

IN PURSUIT OF *YOUR CURE*.™

# Is there an optimal treatment for all pts with ASHL?

**Unlikely!**

Craig Moskowitz, MD  
Director of Mentoring and Academic Development  
Sylvester Comprehensive Cancer Center  
Professor of Medicine, Chair Protocol Review and Monitoring Committee  
Miller School of Medicine  
University of Miami Health System



A Cancer Center Designated by the  
National Cancer Institute

# Disclosures

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

# HOW TO TREAT ASHL: THE CHOICES

## 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?

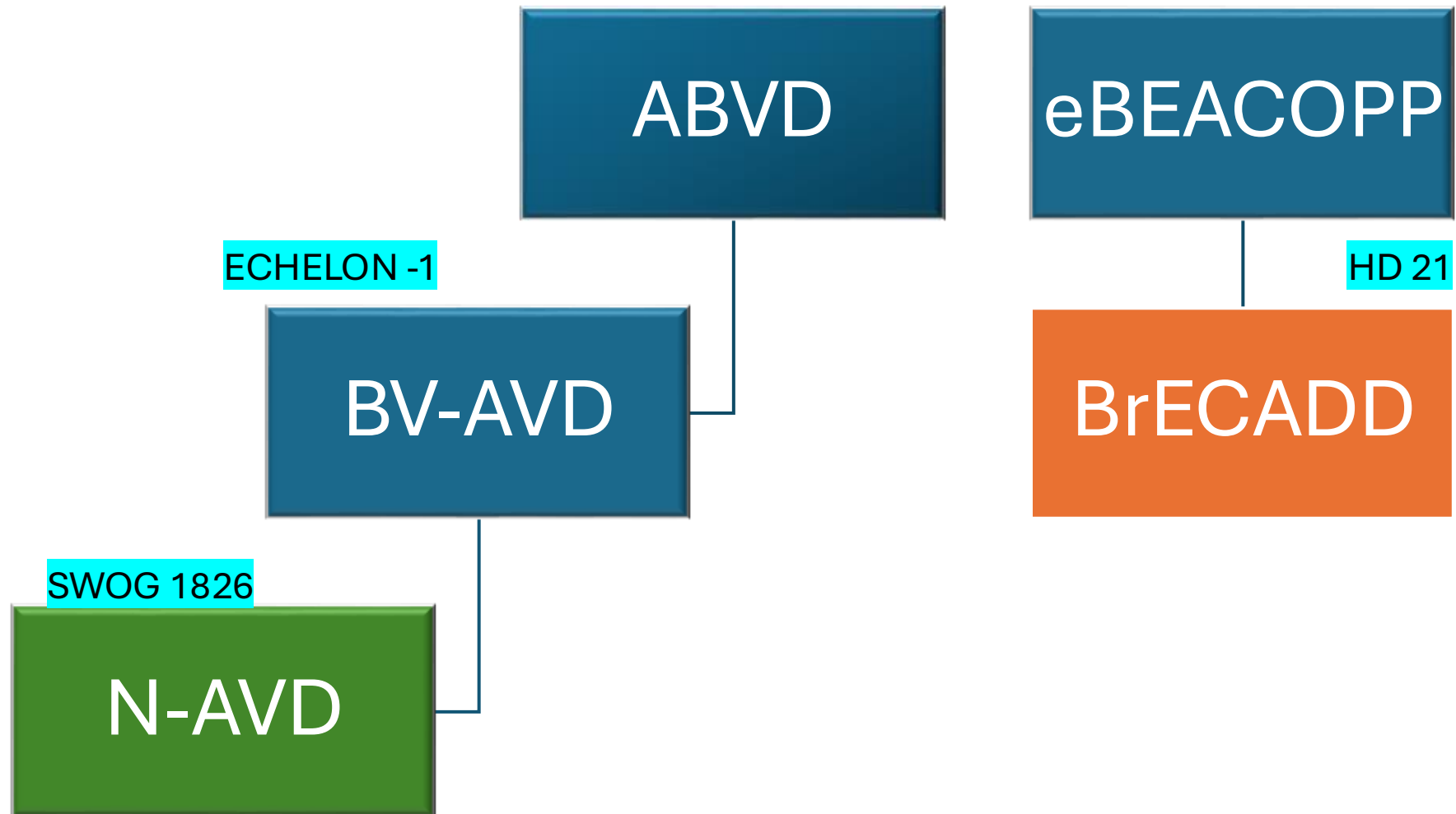
<sup>1</sup>Engert, et al. NEJM 2010; <sup>2</sup>Radford, et al. NEJM 2015; <sup>3</sup>Straus, et al. Blood 2018; <sup>4</sup>Eich, et al. JCO 2010; <sup>5</sup>Tresckow, et al. JCO 2012; <sup>6</sup>Johnson, et al. NEJM 2016; <sup>7</sup>Borchmann, et al. Lancet Onc. 2021; <sup>8</sup>Ansell, et al. 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

A microscopic image of tissue, likely a histological section, showing numerous cells with dark purple nuclei and lighter pink cytoplasm and extracellular matrix. The text is overlaid on the image in green font with a semi-transparent background.

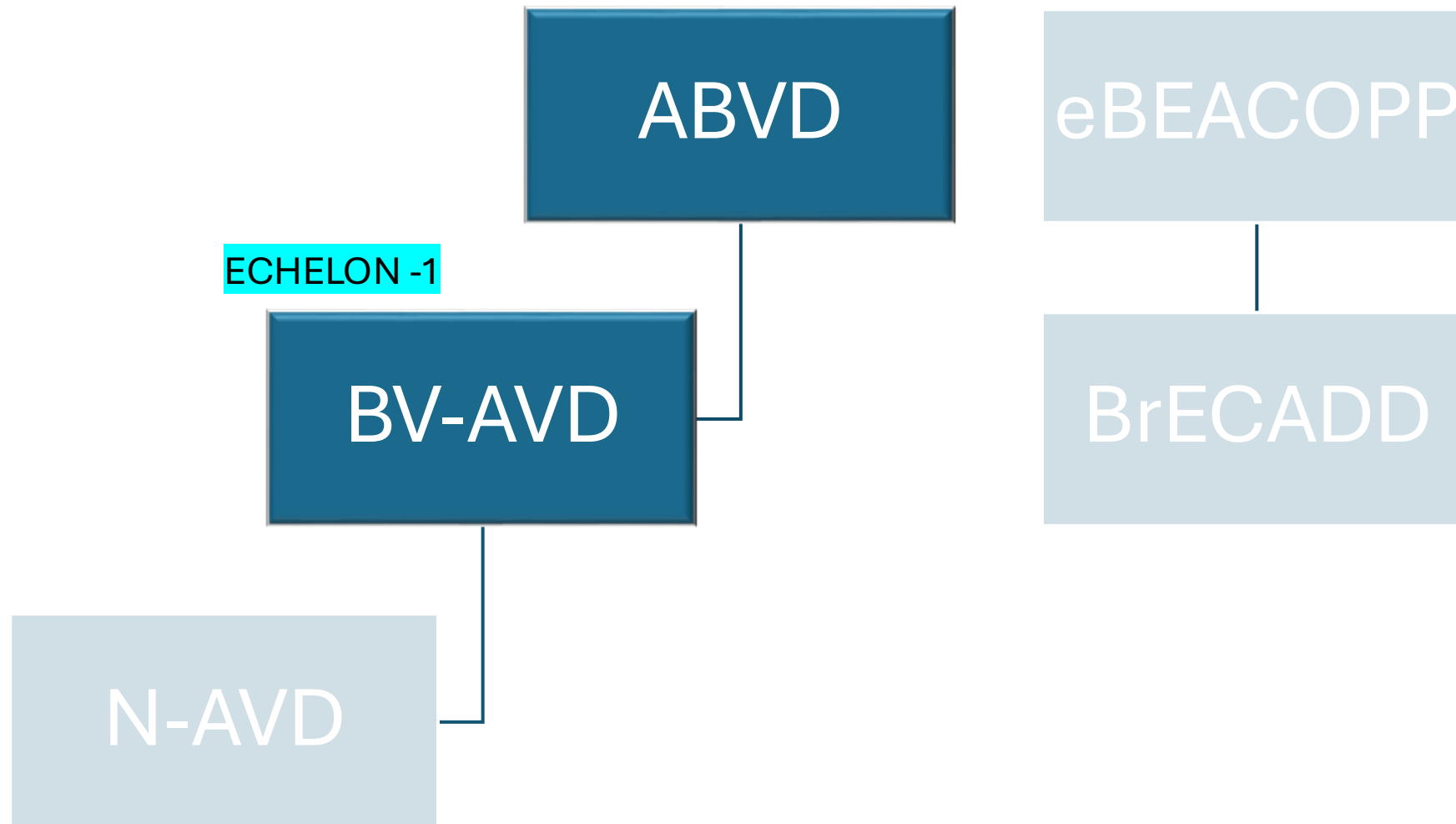
**ASHL: Sad but True (Metallica)  
the era of ABVD is over**

