

Hodgkin Lymphoma

Status of the art of treatment

Peter Borchmann
German Hodgkin Study Group
University of Cologne, Germany

Which statement regarding 1st line treatment of early stage HL is correct?

1. The differentiation between early favourable and unfavourable stage HL does not reflect different prognostic subgroups any longer
2. PET guided omission of RT in early favourable HL results in a significant loss of tumor control as determined by PFS
3. Early interim PET+ guided escalation of ABVD to BEACOPPesc does not improve the outcome (PFS/OS) in early unfavourable HL
4. Consolidating radiotherapy puts the majority of female patients at high risk for second breast cancer

GHSQ staging and treatment concepts

	Stage			
Risk factor	IA, IB, IIA	IIB	IIIA, IIIB	IVA, IVB
No	Early favourable			
≥ 3 LN- areas				
Elevated ESR				
Large mediastinal mass				
Extranodal disease				

„State of the art“ early favourable stage HL: The GHSG HD10 study

CS I/II, no RF

4 x
ABVD

4 x
ABVD

2 x
ABVD

2 x
ABVD

30 Gy IF

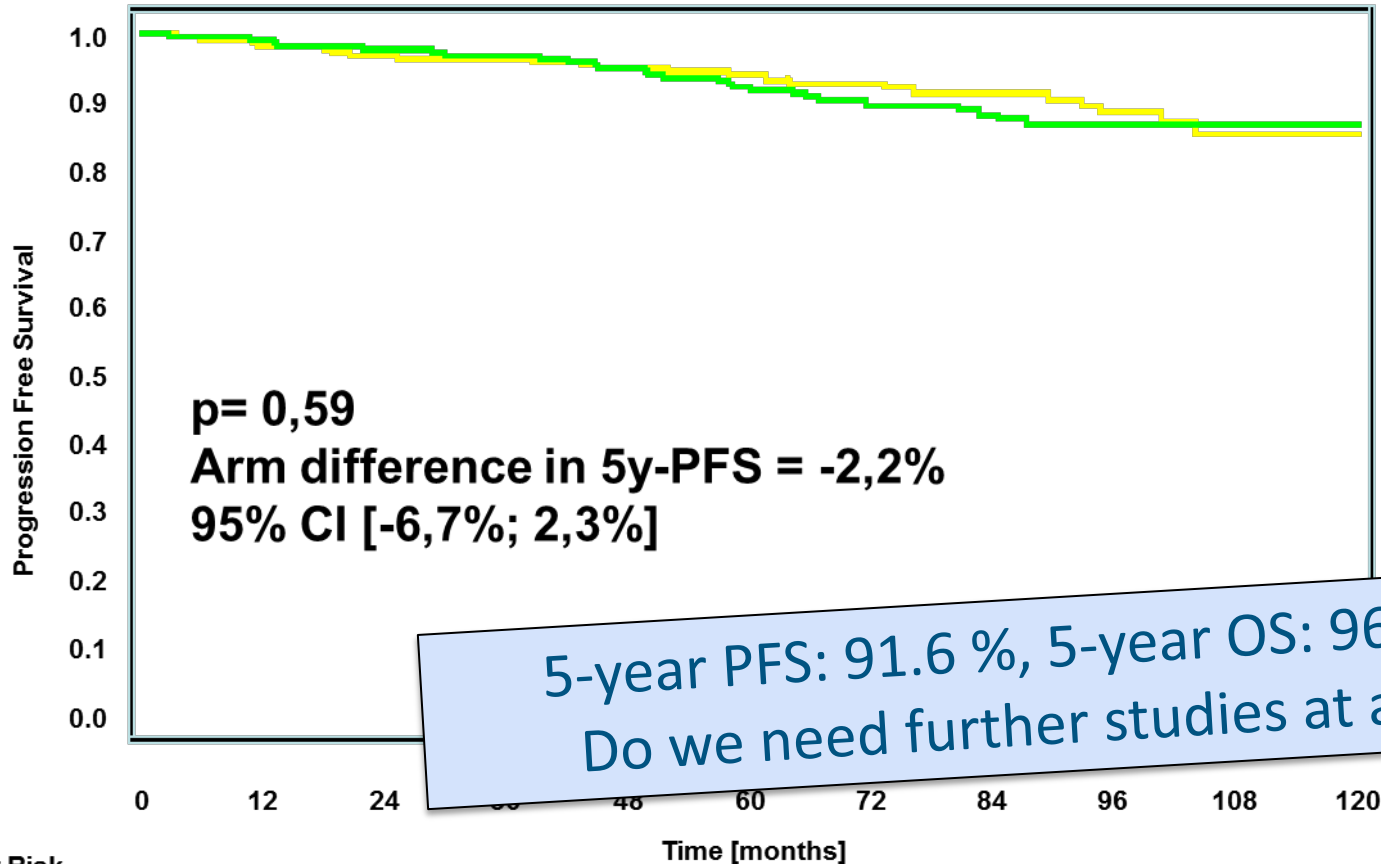
20 Gy IF

30 Gy IF

20 Gy IF

objective: to show non-inferiority (6%)

