FONDAZIONE ITALIANA LINFOMI

IMMUNOTERAPIA E FARMACI BIOLOGICI NEL TRATTAMENTO DEI LINFOMI E LLC: ATTUALITÀ E FUTURO

Il linfoma di Hodgkin in stadio avanzato in I linea: oltre ABVD?

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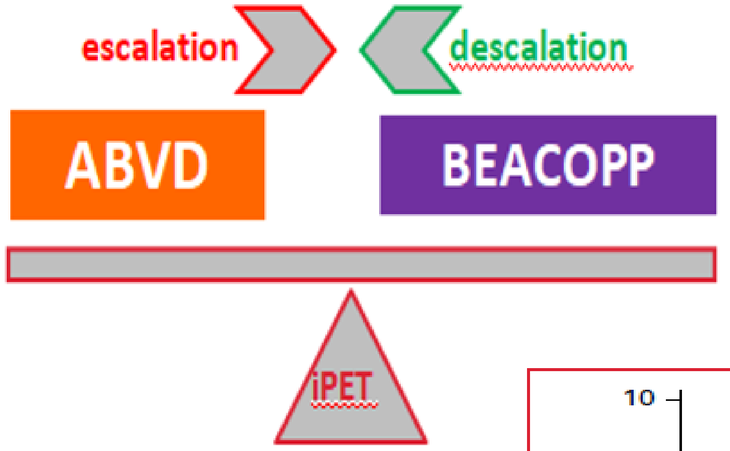
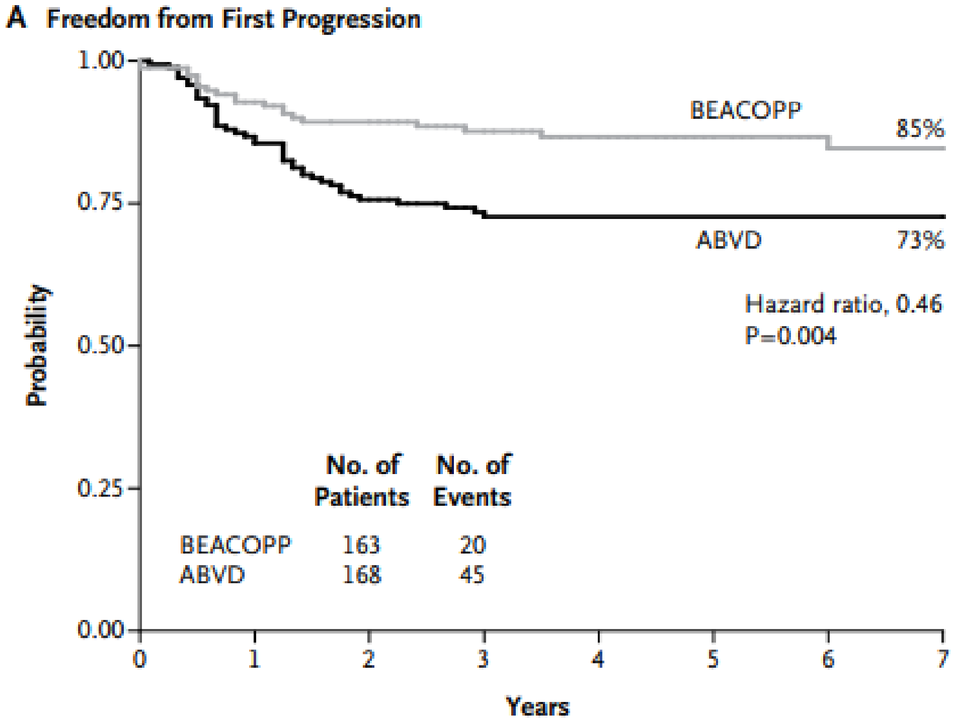
Disclosures of Chiara Rusconi

Research support PI	–
Consultant	–
Major stockholder	–
Honoraria	Celgene, Gilead, Lilly, Takeda
Scientific advisory board	Lilly, Takeda