**unfortunately not in ESHL, the major unmet need in  
this disease!**

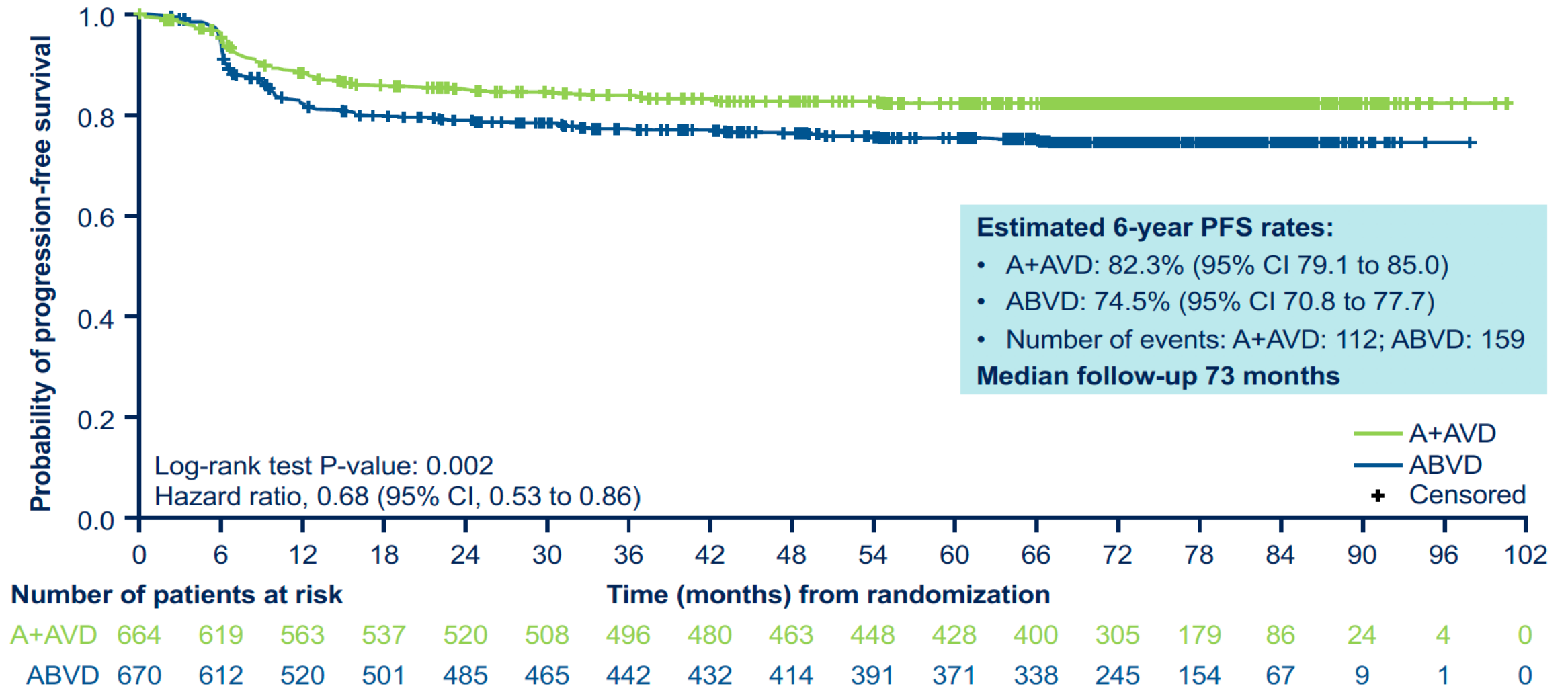
# THE PHASE III TRIALS



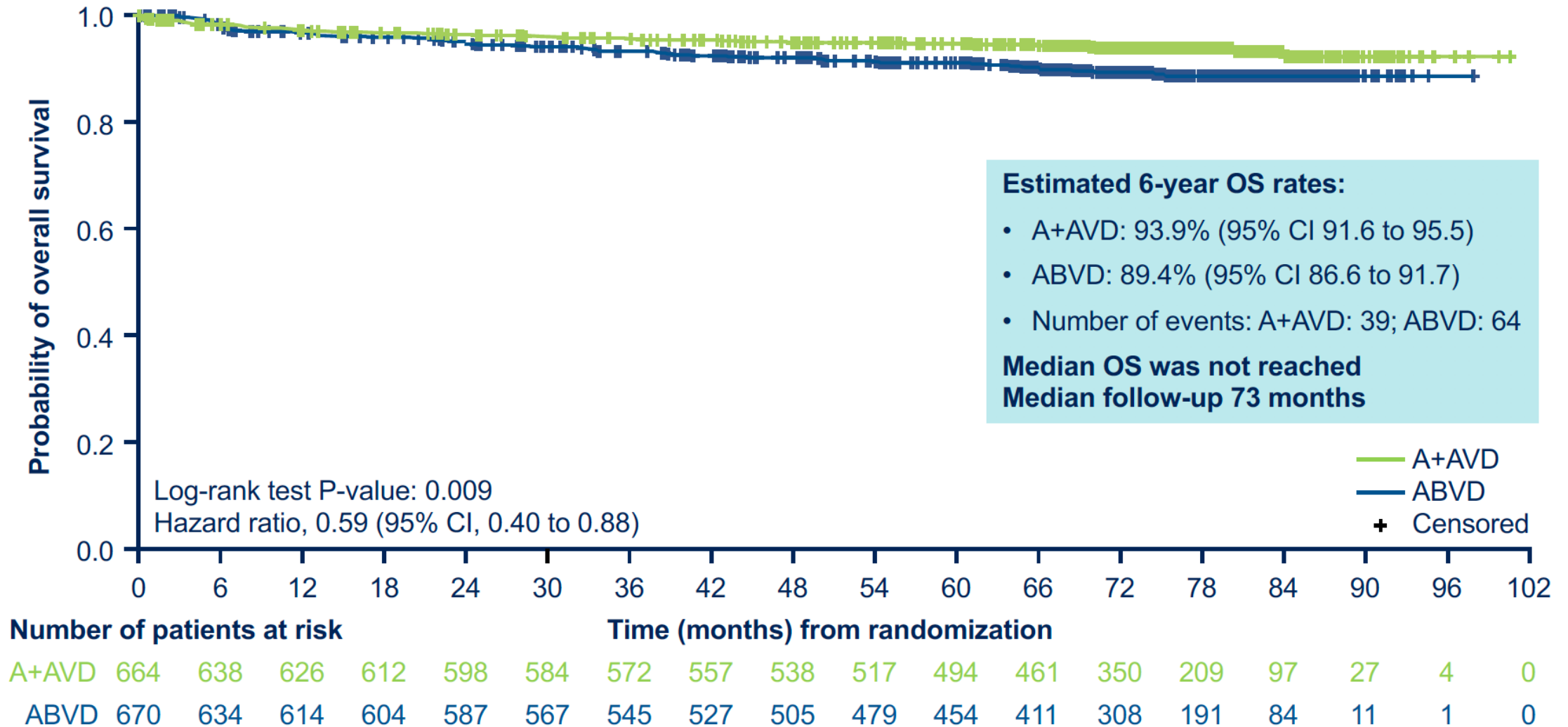
# THE PHASE III TRIALS: ECHELON-1 (stage III/IV)



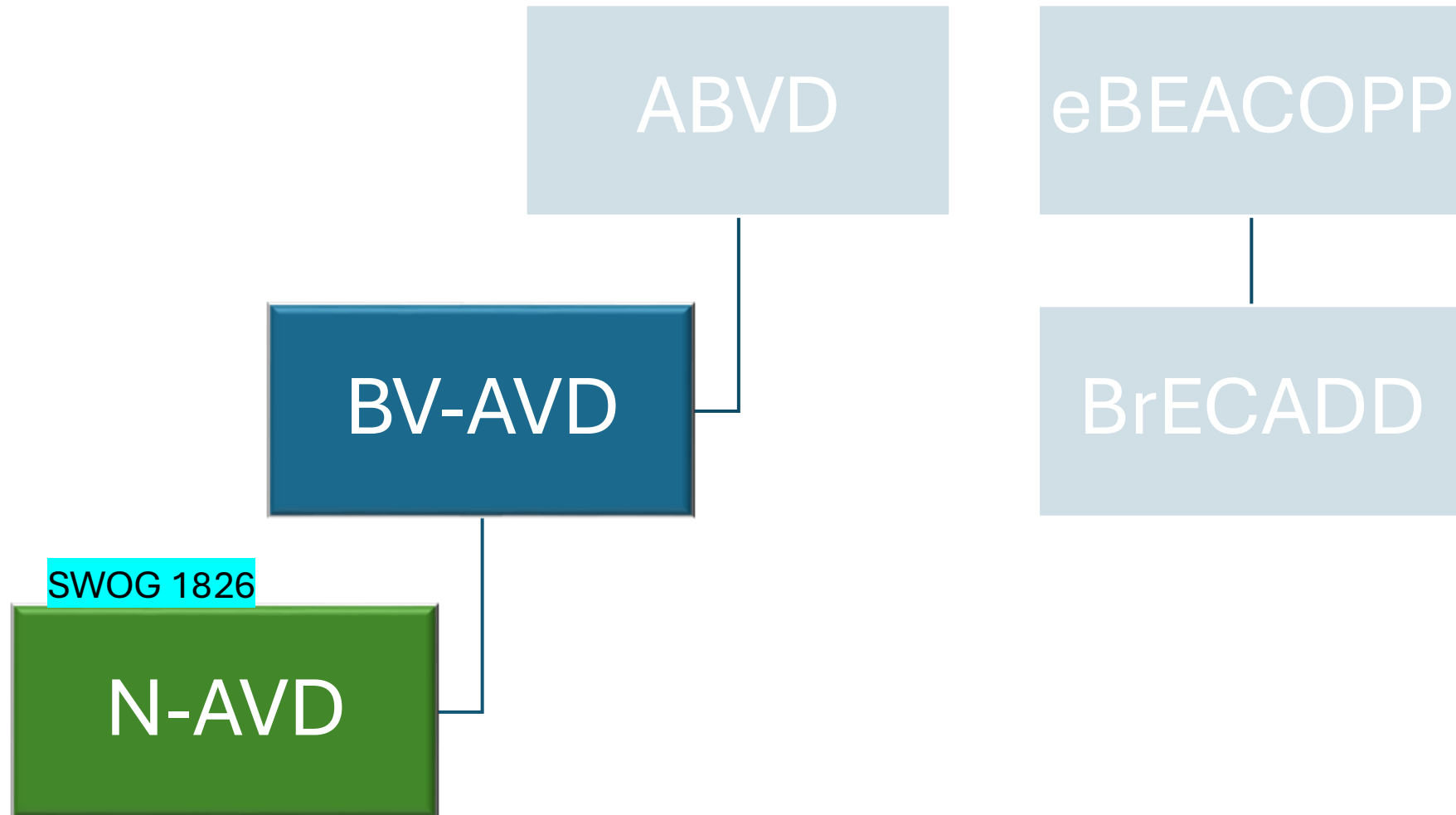
# ECHELON-1: 6-year follow-up shows sustained PFS benefit of BV-AVD



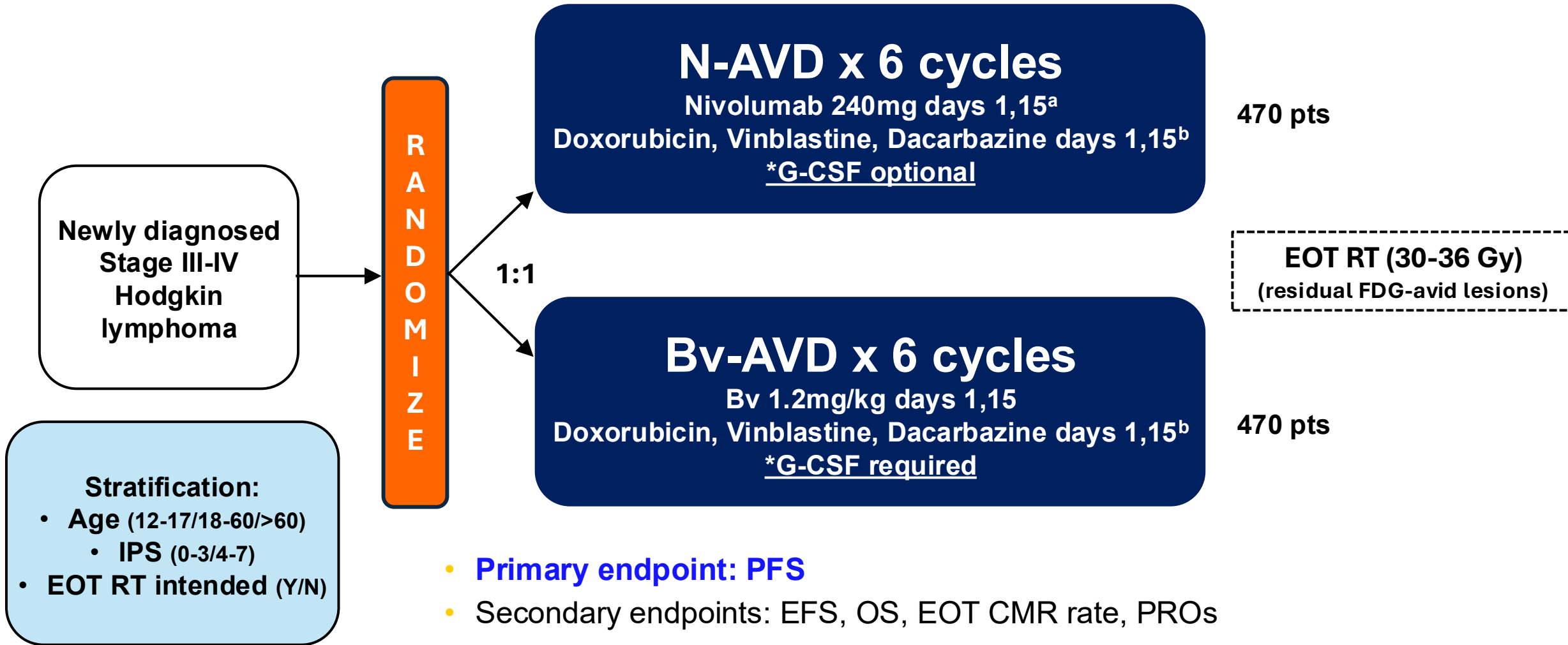
# ECHELON-1: At 6 years, BV-AVD significantly improved overall survival



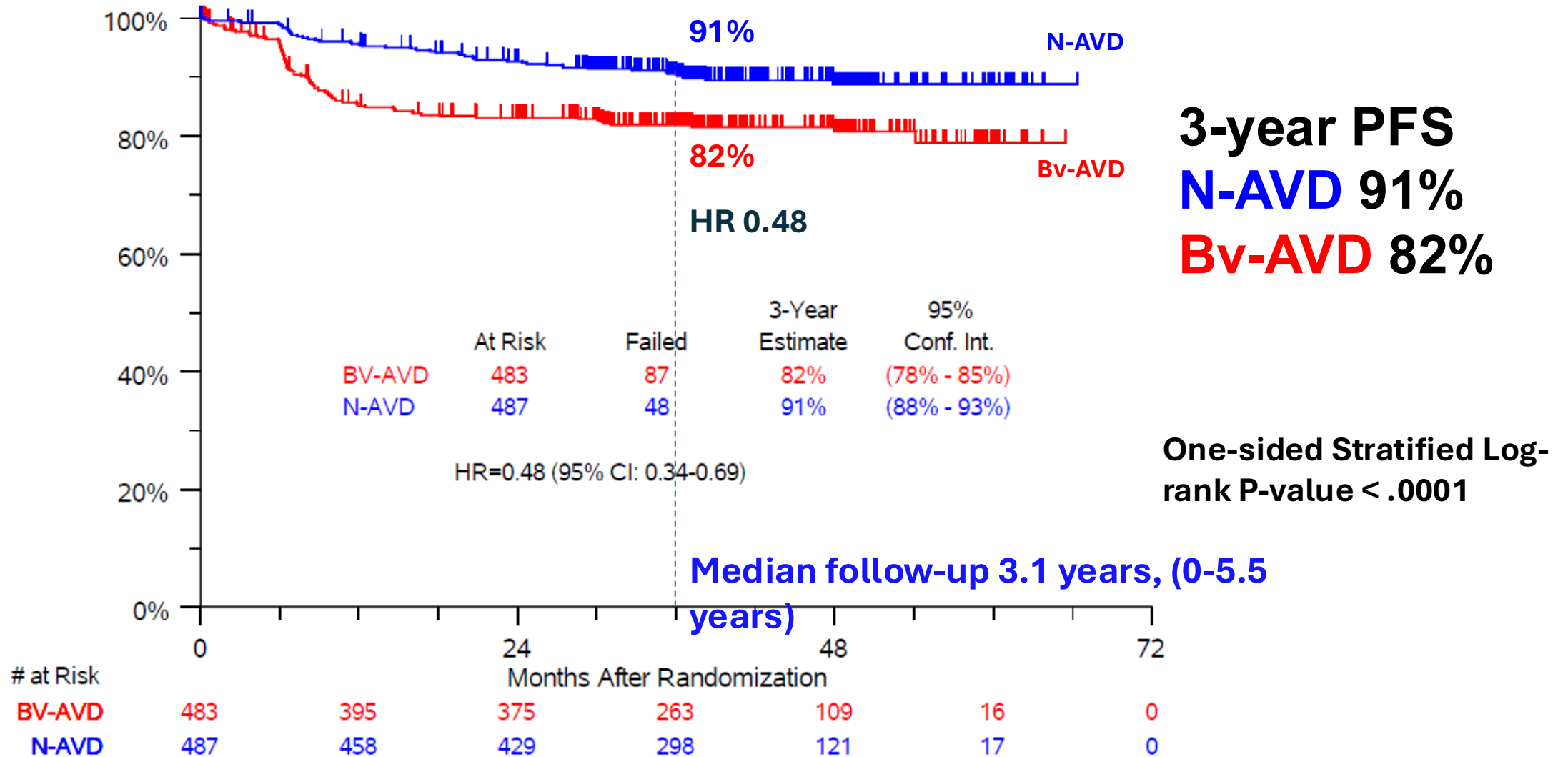
# THE PHASE III TRIALS: SWOG 1826 (stage III/IV)



