

# Choice of Therapy for Early-stage Hodgkin Lymphoma

*David Hodgson MD, MPH, FRCPC*

*Professor, Radiation Oncology*

*University of Toronto*

*Princess Margaret Cancer Centre*

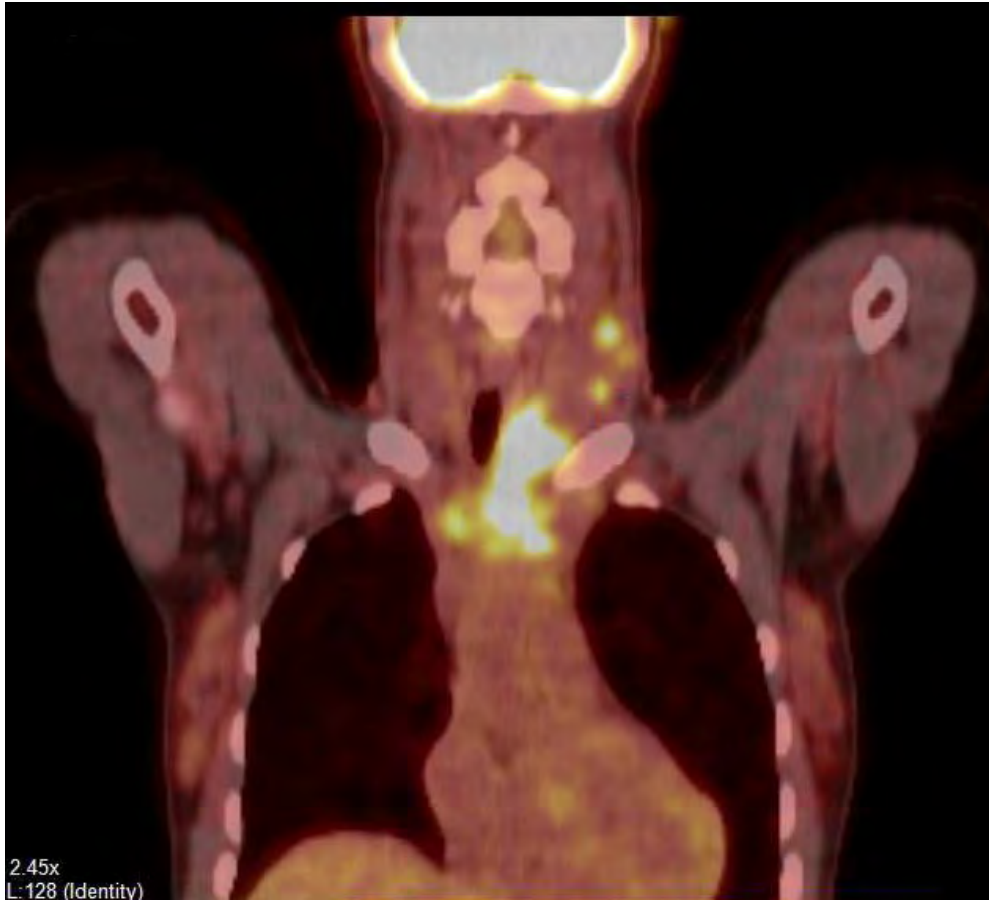
*Medical Director, Pediatric Oncology Group of Ontario*



# Introduction

- Case presentations: low, intermediate risk early stage.
- Review pivotal trials that inform the role of RT.
- Radiotherapy avoidance strategies.
- Review clinical considerations that guide decision making in borderline cases.
- Novel agents in treatment of early stage HL.

# Early Favourable Hodgkin Lymphoma

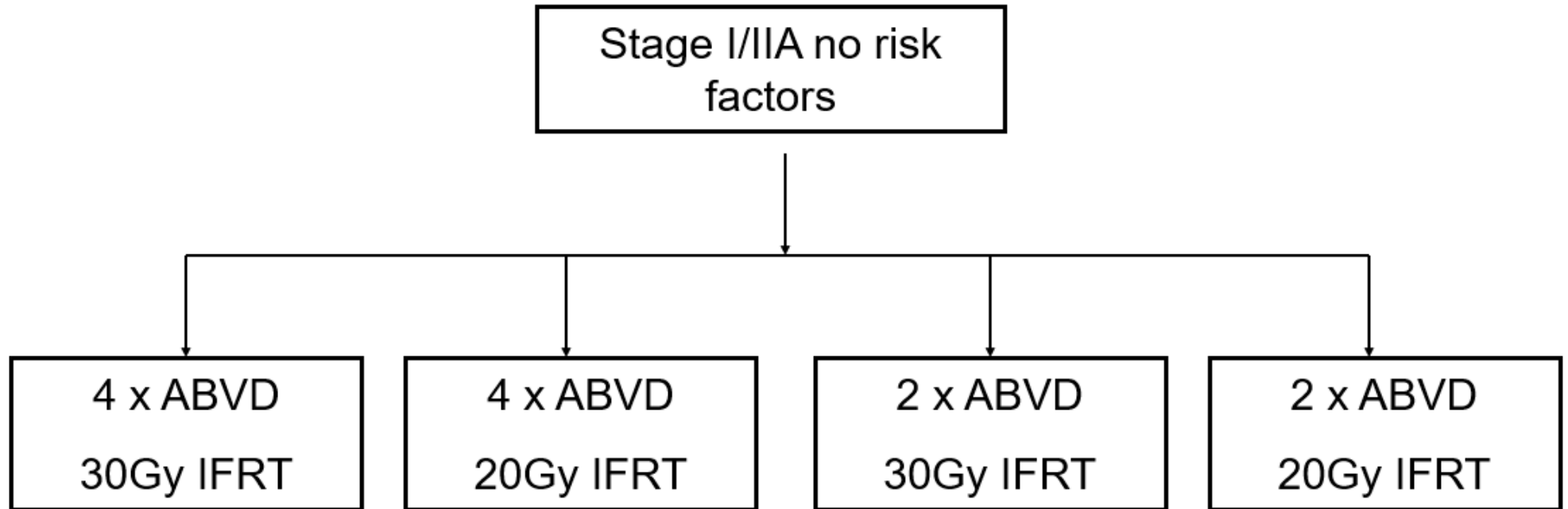


- 25 year old female
- Brief history of left sided neck lymphadenopathy
- Bx – NS HL
- CT/PET: involvement of left neck and mediastinum, no bulk
- ESR 10mm/hr
- Hb 125 g/L

# Favorable (GHSB criteria)

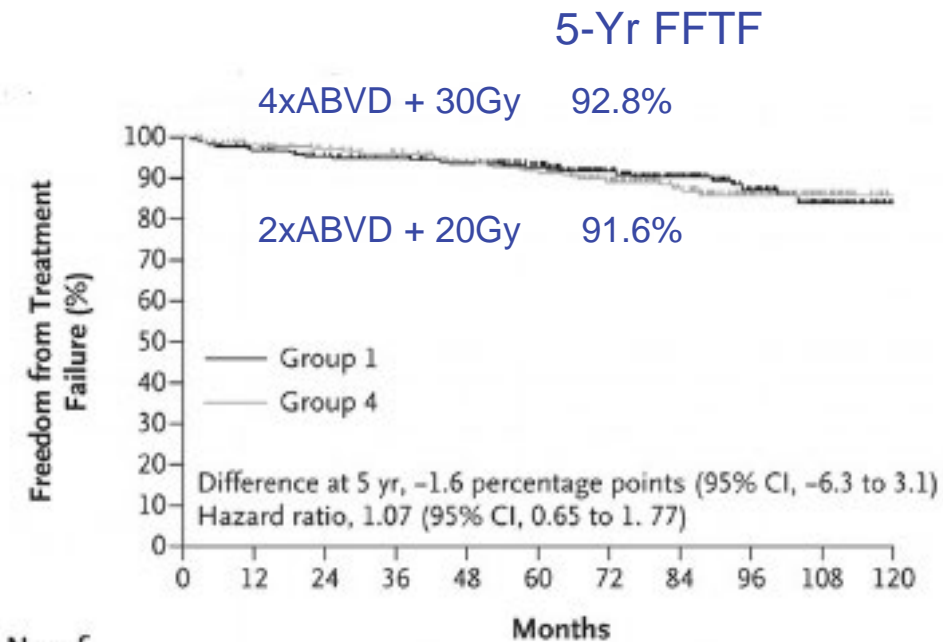
- *1-2 sites of involvement*
  - *left and right neck separate sites*
  - *neck and SCF, infraclavicular nodes are one site*
  - *hila and mediastinum same site*
- No large mediastinal adenopathy
  - <1/3 diameter of the chest
- No extranodal involvement
- Favorable ESR/B-symptom profile
  - <50mm/hr, no “B” symptoms; <30 mm/hr, with “B” symptoms

# GHSB HD10 - Favorable Risk HL



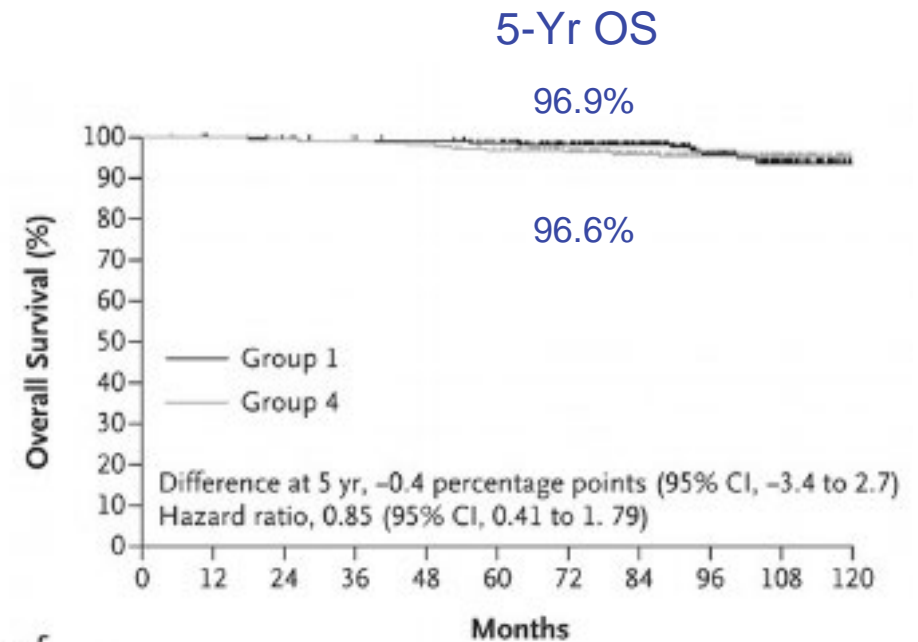
# GHSB HD10

No Significant Difference Between Most Intensive and Least Intensive



No. of Patients at Risk

Group 1	298	277	264	255	239	217	167	121	74	35	3
Group 4	299	275	265	252	239	199	151	110	66	28	4



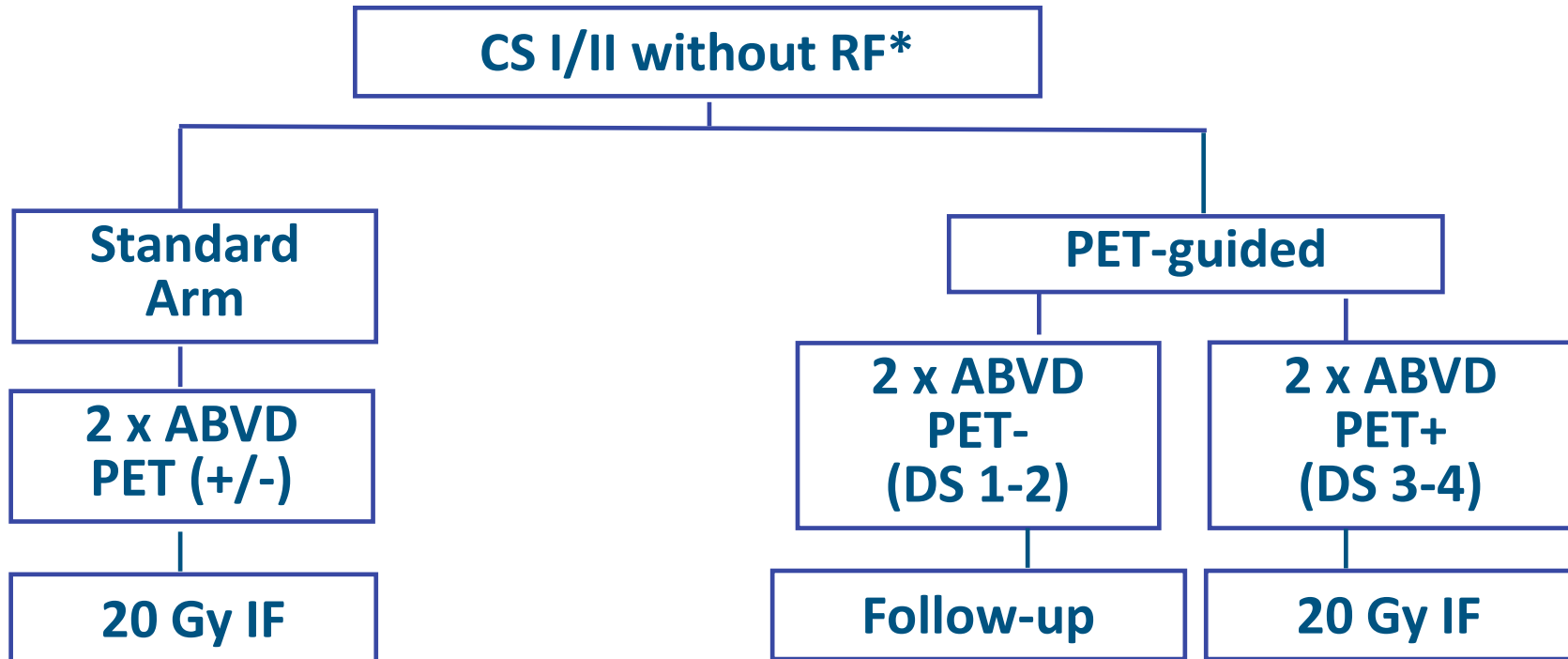
No. of Patients at Risk

Group 1	298	293	289	286	283	271	240	182	116	63	12
Group 4	299	298	293	289	285	273	241	182	122	64	16

