

IN PURSUIT OF *YOUR CURE.*<sup>™</sup>

# Hodgkin Lymphoma 2024

3 questions that need answering

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A Cancer Center Designated by the  
National Cancer Institute

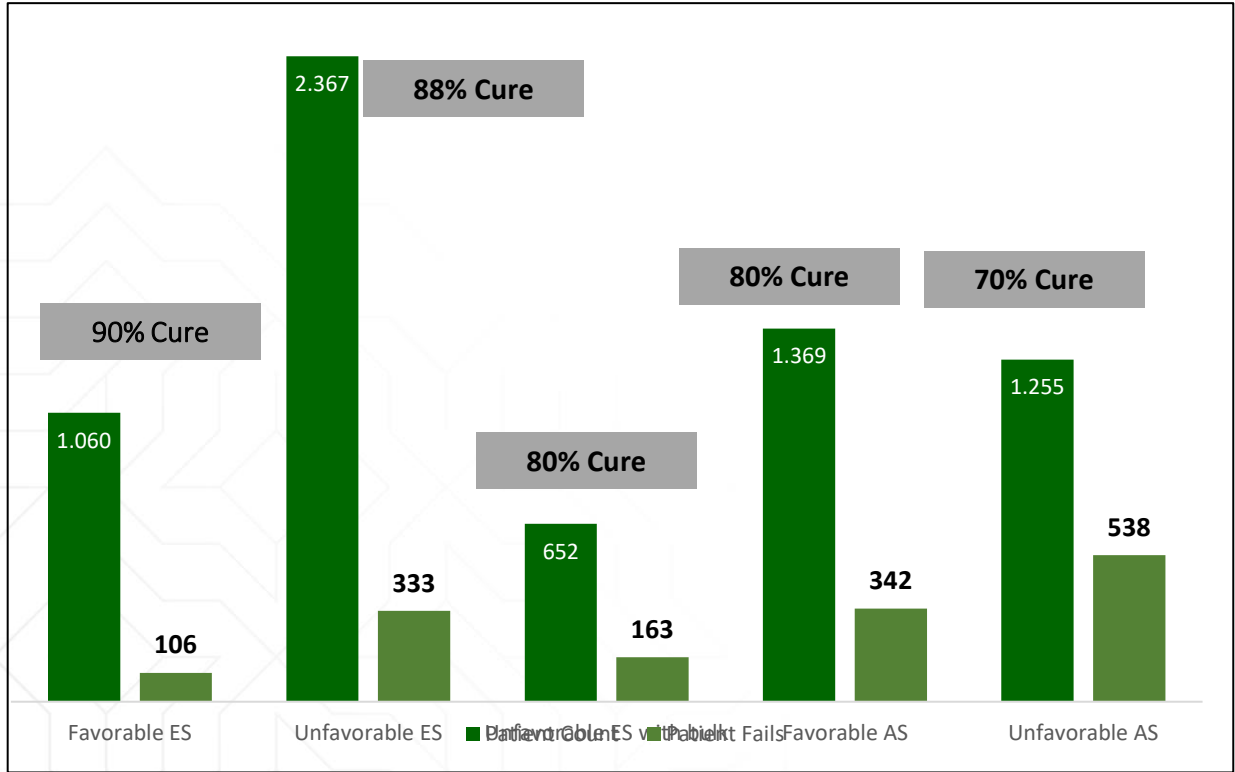
- Research support-ADC therapeutics, Merck, Seattle Genetics, Astra Zeneca
- Scientific Advisory Board-ADC therapeutics, Merck, Takeda, Merck, Seattle Genetics, Astra Zeneca, Incyte, Genmab

# Hodgkin Lymphoma by the Numbers:

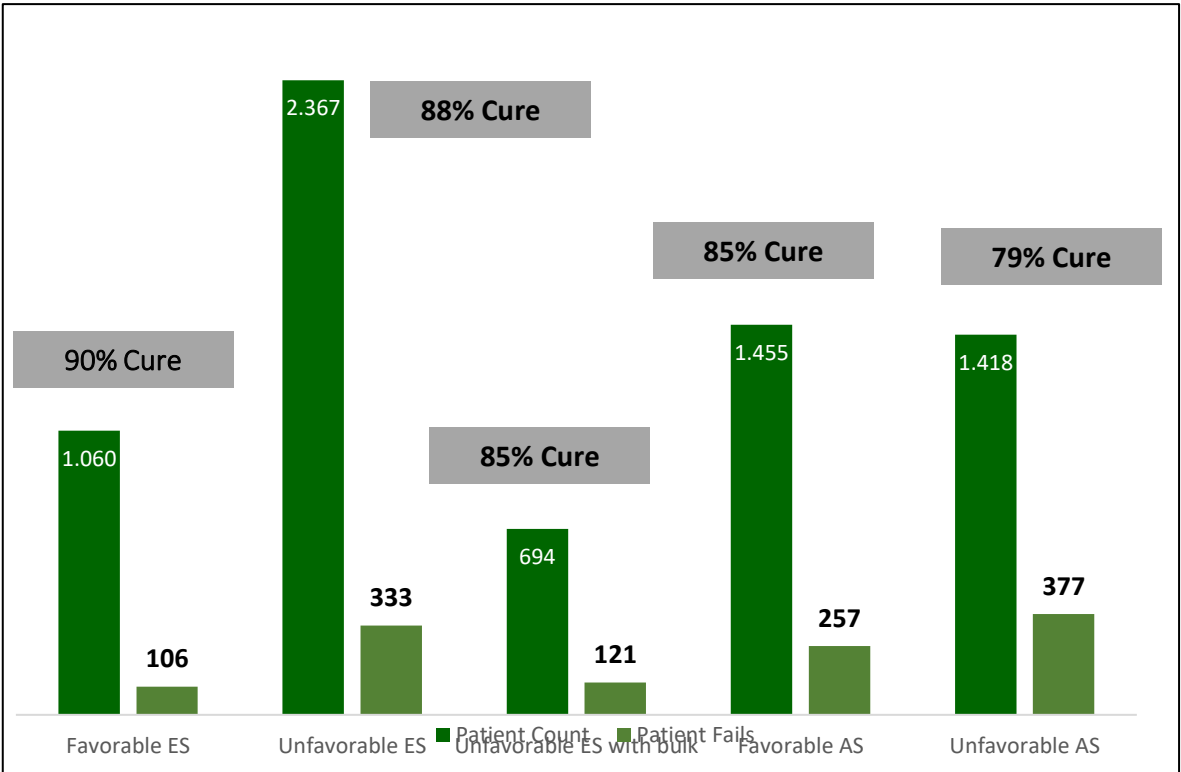
ES-F (13%) ES-U (33%), ES-UB (10%) AS-F (21%) AS-U (22%)

Optimal upfront treatment 8,150 patients (Pre BV)

Optimal upfront treatment 8,150 patients (post BV)



1484 pts need SLT



1194 pts need SLT

700 pts >70 excluded; 8,850 cases per year, 4850 male 4000 female

# The 3 questions

- **Should Radiation therapy be eliminated in ESHL**
- **Is N-AVD superior to Brentuximab based chemotherapy in ASHL**
- **When frontline therapy fails do all transplant-eligible patients need HDT/ASCT**

# Have we made progress?

## Standard treatment at time of HL in 2000 in US

4-6 cycles of ABVD or MOPP/ABV+/-D and Rt standard management for ESHL without tumor bulk

6 cycles and RT for bulky disease

6 cycles of ABVD or MOPP/ABV hybrid; other hybrid regimens for ASHL +/- RT

## Standard treatment for HL 2022

- 3-4 cycles of ABVD without RT early stage without tumor bulk
- 6 cycles of ABVD without RT if PET negative post treatment is common for bulky disease
- BV-AVD is becoming for standard of ASHL, no role for RT

