¿La inmunoquimioterapia supera la necesidad de Individualización en Linfoma de Hodgkin?

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Conflicto de Interés

- Research funding: Bristol Myers Squibb, Genentech, Merck, Pfizer
- Consultancy: Bristol Myers Squibb, Genentech, Merck, AstraZeneca, Genmab, Pfizer, Abbvie, Allogene Therapeutics, Lilly

Resumen

- Individualization remains the standard in early stage cHL
- New standards of care in frontline treatment of cHL
  - BV
    - BV-AVD
    - BrECADD
  - PD-1 Blockade
    - Nivolumab-AVD
  - How to choose – individualization of treatment?

Estadio Temprano

Estadio Temprano Favorable

Early Stage Favorable cHL

Perform PET after ABVD x 2

HD10

- CMT desired
- GHSG Favorable
- Mediastinal/axillary: M or F > 30y

5y FFTF
91.2%

ABVDx2 + 20Gy

H10F

- CMT desired
- EORTC Favorable
- Mediastinal/ax: M or F > 30y

ABVDx3 + 30Gy

5y PFS
99%

RAPID

- No RT desired
- PET2 DS 1-2

3y PFS
90.8%

ABVDx3

ABVDx4 + RT

PFS 87.6% (incl DS3)

CALGB

- No RT desired
- PET2 DS 1-2

ABVDx4

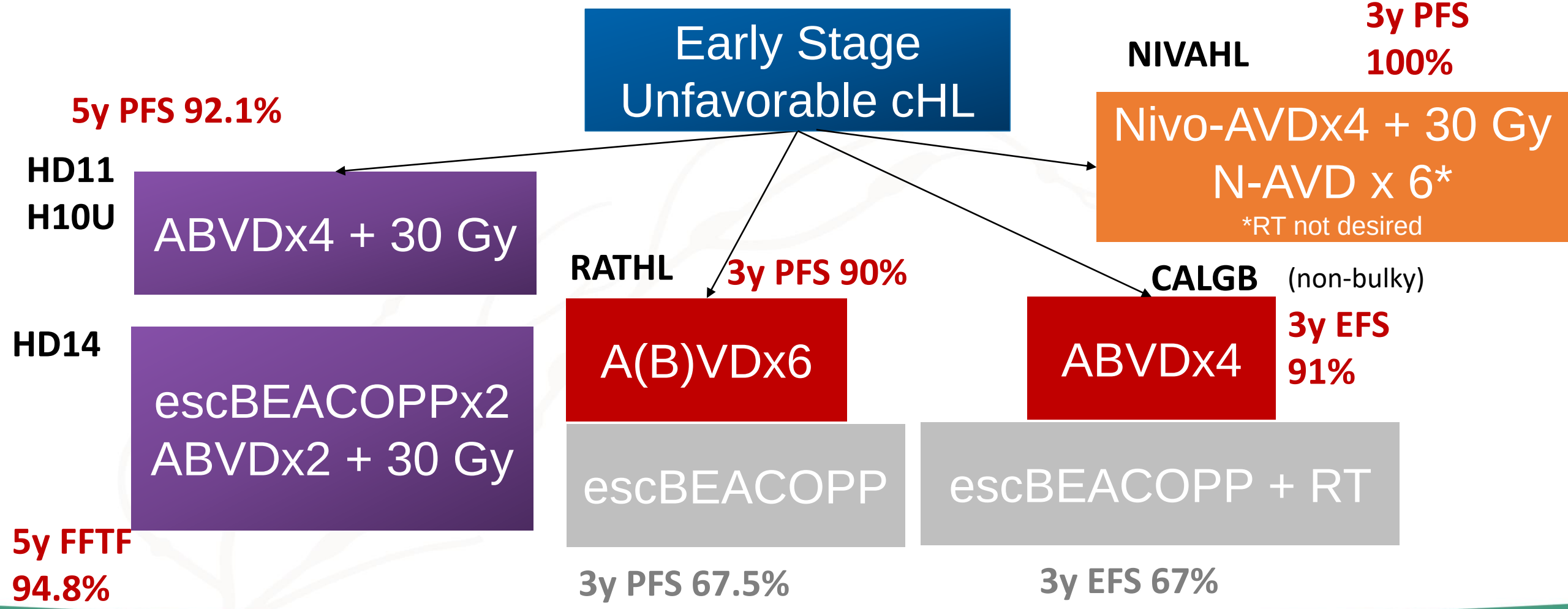
3y EFS
91%

escBEACOPP + RT

3y EFS 67%

Engert A et al. N Engl J Med 2010, Andre MPE et al. JCO 2017,
Straus D et al. Blood. 2018, Radford J et al. NEJM 2015

Estadio Temprano Desfavorable



Eich HT et al. JCO 2011, von Tresckow B et al. JCO 2012, Straus D et al. Blood. 2018, Johnson P et al. NEJM 2016

Estadio Avanzado

Advanced Stage cHL

RATHL

A(B)VDx6

escBEACOPP

HD18

escBEACOPP

AHL2011

escBEACOPPx2
ABVDx4

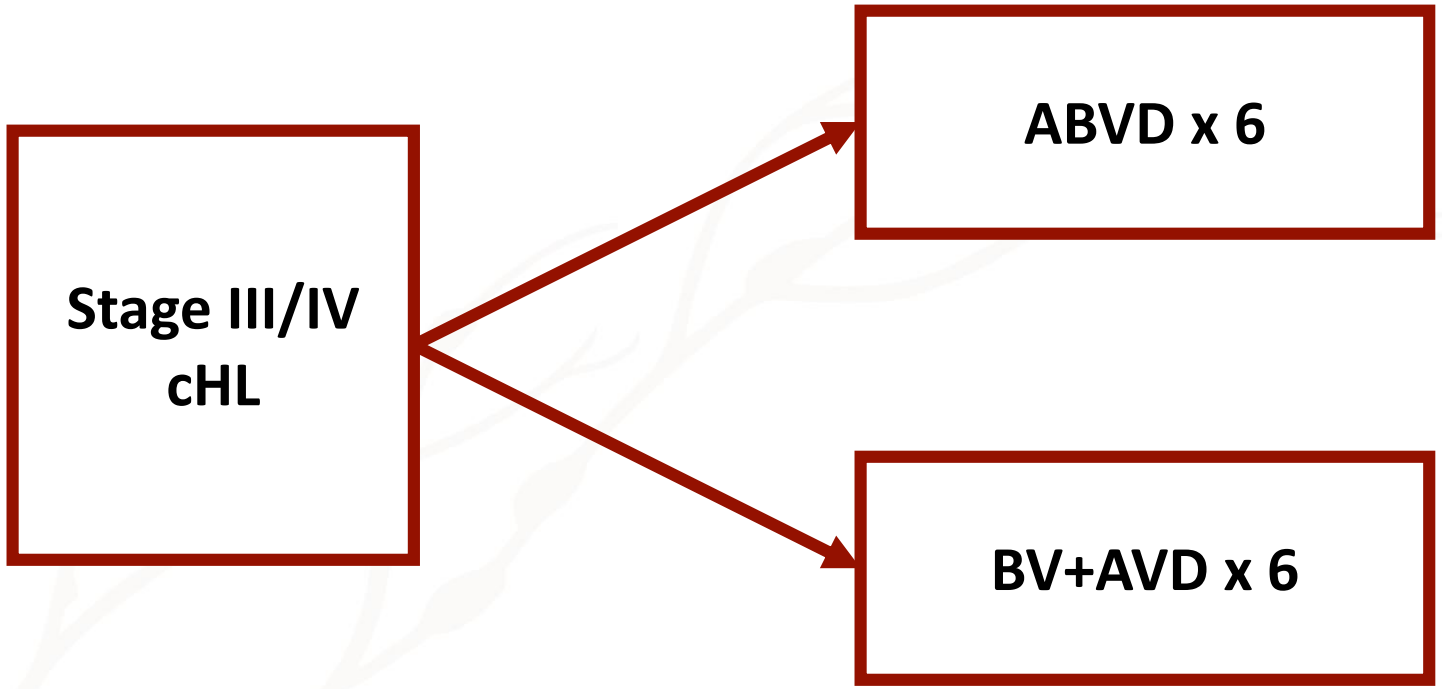
Pediatric approach

ABVE-PC +/- RT

OEPA-COPDAC +/- RT

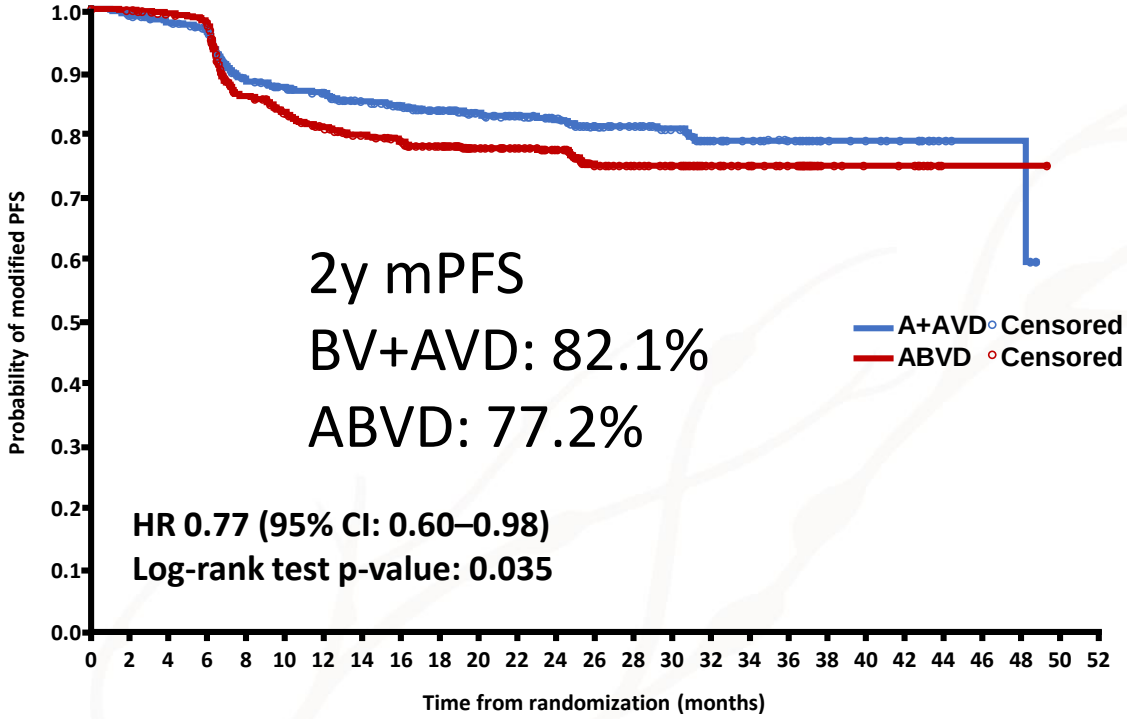
Ansell SM, et al. NEJM 2022, Borchmann P et al. Lancet 2018, Casasnovas O et al. *Lancet Oncol* 2019, Johnson P et al. NEJM 2016

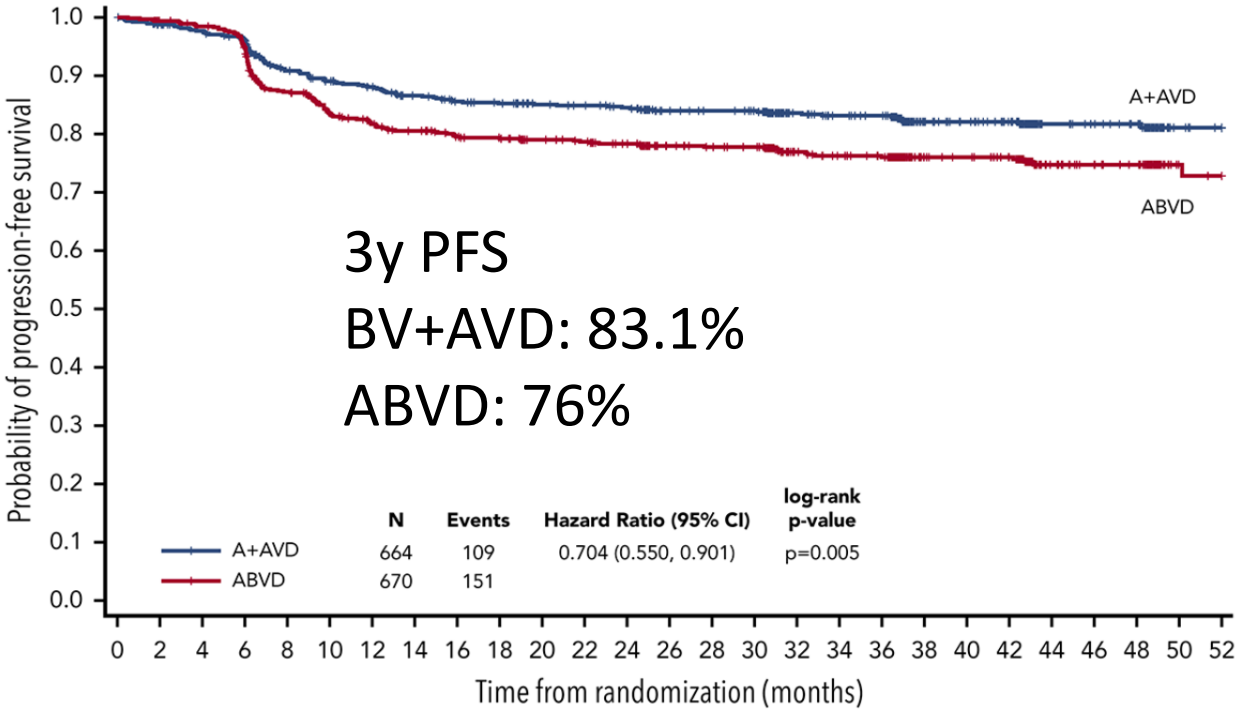
ECHELON-1: BV+AVD en cHL de estadio avanzado



Connors et al. *NEJM* online 2017, Straus D, et al Blood 2020

ECHELON-1: BV+AVD en cHL de estadio avanzado





Connors et al. *NEJM* online 2017, Straus D, et al Blood 2020

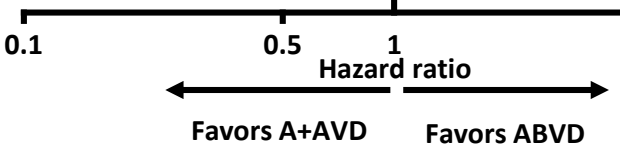
BV-AVD: mas neutropenia febril y neuropatía