# Advantages of “2+20”

- Treatment time is short: 2.5 months
- Grade III/IV acute treatment toxicity is significantly less frequent than with 4 cycles of ABVD (33.2% vs. 51.7%,  $P < 0.001$ ):
  - hematologic (15% vs. 24%)
  - infectious (1.7% vs. 5.1%)
  - hair loss (15.2% vs. 28.1%)
- Minimizes exposure to cardiotoxic agents
- Less bleomycin toxicity
- Reduced normal tissue radiation exposure

# Early-favorable HL: HD16

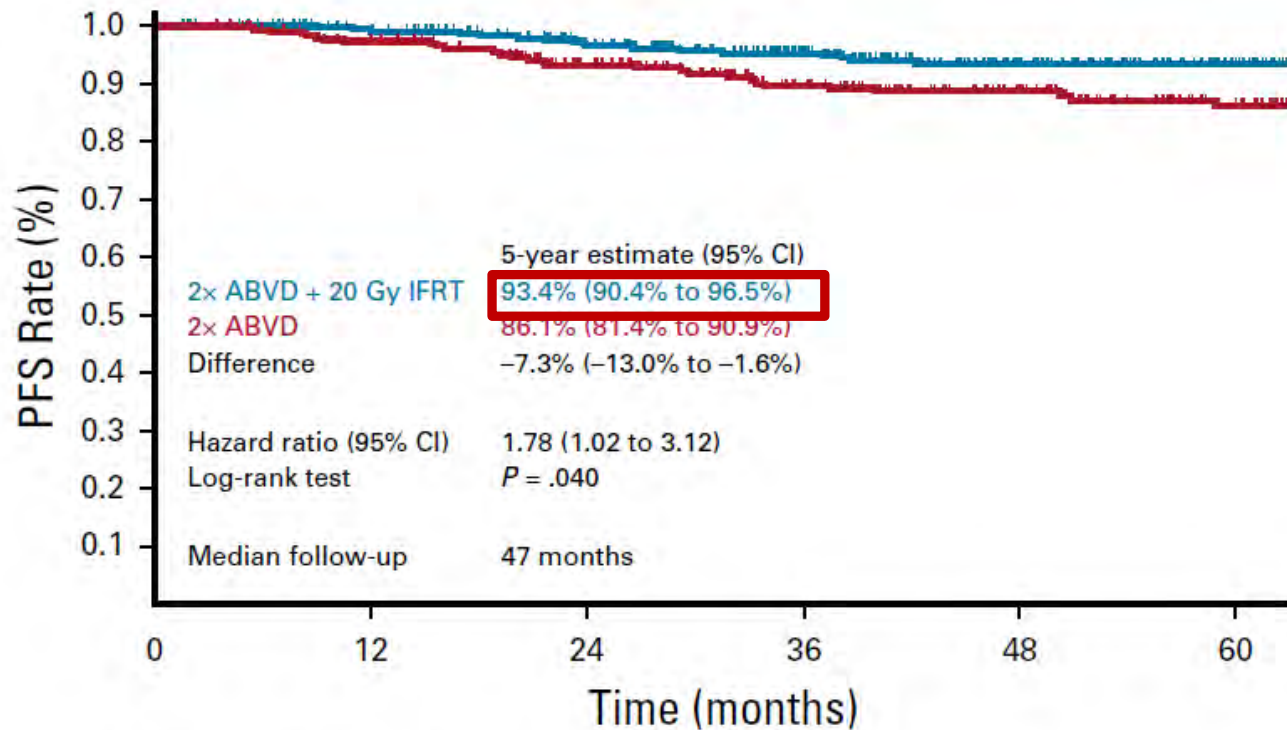


\*a) large mediastinal mass; b) extranodal disease; c) high ERS; d) 3 or more areas



# Ommission of RT in PET2-negative Cases Significantly Increases Relapse Risk After ABVD x 2

## No Difference in Overall Survival



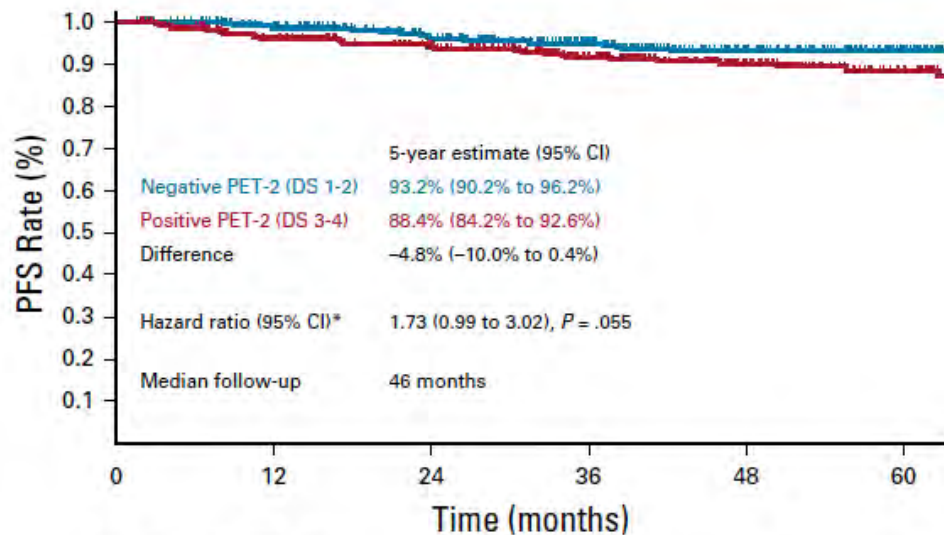
93% 5-yr PFS  
86%

No. at risk (No. censored):

328 (0)	307 (19)	268 (50)	212 (103)	149 (162)	97 (214)
300 (0)	280 (12)	239 (42)	179 (94)	134 (137)	85 (183)

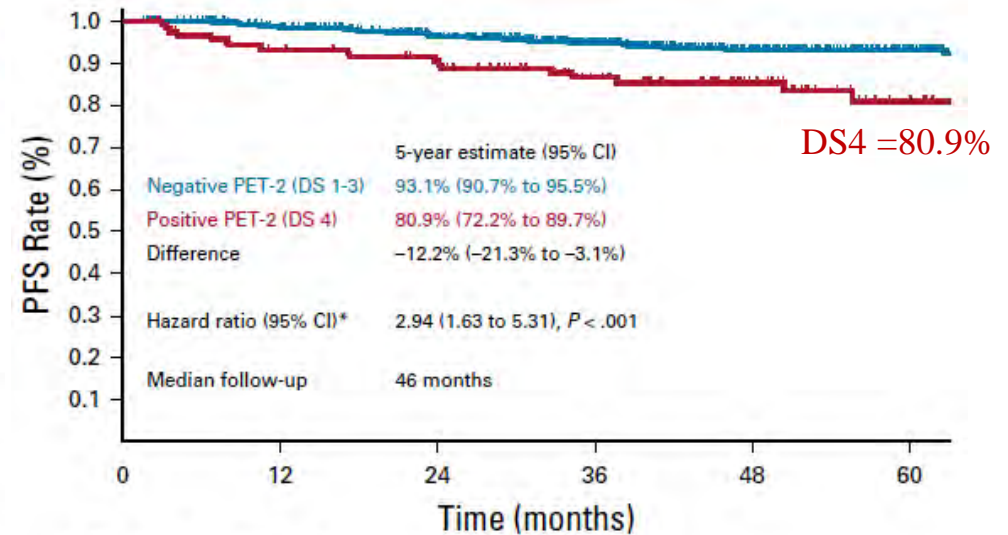
# Impact of PET2 Deauville Score (PFS)

Deauville 1-2 vs 3-4  
(Among RT-treated patients)



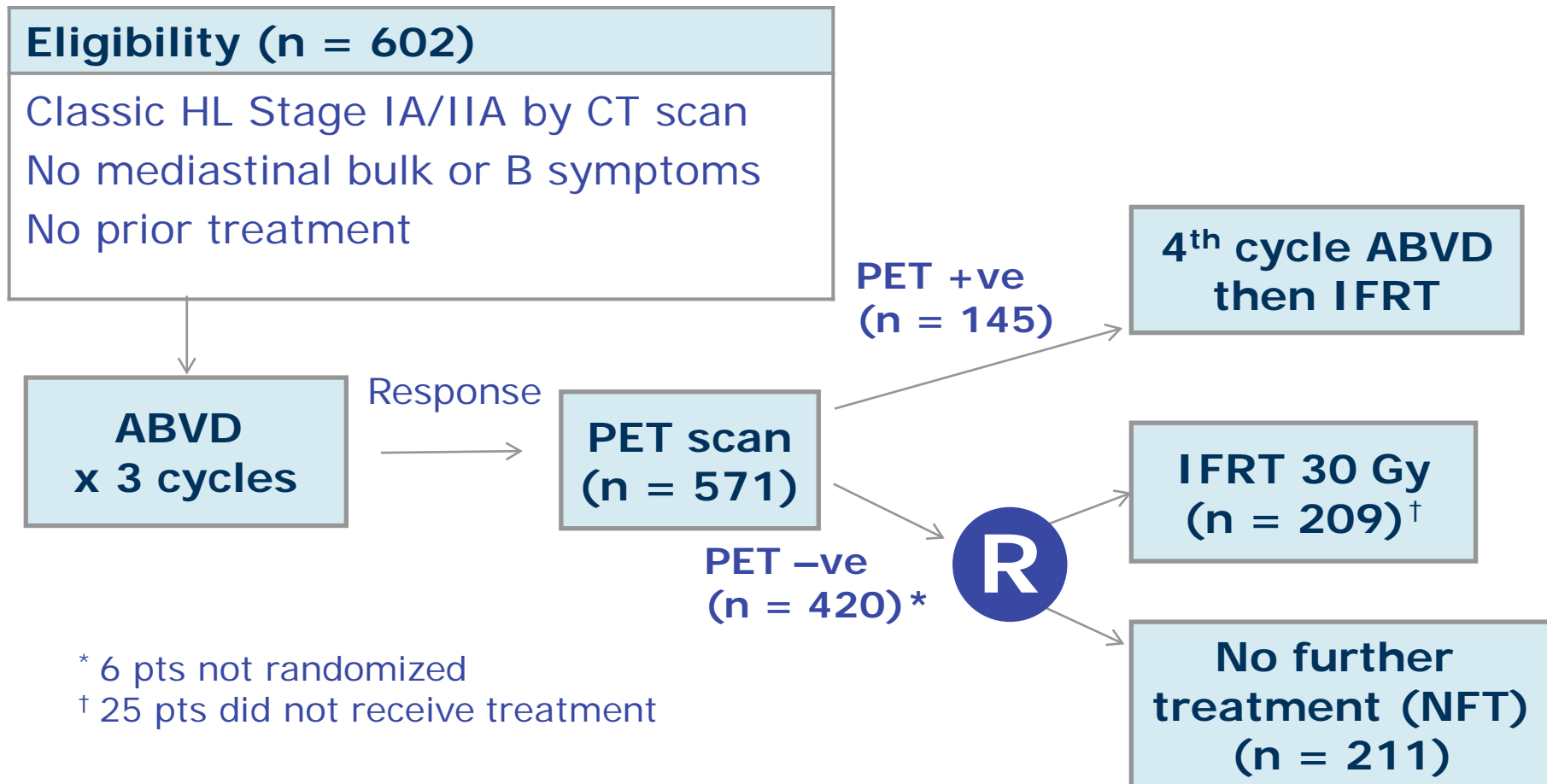
No. at risk (No. censored):					
353 (0)	327 (23)	285 (56)	223 (115)	157 (177)	102 (232)
340 (0)	304 (24)	277 (45)	213 (102)	141 (171)	76 (234)

Deauville 1-3 vs 4  
(Among RT-treated patients)



No. at risk (No. censored):					
571 (0)	524 (40)	464 (88)	360 (186)	246 (294)	150 (390)
122 (0)	107 (7)	98 (13)	76 (31)	52 (54)	28 (76)

