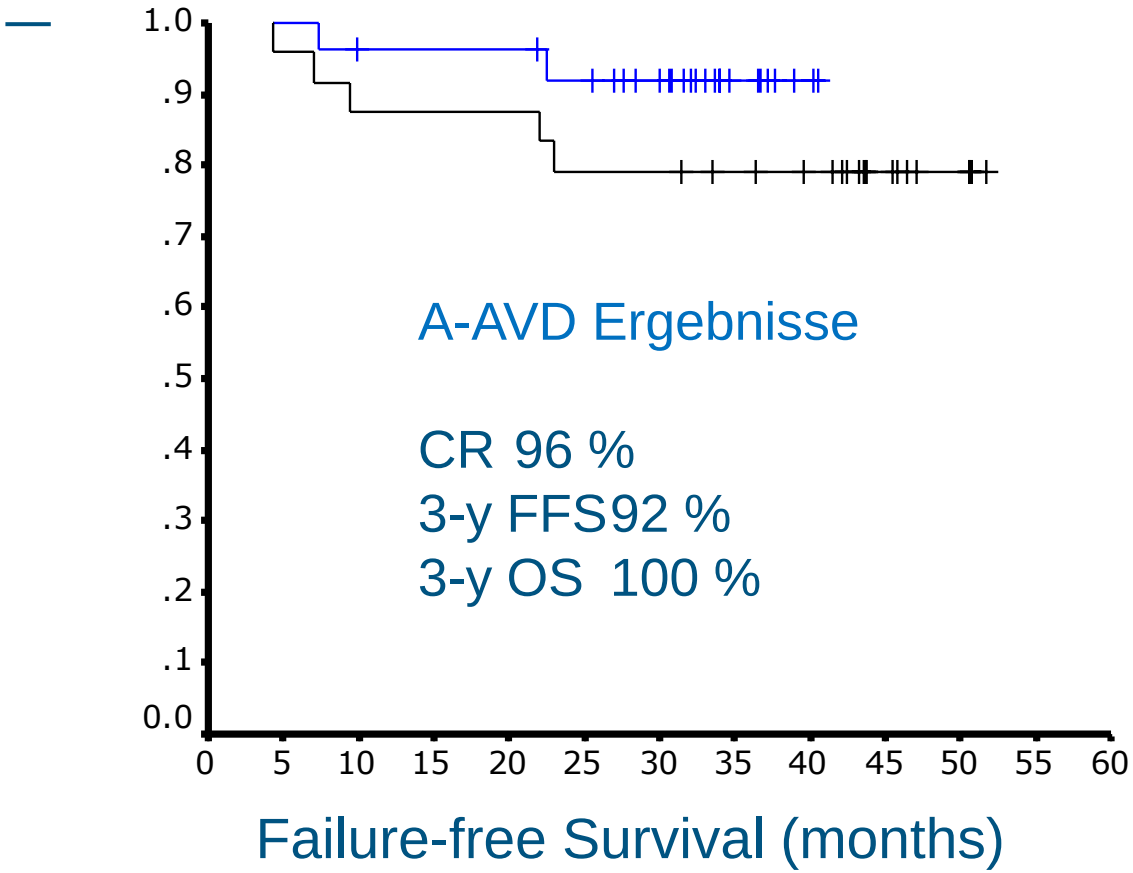
* Per Investigator

** Patient had Grade 5 pulmonary toxicity prior to end of frontline therapy

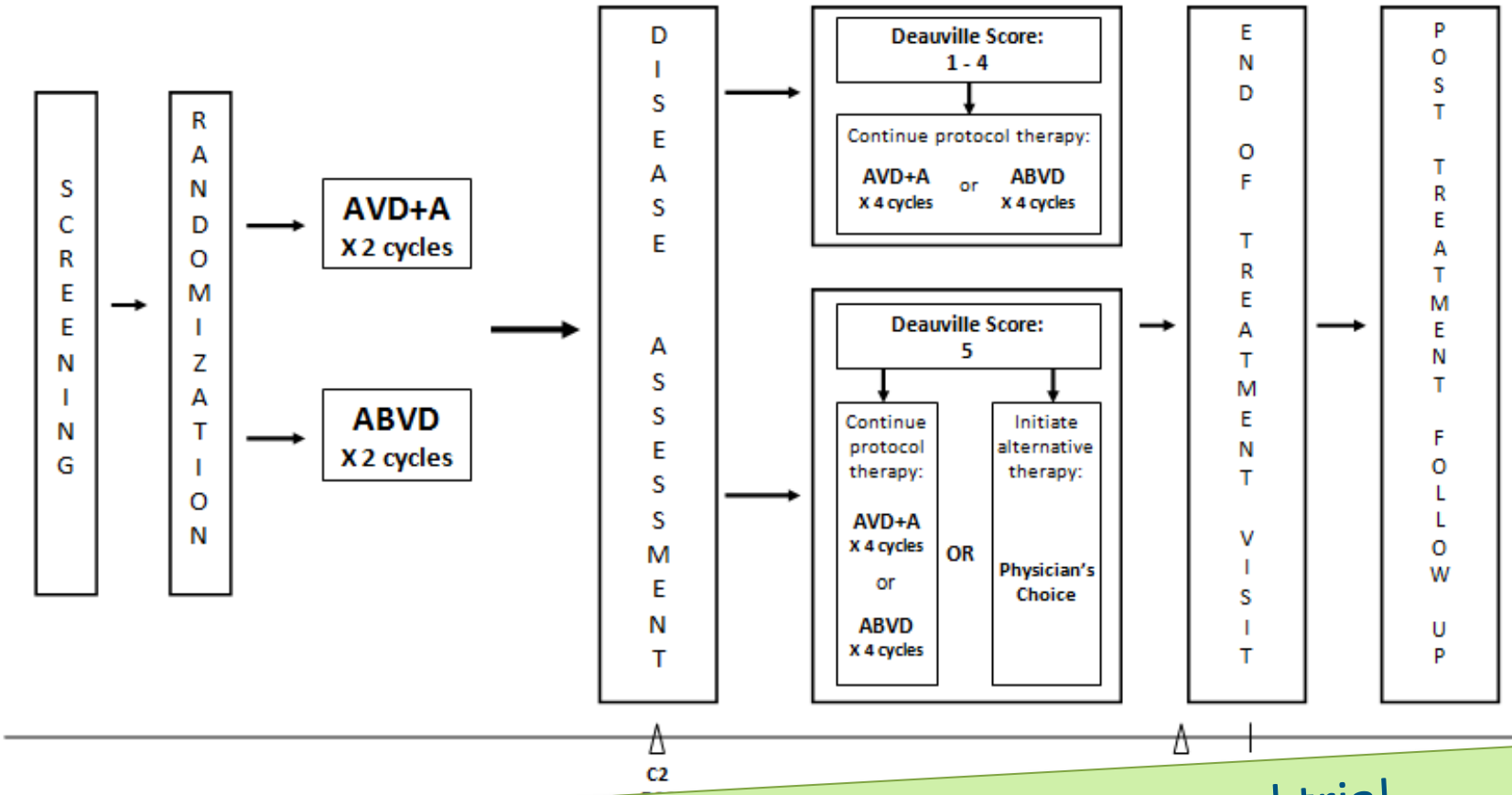
Ansell SM, et al. ASH 2012, Atlanta, GA, USA (Abstract 798)

A(B)VD-A failure free survival

Connors et al., ASH, 2014, abs 624



Phase III study of A-AVD vesus ABVD in advanced stage HL (NCT01712490)