	BV+AVD	ABVD
Grade ≥3 AE	549 (83%)	343 (66%)
SAE	284 (43%)	178 (27%)
PN all grades	55%	30%
PN grade ≥ 3	9%	1%
SAE of febrile neutropenia, sepsis, infection, neutropenia	33% no G-CSF ppx 24% G-CSF ppx	17% no G-CSF ppx 9% G-CSF ppx

Connors JM et al NEJM 2017

Individualización con BV-AVD

Subgroup	A+AVD	ABVD	
Overall	117/664 (17.6)	146/670 (21.8)	0.77 (0.60–0.98)
Age <60 years	93/580 (16.0)	117/568 (20.6)	0.73 (0.56–0.96)
Age ≥60 years	24/84 (28.6)	29/102 (28.4)	1.01 (0.59–1.73)
Age <45 years	70/451 (15.5)	83/423 (19.6)	0.73 (0.53–1.01)
Age ≥45 years	47/213 (22.1)	63/247 (25.5)	0.86 (0.59–1.26)
Region: Americas	41/261 (15.7)	58/262 (22.1)	0.65 (0.44–0.97)
Region: North America	38/250 (15.2)	57/247 (23.1)	0.60 (0.39–0.90)
Region: Europe	62/333 (18.6)	74/336 (22.0)	0.83 (0.59–1.17)
Region: Asia	14/70 (20.0)	14/72 (19.4)	0.91 (0.43–1.93)
IPS: 0–1	22/141 (15.6)	25/141 (17.7)	0.83 (0.47–1.48)
IPS: 2–3	57/354 (16.1)	68/351 (19.4)	0.79 (0.56–1.13)
IPS: 4–7	38/169 (22.5)	53/178 (29.8)	0.70 (0.46–1.07)
Stage III	40/237 (16.9)	43/246 (17.5)	0.92 (0.60–1.42)
Stage IV	77/425 (18.1)	102/421 (24.2)	0.71 (0.53–0.96)
B symptoms: Present	77/399 (19.3)	94/381 (24.7)	0.74 (0.55–1.01)
B symptoms: Absent	40/265 (15.1)	52/289 (18.0)	0.79 (0.52–1.20)
Extranodal sites: 0	40/217 (18.4)	39/228 (17.1)	1.04 (0.67–1.62)
Extranodal sites: 1	36/217 (16.6)	45/223 (20.2)	0.75 (0.48–1.16)
Extranodal sites: >1	39/194 (20.1)	57/193 (29.5)	0.67 (0.44–1.00)
Gender: Male	64/378 (16.9)	90/398 (22.6)	0.71 (0.51–0.97)
Gender: Female	53/286 (18.5)	56/272 (20.6)	0.86 (0.59–1.26)

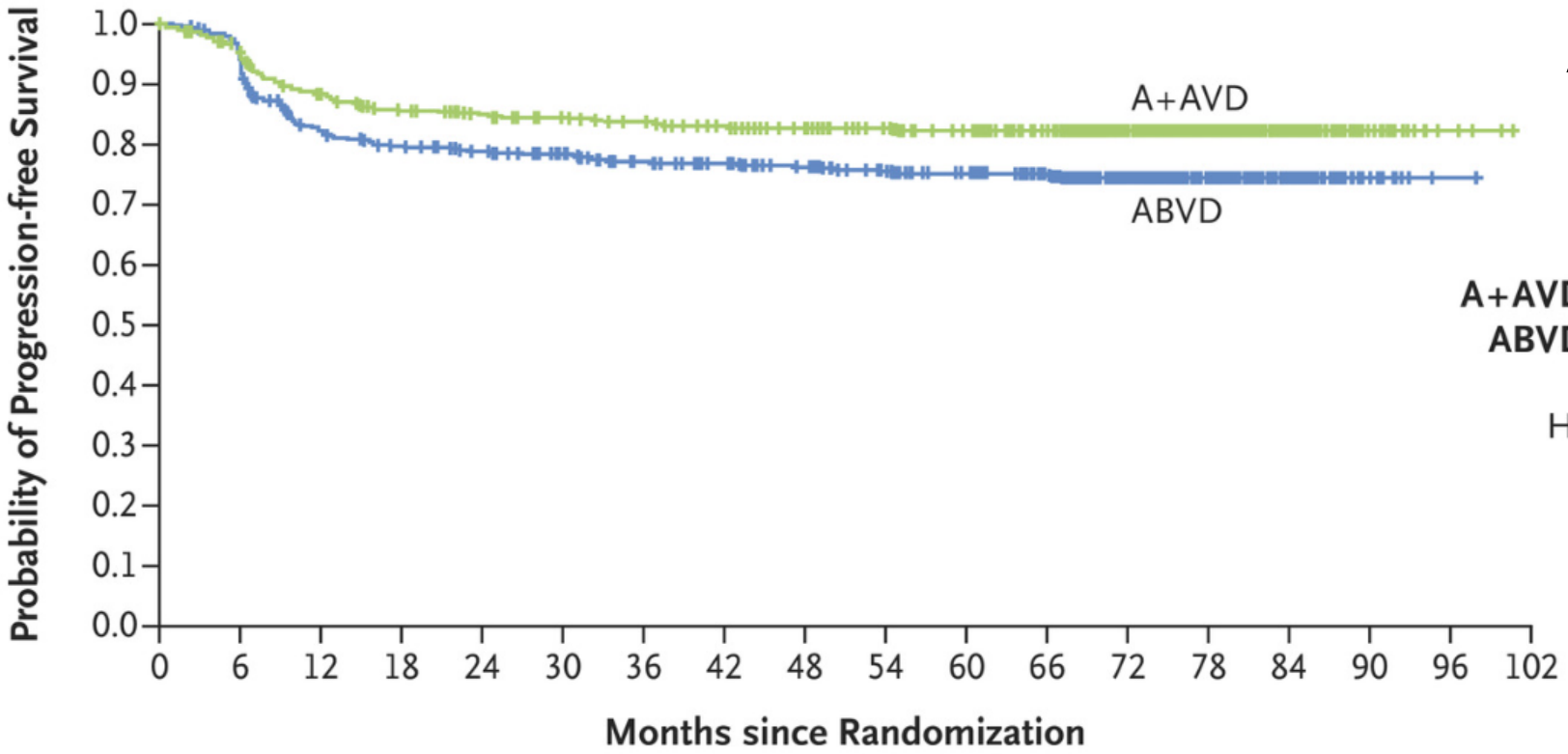


Younger patients
North American pts
Extranodal sites > 1
Stage IV

Connors et al. *NEJM* online 2017, Straus D, et al Blood 2020

E-1: BV-AVD tiene beneficio de SLP

6y PFS
BV-AVD 82.3%
ABVD 74.5%

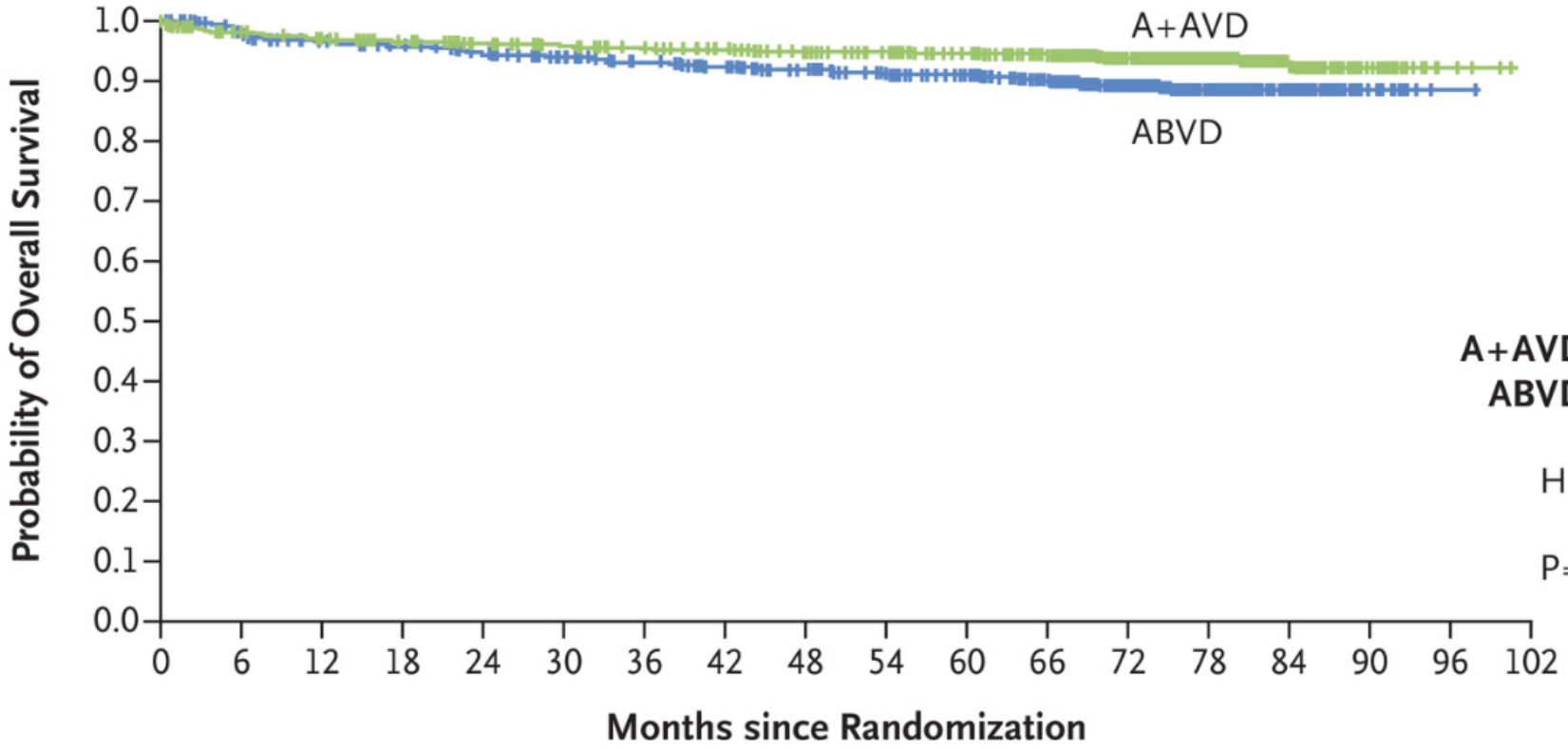


No. of Events	
A+AVD	112
ABVD	159

Hazard ratio for disease progression or death, 0.68 (95% CI, 0.53–0.86)

Ansell SM, et al. NEJM 2022.

BV-AVD beneficio modesto en supervivencia global



6y OS
BV-AVD 93.9%
ABVD 89.4%

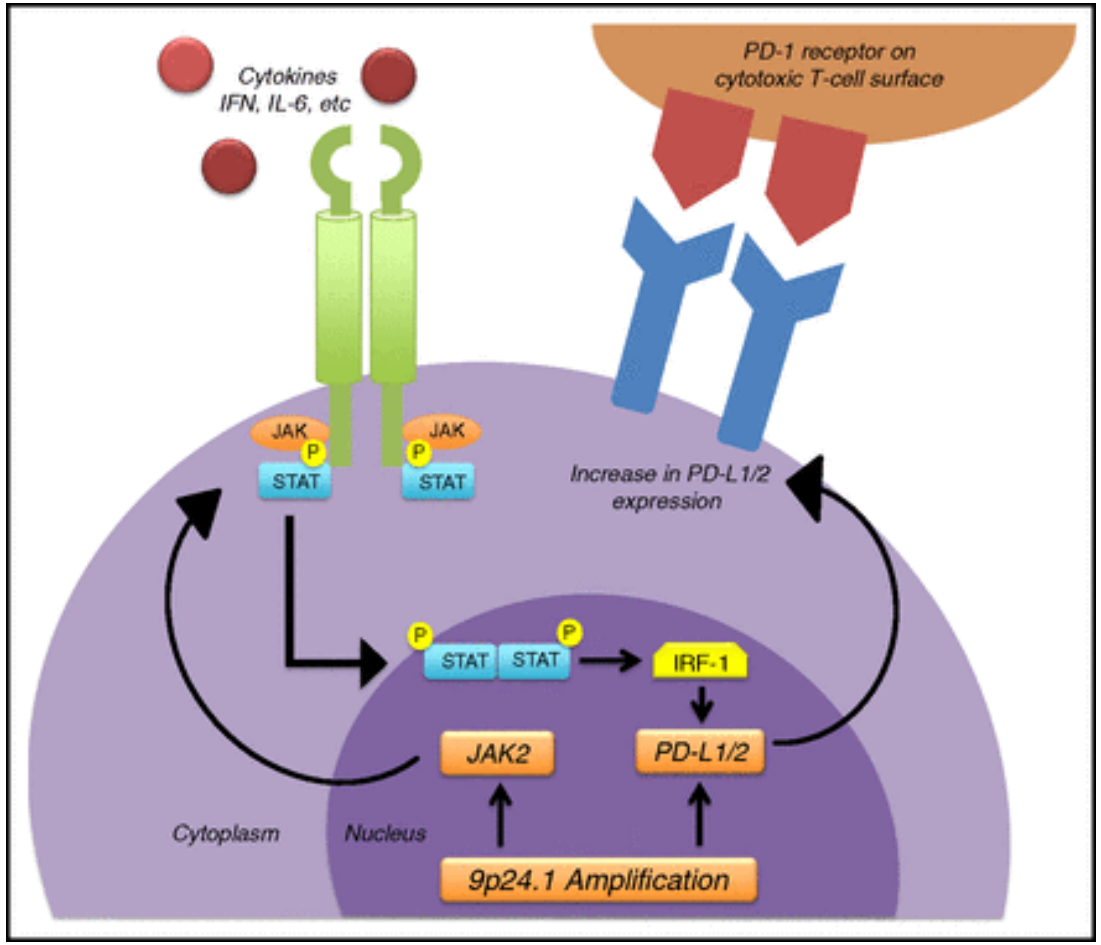
No. of Deaths	
A+AVD	39
ABVD	64

Hazard ratio for death, 0.59
(95% CI, 0.40–0.88)
P=0.009 by log-rank test

Ansell SM, et al. NEJM 2022

PD-1 en Linfoma de Hodgkin

- 9p24.1 alteration directly results in PD-L1/2 expression on RS cells
- 9p24.1 alteration increases JAK2 expression, which can induce PD-L1/2 expression on RS cells
- EBV infection induces PD-L1 expression on RS cells
- Tumor-associated macrophages express PD-L1 in the HL TME