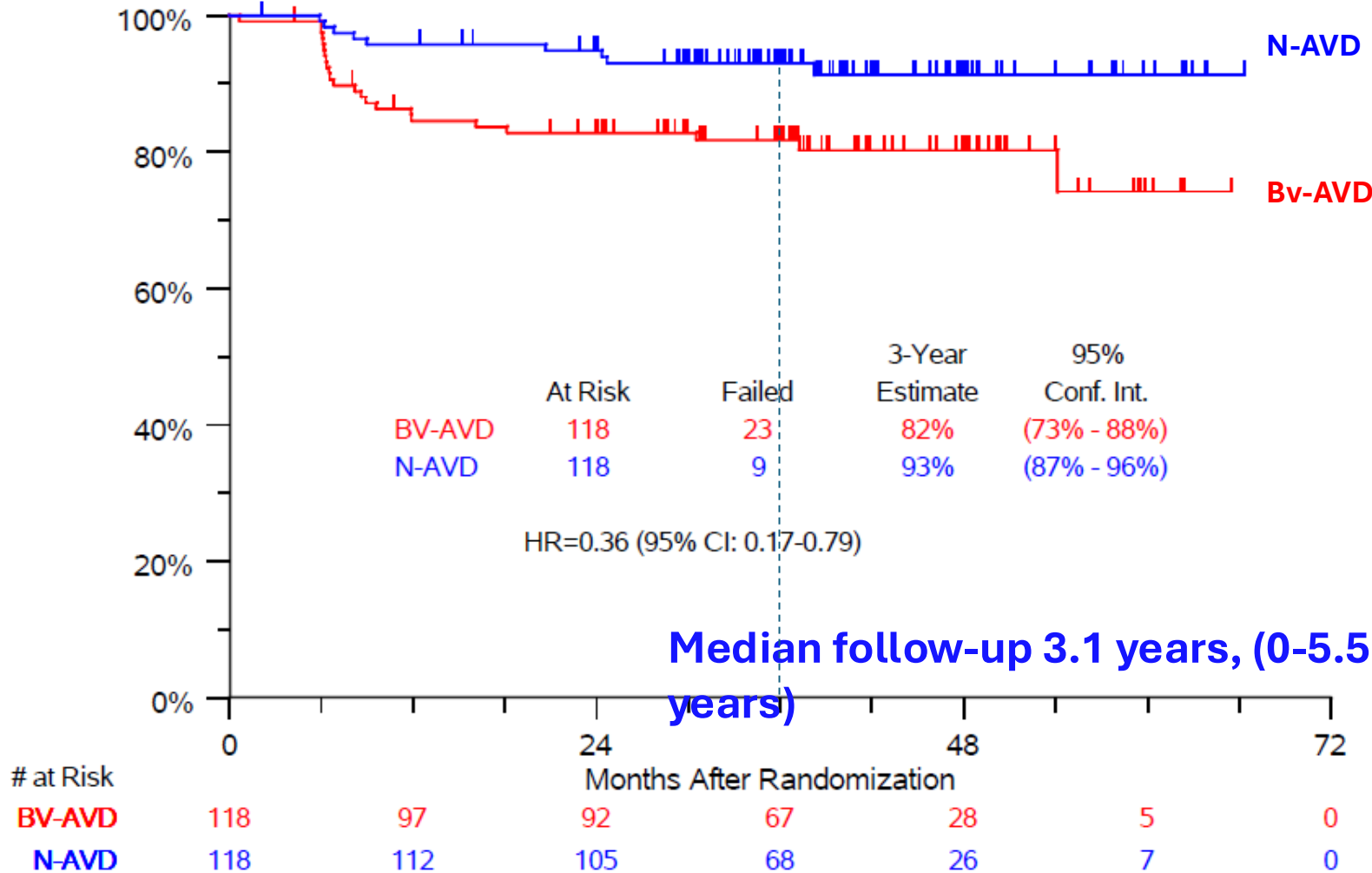
# SWOG 1826: BV-AVD vs N-AVD in 1L ASHL



# PFS benefit of N-AVD sustained with 3y follow-up



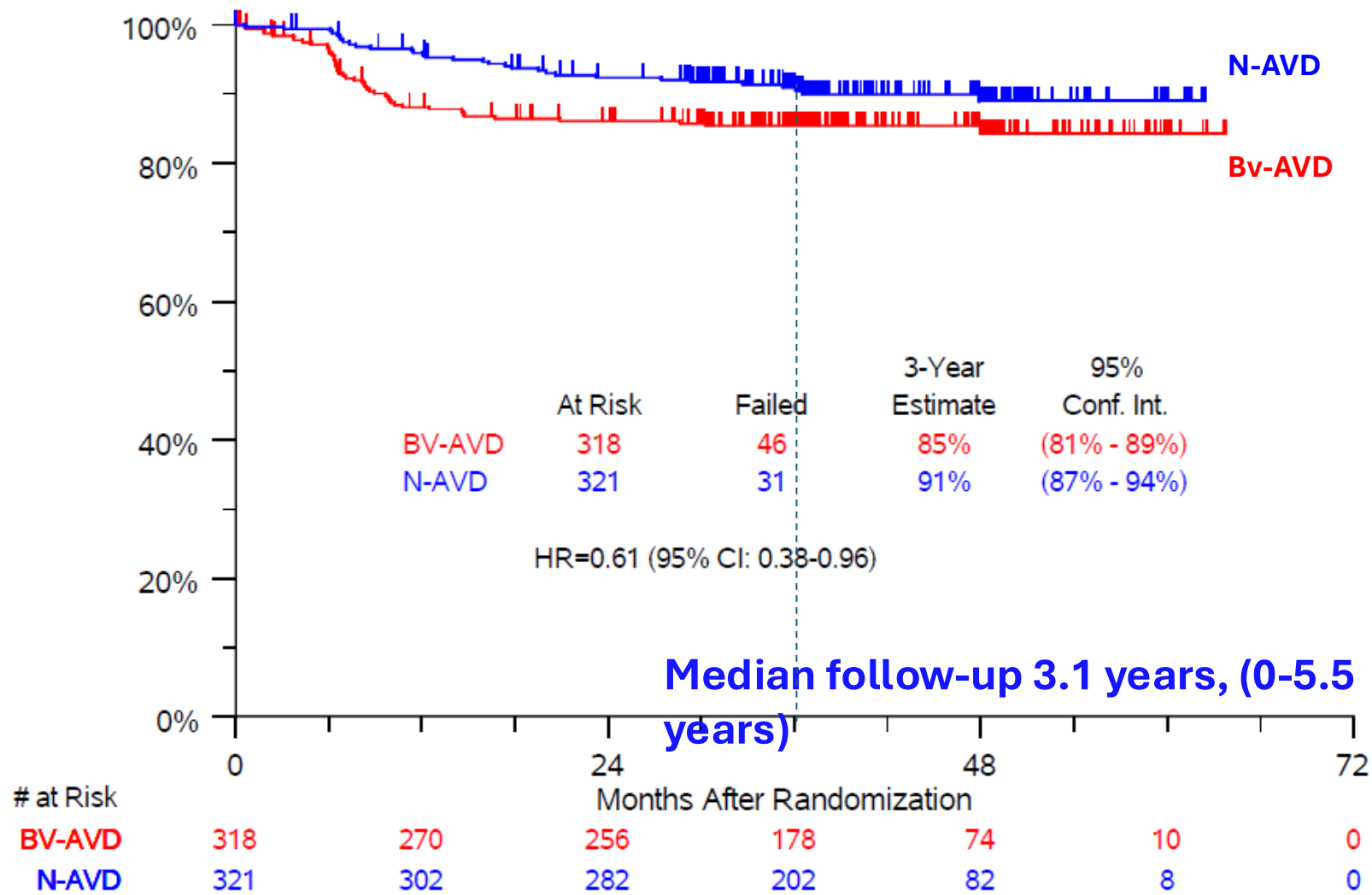
# N-AVD prolongs PFS in adolescents



**3-year PFS**  
**N-AVD 93%**  
**BV-AVD 82%**

One-sided Stratified  
 Log-rank P-value = .004

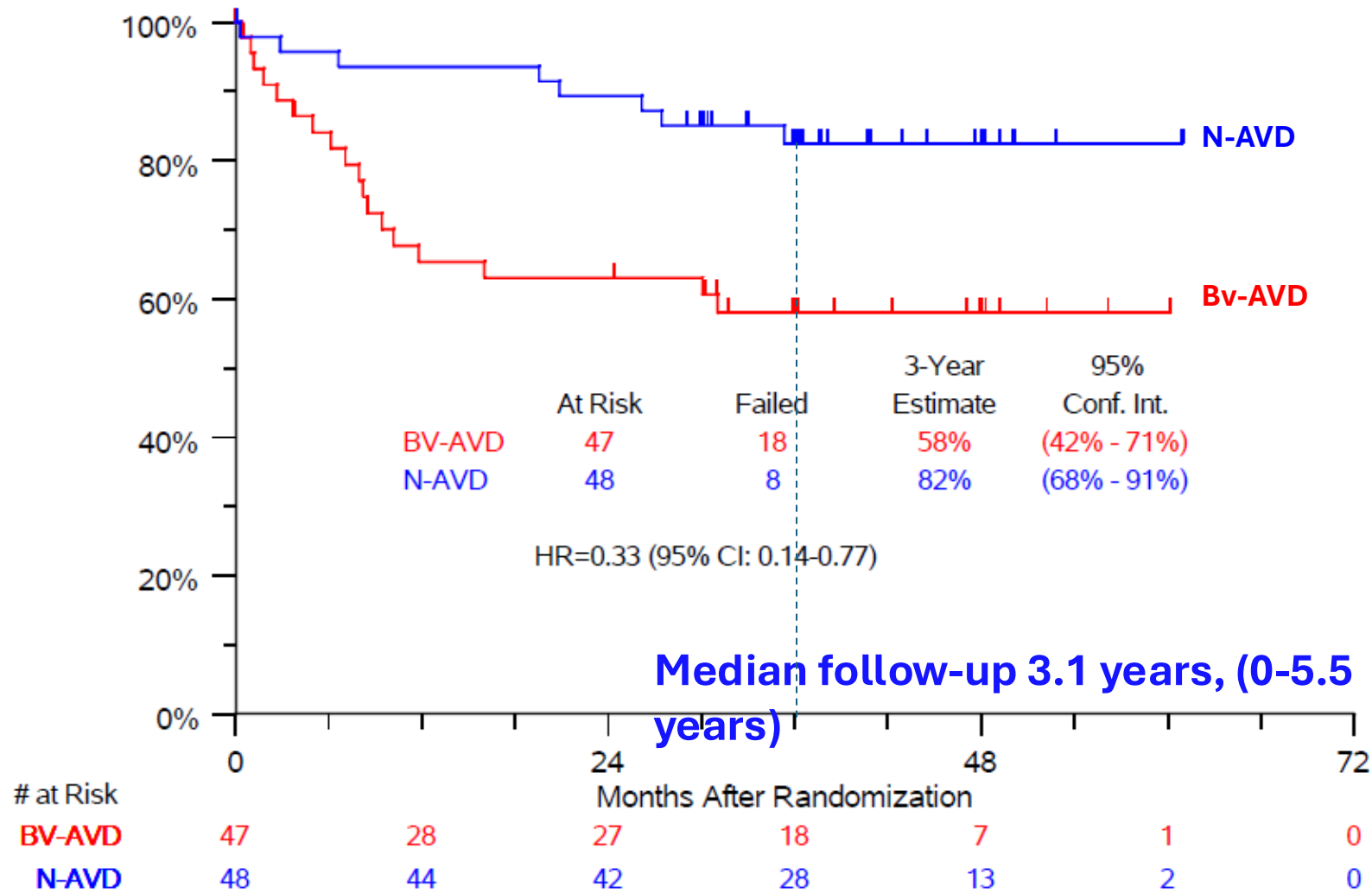
# N-AVD prolongs PFS in 18-60 year-old adults