HD10: Strongest (A, 4xABVD + 30Gy) vs weakest (D, 2xABVD + 20Gy) group

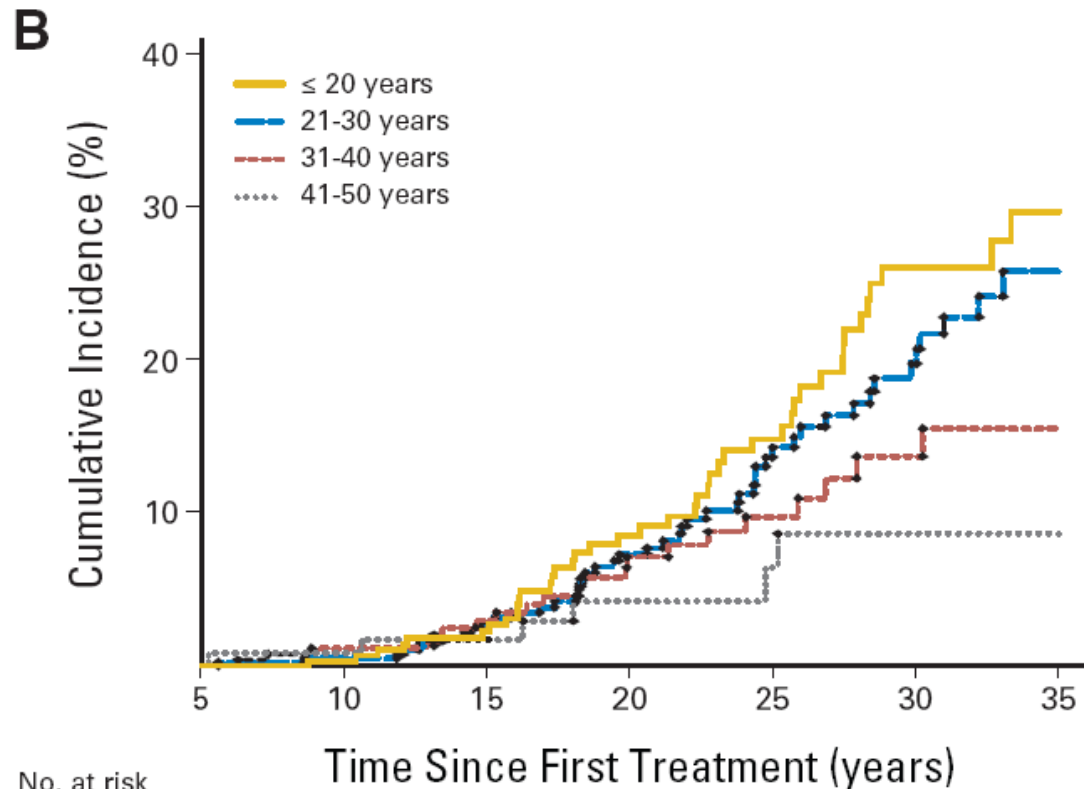


Pts. at Risk

	0	12	24	36	48	60	72	84	96	108	120
A	298	285	272	263	247	224	172	124	77	34	2
D	299	283	273	260	247	204	155	114	69	28	4

Long term risk of Rx: Cumulative breast cancer incidence in women

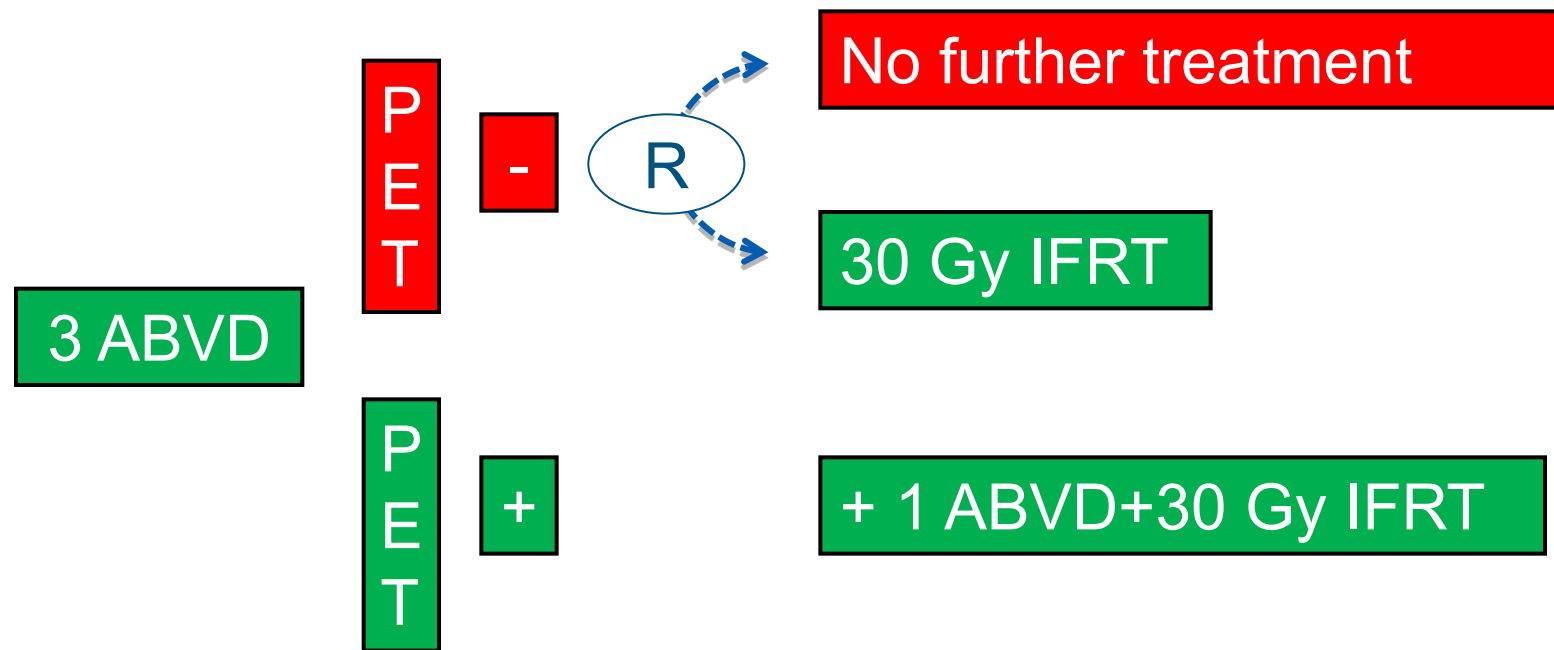
(1,122 female 5-year survivors treated for HL <51 years between 1965 and 1995)



No. at risk	5	10	15	20	25	30	35
≤ 20	311	279	203	136	81	41	11
21-30	426	375	262	168	90	46	9
31-40	264	224	162	94	29	25	5
41-50	121	102	73	52	25	11	4

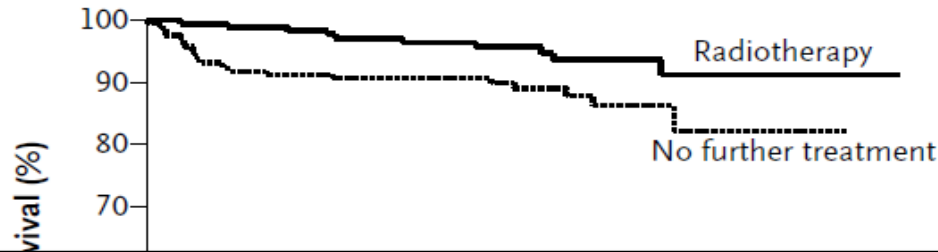
PET guided omission of Rx: the RAPID trial

Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. The UK NCRI RAPID **non-inferiority trial (lower margin 7%).**



RAPID: PFS PET-negative patients (per protocol, n=392)

B Per-Protocol Analysis



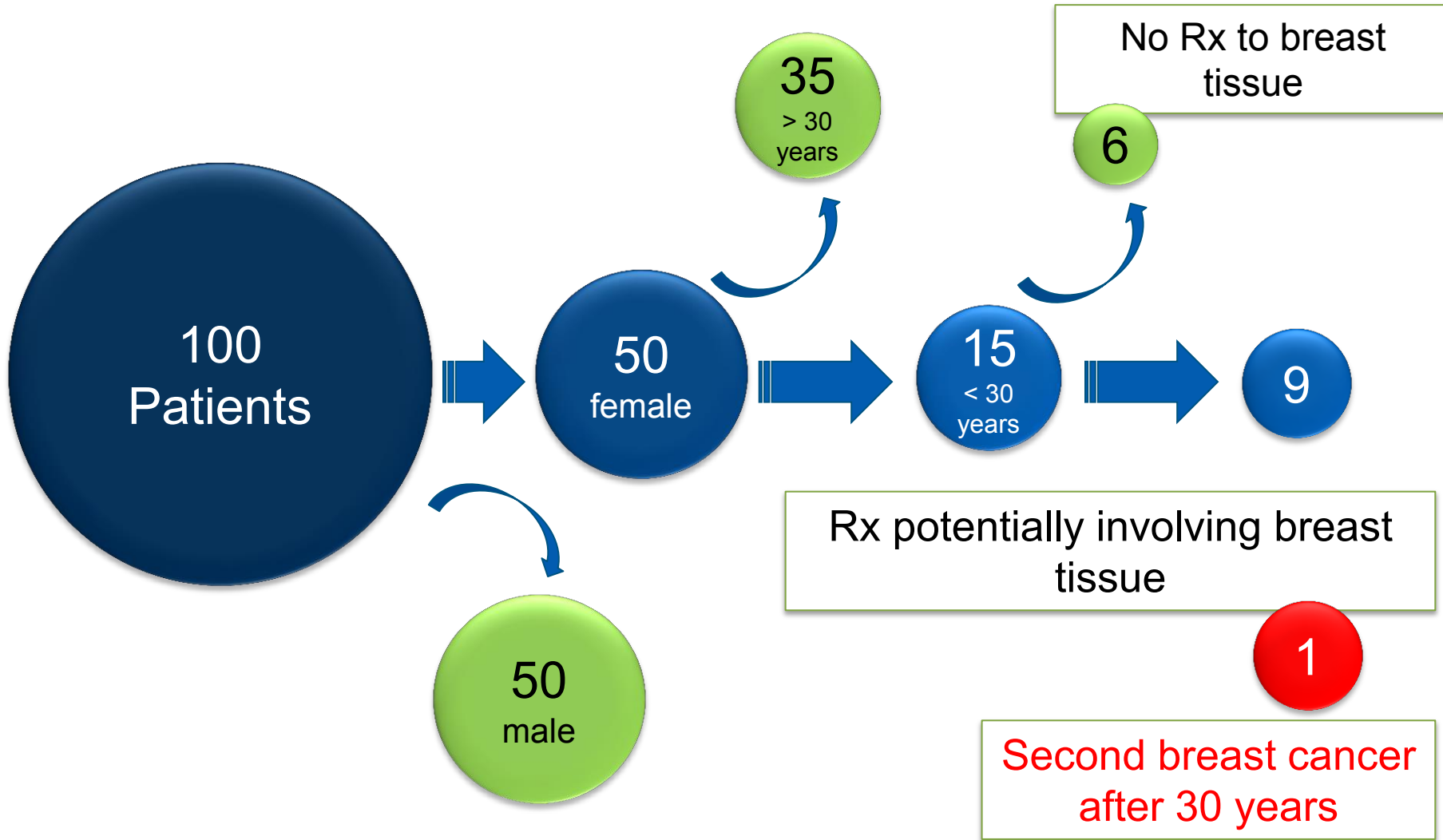
1. Radiotherapy *improves* the PFS significantly in PET-negative (!) patients
2. This is the same result as in the EORTC10 trial (Raemaekers et al., JCO): evidence for this observation is good.
3. Nonetheless, omission of Rx for PET negative patients has been recommended (Longo, NEJM). SOC?

