

IN PURSUIT OF *YOUR CURE*.™

# Hodgkin Lymphoma 2024

3 questions that need answering

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A Cancer Center Designated by the  
National Cancer Institute



# The winds of change are here-The Scorpions

## Stage III/IV

BV+AVD x 6<sup>8</sup>

RATHL (ABVDx6)<sup>6,9</sup>

escBEACOPP x 4<sup>11</sup>

BreCADD x 4<sup>12</sup>

Nivo+AVD x 6<sup>13</sup>

### Key:

 I have not given at UM

 Should we still give BV-AVD?

<sup>1</sup>Engert, et al. NEJM 2010; <sup>2</sup>Radford, et al. NEJM 2015; <sup>3</sup>Straus, et al. Blood 2018; <sup>4</sup>Eich, et al. JCO 2010; <sup>5</sup>Tresckow, et al. JCO 2012; <sup>6</sup>Johnson, et al. NEJM 2016; <sup>7</sup>Borchmann, et al. Lancet Onc. 2021; <sup>8</sup>Ansell, et al. N Engl J Med (2022) 387;4: 310-320; <sup>9</sup>LaCasce et al, JCO 2022; <sup>10</sup>Evens AM, et al. JCO 2018; <sup>11</sup>Borchmann, et al. Lancet 2017; 390:2790-802; <sup>12</sup>Borchmann, et al. Lugano 2023; <sup>13</sup>Herrera, et al. Lugano 2023; <sup>14</sup>Pallawi, et al. Lugano 2023

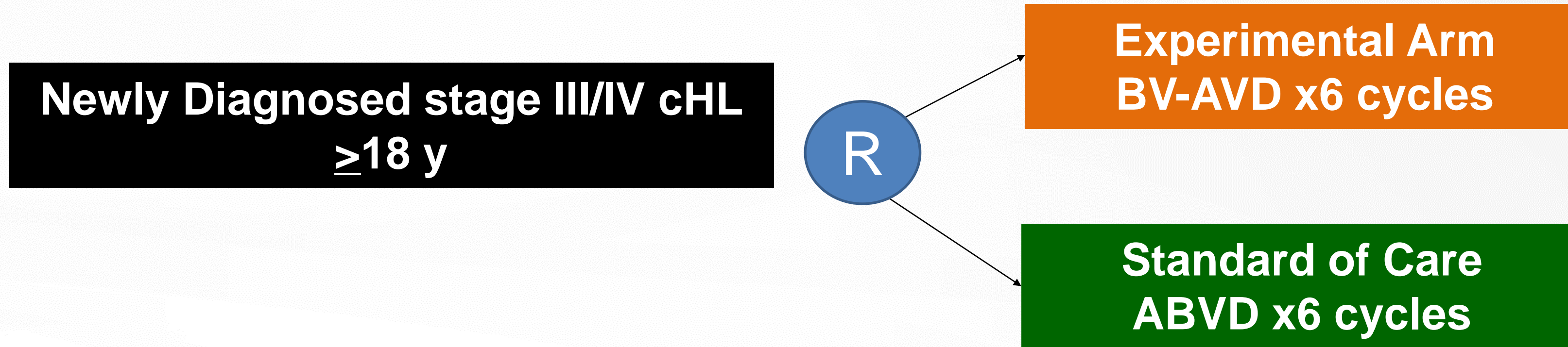




# **The Phase III studies**



# Phase III Frontline HL (ECHELON-1)



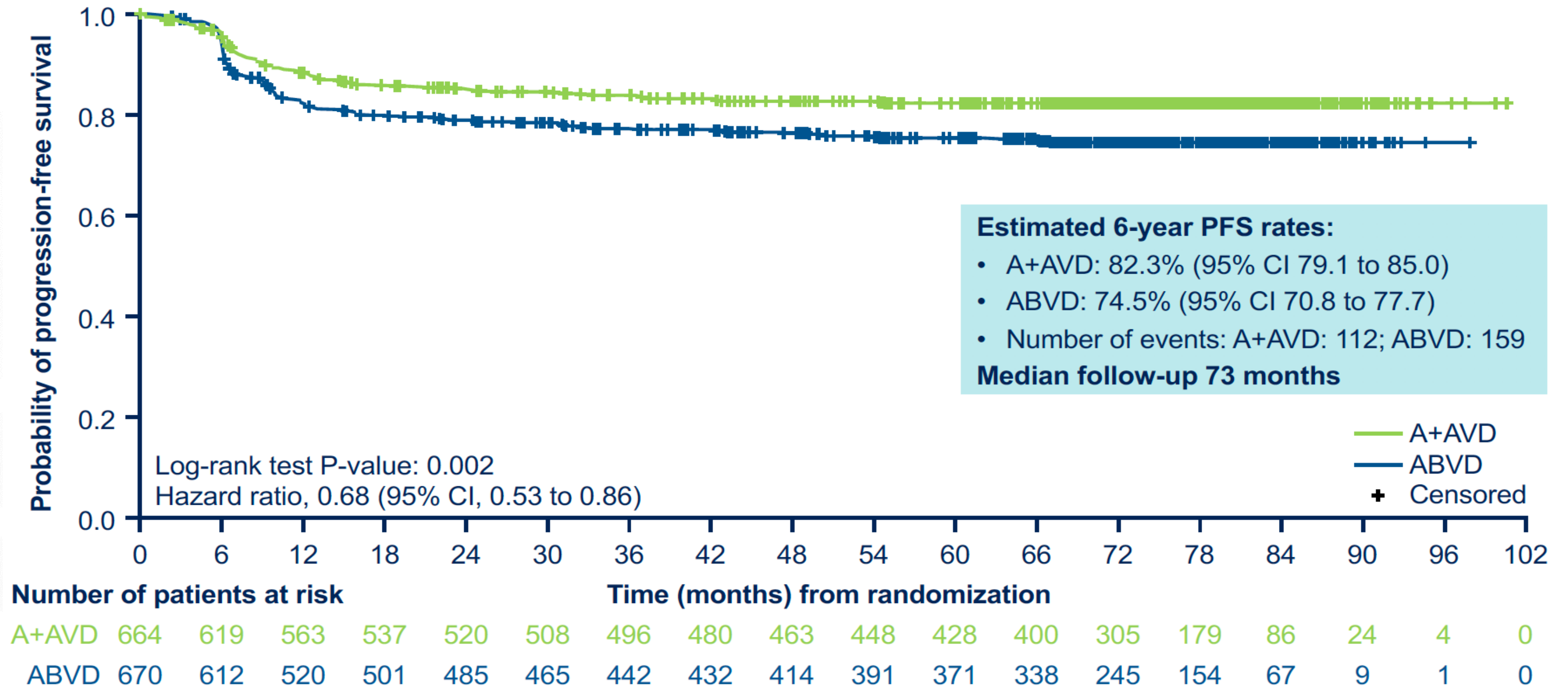
N=1334

Primary endpoint: improvement in 2 year modified PFS (mPFS)

Secondary Outcome Measures: Overall survival

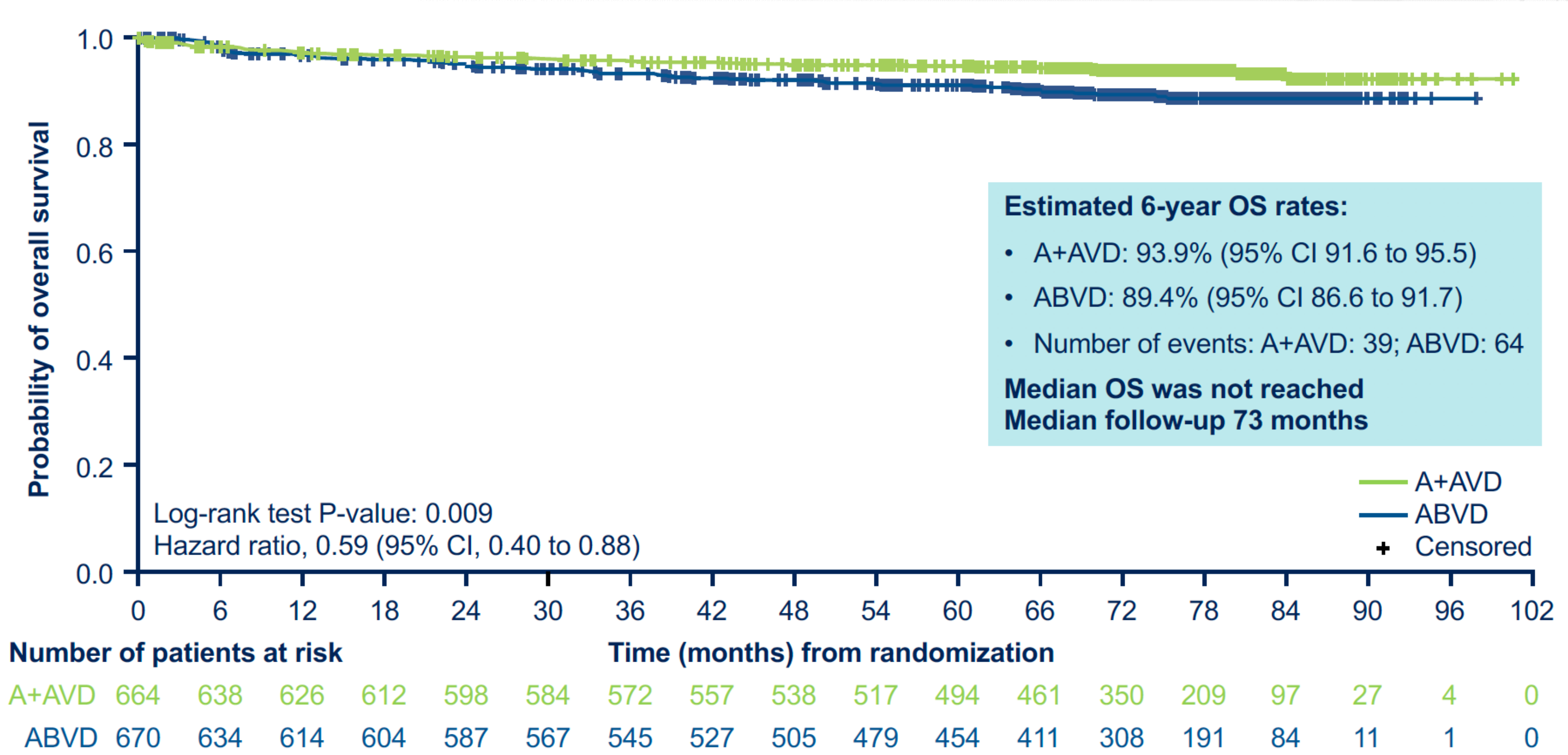


# ECHELON-1: 6-year follow-up shows sustained PFS benefit of BV-AVD





# ECHELON-1: At 6 years, BV-AVD significantly improved overall survival





# BV-AVD: G-CSF required and ongoing

# neuropathy

Events	BV+AVD n=662	ABVD n=659
<b>Febrile neutropenia</b>		
No G-CSF	119/579 (21%)	49/616 (8%)
Received G-CSF	9/83 (11%)	3/43 (7%)
<b>Peripheral neuropathy</b>		
Any grade	443 (67%)	286 (43%)
<b>Ongoing @ 5 years</b>	<b>127 (19%)</b>	<b>59 (9%)</b>
Grade 1	74 (11%)	39 (2%)
Grade 2	38 (6%)	16 (2%)
Grade 3	14 (2%)	4 (<1%)
Grade 4	1 (<1%)	
<b>Pulmonary toxicity</b>		
Any grade	12 (2%)	44 (7%)
Grade ≥3	5 (<1%)	21 (3%)



# HD21 – BrECADD vs BEACOPP

Drug	Day	BEACOPP <sup>1</sup> Dose (mg/m <sup>2</sup> )	BrECADD Dose (mg/m <sup>2</sup> )	Potential <u>improvement</u>
Bleomycin	8	10	-	<u>lung tox</u>
Etoposide	1-3	<b>200</b>	<b>150</b>	<u>hem tox, transfusion frequency</u>
<u>Doxorubicin</u>	1	<b>35</b>	<b>40</b>	
<u>Cyclophosphamide</u>	1	<b>1250</b>	<b>1250</b>	
<u>Vincristine</u>	8	1.4	-	<u>neuropathy</u>
Brentuximab vedotin	1	-	<b>1.8 mg/kg</b>	
Procarbazine	1-7	100	-	<u>gonadal tox, sAML/MDS</u>
<u>Prednisone</u>	1-14	40	-	<u>weight, bone, infections</u>
Dacarbazine	2-3	-	<b>250</b>	
Dexamethasone	1-4	-	<b>40</b>	



# HD21 – BrECADD vs BEACOPP

## Randomisation

2 x eBEACOPP

2 x BrECADD

## PET2/CT Staging

PET2 neg.

PET2 pos.

PET2 neg.

PET2 pos.

2x  
eBEACOPP

4x  
eBEACOPP

2x  
BrECADD

4x  
BrECADD

End of therapy staging: PET-positive RD consolidative radiotherapy, PET-negative FU

PET-neg = Deauville Score 1-3

Co-primary endpoints:

-Non-inferiority PFS

-Reduction in treatment related morbidity



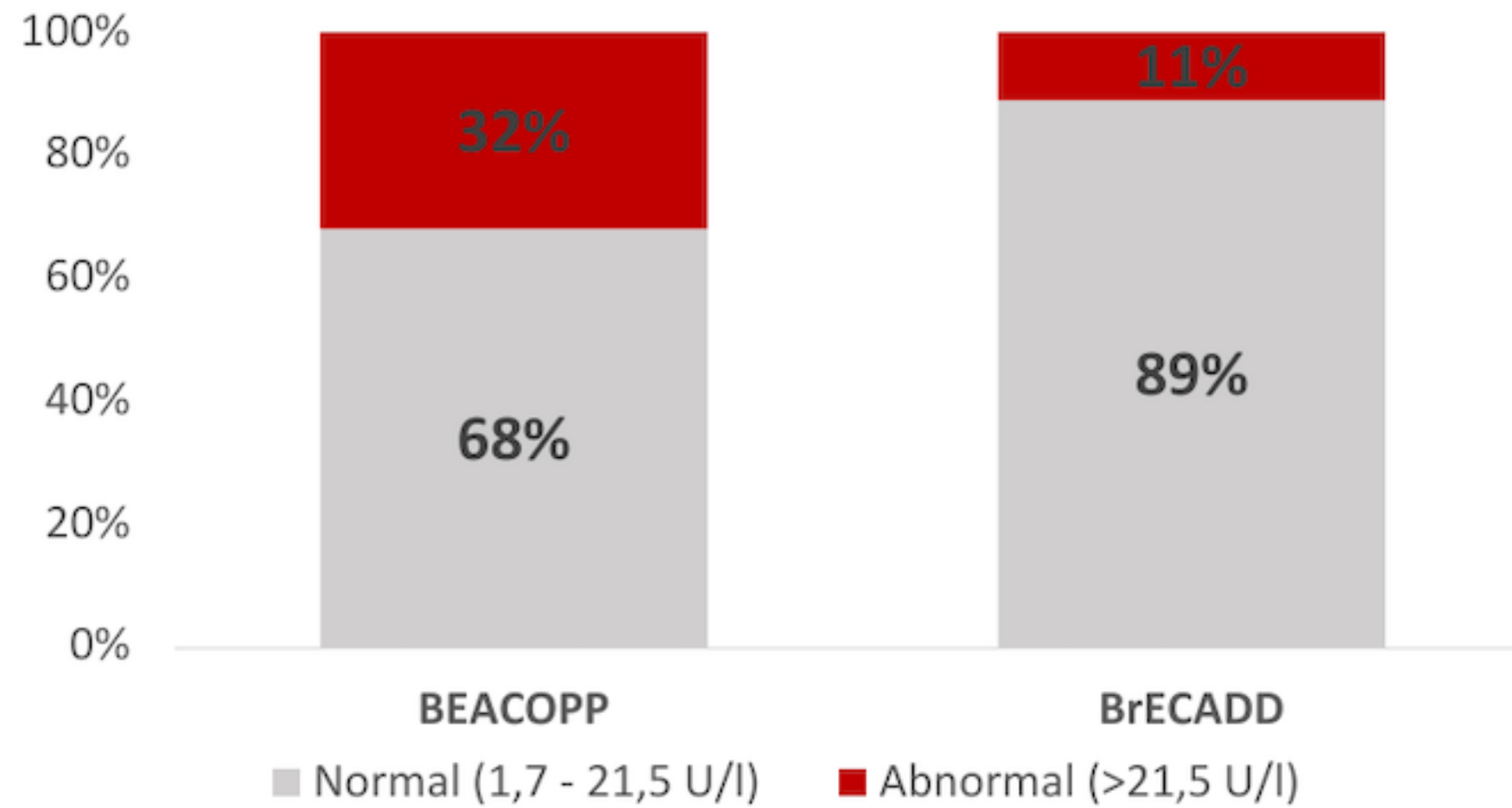
# HD21 – BrECADD vs BEACOPP: Toxicity

<u>Toxicity</u>	eBEACOPP (%)	BrECADD (%)
<u>Anemia (at least 1 red cell transfusion)</u>	22	8
<u>Thrombocytopenia (at least 1 platelet transfusion)</u>	13	6
	eBEACOPP (%)	BrECADD (%)
<u>Sensory PNP</u>		
All grades	49	38
Grade 2	14	6
Grade 3	2	1
	eBEACOPP (%)	BrECADD (%)
<u>Treatment related mortality</u>	< 1%	0%

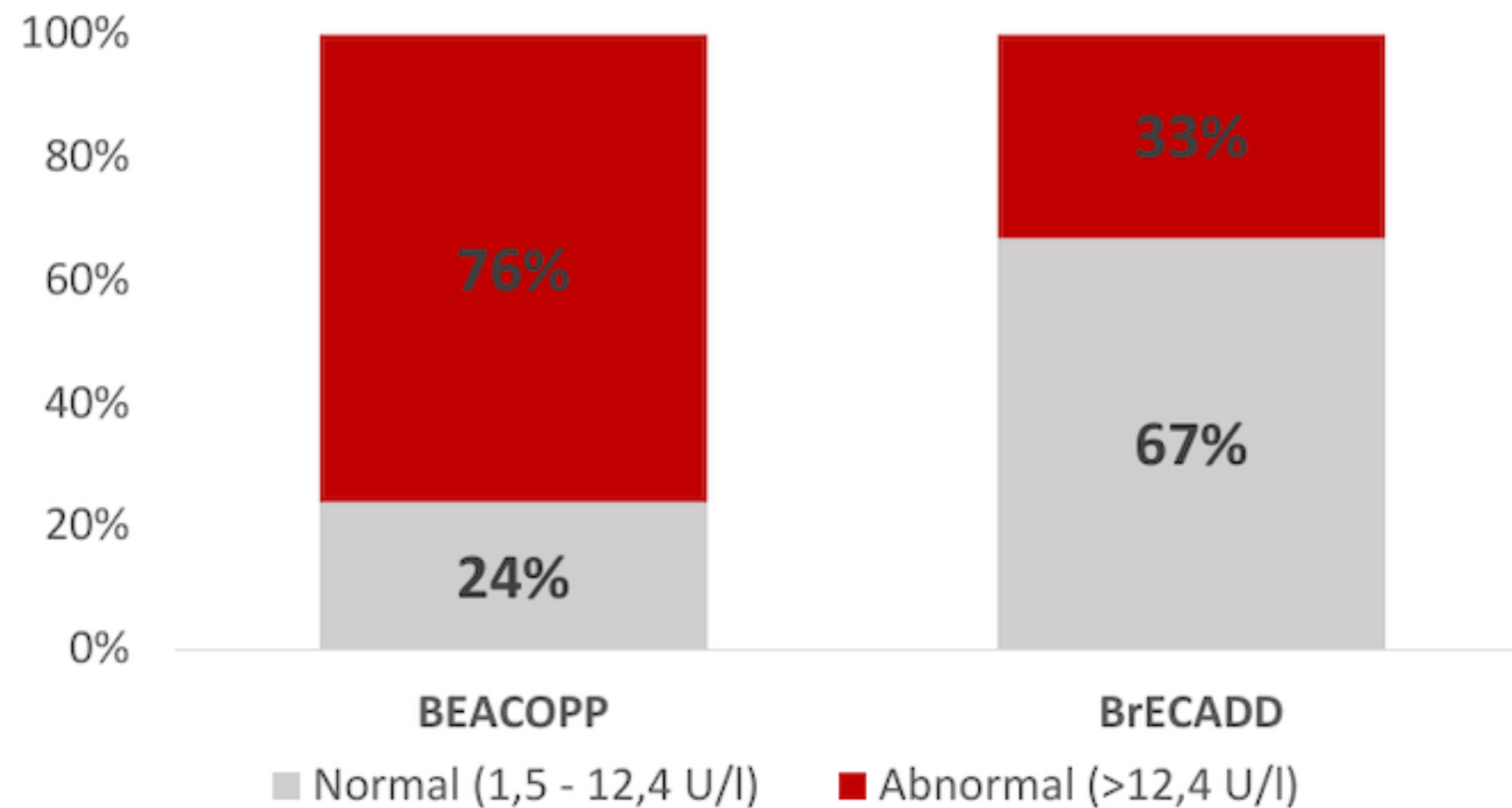


# HD21 – BrECADD vs BEACOPP: Fertility

**Figure 1** Recovery of FSH in females (18-39), mean Fu12-Fu24



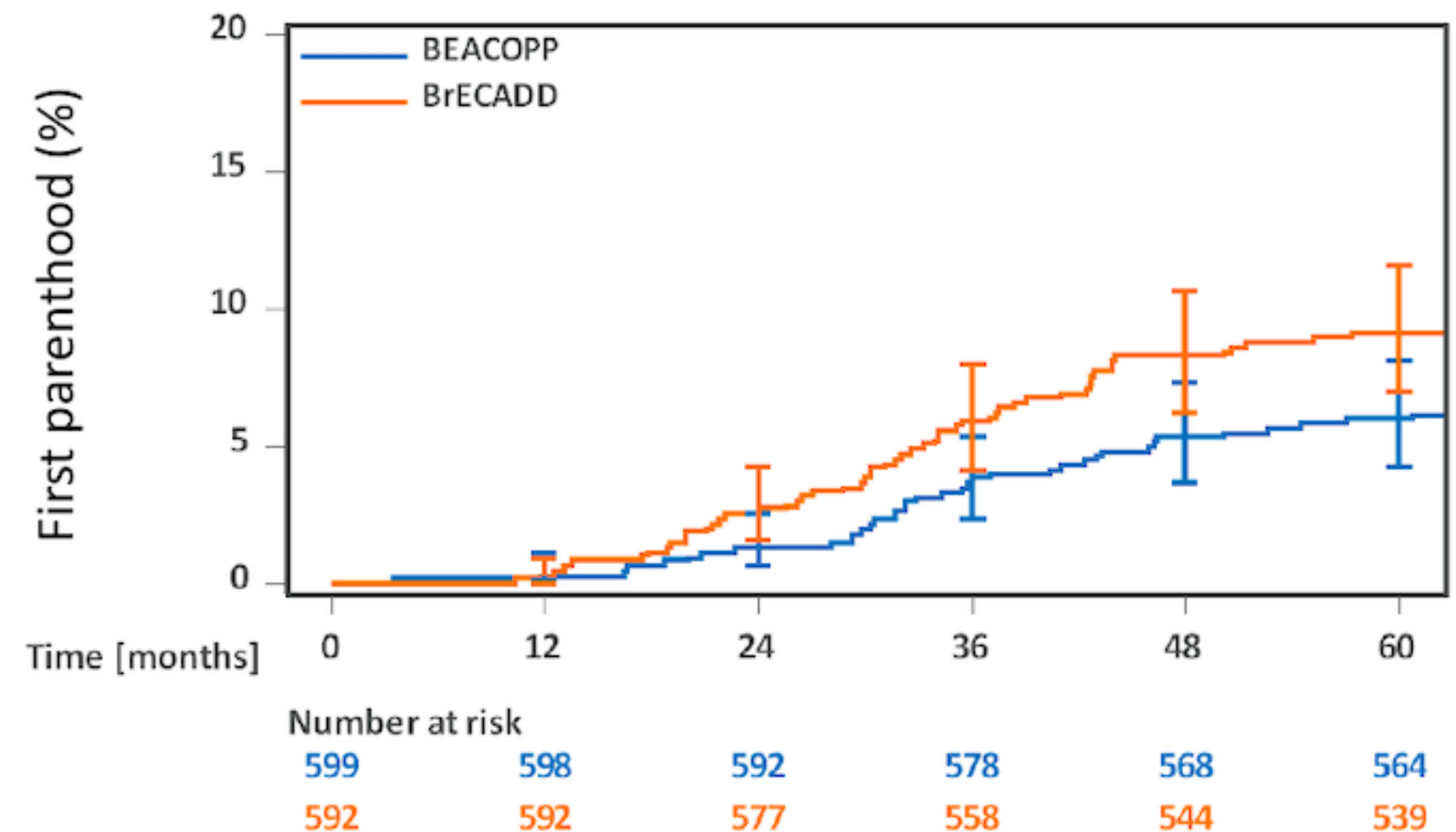
**Figure 2** Recovery of FSH in males (18-49), mean Fu12-Fu24