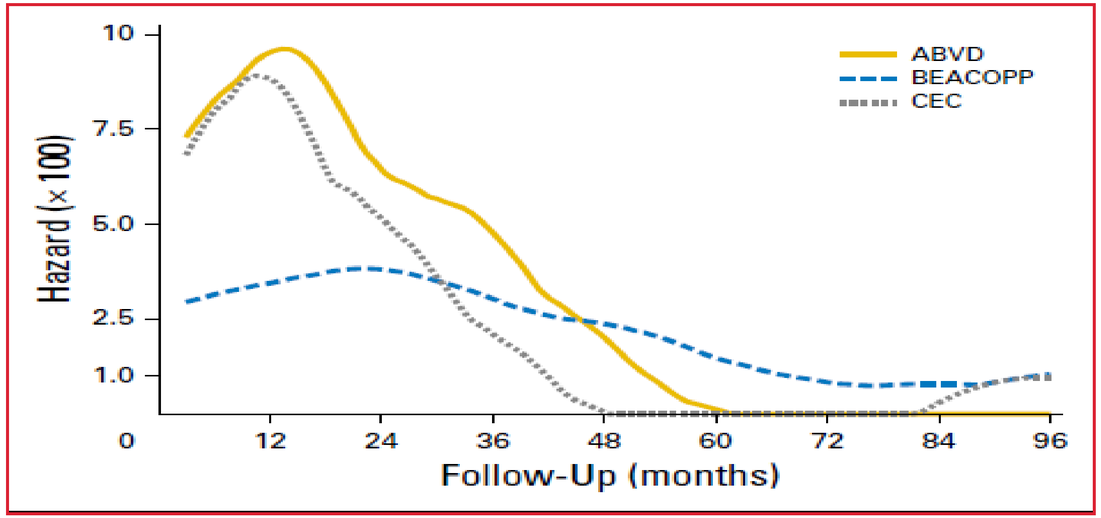
ABVD versus BEACOPP





Viviani S et al, NEJM 2011

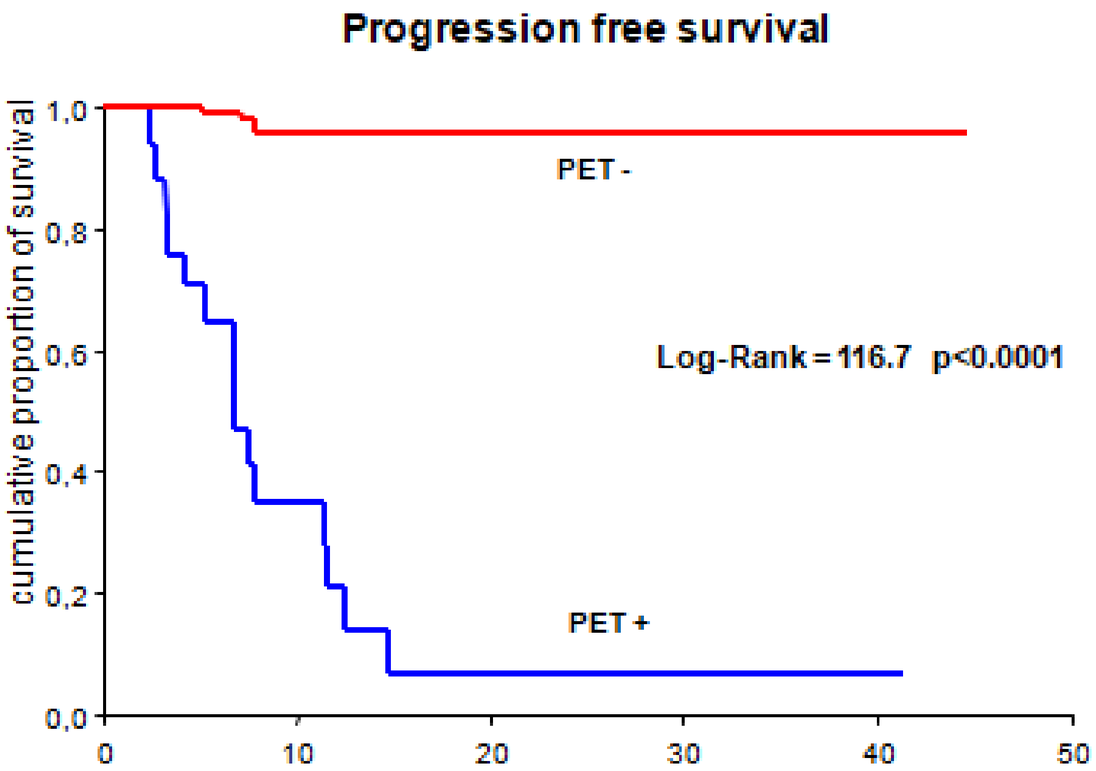
HD2000



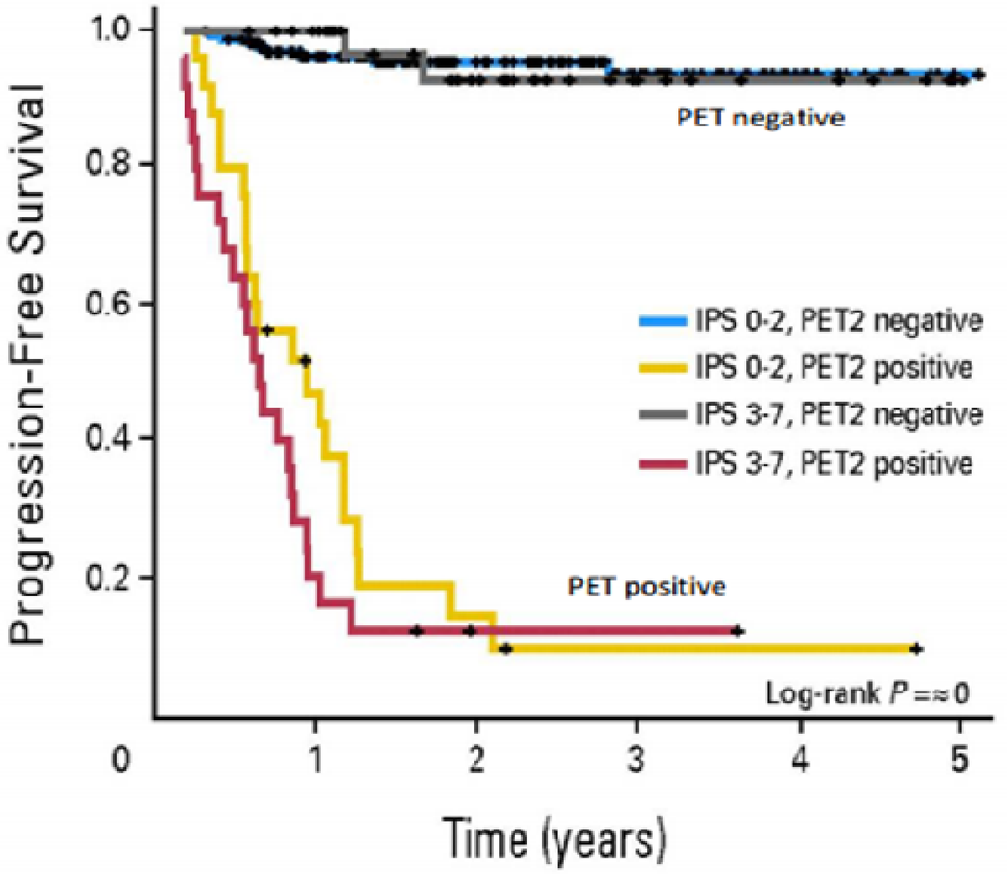
Second malignancies cumulative incidence rate@10 ys: 0.9% ABVD vs 6.6% CEC vs 6% BEACOPP (p= 0.02)

Merli F et al, JCO 2016

Interim PET: Hodgkin Lymphoma's Paradigm



Gallamini et al, Haematologica 2006



Gallamini et al, JCO 2007

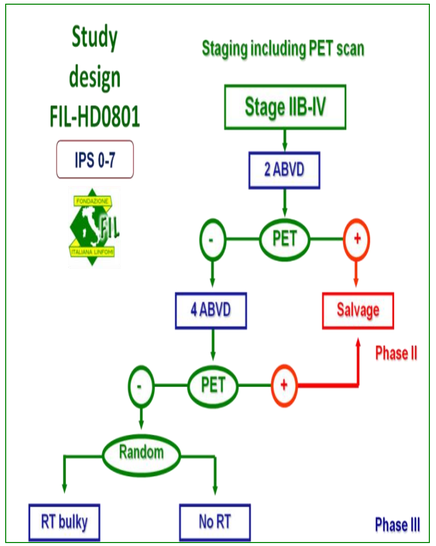
Advanced Stage: PET-driven studies

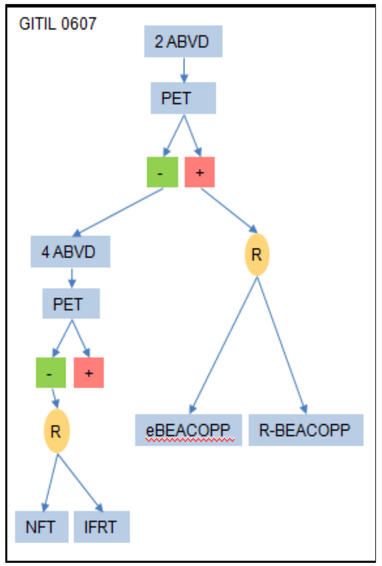
Intensification | DE-Escalation

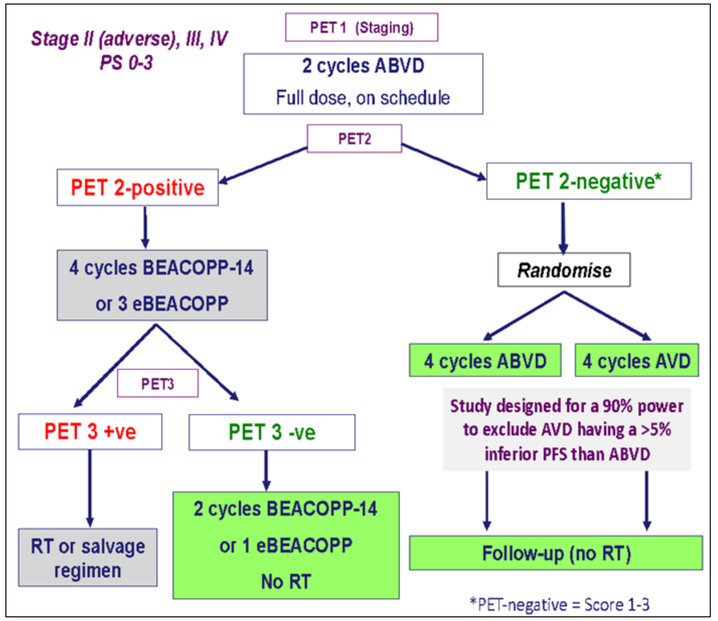
- **HD0801 (FIL)** Zinzani PL et al, JCO 2016 — IN
- **HD0607 (GITIL/FIL)** Gallamini A, JCO 2018 — IN
- **RATHL (UK)** Johnson P et al, NEJM 2016 — IN DE
- **S0816 (SWOG)** Stephens D. et al, ASH 2018 — IN
- **HD18 (GHSG)** Borchmann P et al, Lancet 2017 — IN DE
- **AHL2011 (Lysa)** Casasnovas et al, Lancet Oncol 2019 — DE

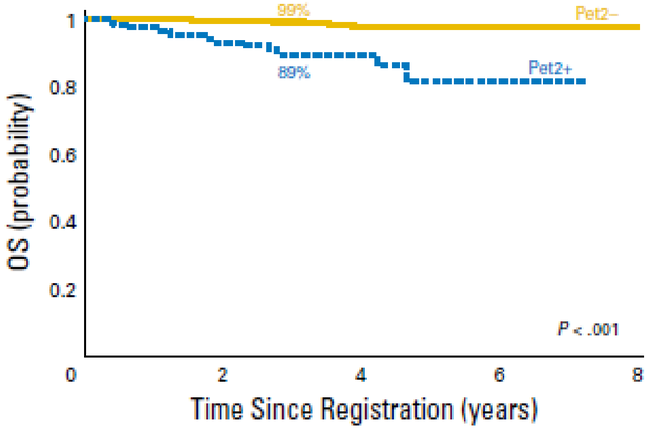
PET-driven studies: intensification

Gallamini A et al, JCO 2018

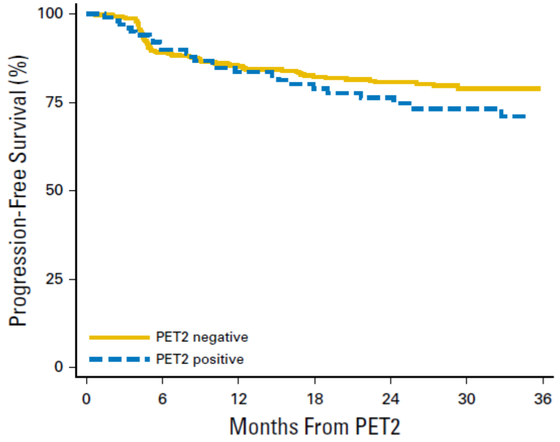






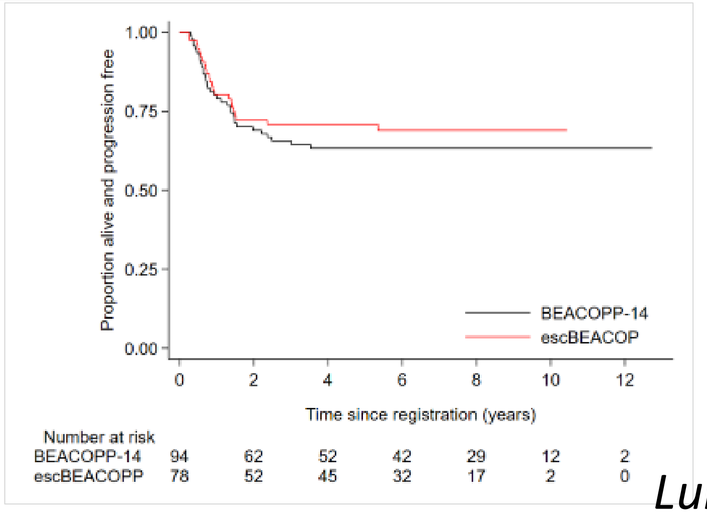


No. at risk		Events		Events		Events		Events	
Pet2–	630	3	583	9	169	0	42	0	0
Pet2+	150	10	116	4	37	2	4	0	0



No. at risk							
PET2 negative	409	354	296	228	191	81	20
PET2 positive	101	87	77	64	50	40	28