Months since Randomization

No. at Risk

Radiotherapy	183	180	172	161	130	99	58	33	13	2	0
No further treatment	209	202	194	165	139	97	56	18	6	0	0

Should we expose ~ 85% of our patients to an increased risk for relapse, though they do not have a risk for developing second breast cancer at all?



GHSG staging and treatment concepts

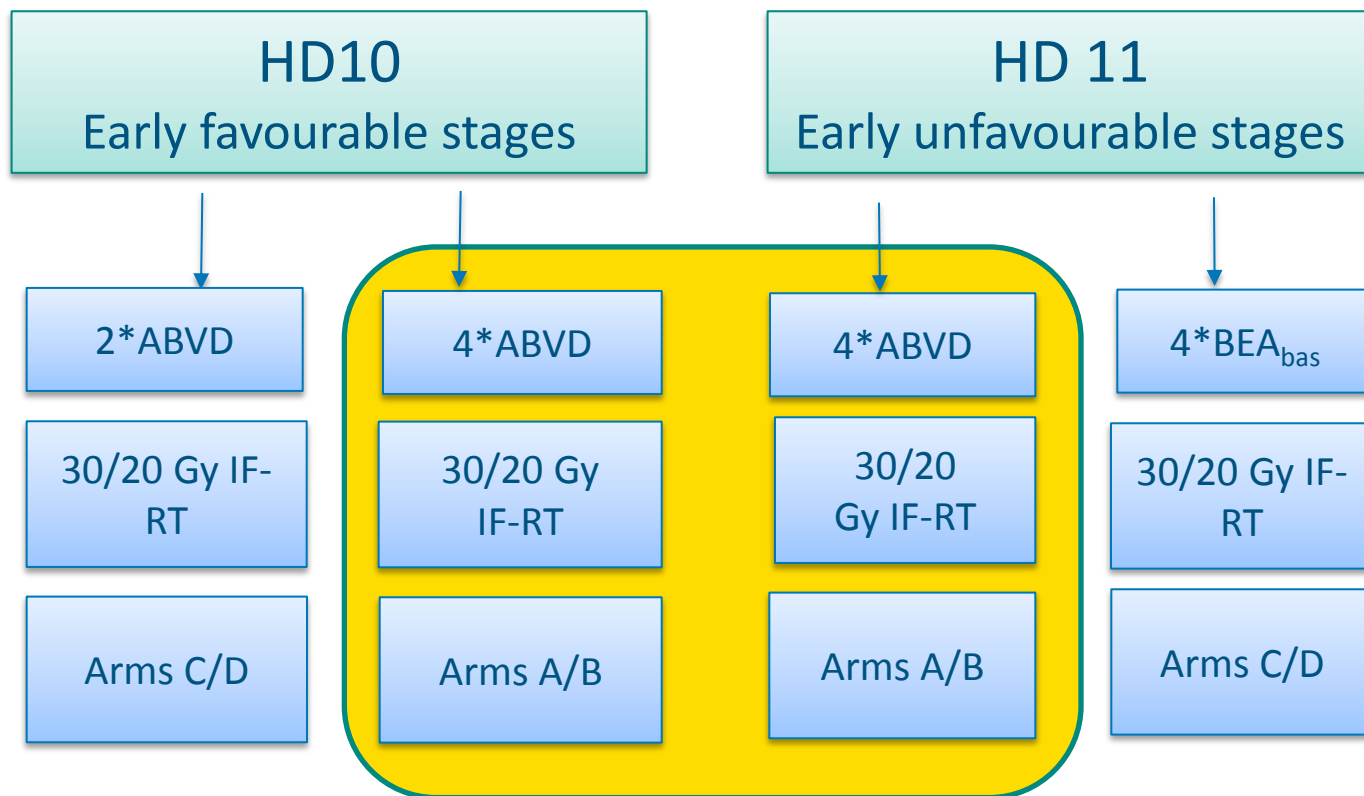
	Stage			
Risk factor	IA, IB, IIA	IIB	IIIA, IIIB	IVA, IVB
No	Early favourable			
≥ 3 LN- areas				
Elevated ESR				
Large mediastinal mass				
Extranodal disease				

2x ABVD plus 20Gy IF-RT (HD10) still is a reasonable SOC

GHSG staging and treatment concepts

	Stage			
Risk factor	IA, IB, IIA	IIB	IIIA, IIIB	IVA, IVB
No				
≥ 3 LN- areas	Early unfavourable			
Elevated ESR				
Large mediastinal mass				
Extranodal disease				

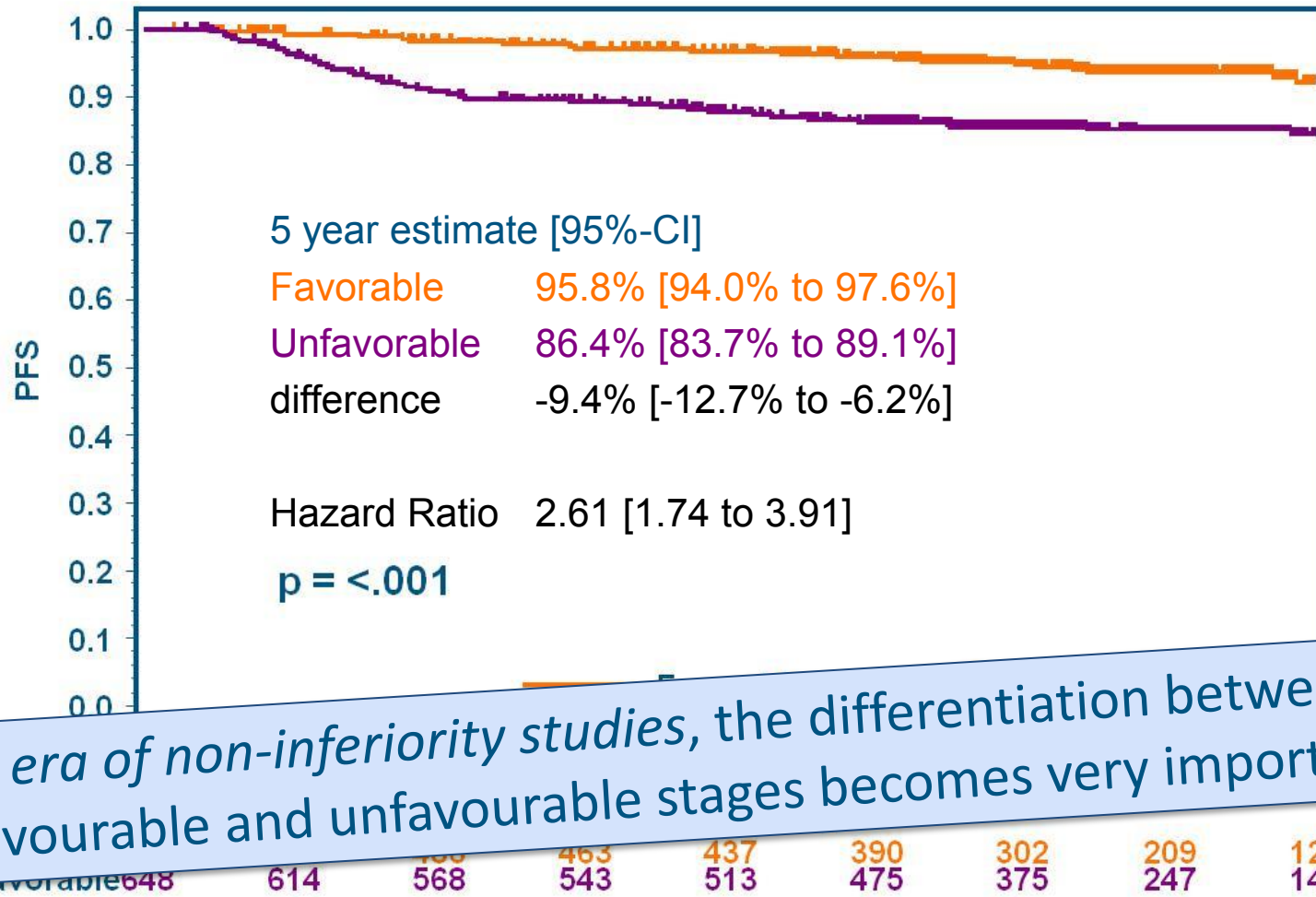
Different stages, same treatment: the GHSG experience