**Table 1** Pregnancy rate (%) at 46 months of median follow up

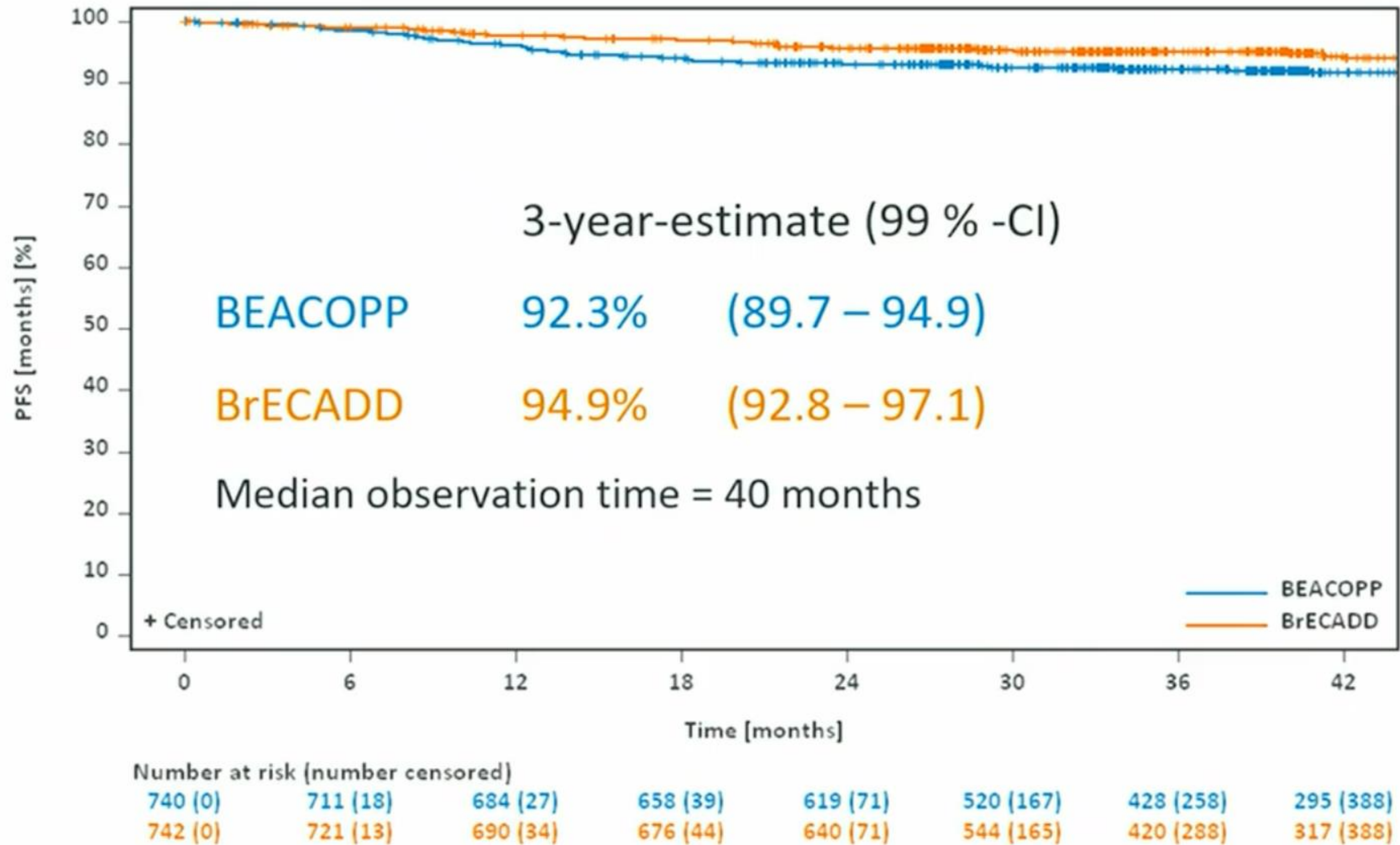
Pregnancy rate (%)	Male (n= 704)	Female (n=496)
BEACOPP	2.8	15.9
BrECADD	6.3	16.8

**Figure 3** Cumulative Incidence plot of first parenthood in HD21





# GHSB HD21: BrECADD is non-inferior to escBEACOPP

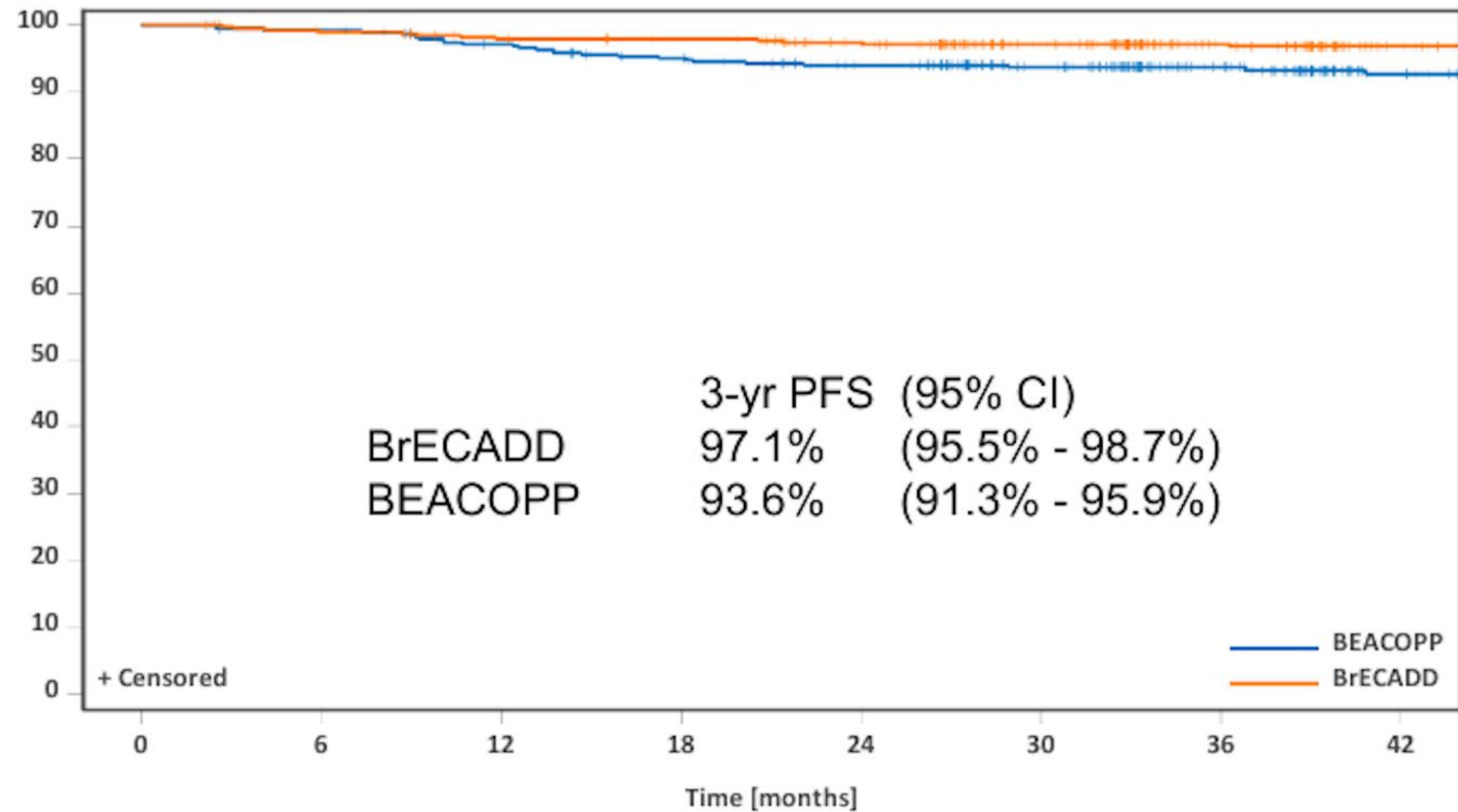




# BrECADD: 3-year PFS

PET-2 neg: 59% of pts

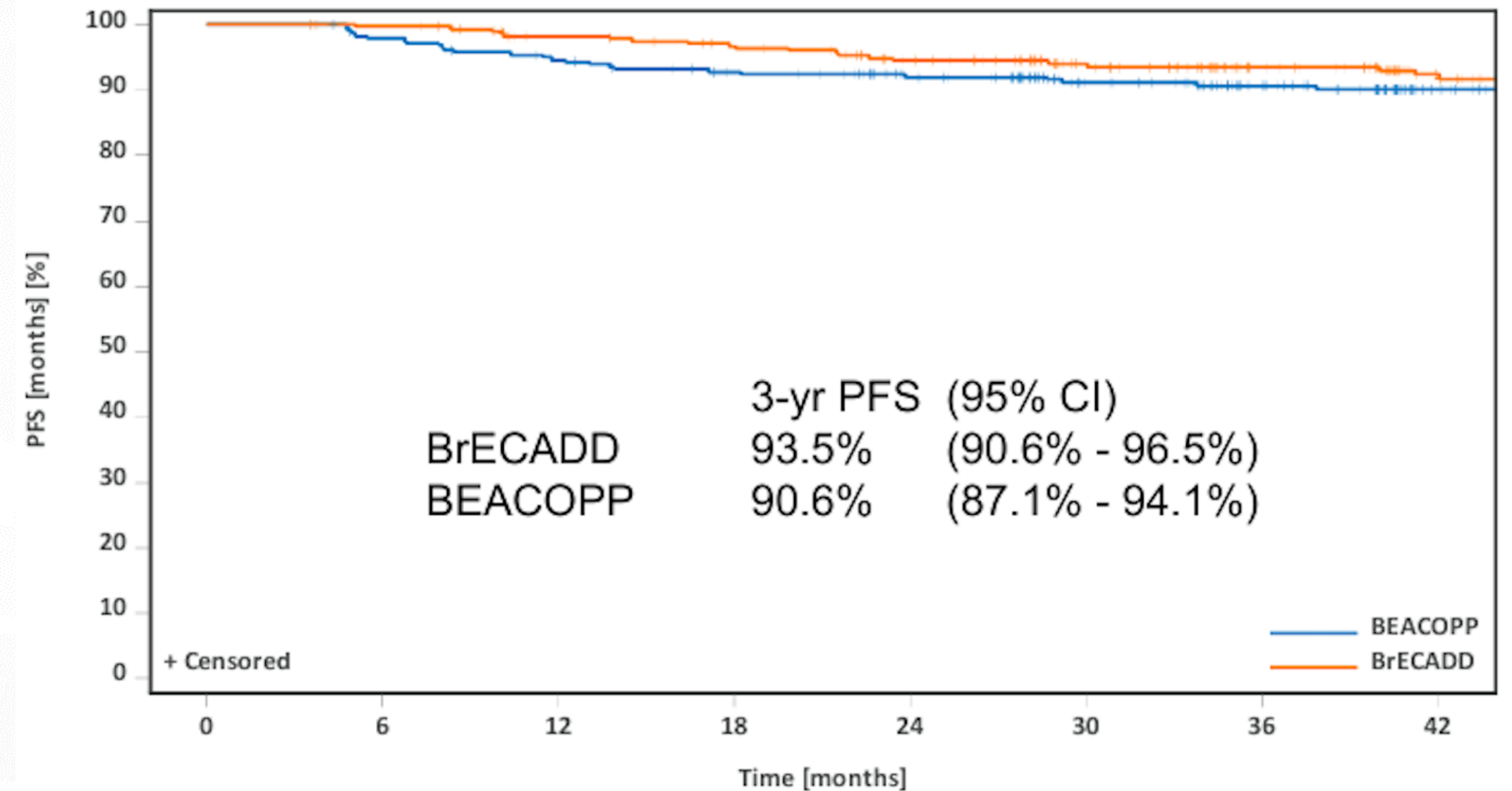
**Figure 3** PFS in PET2-neg patients according to treatment arm



Number at risk (number censored)		0		6		12		18		24		30		36		42	
BrECADD	435 (0)	431 (1)	415 (8)	400 (14)	378 (31)	319 (89)	255 (153)	171 (235)									
BEACOPP	432 (0)	423 (5)	410 (13)	405 (18)	385 (36)	324 (96)	241 (179)	173 (246)									

PET-2 pos: 41% of pts

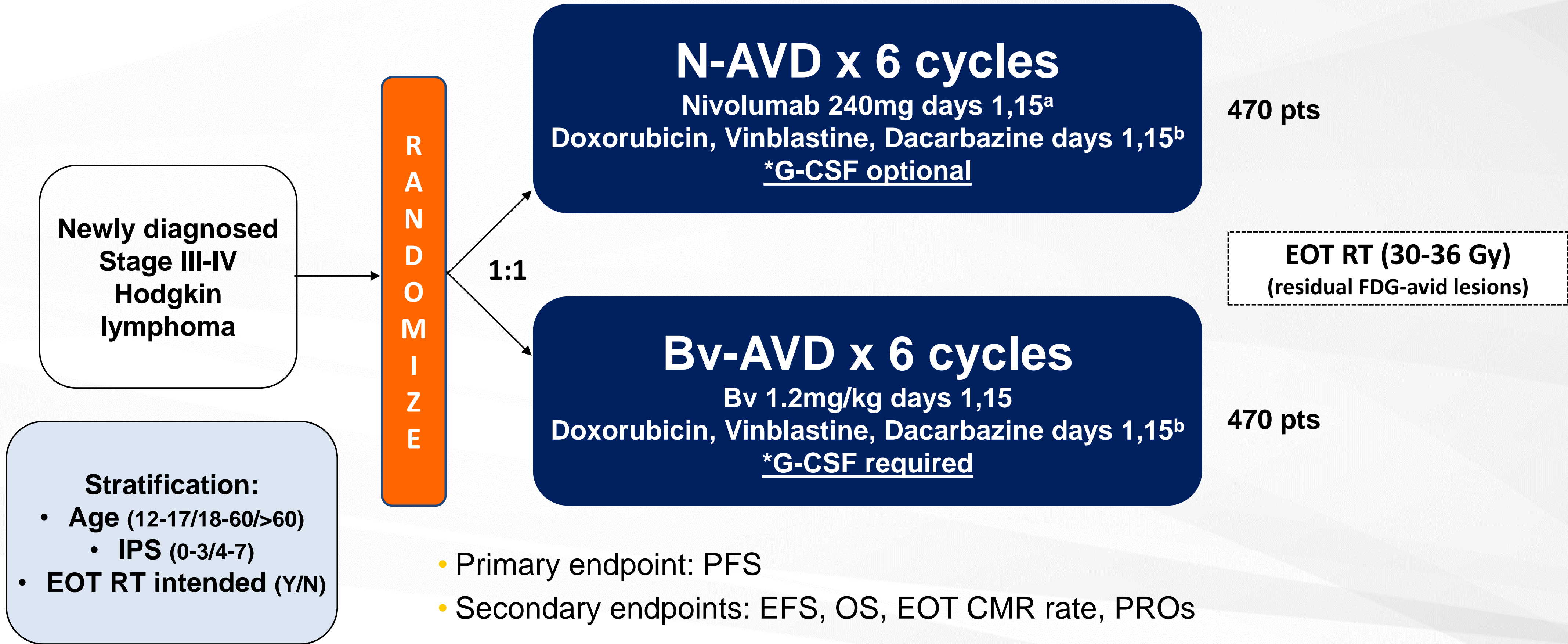
**Figure 4** PFS in PET2-pos patients according to treatment arm



Number at risk (number censored)		0		6		12		18		24		30		36		42	
BrECADD	280 (0)	272 (2)	261 (4)	250 (10)	234 (24)	194 (62)	166 (89)	119 (135)									
BEACOPP	284 (0)	281 (2)	265 (14)	257 (18)	242 (27)	211 (57)	171 (96)	139 (126)									



# S1826 Study Design





# Baseline Characteristics

Baseline characteristics	N-AVD n=489 N (%)	Bv-AVD n=487 N (%)
<b>Age, median (range)</b>	<b>27 (12-83)</b>	<b>26 (12-81)</b>
<b>12-17 years</b>	<b>120 (25%)</b>	<b>117 (24%)</b>
<b>18-60 years</b>	<b>323 (66%)</b>	<b>323 (66%)</b>
<b>≥ 61 years</b>	<b>46 (9%)</b>	<b>47 (10%)</b>
<b>Female Sex</b>	<b>218 (45%)</b>	<b>213 (44%)</b>
<b>Race</b>		
<b>White</b>	<b>375 (77%)</b>	<b>364 (75%)</b>
<b>Black</b>	<b>57 (12%)</b>	<b>56 (11%)</b>
<b>Asian</b>	<b>11 (2%)</b>	<b>17 (3%)</b>
<b>Other/Unknown</b>	<b>46 (9%)</b>	<b>50 (10%)</b>
<b>Hispanic</b>	<b>68 (14%)</b>	<b>59 (12%)</b>



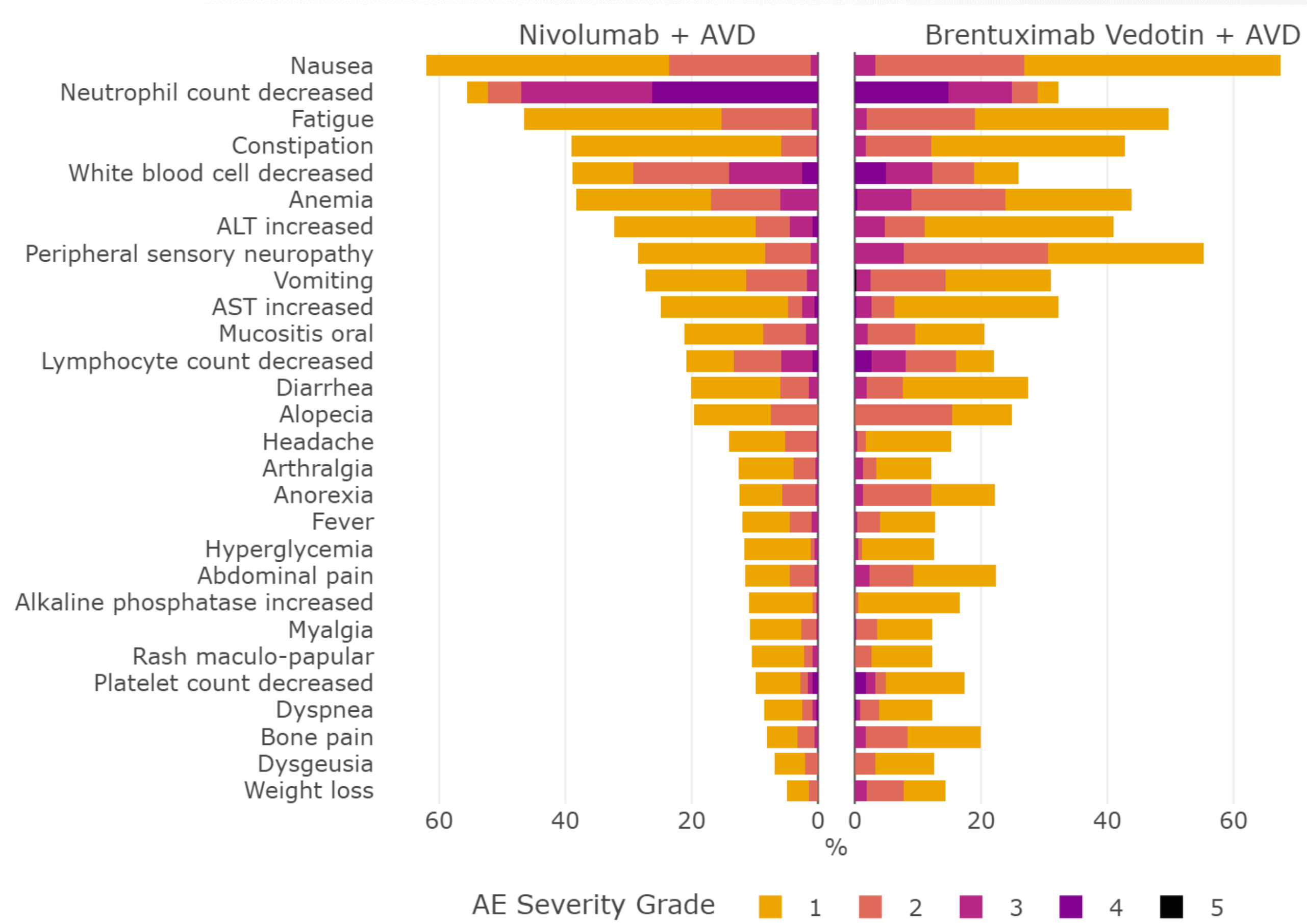
# S1826 Baseline Characteristics

Baseline characteristics	N-AVD n=489 N (%)	Bv-AVD n=487 N (%)	Baseline characteristics	N-AVD n=489 N (%)	Bv-AVD n=487 N (%)
<b>Age, median (range)</b>	<b>27 (12-83)</b>	<b>26 (12-81)</b>	<b>Stage</b>		
12-17 years	120 (25%)	117 (24%)	III	187 (38%)	167 (34%)
18-60 years	323 (66%)	323 (66%)	<b>IV</b>	<b>301 (62%)</b>	<b>317 (65%)</b>
≥ 61 years	46 (9%)	47 (10%)	Not reported	1 (0.2%)	3 (1%)
<b>Female Sex</b>	<b>218 (45%)</b>	<b>213 (44%)</b>	<b>B symptoms present</b>	<b>286 (58%)</b>	<b>274 (56%)</b>
<b>Race</b>			<b>IPS Score</b>		
White	375 (77%)	364 (75%)	0-3	331 (68%)	330 (68%)
<b>Black</b>	<b>57 (12%)</b>	<b>56 (11%)</b>	4-7	158 (32%)	157 (32%)
Asian	11 (2%)	17 (3%)	<b>Bulky disease &gt; 10cm</b>	<b>155 (32%)</b>	<b>131 (27%)</b>
Other/Unknown	46 (9%)	50 (10%)	<b>HIV+</b>	<b>10 (2%)</b>	<b>5 (1%)</b>
<b>Hispanic</b>	<b>68 (14%)</b>	<b>59 (12%)</b>			