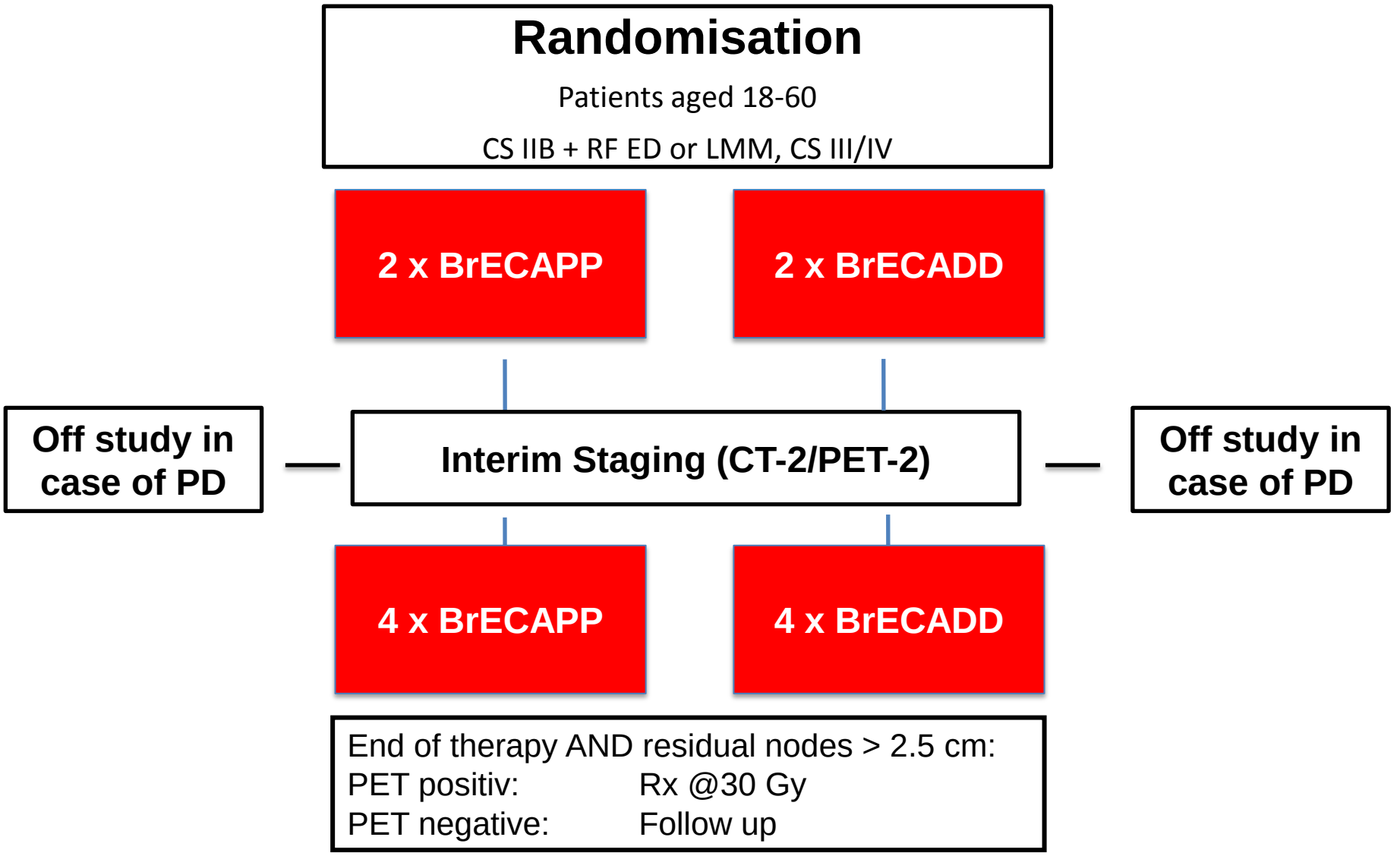
Worldwide recruiting industry sponsored trial

Primary endpoint PFS: Estimates in C25003 (ECHELON I)

PFS @ 3 years for stage III/IV patients

	6x ABVD C 25003	6x AVD-A C 25003
PFS	**75** expected	**82,5** expected

Targeted BEACOPP: Study flow



Can we define patients at risk for treatment related mortality (TRM)?

Risk Factor		Score
Age	**<40**	0
	40-49	1
	≥50	2
ECOG / Karnofsky	<2 or ≥80	0
	=2 or <80	1

Wongso et al., JCO, 2013