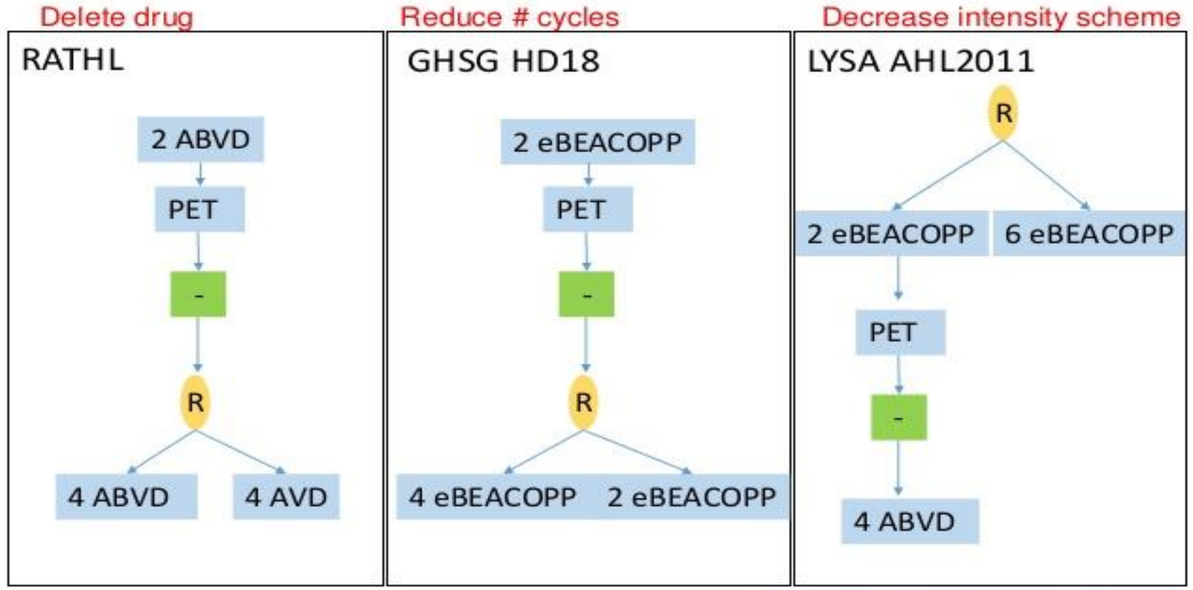
Zinzani PL et al, JCO 2016



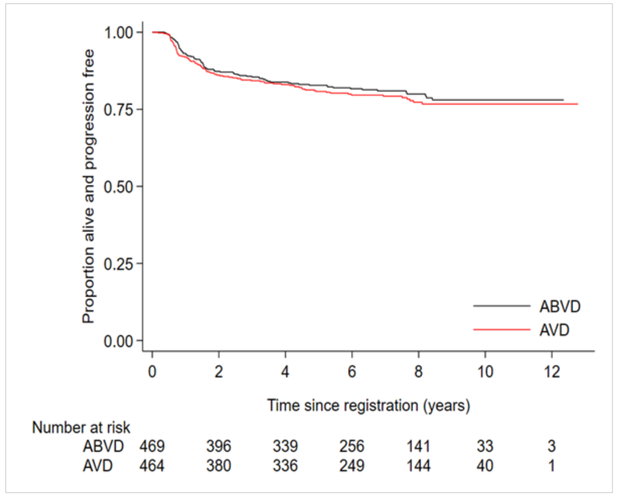
Number at risk							
BEACOPP-14	94	62	52	42	29	12	2
escBEACOPP	78	52	45	32	17	2	0

Luminari S et al, JCO 2024

PET-guided de-escalation
randomized trials in advanced stages

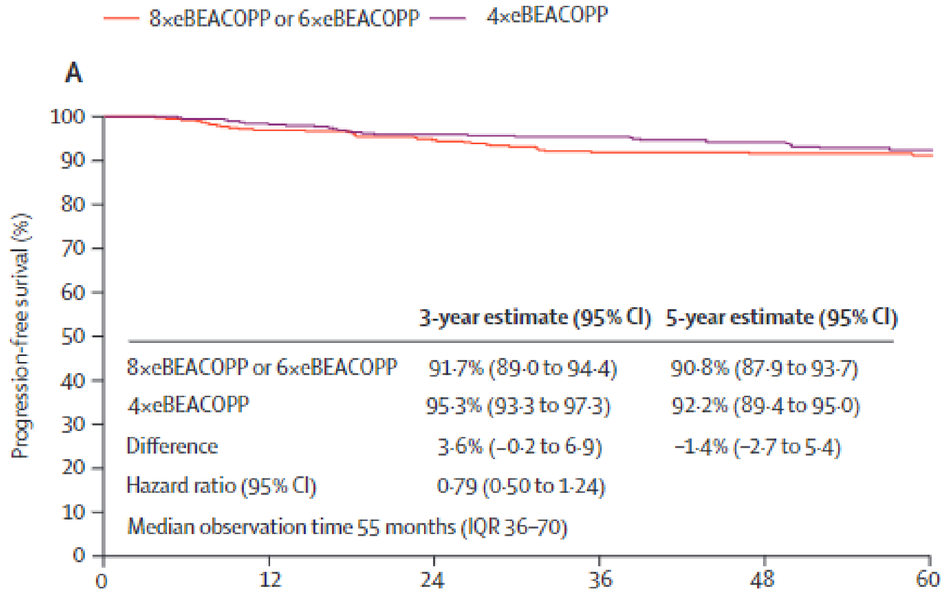


Courtesy of Peter Johnson, adapted

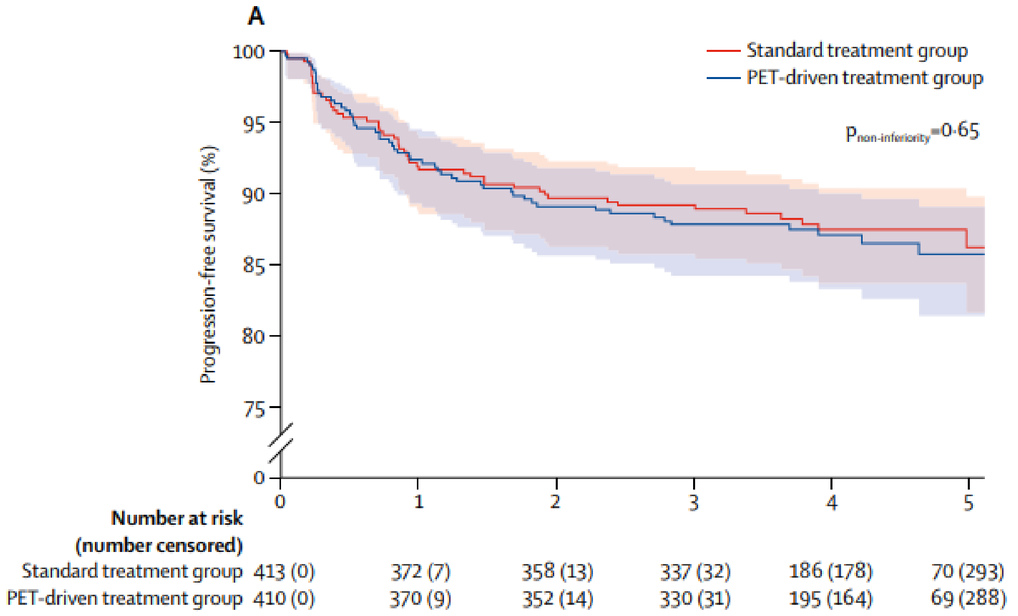


At 3 years: ABVD - AVD = 1.3% (- 3.8 to +4.7) within pre-defined non-inferiority margin of 5%