Engert A; NEJM 2010

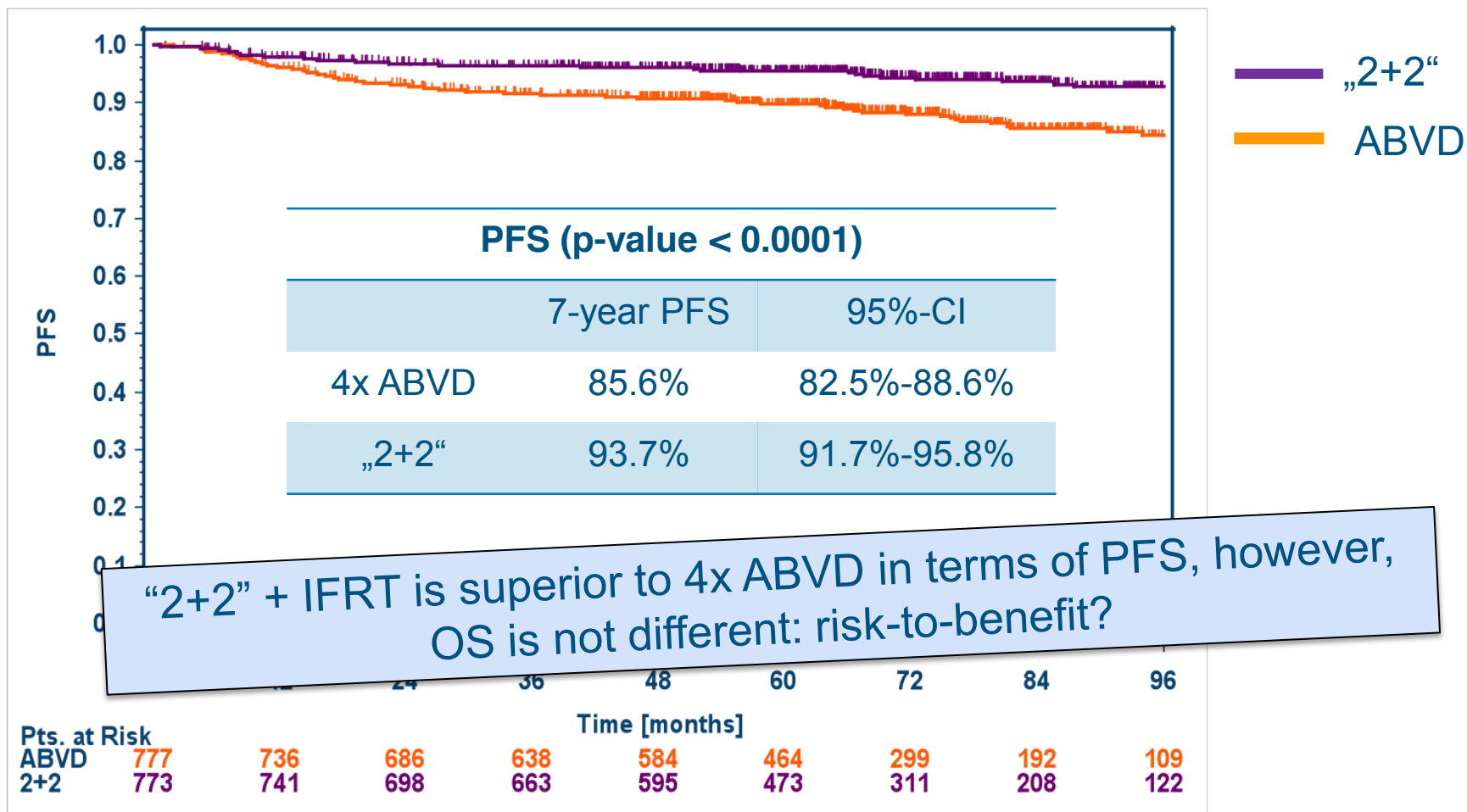
Eich HT, JCO 2011

Progression free survival



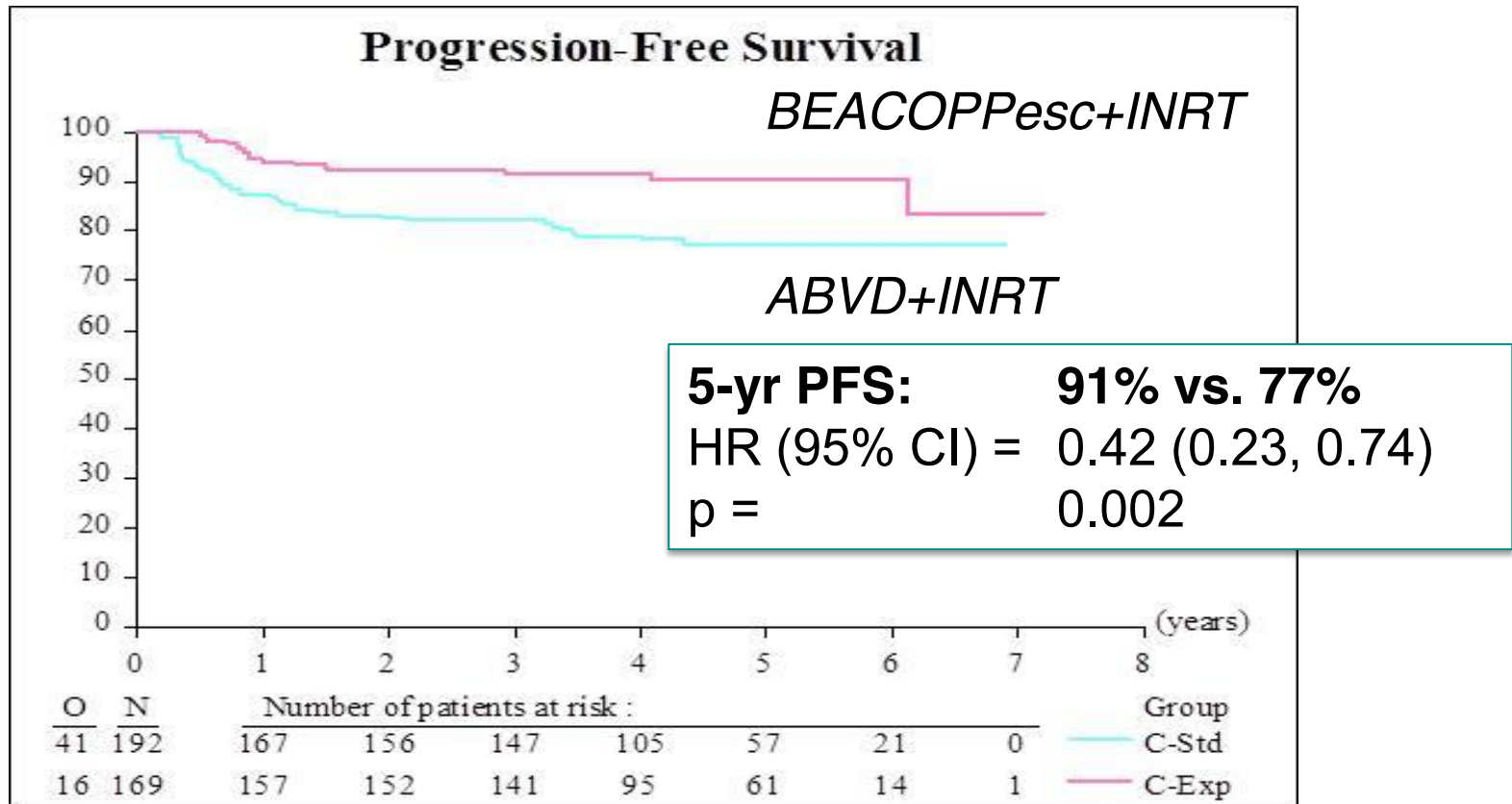
In the era of non-inferiority studies, the differentiation between early favourable and unfavourable stages becomes very important.