# UK RAPID Study



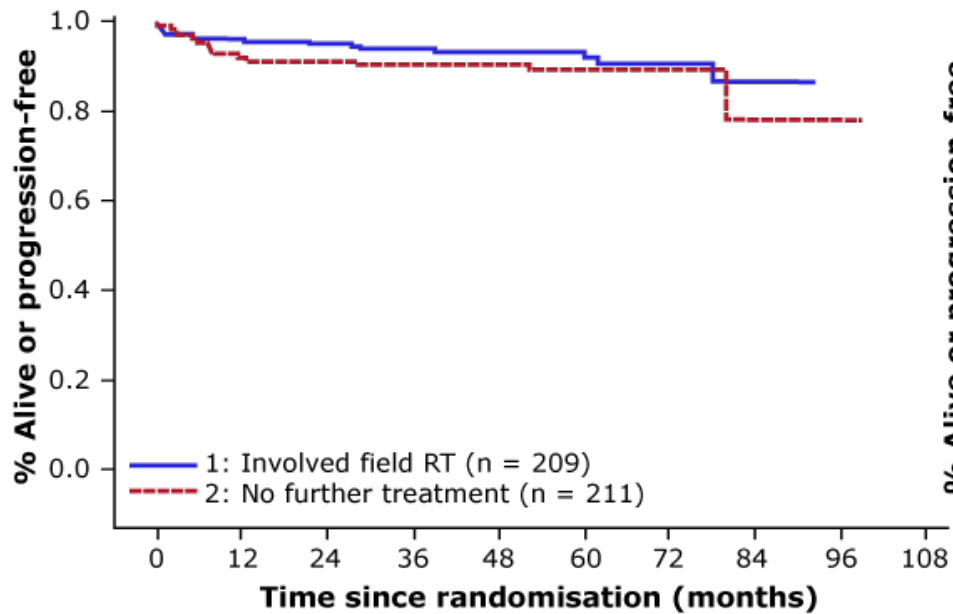
\* 6 pts not randomized

† 25 pts did not receive treatment

# UK RAPID

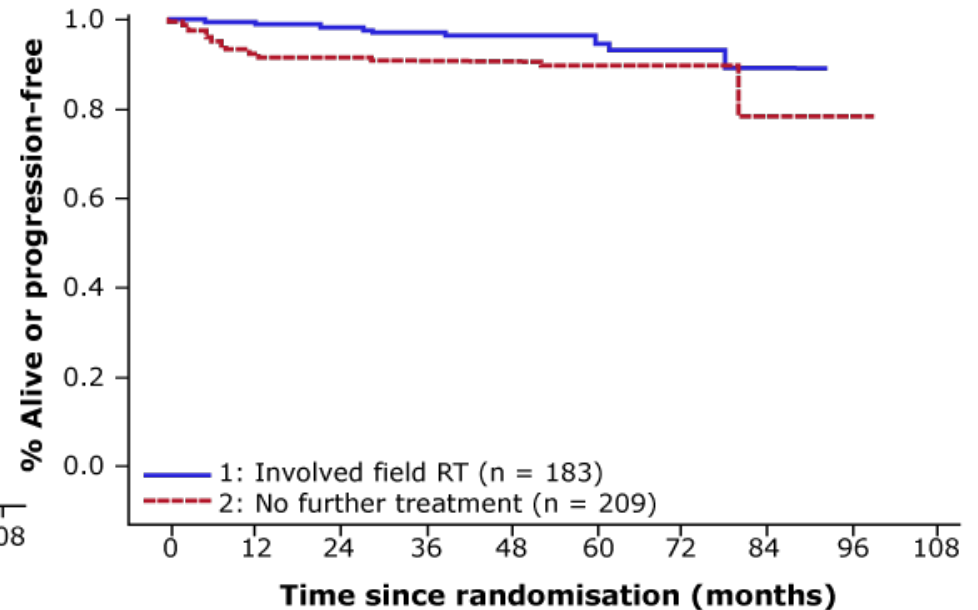
## PFS in the PET-Negative Population

ITT population (n = 420)



3-year PFS: 94.5% vs 90.8%  
HR 1.51 in favor of IFRT,  $p = 0.23$

Per protocol analysis of patients who received allocated treatment (n = 392)



3-year PFS: 97% vs 90.7%  
HR 2.39 in favor of IFRT,  $p = 0.03$

# Summary – Early (very) Favourable HL

- After 2 cycles of ABVD (and likely after 3 cycles), “radiotherapy cannot be omitted from CMT without clinically relevant loss of tumor control.”
- In early-stage favorable HL, a positive PET after two cycles ABVD indicates a high risk for treatment failure, particularly when a Deauville score of 4 is used as a cutoff for positivity.
  - PET scan after 2 cycles remains relevant even if RT is planned for PET-negative patients.

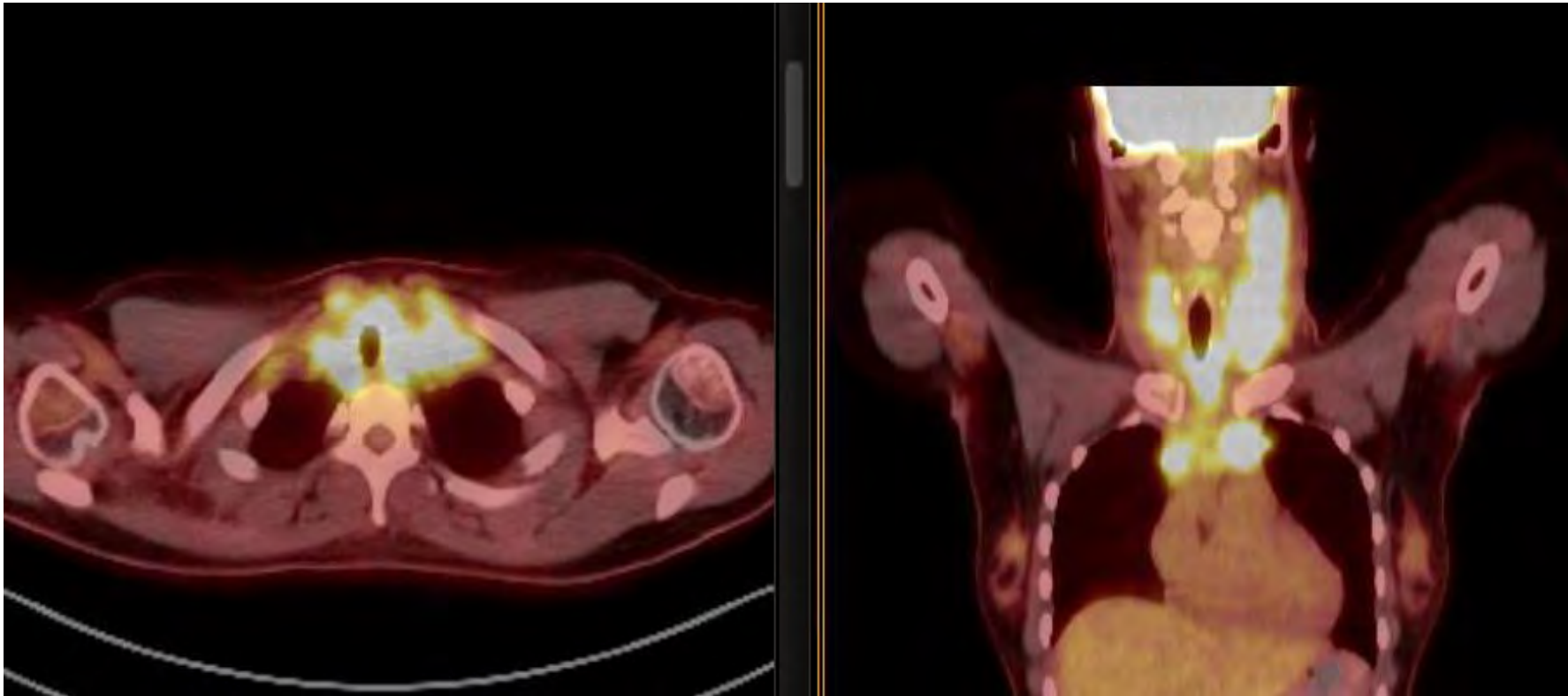
# Back to the Case



- Rx dose – 20Gy in 10F
- Mean heart dose = 0.60Gy
- Mean breast dose
  - Left = 0.26 Gy
  - Right = 0.21 Gy

## Case 2:

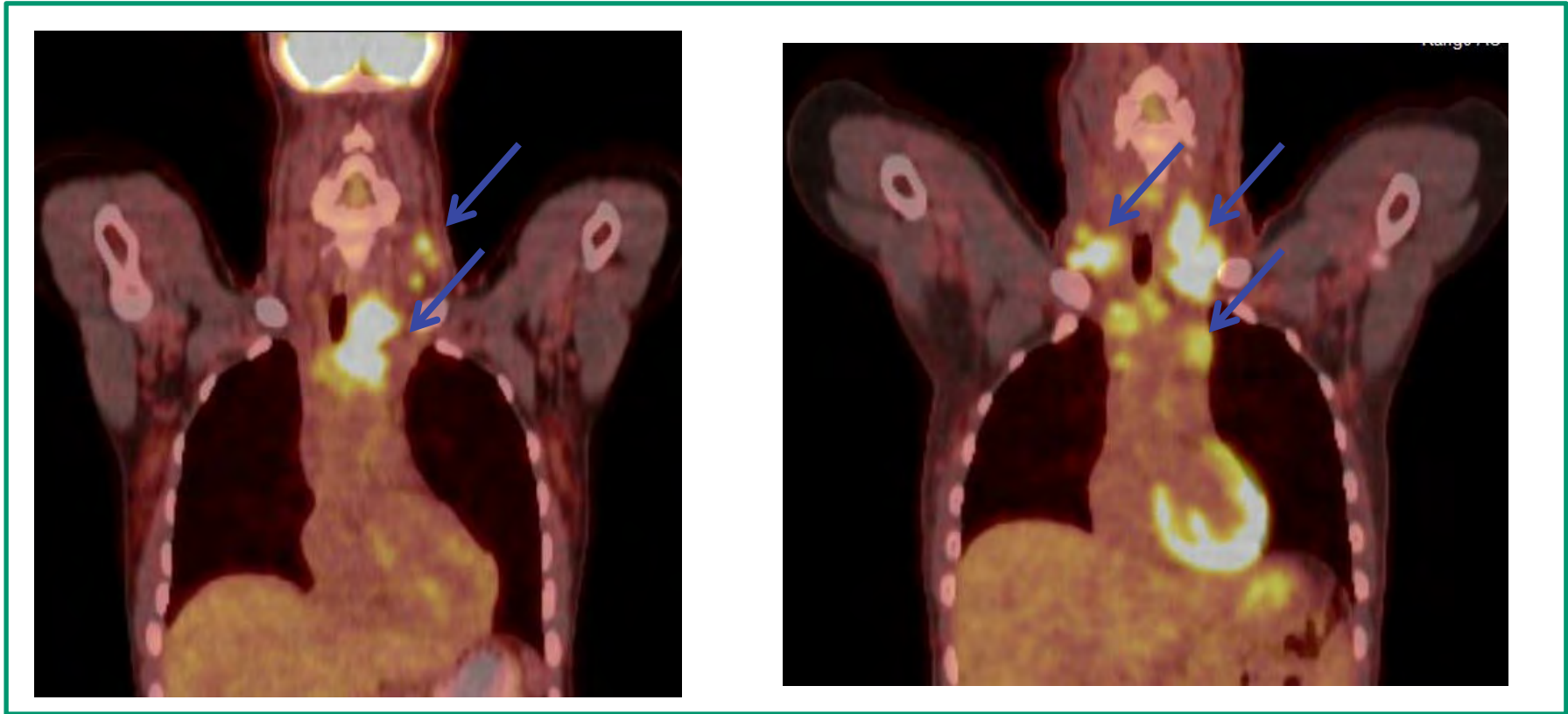
28 yo female IIA HL, 3 sites, no bulk, ESR normal