Luminari S et al, JCO 2024

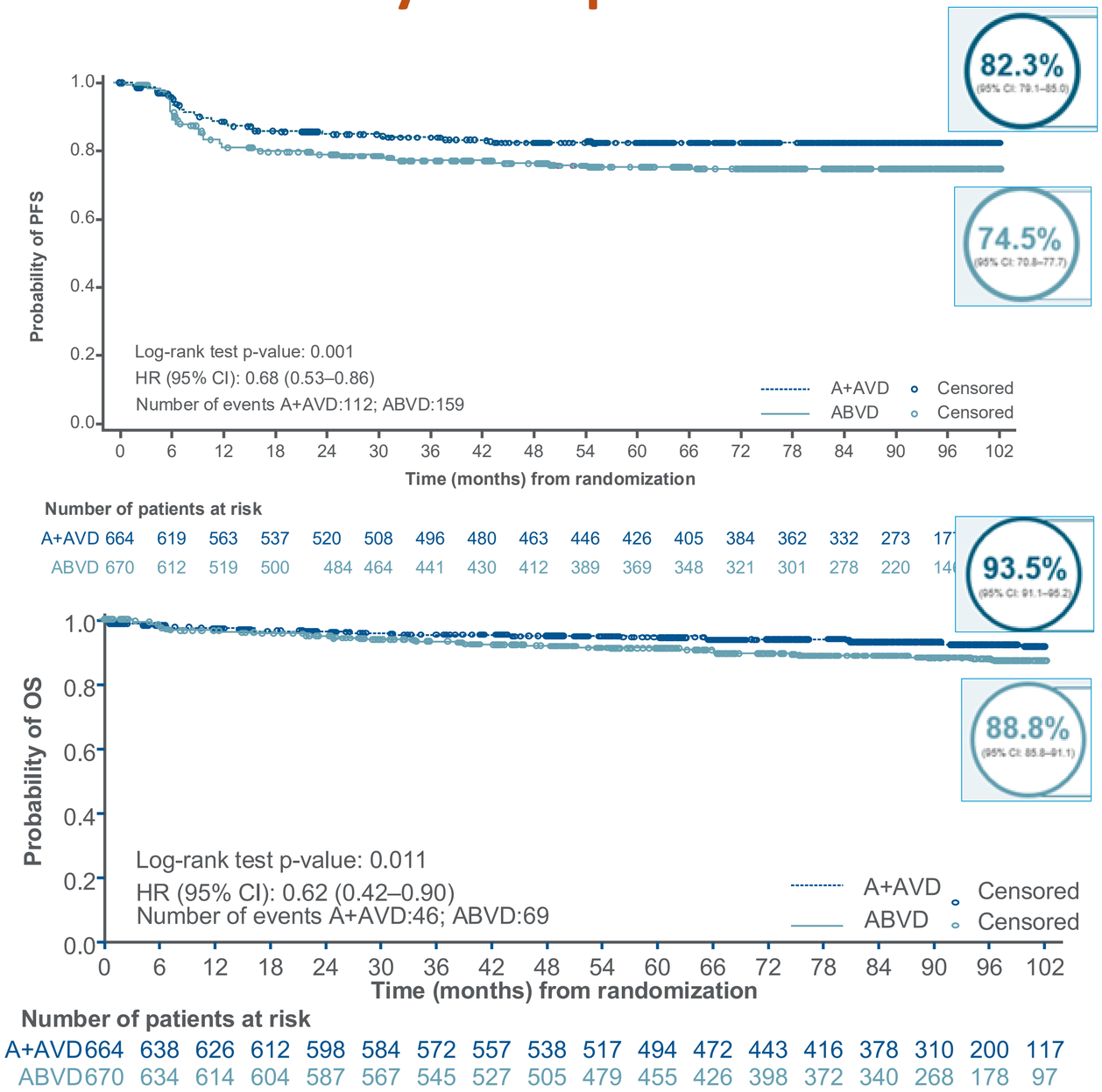


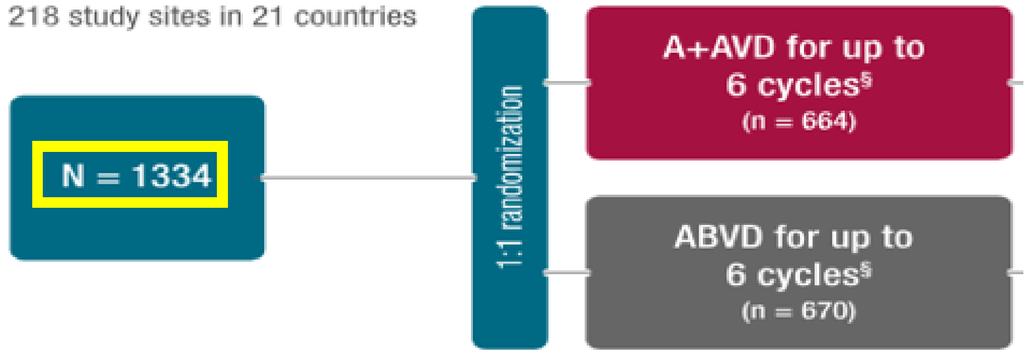
Borchmann P et al, Lancet 2017



Casasnovas RO, Lancet Oncol 2019

ECHELON-1: 7-years update



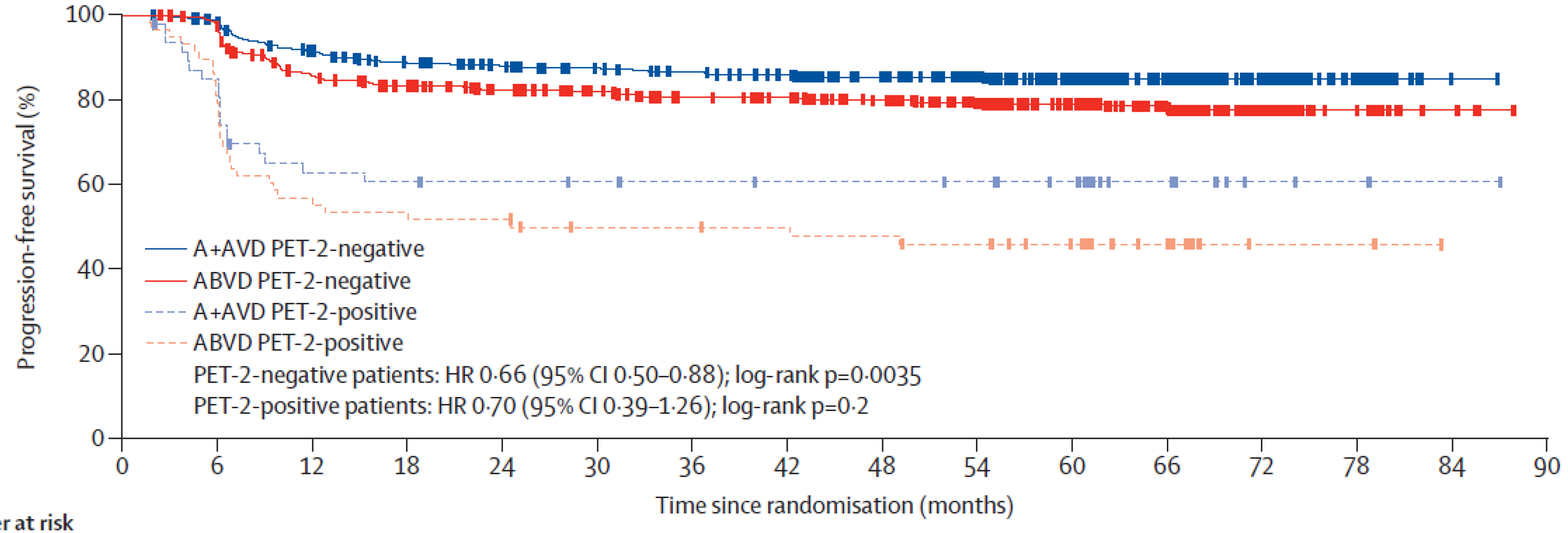


- **A+AVD** (brentuximab vedotin 1.2 mg/kg)
- **ABVD**

Events	A+AVD (n=662)	ABVD (n=659)
	No of events, n (%)	No of events, n (%)
All deaths	**46 (7)**	**69 (10)**
Disease-related	22 (3)	30 (5)
Not disease-related	24 (4)	38 (6)
Unknown	0 (0)	1 (<1)
Deaths >30 days after last dose of frontline therapy	**37 (6)**	**56 (8)**
Disease-related	19 (3)	26 (4)
Not disease-related*	18 (3)	29 (4)
Unknown	2 (<1)	7 (1)
Deceased	3 (<1)	0 (0)
Cardiac arrest	2 (<1)	0 (0)

Ansell SM et al, NEJM 2022

ECHELON-1 and iPET



Number at risk (number censored)															
A+AVD PET-2-negative	588 (0)	572 (6)	526 (13)	500 (23)	484(35)	472 (44)	460 (52)	444 (64)	417 (88)	386 (119)	312 (191)	189 (314)	98 (405)	36 (467)	1 (502)	0 (503)
ABVD PET-2-negative	578 (0)	558 (4)	483 (13)	463 (20)	442(36)	424 (52)	400 (68)	392 (76)	368 (97)	334 (128)	271 (190)	170 (290)	70 (388)	20 (438)	4 (454)	0 (458)
A+AVD PET-2-positive	47 (0)	39 (1)	28 (2)	27 (2)	26(3)	25 (4)	24 (5)	23 (6)	23 (6)	22 (7)	18 (11)	10 (19)	3 (26)	2 (27)	1 (28)	0 (29)
ABVD PET-2-positive	58 (0)	46 (0)	32 (0)	31 (0)	30(0)	26 (3)	26 (3)	25 (4)	24 (4)	22 (5)	18 (9)	8 (19)	2 (25)	2 (25)	0 (27)	0 (27)

5-ys PFS: 82.2% vs 75.3%

Straus D et al, Lancet Hematol 2021

ECHELON-1: Overall Survival – Multivariate analysis

- **overall survival benefit with A+AVD (hazard ratio for death, 0.53; 95% CI, 0.34 to 0.83)**

- covariates with greatest evidence of association with OS:
  - age
  - nonWhite race
  - ECOG PS score
  - **PET2 status (negative or positive)**

6-year OS estimates favored A+AVD over ABVD among both

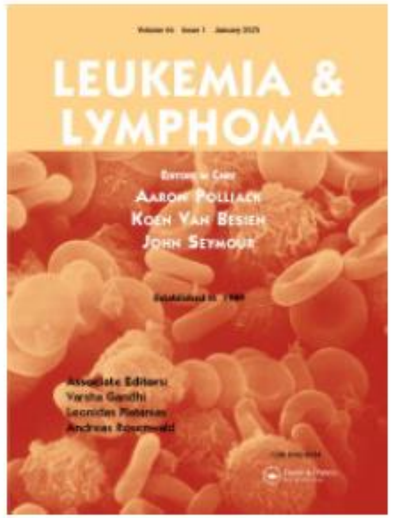
- **PET2-negative** patients (94.9% vs. 90.6%; HR for death, 0.54; 95% CI, 0.34 to 0.86)
- **PET2-positive** patients (95% vs. 77%; HR ratio, 0.16; 95% CI, 0.04 to 0.72)