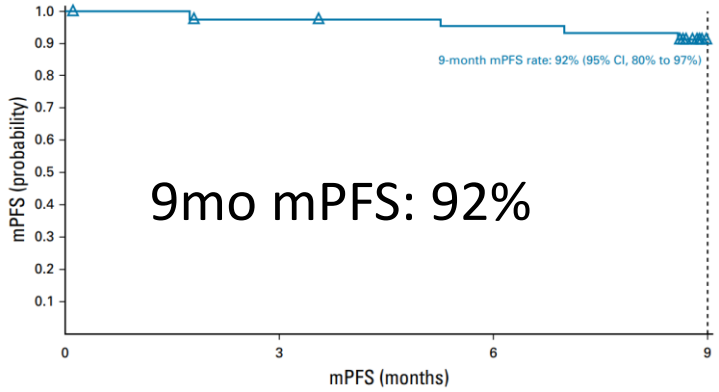


- Cabanillas F and Rivera N. Blood 2017, Green MR et al Blood 2010, Green MR et al. CCR 2012, Carey CD et al. Blood 2017

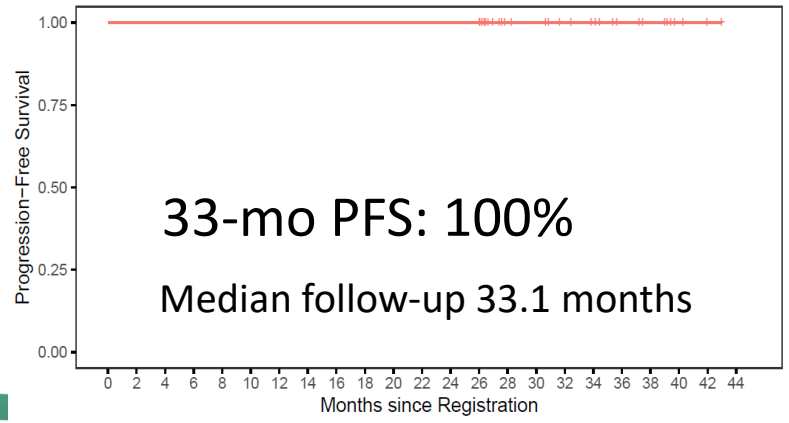
Ensayos clínicos iniciales con PD1 de 1a linea

- Studies of frontline PD-1 blockade in cHL have been promising[10,11,12,13]
  - N-AVD well-tolerated
  - Excellent PFS

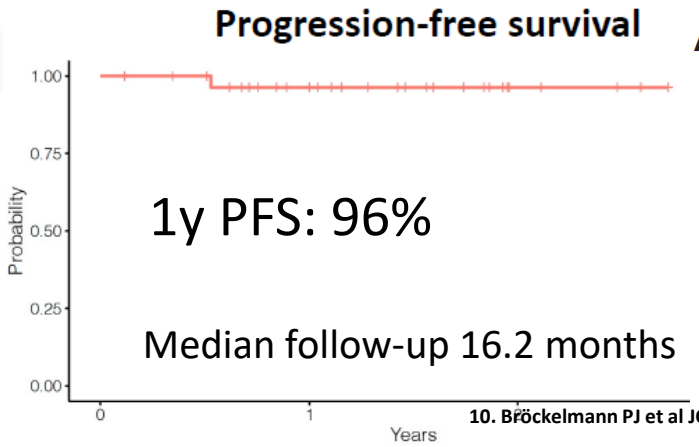
1L Nivolumab-AVD in advanced stage cHL



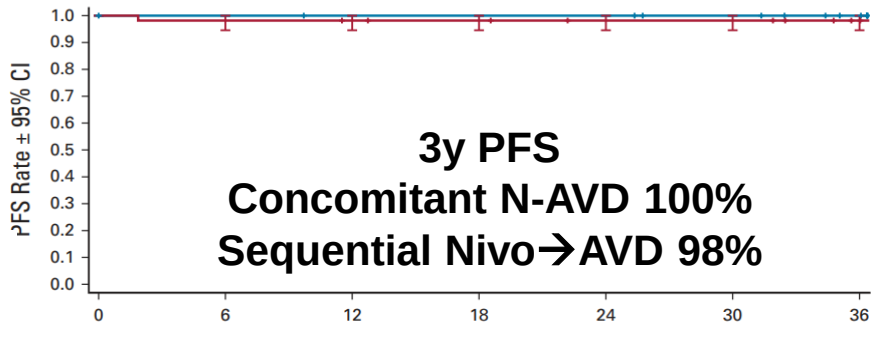
Sequential Pembro-AVD in cHL



Concurrent Pembro-AVD in cHL

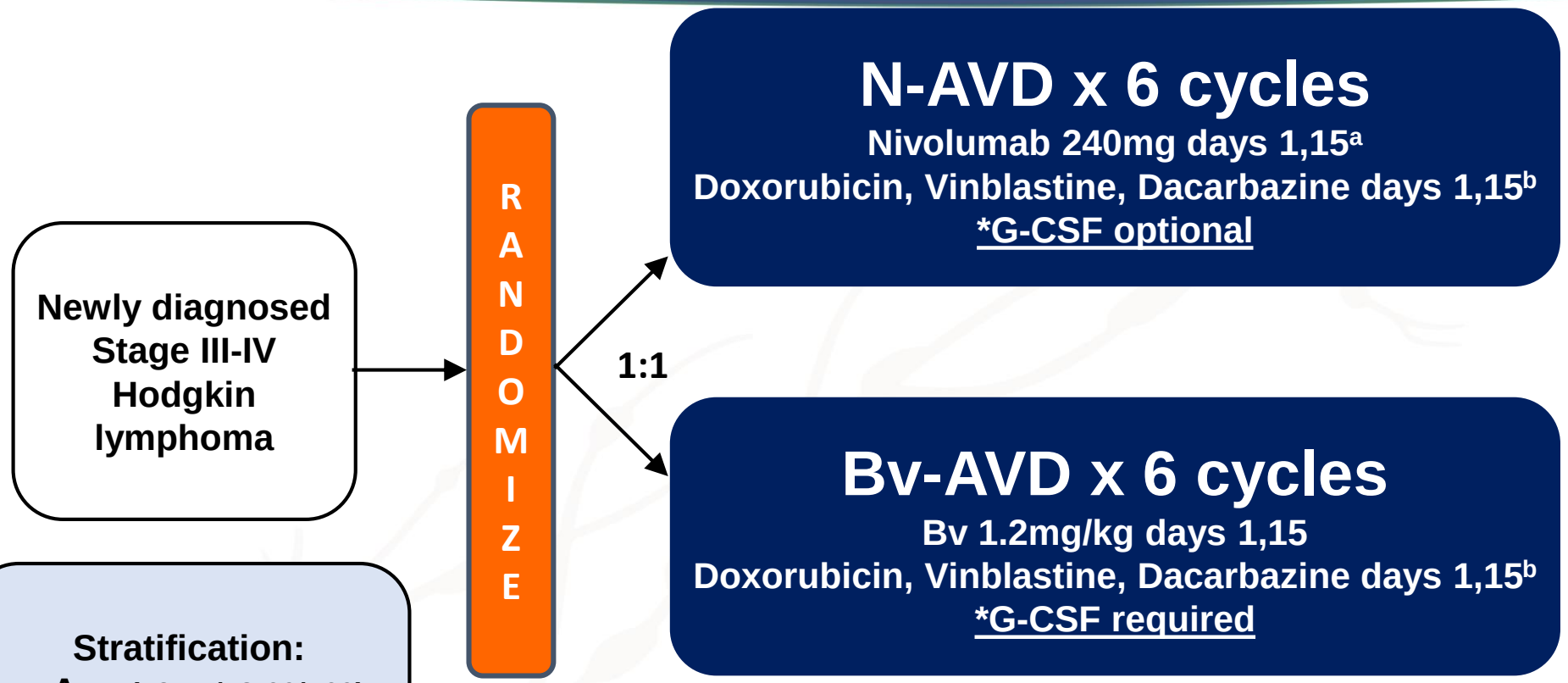


1L Nivolumab-AVD in early stage cHL



10. Bröckelmann PJ et al JCO. 2023 11. Ramchandren R et al JCO 2019 12. Allen PB, et al Blood. 2021 13. Lynch RC et al Blood 2023

S1826 Diseño



- Primary endpoint: PFS
- Assume 84% 2-year PFS for BV-AVD, 90% 2-year PFS in N-AVD, final analysis @ 179 events

Herrera, AF et al. ASCO 2023.

[a] Nivolumab 3mg/kg for ages ≤ 17, max 240mg
[b] Conventional doses of AVD: Stephens DM et al Blood 2019, Ansell SM et al NEJM 2022

Con el Aval:

S1826 Características basales

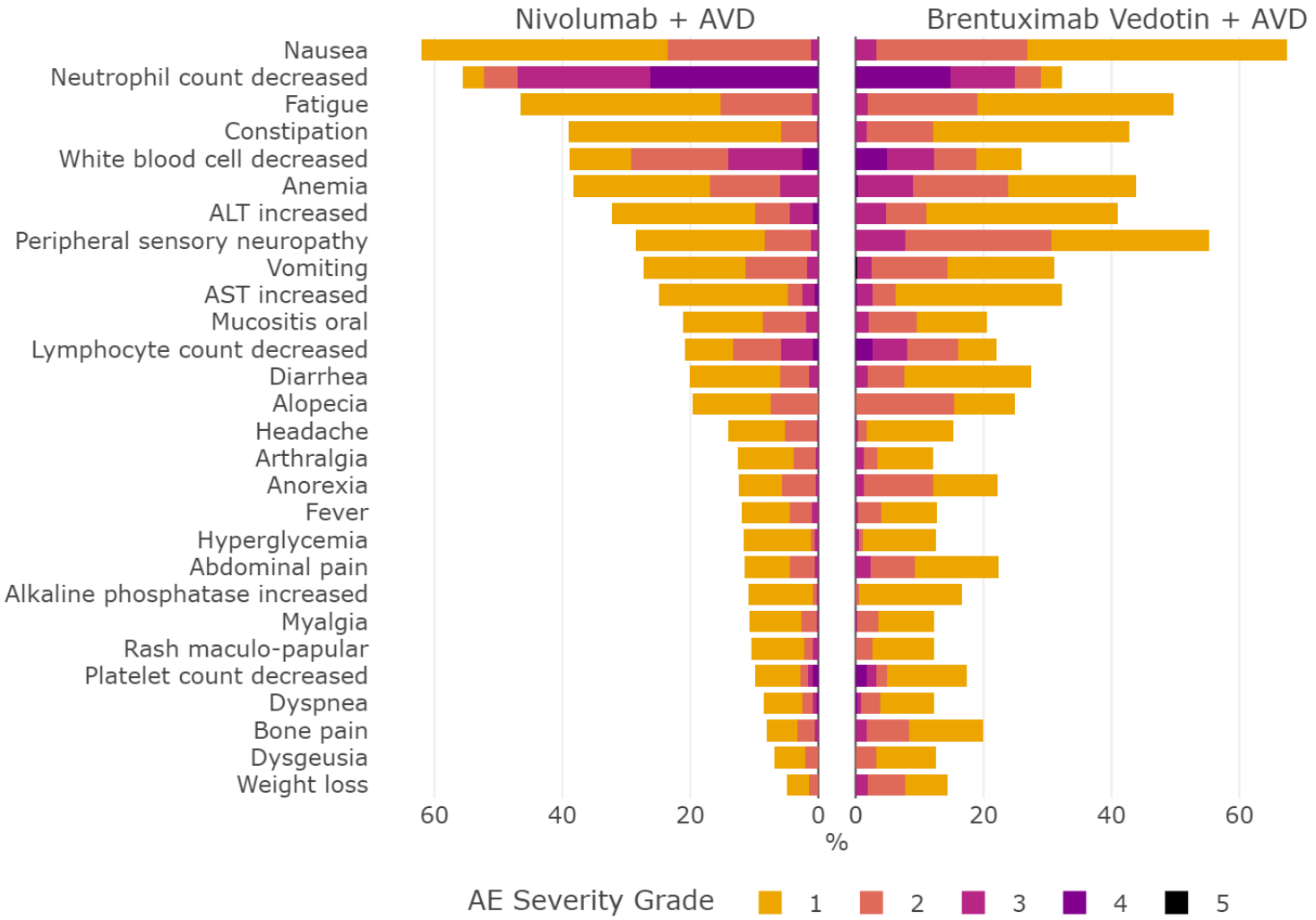
Baseline characteristics	N-AVD n=487 N (%)	Bv-AVD n=483 N (%)
Age, median (range)	27 (12-83)	26 (12-81)
12-17 years	118 (24%)	118 (24%)
18-60 years	321 (66%)	318 (66%)
≥ 61 years	48 (10%)	47 (10%)
Female Sex	216 (44%)	210 (43%)
Race		
White	372 (76%)	361 (75%)
Black	58 (12%)	56 (12%)
Asian	11 (2%)	17 (4%)
Other/Unknown	46 (9%)	49 (10%)
Hispanic	66 (14%)	58 (12%)

Baseline characteristics	N-AVD n=487 N (%)	Bv-AVD n=483 N (%)
Stage		
III	185 (38%)	168 (35%)
IV	302 (62%)	315 (65%)
B symptoms present	288 (59%)	273 (57%)
IPS Score		
0-3	332 (68%)	328 (68%)
4-7	155 (32%)	155 (32%)
Bulky disease > 10cm	156 (32%)	127 (26%)
HIV+	11 (2%)	5 (1%)

Representative study, inclusive of high-risk pts

Herrera, AF et al. N Eng J Med. 2024 Oct 17;391(15):1379-138.

N-AVD se toleró mejor que BV-AVD.



Herrera, AF et al. ASCO 2023 LBA4.