# ABVD x2 + 20Gy Eligibility

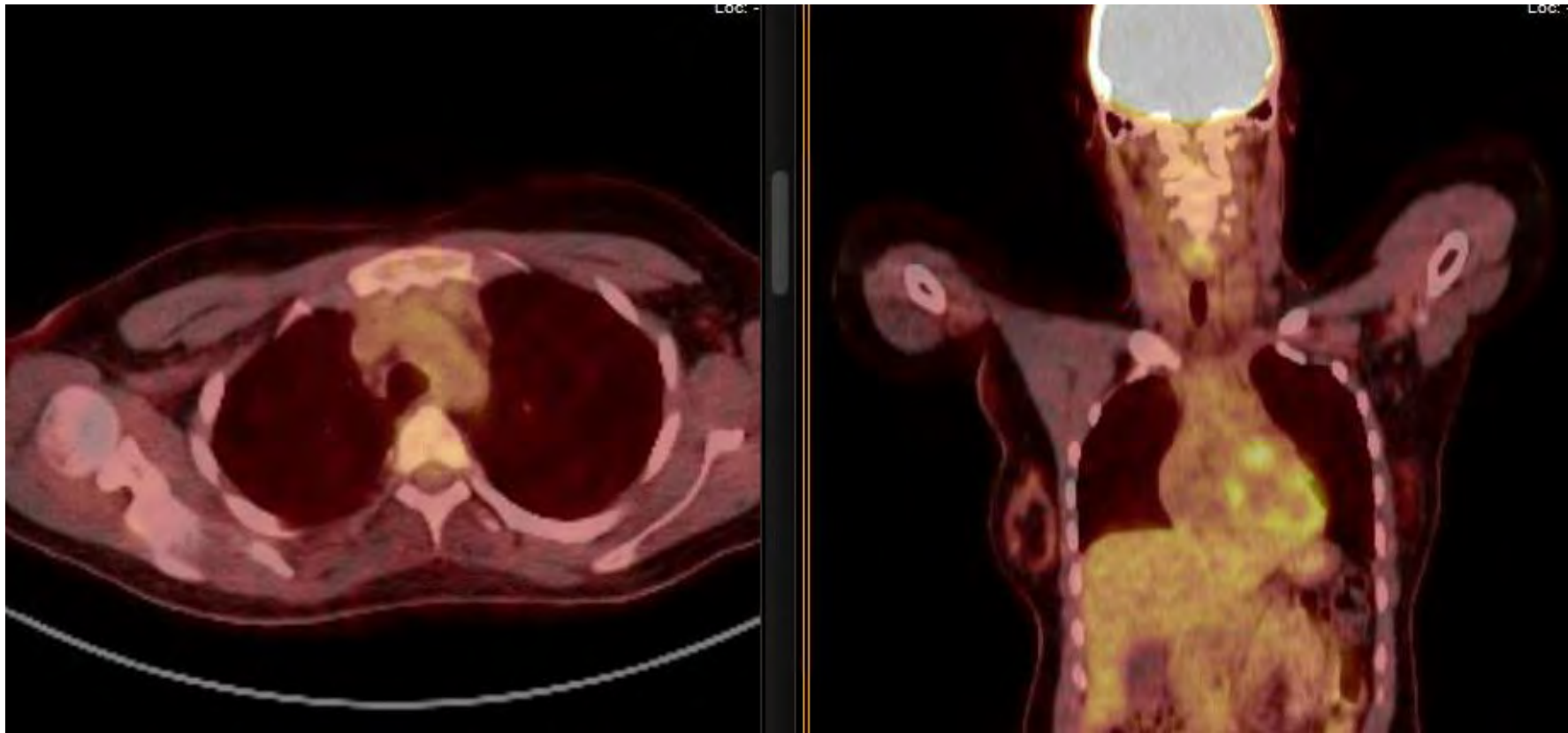
Eligible

Ineligible





## Post ABVD x 2: PET = Deauville 2 (negative)



J Clin Oncol 35:1786-1794, 2017

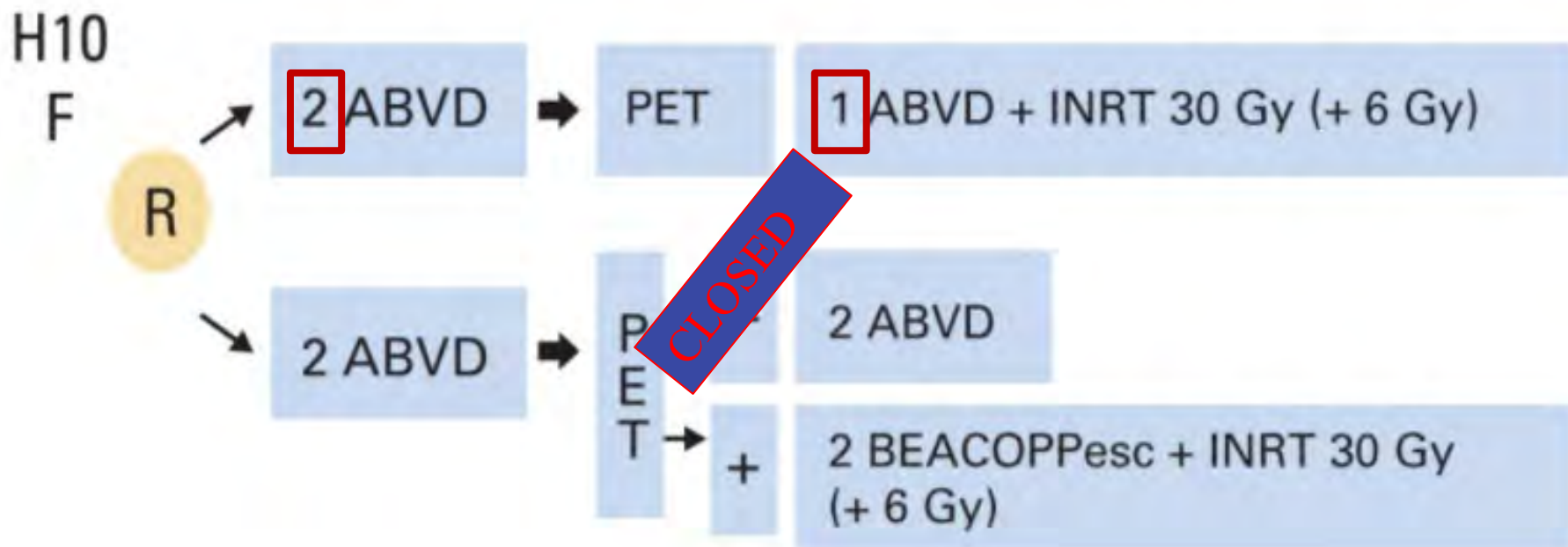
# ABVD +/- RT: EORTC/LYSA/FIL H10

Can RT be Omitted in PET2 -'ve Patients?

- age 15 to 70 years
- supradiaphragmatic stage I and II HL
- Early unfavourable (U): at least one of the following criteria:
  - age >50 years
  - > three nodal areas
  - mediastinal-thoracic ratio  $\geq 0.35$
  - ESR > 50mm/hr and no B symptoms or >30 mm/hr with B symptoms
- Early favourable (F): all others).

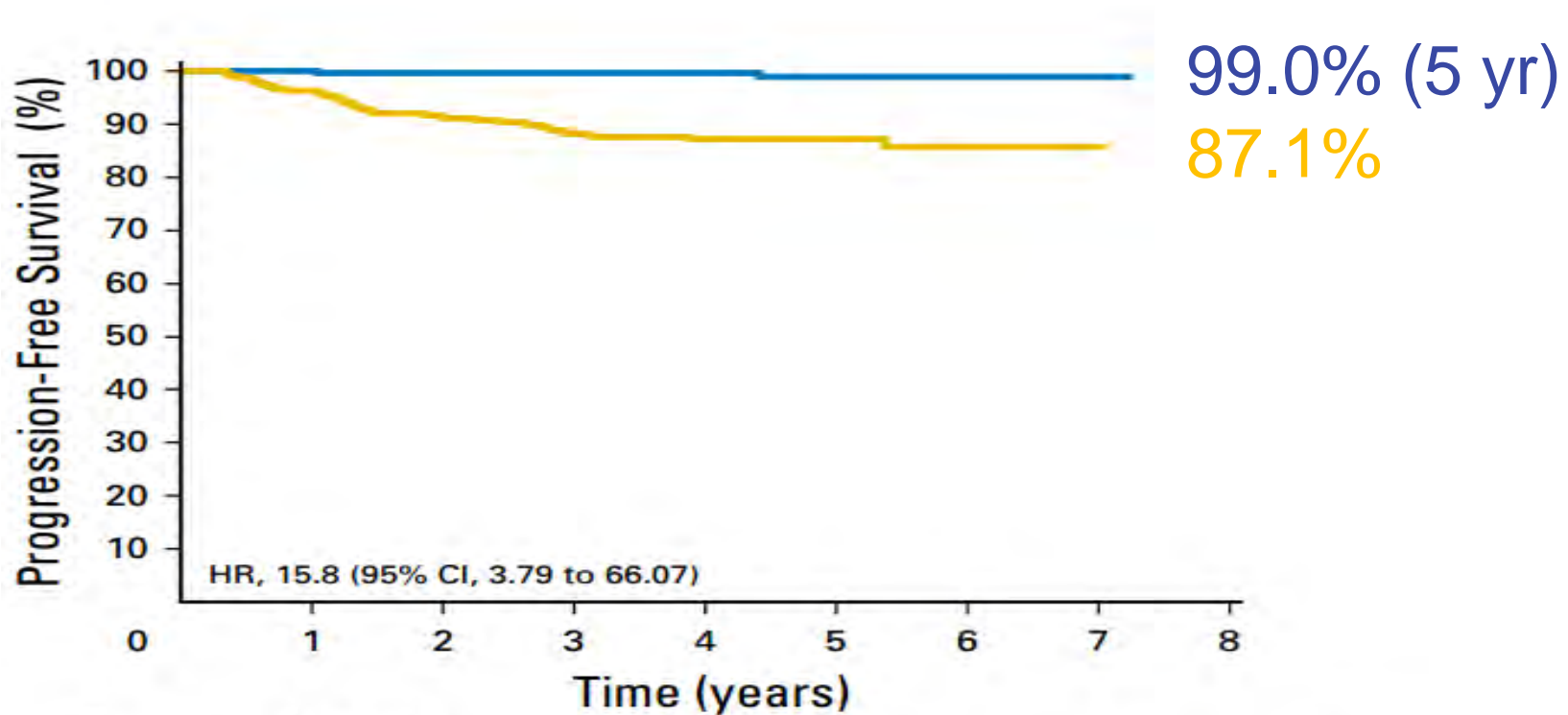
# ABVD alone vs ABVD + RT: EORTC H10

Can RT be Omitted in PET2 -'ve Patients?



# EORTC/LYSA/FIL H10

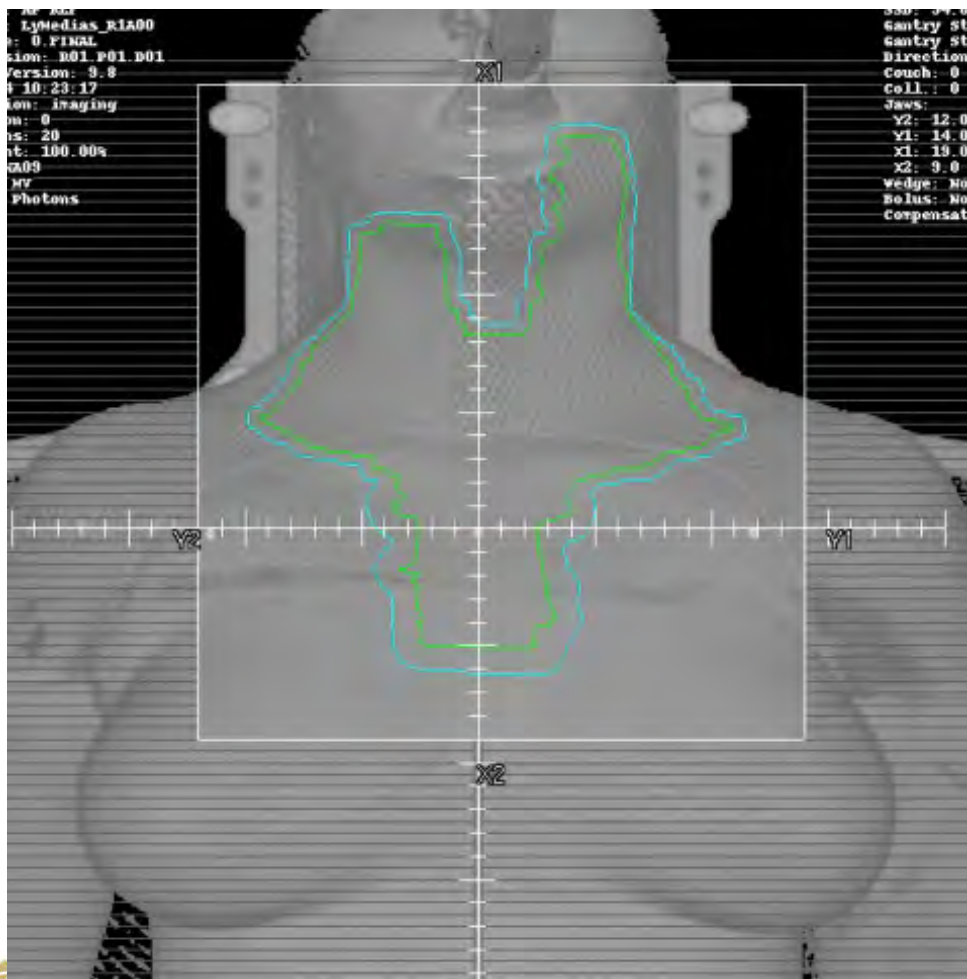
PET2 Negative Early Favorable +/- RT



O	n	No. at risk:								
2	227	223	221	216	203	112	25	2	2	— ABVD + INRT
31	238	228	214	198	177	105	29	2	2	— ABVD only