Ansell SM et al, NEJM 2022

Real-world studies of frontline BV+AVD therapy for HL

Study	Patients	Baseline characteristics	Median follow-up	PFS	OS
Steiner R, et al. 2023: Retrospective, multi-center cohort study (N=179)[1]	Stage III/IV HL treated with BV+AVD	Median age, years: 37 (18–79); 21% ≥60 years Stage III/IV: 27%/73%	27.4 months	1-year PFS: 90.3%	2-year OS: 98.5%
Bowers J, et al. 2023: Retrospective, multi-center cohort study (N=153)[2]	Stage III/IV HL 6 cycles BV+AVD planned	Median age, years: 35 (18–76); 22% >60 years Stage III–IV: 92%*	24 months	2-year PFS: 82.7%	2-year OS: 97.4%
Rusconi C, et al. 2024: Retrospective, multi-center cohort study (N=99)[4]	Stage IV HL treated with BV+AVD (≥1 cycle)	Median age: 39 yrs 11% >65 years Stage IV: 100%	14.4 months	1-year PFS: 84.1%	1-year OS: 96.9%
Assanto G, et al. 2024: Retrospective, multi-center cohort study (N=168)[5]	Stage IV HL treated with BV+AVD (or ABVD)	Median age: 37 yrs BV+AVD, 34 yrs ABVD ≥65 yrs; 11.1% BV+AVD, 8.3% ABVD Stage IV: 100%	BV+AVD: 16 months ABVD: 40 months	EOT: CR (BV+ABVD 83% ABVD 83.3%	NR

- *8% (13) had Stage I–II cHL; †7% (1) had Stage II cHL.
- ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AVD, doxorubicin, vinblastine, dacarbazine; BV, brentuximab vedotin; CR, complete response; (c)HL, (classical) Hodgkin lymphoma; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
- 1. Steiner R, et al. *Blood Adv.* 2023;7:7485–93; 2. Bowers J, et al. *Blood Adv.* 2023;7:6630–8; 3. Cai Q, et al. *Blood.* 2022;140(Suppl 1):12035–6. 4. Rusconi C, et al. Presented at EHA, 13–16 June 2024, Madrid, Spain: Abstract P1096; 5. Assanto GM, et al. Presented at EHA, 13–16 June 2024, Madrid, Spain: Poster P1080.



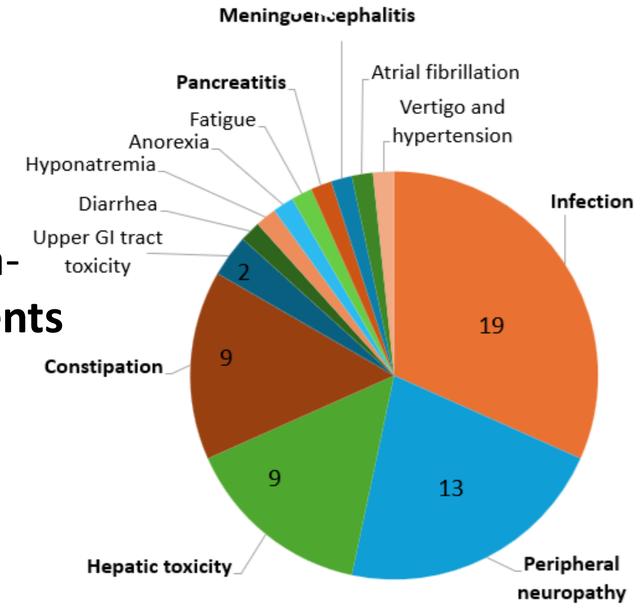
Interim-PET predicts progression-free survival in stage IV Hodgkin lymphoma treated with upfront brentuximab vedotin-AVD

Chiara Rusconi, Angelica Barone, Andrea Visentin, Benedetta Bianchi, Vittorio Ruggero Zilioli, Andrea Bernardelli, Sara Iadecola, Edoardo Olivari, Francesca Gaia Rossi, Manuel Gotti, Caterina Cecchetti, Benedetta Puccini, Silvia Franceschetti, Alfredo Molteni, Sara Steffanoni, Fabrizio Marino, Anna Vanazzi, Anna Guidetti, Michele Merli, Federico Mazzon, Alfredo Marchetti, Alessandro Cellini, Cristina Muzi, Rosalba Miceli, Carlo Visco, Alessandro Re & Paolo Corradini

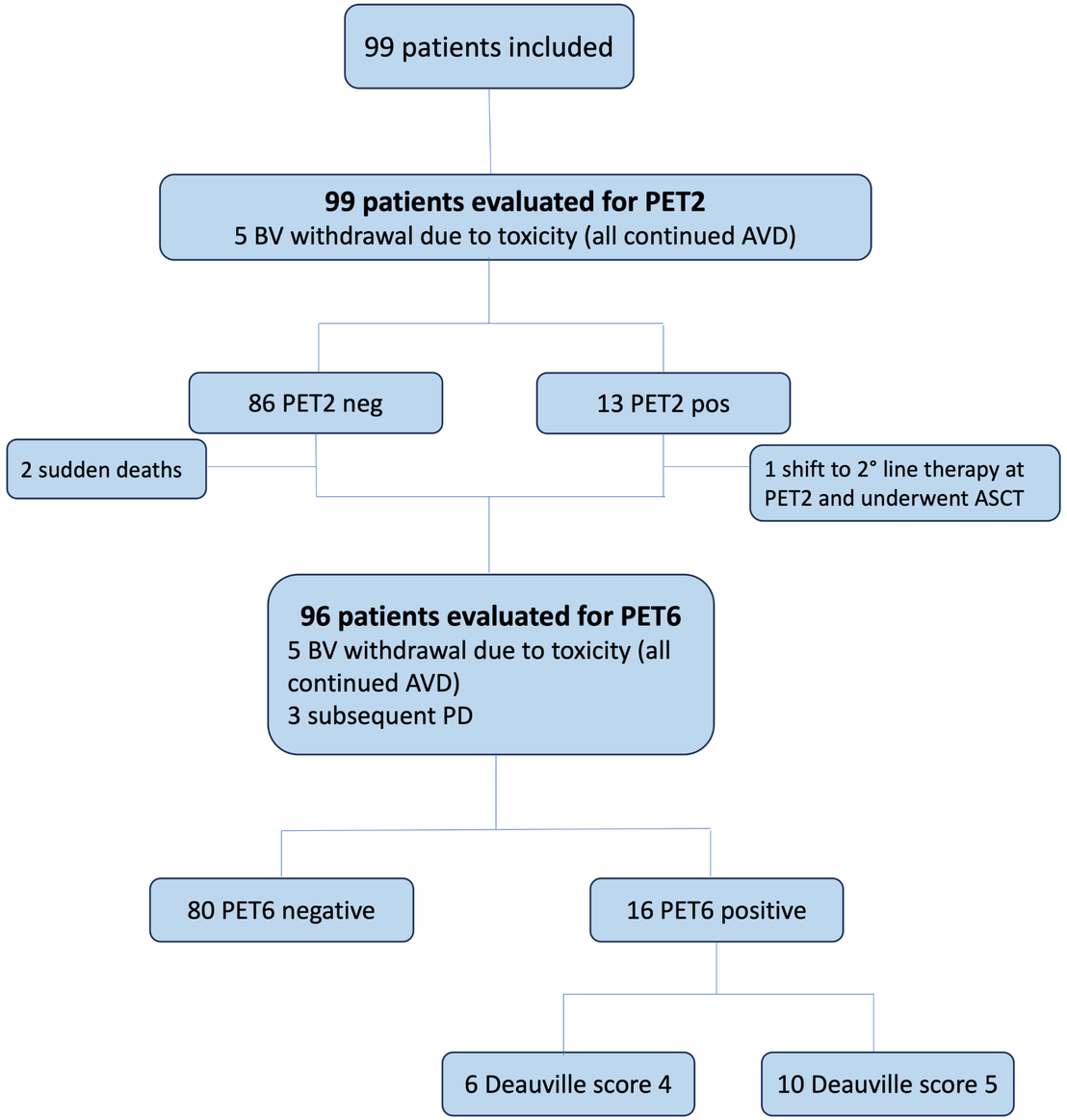
	Patients = 99
Male sex, n (%)	60 (60.6)
Age, median (range)	36 (18-82)
Age > 65, n (%)	11 (11.1)

	Patients = 99
Hasenclever score ≥ 4, n (%)	47 (47.5)
B symptoms, n (%)	72 (72.7)
Bulky, n (%)	28 (28.3)
Skeletal involvement, n (%)	66 (66.7)
N° of extranodal sites ≥ 2, n (%)	34 (34.3)

44.4% patients experienced a G3-4 extra-hematological toxicity, for a total of **60 events**



Grade ≥ 3 extra-hematological toxicity



Feasibility

- 83.8% (83) patients completed all planned 6 cycles
- **16.2% (16) patients did not complete 6 cycles of BV-AVD:**