## Standard treatment for HL 2024?

# I am not sure we are curing more Pts

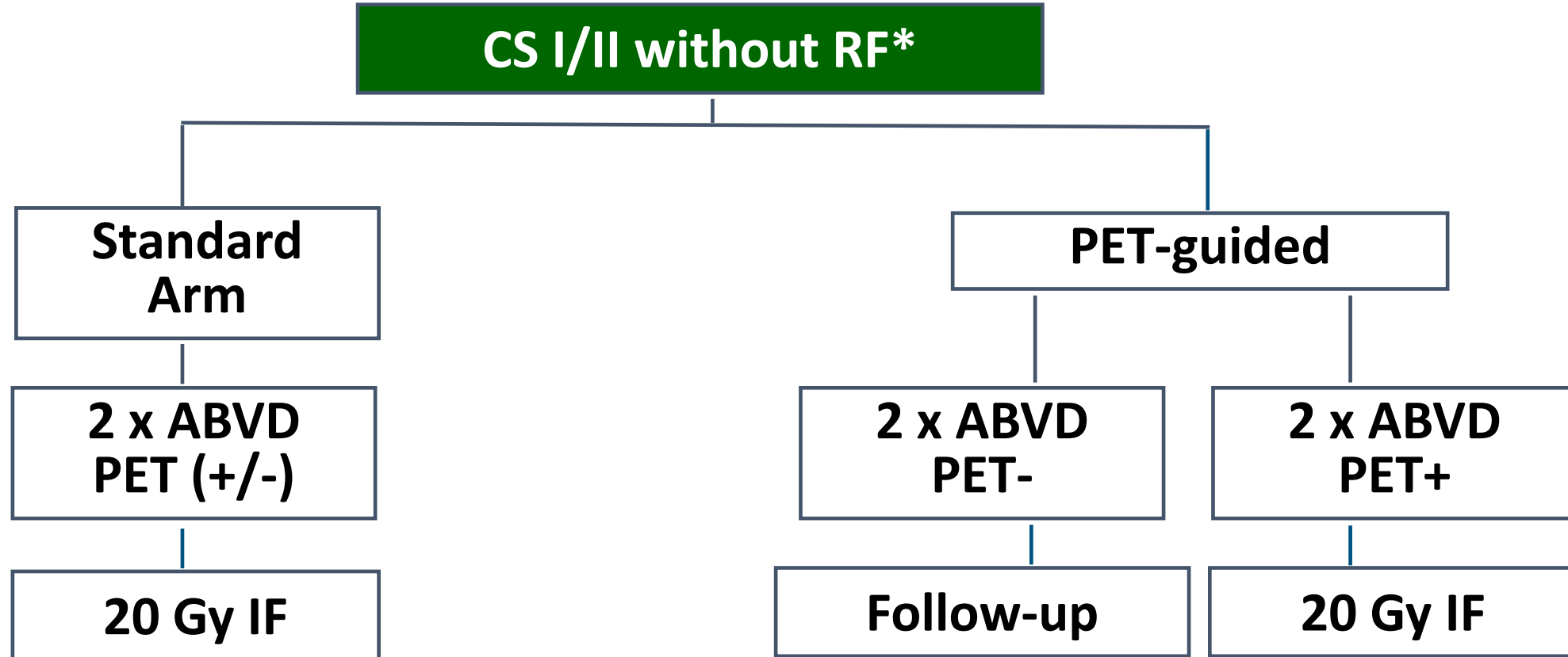
- With optimal therapy in each cohort, less pts with ASHL need SLT/ASCT
- With less treatment for ESHL and the near elimination of ISRT, more pts are relapsing
- Clinical research has moved in a direction to maintain the cure rate of patients with HL and decrease long term side effects
- Luckily in the second-line setting we are curing more patients!
- Don't we want to cure more pts upfront?

# Should we stop administering RT to patients with ESHL?

Patients want to be cured with the least amount of therapy and with minimal toxicity

# GHSB HD16 trial

Early-favorable HL



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



# GHSB HD16 trial

Questions to be addressed

## Primary objectives

- (1) Can RT be omitted from standard CMT without relevant loss of tumor control in PET-2 negative HL patients?**
- (2) Does a positive PET after 2xABVD represent a risk factor for PFS among patients treated with standard CMT?**

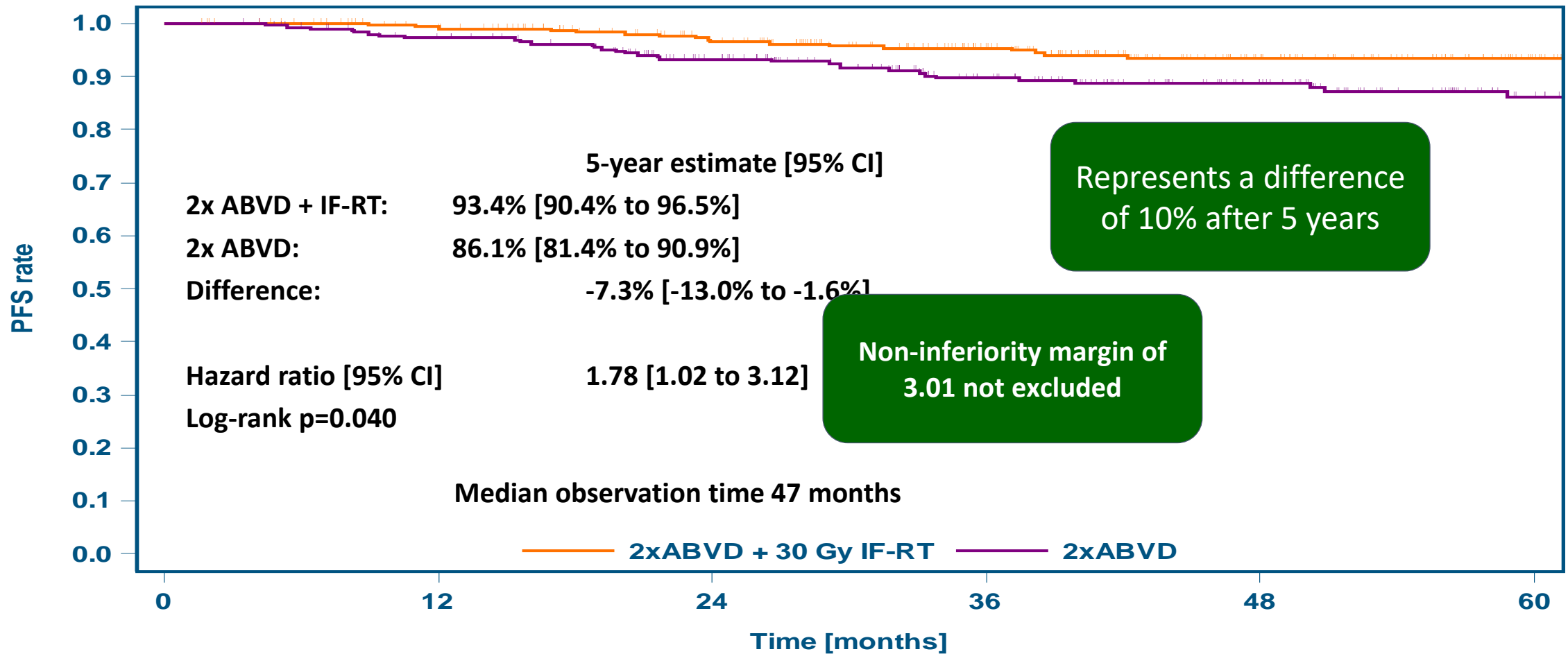
# Progression and relapse

## PET-negative patients

		<b>2xABVD + IF-RT</b> N=328	<b>2xABVD</b> N=300
		%	%
<b>Type of pd/relapse</b>	<b>Progression</b>	<b>0</b>	<b>0.3</b>
	<b>Early relapse</b>	<b>0.6</b>	<b>3.0</b>
	<b>Late relapse</b>	<b>4.0</b>	<b>6.3</b>
<b>In-field pd/relapse</b>		<b>2.1</b>	<b>8.7</b>
<b>Any pd/relapse</b>		<b>4.6</b>	<b>9.7</b>