Escalating from ABVD to BEACOPP (“2+2”) in early unfavourable HL: PFS difference after 7y FU in the GHSG HD14 trial



“2+2” for patients at high risk for failure with ABVD only: The EORTC H10 study

Early un/favourable PET2+ patients (after 2x ABVD) were randomized to receive either 2x ABVD or 2x eBEACOPP



GHSQ staging and treatment concepts

	Stage			
Risk factor	IA, IB, IIA	IIB	IIIA, IIIB	IVA, IVB
No				
≥ 3 LN- areas				
Elevated ESR	Early unfavourable			
Large mediastinal mass				
Extranodal disease				

4x "chemo" (ABVD, 2+2 upfront, 2+2 PET adapted), plus IF-RT ad 30 Gy

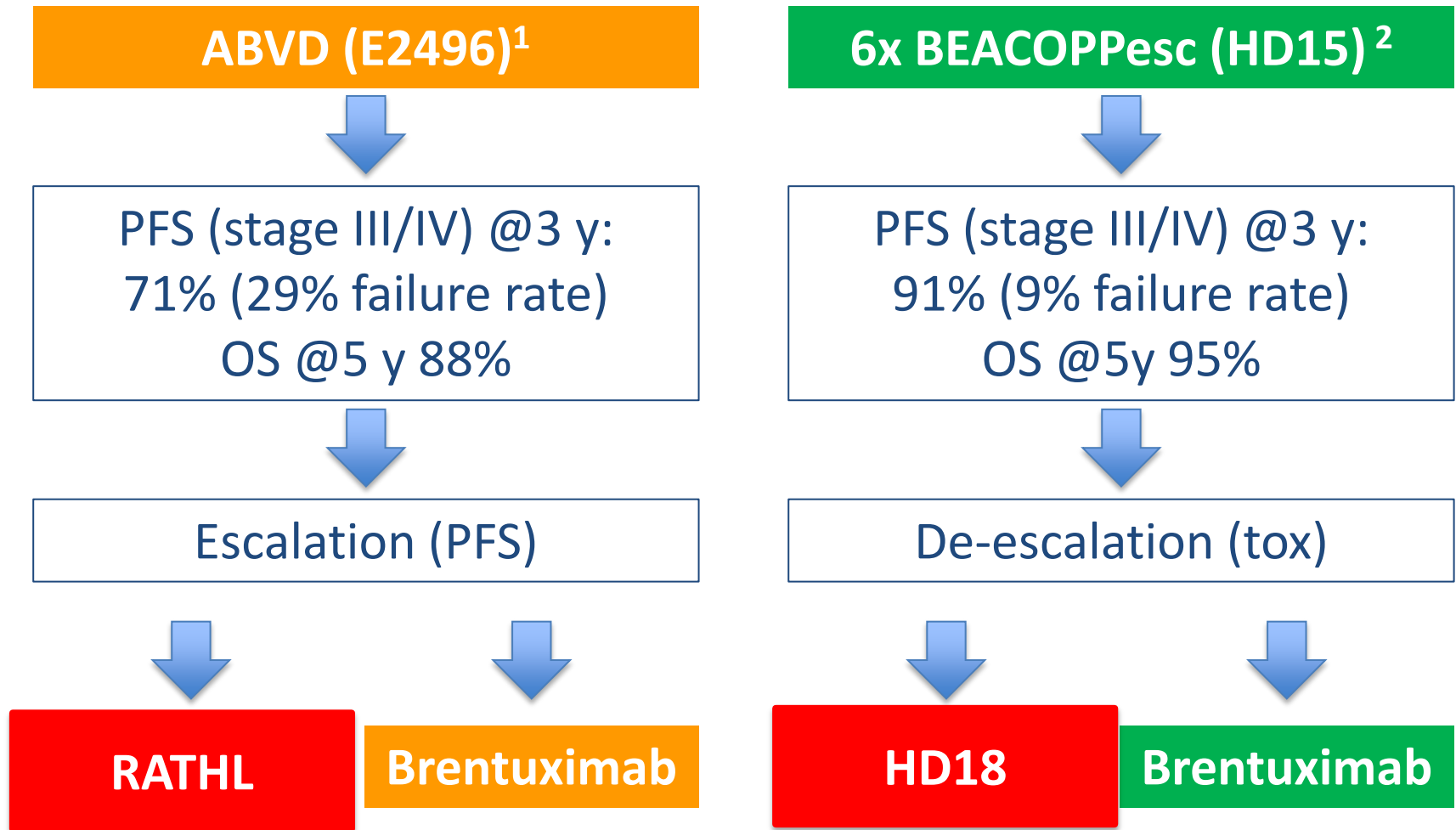
GHSQ staging and treatment concepts

	Ann Arbor Stage			
Risk factor	IA, IB, IIA	IIB	IIIA, IIIB	IVA, IVB
No			Advanced stages	
≥ 3 LN- areas				
Elevated ESR				
Large mediastinal mass				
Extranodal disease				

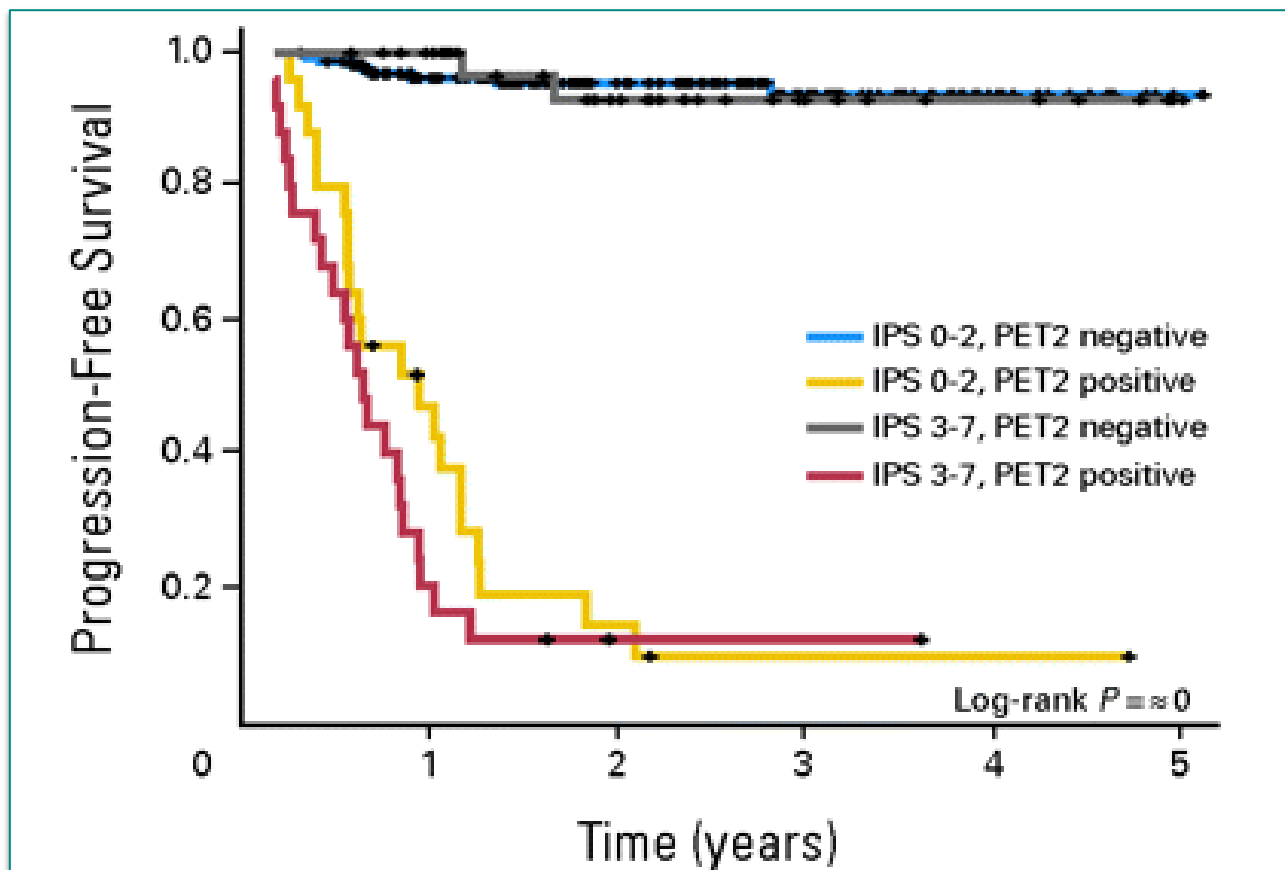
Which statement regarding 1st line treatment of advanced stage HL is correct?