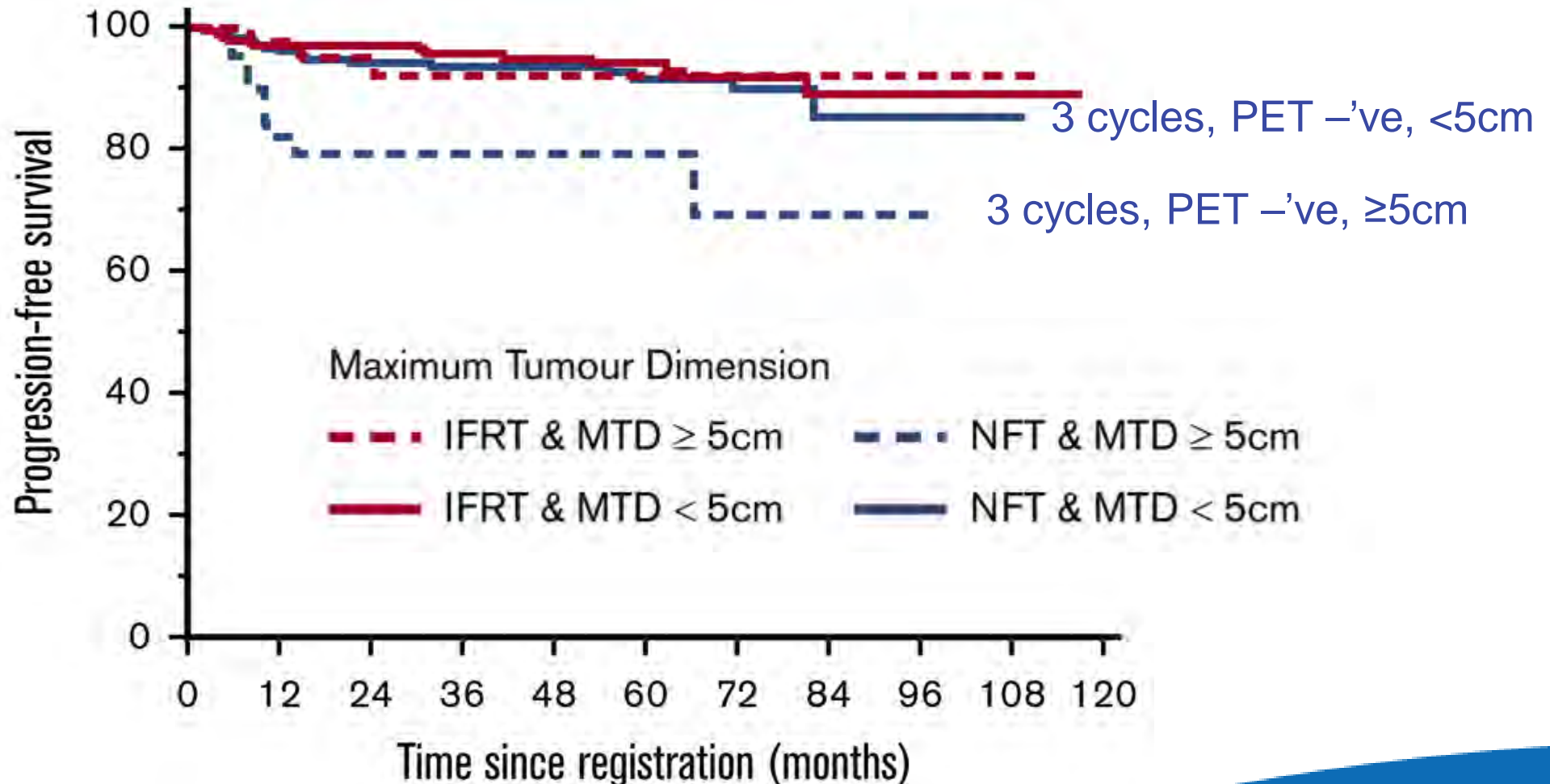
Mean heart dose = 5.5Gy

Mean bilateral breast dose = 0.75Gy



# ABVD alone – who and how many cycles?

## Effect of Bulk on UK RAPID Outcome



# RT Avoidance: ABVD x 4 in PET2 Negative

CALGB 50604  
I-IIA/B non-bulky

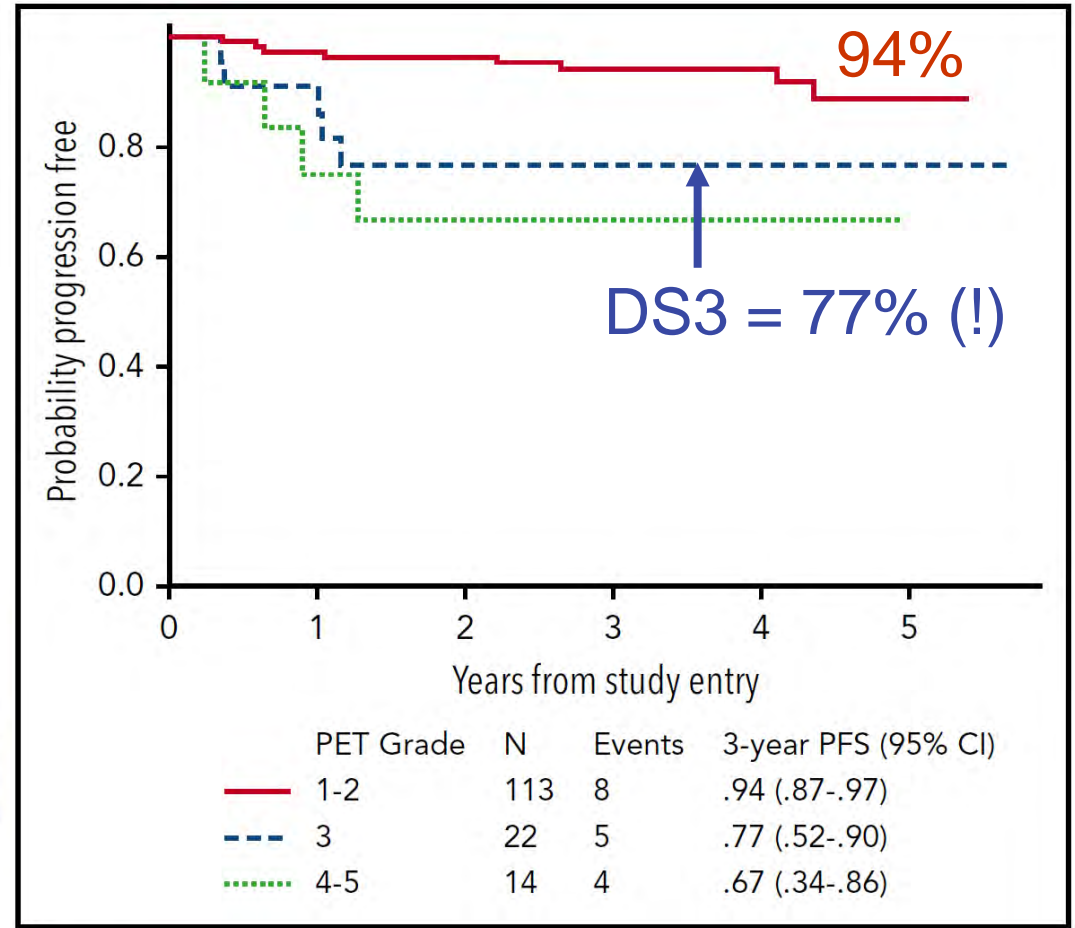
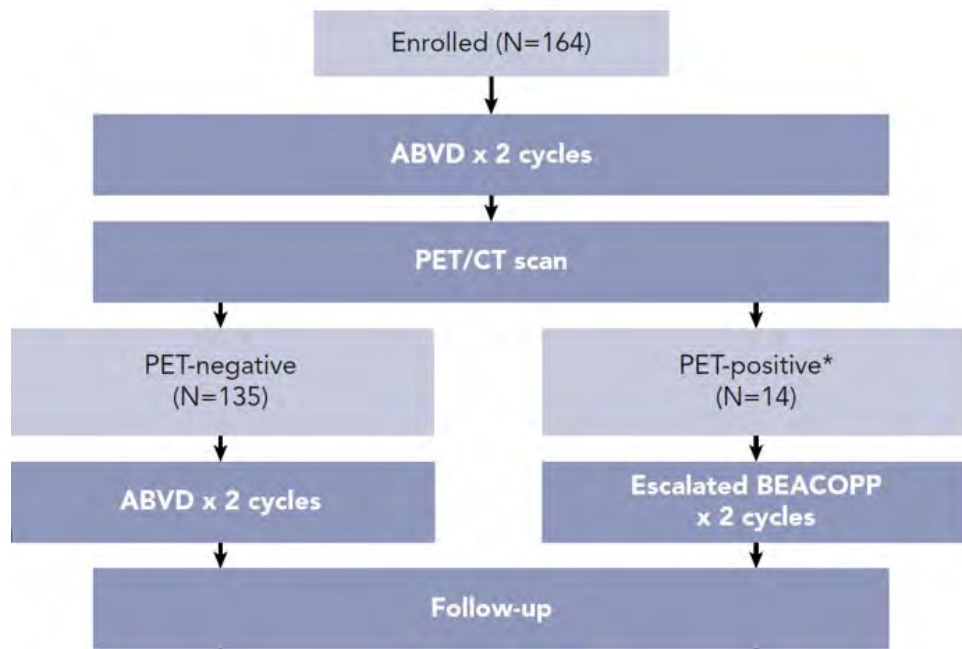
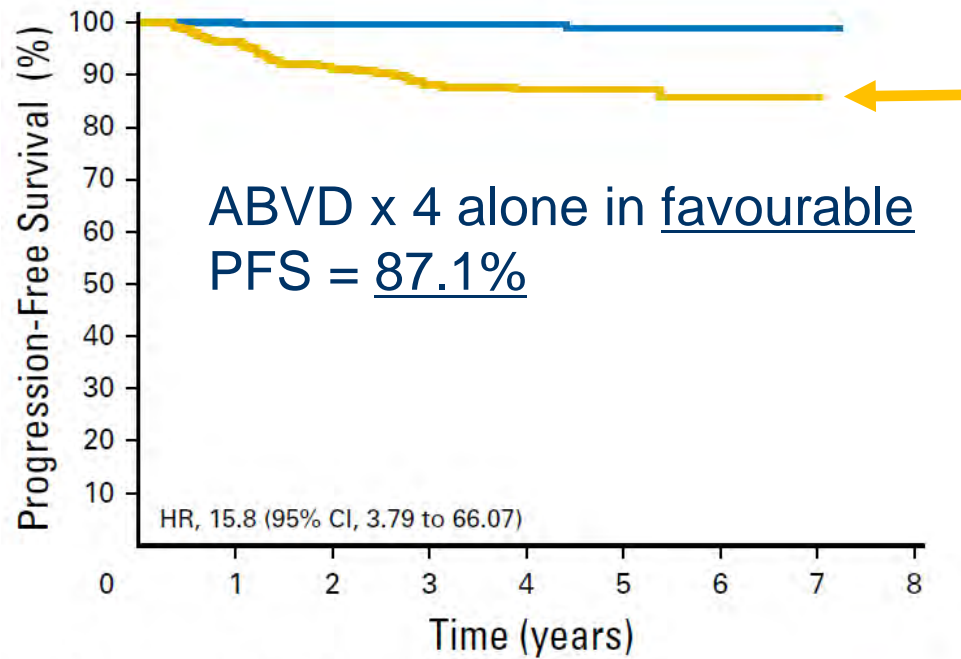


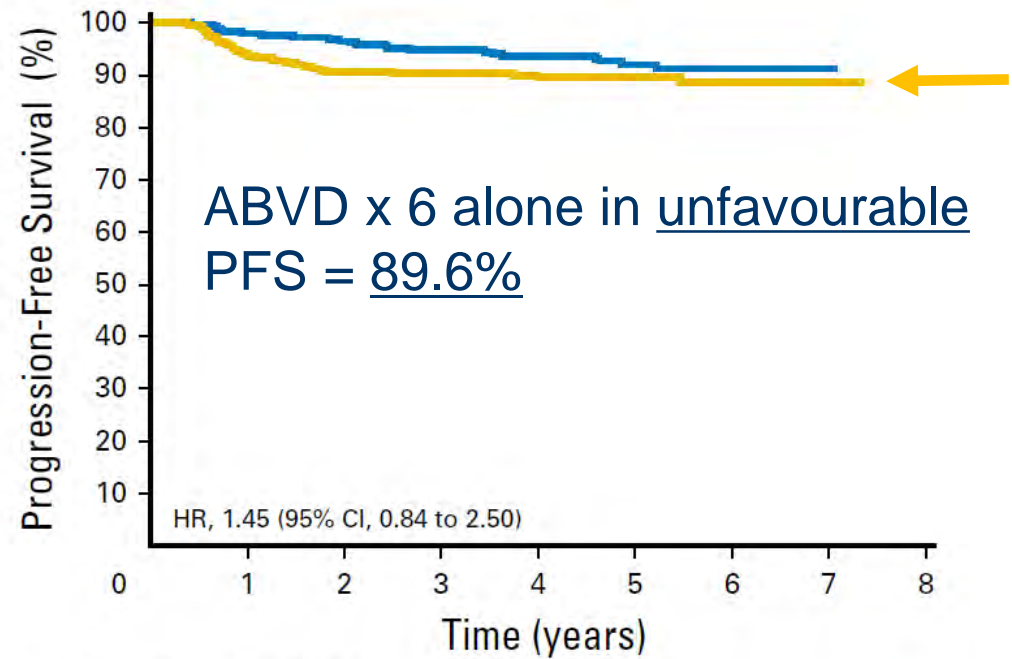
Figure 4. PFS for patients according to interim PET Deauville scores 1 to 2 vs 3 vs 4 to 5.

# ABVD-alone: How Many Cycles?

## H10 Results PET2 -'ve



O	n	No. at risk:							
2	227	223	221	216	203	112	25	2	— ABVD + INRT
31	238	228	214	198	177	105	29	2	— ABVD only

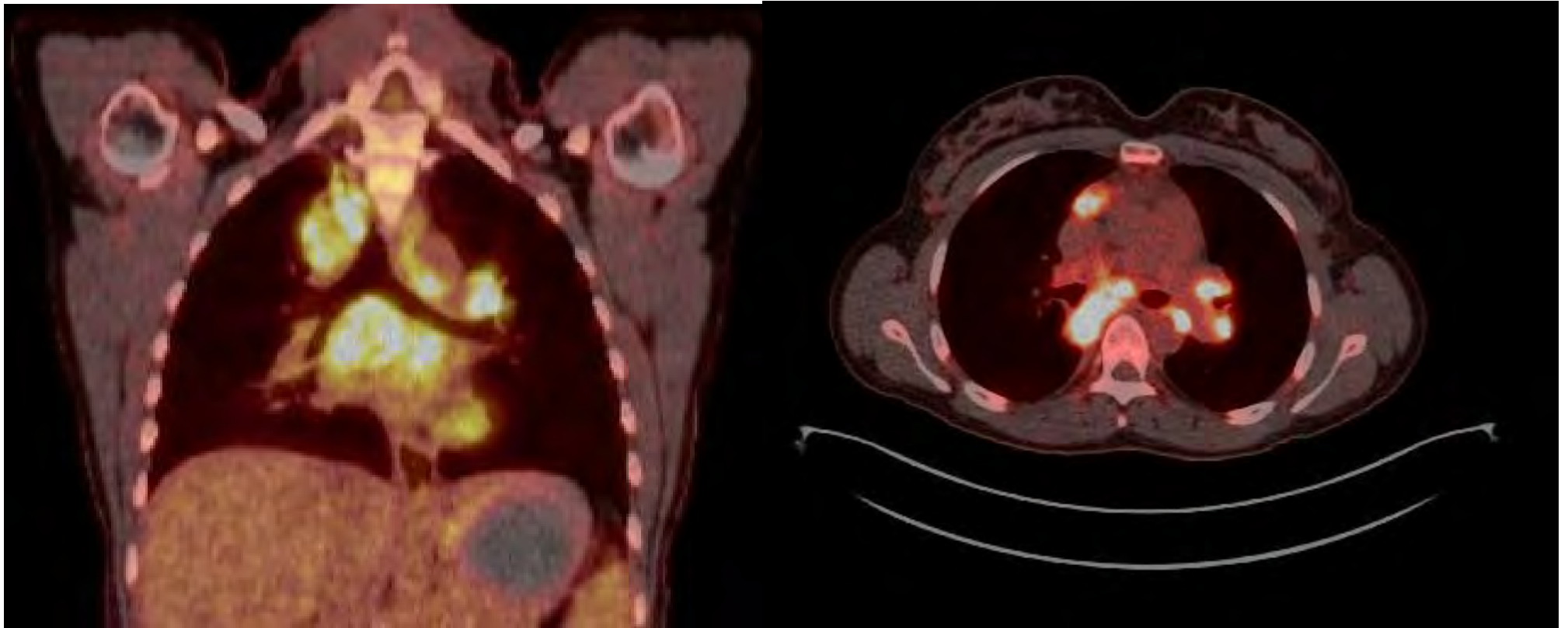


O	n	No. at risk:							
22	292	284	277	265	246	147	35	3	— ABVD + INRT
32	302	282	266	261	242	145	36	2	— ABVD only