**Representative study, inclusive of high-risk pts**

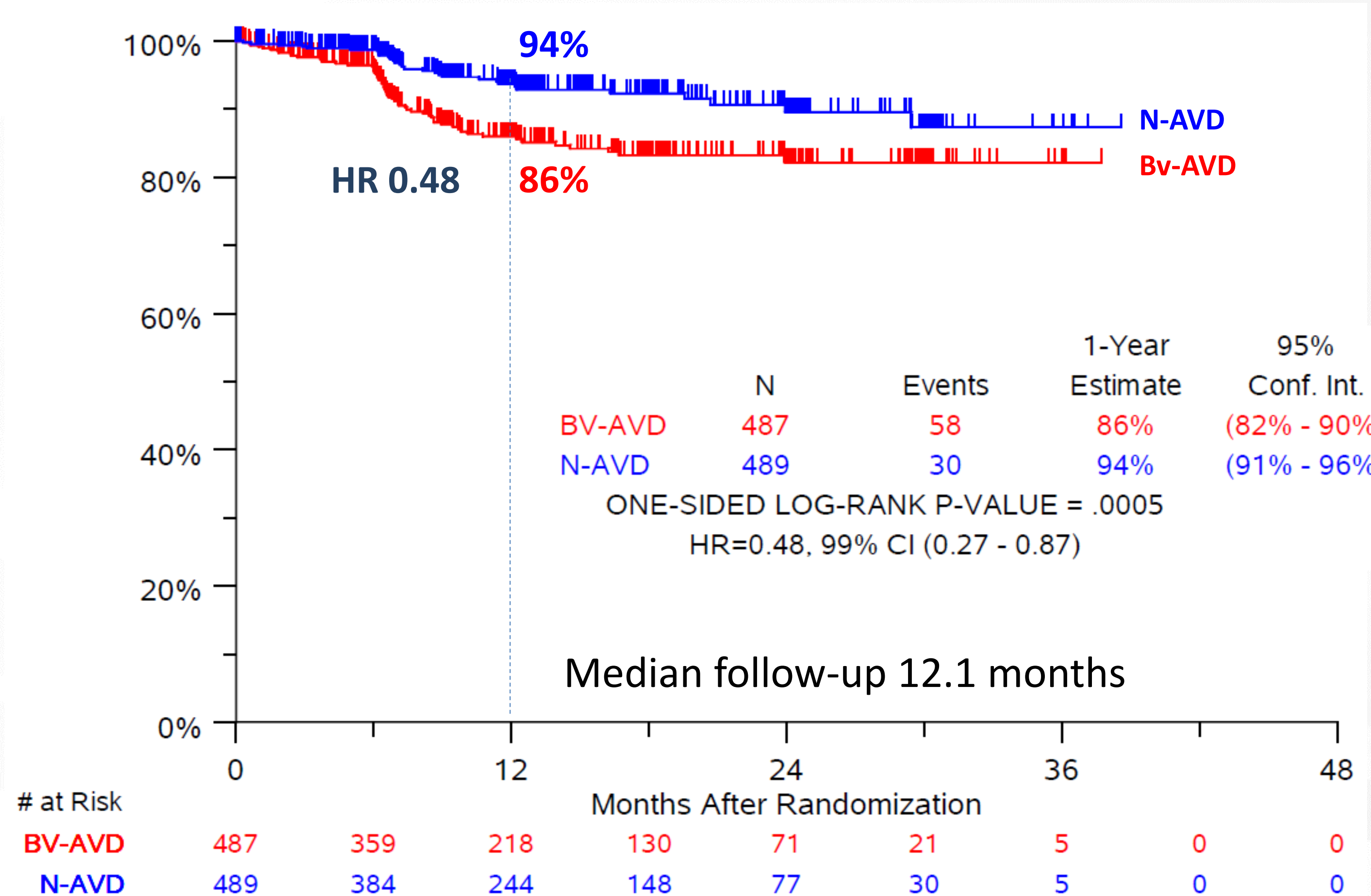


# Adverse Events in $\geq 10\%$





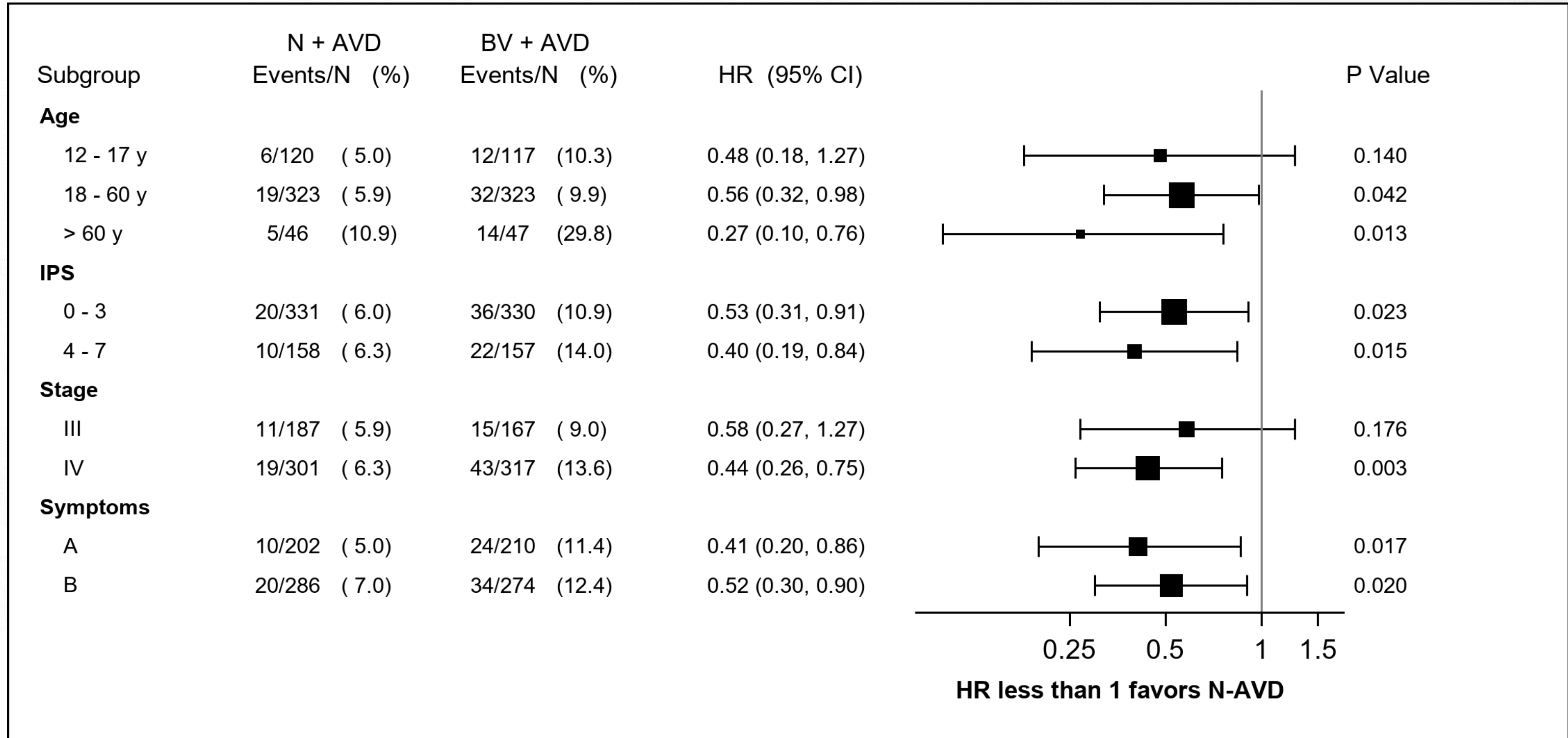
# N-AVD improves PFS compared to Bv-AVD



**1-year PFS**  
**N-AVD 94%**  
**Bv-AVD 86%**



# PFS benefit consistent across subgroups



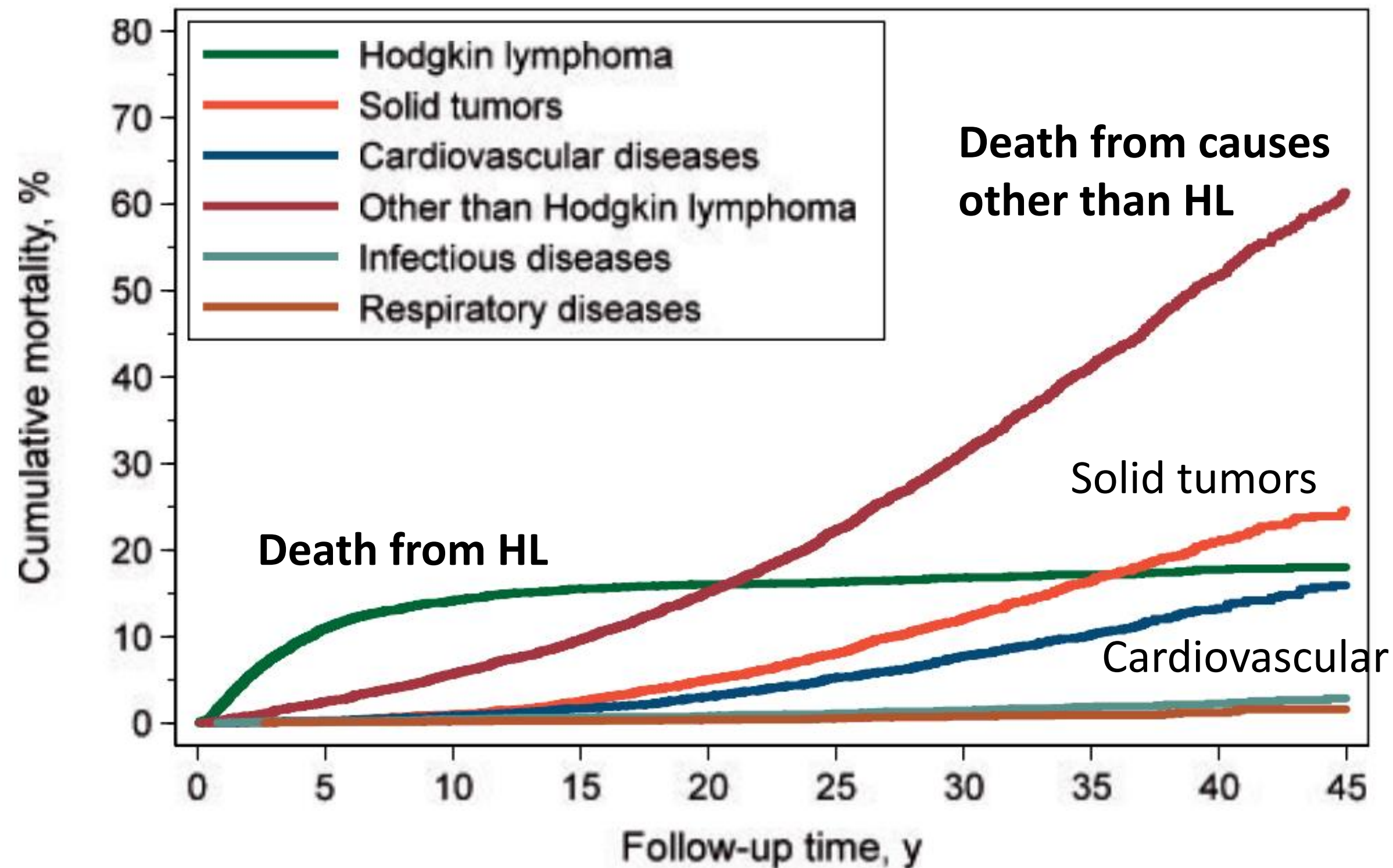


# Lets compare

- **ABVD**-Best Approach-PET-adapted therapy, Echelon 1 on Deauville 5 could change tx
  - No one wants to give Bleomycin
  - It is cheap! 6 months of tx
  - But other treatments are better
- **BV-AVD**-OS advantage over ABVD; G-CSF is mandated;
  - Neuropathy; in my opinion more toxic than ABVD
  - 6 months of therapy
  - I believe interim PET is useful
  - Clear step forward
- **BRECADD**-equivalent for BEACOPP and less toxic
  - 60 percent of pts are treated for only 3 months; interim PET 2 +/- do the same
  - The schedule is cumbersome, 4 yr f/u at ASCO
  - Results are superior to BV-AVD
- **N-AVD**
  - Well tolerated, interim PET data unknown
  - With short f/u superior to BV-AVD
  - Not superior to BRECADD
  - 6 months of tx



# Choose therapy wisely



## Late effects of **modern** therapy...

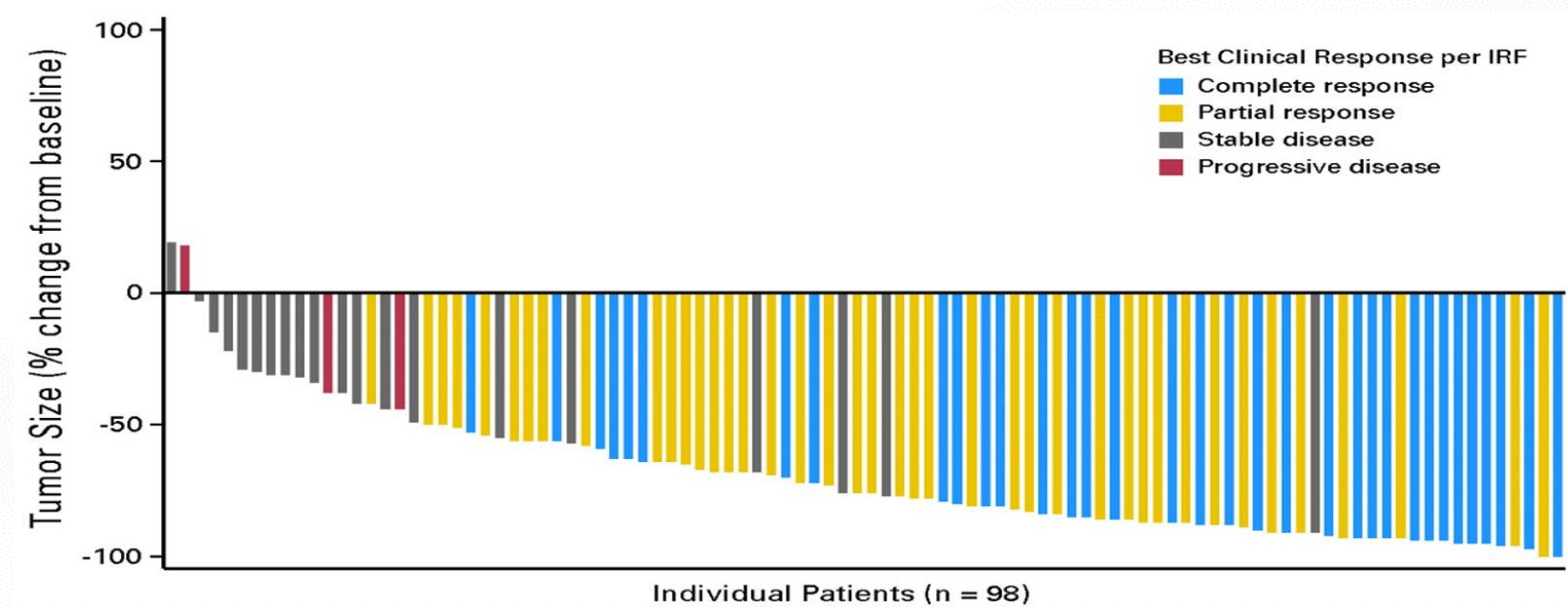
- 5 years after BV-AVD: peripheral neuropathy persists in 19%
- 10-15% hypothyroidism after anti-PD-1 therapy; I would not administer to anyone with an underlying immune related disorder

de Vries, et al. JNCI J Natl Cancer Inst (2021) 113(6): 760-769

Straus, et al. Lancet Haematol (2021) 8: e410-21

Moskowitz AJ, et al. J Clin Oncol (2021) 39:3109-3117

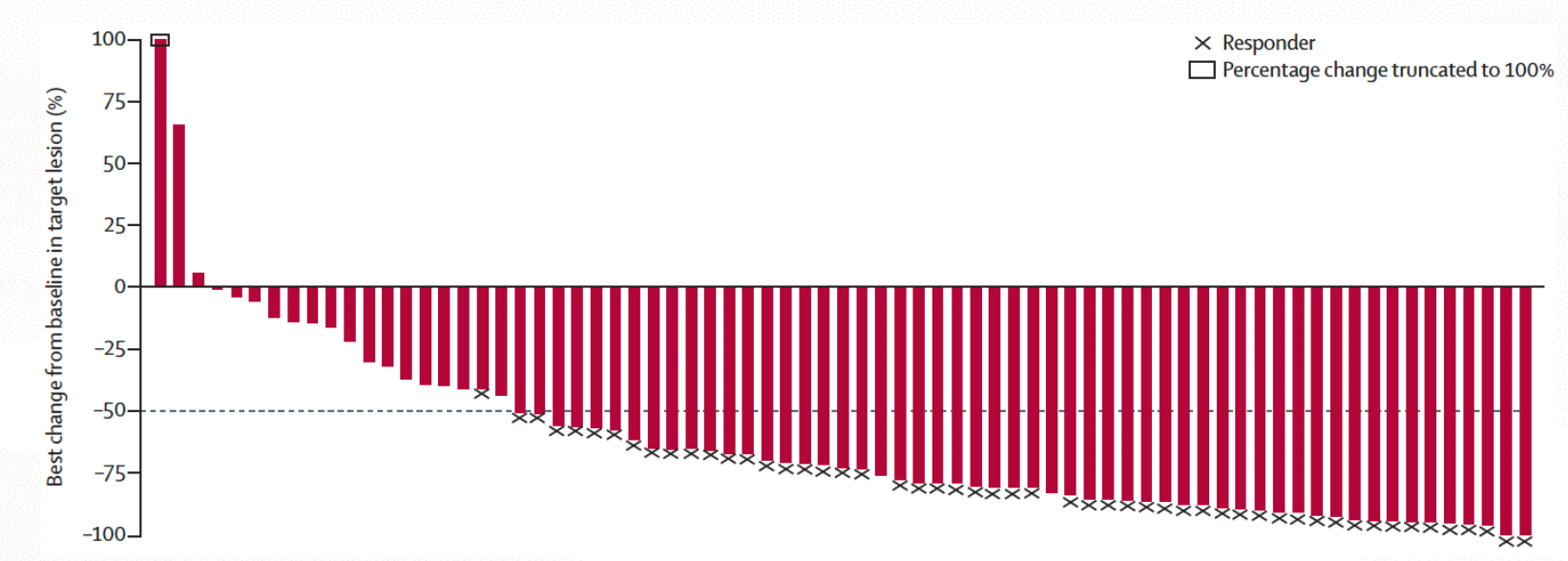




**Efficacy in relapsed/refractory setting:**

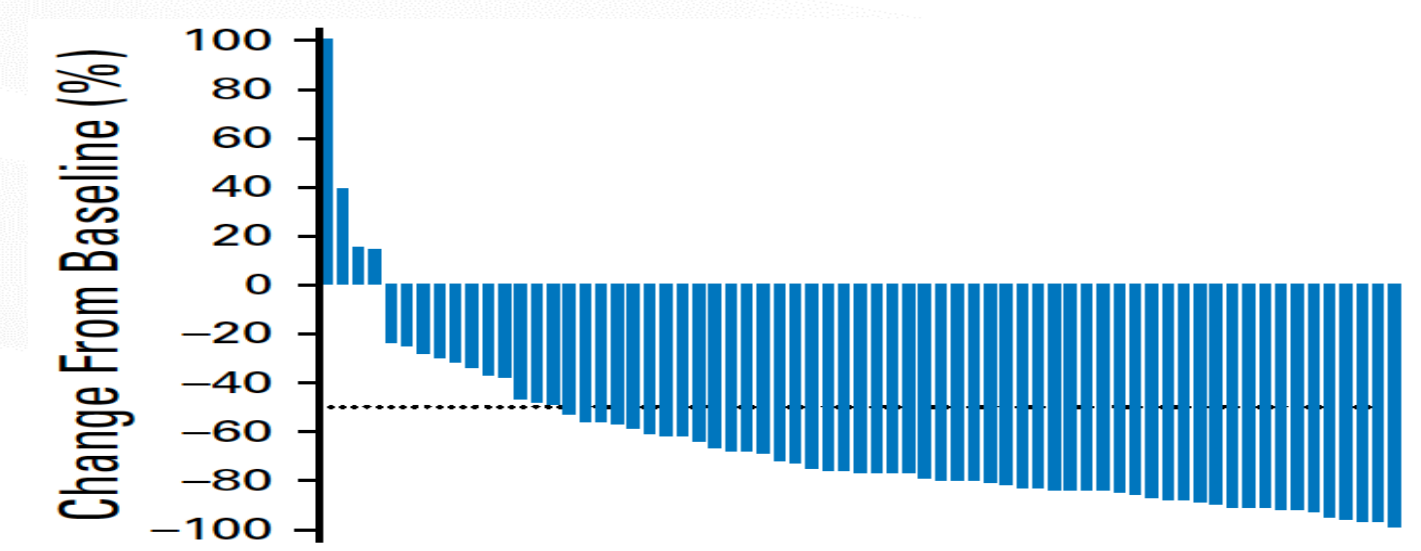
## Brentuximab vedotin

76% ORR  
36% CR



## Nivolumab

66% ORR  
22% CR



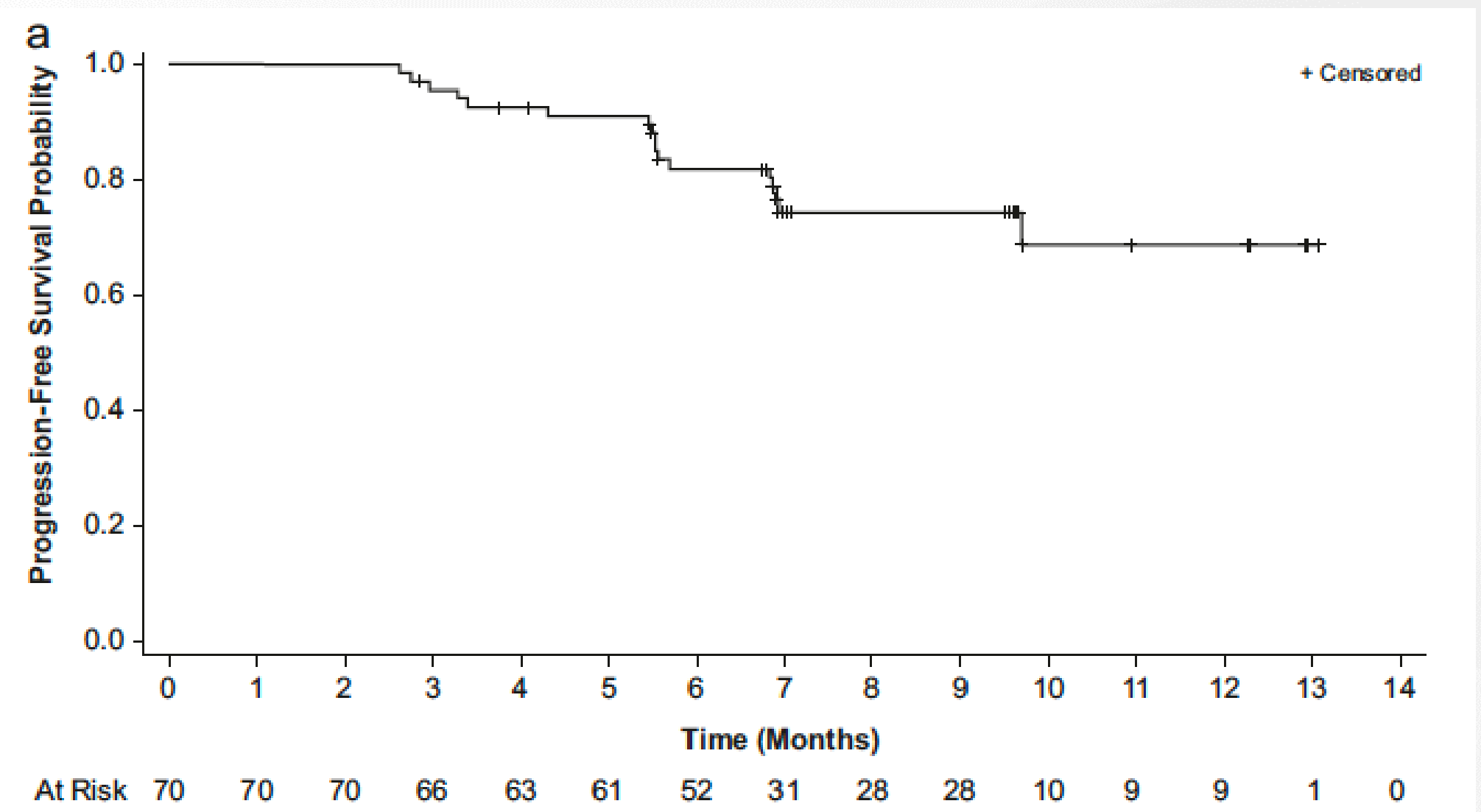
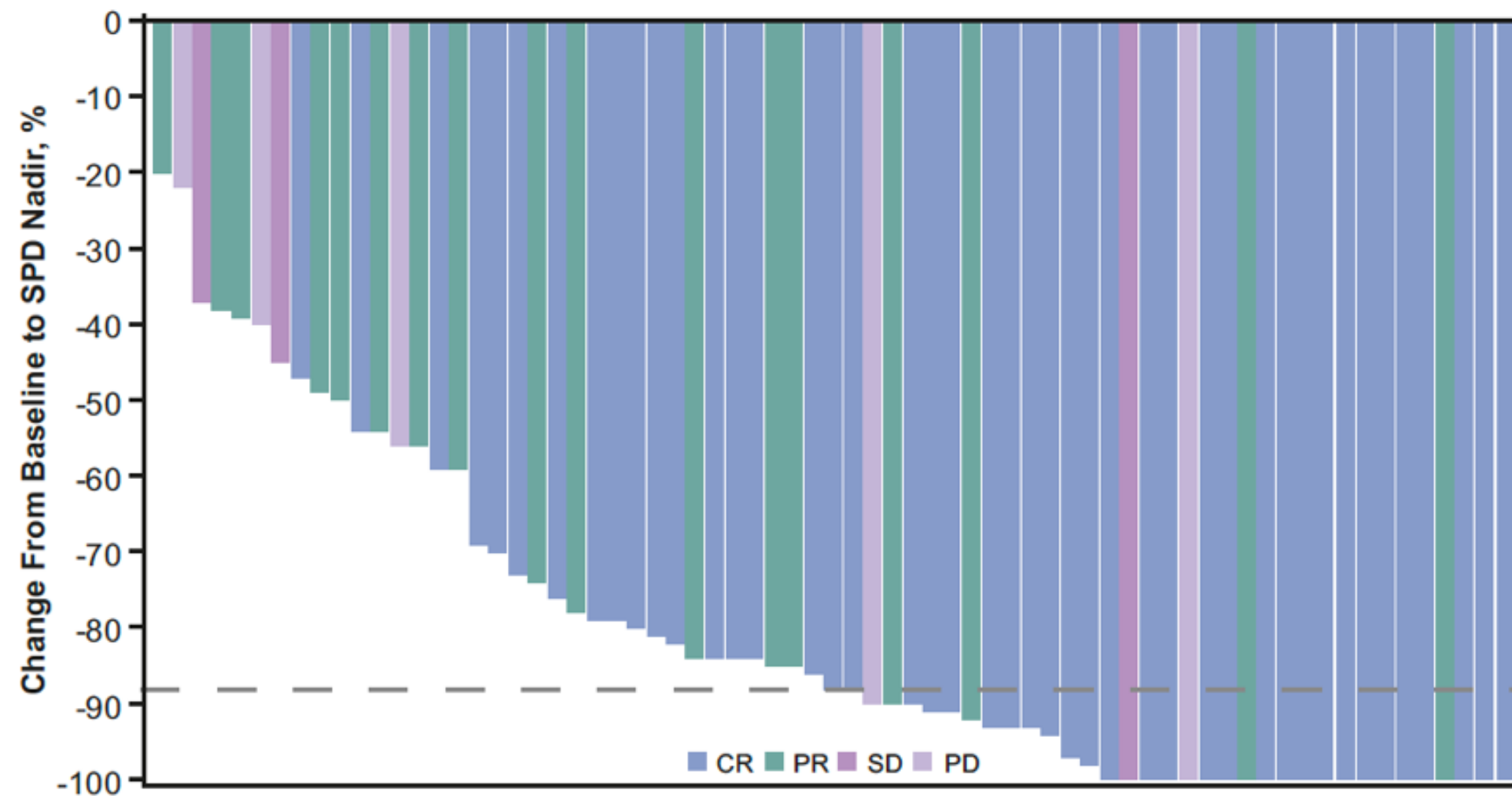
## Pembrolizumab