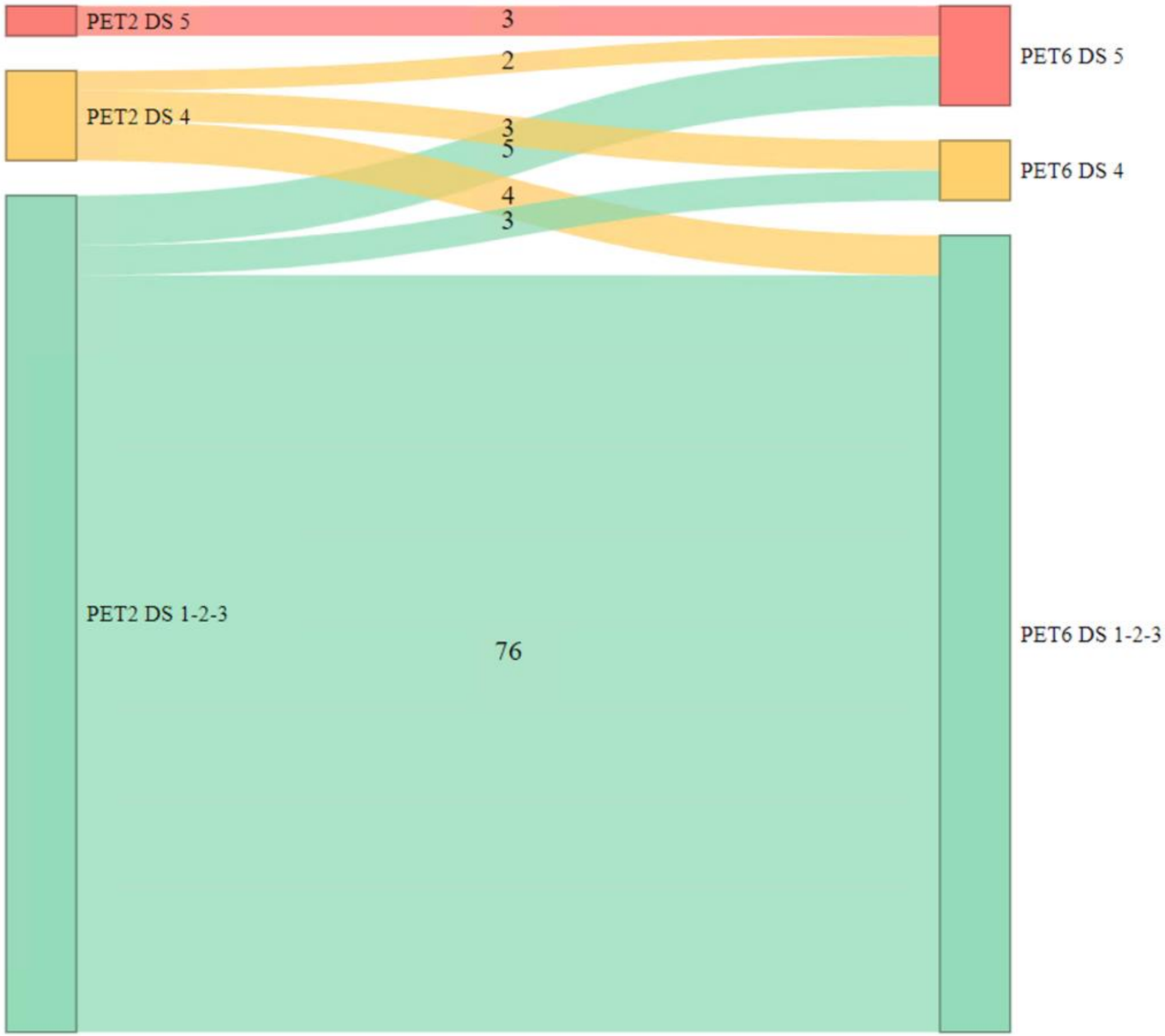
  10 BV discontinuations because of toxicities

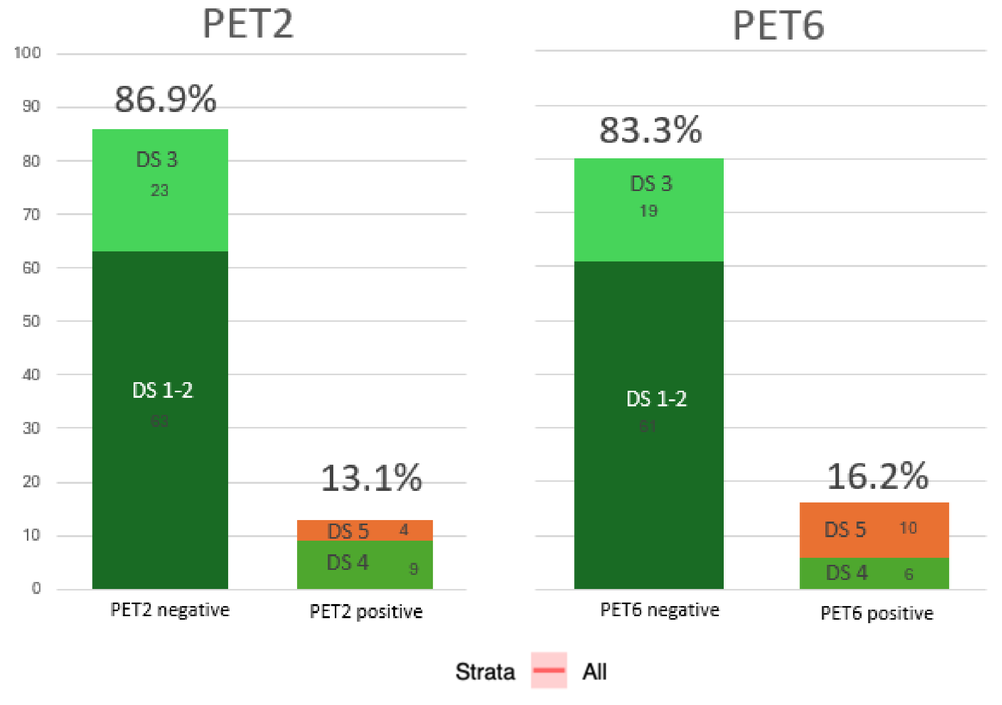
  - **Peripheral neuropathy 6**
  - Diarrhea 1
  - Infection 1
  - Pancreatitis 1
  - Fatigue 1

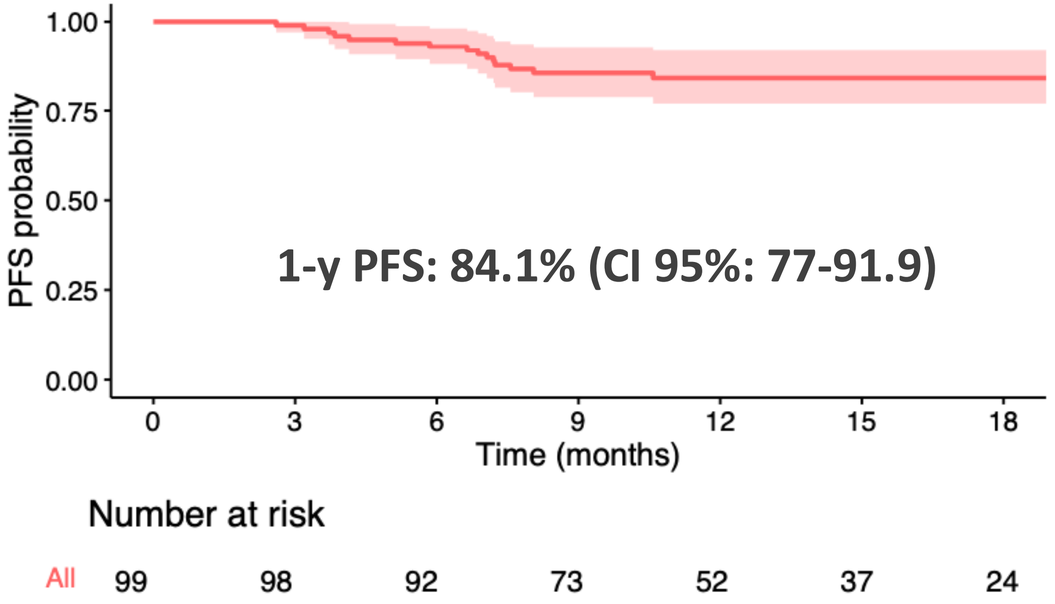
  4 patients shifted to 2° line therapy because of progressive disease (PD)