1. PET2 guided escalation of ABVD to BEACOPPesc equals the outcome (PFS) to early interim PET- patients treated with ABVD alone in advanced stage HL
2. PET2 negative after 2x ABVD patients have a PFS of around 95 % at 3y confirming the high negative predictive value of PET2.
3. PET2 positive patients after 2x eBEACOPP have a dismal prognosis
4. PET2 has a different positive predictive value depending on the treatment strategy (e.g. ABVD, BEACOPP, cons. Rx)

Current international standards and approaches in advanced stage HL

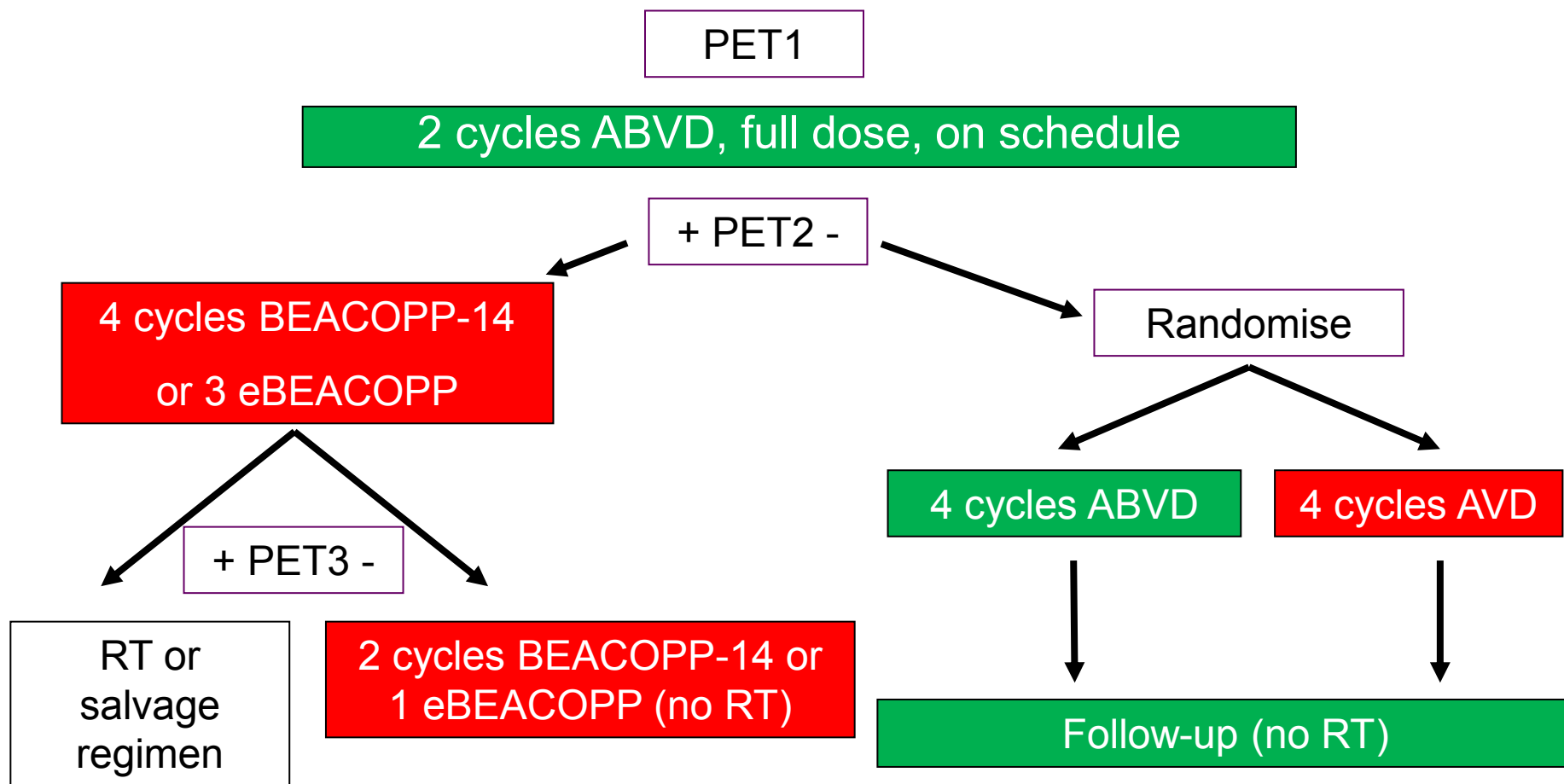


If we cannot predict the individual prognosis *before* treatment, maybe we can do better taking into account the *early response*?

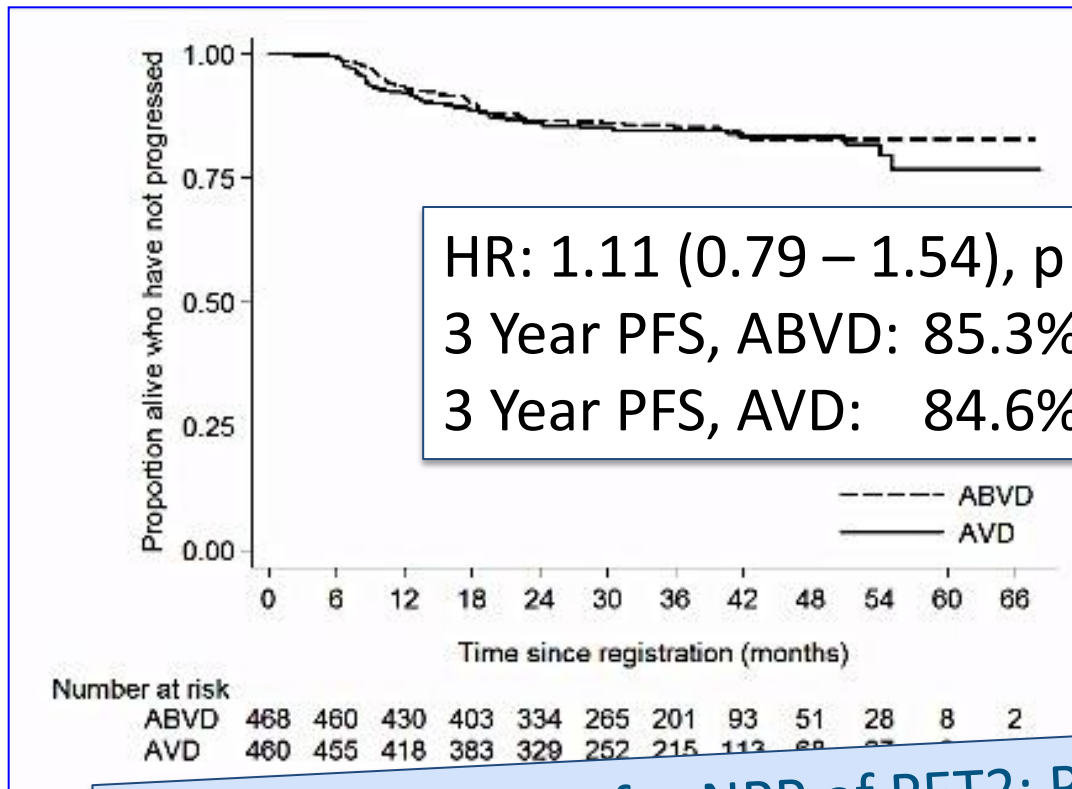


Early interim PET overcomes the international prognostic score (IPS)