pd = progressive disease

# HD16: Progression-free survival PET-negative patients



number at risk

328  
300

307  
280

268  
239

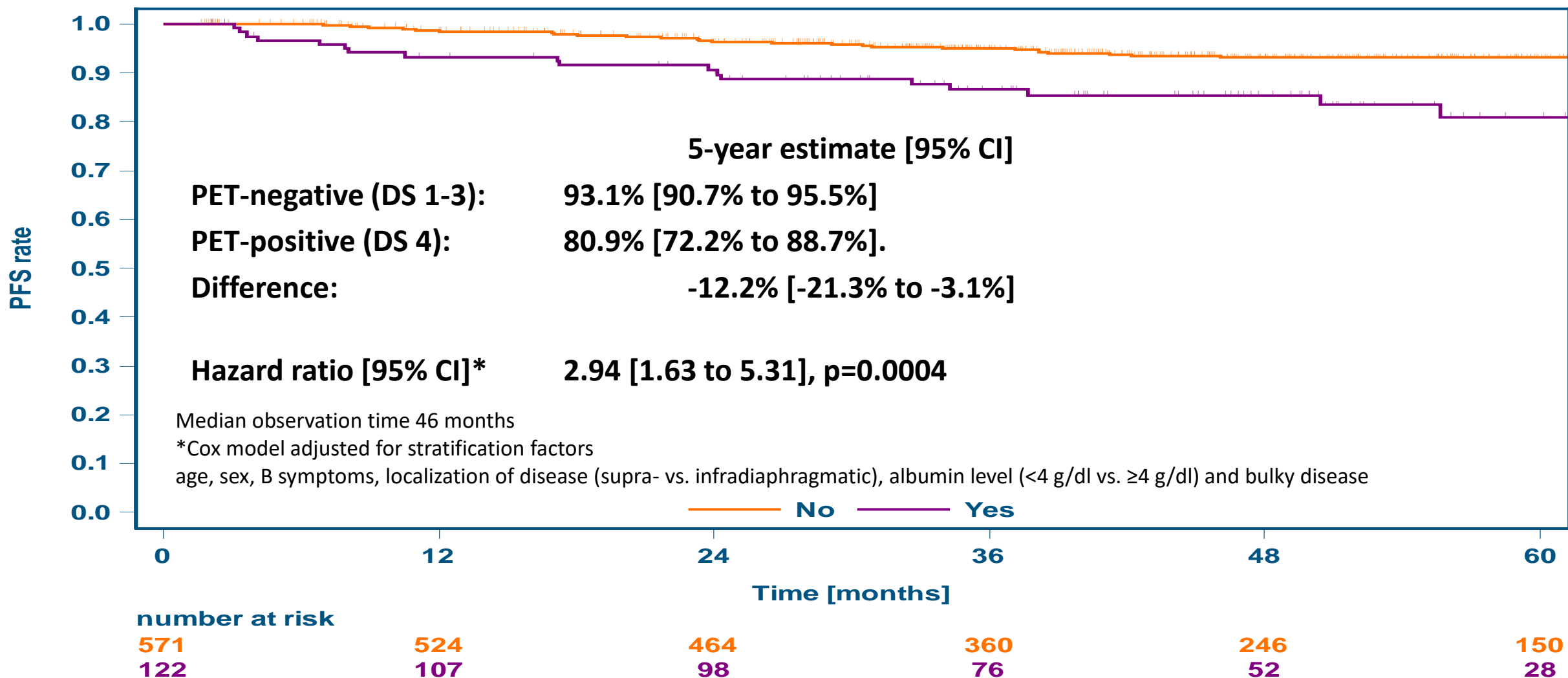
212  
179

149  
134

97  
85

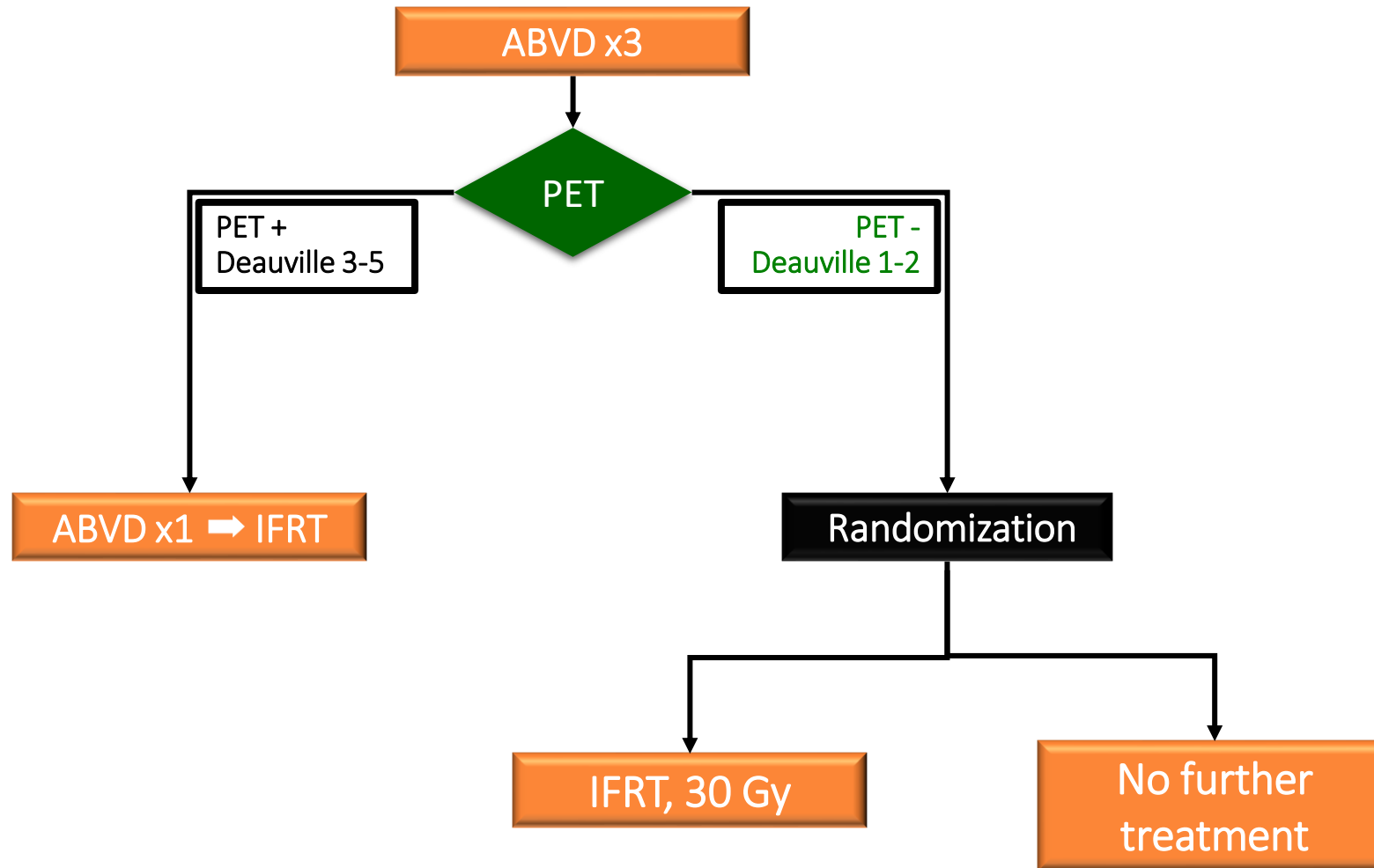
# HD16: Progression-free survival

## Patients receiving radiotherapy: DS1-3 vs DS4



# RAPID: Schema

Radford, et al, N Engl J Med. 2015 Apr 23;372(17):1598-607

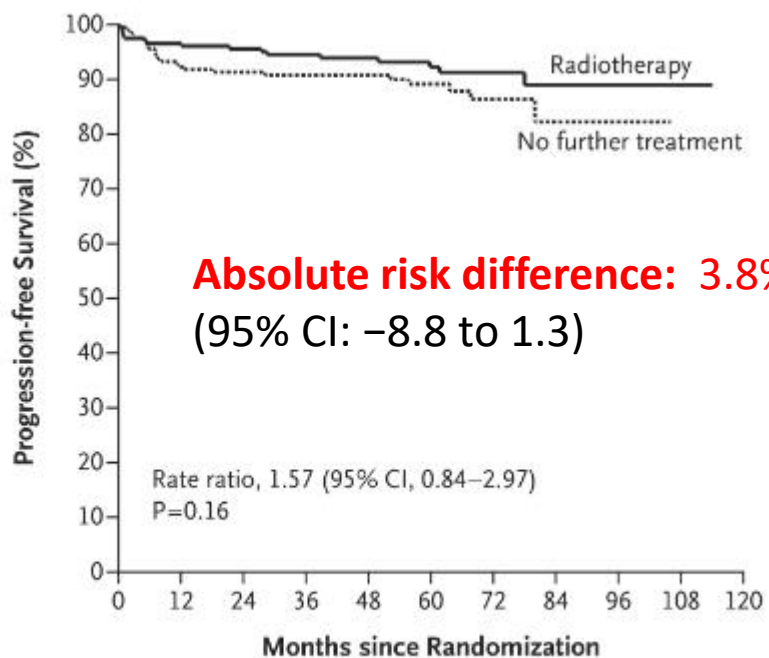


# UK NCRI RAPID Trial

PFS from randomization in the PET –ve population (ITT N=420; PP N=392)

Radford *et al* N Engl J Med 2015

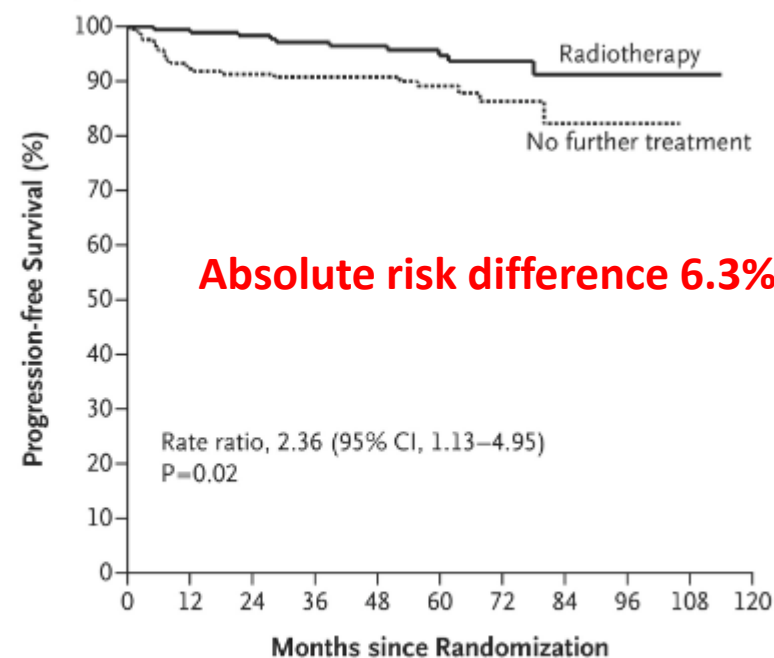
A Intention-to-Treat Analysis



No. at Risk

Radiotherapy	209	198	188	170	134	99	57	30	13	2	0
No further treatment	211	190	181	153	129	89	50	14	5	0	0