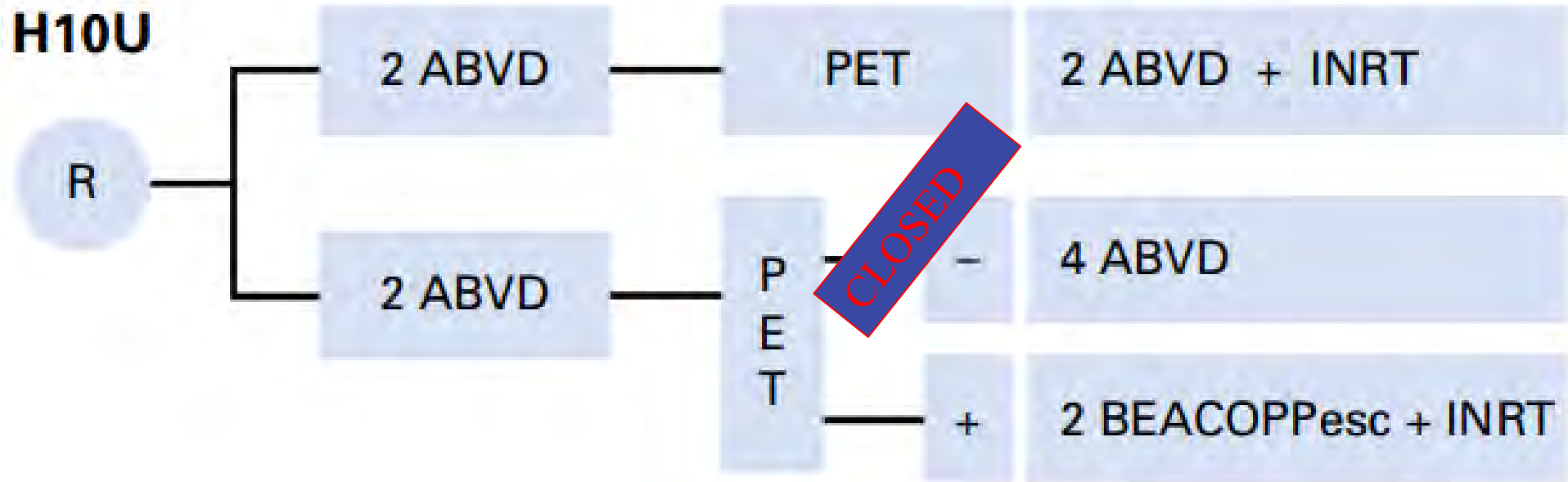
# Early Unfavourable HL

IIA, 3 sites, elevated ESR, + bulk



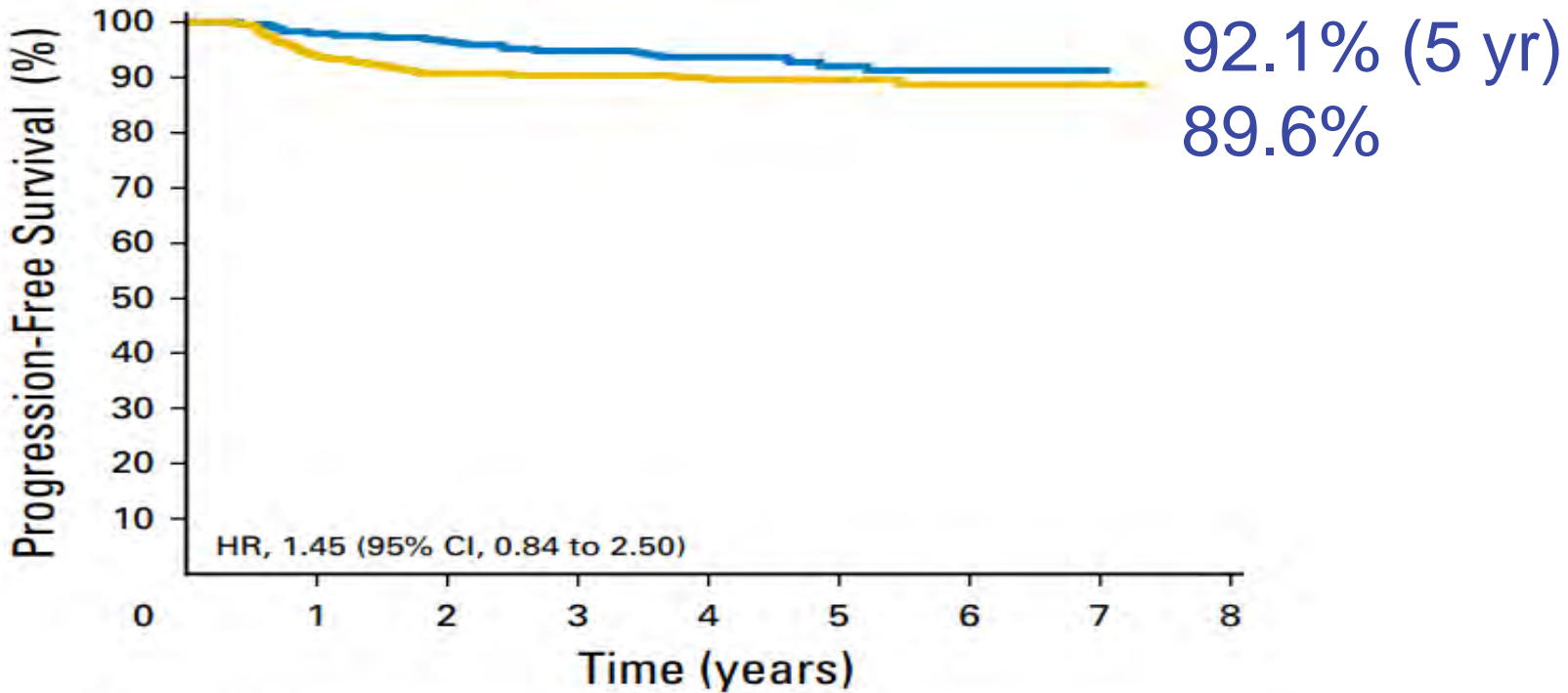
# ABVD alone vs ABVD + RT:

EORTC/LYSA/FIL H10 - Early Unfavourable



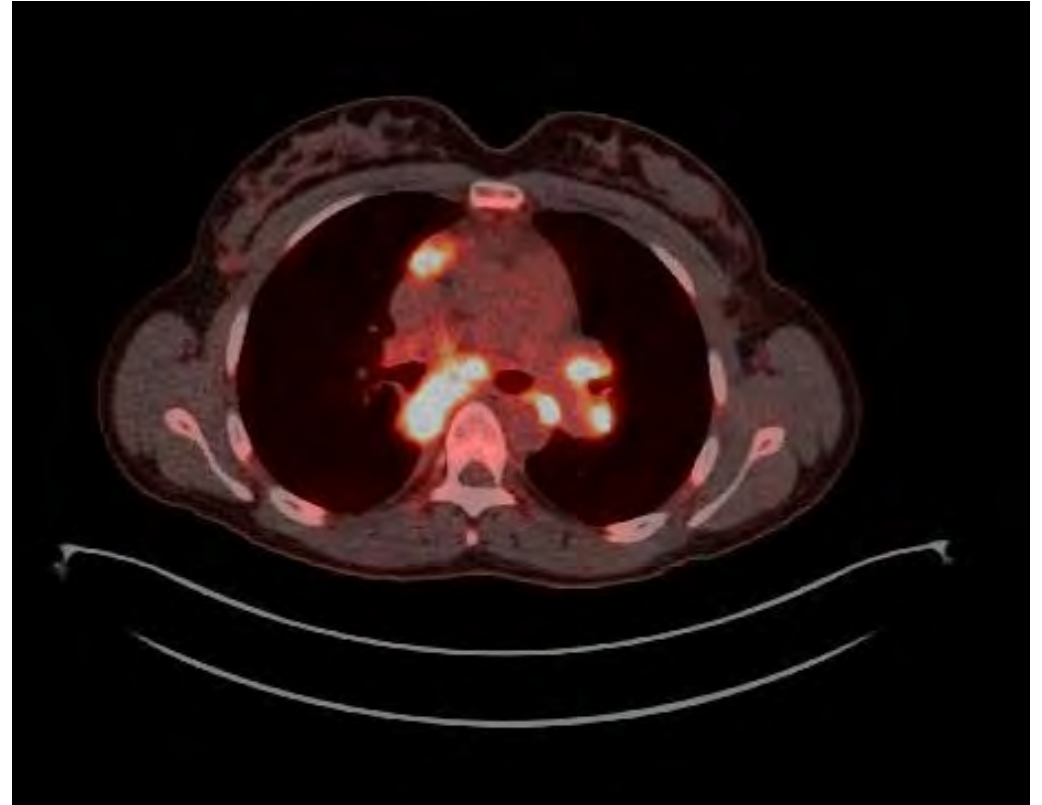
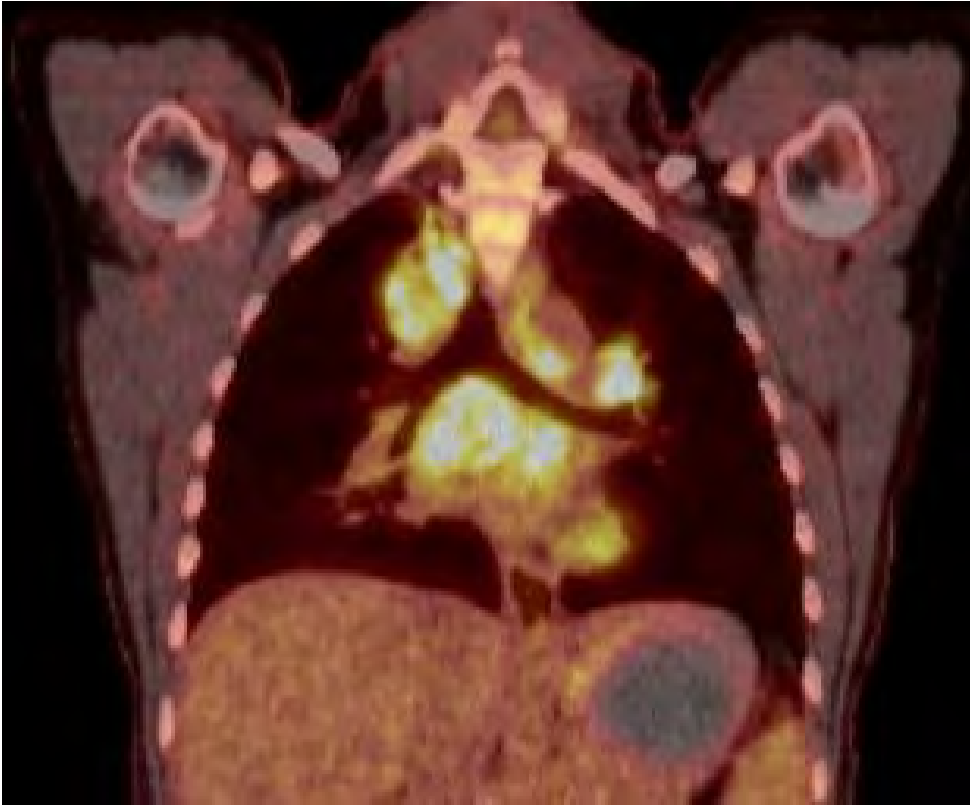
# EORTC/LYSA/FIL H10

PET2 Negative Early Unfavorable +/- RT

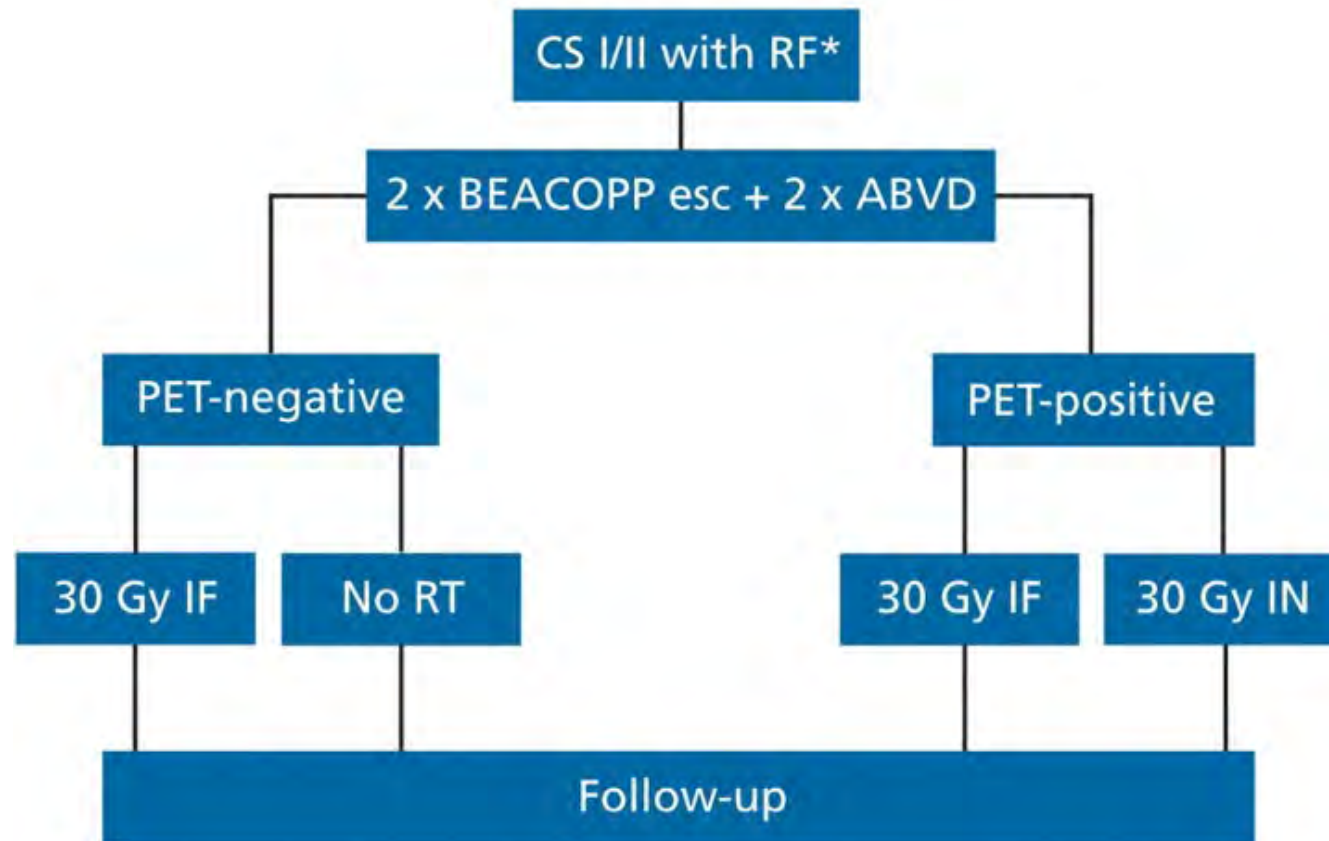


O	n	No. at risk:								
22	292	284	277	265	246	147	35	3	—	ABVD + INRT
32	302	282	266	261	242	145	36	2	—	ABVD only