RATHL: study-design

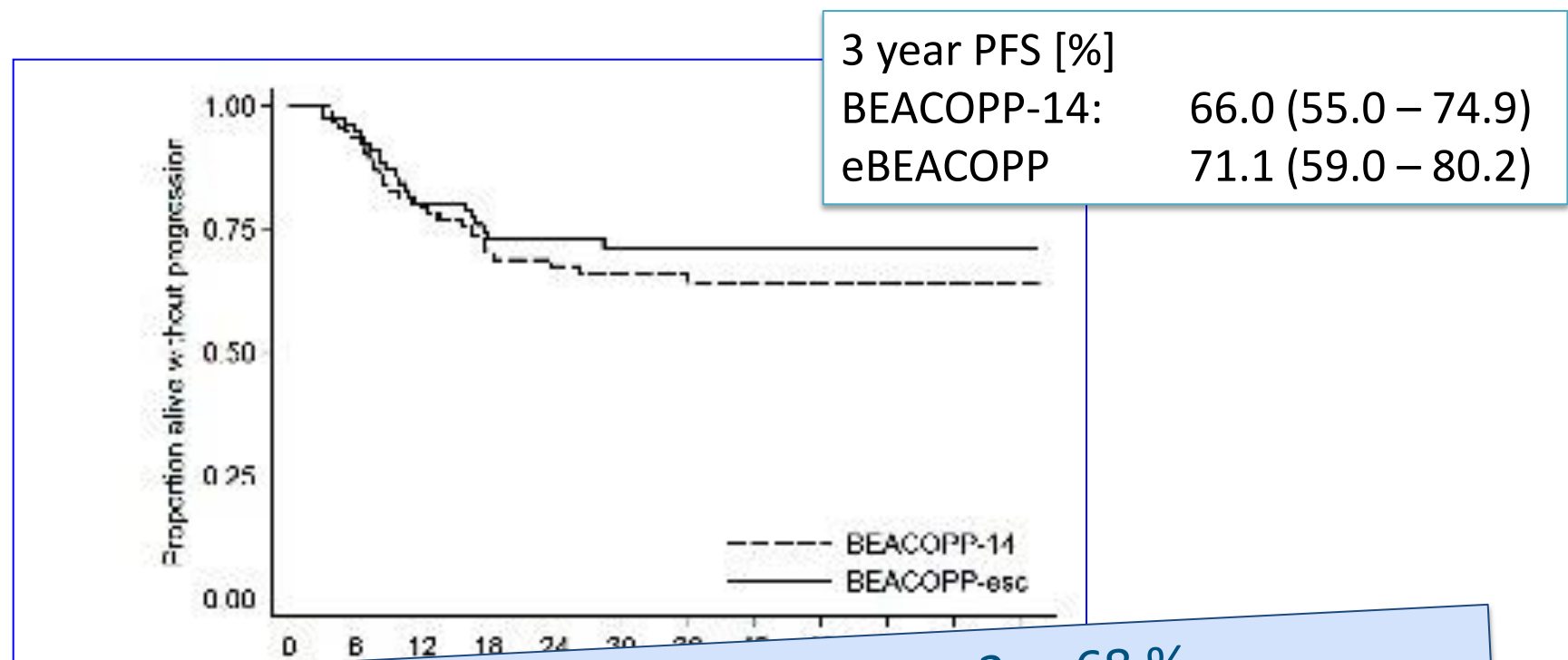


ABVD versus AVD in PET2 negative patients (Median FU 36.3 months)



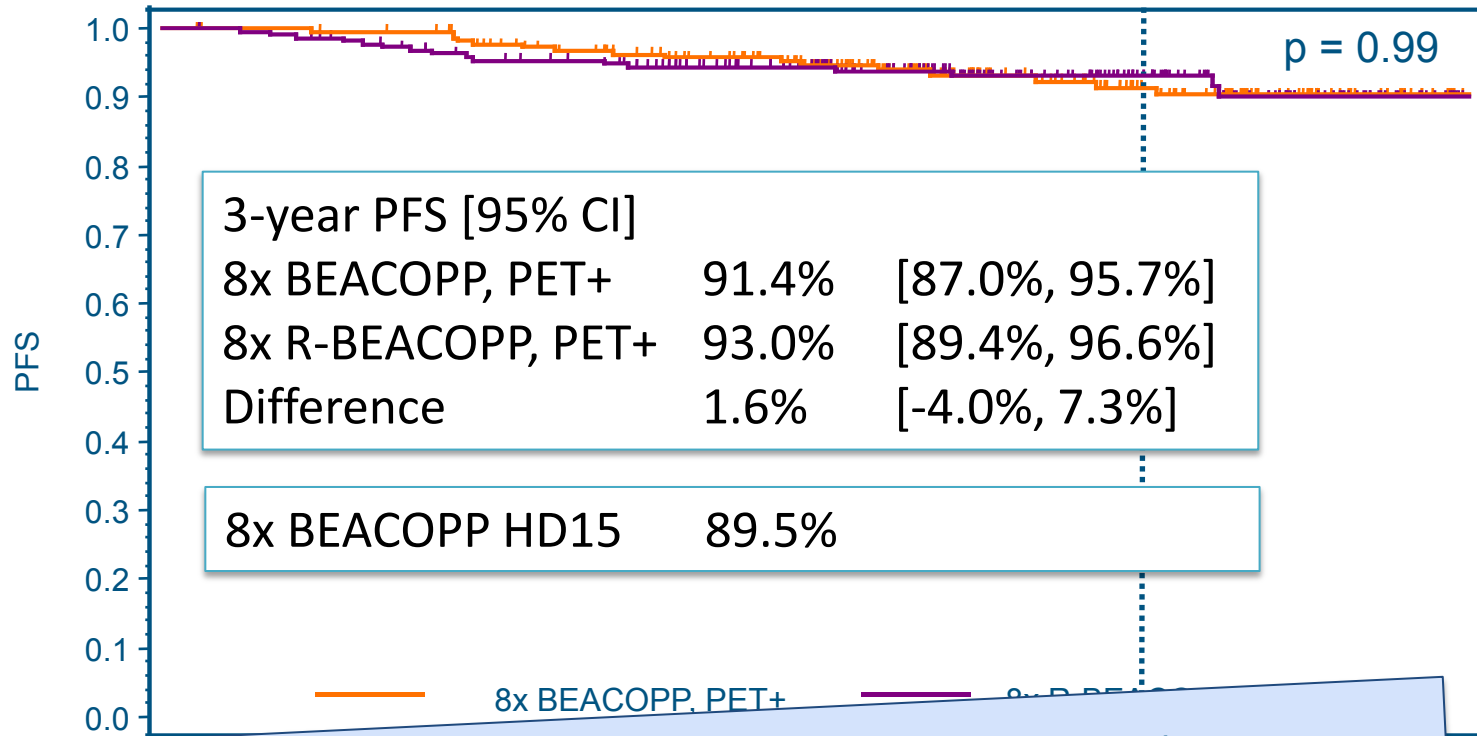
Assumption for NPP of PET2: PFS 95% at 3 years.
Observed PFS at 3 years: 85%. NPP of PET?

PFS for PET2 positive patients



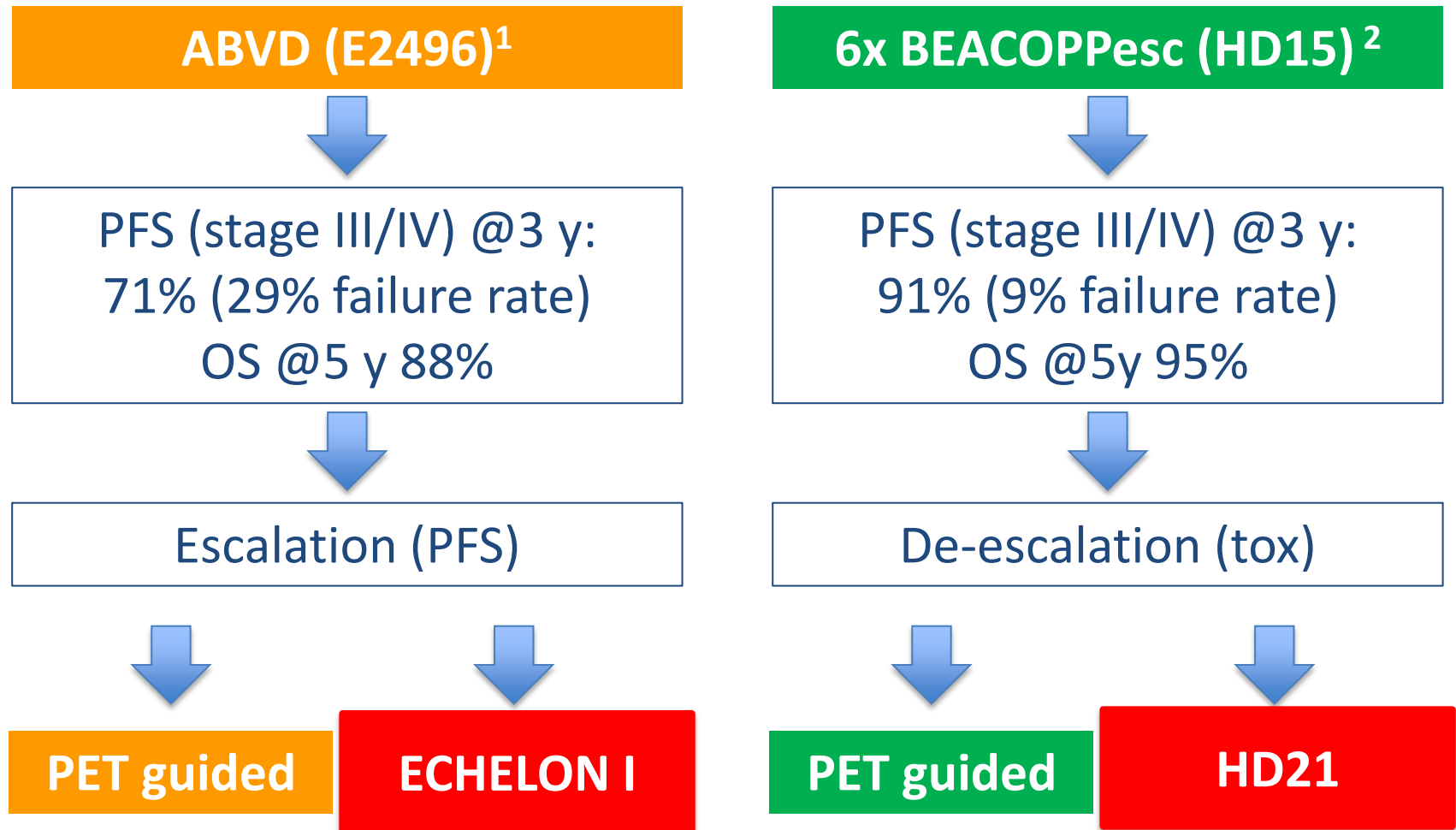
1. 2x ABVD, PET+, BEACOPP, PFS at 3 y: 68 %
2. Positive predictive value of PET might be overcome by intensification to BEACOPP?