**3-year PFS**  
**N-AVD 91%**  
**Bv-AVD 85%**

One-sided Stratified  
 Log-rank P-value =  
 .015

# N-AVD prolongs PFS in older adults

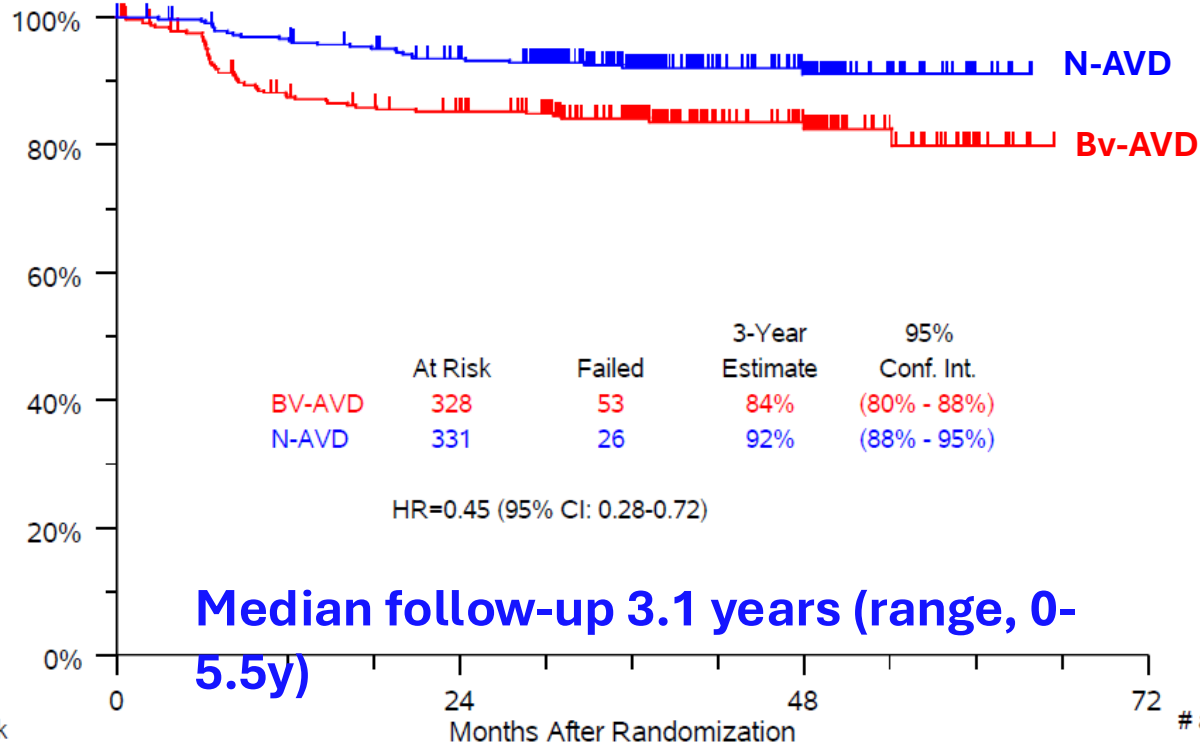


**3-year PFS**  
**N-AVD 82%**  
**Bv-AVD 58%**

One-sided Stratified  
 Log-rank P-value =  
 .003

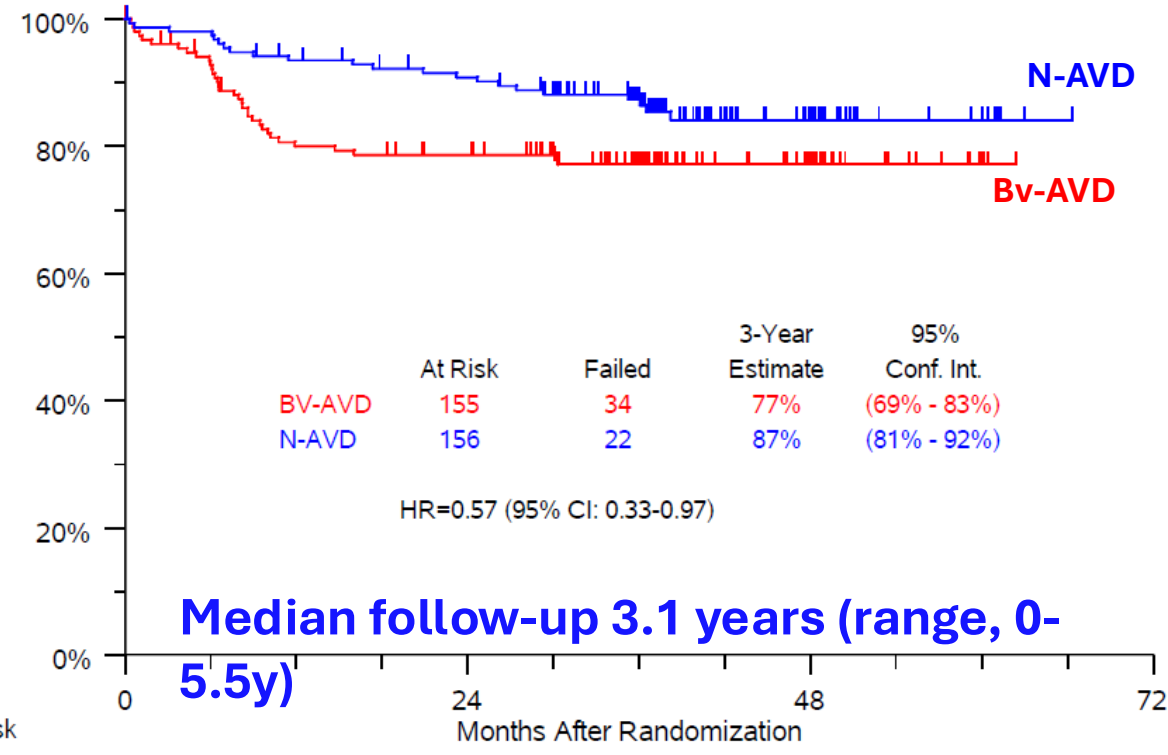
# N-AVD prolongs PFS in low and high-risk IPS

## IPS 0-3



Two-sided Log-rank P-value = 0.0006

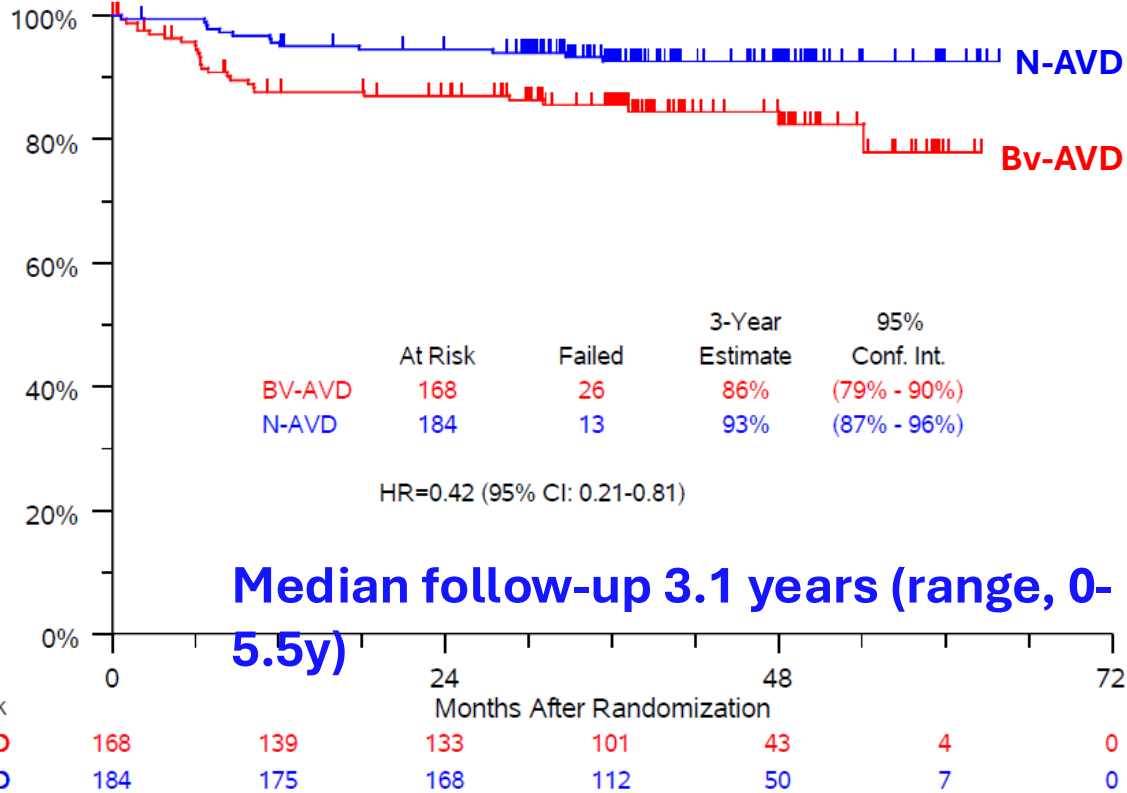
## IPS 4-7



Two-sided Log-rank P-value = 0.04

# N-AVD prolongs PFS in Stage III and Stage IV cHL

## Stage III

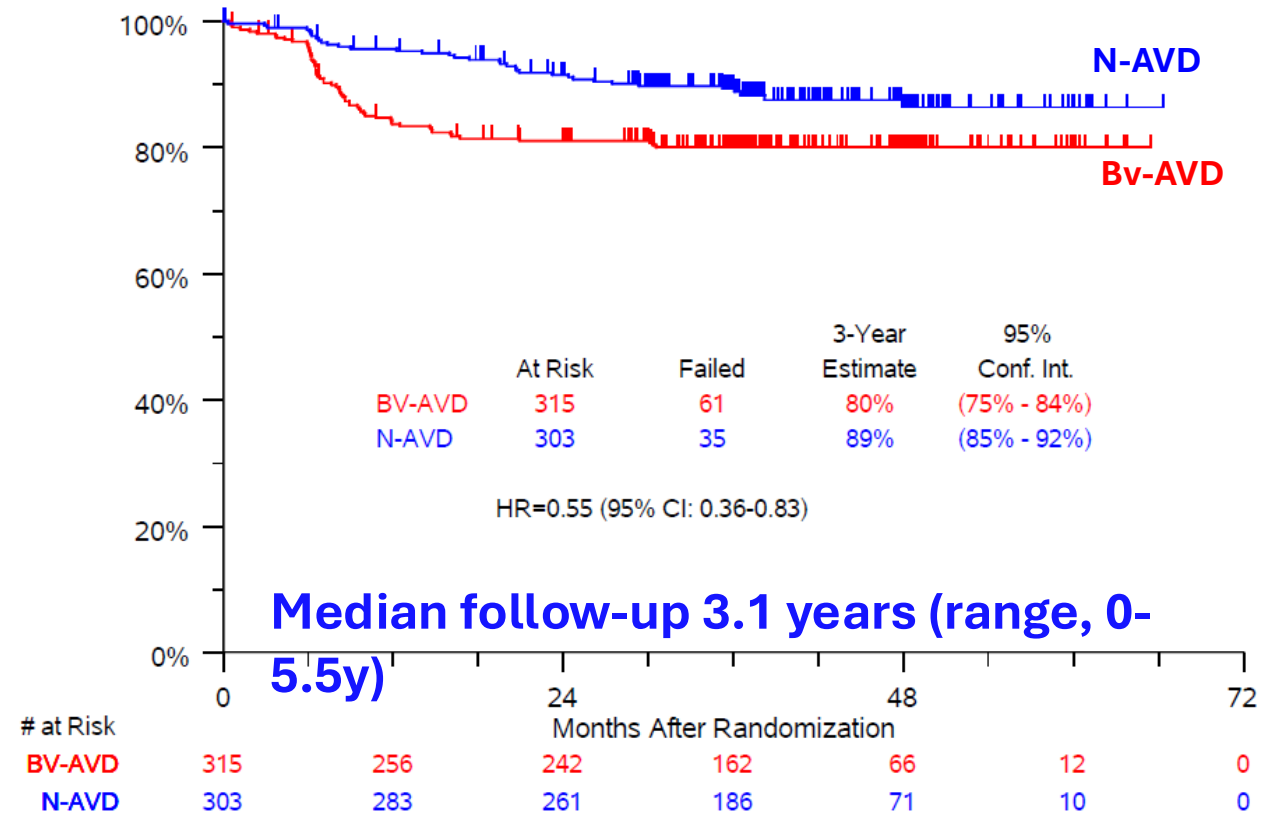


Median follow-up 3.1 years (range, 0-5.5y)