72% ORR  
22% CR

Younes, et al. *JCO* 2012  
Younes, et al. *Lancet Oncol* 2016  
Chen, et al. *JCO* 2017



# Tislelizumab clinical data



## Song et al (2020) Leukemia

- 70 pts, median age 33y, median prior lines 3, mostly BV naïve, 52% refractory, 82% not suitable ASCT
- Median FU 9.8mo; 24% discontinued Rx
- ORR: 87%; CRR: 63% (52% CRR in primary refractory)
- Infusion reactions 36% (1 G3); 4 pts discontinued due to irAE (3 pneumonitis; 1 renal injury)



**Can we tailor treatment of the patient, if no clinical trial is available**

**Active drugs – able to overcome risk**

**Ability to stratify patients into risk groups**

**Accurate markers of interim treatment response**

**We need to give less treatment; 6 cycles is too many!**



# IPS: International Prognostic Score for Advanced Stage HL (works for ABVD)

## Factors

Albumin <4 g/dl

Hgb <10.5 g/dl

Male

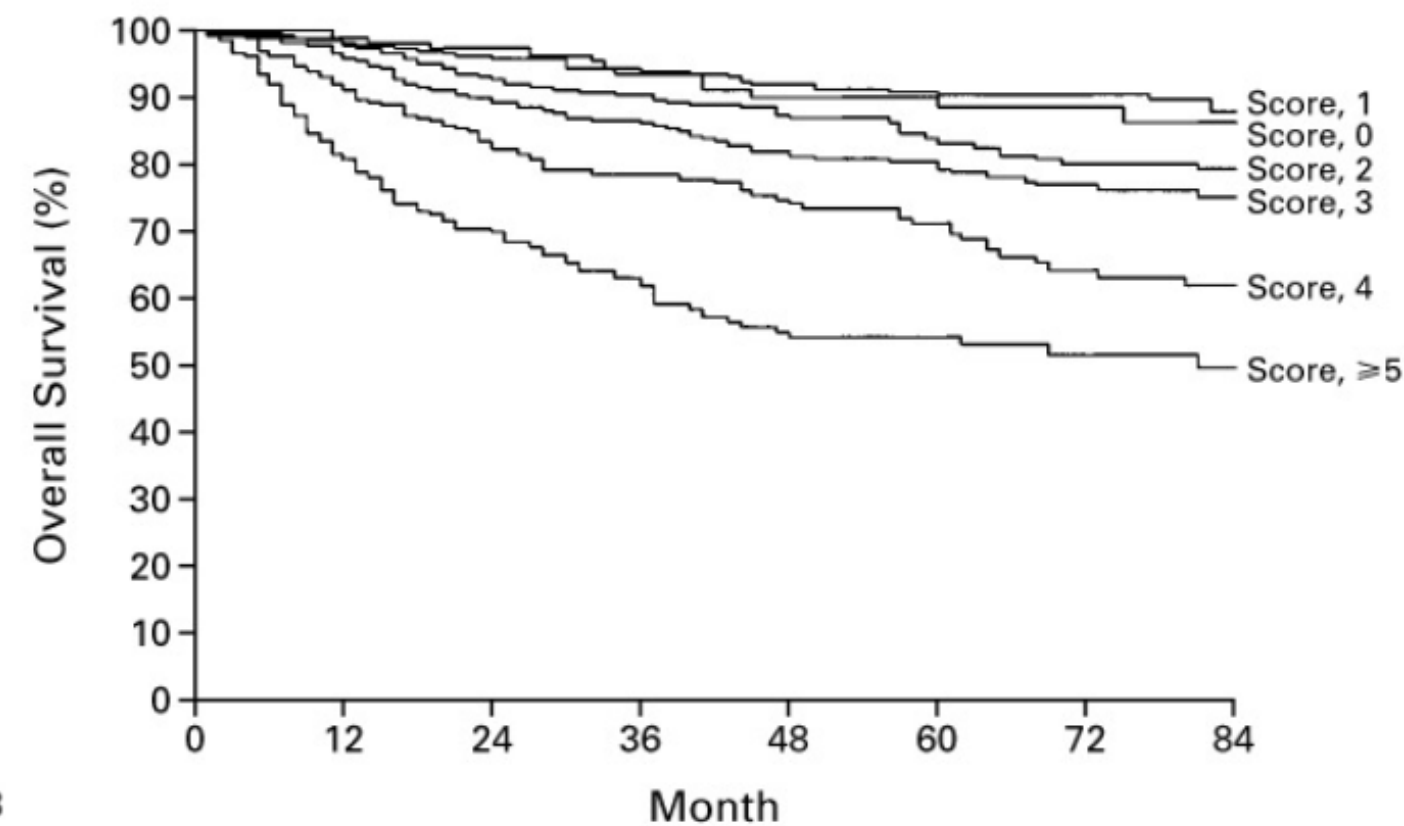
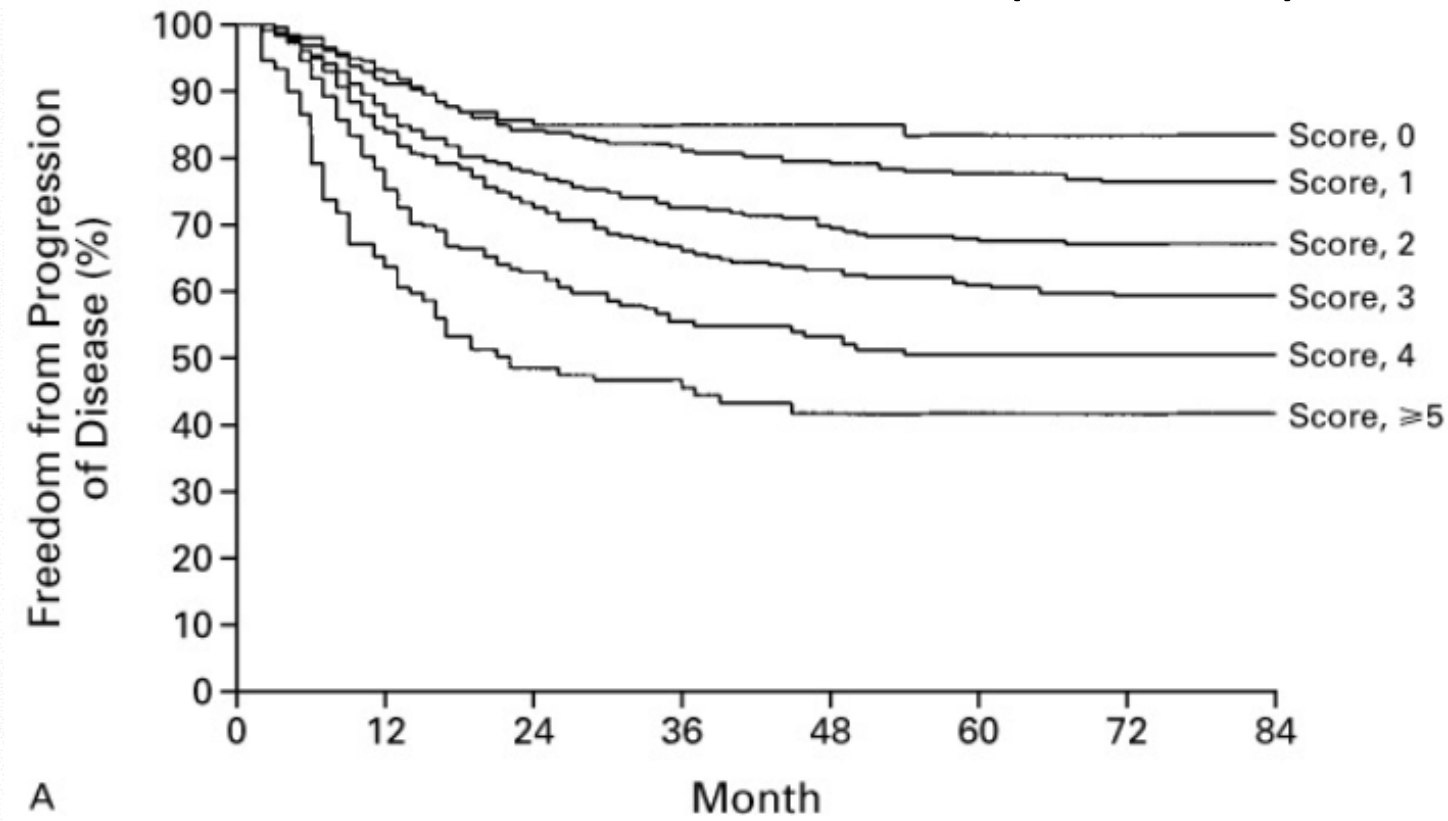
Age ≥ 45

Stage IV

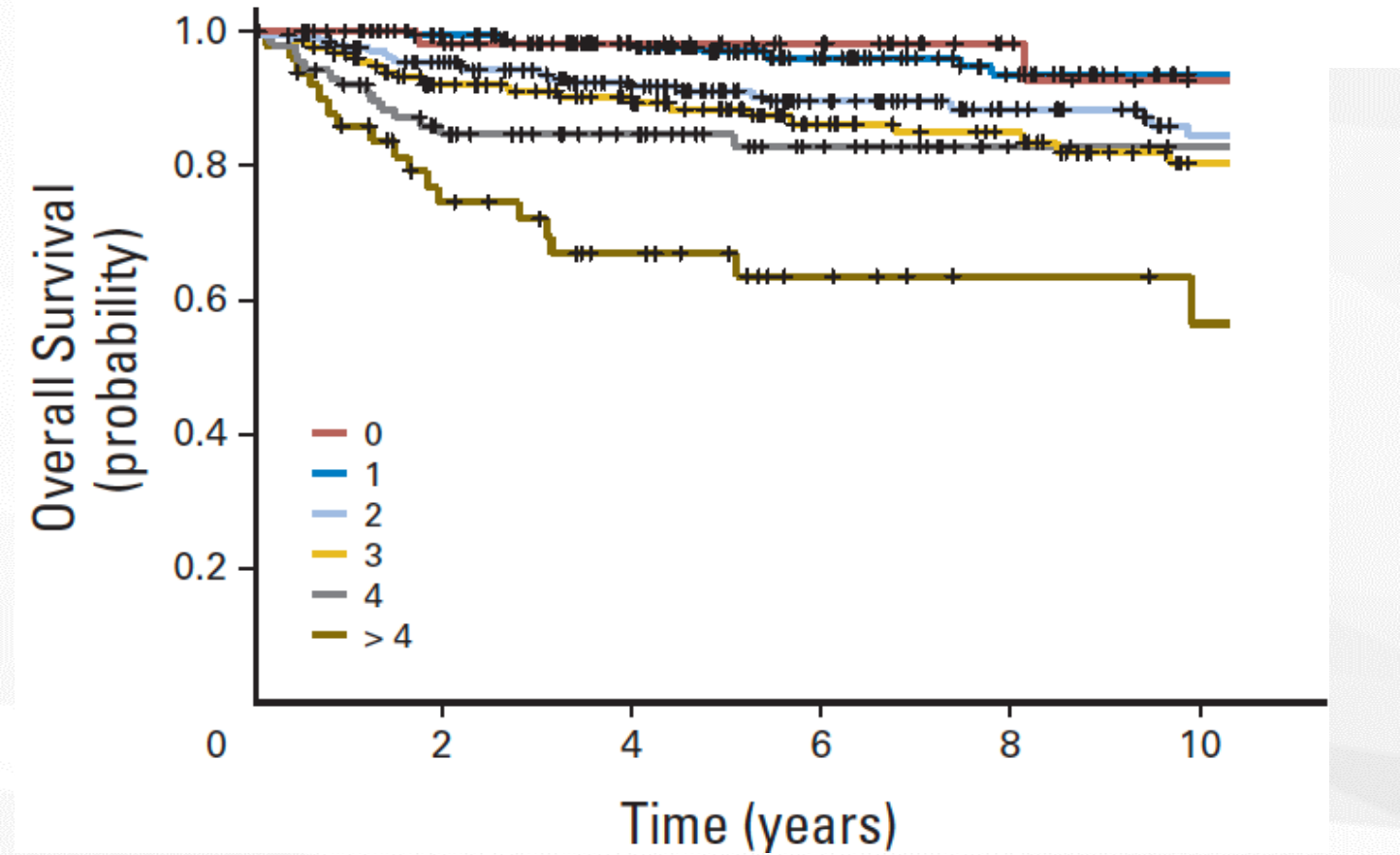
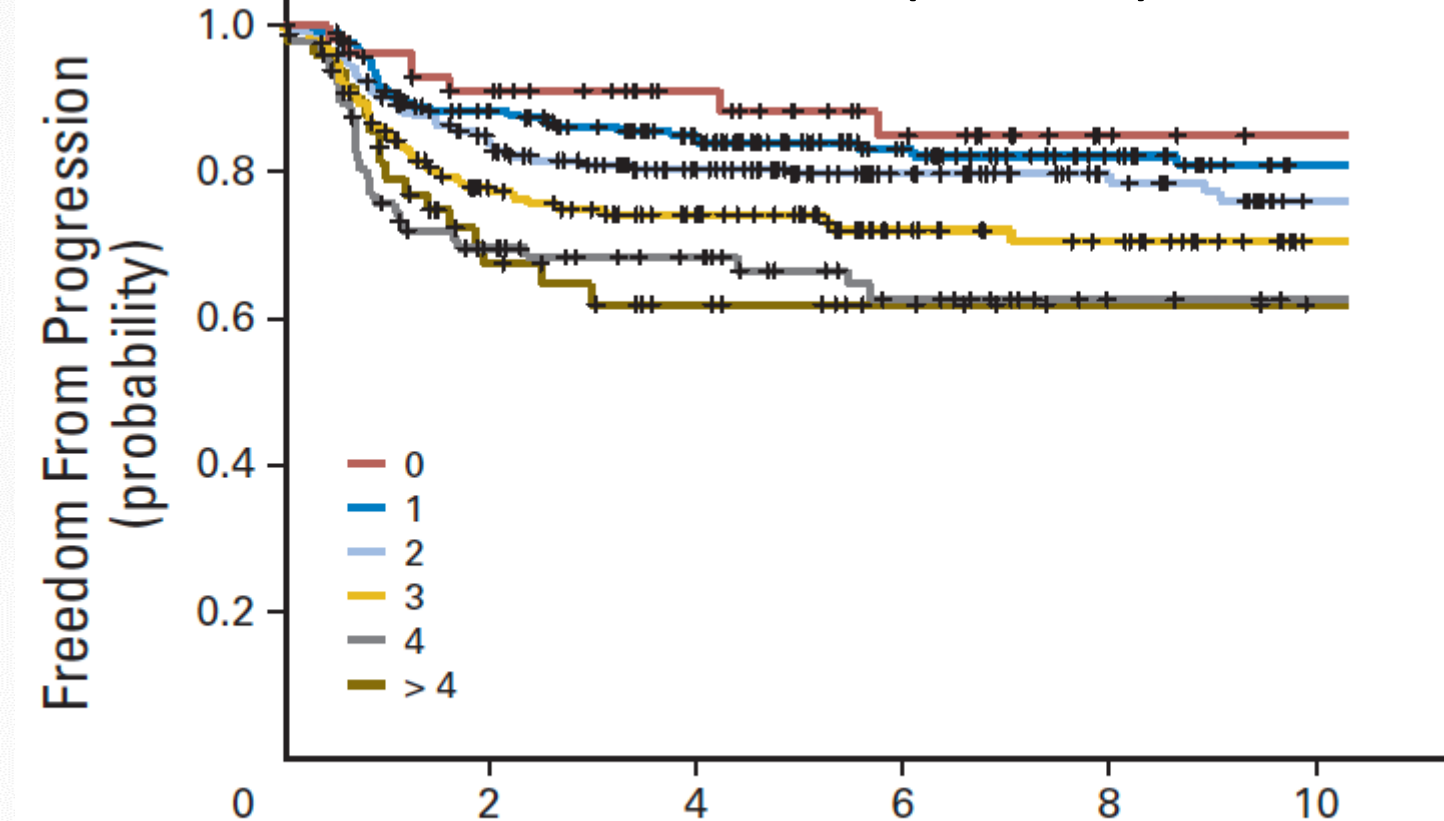
WBC ≥ 15

ALC < 600 or < 8%

Hasenclever, 1998 (n=5141)



BCCA, 2012 (n=740)





# ADVANCED STAGE HODGKIN LYMPHOMA INTERNATIONAL PROGNOSTIC INDEX (A-HIPI)

Validation using continuous variables and modern databases

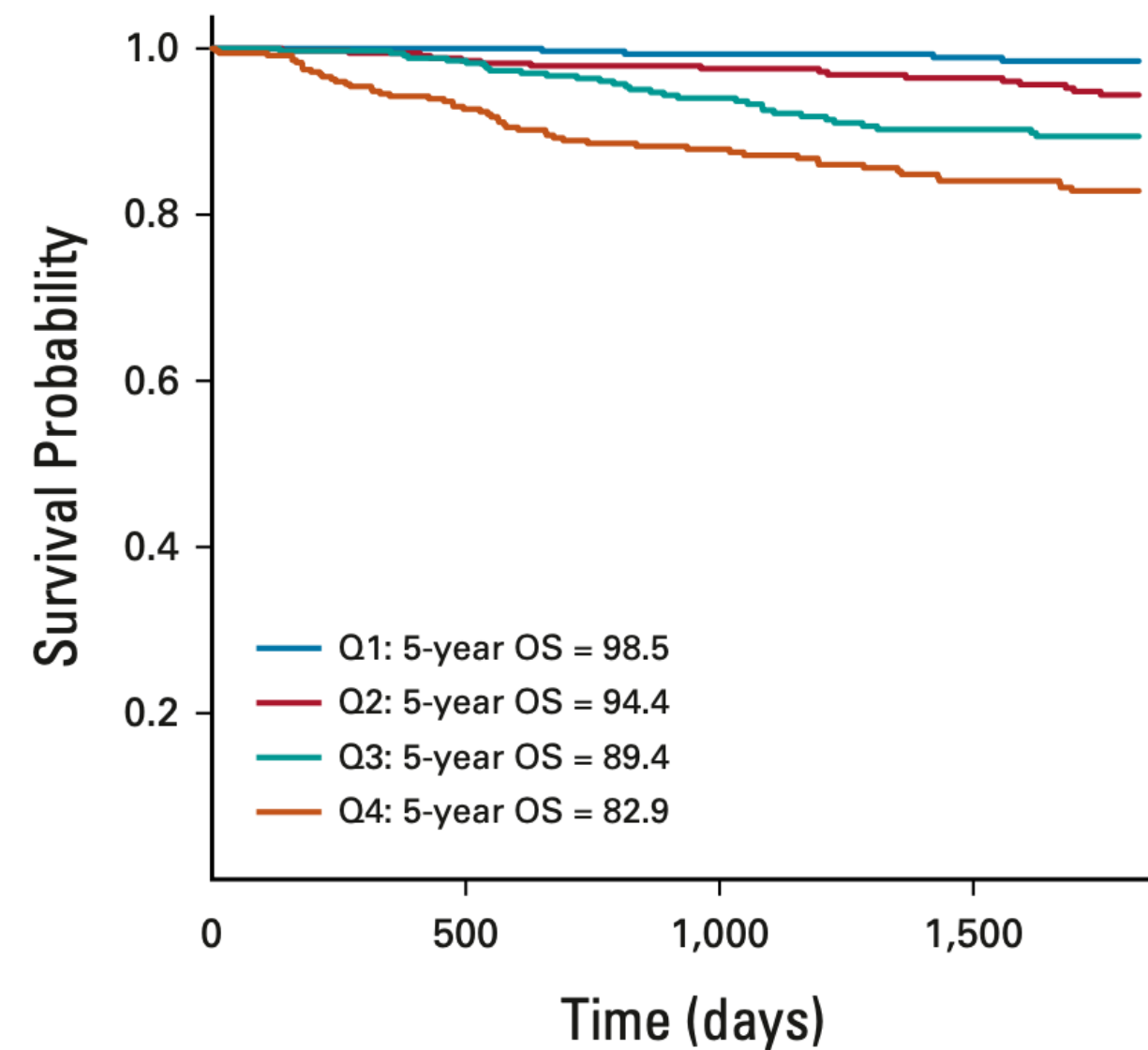
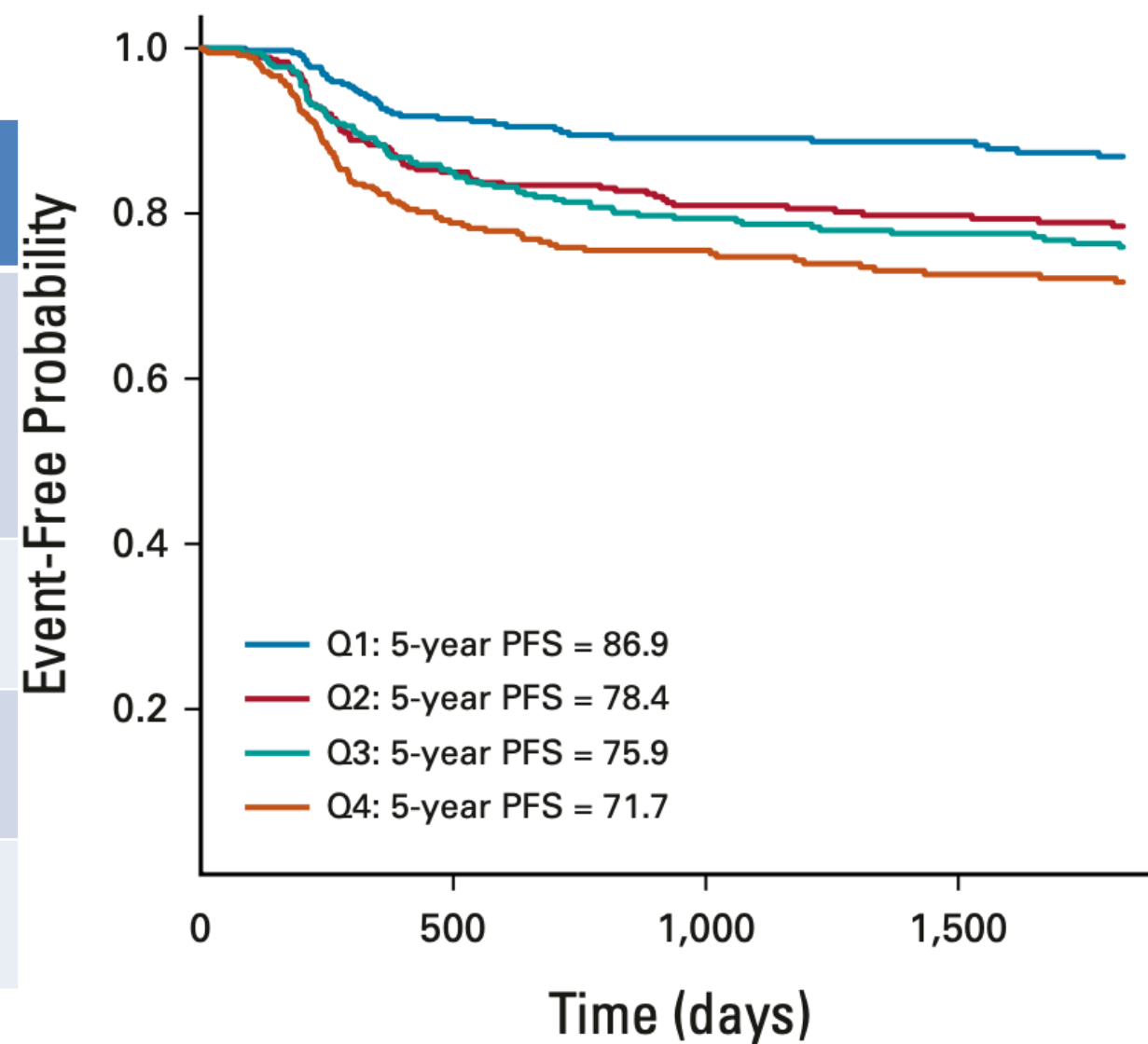
## Factors (PFS)