N-AVD se toleró mejor que BV-AVD

	Received G-CSF	Gr ≥ 3 neutropenia	Febrile neutropenia	Gr ≥ 3 infections, infestations	Sepsis	Bone pain
N-AVD (n = 482)	56%	48%	6%	5%	2%	8%
BV-AVD (n = 476)	97%	26%	7%	7%	3%	20%

	Peripheral sensory Neuropathy All Gr/Gr 2+	Peripheral motor neuropathy All Gr/Gr 2+	Thyroid dysfunction	ALT increased	Pneumonitis	Colitis
N-AVD (n = 482)	29%/9%	4%/1%	10%	33%	2%	1%
BV-AVD (n = 476)	56%/32%	7%/5%	1%	42%	3%	1%

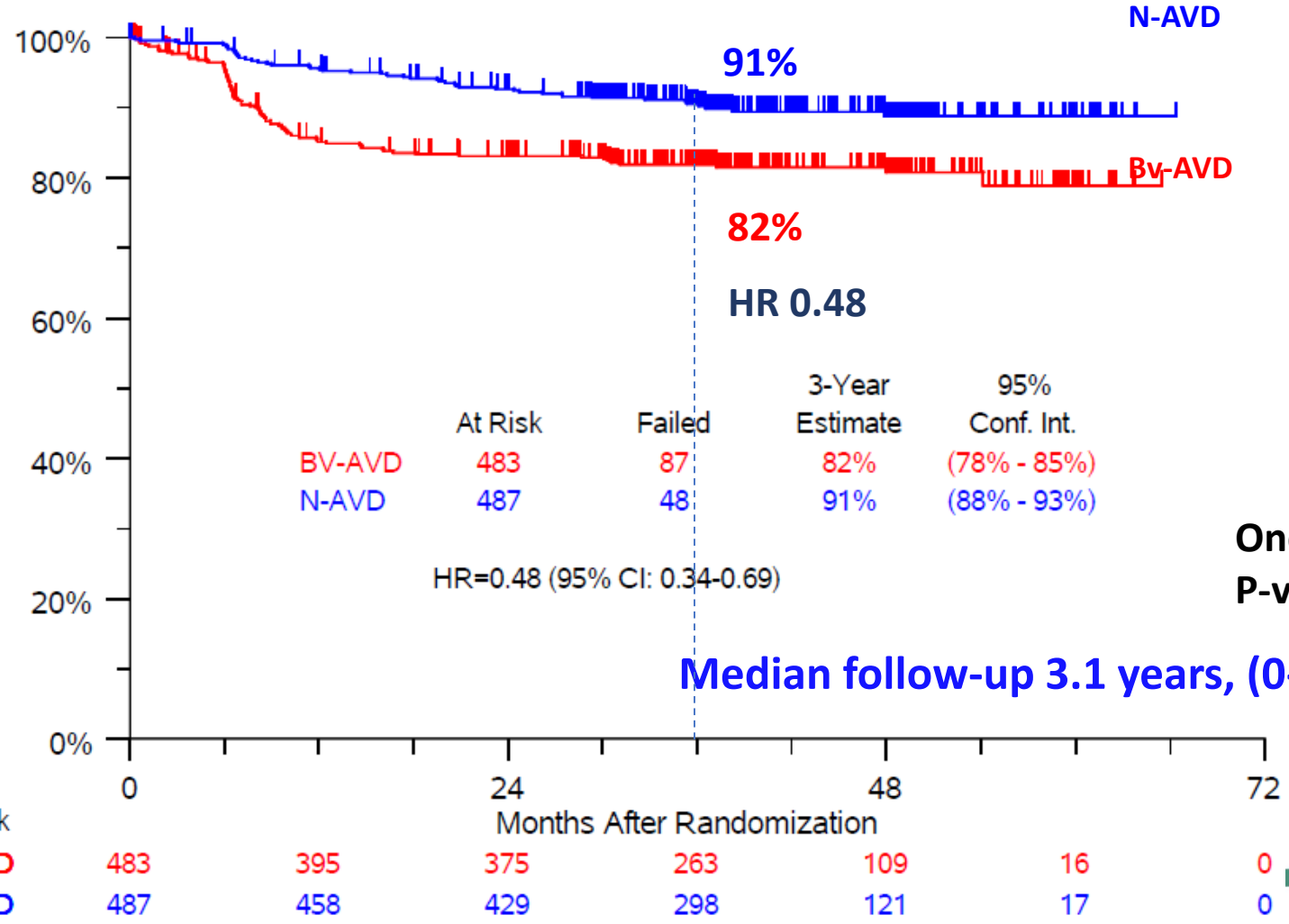
Herrera, AF et al. N Eng J Med. 2024 Oct 17;391(15):1379-138.

Suspensión del tratamiento y fallecimientos

Disposition	N-AVD (n=487) N (%)	Bv-AVD (n=483) N (%)
Completed treatment	450 (92.4%)	425 (88%)
Discontinued all treatment early	**37 (7.6%)**	**58 (12%)**
Adverse event	20 (4.1%)	20 (4.1%)
Refusal unrelated to AE	9	13
Progression/relapse	**0 (0%)**	**9 (1.9%)**
Death on treatment	**3 (0.6%)**	**8 (1.7%)**
Other – not protocol specified	5	8
Any discontinuation Bv or Nivolumab	**46 (9.4%)**	**107 (22.2%)**
Dose reduction	**NA**	**129 (26.7%)**
Received radiotherapy	**3 (0.6%)**	**4 (0.8%)**

Herrera, AF et al. N Eng J Med. 2024 Oct 17;391(15):1379-138.

Beneficio en supervivencia libre de progresión con N-AVD



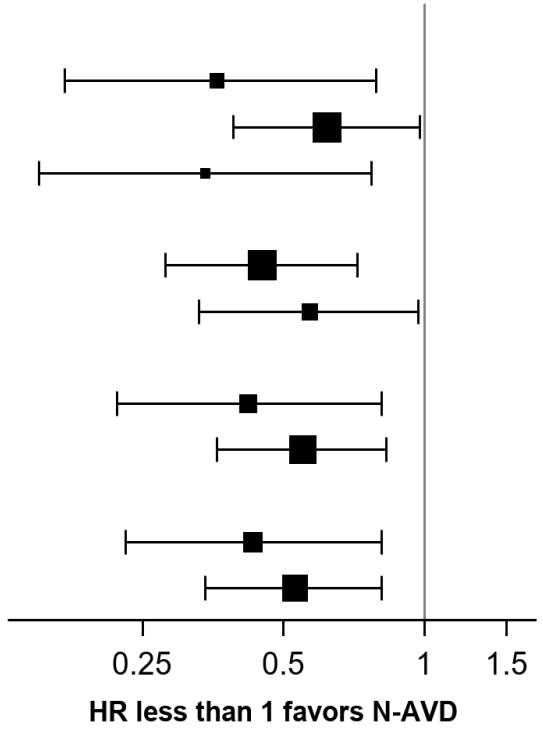
3-year PFS
N-AVD 91%
Bv-AVD 82%

One-sided Stratified Log-rank
P-value < .0001

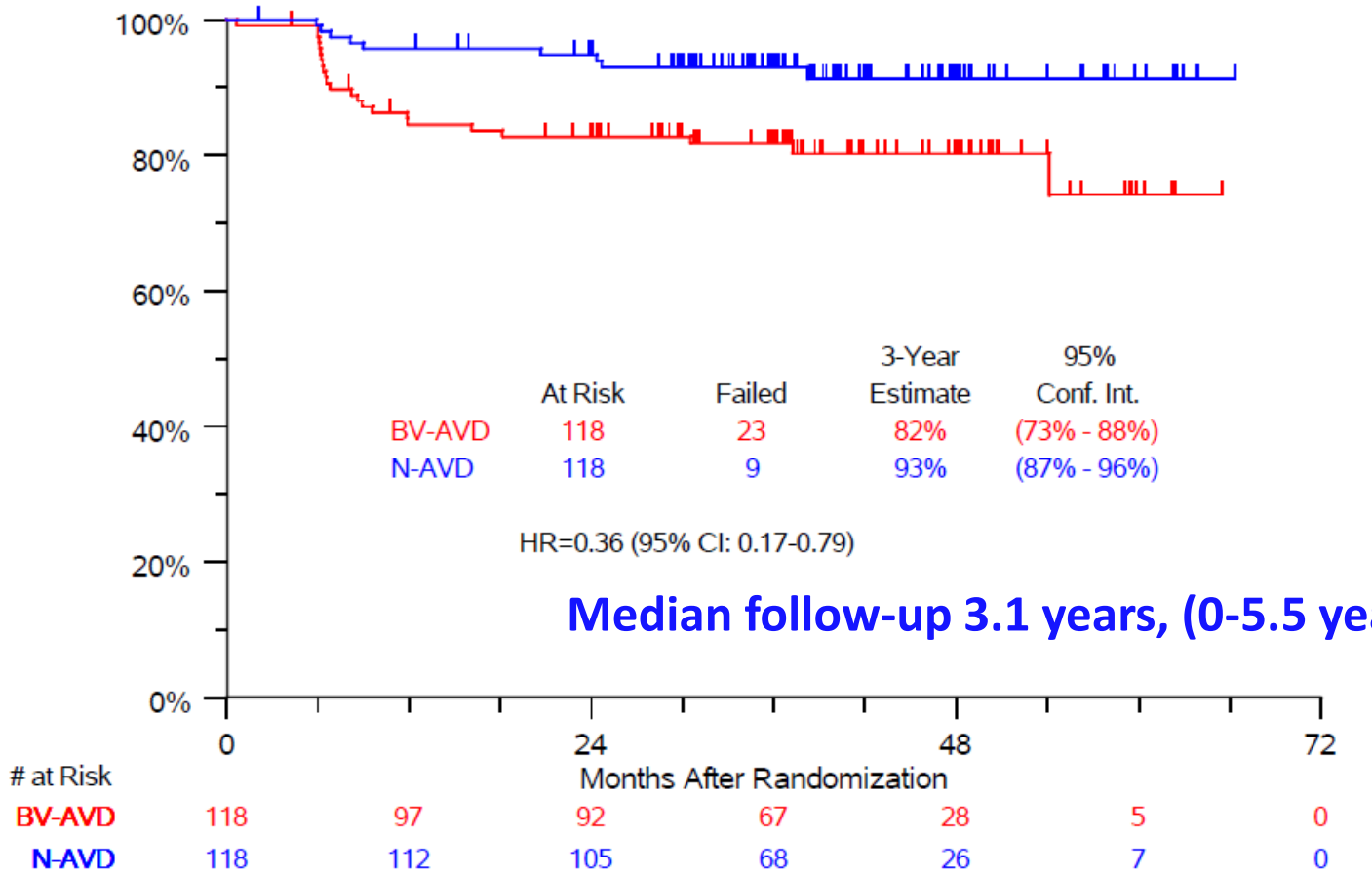
Median follow-up 3.1 years, (0-5.5 years)

Beneficio en supervivencia libre de progresión en todos los subgrupos

Subgroup	N + AVD Events/N (%)	BV + AVD Events/N (%)	Hazard Ratio for Disease Progression or Death (95% CI)
Age			
12 - 17 y	9/118 (7.6)	23/118 (19.5)	0.36 (0.17, 0.79)
18 - 60 y	31/321 (9.7)	46/318 (14.5)	0.62 (0.39, 0.98)
> 60 y	8/48 (16.7)	18/47 (38.3)	0.34 (0.15, 0.77)
IPS			
0 - 3	26/331 (7.9)	53/328 (16.2)	0.45 (0.28, 0.72)
4 - 7	22/156 (14.1)	34/155 (21.9)	0.57 (0.33, 0.97)
Stage			
III	13/184 (7.1)	26/168 (15.5)	0.42 (0.22, 0.81)
IV	35/303 (11.6)	61/315 (19.4)	0.55 (0.36, 0.83)
Symptoms			
A	14/199 (7.0)	32/210 (15.2)	0.43 (0.23, 0.81)
B	34/288 (11.8)	55/273 (20.1)	0.53 (0.34, 0.81)



Beneficio con N-AVD en adolescentes



	At Risk	Failed	3-Year Estimate	95% Conf. Int.
BV-AVD	118	23	82%	(73% - 88%)
N-AVD	118	9	93%	(87% - 96%)

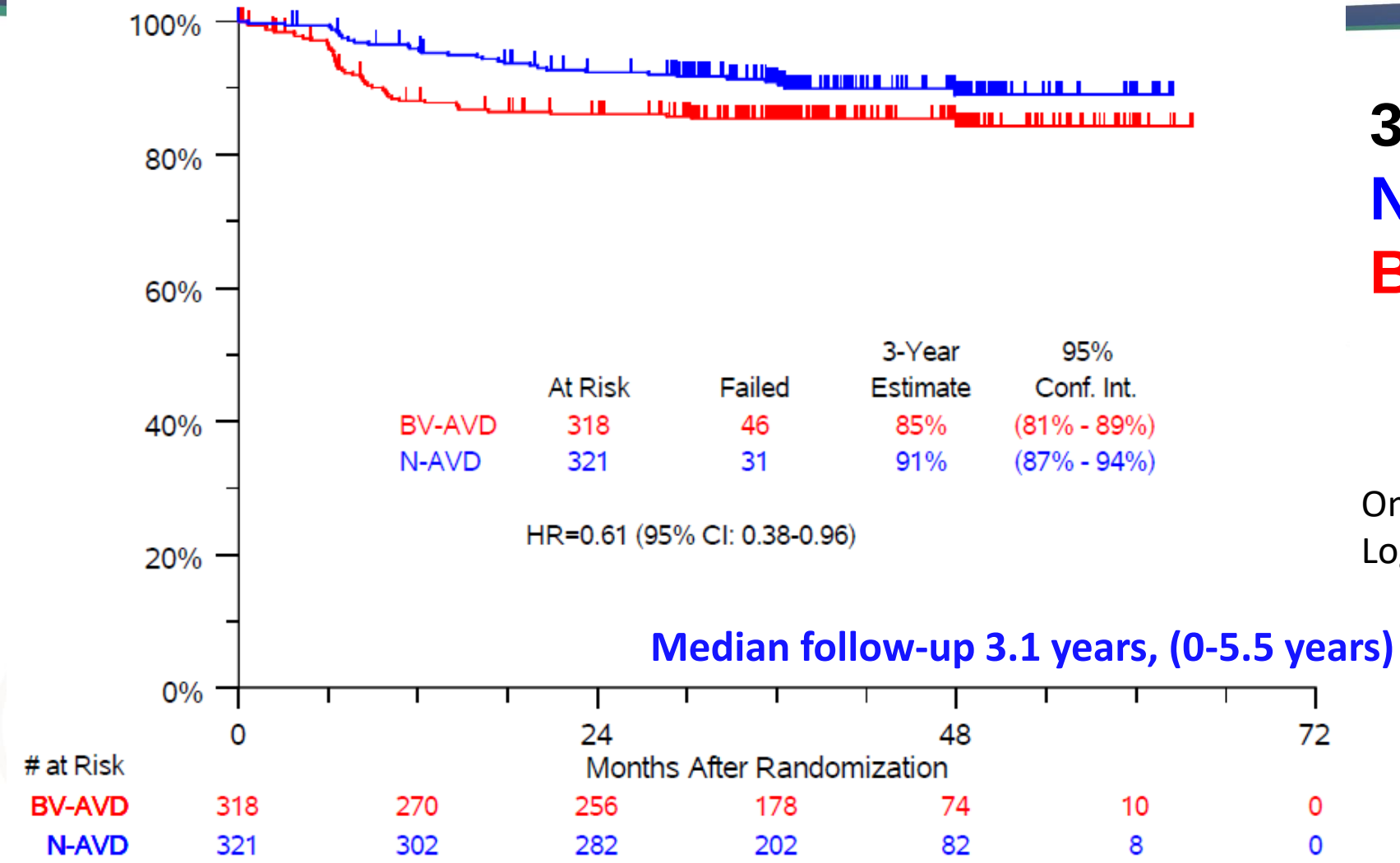
HR=0.36 (95% CI: 0.17-0.79)