Two-sided Log-rank P-value = 0.008

Presented by: Alex F. Herrera, MD

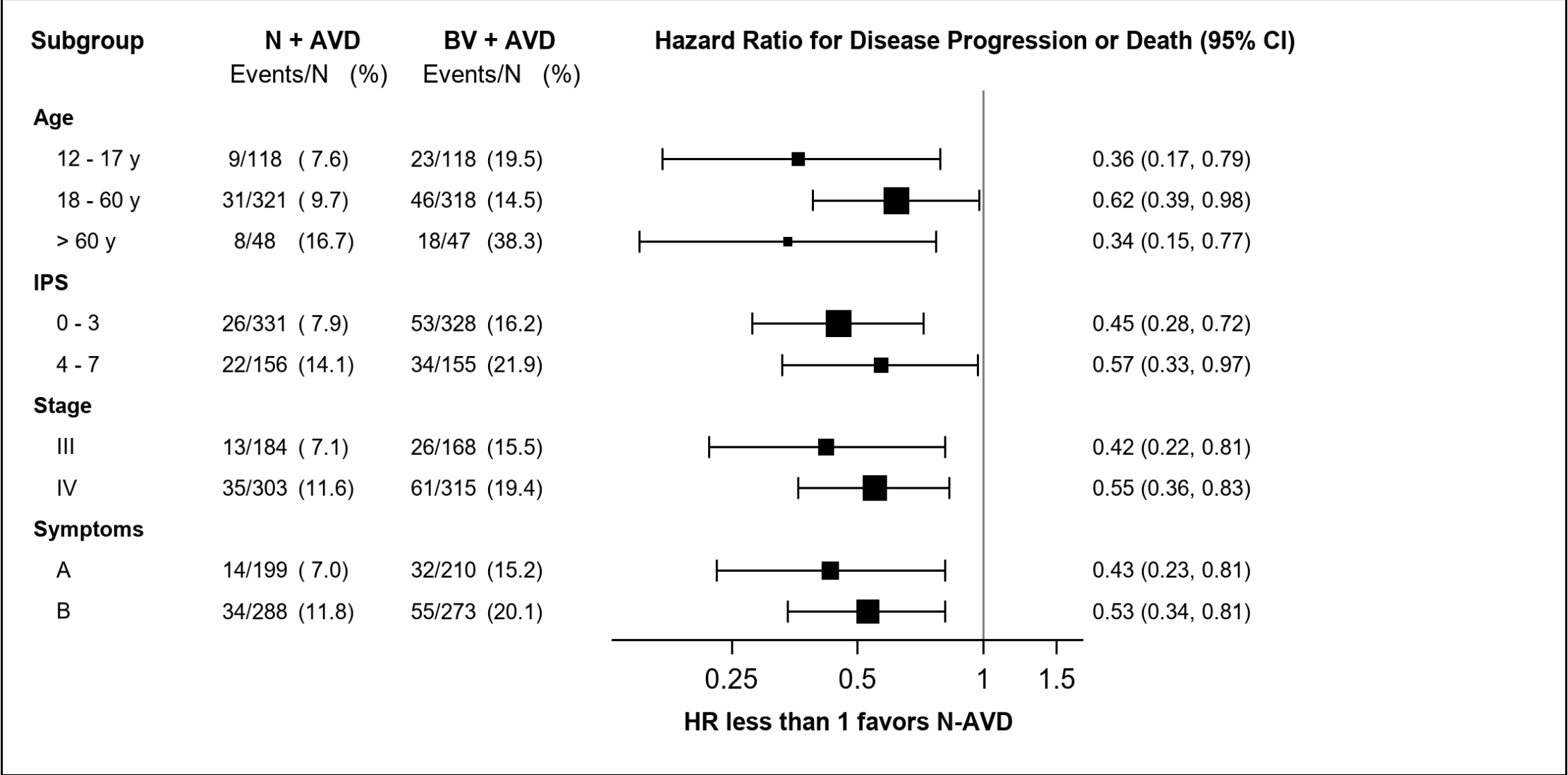
## Stage IV



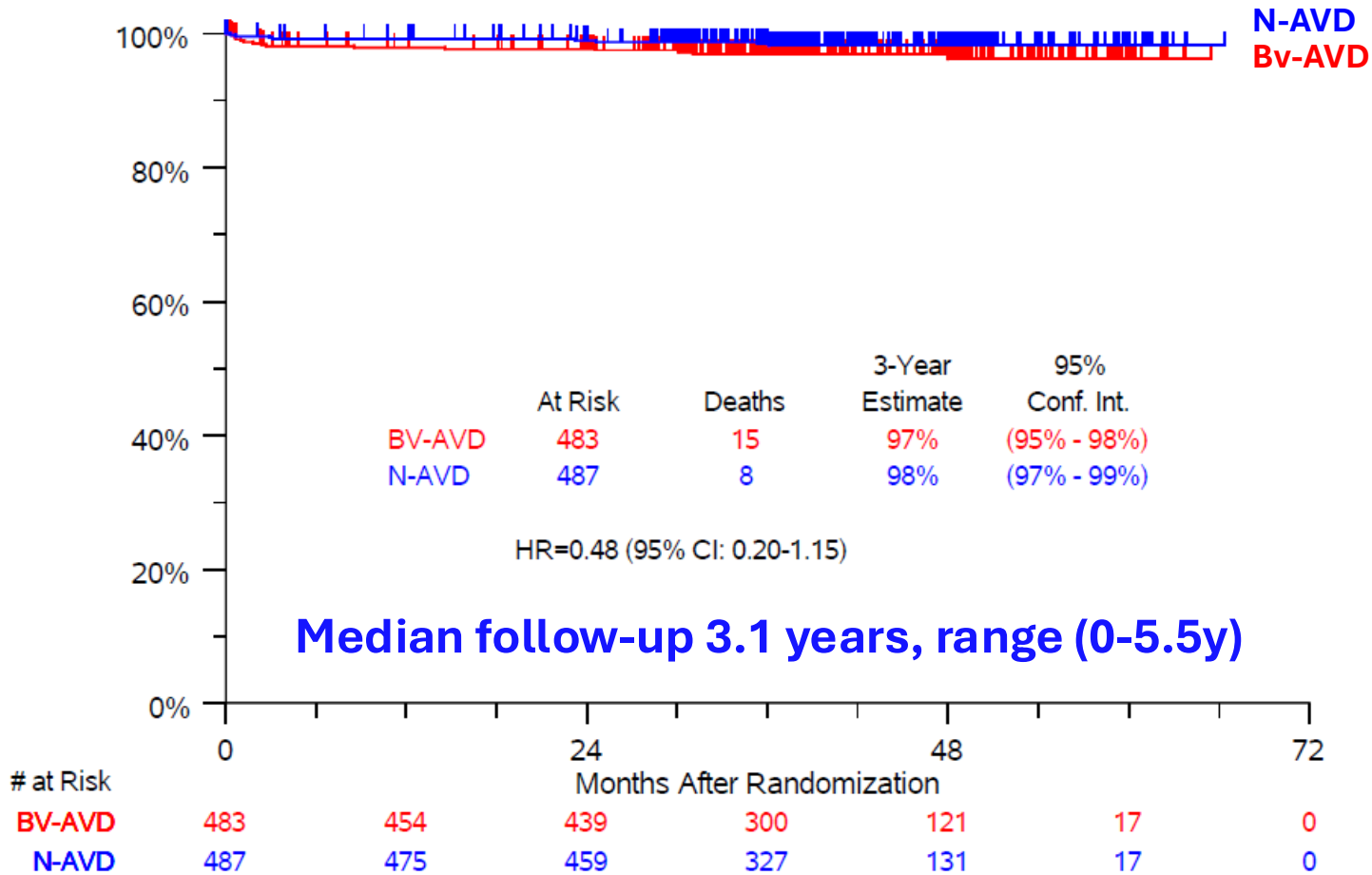
Median follow-up 3.1 years (range, 0-5.5y)

Two-sided Log-rank P-value = 0.004

# PFS benefit consistent across subgroups at 3y



# Overall Survival



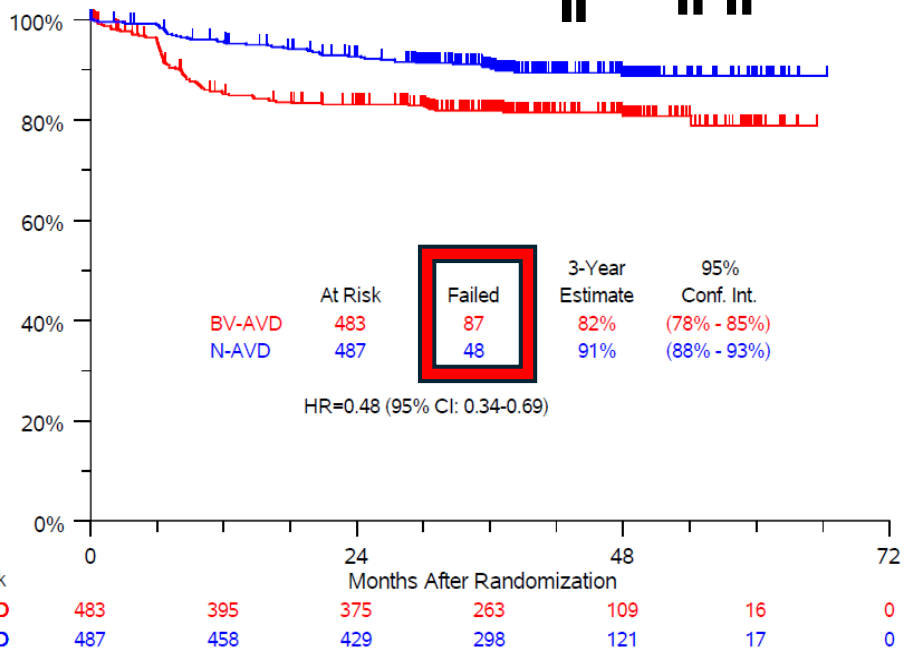
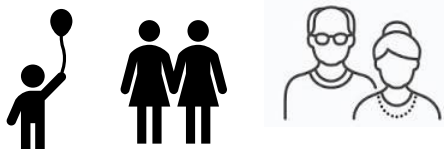
Cause of Death	N-AVD N=487	BV-AVD N=483
Infection/Sepsis	5	6
Lymphoma	1	2
Medical issues other than cancer	2	4
New primary cancer	0	1
Unknown	0	2
<b>Total</b>	<b>8</b>	<b>15</b>

# S1826 3-Year Update Conclusions

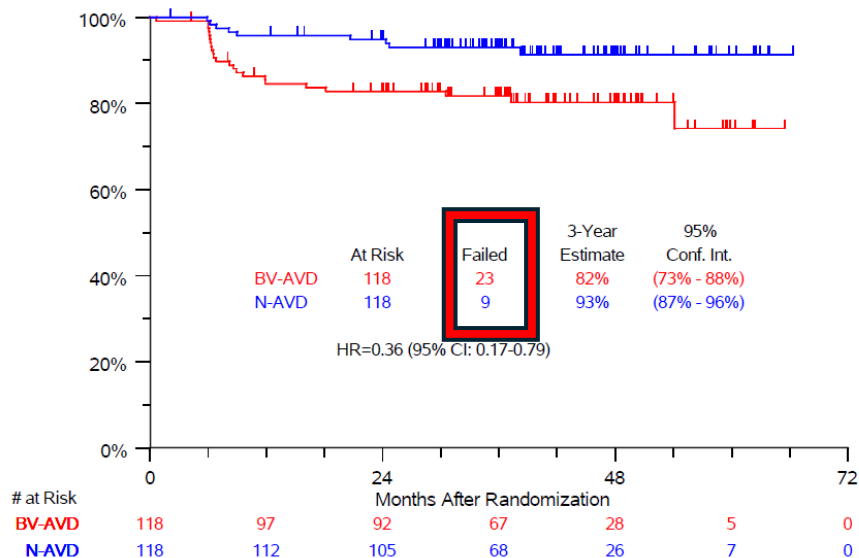
- **PFS benefit with N-AVD over Bv-AVD in advanced stage cHL sustained at 3 years of follow-up**
  - PFS benefit consistent across subgroups, including all age strata
  - N-AVD > BV-AVD in high-risk patients
    - Longer PFS in low and high IPS score groups
    - Longer PFS in stage III and stage IV patients
  - Low rate of second cancers with short follow-up
- **These data support N-AVD as a standard regimen for advanced stage cHL**
  - NCCN Guidelines category 1 recommendation

# S1826 3-Year Update Conclusions: A Closer Look at Who Benefits

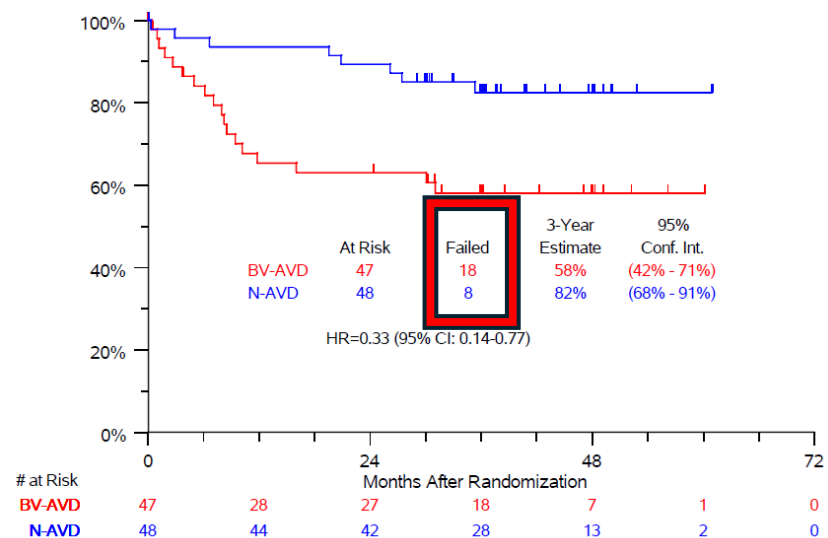
## SWOG 1826 ALL DATA



Statistically significant difference for patients 18-60? SWOG projected 3 yr estimates, One-sided Stratified Log-rank P-value = .015 but will need to follow data



PEDIATRIC



OLDER ADULT

# THE BIG DEBATE -N-AVD vs BRECAD

- Lets remember that ASHL is stage III/IV, not stage IIB(X,E)
- Length of Treatment: 3 -4.5 months vs 6 months
- Toxicity-is 6 months of N-AVD easier than 3 months of BRECAD?
- RT use-not necessarily a bad thing!
- Special populations
  - Older adults
  - Pediatrics
  - Co-Morbidities

# N-AVD vs BRECAD in Older Populations-

many of the more mature docs in this room-me

## Older patients ( $\geq 60$ years) with cHL

- Comprise 15-25% of all patients with cHL -**33% in Florida**<sup>1,2</sup>
- Often receive attenuated doses and/or fewer cycles due to toxicity<sup>1,3</sup>
- Can suffer from treatment-related mortality
- Experience poor outcomes w/ ABVD and pts  $\geq 65$  not eligible for BEACOPP studies<sup>4,6,7</sup>
- Have not had survival improvements vs younger patients with novel therapies<sup>3,4,5,8</sup>

<sup>1</sup>Proctor et al. Blood 2012.

<sup>2</sup>Stark et al. Br J Haematol 2002.

<sup>3</sup>Evens et al. Haematologica 2022.

<sup>4</sup>Evens et al. BJH 2013.

<sup>5</sup>Evens et al. Blood 2012.