# RT Late-effects likely outweigh benefit. What Are RT-Avoidant Strategies?



# GHSB HD17 Early Unfavourable

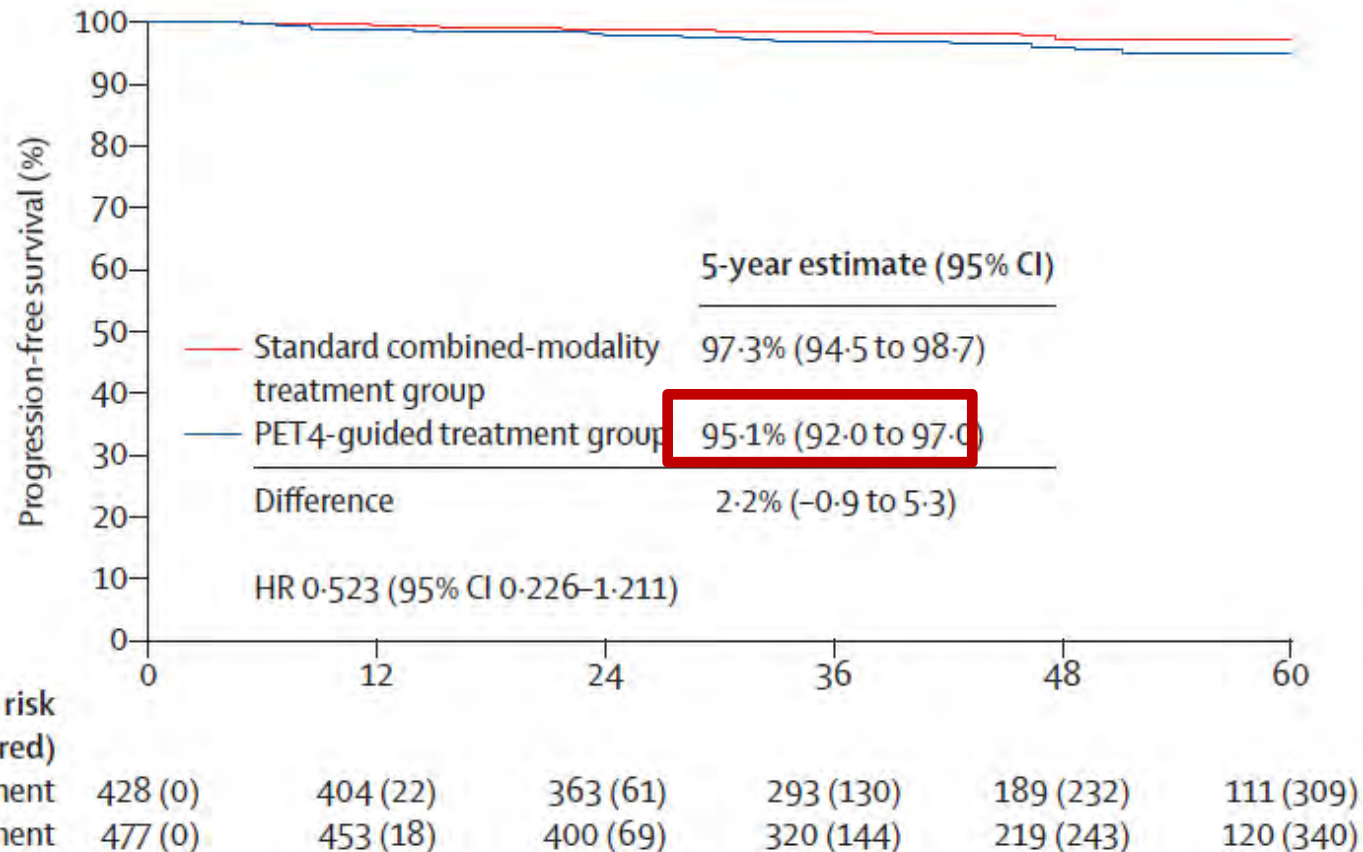


GHSB risk factors:

- >2 involved sites,
- bulky disease,
- extranodal extension,
- ESR > 50 or >30 if B-symptoms are present.

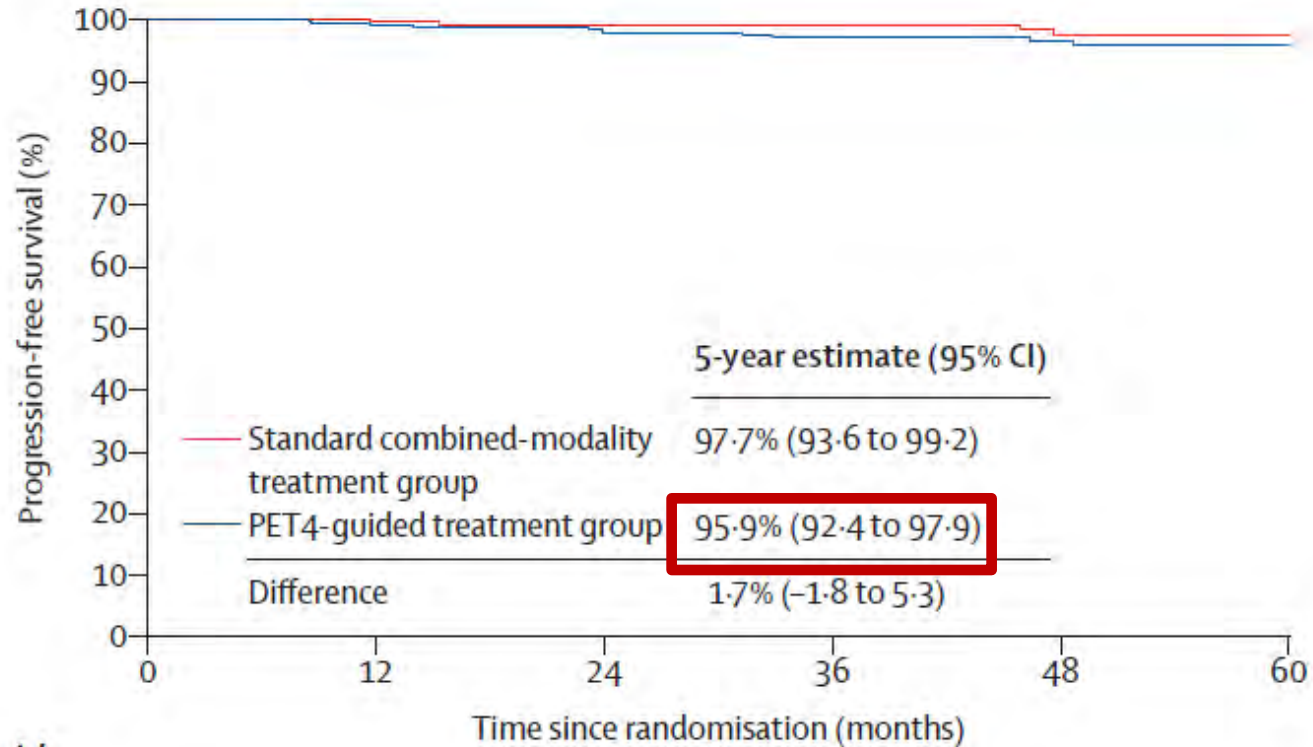
# GHSB HD17 Early Unfavourable

## Progression-free Survival – All Patients



# GHSB HD17 Early Unfavourable

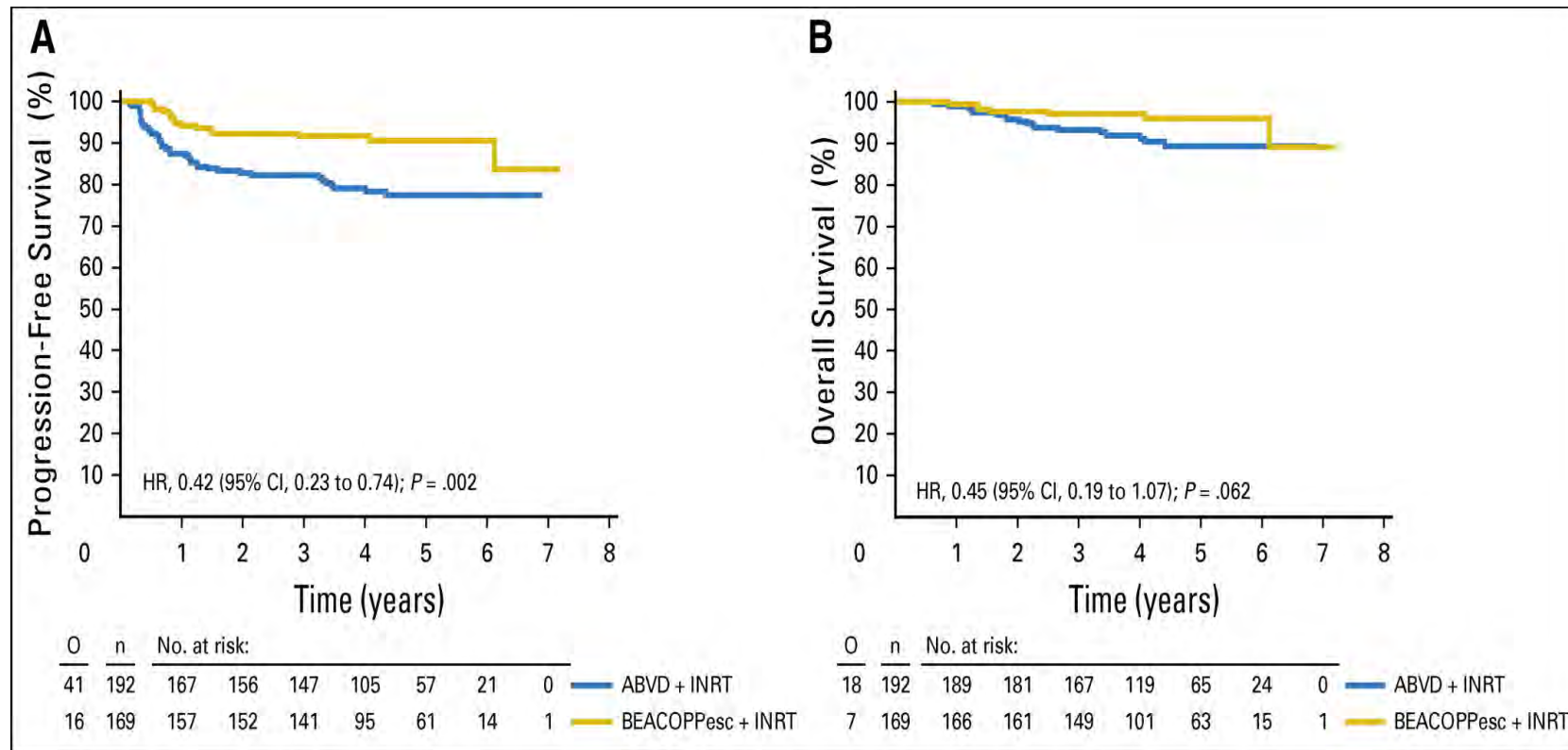
## Progression-free Survival – PET4 –'ve Patients



	Number at risk (number censored)					
Standard treatment	274 (0)	259 (14)	234 (38)	191 (81)	125 (146)	72 (198)
PET4-guided treatment	323 (0)	308 (12)	278 (40)	227 (88)	156 (158)	86 (227)