B Per-Protocol Analysis



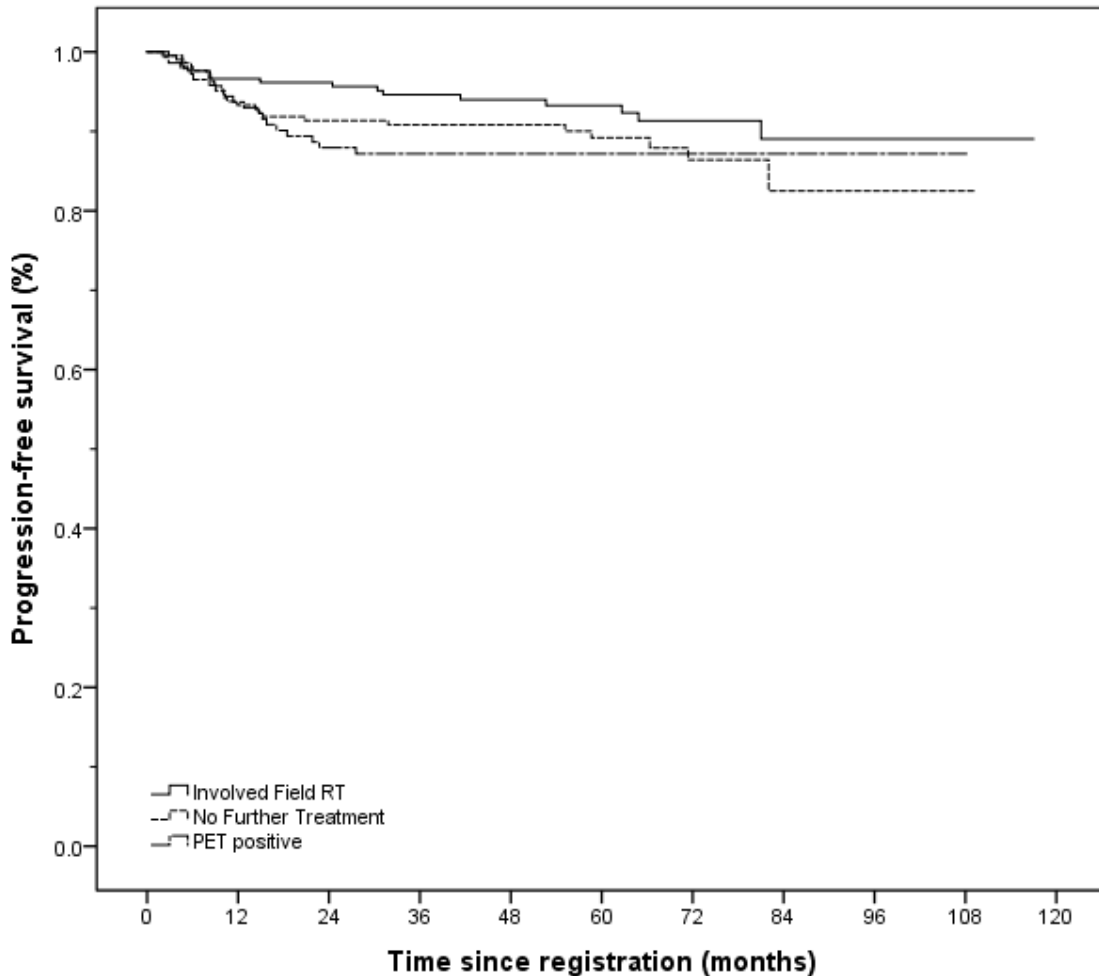
No. at Risk

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

**3 year PFS in ITT population: 94.6% (95%CI 91.5-97.7) IFRT and 90.8% (95%CI 86.9-94.8) NFT**

**3 year PFS in PP population: 97.1% (95%CI 94.7-99.6) IFRT and 90.8% (95%CI 86.8-94.7) NFT**

# RAPID and PET



CMR: PET score 1 or 2

- 5y PFS 91.2% (95% CI: 88.3 – 94.1)

PET positive: PET score 3, 4 or 5

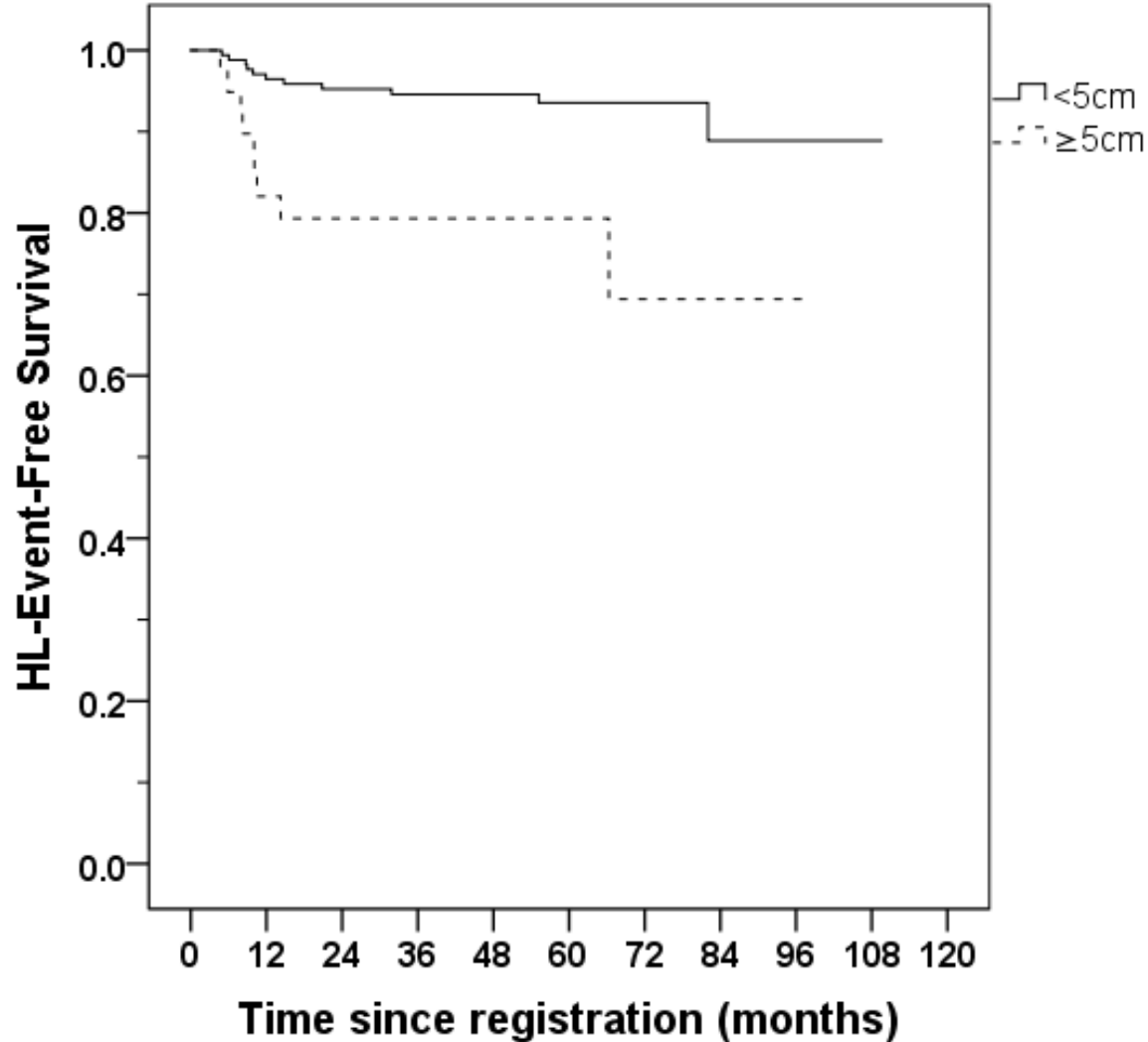
- 5y PFS 87.2% (95% CI: 81.7 – 92.7)

- ***there was no statistically significant difference between any of the treatment arms (ITT basis)***

*How can we improve risk stratification?*

	0	12	24	36	48	60	72	84	96	108	120
IFRT	209	201	196	177	145	110	70	37	14	3	0
NFT	211	206	197	179	152	117	64	24	8	1	0
PET positive	145	141	133	110	87	58	34	16	4	1	0

# RAPID and Tumor Bulk



**5-year EFS:**

**MTD <5cm = 93.6% (n=172)**  
(95% CI: 89.7–97.5)

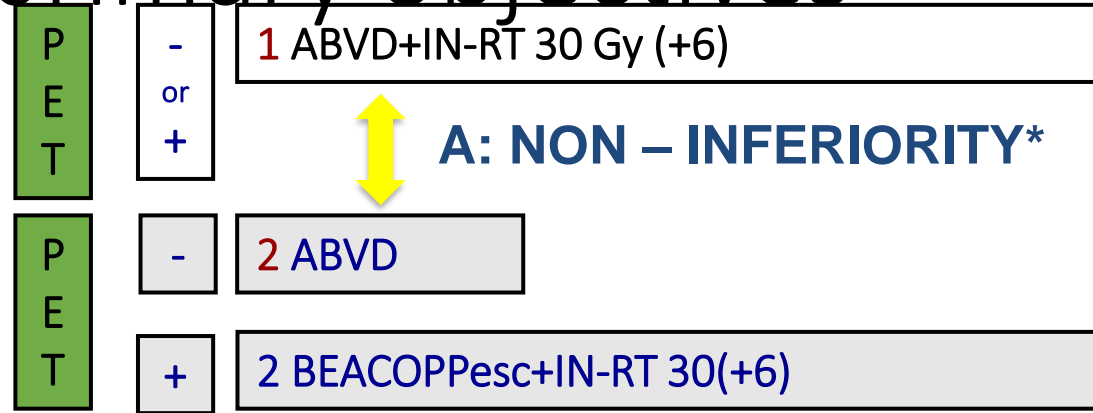
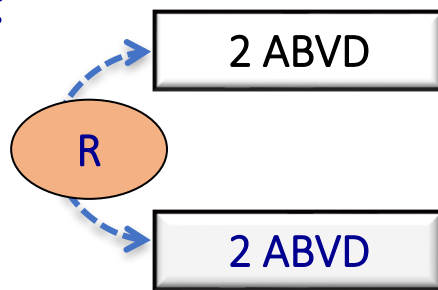
**MTD ≥5cm = 79.3% (n=39)**  
(95% CI: 66.6–92.0)