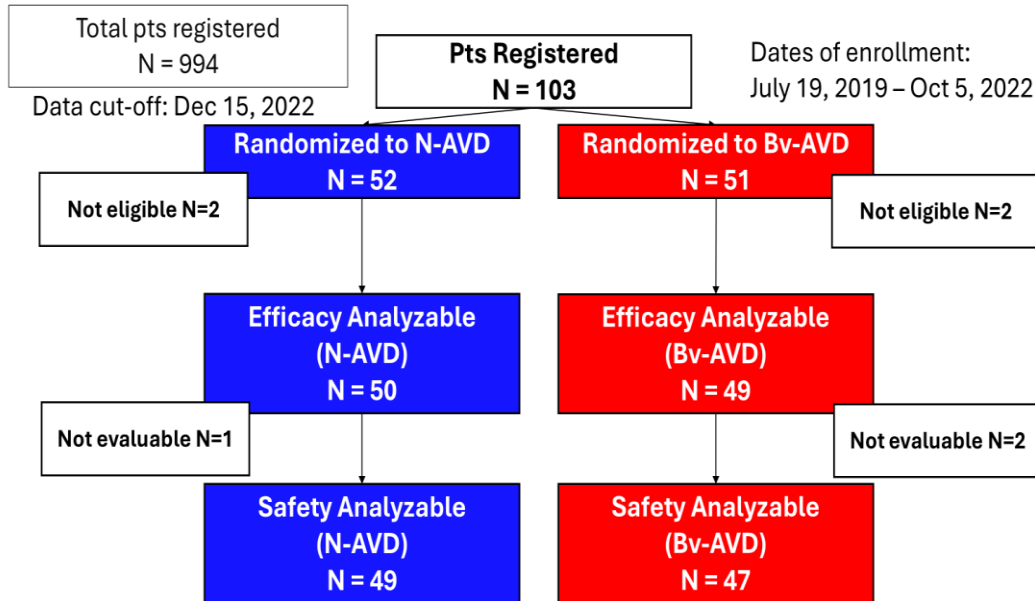
<sup>6</sup>Diehl et al. JCO 1998.

<sup>7</sup>Diehl et al. NEJM 2003.

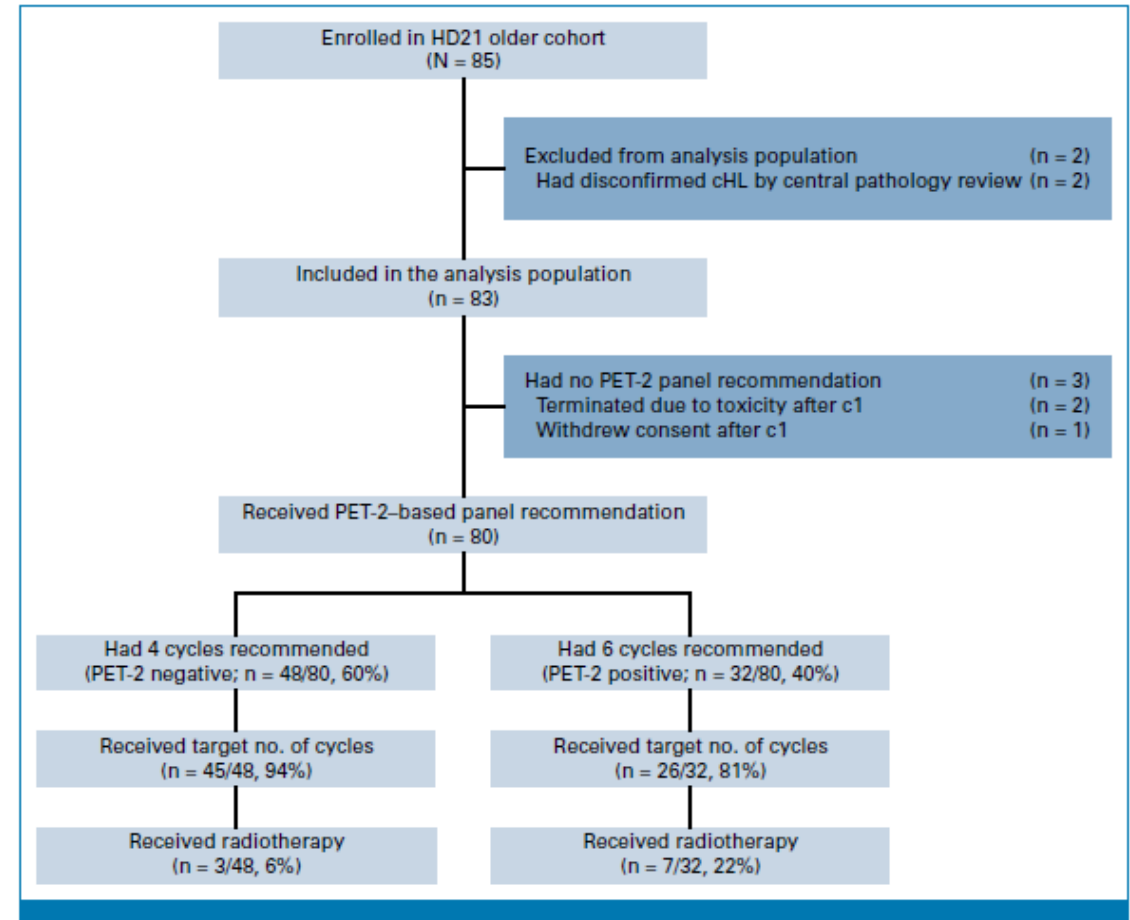
<sup>8</sup>Ansell et al. NEJM 2022.

# SWOG 1826

## S1826 CONSORT Diagram for Patients ≥60 years

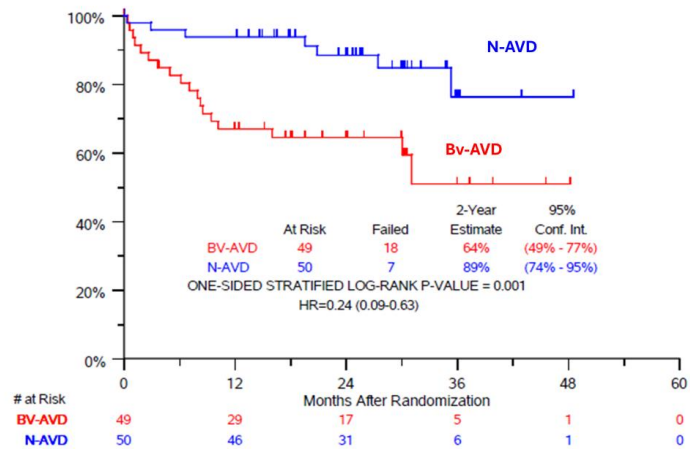


# HD21



# SWOG 1826: Clinical Outcomes

At 2.1y median follow up, PFS benefit of N-AVD over Bv-AVD in older patients with cHL is sustained

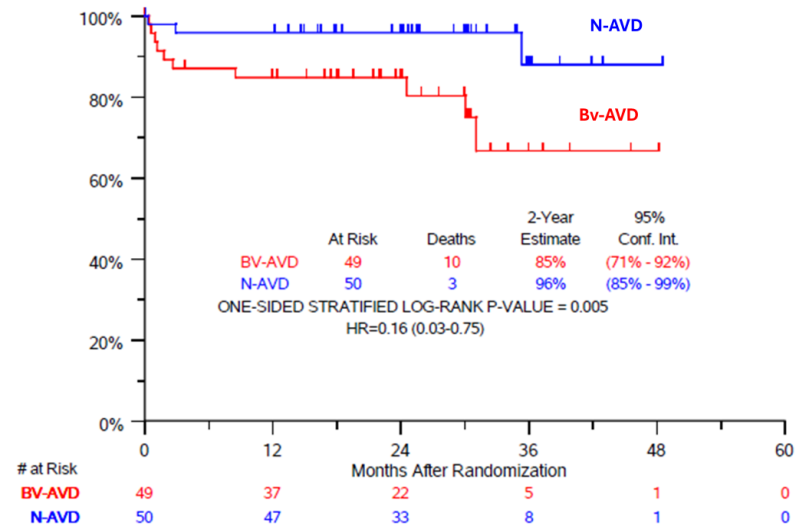


**2-year PFS**  
**N-AVD 89%**  
**Bv-AVD 64%**

Median follow-up  
 2.1y

p-value = 0.001  
 HR=0.24,  
 95% CI (0.09-0.63)

N-AVD improves OS over Bv-AVD in older patients



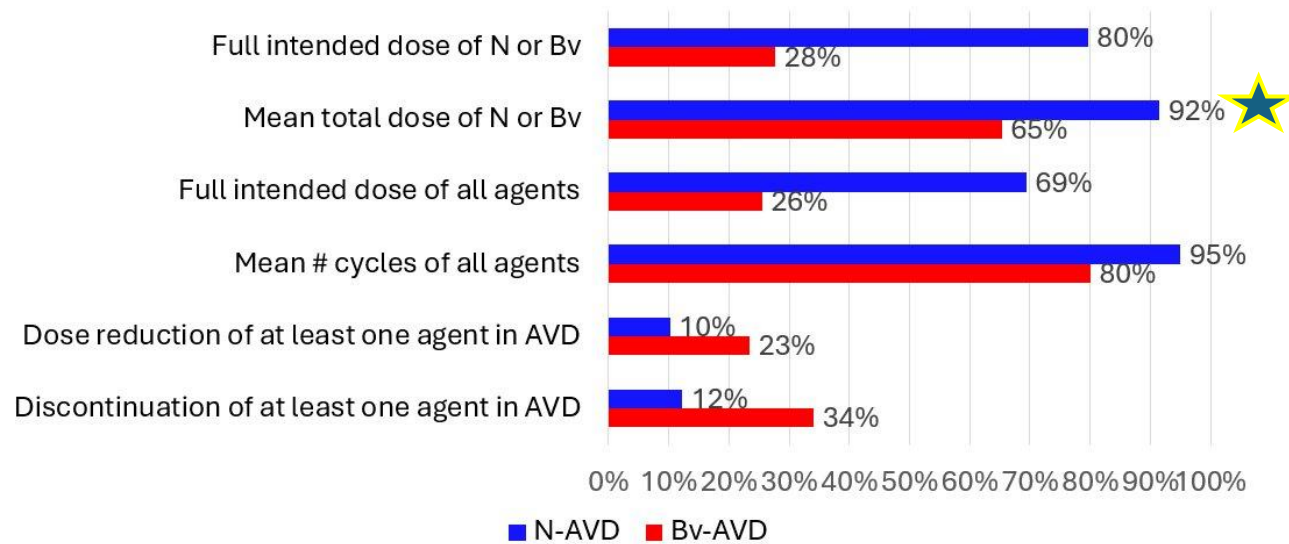
**2-year OS**  
**N-AVD 96%**  
**Bv-AVD 85%**

Median follow-up  
 2.1y

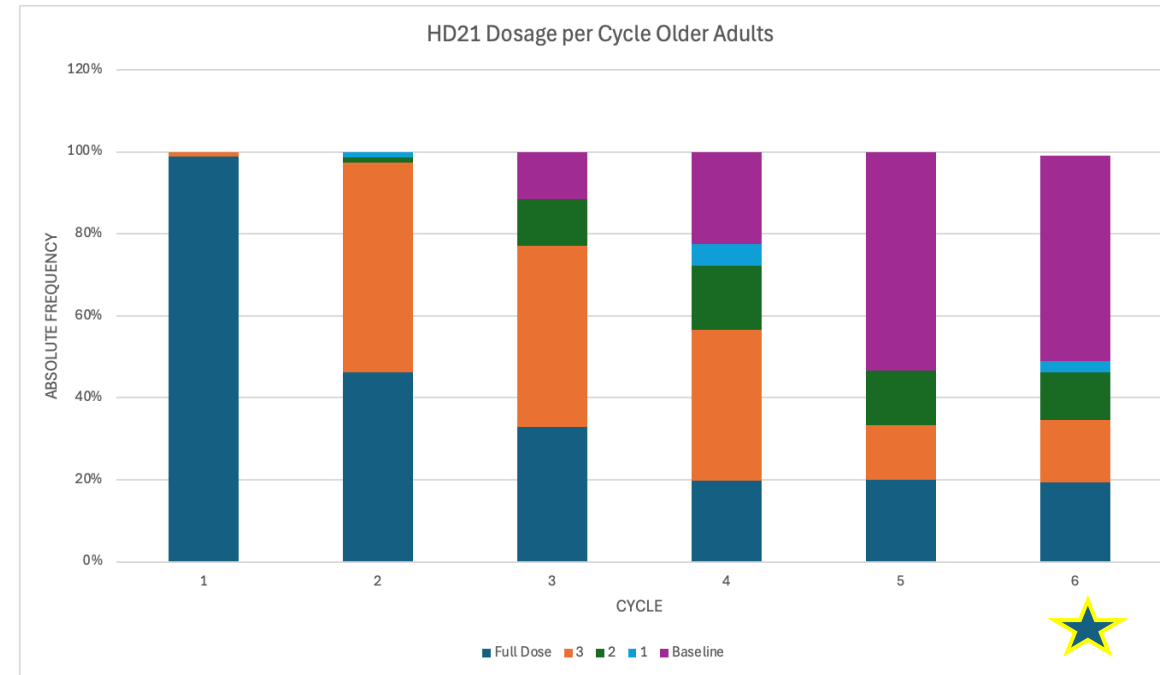
p-value = 0.005  
 HR=0.16,  
 95% CI (0.03-0.75)