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

3-year PFS
N-AVD 93%
Bv-AVD 82%

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

N-AVD en 18-60 year-old adultos

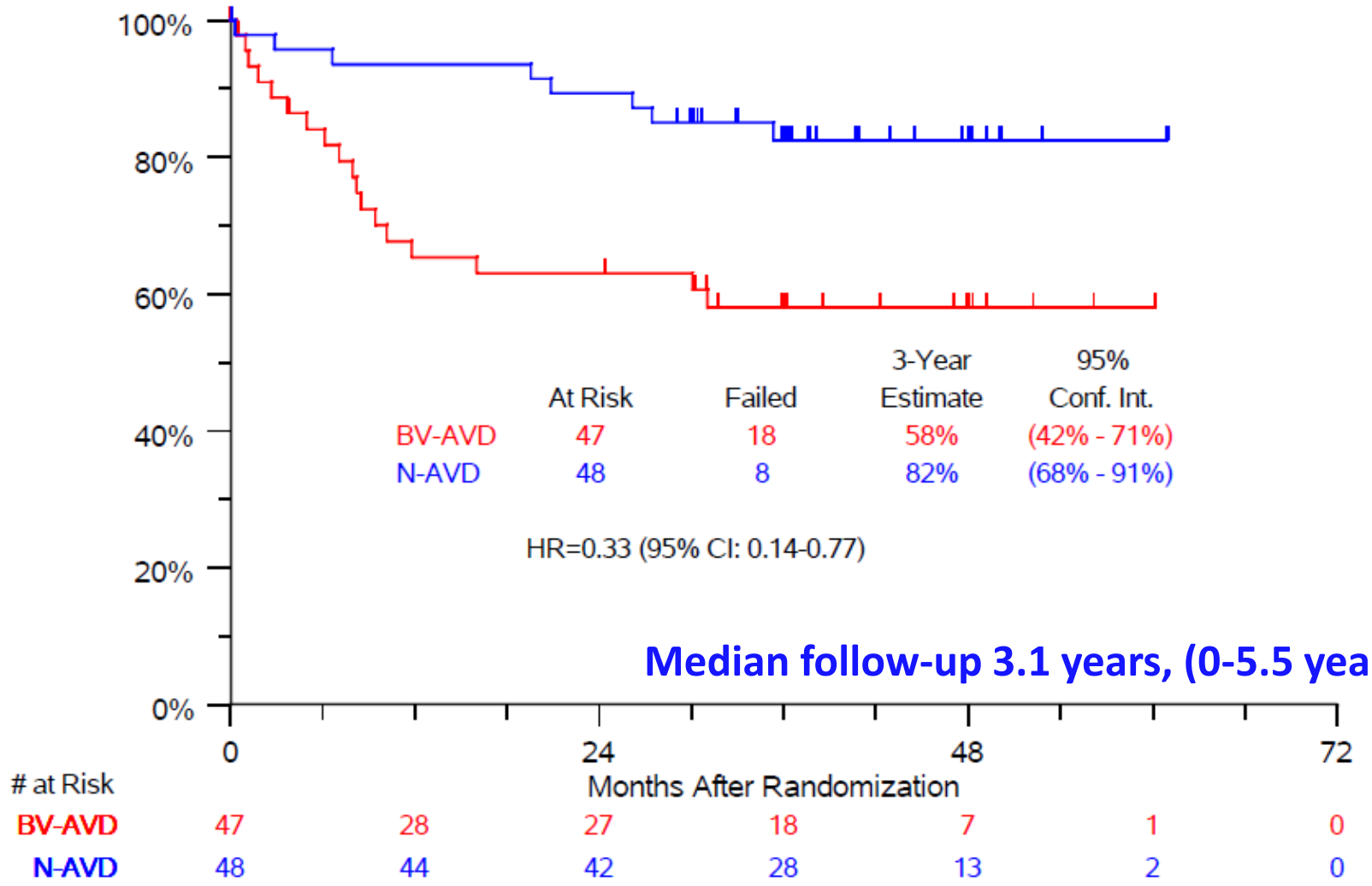


3-year PFS
N-AVD 91%
Bv-AVD 85%

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

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

N-AVD en pacientes mayores



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

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

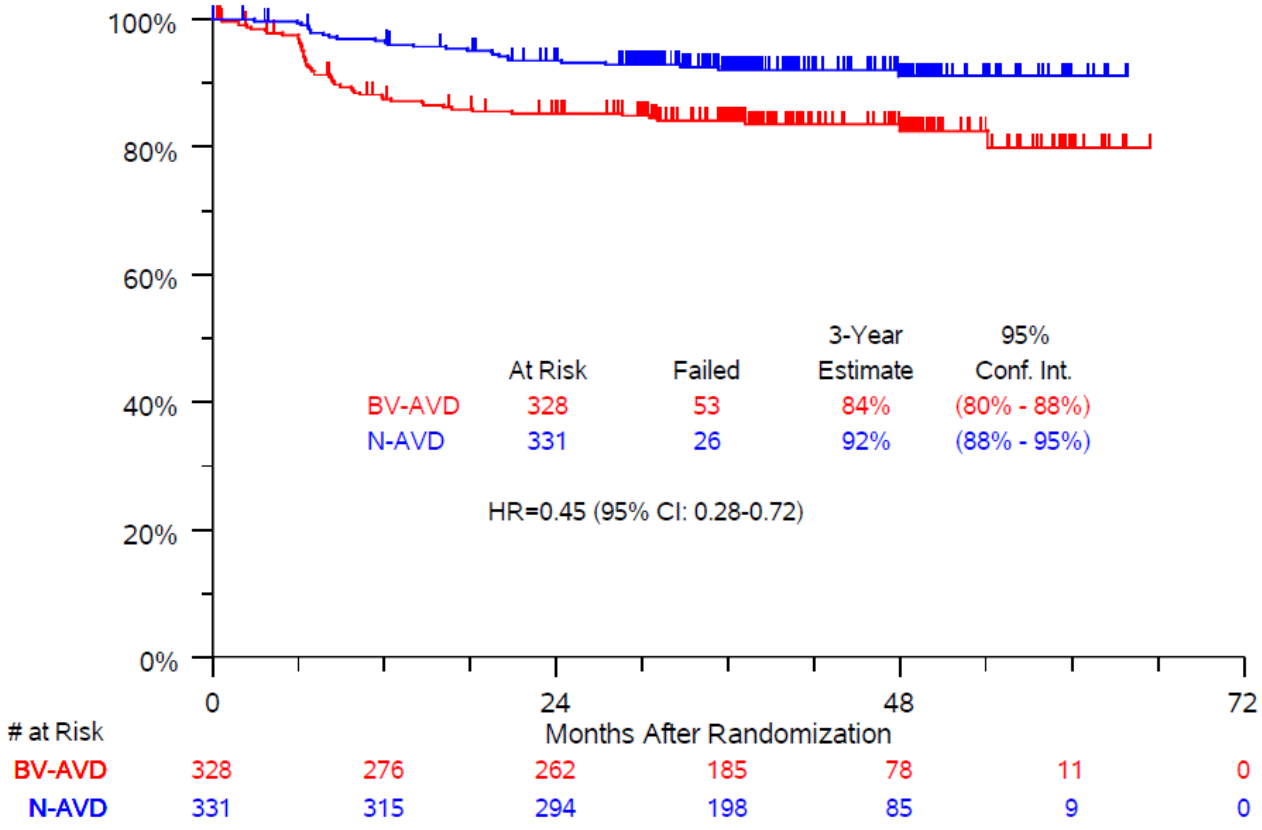
Median follow-up 3.1 years, (0-5.5 years)

Presented by: Alex F. Herrera, MD

Con el Aval:

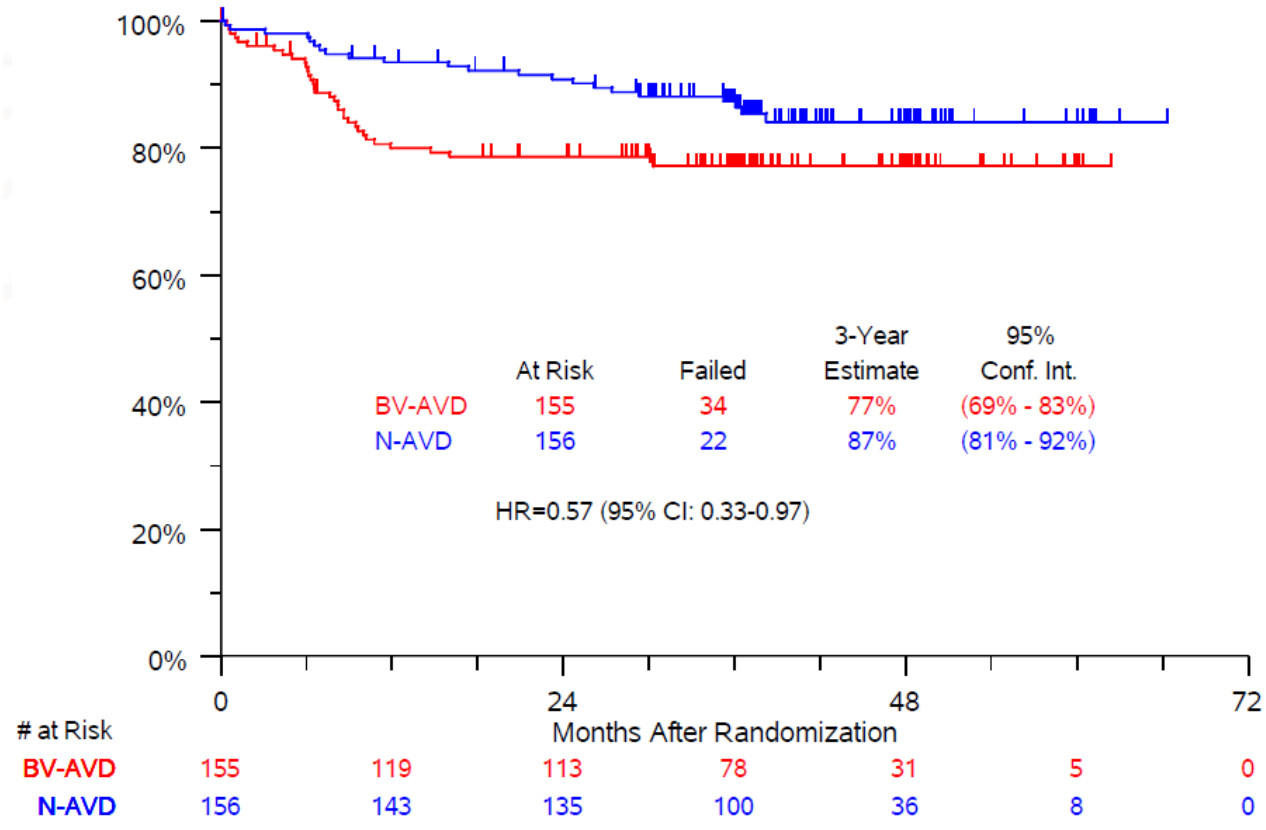
N-AVD en IPS bajo y con IPS alto

IPS 0-3



Two-sided Log-rank P-value = 0.0006

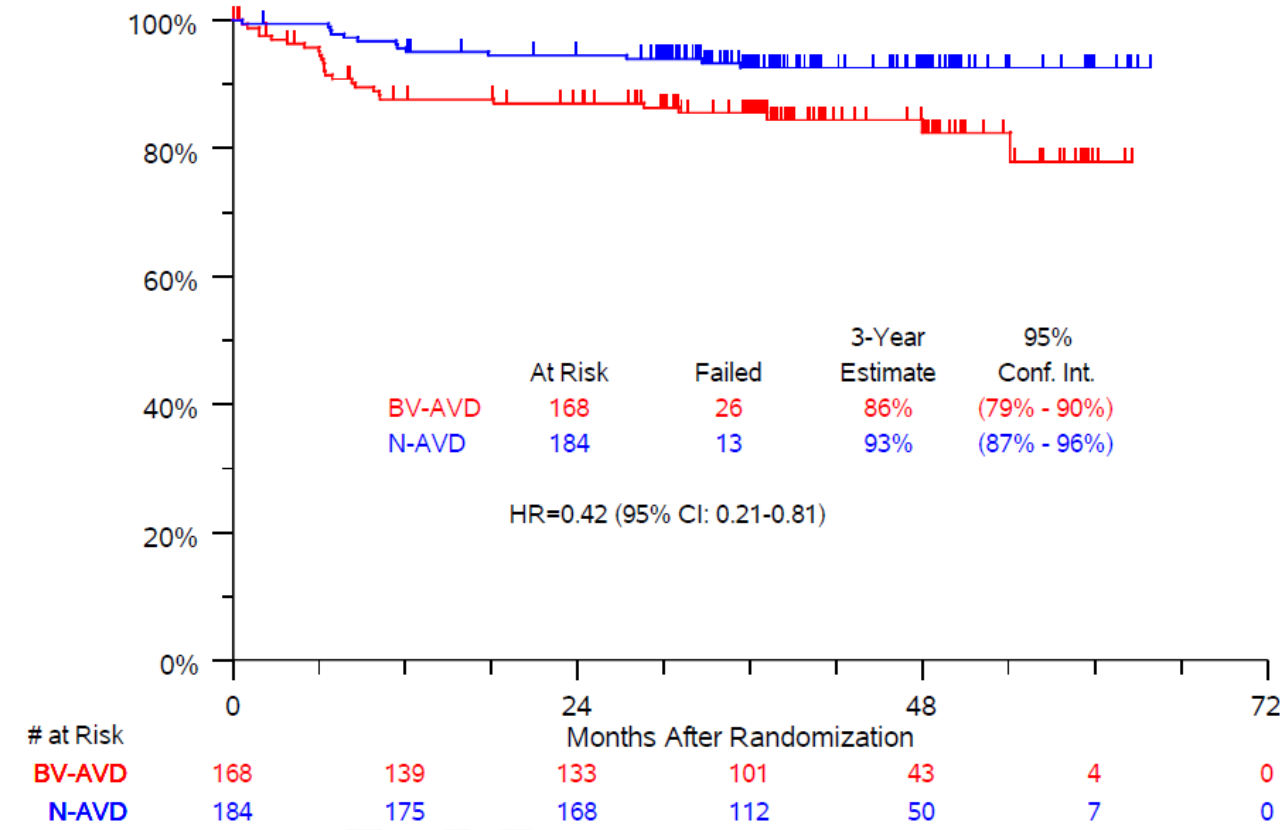
IPS 4-7



Two-sided Log-rank P-value = 0.04

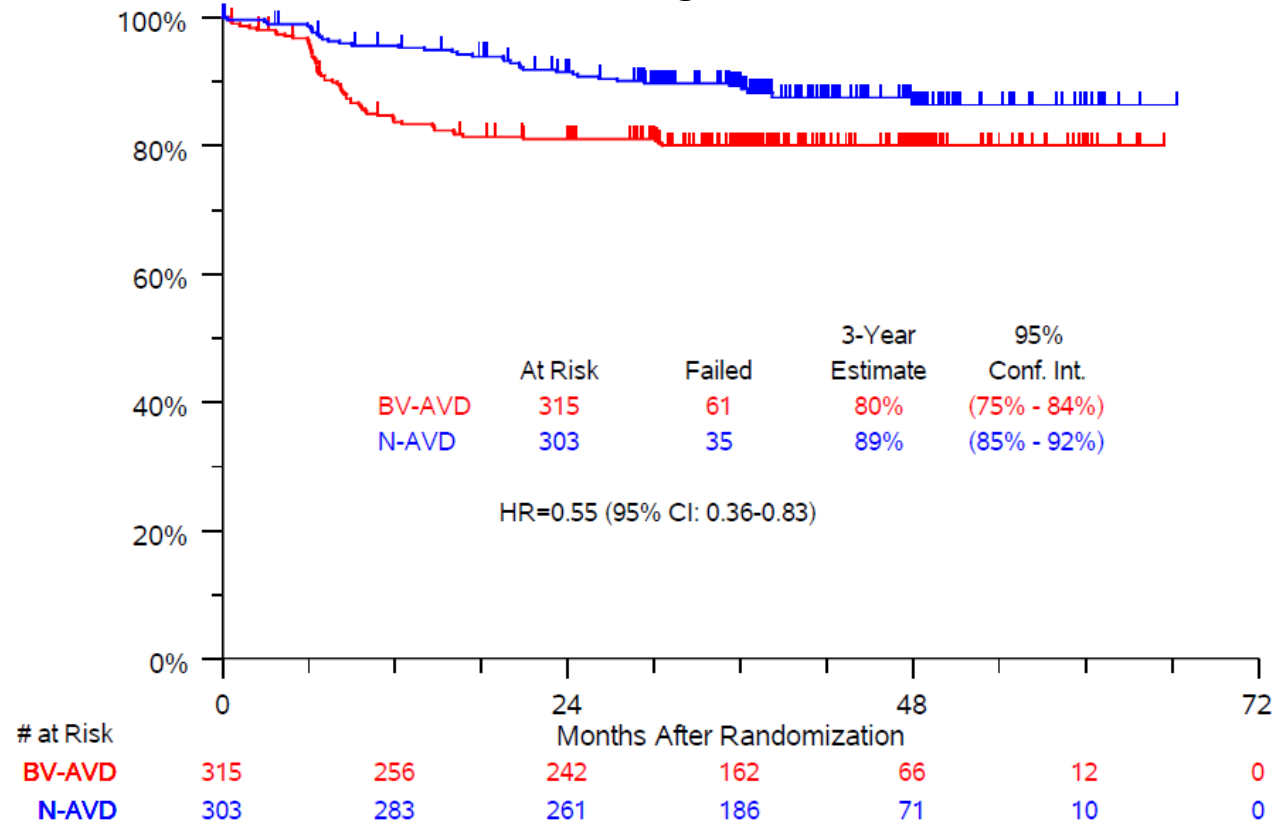
Beneficio con N-AVD en estadio III y IV

Stage III



Two-sided Log-rank P-value = 0.008

Stage IV



Two-sided Log-rank P-value = 0.004

Presented by: Alex F. Herrera, MD

Revisión centralizada de las PET en S1826

Interim

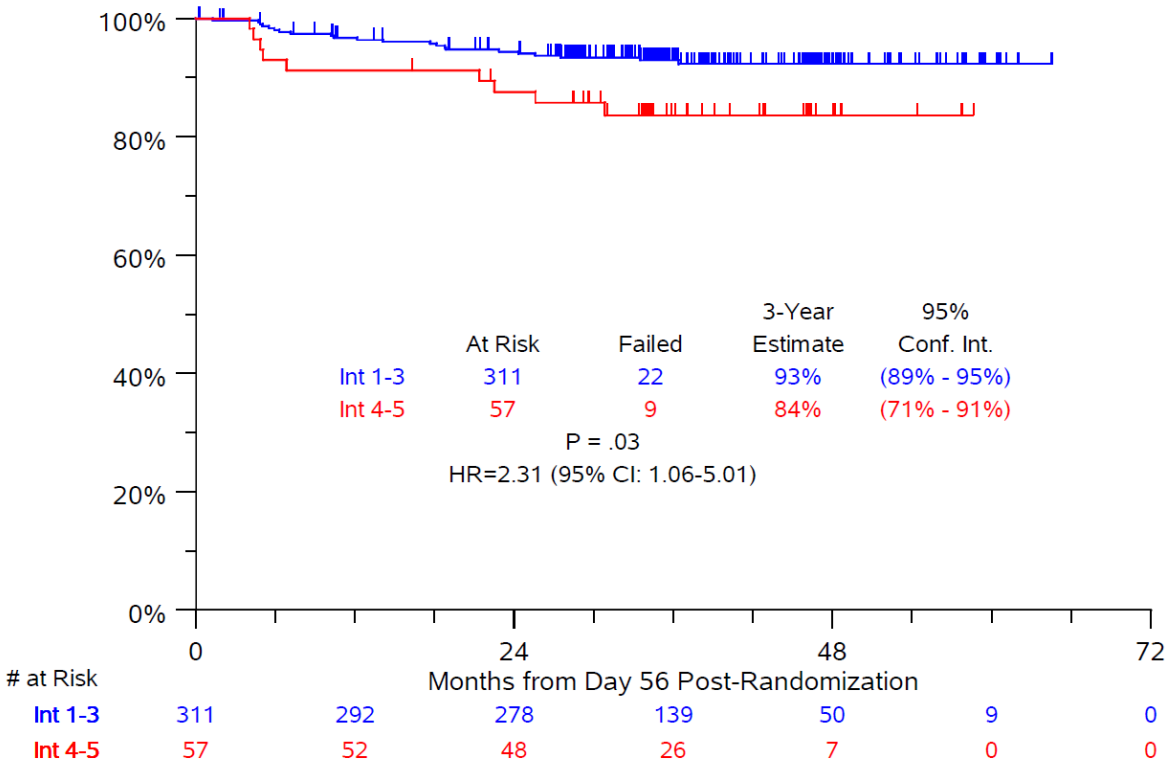
	Total		N-AVD		BV-AVD	
Interim PET/CT Assessed	742	100%	368	100%	374	100%
Deauville Score (DS)						
1	87	11.7%	45	12.2%	42	11.2%
2	396	53.4%	195	53.0%	201	53.7%
3	117	15.8%	71	19.3%	46	12.3%
4	131	17.7%	52	14.1%	79	21.1%
5	11	1.5%	5	1.4%	6	1.6%
DS Group						
DS 1-3	600	80.9%	311	84.5%	289	77.3%
DS 4-5	142	19.1%	57	15.5%	85	22.7%

EOT

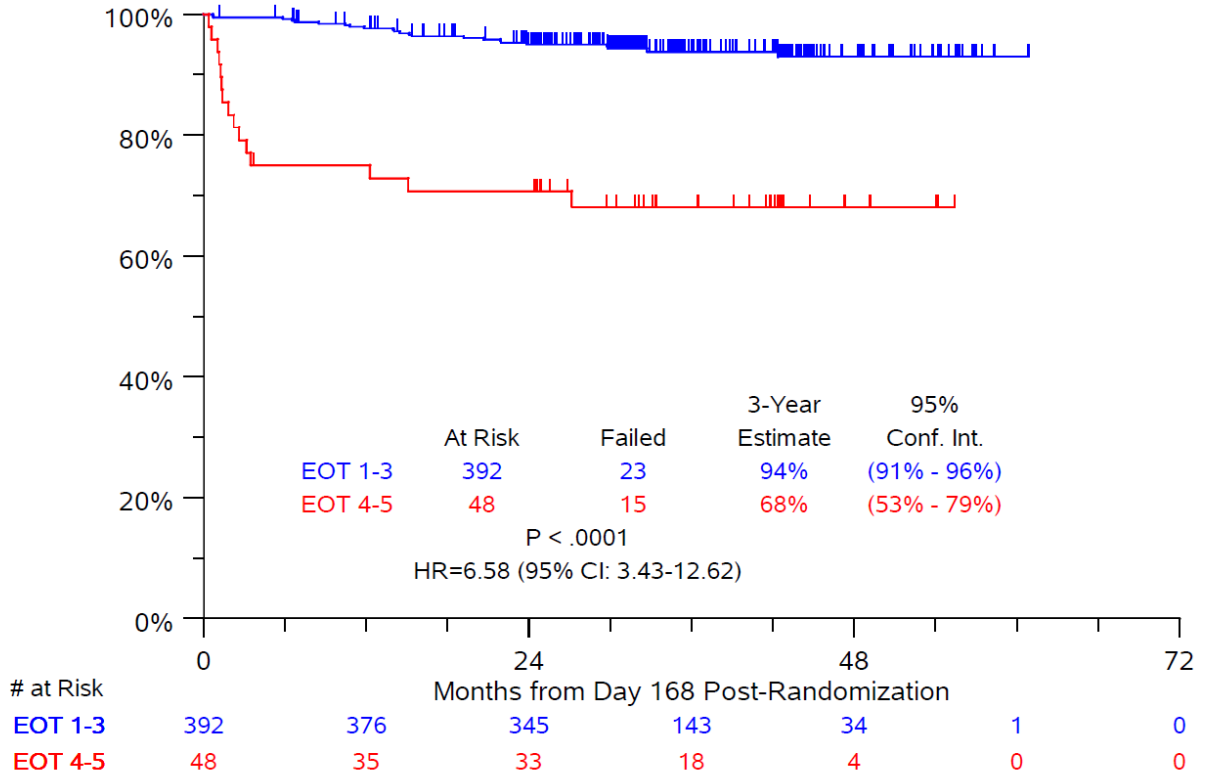
	Total		N-AVD		BV-AVD	
EOT PET/CT Assessed	863	100.0%	440	100.0%	423	100.0%
Deauville Score (DS)						
1	191	22.1%	101	23.0%	90	21.3%
2	501	58.1%	260	59.1%	241	57.0%
3	55	6.4%	31	7.0%	24	5.7%
4	78	9.0%	37	8.4%	41	9.7%
5	38	4.4%	11	2.5%	27	6.4%
DS Group						
EOT 1-3	747	86.6%	392	89.1%	355	83.9%
EOT 4-5	116	13.4%	48	10.9%	68	16.1%