P=0.04

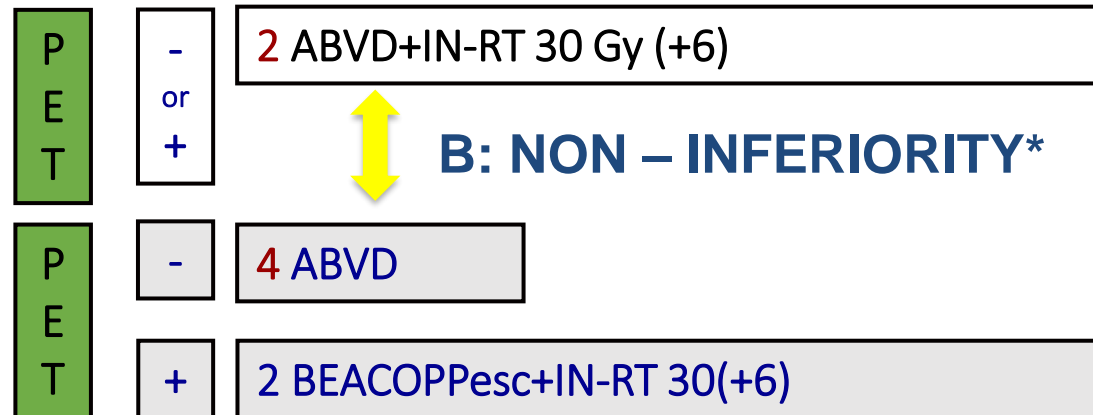
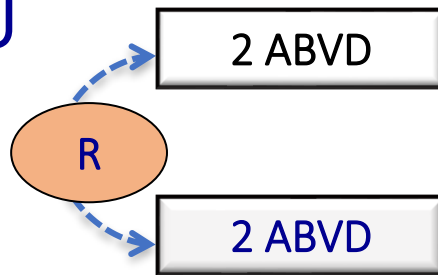


# EORTC/LYSA/FIL H10 study: Study design and primary objectives

H10F



H10U



Primary endpoint : Progression-free survival

\*Non-inferiority: Log-rank comparison, one-sided  $p < 0.025$ ,  
H10F 26 events, HFU 63 events

H10F	Chemo	PET2	CT/RT	# Events	1-yr PFS
Standard	ABVDx2	+/-	INRT	1/188	100%
Experimental	ABVDx2	negative	ABVDx2	9/193	94.9%
		positive	BEACOPPesc x2 + INRT		

H10U	Chemo	PET2	CT/RT	# Events	1-yr PFS
Standard	ABVDx2	+/-	ABVDx2 + INRT	7/251	97.3%
Experimental	ABVDx2	negative	ABVDx4	16/268	94.7%
		positive	BEACOPPesc x2 + INRT		

# I have not eliminated ISRT from my Practice

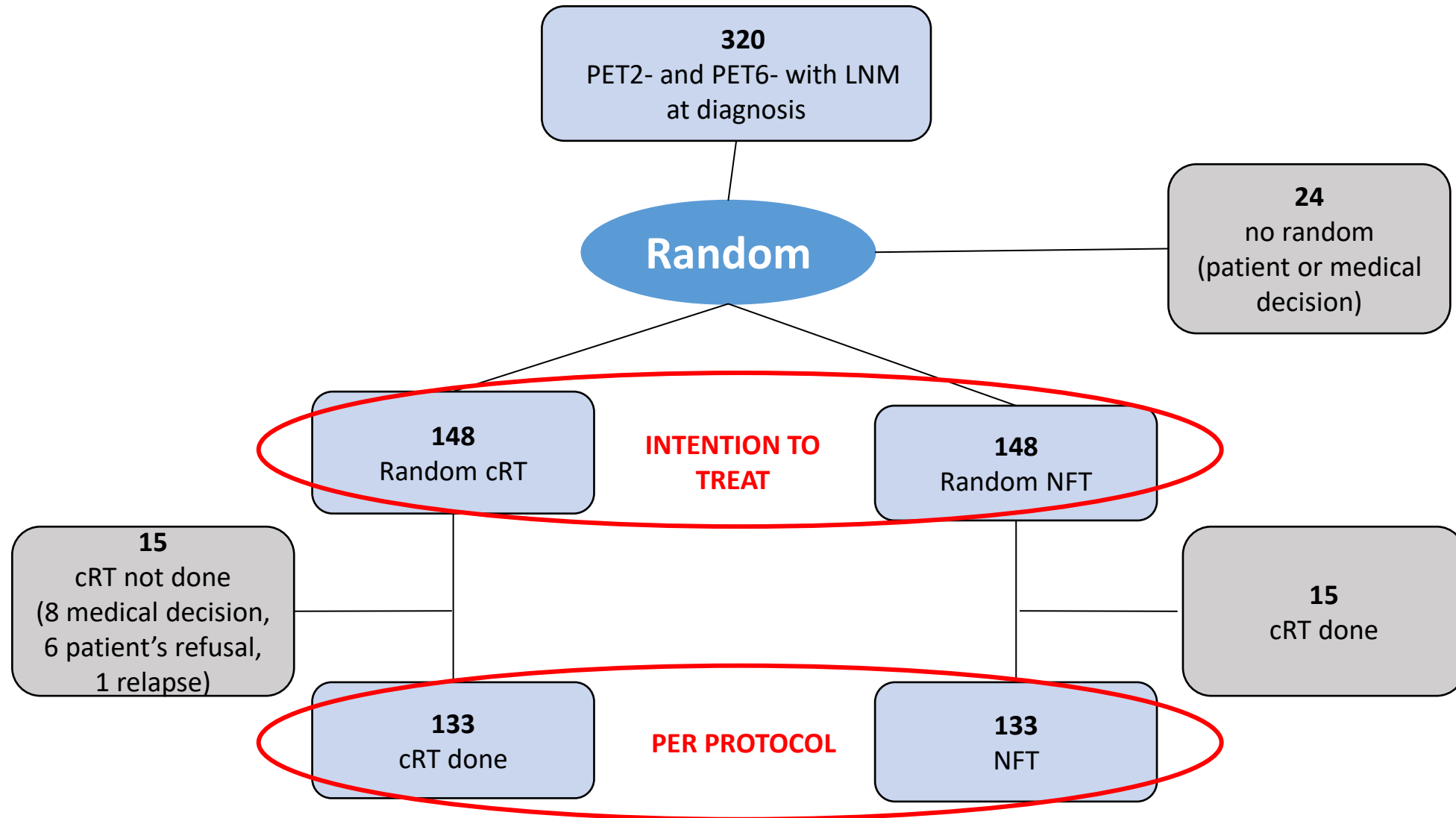
- If the radiation field is small and does not involve breast tissue 2 cycles of ABVD and 20 Gy of ISRT is hard to beat for stage I/II disease
- If pts have a nodal mass of between 5-10 cm the relapse rate is too high if 3 cycles of ABVD is administered without ISRT
- 4 months of ABVD alone is probably equivalent to less chemotherapy with ISRT
- Interim PET is useful when ABVD is administered if therapy will be changed
  
- What about patients with a nodal mass of 10 cm or greater?

# **Consolidation Radiotherapy could be omitted in advanced Hodgkin Lymphoma with large nodal mass in Complete Metabolic Response after ABVD. Final analysis of the randomized GITIL/FIL HD0607 trial.**

Andrea Gallamini MD<sup>1</sup>, Andrea Rossi MD<sup>2</sup>, Caterina Patti MD<sup>3</sup>, Marco Picardi MD<sup>4</sup>, Alessandra Romano MD<sup>5</sup>, Maria Cantonetti MD<sup>6</sup>, Sara Oppi MD<sup>7</sup>, Simonetta Viviani MD<sup>8</sup>, Silvia Bolis MD<sup>9</sup>, Livio Trentin MD<sup>10</sup>, Guido Gini MD<sup>11</sup>, Battistini R<sup>12</sup>, Stephane Chauvie PhD<sup>13</sup>, Laura Bertolotti MD<sup>14</sup>, Chiara Pavoni PhD<sup>2</sup>, Guido Parvis MD<sup>15</sup>, Roberta Zanotti MD<sup>16</sup>, Paolo Gavarotti MD<sup>17</sup>, Michele Cimminiello MD<sup>18</sup>, Corrado Schiavotto MD<sup>19</sup>, Piera Viero MD<sup>20</sup>, Abraham Avigdor MD<sup>21</sup>, Corrado Tarella MD<sup>22</sup> and Alessandro Rambaldi MD<sup>2</sup>