# TOLERABILITY OF TREATMENT

## SWOG 1826



## HD 21

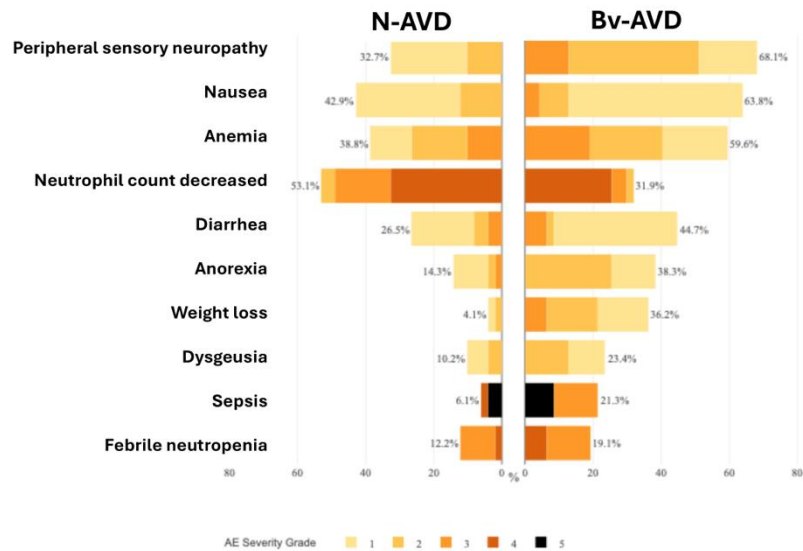


By cycle 6, 50% of patients are at baseline dose

# TOLERABILITY OF TREATMENT

## SWOG 1826

### Key adverse events in $\geq 15\%$ of older patients



## HD 21

Adverse Event	Any Grade, No. (%)	Grade $\geq 3$ , No. (%)
Anemia	81 (98)	57 (69)
Leukopenia	81 (98)	80 (96)
Thrombocytopenia	78 (94)	71 (86)
Gastrointestinal disorders	60 (72)	19 (23)
Infection	55 (65)	39 (47)
Mucositis	47 (57)	14 (17)
Neutropenic fever	46 (55)	46 (55)
Respiratory, thoracic and mediastinal disorders	37 (45)	5 (6)
Skin and subcutaneous tissue disorders	35 (42)	1 (1)
Peripheral sensory neuropathy	33 (40)	1 (1)
Nausea	30 (36)	4 (5)
Nervous system disorder (other than neuropathy)	24 (29)	3 (4)
Cardiac disorders	23 (28)	2 (2)
Renal and urinary disorders	12 (15)	3 (4)
Hepatobiliary disorders	7 (8)	2 (2)
Peripheral motor neuropathy	7 (8)	2 (2)
Drug fever	3 (4)	1 (1)
Allergy	3 (4)	1 (1)
Other <sup>a</sup>	66 (80)	29 (47)
Hematologic TRMB event, No. (%)	60 (72)	
Organ TRMB event, No. (%)	28 (34)	
Any TRMB event, No. (%)	66 (80)	

Abbreviation: TRMB, treatment-related morbidity.

# CONCLUSIONS IN OLDER ADULTS



N-AVD is better tolerated than Bv-AVD and BrECADD with fewer dose reductions and discontinuations



BrECADD is reporting slight improvement in PFS, however, this does not translate to OS benefit



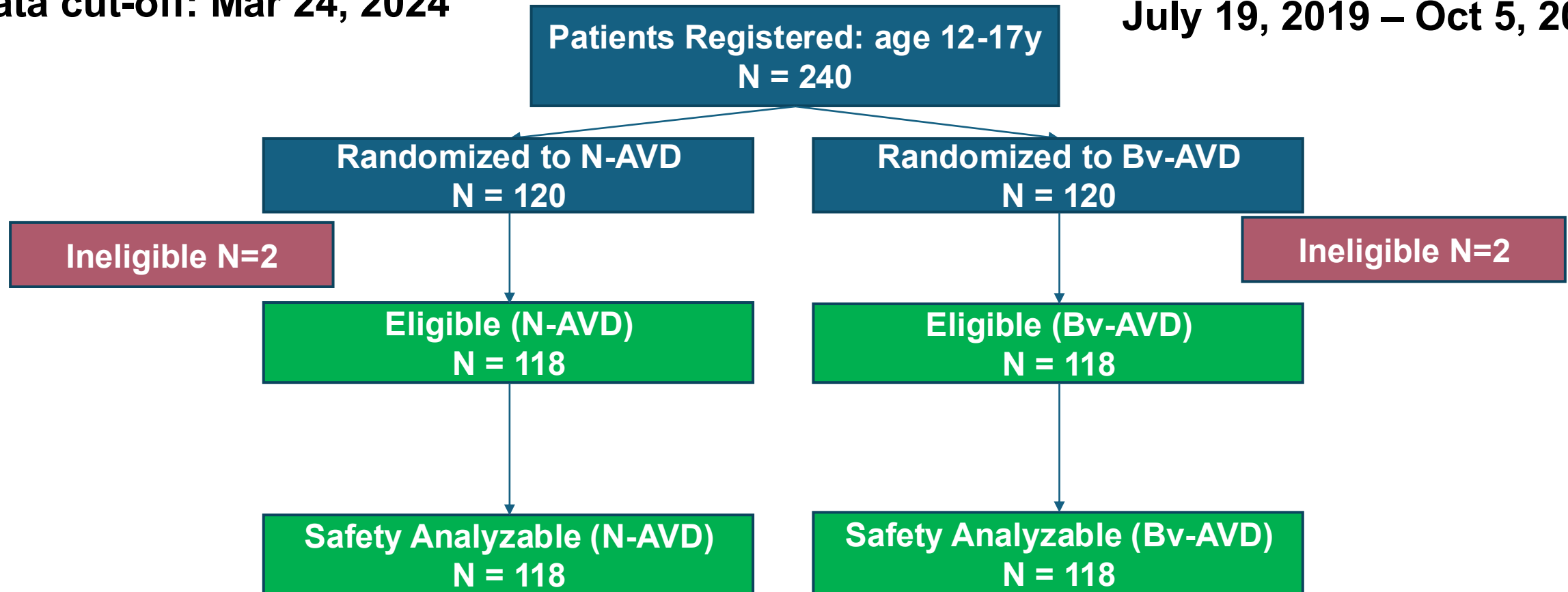
**In my practice, N-AVD is a standard of care for older pts with advanced stage cHL fit for anthracycline-based combination therapy**

# SPECIAL POPULATIONS: PEDIATRICS

## S1826

Data cut-off: Mar 24, 2024

Dates of enrollment:  
July 19, 2019 – Oct 5, 2022

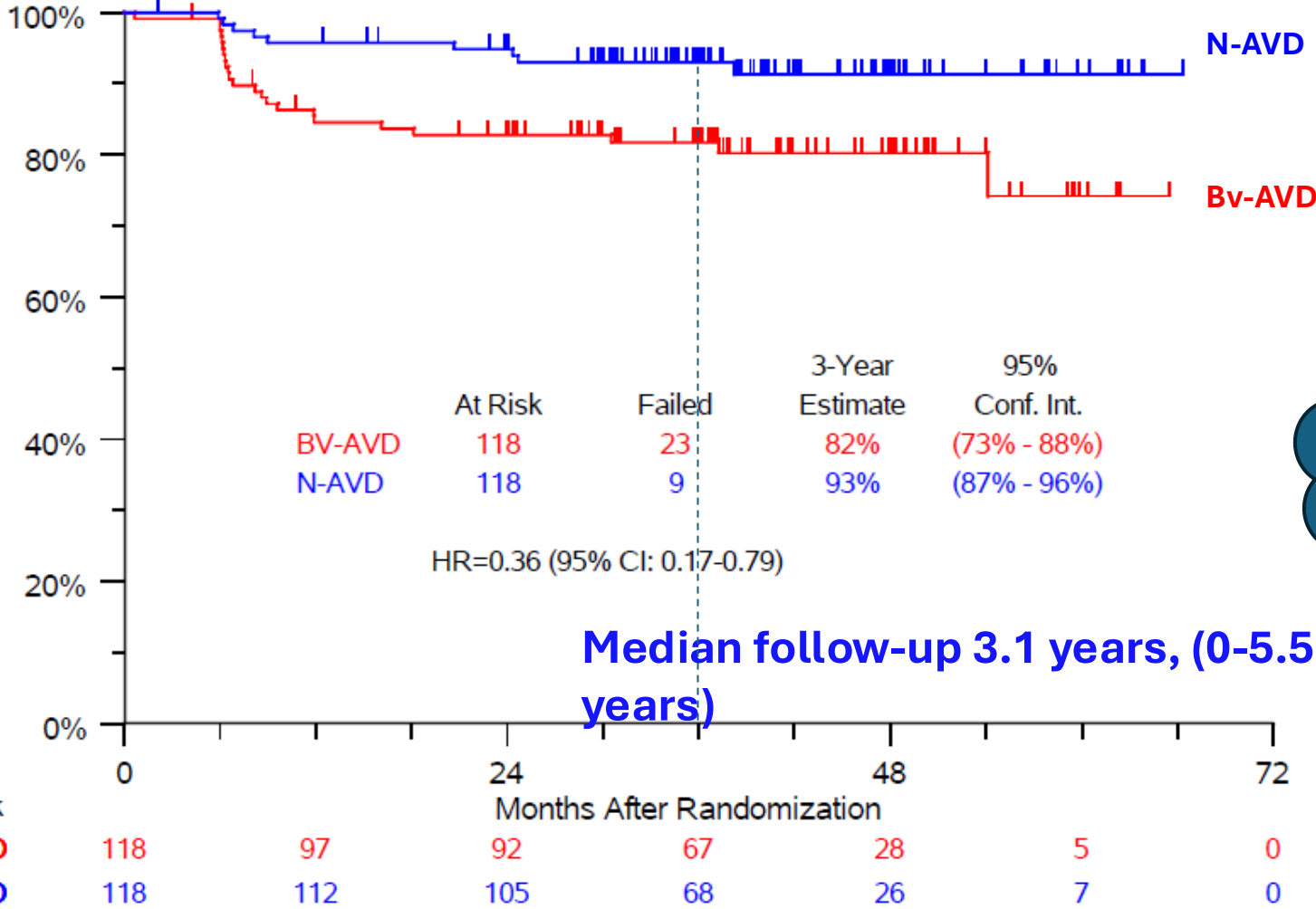


# S1826 Pediatric Cohort

Patient characteristics	N-AVD n=118 N (%)	Bv-AVD n=118 N (%)
Age yrs., median (range)	15.4 (12-17.9)	15.7 (12-17.9)
Female Sex	51 (43%)	65 (55%)
Race		
White	82 (70%)	78 (66%)
Black	18 (15%)	17 (14%)
Asian	0 (0%)	5 (4%)
Other/Unknown	18 (15%)	18 (15%)
Hispanic	24 (20%)	17 (14%)

Disease characteristics	N-AVD n=118 N (%)	Bv-AVD n=118 N (%)
Stage		
III	54 (46%)	47 (40%)
IV	64 (54%)	71 (60%)
B symptoms present	68 (58%)	67 (57%)
IPS Score		
0-3	88 (75%)	82 (66%)
4-7	30 (25%)	36 (30%)
Bulky disease > 10 cm	56 (48%)	46 (39%)

# N-AVD prolongs PFS in adolescents



**3-year PFS**  
**N-AVD 93%**  
**BV-AVD 82%**

HD21 Did NOT include pediatric cohort

One-sided Stratified Log-rank P-value = .004

**Median follow-up 3.1 years, (0-5.5 years)**

# SPECIAL POPULATIONS: CO-MORBIDITIES

- **Peripheral Neuropathy**

- Baseline PN>G1 were excluded from HD21 and  $\geq 2$  were excluded from SWOG
- Incidence of Any grade PN in SWOG1826 and HD21
  - N-AVD: 29%; 1%  $\geq$ G3
  - BV-AVD: 56%; 8%  $\geq$  G3
  - BrECADD: 39%; 1%  $\geq$ G3

- **HIV**

- Excluded from HD21; included in SWOG!

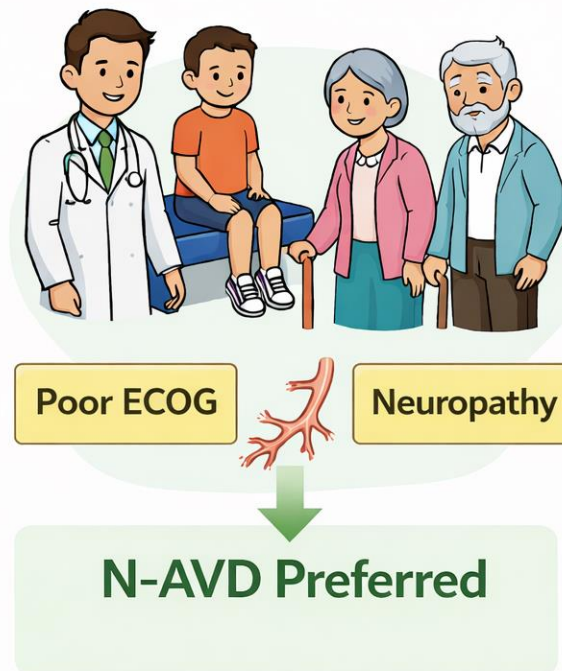
# CONCLUSIONS: N-AVD vs BrECADD

- ❖ Both have a role in the treatment of ASHL
- ❖ I treated 27 pts on SWOG 1826 *and have an IIT with BRECADD*