  2 sudden deaths

Rusconi C et al, Leuk & Lymphoma 2025

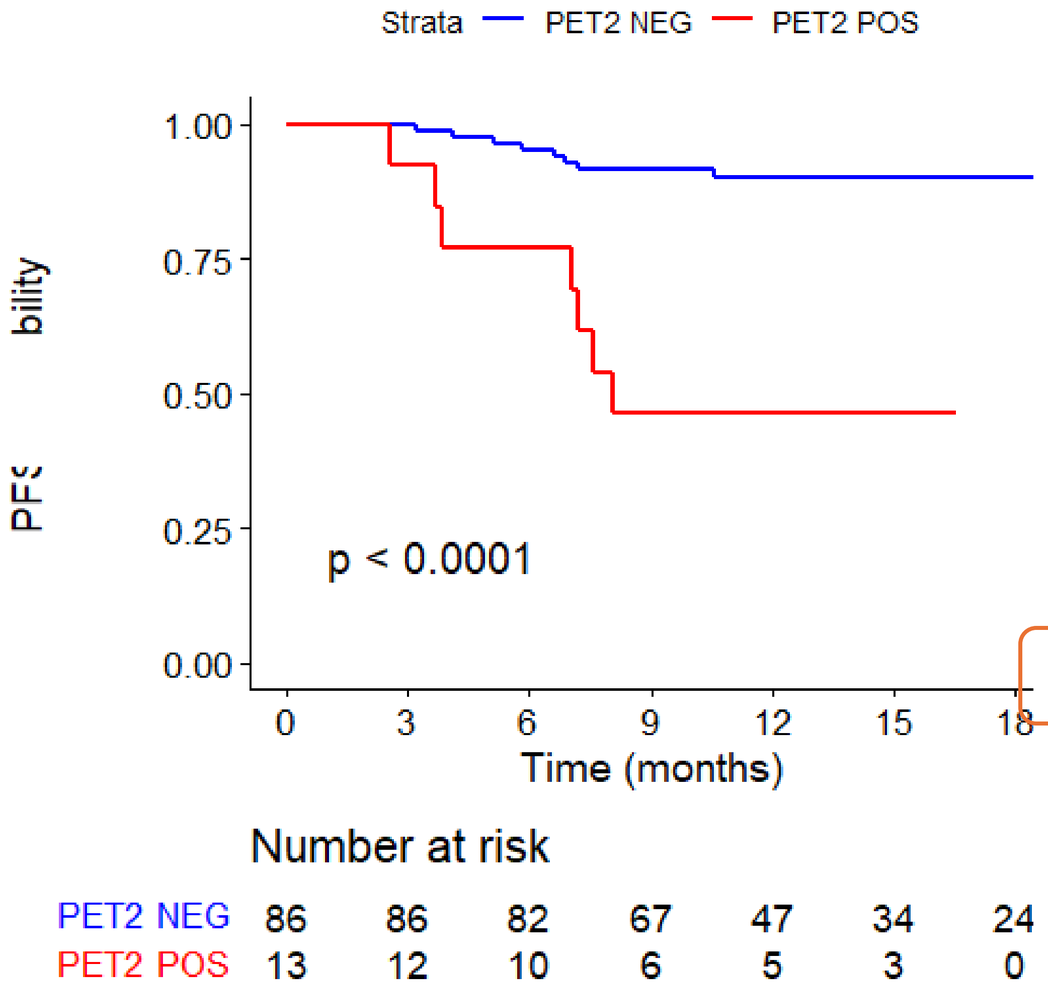




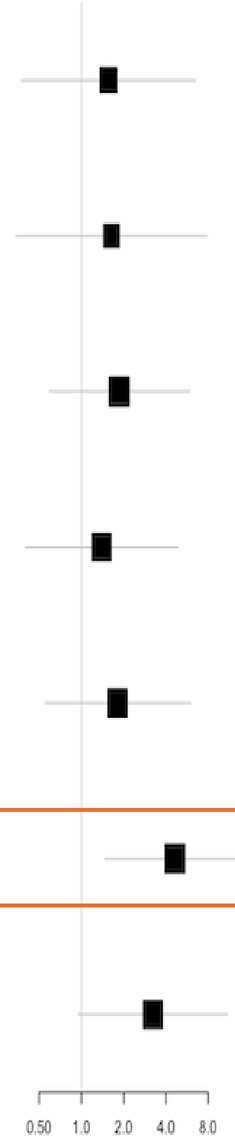


Rusconi C et al, Leuk & Lymphoma 2025

PFS survival



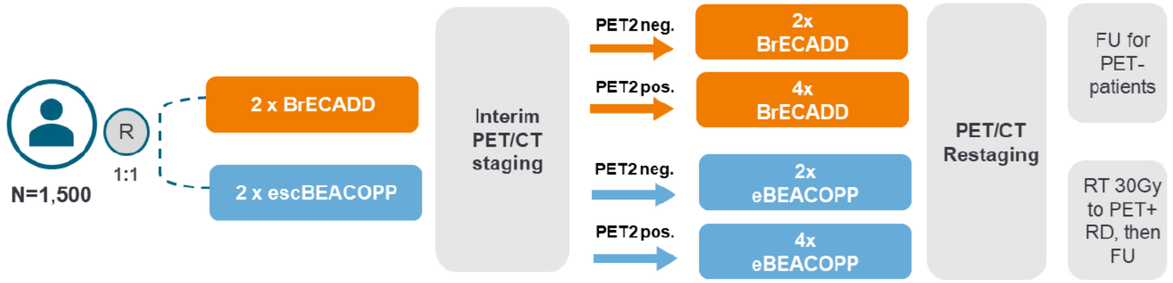
Variable	Comparison	HR	95% CI	p-value
Age	>65 vs <=65 years	1.56	0.37-6.49	0.542
B symptoms	Yes vs No	1.64	0.34-7.9	0.535
Extranodal involvement	>1 vs 0-1	1.86	0.59-5.91	0.293
Bulky	Yes vs No	1.39	0.4-4.88	0.607
Hasenclever score	>=4 vs <4	1.81	0.55-6.02	0.331
PET2 DS	Pos vs Neg	4.64	1.47-14.62	0.009 **
Treatment delay for neutropenia	Yes vs No	3.23	0.95-11	0.061



Rusconi C et al, Leuk & Lymphoma 2025

GHSG HD21 study design and primary endpoints

HD21 is an international randomized, open-label, phase 3 study of BrECADD versus eBEACOPP in adult patients < 60 yo with previously untreated, AS-cHL

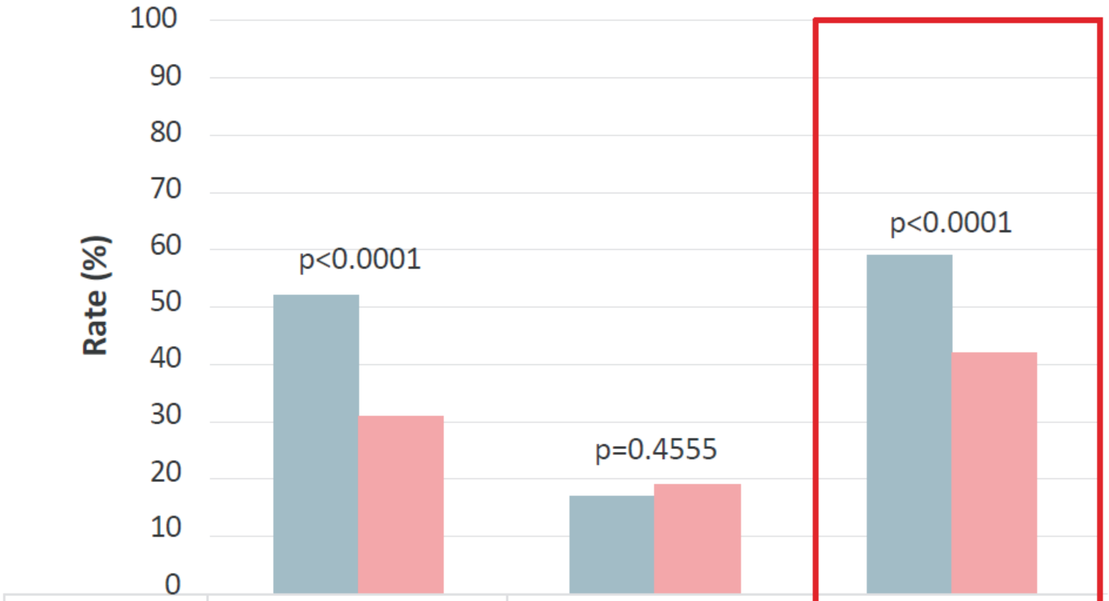


Co-primary objectives:

- Demonstrate **superior tolerability** defined by treatment-related morbidity (TRMB) with BrECADD.
- Demonstrate **non-inferior efficacy** of 4-6 x BrECADD compared with 4-6 x BEACOPP determined by PFS (NI margin 6%, HR to be excluded 1.69)

Drug	Day	escBEACOPP[1] Dose (mg/m²)	BrECADD Dose (mg/m²)	*Potential* improvement
Bleomycin	8	10	-	Lung tox
Etoposide	1–3	200	*150*	Hem tox, transfusion frequency
Doxorubicin	1	35	*40*	
Cyclophosphamide	1	1,250	*1,250*	
Vincristine	8	1.4	-	Neuropathy
Brentuximab vedotin	1	-	*1.8 mg/kg*	
Procarbazine	1–7	100	-	Gonadal tox, sAML/MDS
Prednisone	1–14	40	-	Weight, bone, infections
Dacarbazine	2–3	-	*250*	
Dexamethasone	1–4	-	*40*	