Albumin:  
continuous

Age: continuous

Stage IIB vs III/IV

ALC: continuous



## Factors (OS)

Albumin:  
continuous

Age: continuous

Stage IIB/III vs IV

ALC: continuous

Hgb: continuous

Male vs Female

Bulk

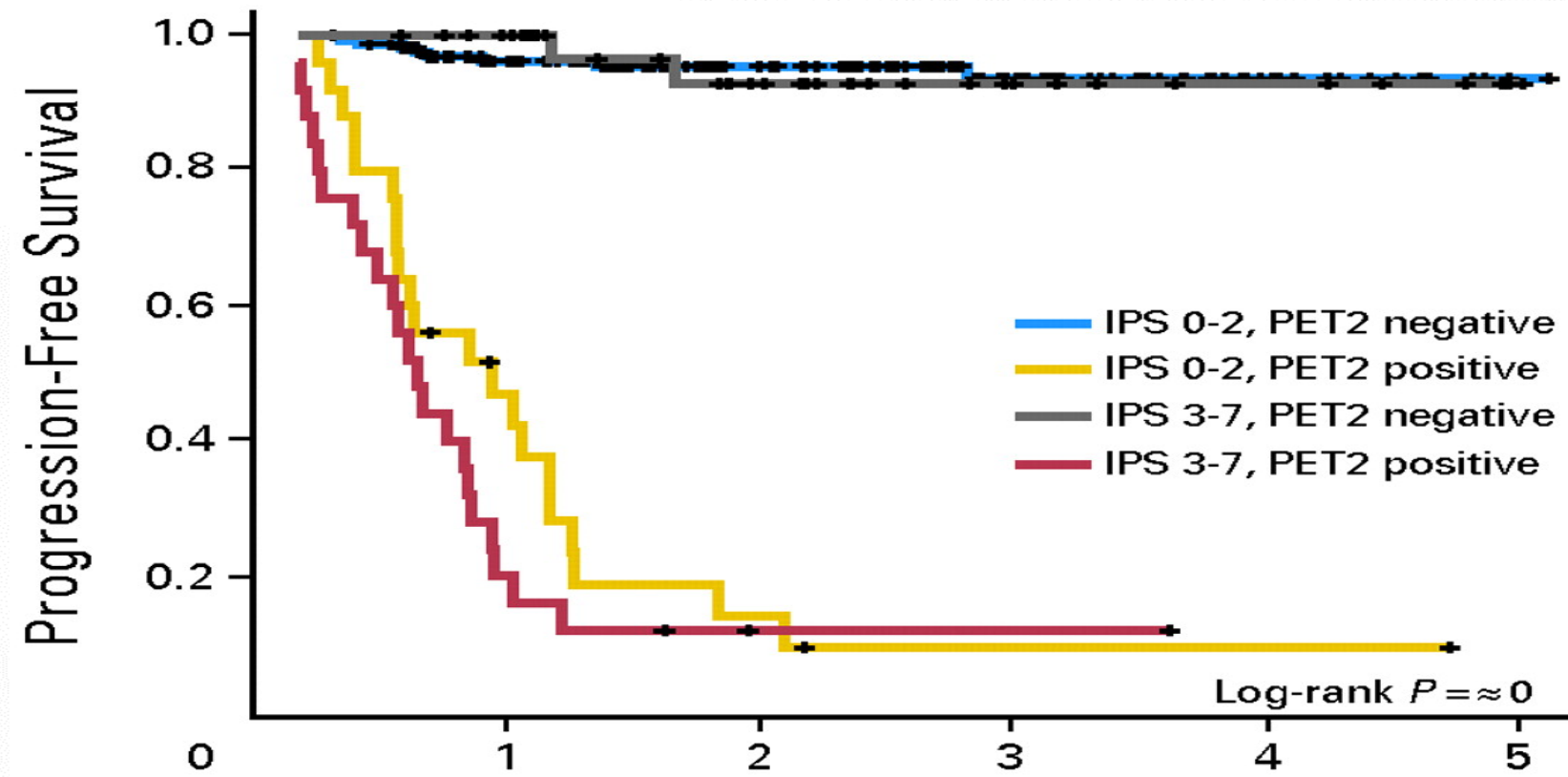
Online calculator: <https://holistic-calculator.web.app/>

Works for ABVD

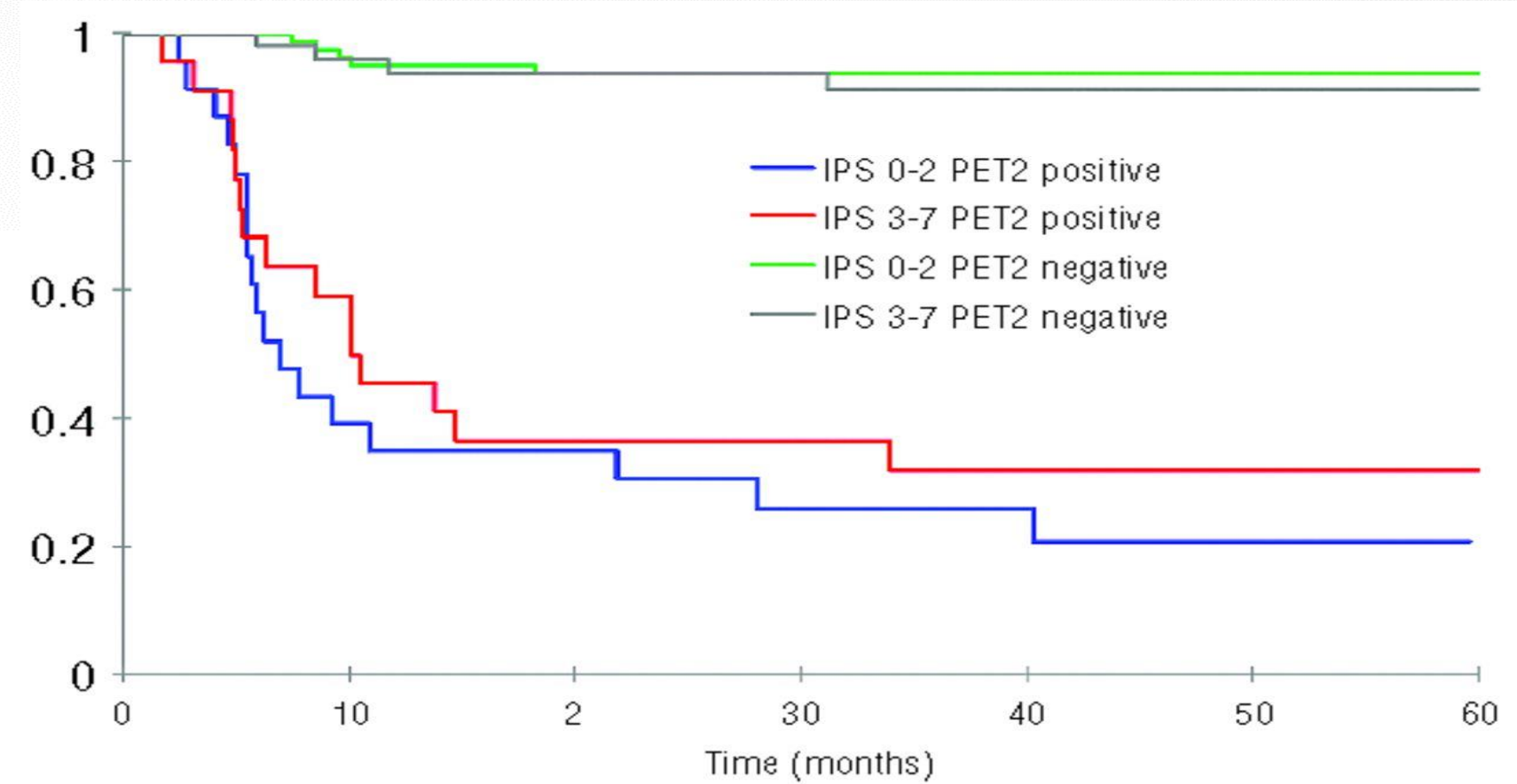


# Predictive power of interim PET

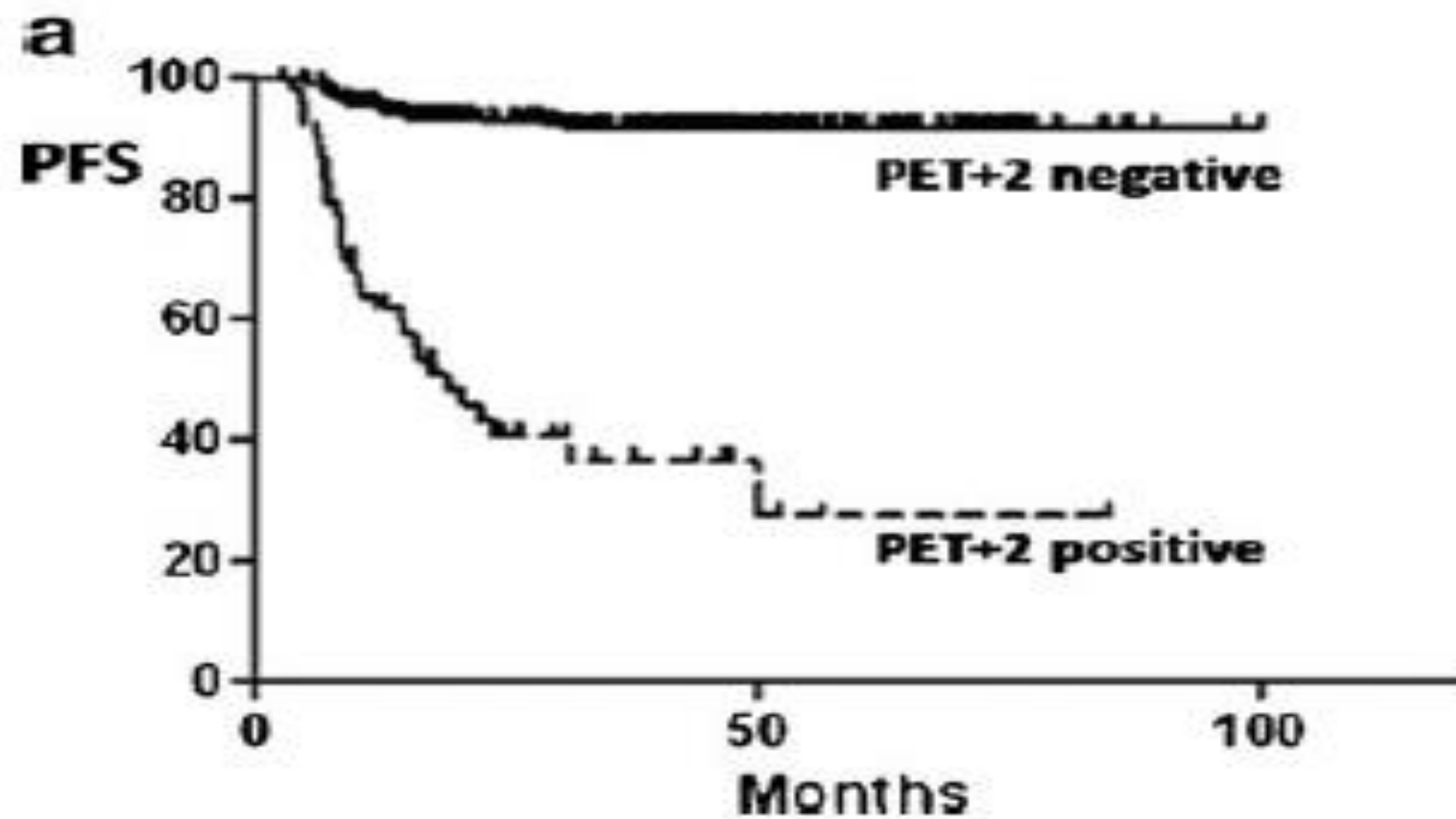
PET-2  
IHP



PET-2  
Deauville  
criteria  
Neg 1-3  
Pos 4-5



PET-2  
IHP



PET-2 predicts for long-term PFS of  
80-90% if negative  
30-35% if positive.(if tx not changed)

Works for ABVD and probably BV-AVD

Gallamini A et al. JCO 2007;25:3746-3752, Gallamini A Haematologica 2014  
99: 1107-1113; Zinzani PL et al. Eur J Nucl Med Imaging (2012) 39:4-12



# Potential new biomarkers for risk stratification and interim response

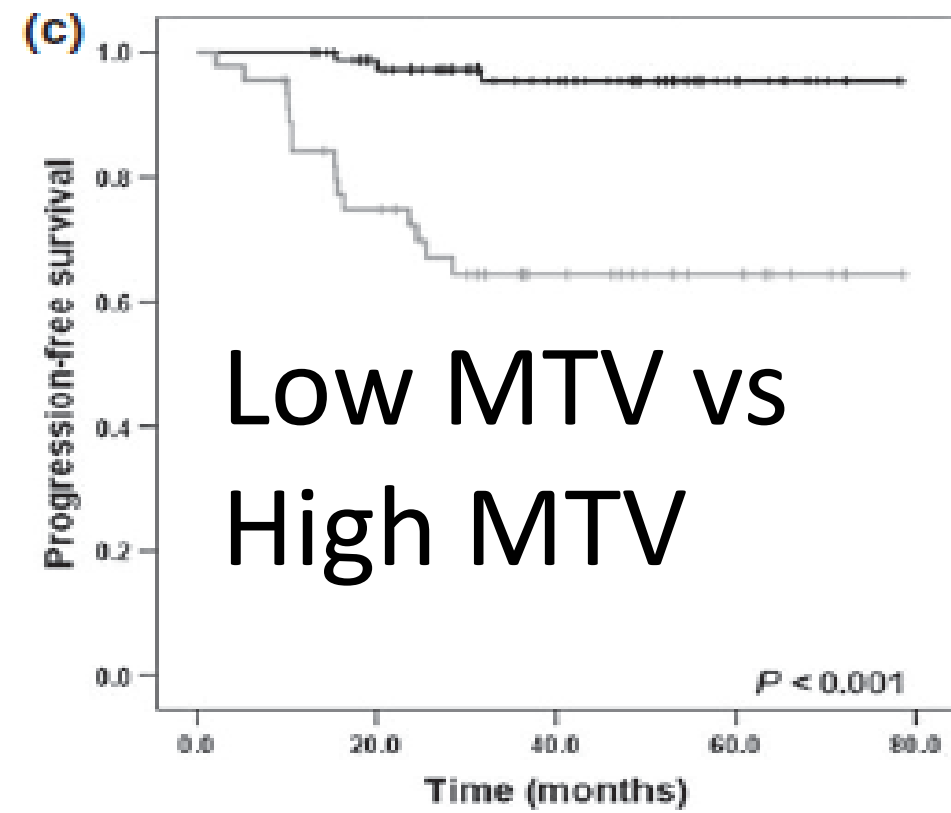
Metabolic tumor volume

ctDNA

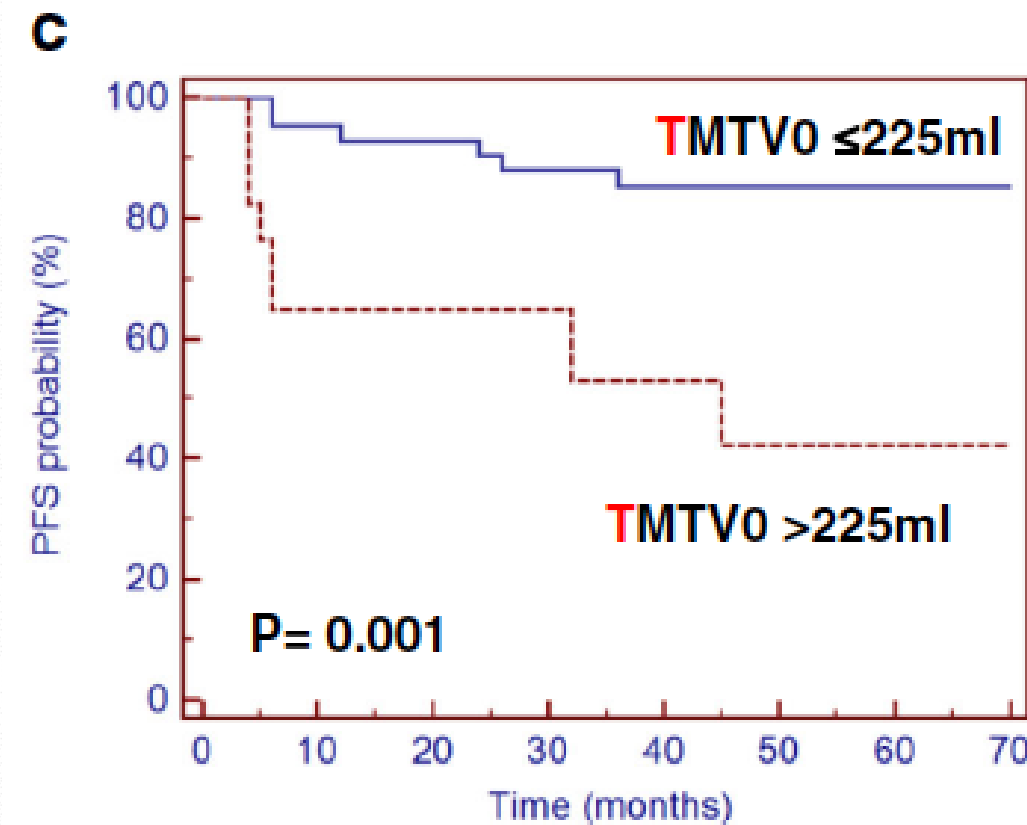


# Future of risk stratification?

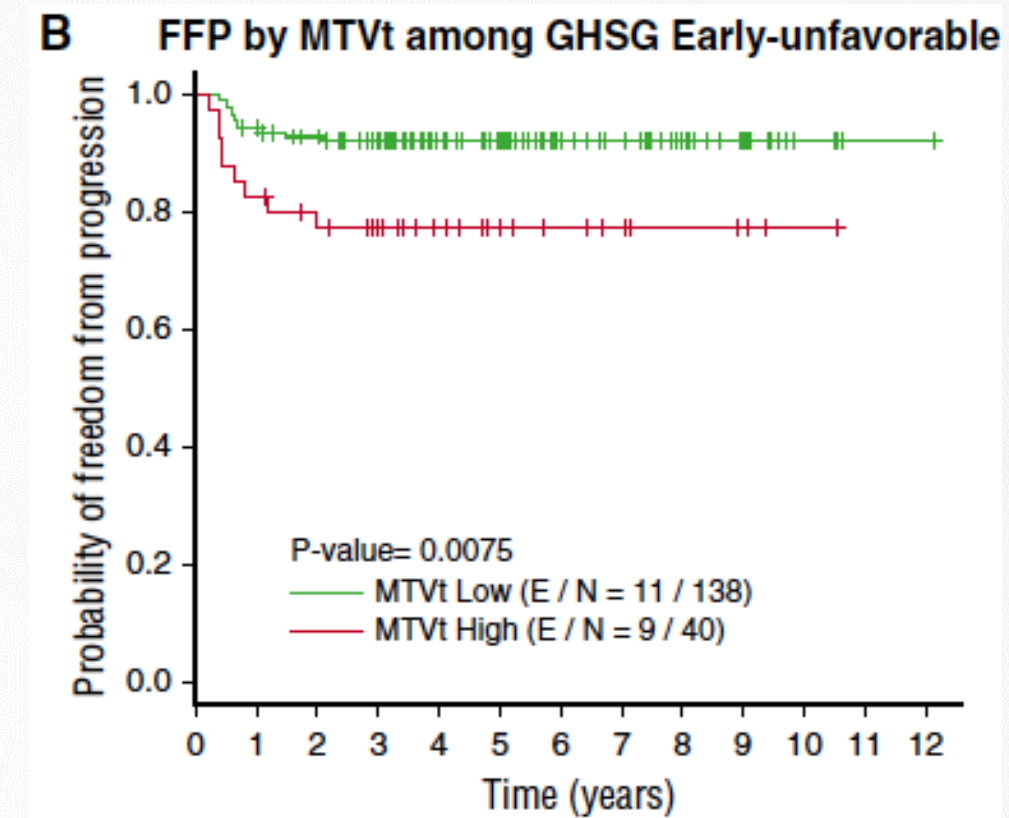
## Prognostic significance of metabolic tumor volume (MTV) in HL