# Consort diagram (N=320)



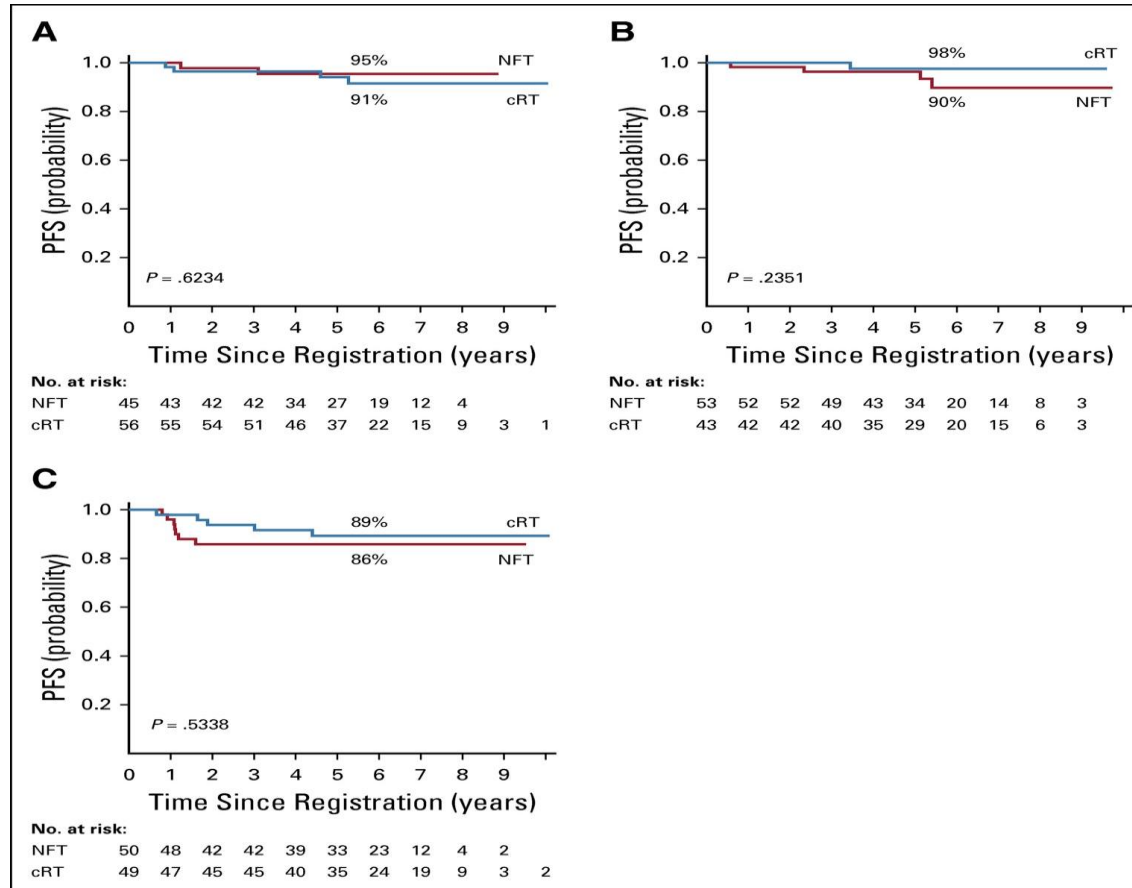


FIG 3. Kaplan-Meier analysis of progression-free survival (PFS) according to the randomization group and the baseline large nodal mass (LNM) size. (A) LNM 5-7 cm. (B) LNM 7-10 cm. (C) LNM > 10 cm (classic bulky). cRT, consolidation radiotherapy; NFT, no further treatment.

# Phase II MSKCC BV-AVD clinical trial

Can BV-replace ISRT?

**COHORT 1**

**Brentuximab vedotin (1.2 mg/kg)+ AVD x 2 cycles**

**PET-CT-2**

**Brentuximab vedotin (1.2 mg/kg)+ AVD x 2 cycles**

**PET-CT-4**

(Deauville 4-5)

(Deauville 1-3)

**Biopsy**

**Bx-**

**30 Gy  
ISRT**

**Bx+**

**Off study**

**Eligibility criteria:**  
- Stage I or II classical Hodgkin lymphoma

**At least 1 unfavorable risk feature:**

- Bulky mediastinal mass ( $\geq 1/3$  MMR on PA CXR or  $\geq 10$ cm by CT)
- ESR  $\geq 50$ mm/h, or ESR  $\geq 30$ mm/h in patient with B-symptoms
- Extranodal involvement
- 3 or more lymph node sites (per GHSG definition)
- Infradiaphragmatic disease



**COHORT 2**

**Brentuximab vedotin (1.2 mg/kg)+ AVD x 2 cycles**

**PET-CT-2**

**Brentuximab vedotin (1.2 mg/kg)+ AVD x 2 cycles**

**PET-CT-4**

(Deauville 4-5)

(Deauville 1-3)

**Biopsy**

**Bx-**

**20 Gy  
ISRT**

**Bx+**

**Off study**

**Eligibility criteria:**

Stage I or II classical  
Hodgkin lymphoma

**At least 1 unfavorable risk  
feature:**

- Disease bulk (>7cm in MTD or MCD)
- ESR  $\geq$  50mm/h, or ESR  $\geq$  30mm/h in patient with B-symptoms
- Extranodal involvement
- 3 or more lymph node sites (per GHSG definition)
- Infradiaphragmatic disease

MSKCC Disease Bulk Definition:  
Kumar et al, Haematologica, 2016

**COHORT 3**

**Brentuximab vedotin (1.2 mg/kg)+ AVD x 2 cycles**

**PET-CT-2**

**Brentuximab vedotin (1.2 mg/kg)+ AVD x 2 cycles**

**PET-CT-4**

**(Deauville 4-5)**

**Biopsy**

**Bx-**

**(Deauville 1-3)**

**30 Gy  
CVRT**

**Bx+**

**Off study**

**Eligibility criteria:**  
• Stage I or II classical Hodgkin lymphoma

**Unfavorable risk feature:**  
– Disease bulk (>7cm in MTD or MCD)

**CONSOLIDATION VOLUME RADIATION (CVRT)**

- Novel RT field
- Treat only post-chemo, PET-negative residual CT abnormalities ≥

**COHORT 4**

**Brentuximab vedotin (1.2 mg/kg)+ AVD x 2 cycles**

**PET-CT-2**

**Brentuximab vedotin (1.2 mg/kg)+ AVD x 2 cycles**

**PET-CT-4**

(Deauville 4-5)

(Deauville 1-3)

**Biopsy**

**Bx-**

**No RT**

**Bx+**

**Off study**

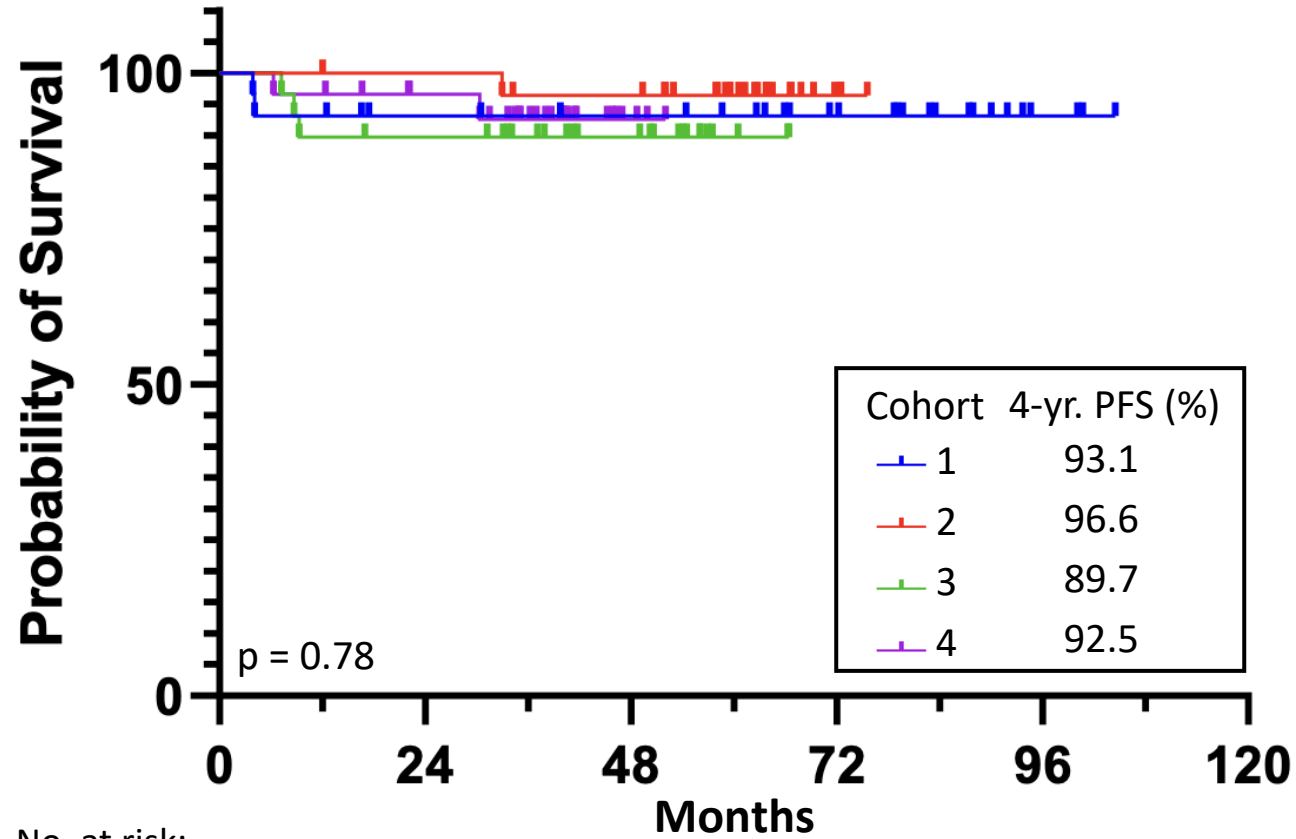
**Eligibility criteria:**  
• Stage I or II classical Hodgkin lymphoma