N-AVD: PET tiene valor minimo pronóstico

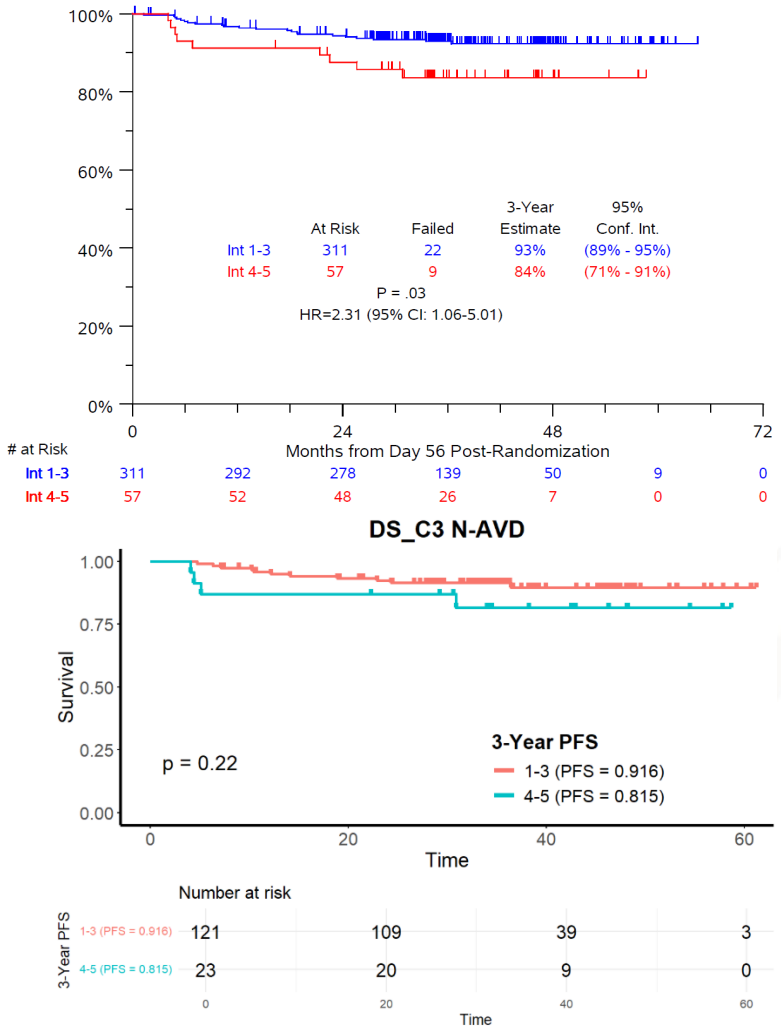
Interim

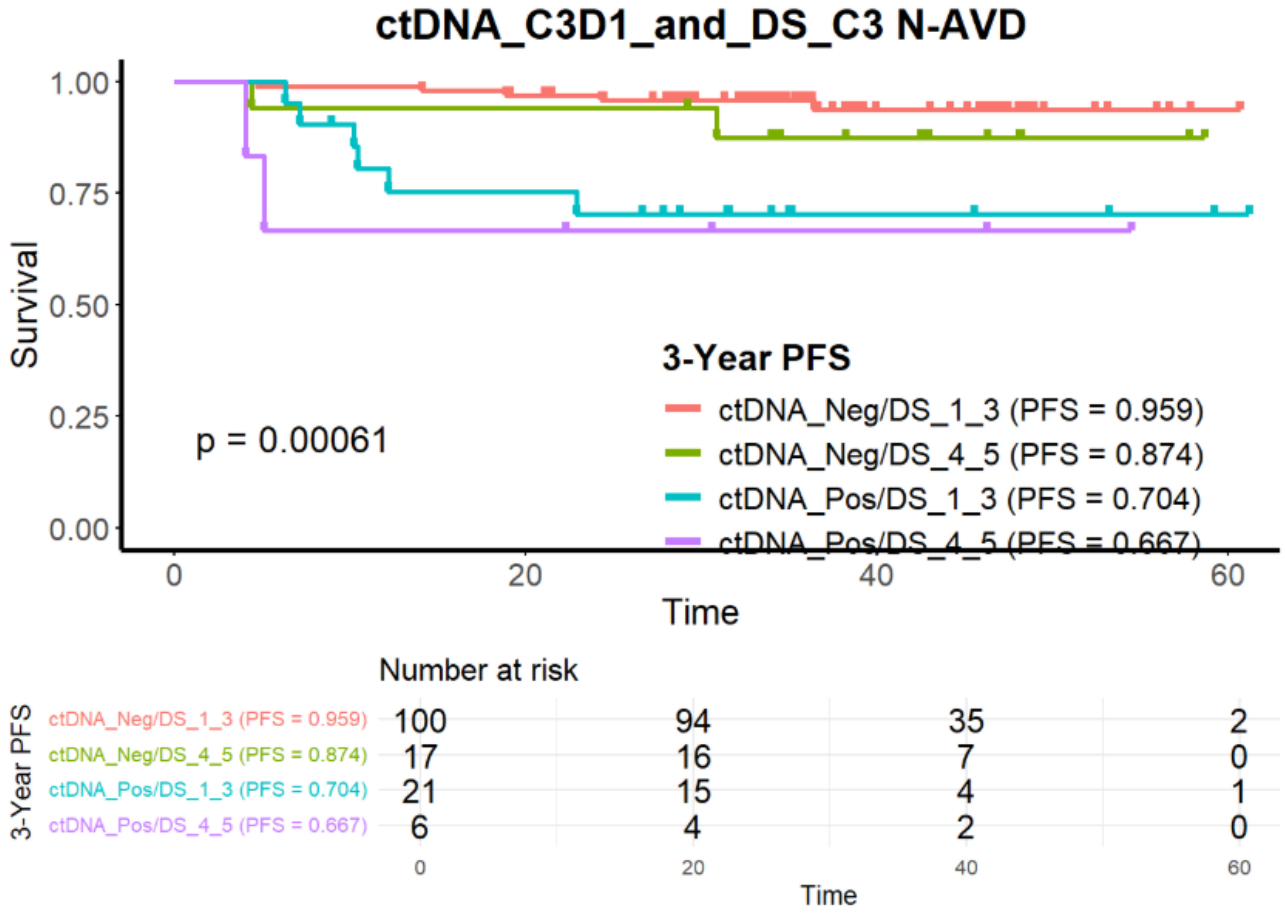


EOT



N-AVD C3D1: ctDNA y PET

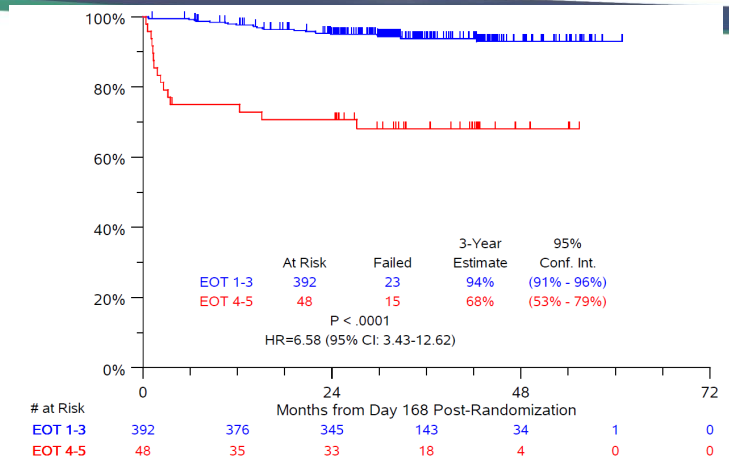


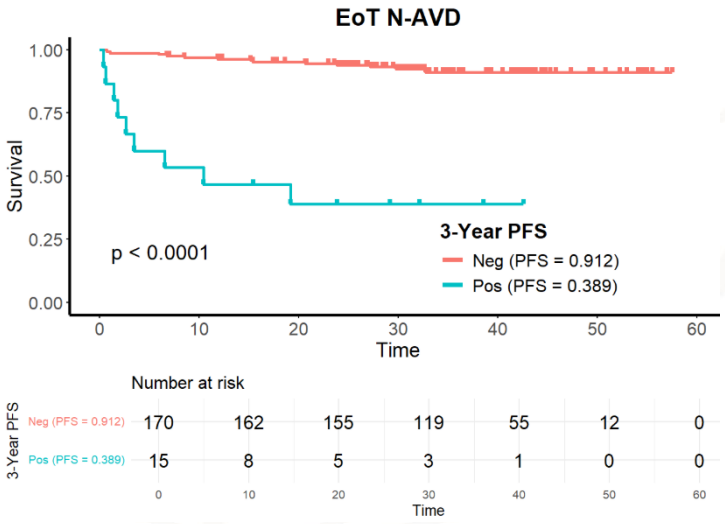


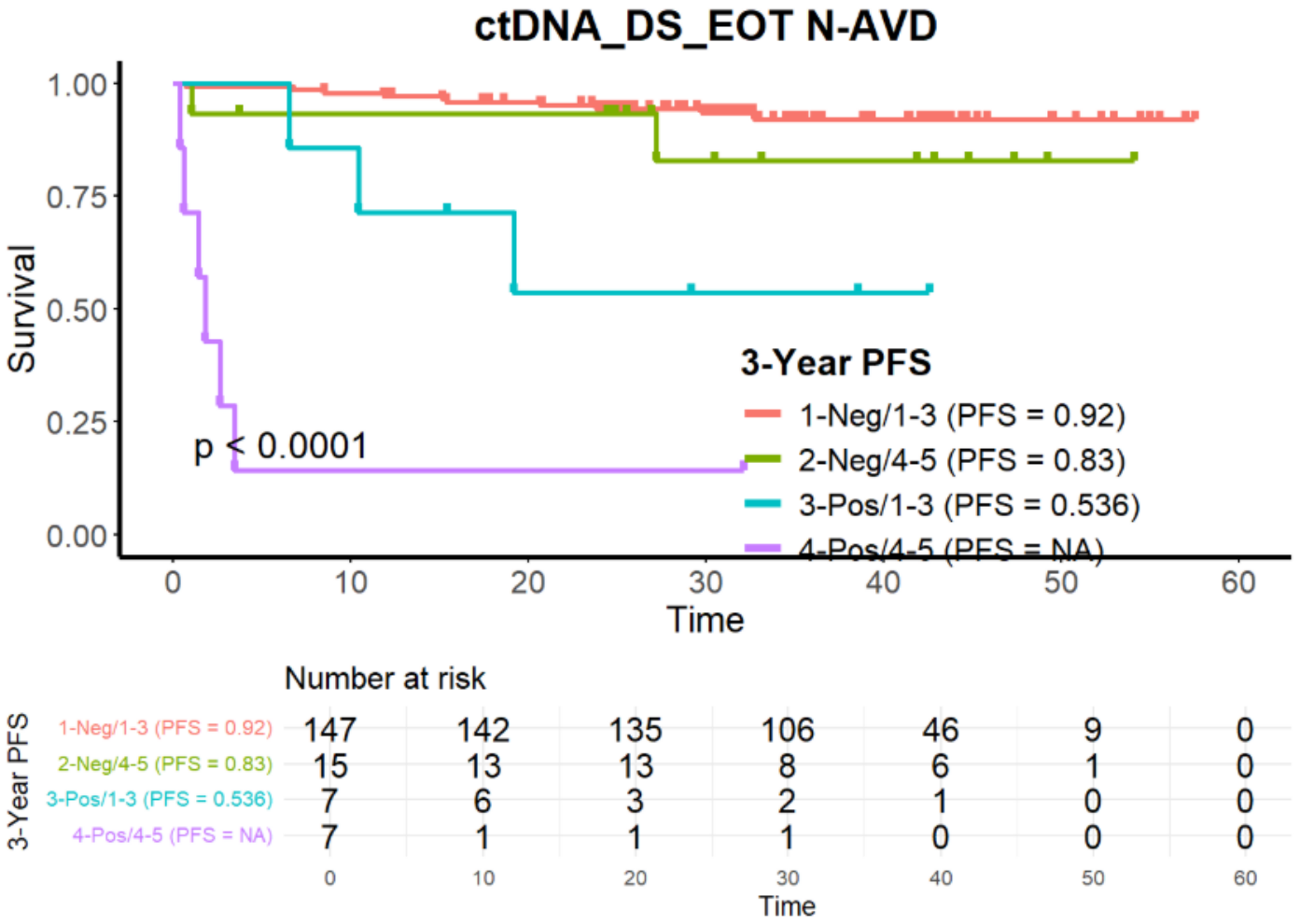
Presented by: Alex F. Herrera, MD

Con el Aval:

N-AVD EOT: integration of PET and ctDNA







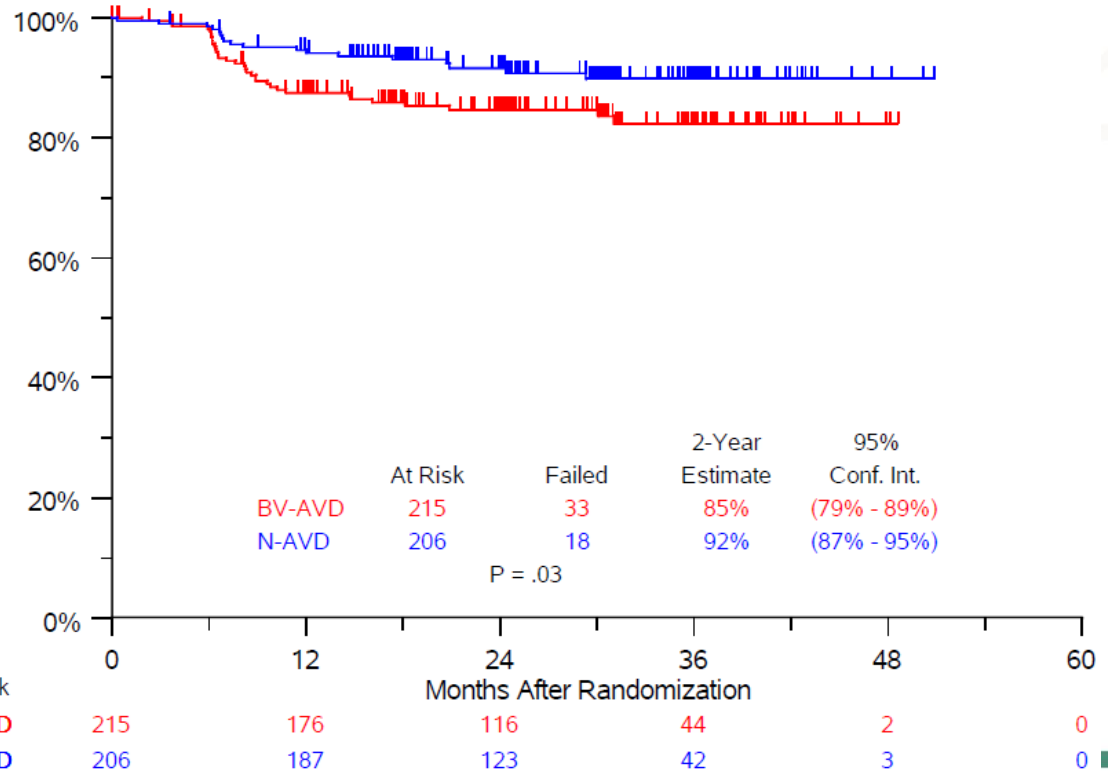
Presented by: Alex F. Herrera, MD

Con el Aval:

N-AVD > BV-AVD en EBV- and EBV+ cHL

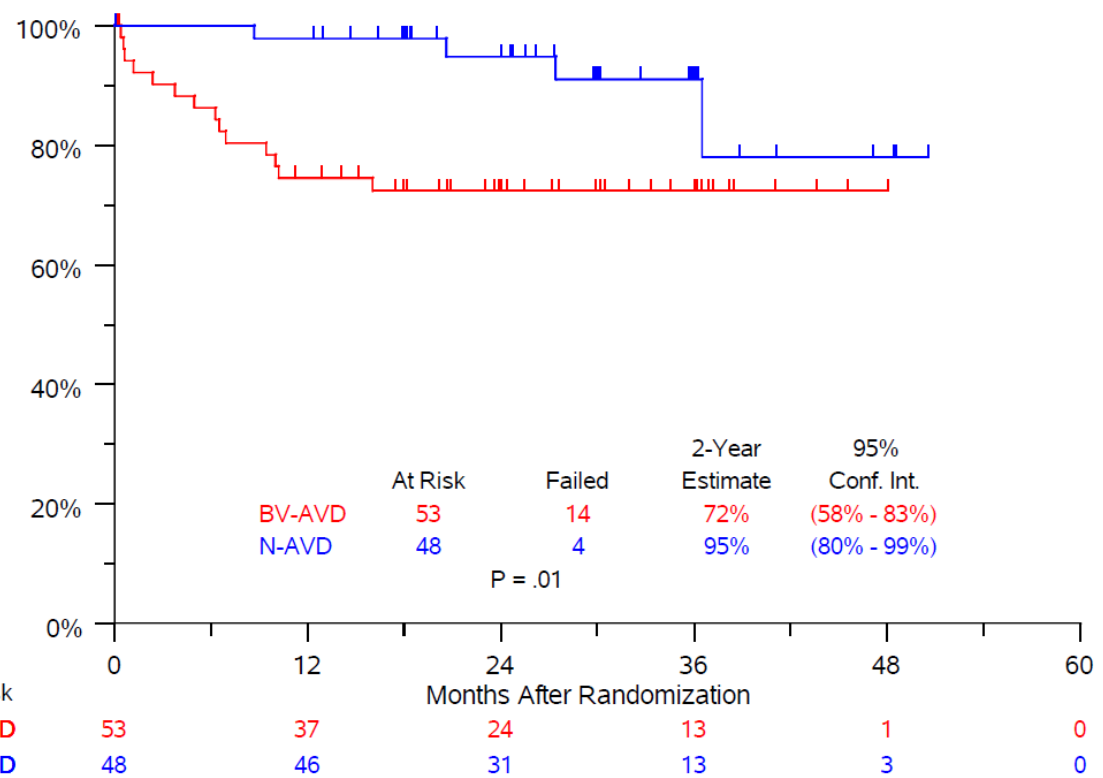
EBV-

2-year PFS
N-AVD 92%
Bv-AVD 85%



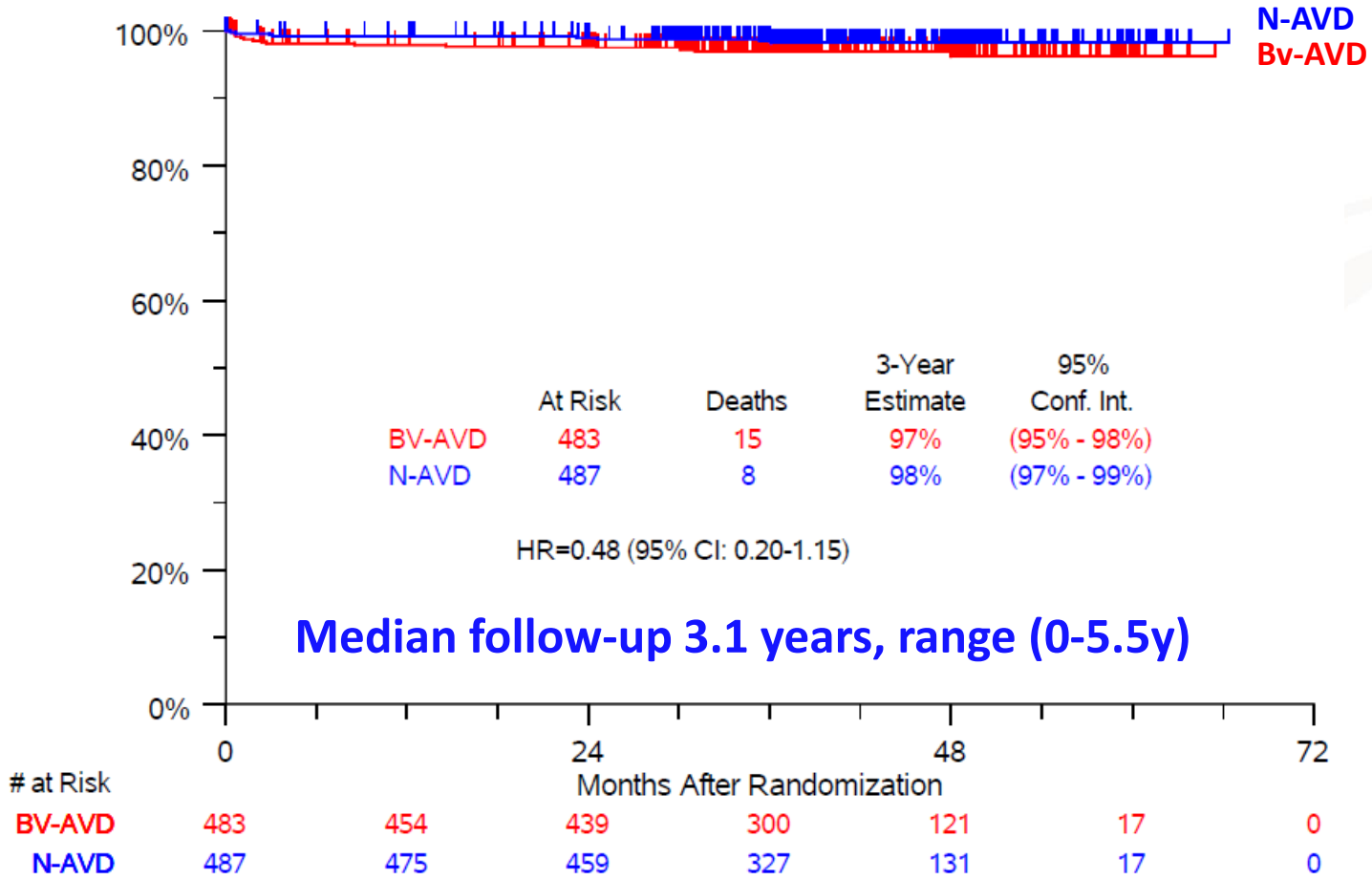
EBV+

2-year PFS
N-AVD 95%
Bv-AVD 72%



Ahmed S et al. ICML 2025

Supervivencia global

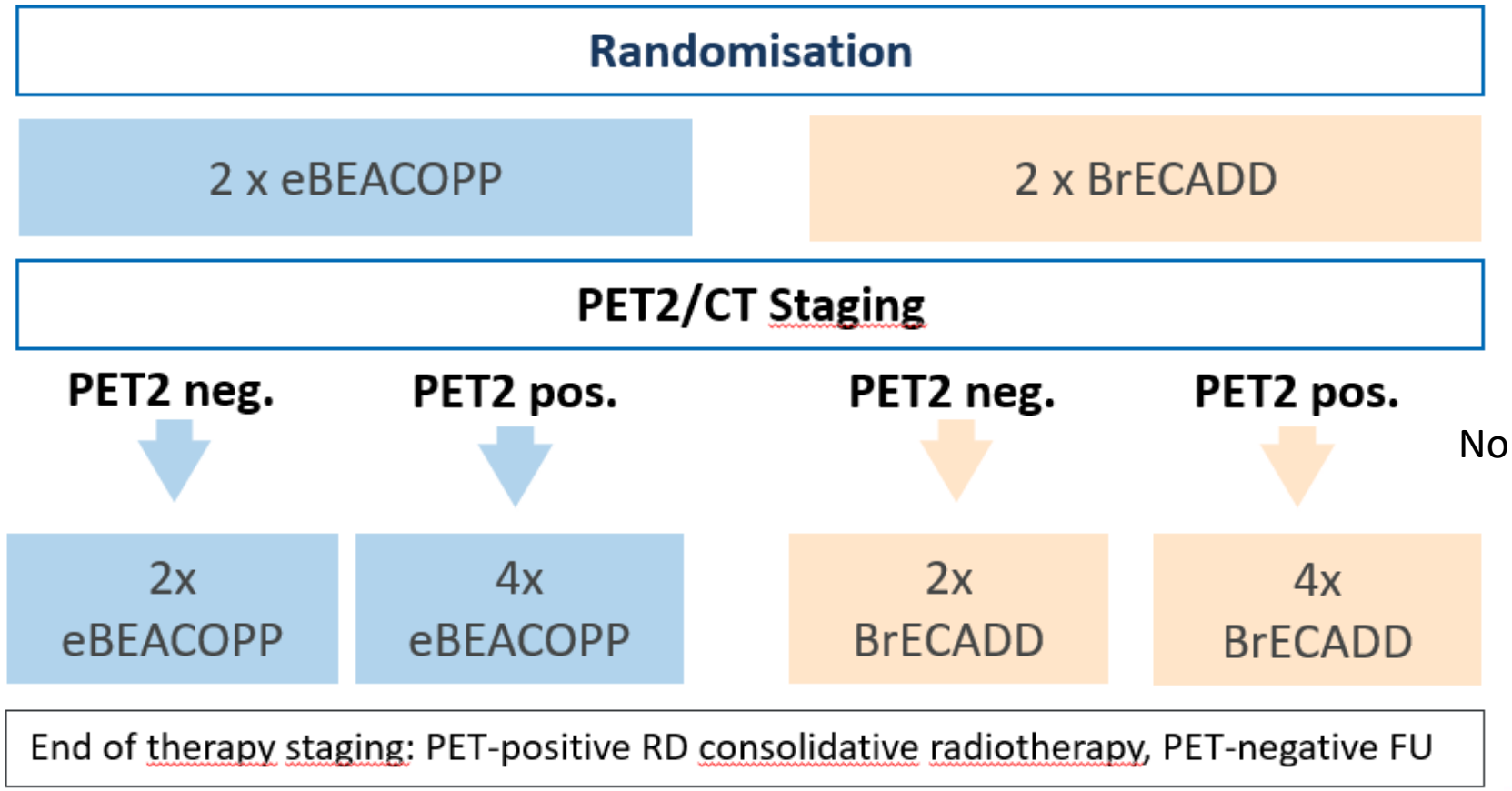


Cause of Death	N-AVD N=487	BV-AVD N=483
Infection/Sepsis	5	6
Lymphoma	**1**	**2**
Medical issues other than cancer	2	4
New primary cancer	0	1
Unknown	0	2
Total	**8**	**15**

Presented by: Alex F. Herrera, MD

Herrera, AF et al. N Eng J Med. 2024 Oct 17;391(15):1379-138

HD21: Reduciendo toxicidad de escBEACOPP



Non-inferiority design

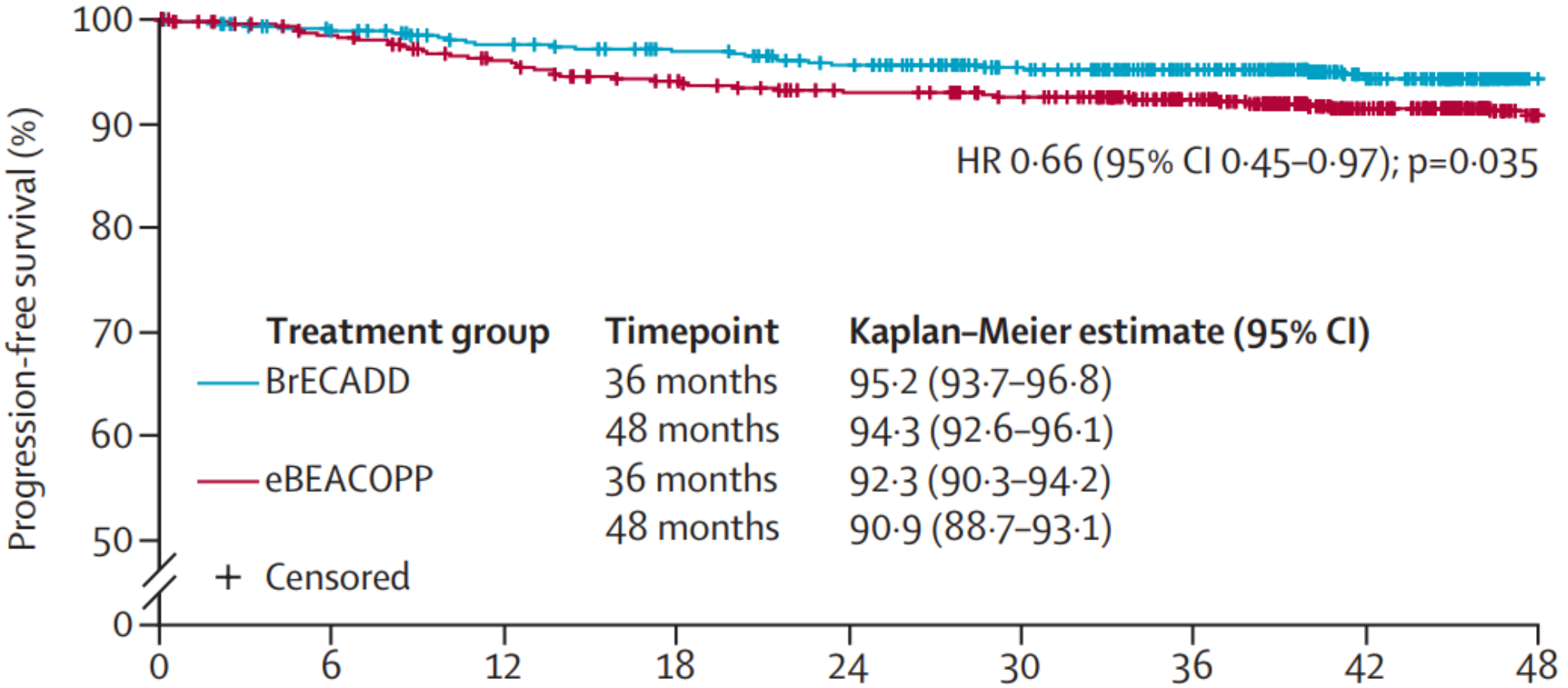
Borchmann P et al, ICML 2023

BrECADD fue mejor tolerado que BEACOPP

Adverse event, n (%)	BrECADD (n=738)		escBEACOPP (n=732)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Neutropenic fever	194 (28)	193 (28)	144 (21)	141 (21)
Infection	358 (49)	150 (20)	335 (46)	138 (19)
Peripheral sensory neuropathy	287 (39)	10 (1)	360 (49)	17 (2)
Peripheral motor neuropathy	28 (4)	3 (<1)	31 (4)	1 (<1)
Respiratory, thoracic, and mediastinal disorders	282 (38)	24 (3)	347 (47)	34 (5)
Treatment related morbidity				
Anemia, thrombocytopenia, or infection of CTCAE grade 4	231 (31)		382 (52)	
Organ toxicity of CTCAE grade 3–4	139 (19)		126 (17)	
Treatment-related morbidity	312 (42)		430 (59)	

Borchmann P, et al. *Lancet*. 2024;404:341–352.

HD21: BrECADD >> escBEACOPP



Borchmann P et al, Lancet 2024

BrECADD vs N-AVD toxicidad hematológica

Toxicity	Frequency (%)
Gr ≥ 3 anemia	30% (vs 6%)
PRBC transfusion	24%
Gr ≥ 3 thrombocytopenia	55% (vs 2%)
Platelet transfusion	17%
Gr ≥ 3 leukopenia	87% (vs 47%)
Febrile neutropenia	28% (vs 5%)
Gr ≥ 3 infection	20% (vs 5%)

- Use of consolidative radiation: BrECADD 14% vs S1826 < 1%

Individualización: Pros/Cons de N-AVD vs BrECADD

Nivo-AVD

- Tolerability
  - Pros: less heme/infectious/GI tox; older pts can tolerate
  - Cons: Immune tox, more anthracycline
- Efficacy
  - No direct comparison, no clear difference
- Duration
  - 24 wks, longer than BrECADD, esp PET2 neg
- Logistics
  - Familiarity globally with PD1 blockade
  - Q2 week dosing

BrECADD

- Tolerability
  - Pros: no immune tox, less anthracycline
  - Cons: more heme/infectious/GI tox, toxic in older pts
- Efficacy
  - No direct comparison, no clear difference
- Duration
  - 12-18 wks, shorter than N-AVD, esp PET2 neg
- Logistics
  - Daily dosing x 3-4 days
  - Transfusions, ~30% febrile neutropenia

Individualización en Linfoma de Hodgkin

- Role of PET for personalization of treatment
  - Early stage disease: PET-adapted therapy remains standard
  - Advanced stage disease: evolving role for PET
    - N-AVD: no role for PET adaptation
    - BrECADD: key role for PET adaptation
    - BV-AVD: no role for PET adaptation
    - ABVD: key role for PET adaptation
- Individualization remains important
  - Patient preferences may guide choices – acute toxicity, treatment duration, use of radiation
  - Patient characteristics may guide choices – (e.g. older age favors N-AVD)

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