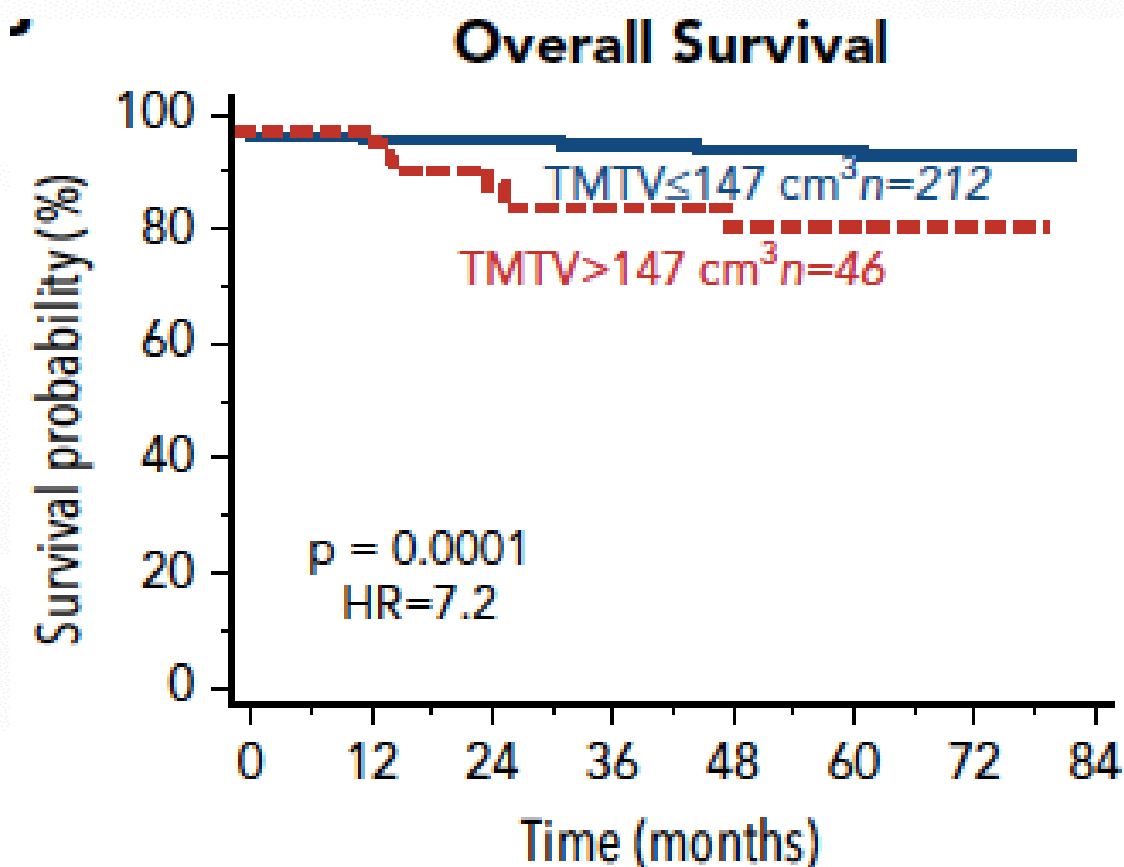
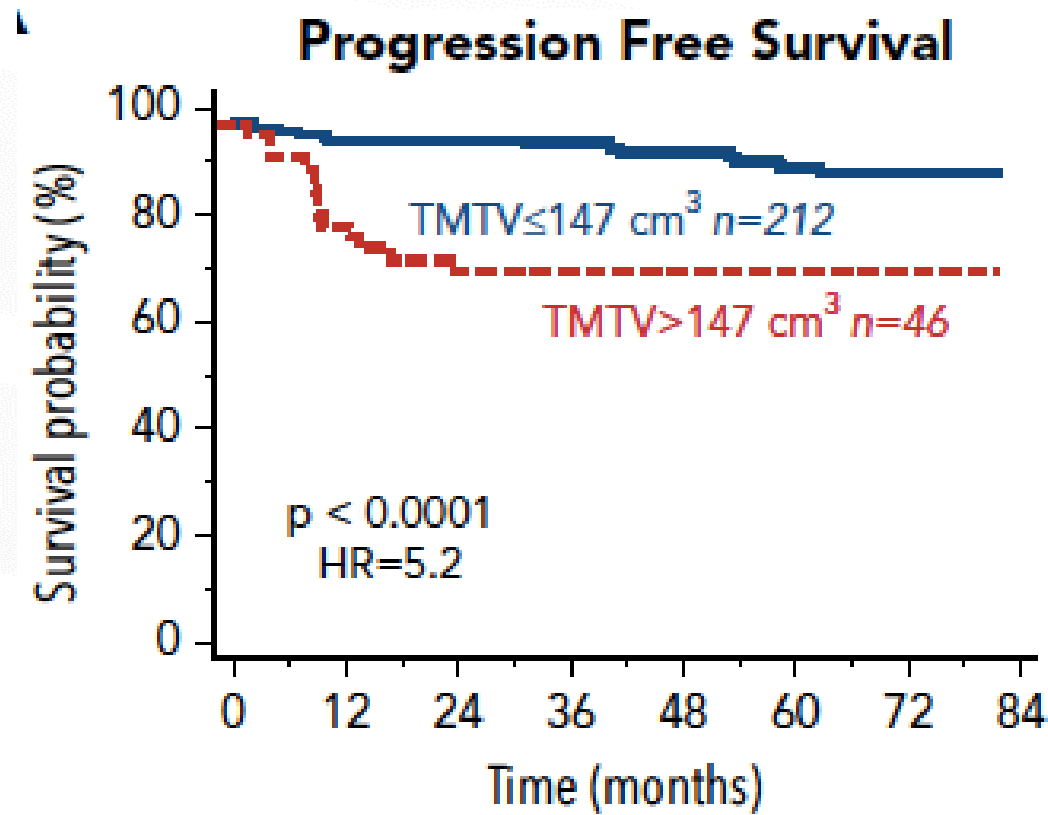
Song, et al. Cancer Science. 2013



Kanoun, et al. EJNMMI. 2014



Akhtari, et al. Blood. 2018



MTV predicts PFS and OS in EORTC H10 study

Cottreau, et al. Blood. 2018

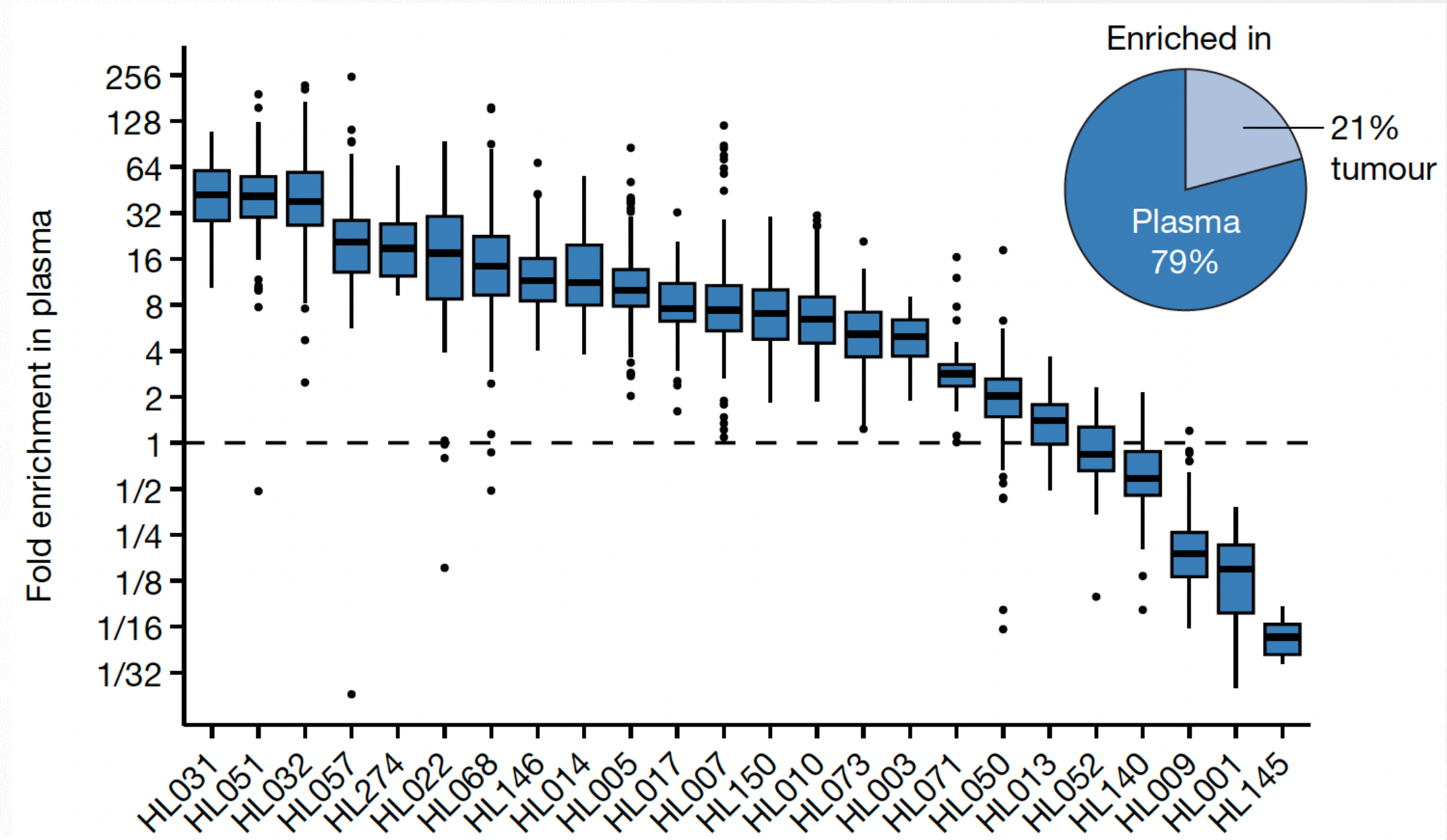
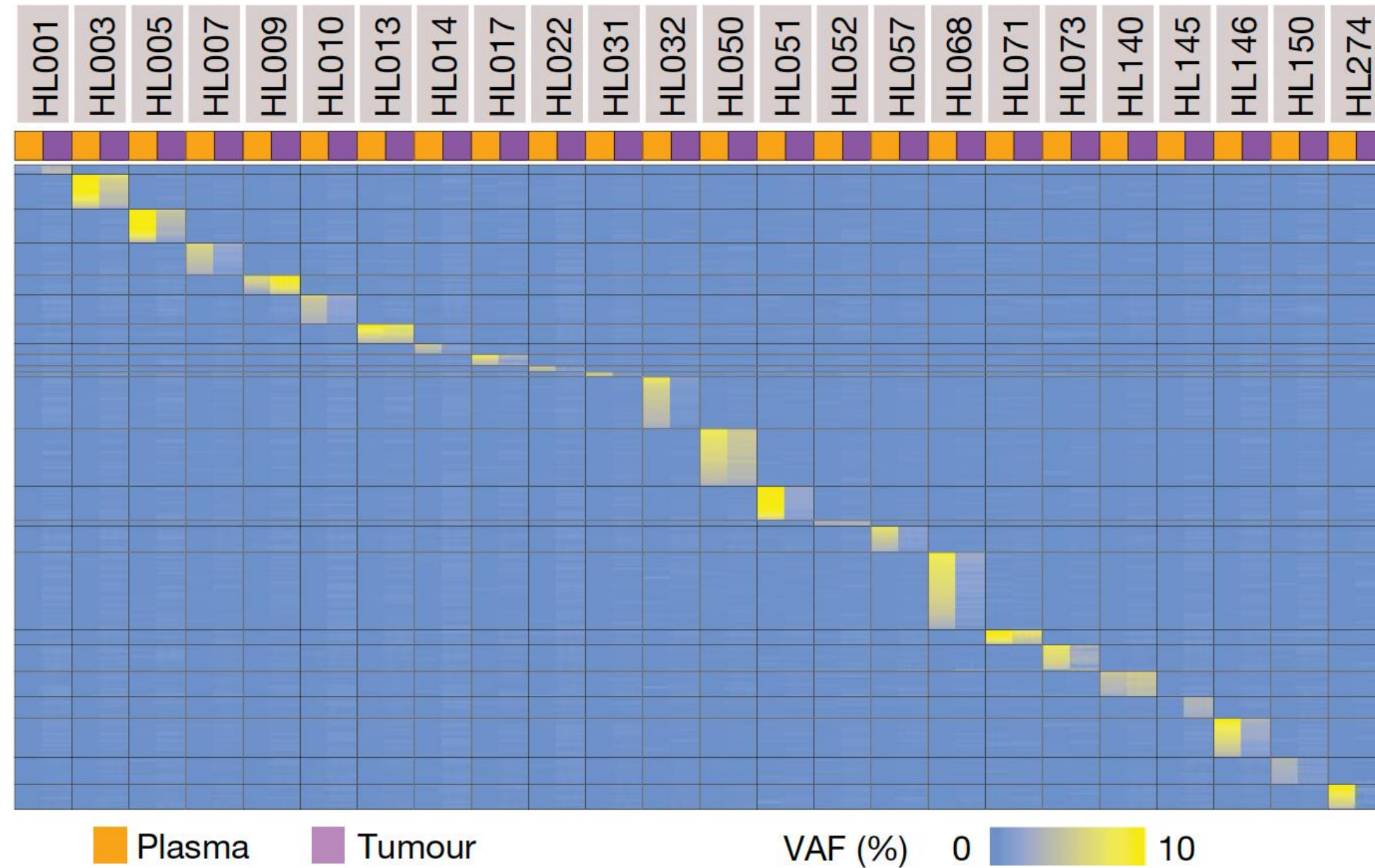
Works for ABVD



# Promise of ctDNA for HL

ctDNA recapitulates tumor-derived DNA

Greater enrichment of tumor DNA in **plasma** than in tumor



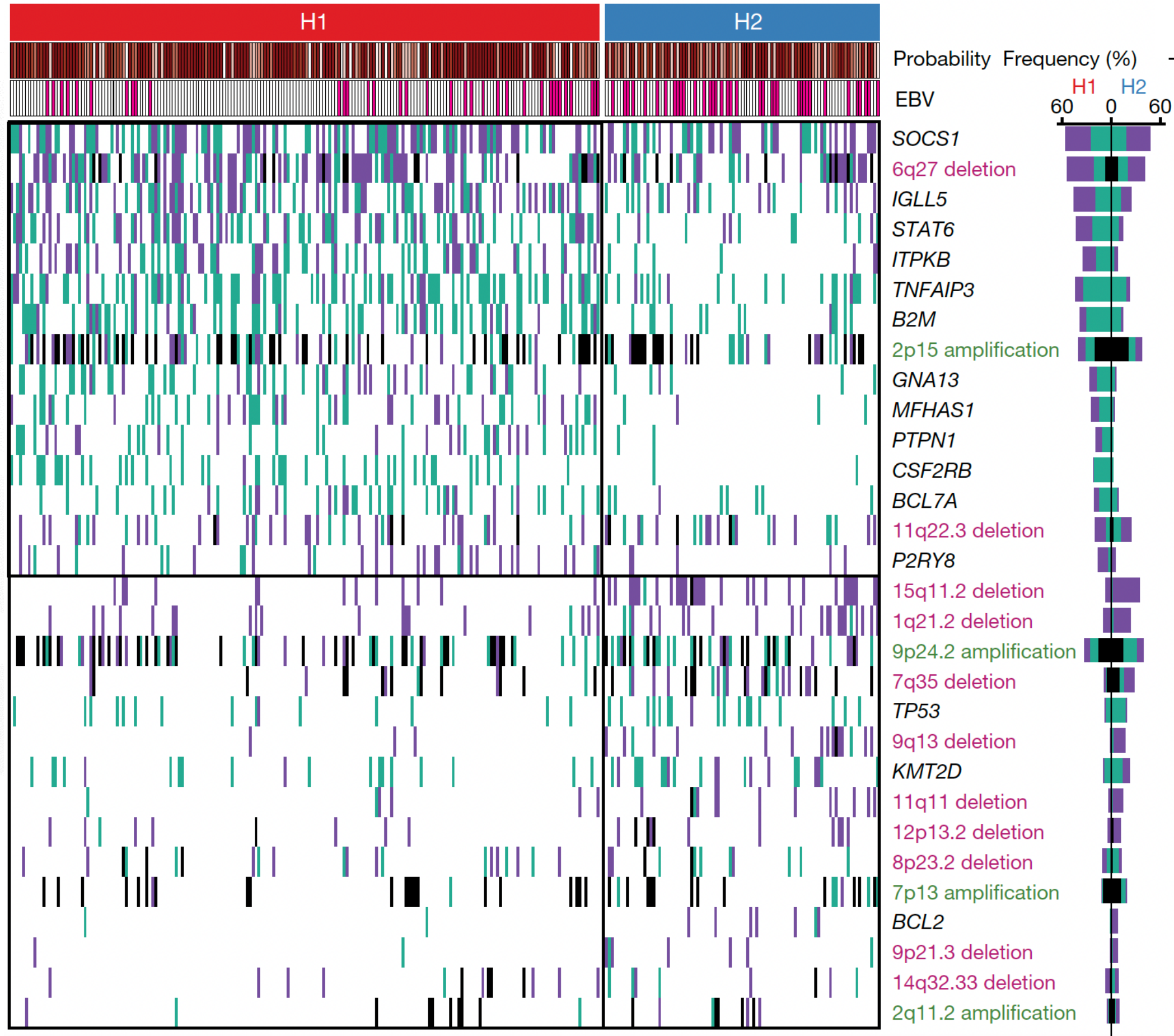
Alig, et al. Distinct Hodgkin lymphoma subtypes defined by noninvasive genomic profiling. Nature. Available online November 28 2023. ASH abstract #177



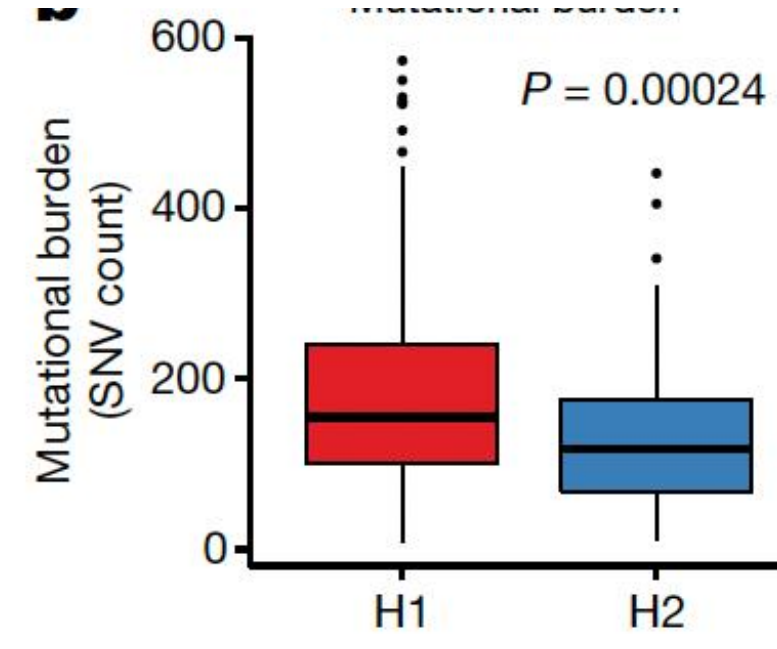
# Two distinct genetic

**NFkB/STAT/PI3K/B2M**

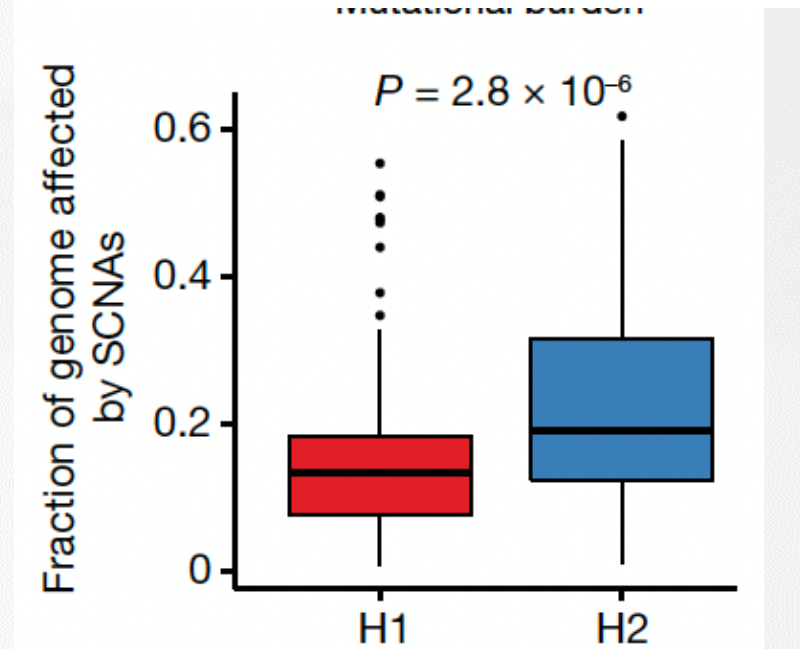
**Genomic instability/  
TP53/KMT2D**



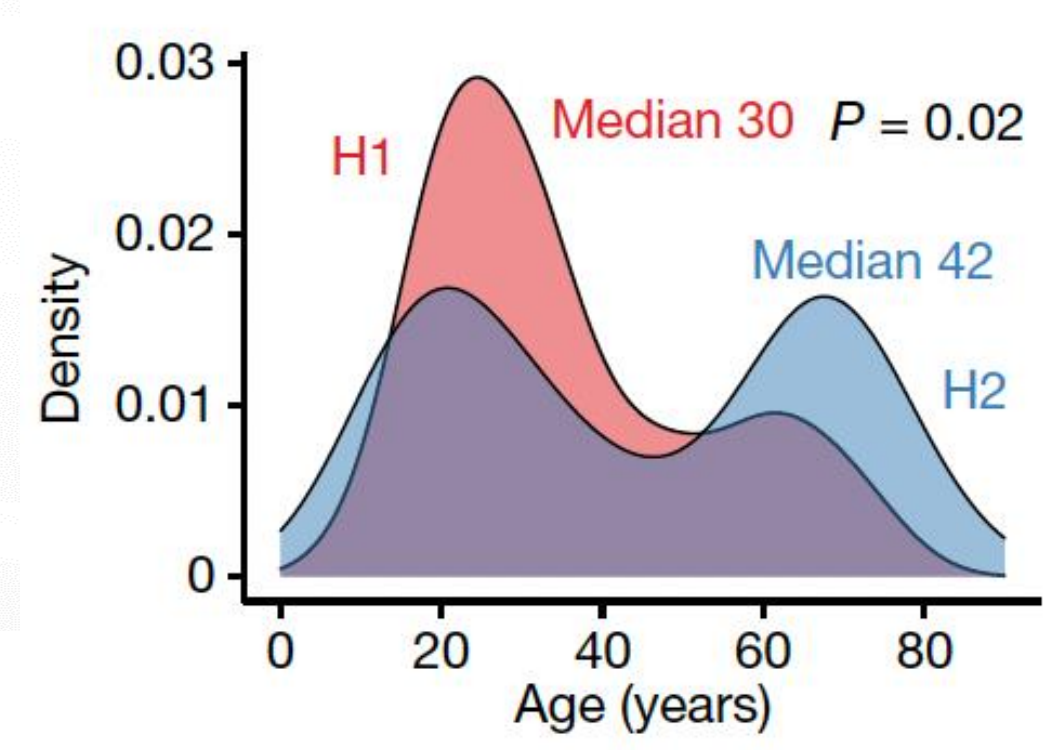
**H1: higher single-nucleotide variants**