**Unfavorable risk feature:**  
– Disease bulk (>7cm in MTD or MCD)

# Results: Baseline Characteristics

Characteristic	Cohort 1, No. (%)	Cohort 2, No. (%)	Cohort 3, No. (%)	Cohort 4, No. (%)	Total, No. (%)
No. of patients	30	29	29	29	117
Age, median	31	33	31	30	32
Male	16 (53)	17 (59)	15 (52)	11 (38)	59 (50)
Stage II	30 (100)	29 (100)	28 (97)	28 (97)	115 (98)
<b>Unfavorable risk features</b>					
MSK Bulk (> 7 cm)	23 (77)	20 (69)	<b>29 (100)</b>	<b>29 (100)</b>	<b>101 (86)</b>
Traditional Bulk	12 (40)	9 (31)	6 (21)	7 (24)	32 (27)
Elevated ESR	20 (67)	12 (41)	12 (41)	17 (59)	61 (52)
B symptoms	15 (50)	11 (38)	8 (28)	12 (41)	46 (39)
EN Site	9 (30)	6 (21)	4 (14)	5 (17)	24 (21)
> 2 nodal sites	13 (43)	21 (72)	10 (34)	22 (76)	66 (56)
Infradiaphragmatic	1 (3)	1 (3)	1 (3)	1 (3)	4 (3.4)

# Results: PFS by Cohort

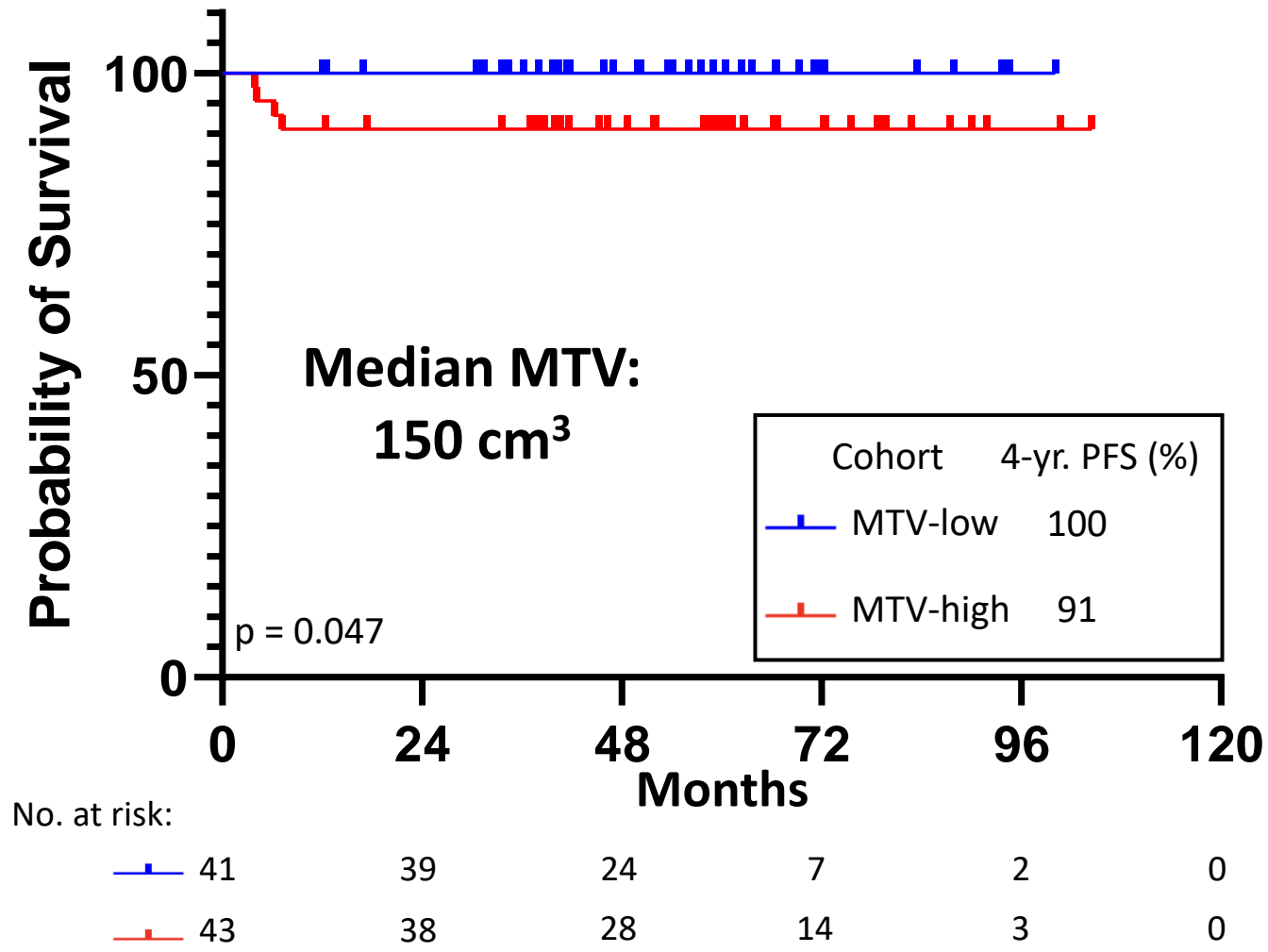


Cohort Descriptions	
1	30-Gy ISRT
2	20-Gy ISRT
3	30-Gy CVRT
4	No RT

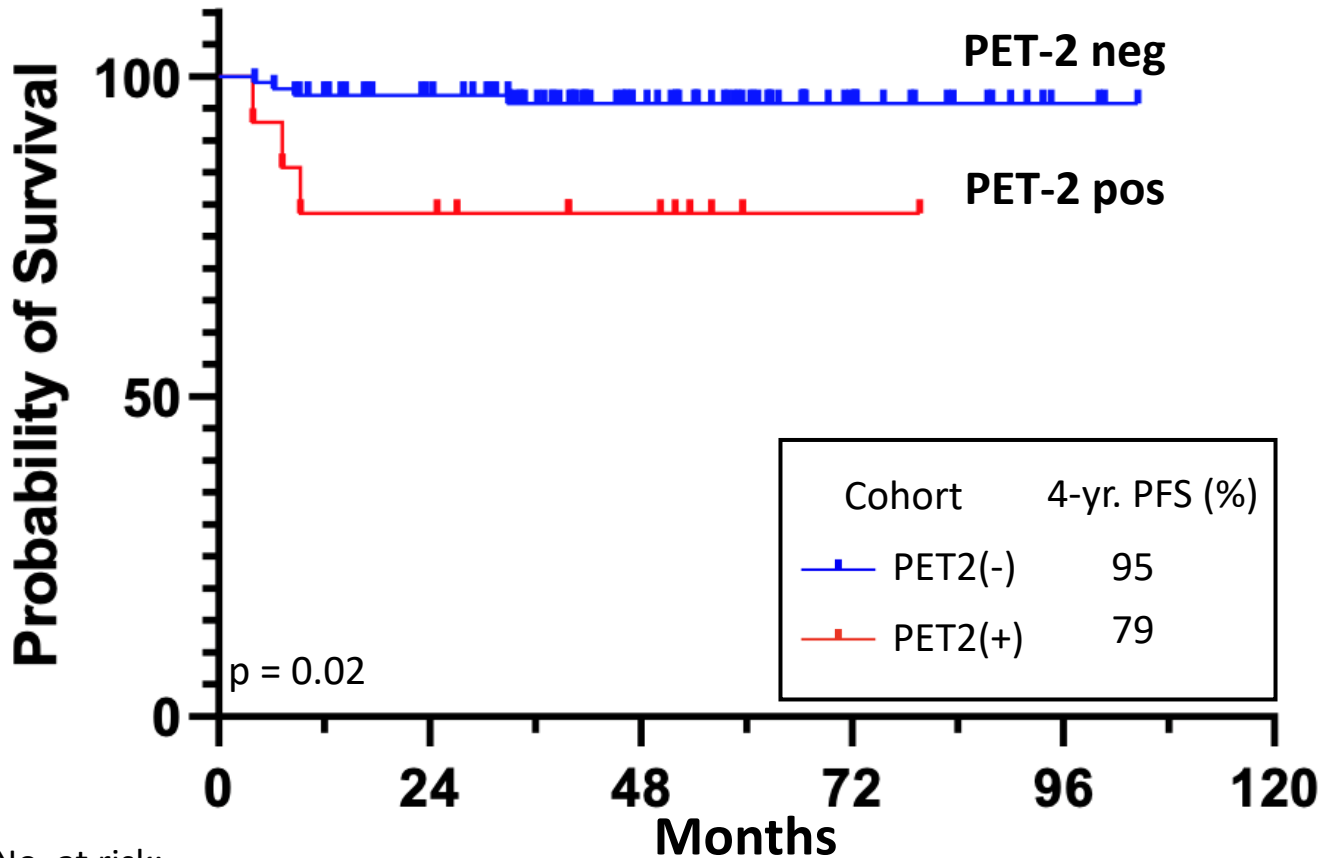
No. at risk:

29	25	23	16	4	0
29	29	27	5	0	0
29	26	17	1	0	0
29	24	4	0	0	0

# Results: PFS by Baseline MTV



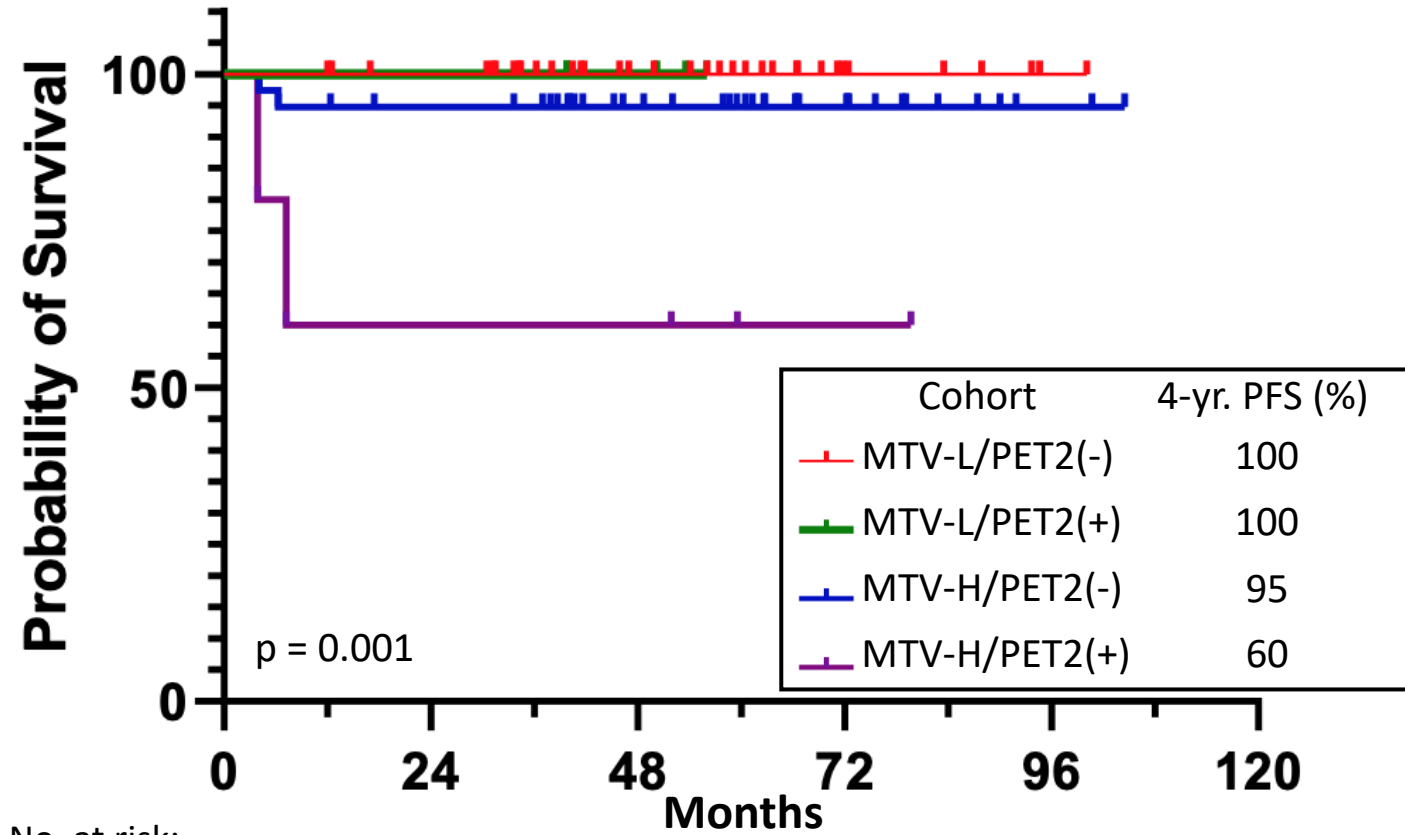
# Results: PFS by PET2



No. at risk:

101	87	51	19	4	0
14	12	10	2	0	0

# Results: PFS by Combined MTV/PET2



No. at risk:

—	36	33	20	6	1	0
—	5	5	3	0	0	0
—	38	34	24	12	2	0
—	5	3	3	1	0	0



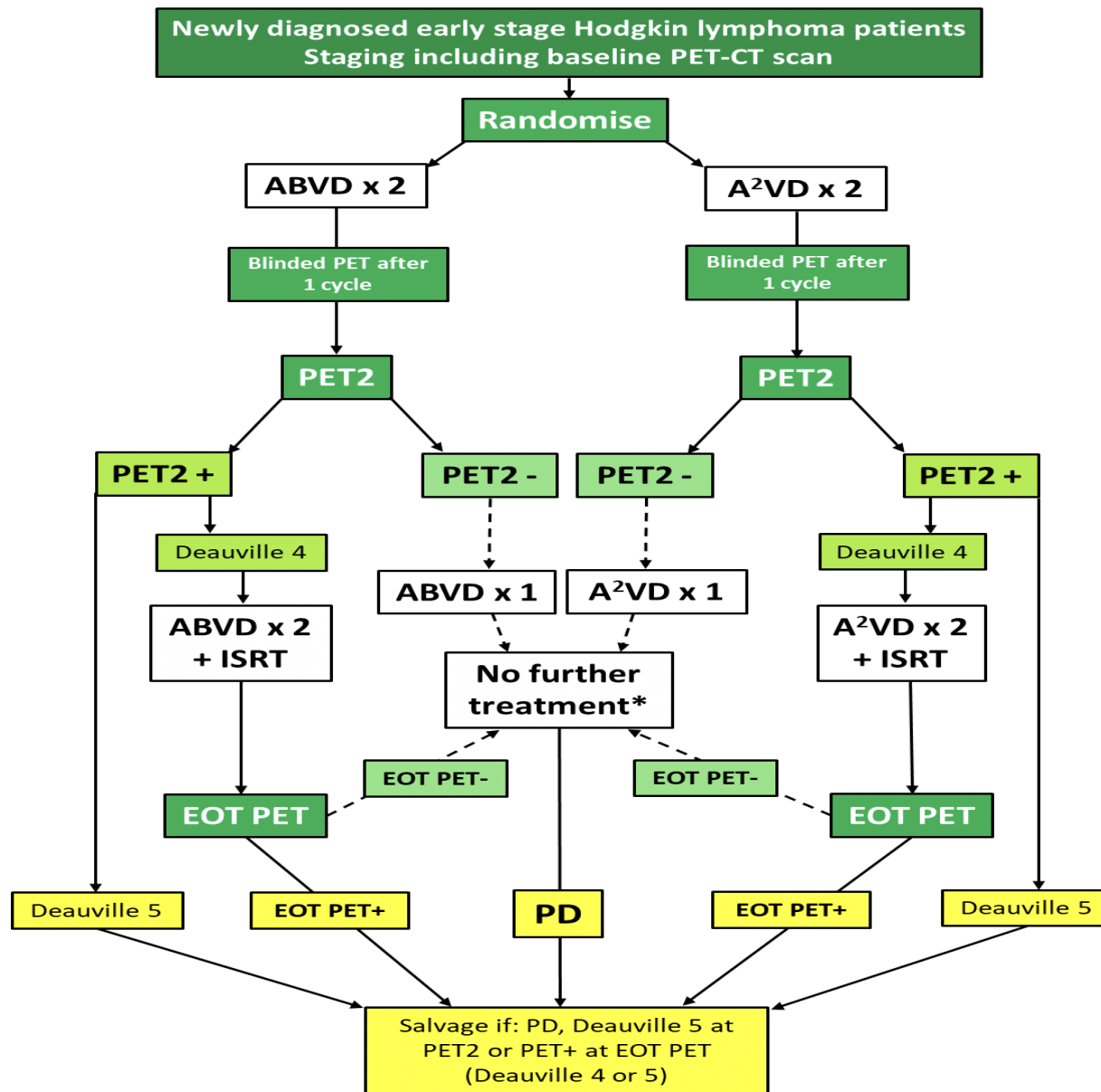
# Conclusions

- Short-course BV-AVD x 4 in ES UF HL remains a highly active regimen at 4 years, even in the absence of consolidative RT in patients with bulk.
  - Late events are rare.
  - Baseline MTV and PET2 had significant associations with PFS.
- 
- There is no Phase III data supporting this claim.....

# Brentuximab Vedotin vs. ISRT

For ESHL

Pts with single nodal mass >5cm, may get ISRT if determined prior to enrollment



RADAR STUDY:  
INTERNATIONAL  
PHASE III STUDY  
STAGE I/IIA; < 10  
CM

# Reasonable Conclusions for ESHL

- In patients receiving only 2 cycles of chemo, ISRT is essential
- In patients receiving 3 cycles of chemo with a negative PET, if nodal mass is between 5-10 cm; RT should be considered
- In patients receiving 4 cycles of ABVD (score 1-2); Use of RT is not necessary; score 3 in masses > 5 cm I would consider radiation
- In patients receiving BV-AVD for 4 cycles; use of RT is not necessary if PET 2 and 4 are negative and if somehow insurance will approve this treatment
- In patients receiving full course ABVD there is no role for RT if PET and PET 6 are negative

I want to thank the HL patients for  
participating in these research studies  
over the past 32 years

as well as the Lymphoma faculty at MSKCC where I spent 25 years of my life and lymphoma  
faculty at SCCC

## Lymphoma Service-Sylvester Comprehensive Cancer Center, University of Miami Health System

- Izidore Lossos
- Juan Alderuccio
- Alvaro Alencar
- Georgio Pongas
- Michelle Stanchina
- Juan Ramos
- Joe Rosenblatt
- Jonathan Schatz
- Craig Moskowitz



We see 1000 lymphoma consults each year