# What if PET2 is Positive (DS4)?

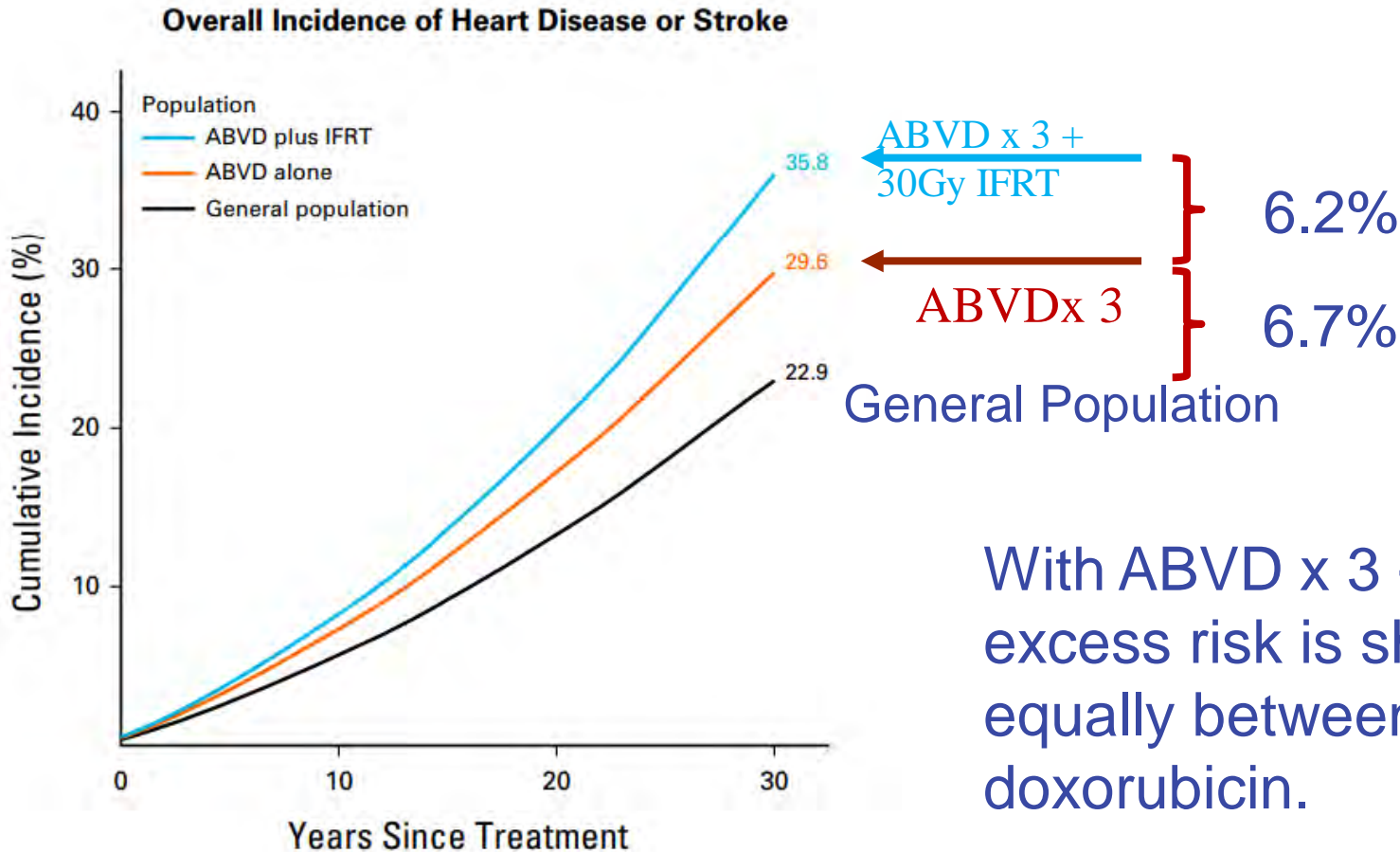
## Escalate to BEACOPP + ISRT/INRT





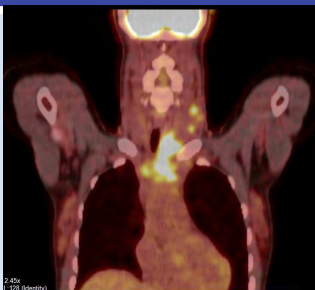
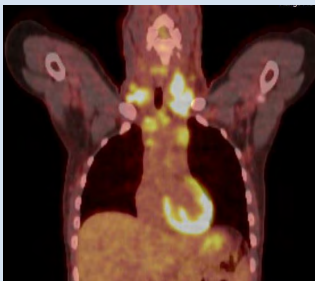
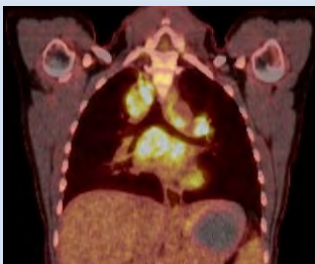
# Balancing Late Effects

## Attribution of Heart Disease – UK RAPID



With ABVD x 3 + 30Gy IFRT excess risk is shared about equally between RT and doxorubicin.

# Summary

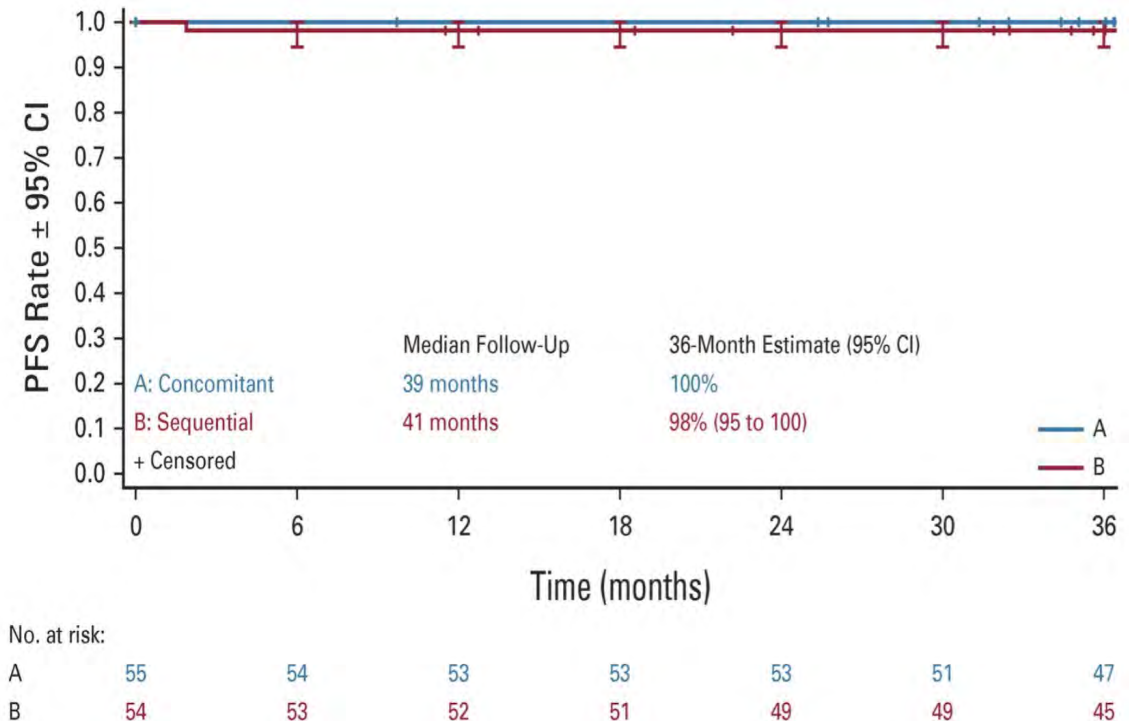
Clinical Category		CMT Approach	RT Avoidant
Early Favourable (1-2 sites) PET2 negative		ABVD x 2 + 20Gy	ABVD x 3-4 if <5cm bulk
Early Favourable (3 sites) PET2 negative		ABVD x 3 + 30Gy	ABVD x 4-6
Early Unfavourable PET2 negative		ABVD x 4 + 30Gy	<ul style="list-style-type: none"> <li>• BEACOPP-containing regimen (e.g. GHSG HD17)</li> <li>• ABVD x 6</li> </ul>

# Novel Agents: GHSG NIVAHL Trial

## Randomized Phase 2 – Early Unfavourable

- 4 × cycles of N-AVD vs sequential treatment with 4xnivo, 2xN-AVD, and 2xAVD; group B)
- both consolidated by 30 Gy involved-site radiotherapy (IS-RT).

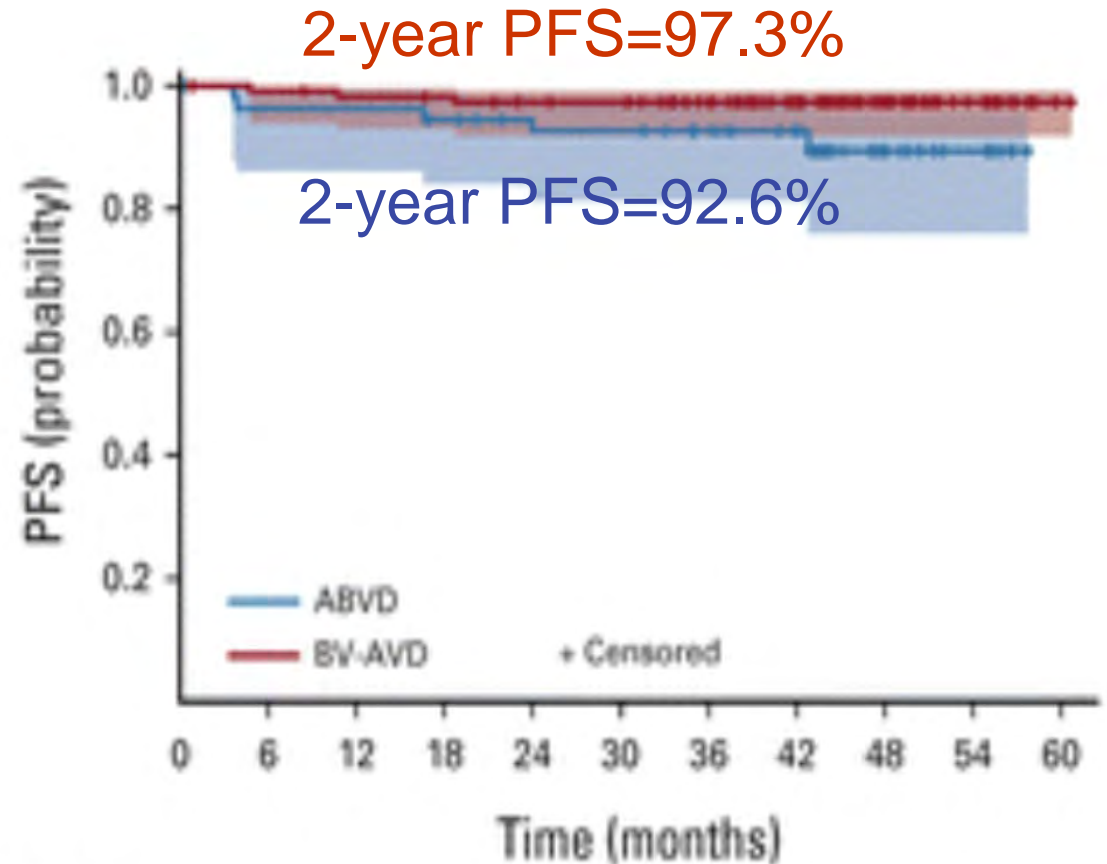
3-year PFS = 99-100%



# Novel Agents: BREACH Trial

Randomized Phase II – EORTC/LYSA Early Unfavourable

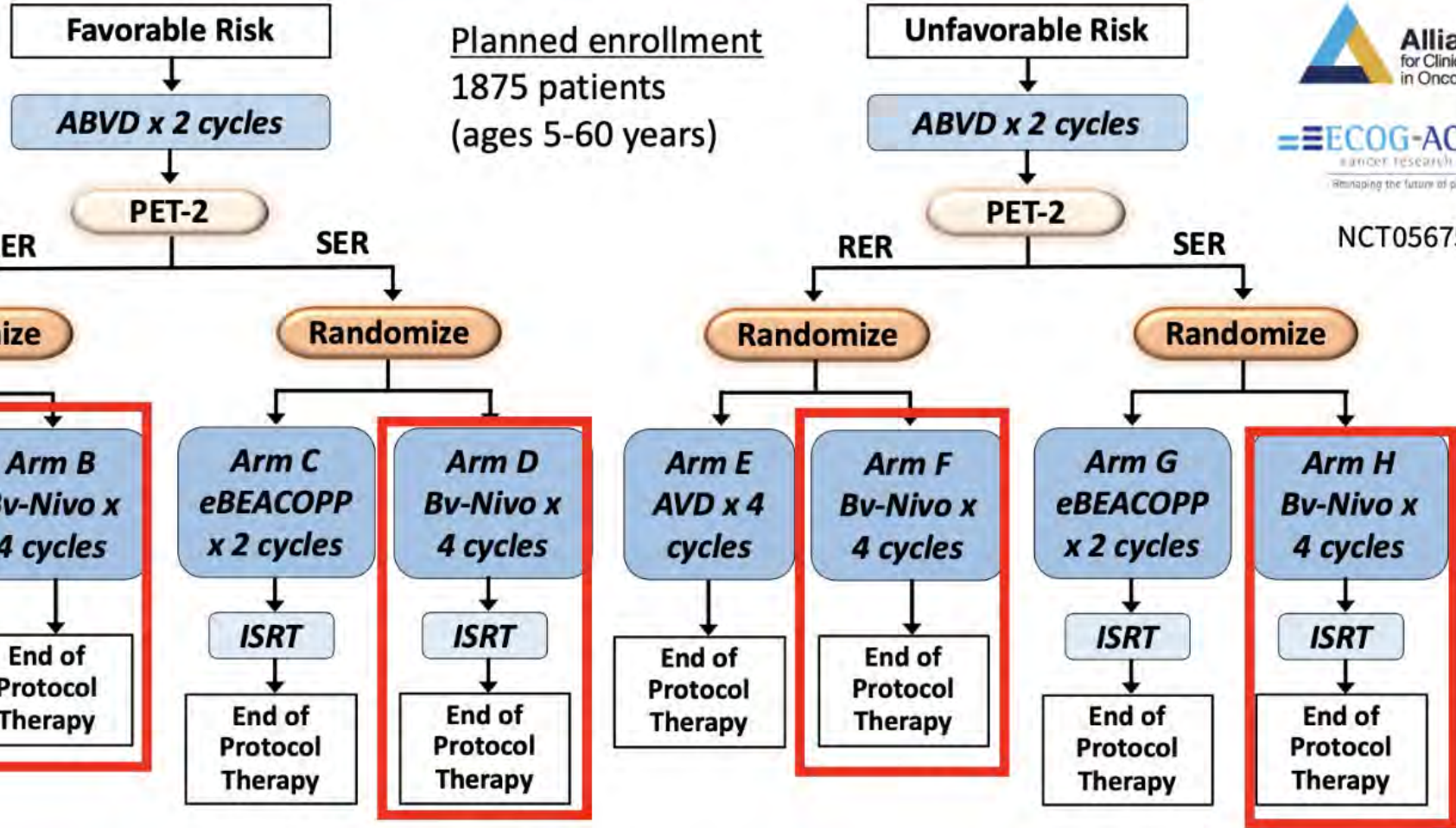
- 4x BV-AVD vs 4x ABVD.
- all get 30 Gy ISRT.
- Bv increased PET2 negative rate by 6.9%
  - (82.3% v 75.4%)



No. at risk:

ABVD	57	53	53	51	47	47	42	33	15	7	0
BV-AVD	113	111	109	108	105	104	97	80	44	17	2

# Standard therapy vs. immuno-oncology for children and adults with newly diagnosed stage I and II classic HL: AHOD 2131



NCT05675410

# Summary

- Treatment for early stage HL (favourable and unfavourable) should produce PFS > 90%
- Currently, interim PET response remains an important method of tailoring treatment intensity.
- For early favourable disease, ISRT/INRT allows minimization of chemotherapy exposures for rapid responders and is integrated into management for slow responders.
- Early results with novel agents are very promising.
  - Currently used with ISRT/INRT but will lead to trials of RT avoidance.

A nighttime photograph of a city skyline, likely Toronto, featuring the CN Tower and a large stadium illuminated in blue. The city lights are reflected in the water in the foreground. The sky is a deep blue, and the overall scene is vibrant and colorful.

**Thank you**