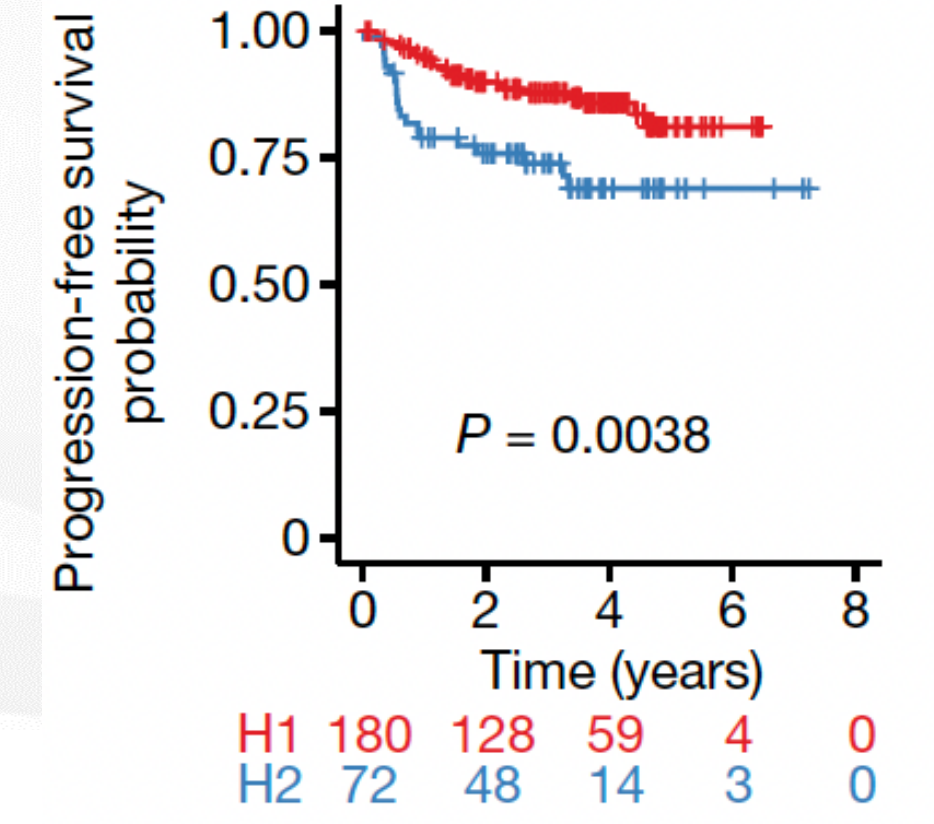
**H2: higher copy number variation**



**H1: enriched in younger**



**H1: improved prognosis**



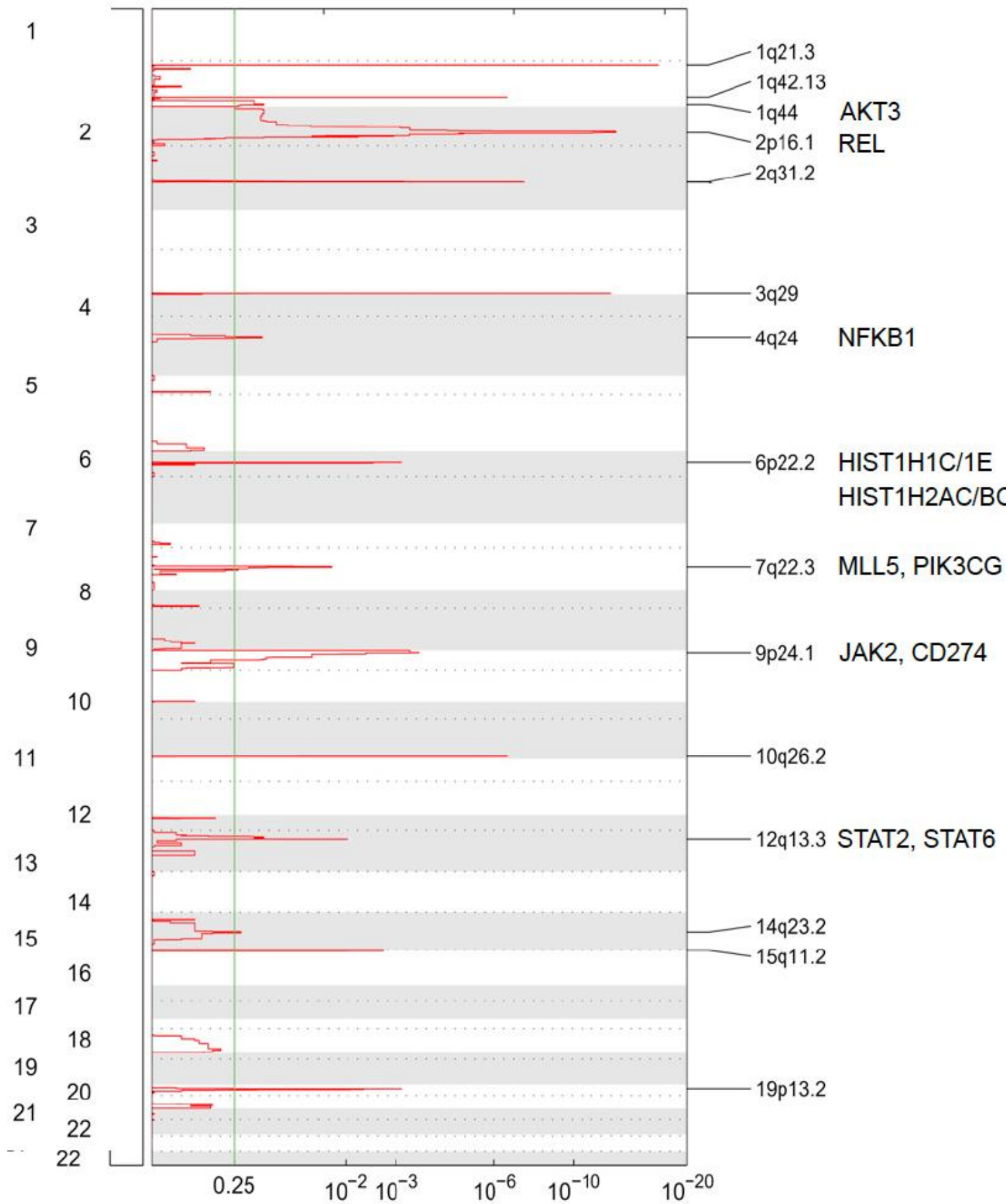
Alig, et al. Distinct Hodgkin lymphoma subtypes defined by noninvasive genomic profiling. Nature. Available online November 28 2023. ASH abstract #177



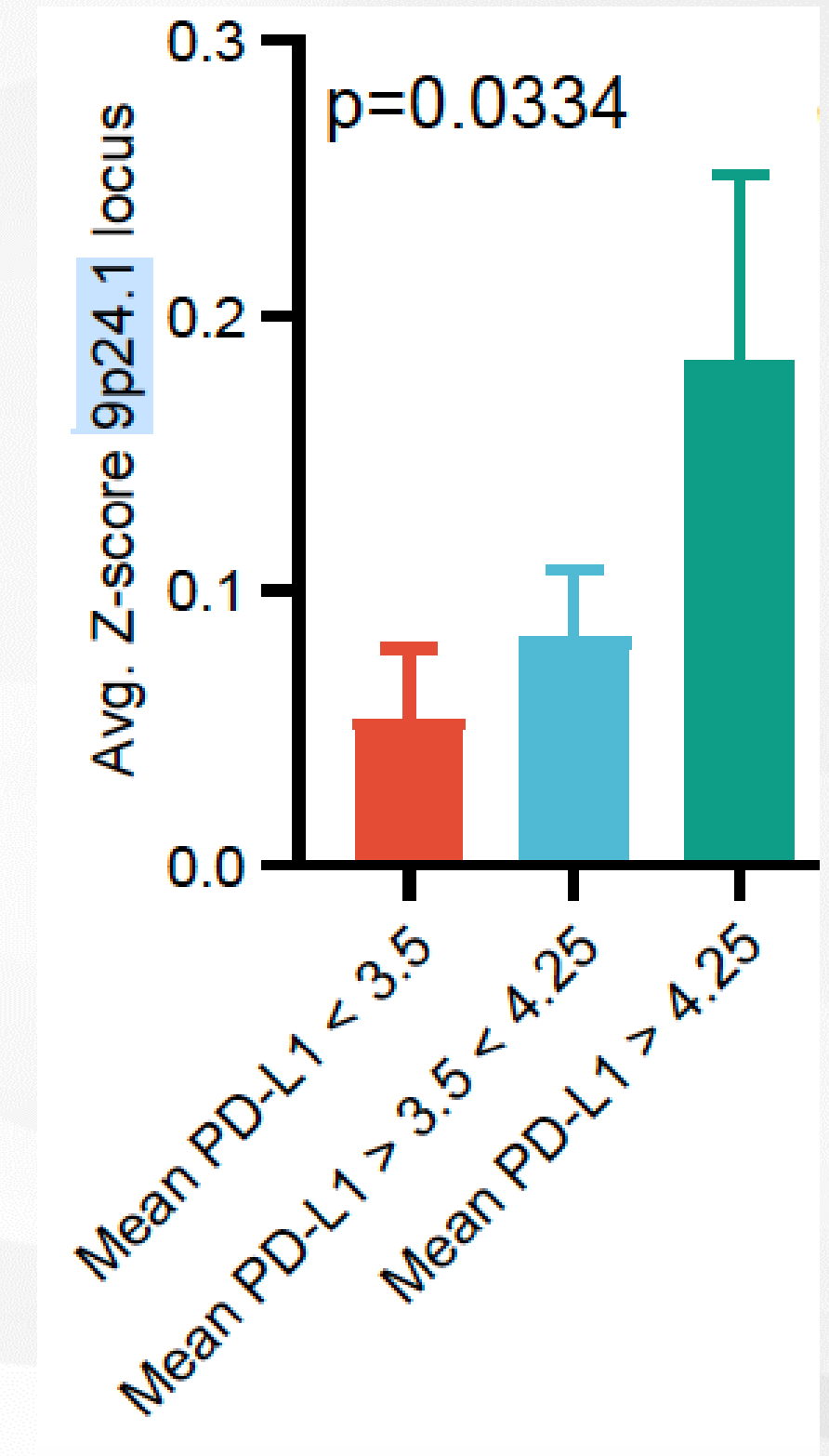
# 9p24.1 amplification can be

by ctDNA

9p24.1 by FISH correlates with ctDNA

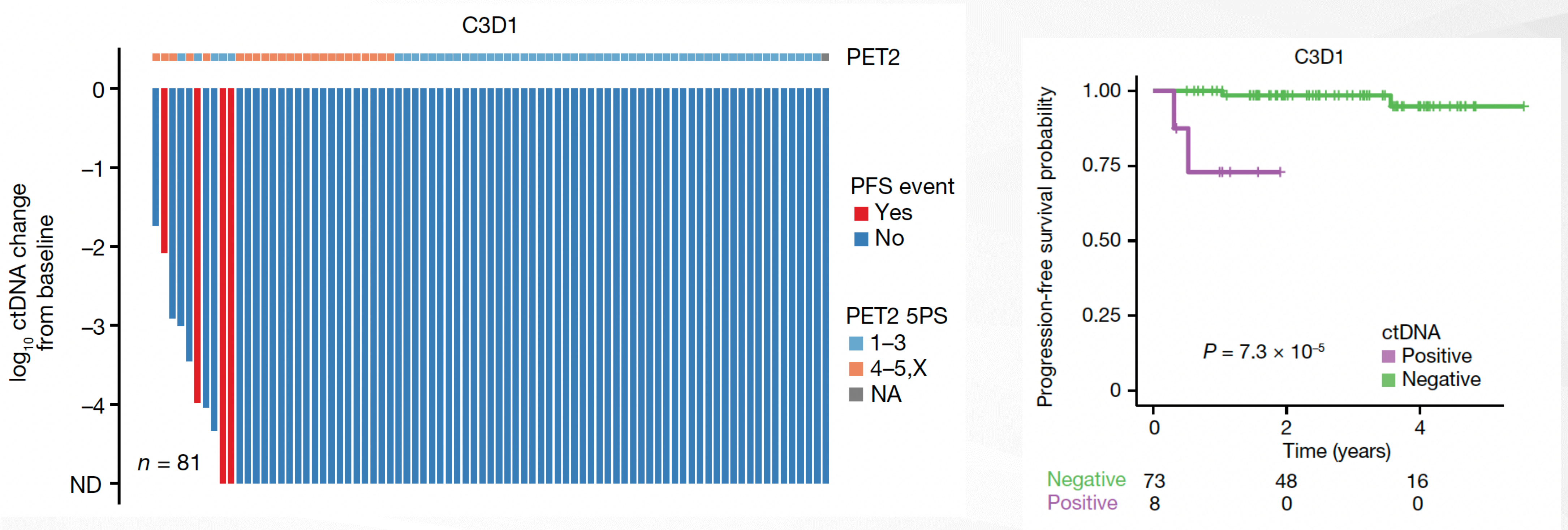


9p24.1 copy gain on ctDNA





# Interim ctDNA may perform better



Alig, et al. Distinct Hodgkin lymphoma subtypes defined by noninvasive genomic profiling. Nature. Available online November 28 2023. ASH abstract #177



# Age HL in older

patients

**Age  $\geq$  60-me!**

**BV-AVD-BV<sup>1</sup>**

**Nivo+AVD x 6<sup>2,3</sup>**

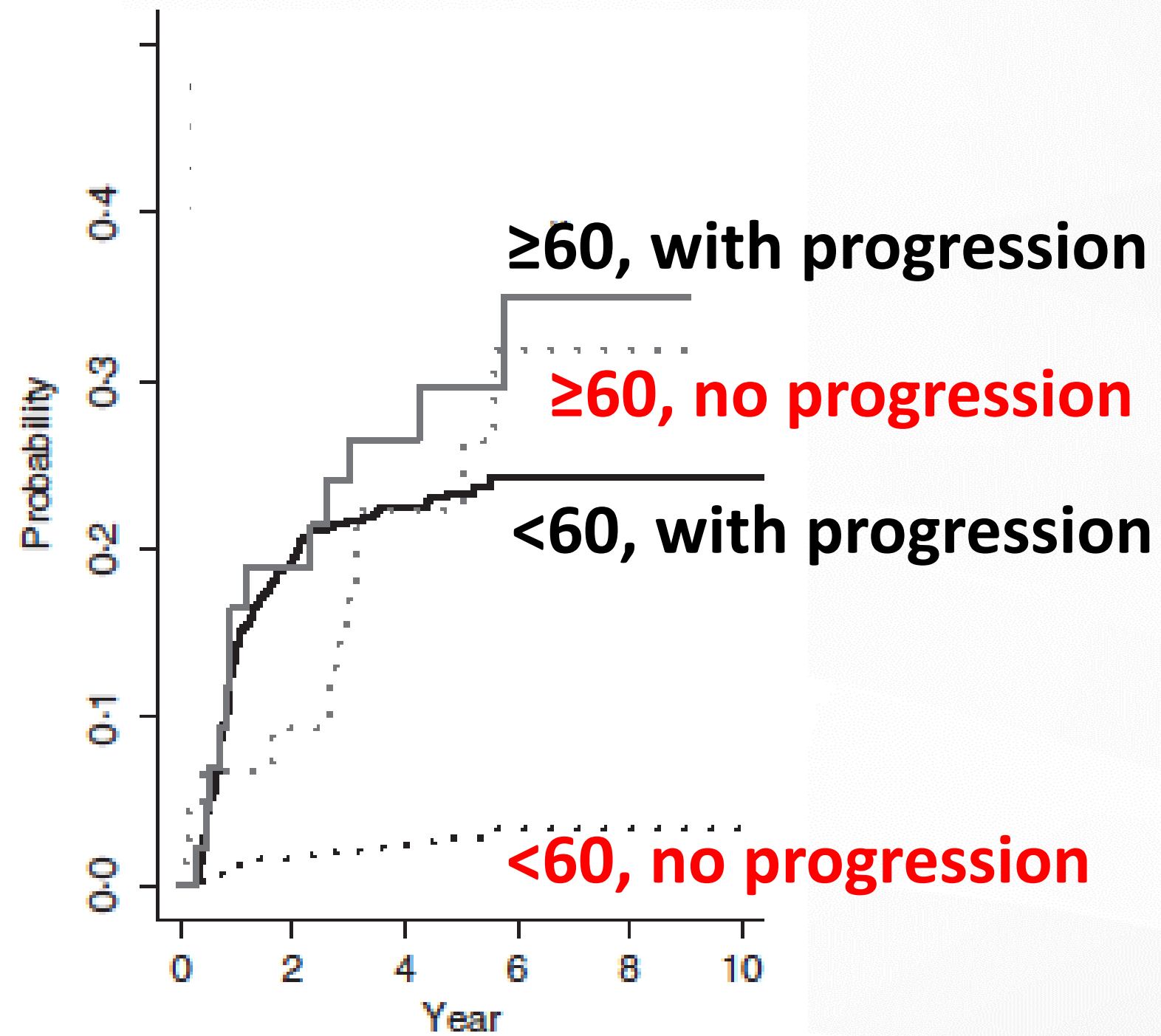
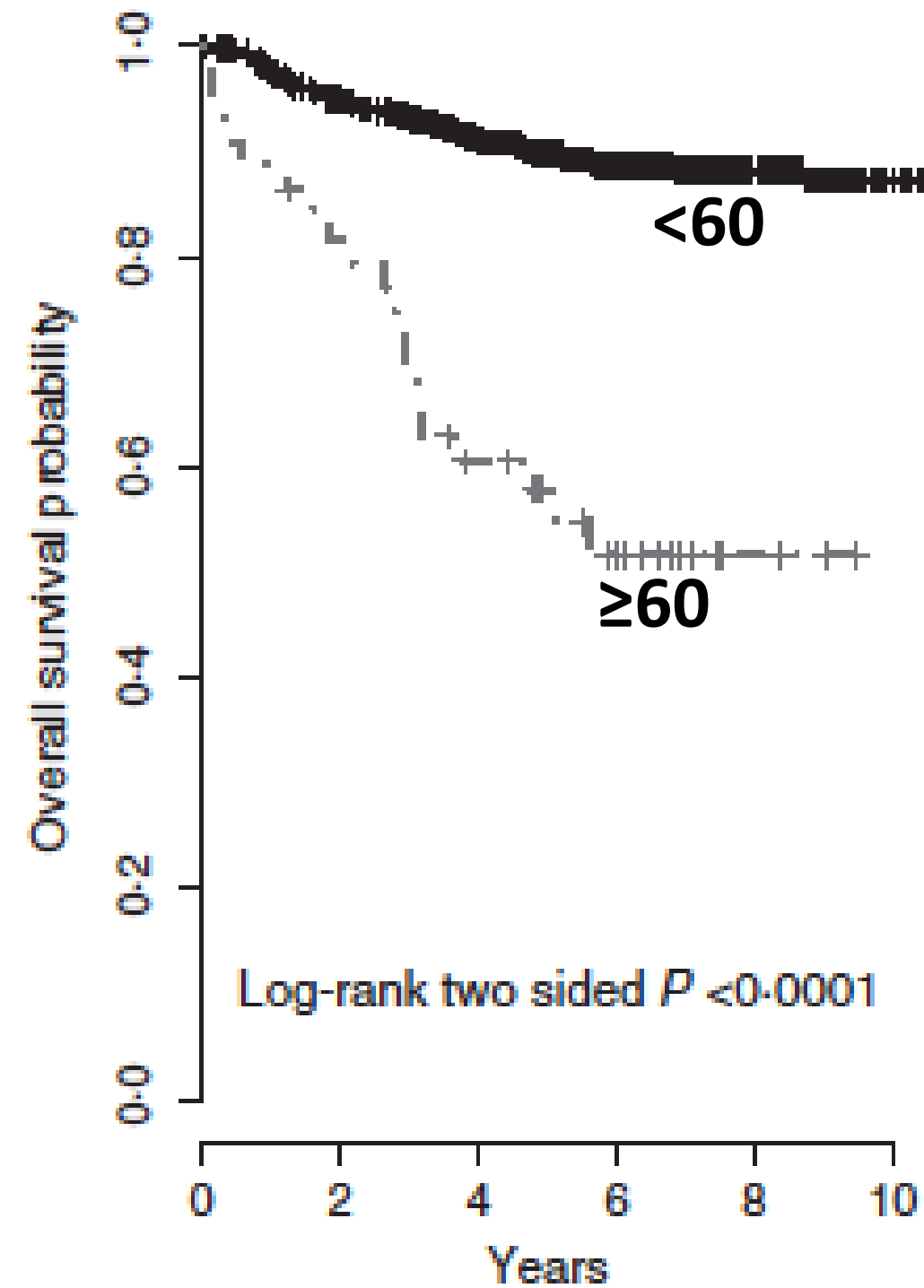
**Key:**

 SOC

 New SOC?



# Less favorable outcomes primarily due to treatment-related toxicity



## Among patients $\geq 60$ :

- 43% bleomycin lung toxicity with ABVD
- 64% grade  $\geq 4$  neutropenia
- 9% treatment related mortality

E2496: ABVD vs Stanford V

Competing risk analysis



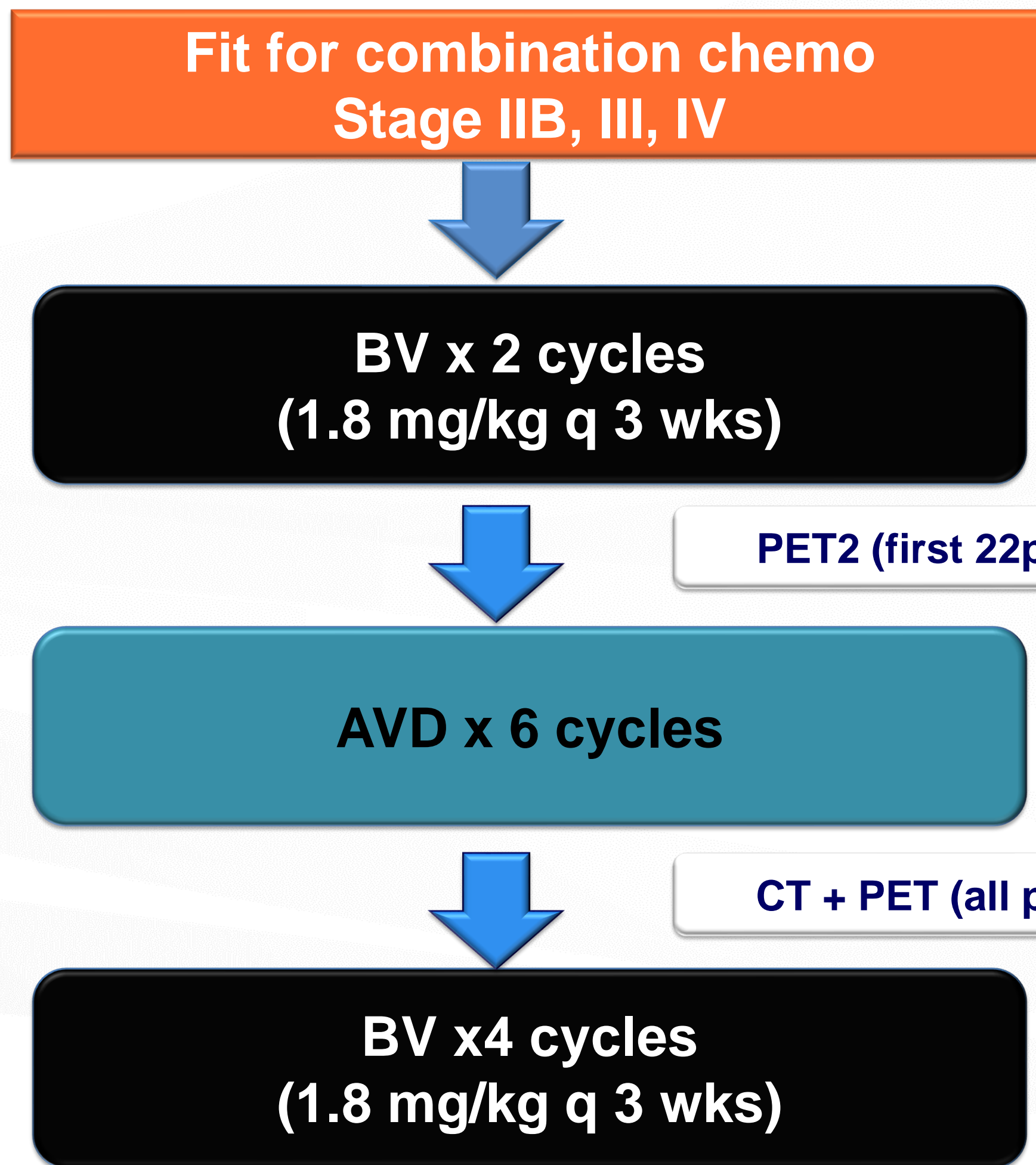
## Front-line palliative therapy with BV for age $\geq 60$

Treatment	n	ORR	CR	Median PFS
BV alone <sup>1</sup>	27	92%	73%	10.5 months
BV plus bendamustine <sup>2</sup>	20	<b>Closed early due to toxicity</b>		
BV plus dacarbazine <sup>3</sup>	22	95%	64%	46 months
BV plus nivolumab <sup>3</sup>	21	86%	67%	NR (med f/u 51.6 mo)

<sup>1</sup>Forero-Torres A, et al. Blood (2015) 26:2798-2804; <sup>2</sup>Friedberg JW, et al. Blood (2017) 130: 2829-2837; <sup>3</sup>Friedberg, et al. Blood 2023



# Sequential BV and AVD for patients ≥60



PET2 (first 22pts)