3y PFS of PET2 positive patients in the GHSG HD18 study (8x eBEACOPP +/- R)

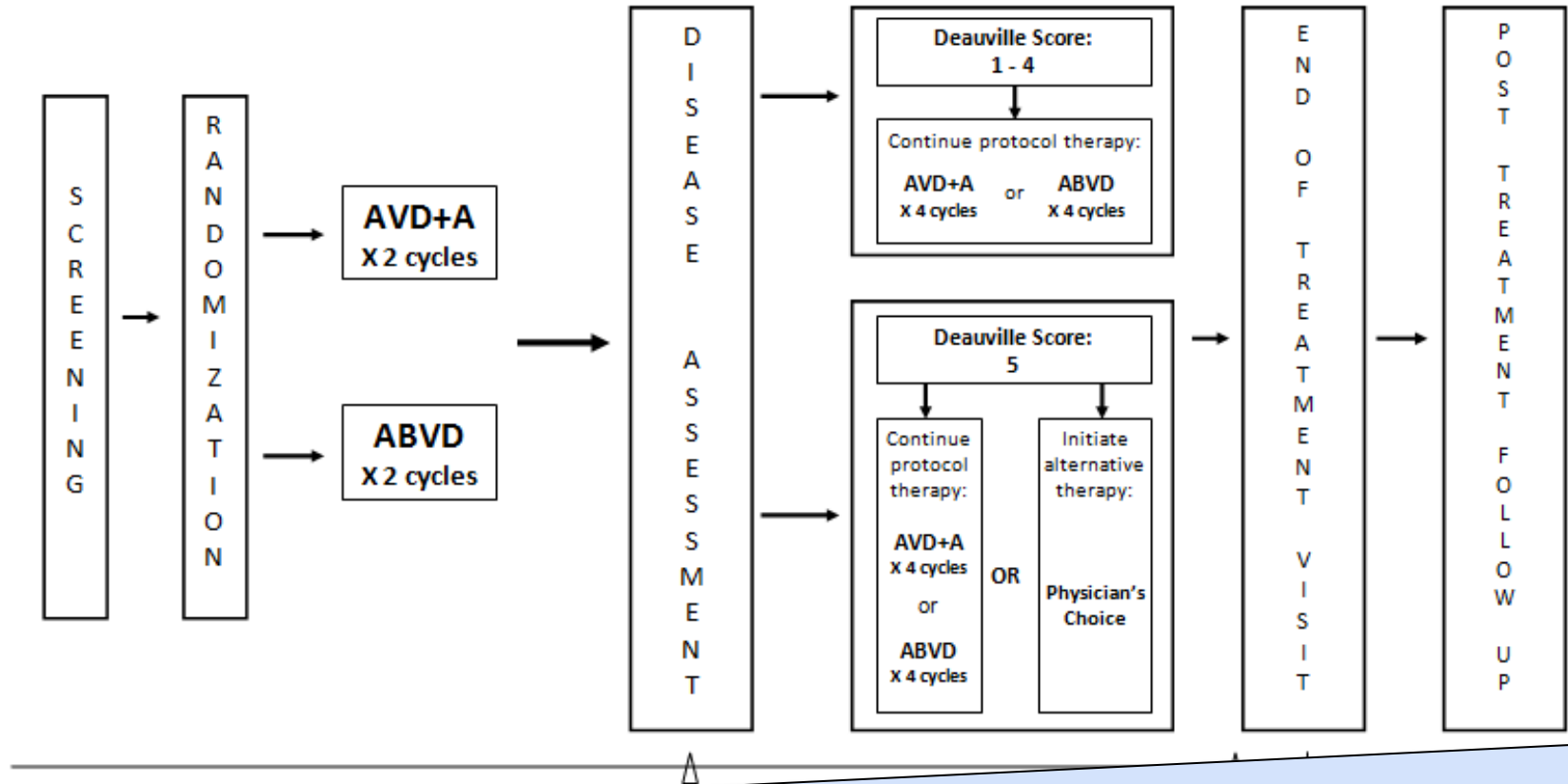


1. There is no (!) positive predictive value of PET in HD18 at all
2. 3y PFS in HD18 91% vs 68% in RATHL: are the first two cycles decisive?

Current international standards and approaches



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



Primary endpoint: improvement of PFS from 75% to 82,5% at 3 y (?)

targeted BEACOPP: Phase II

Drug	day	BEACOPP	BrECAPP	BrECADD
Bleomycin	8	10		
Etoposide	1-3	200	200	150
Doxorubicin	1	35	35	40
Cyclophosphamide	1	1250	1250	1250
Vincristine	8	1.4		
			1.8	1.8
Procarbazine	1-7	100	100	
Prednisone	1-14	40	40	
				250
				40

Results for BrECADD (compared to HD18, current results)

- Primary endpoint CR after Ctx reached (BrECADD 88%, HD18: 88%)
- Hematological toxicity grade 3/4: 80 % versus 93 %
- Non-Hem toxicity grade 3/4: 2 % versus 14,7 %

The GHSG HD21 study

randomization

2 x BEACOPP esc

2 x BrECADD

PET/CT Staging

First GHSG NI-study with a co-primary endpoint:

1. Non-inferiority for PFS
2. Superiority for treatment related morbidity

4x
BEACOPP esc

4x
BrECADD

End of therapy AND residual nodes > 2.5 cm:

PET positiv:

Rx

PET negativ:

Follow up

1. Early favourable HL:

- The negative predictive value of PET does not allow omission of radiotherapy without significant loss of tumor control (RAPID, EORTC H10)
- A loss of tumor control might be acceptable, but the degree needs to be defined upfront (RAPID, EORTC H10) and should be regarded afterwards. However, the determination of an acceptable loss of efficacy is challenging!

2. Early unfavourable HL:

- The positive predictive value of PET2 after 2x ABVD does allow restriction of eBEACOPP to high risk patients (EORTC H10), if followed by Rx, with superior PFS and OS compared to 4x ABVD in this subgroup of patients.

3. Advanced stage HL:

- The negative and positive predictive value of PET2 might change over time (Gallamini 2007, RATHL), and might be dependent on the treatment itself (RATHL, HD18)
- The potential benefit of Brentuximab vedotin will depend on the comparator. For example, the target PFS of 82,5 % at 3y (ECHELON I) would be a negative result in any GHSQ study (3y PFS 91 % in HD15 already).

Thank you very much for your attention!

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