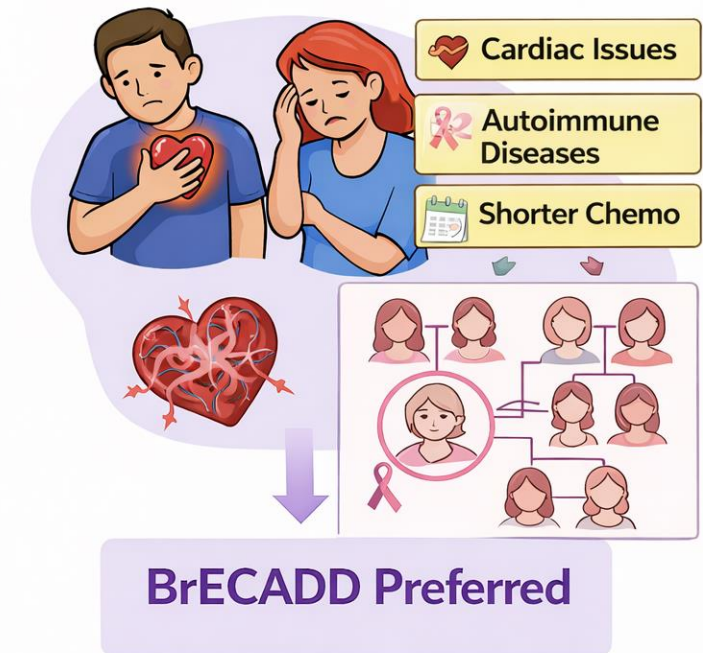
## ❖ Things to Consider

- Age
- Co-morbidities including cardiac, autoimmune, neuropathy
- Duration of therapy- patient scheduling, distance from doctor/infusion center, cost to patient
- Functional status
- Stage (IIB appropriate for BrECADD)- RT is still allowed for bulky disease

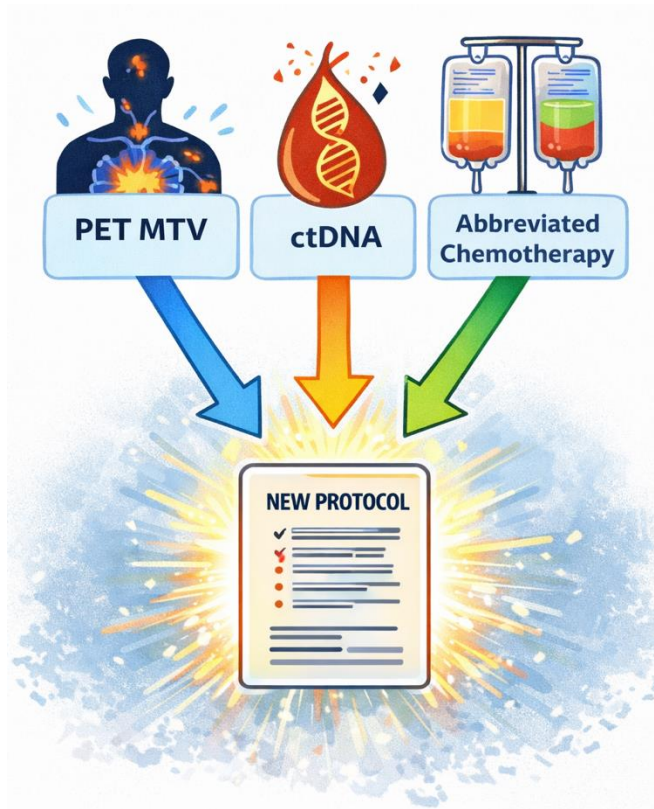
For pediatric, elderly (>60),  
poor ECOG, neuropathy:



For cardiac issues, autoimmune diseases,  
desire for shorter chemo,  
family history of breast cancer:



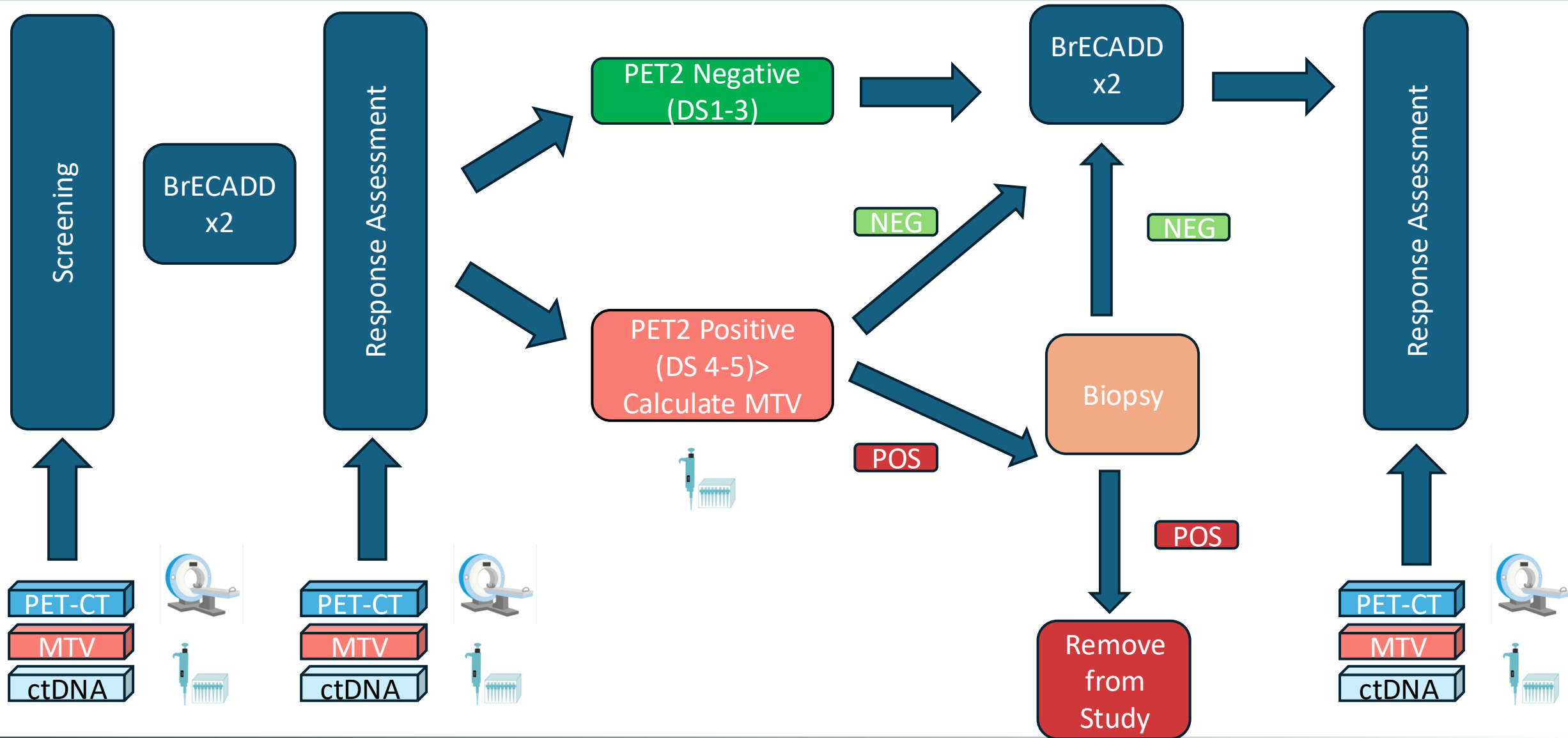
# NEXT STEPS: How can we improve?



- HD21 introduced BrECADD regimen which showed excellent PFS and OS despite the majority of patients (64%) receiving only 4 cycles of chemoimmunotherapy; pts with IIB included
- A high percentage of patients may have false positive PET2 based on DS, thus MTV-2 and ctDNA should be integrated into treatment algorithms prospectively to better understand why 36% of interim PET are positive
- Given the high efficacy of BrECADD, integration of MTV and ctDNA into treatment algorithms may enhance the ability to prognosticate before and throughout treatment.

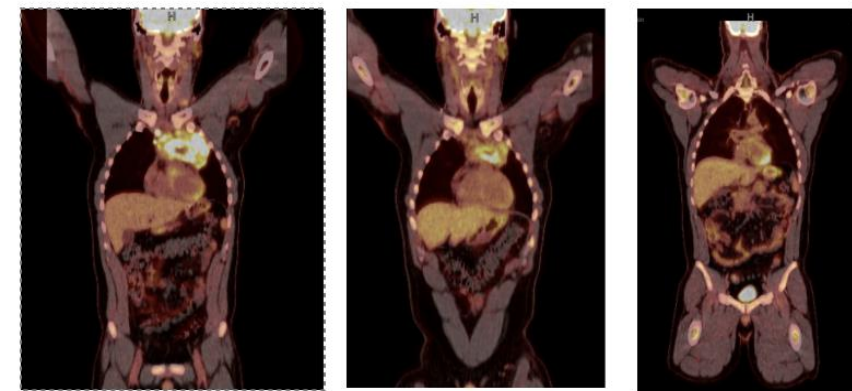
We hypothesize that BrECADD can be administered for fewer cycles with preserved efficacy and reduced short- and long-term toxicity by incorporating MTV alongside Deauville scoring in PET2-based response assessment. While MTV will not directly inform treatment de-escalation in this trial, ctDNA will be evaluated as a complementary biomarker to improve confidence in response assessment and inform future response-adapted strategies.

# STUDY SCHEMA-pts seen weekly



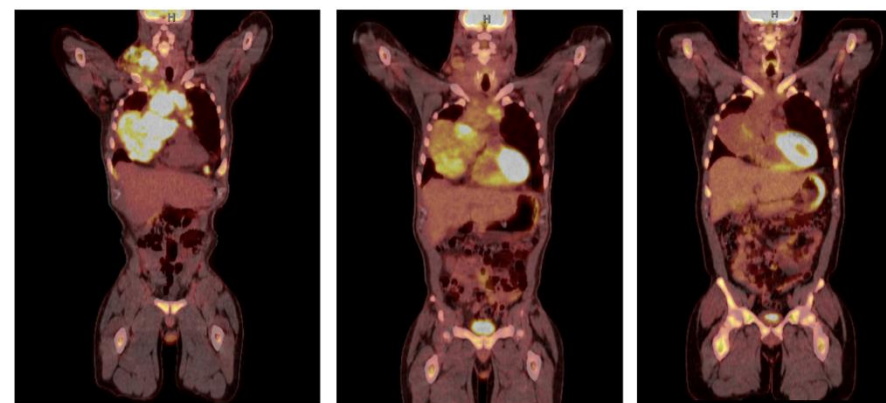
PET remains a problem in HL

### Case #1:



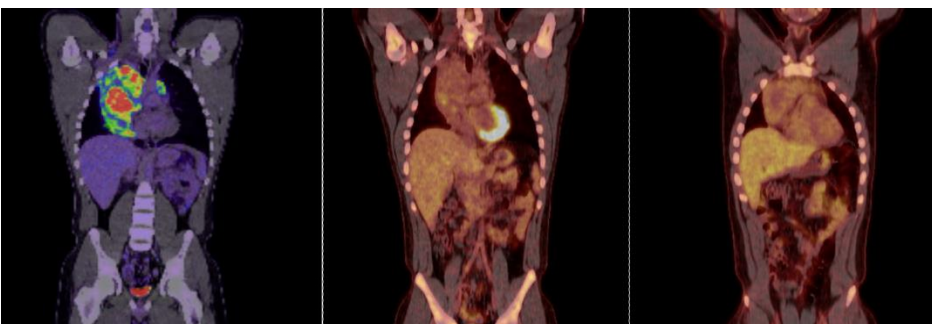
29M, Stage IV-X (11cm mass)--> PET2 with DS5--> MTV 13.6--> Biopsy negative--> completed BrECADD -CMR-receiving proton beam RT

### Case #2:



35M, Stage IV-X (15cm)--> PET2 with DS5--> MTV 65.6--> Biopsy Positive--> removed from study; given P-GVD x4 , CMR, receiving proton beam RT

### Case #3



18M, Stage IV (17.5 cm)--> PET2 with DS4 --> MTV 0--> No Biopsy--> completed BrECADD -CMR, receiving proton BEAM RT

It is very reasonable to radiate patients with bulky HL when PET imaging is unclear

# 5-24/-2/25 (9 months since study opened)

- At UM we treated 40 pts with ASHL
  - I treated 32 of the pts myself
- 19 on BRECADD study-18 achieved a CR; no pt had more than 4 cycles of tx
  - All pts get fluid and blood work day 8 and 15
- 3 pts treated with BRECADD off study-2 with Ulcerative colitis and one with RA
- 3 pts older than 75 with comorbidity -nivo only bridge to vinblastine or BV
- 15 pts treated with N-AVD
  - 7 pts older than 60
  - 4 pts refused protocol
  - 3 pts lived too far away to be seen weekly
  - 1 pts was 17

# FUTURE DIRECTIONS

- Upfront individualized risk stratification based on ctDNA sequencing
- MRD assessment during treatment
- Individualized treatment regimens based on molecular subtype?
- **Reduce the number of cycles of N-AVD**
  - **Remember breast cancer and cardiac risk increases with doxorubicin dosing**

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

**As well as the Lymphoma Faculty at SCCC and MSKCC**

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

- Izidore Lossos
- Juan Alderuccio
- Alvaro Alencar
- Georgio Pongas
- Juan Ramos
- Ashley Rose
- Joe Rosenblatt
- Jonathan Schatz
- Michele Stanchina
- Assad Trabolssi
- Craig Moskowitz



We see 1100 lymphoma consults each year

# Which study has a survival advantage

- BRECADD vs BEACOPP
- N-AVD vs BV-AVD
- BV-AVD vs ABVD
- N-AVD vs BV-AVD-pediatric pts
- N-AVD vs BV-AVD-older pts

# What is advanced stage HL?

- Stage III-IV
- Stage IIX-IV
- Stage IIB-IV
- Stage IIE-IV
- Stage IV

# Which therapy is optimal?

- BV-AVD for 66 yr. old male with stage III disease
- N-AVD for a 23 yr. old female with stage IV disease and history of Ulcerative colitis
- N-AVD for 76 yr. old male with stage IV disease
- BRECADD for a 16 yr. old male with stage IIB disease
- BRECADD for a 34 yr. old female BRCA1 positive with Stage IIE disease