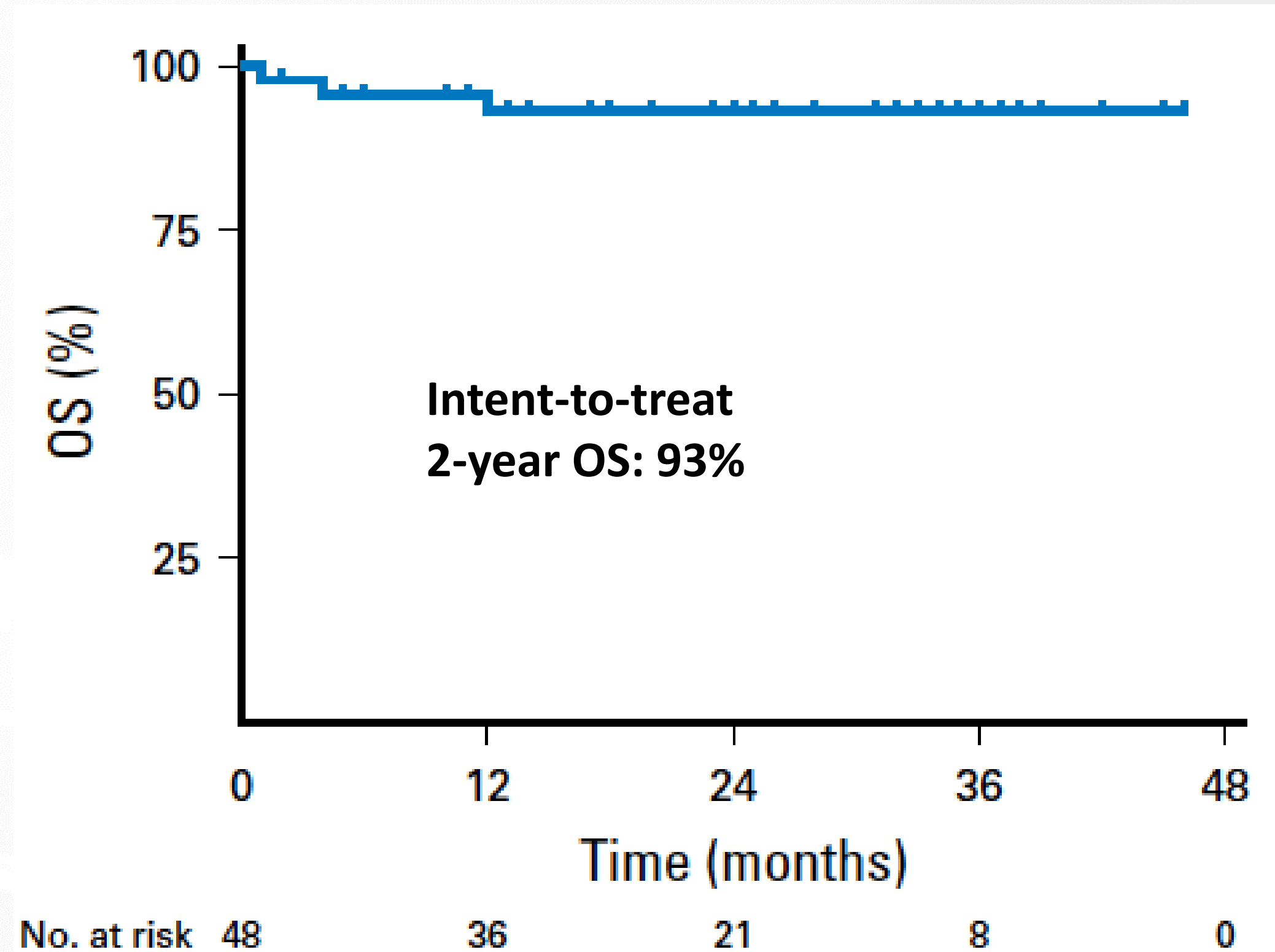
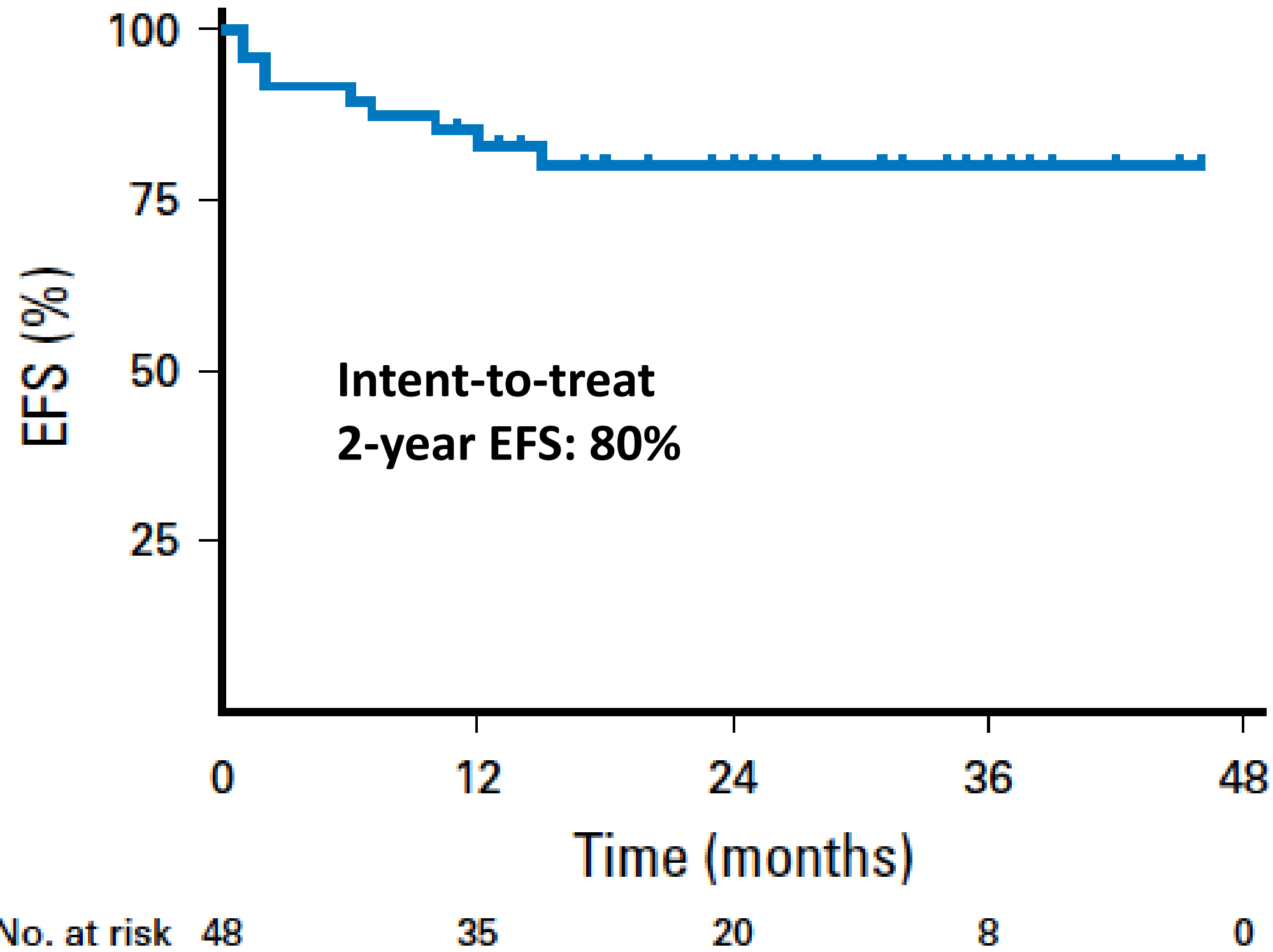
CT + PET (all pts)

## 48 patients enrolled

- 52% age 60-70; 17% >80
- 81% stage III or IV
- 58% IPS 3-7
- 10% disease bulk (10cm)



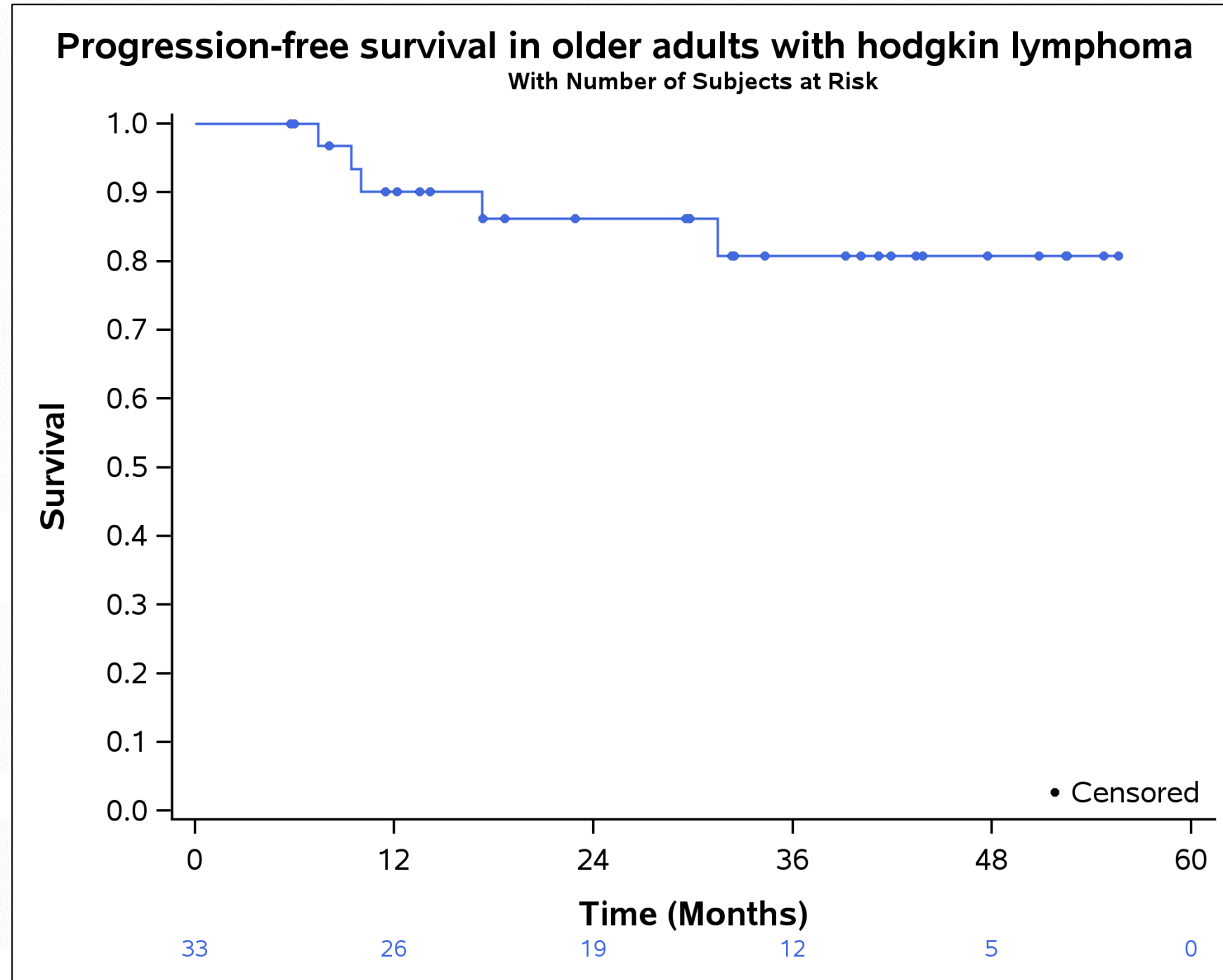
# Sequential BV and AVD for patients $\geq 60$ years old



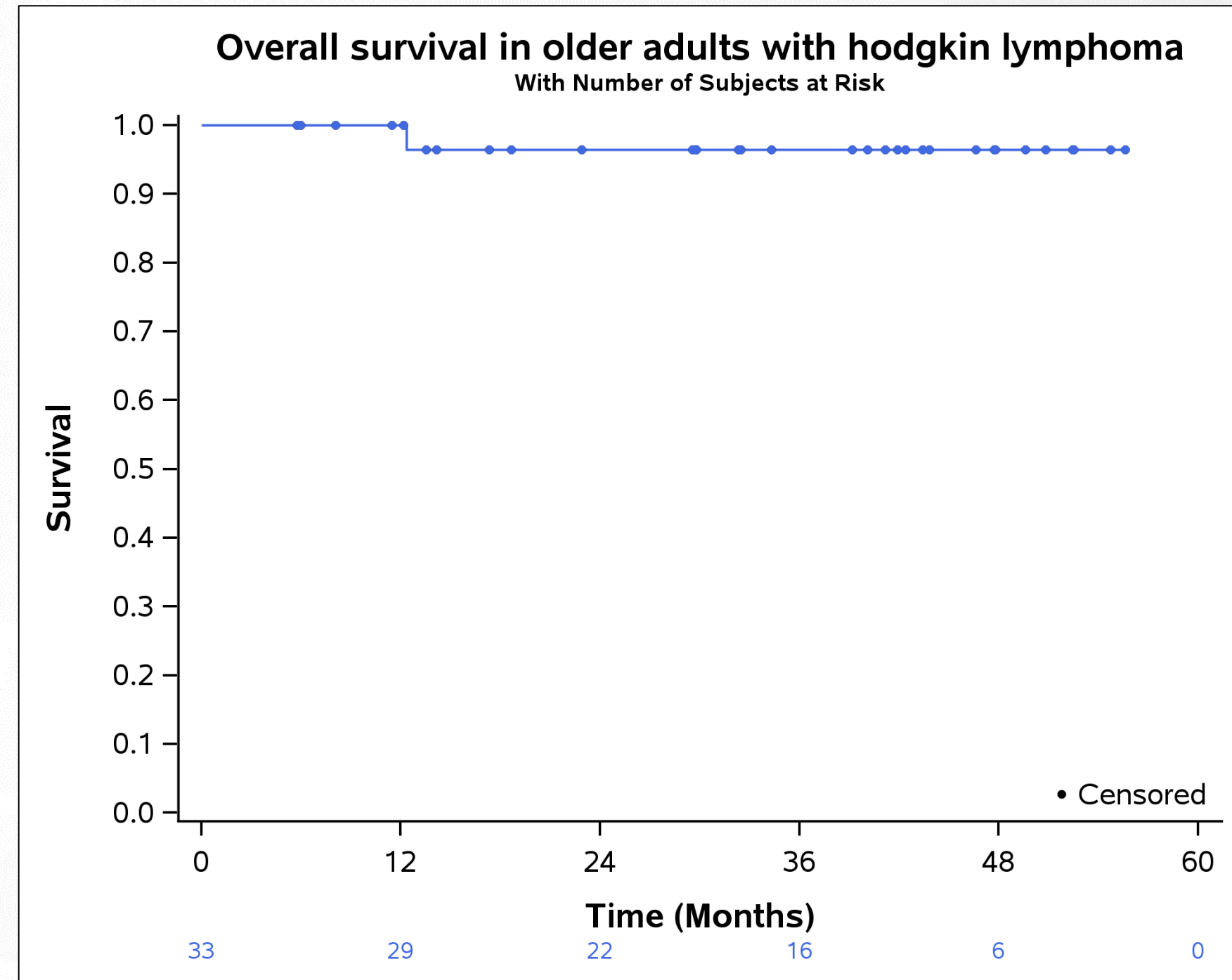


# Phase II study of N-AVD for pts age $\geq 60$ (n=37, 33 evaluable)

## Nivo+AVD x 6



**2-year PFS 86.2% (95% CI: 74-100%)**



**2-year OS 96.4% (95%CI: 90-100%)**

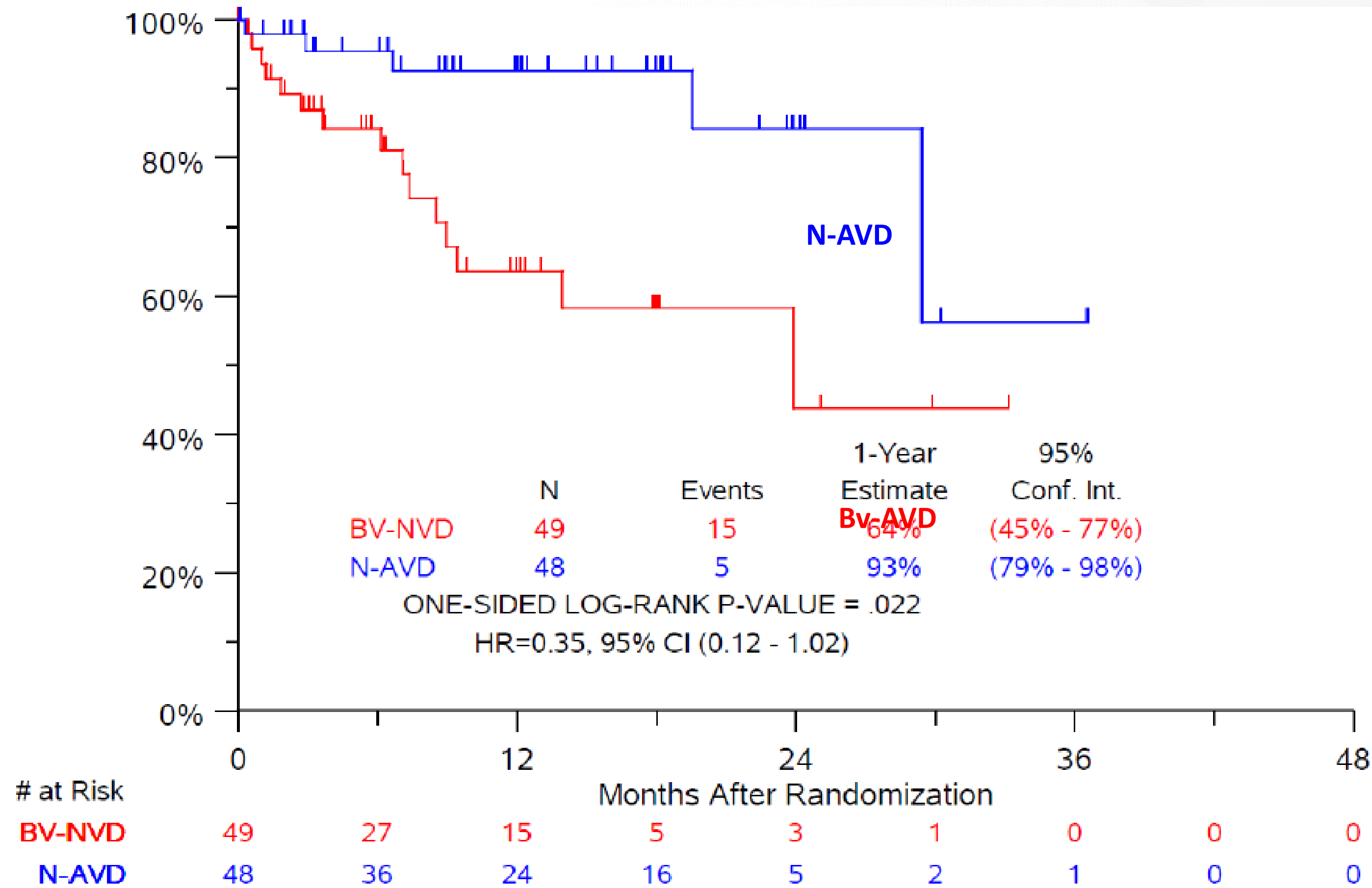


# S1826 (N-AVD vs BV-AVD) Older Pts

Baseline characteristics	N-AVD N = 48 N (%)	Bv-AVD N = 49 N (%)	Baseline characteristics	N-AVD N = 48 N (%)	Bv-AVD N = 49 N (%)
Age, median (range)	66.4 (60-84 y)	67.1(60-87 y)	Stage III	16 (33%)	22 (45%)
Age 60-69	31 (65%)	36 (74%)	IV	32 (67%)	27 (55%)
Age 70-79	14 (29%)	12 (24%)	B symptoms present	25 (52%)	27 (55%)
Age ≥80	3 (6%)	1 (2%)	IPS Score		
Female Sex	19 (40%)	18 (37%)	0-3	24 (50%)	27 (55%)
Race			4-7	24 (50%)	22 (45%)
White	43 (90%)	40 (82%)	Bulky disease > 10cm	7 (15%)	5 (10%)
Black	1 (2%)	2 (4%)	HIV+	0 (0%)	1 (2%)
Asian	1 (2%)	1 (2%)	Elevated bilirubin	4 (8%)	4 (8%)
Other/Unknown	3 (6%)	6 (12%)			
Hispanic	5 (10%)	5 (10%)			



# N-AVD markedly improves PFS over Bv-AVD in older patients with cHL



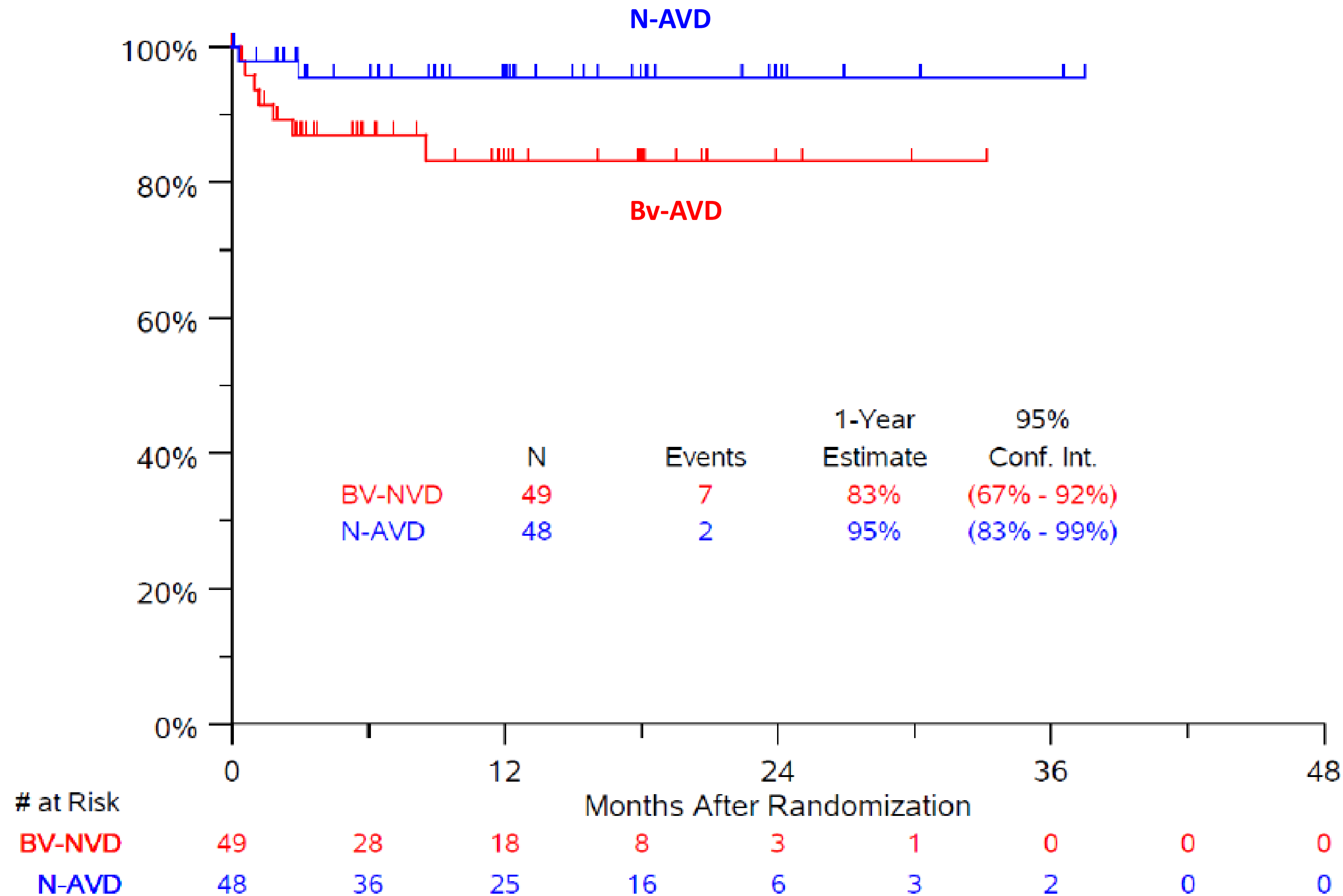
**1-year PFS**  
**N-AVD 93%**  
**Bv-AVD 64%**

Median follow-up  
 12.1 months

p-value = 0.022  
 HR=0.35,  
 95% CI (0.12-1.02)



# Fewer deaths occurred on N-AVD



**1-year OS**  
**N-AVD 95%**  
**BV-AVD 83%**

Median follow-up  
 12.1 months

p-value = 0.091  
 HR=0.35,  
 95% CI (0.07-1.75)



# Majority of deaths on Bv-AVD due to infection/sepsis

Cause of death	N-AVD	Bv-AVD
Infection	1	3
Sepsis	1	2*
Pneumonitis	0	1
Unknown	0	1
<b>Total OS events</b>	<b>2</b>	<b>7</b>

***Non-relapse mortality***  
***N-AVD 4% vs Bv-AVD 14%***



## Front-line treatment of advanced stage HL

Nivo-AVD replacing BV-AVD as treatment of choice

BrECADD represents reasonable alternative to nivo-AVD

Nivo-AVD represents good option for patients over 60

ctDNA, MTV may aid in individualizing therapy in future




## **Two of my pts currently receiving BRECADD**

28 year old female with stage IV disease and ulcerative colitis

21 year old male stage 3 disease with graves disease and type 1 DM





**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



Griffen Cancer Research Building



Gemma, Dylan and Ethan

We see 1000 lymphoma consults each year