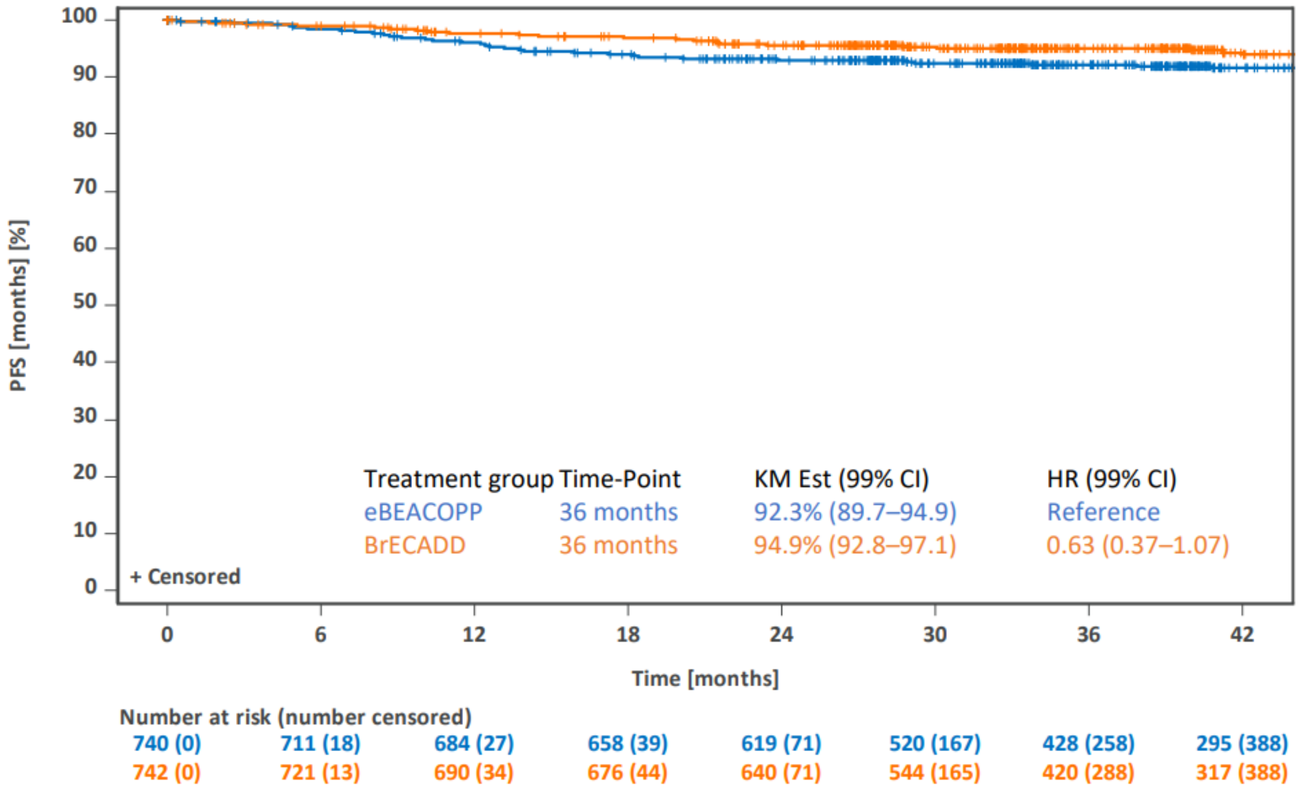
Acute treatment-related morbidity

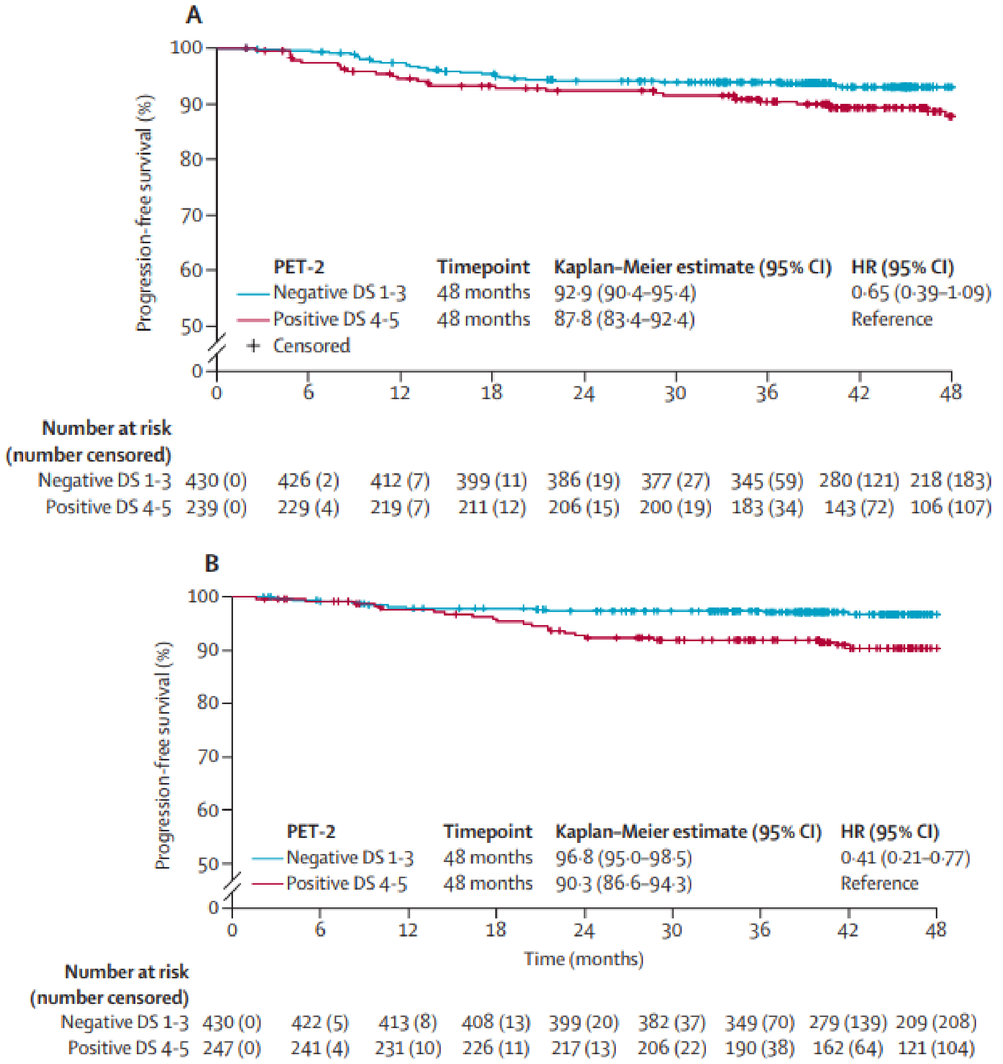


	Anemia, thrombocytopenia, or infection Grade ≥4	Organ toxicity Grade ≥3	TRMB
escBEACOPP (%)	52	17	59
BrECADD (%)	31	19	42

Borchmann P et al, Lancet 2024

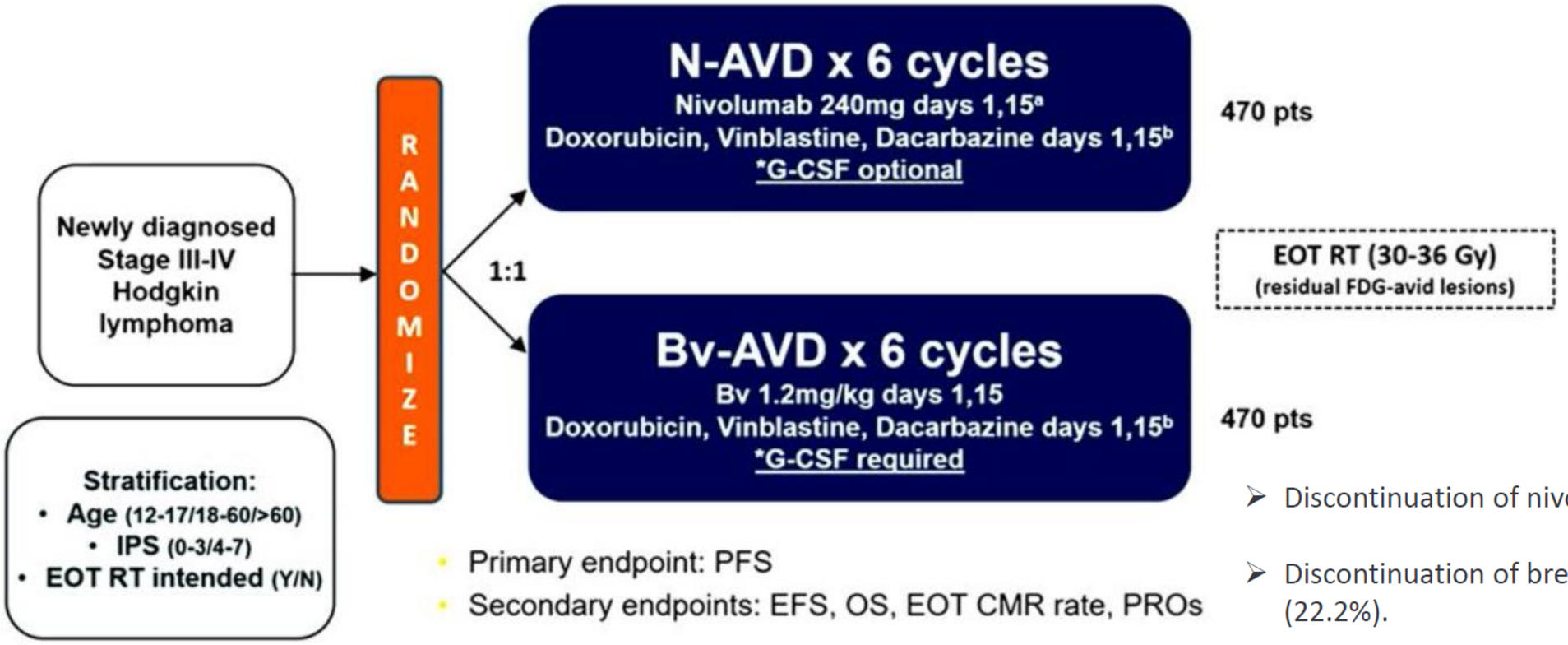
HD21: PFS





Borchmann P et al, Lancet 2024

S1826 Study Design



- Primary endpoint: PFS
- Secondary endpoints: EFS, OS, EOT CMR rate, PROs

- Discontinuation of nivolumab: 46 patients (9.4%).
- Discontinuation of brentuximab vedotin: 107 patients (22.2%).
- Dose reduction of brentuximab vedotin: 129 patients (26.7%).
- Dose reduction of nivolumab was not permitted.
- Dexrazoxane was administered in 273 patients (28.1%). Similar use across groups and primarily in adolescent patients ([79.7%] 12 to <18 years of age)

Safety

Toxicity	N+AVD, n=483, N (%)		BV+AVD, n=473, N (%)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
PN				
Peripheral sensory neuropathy	138 (29)	6 (1)	262 (55)	37 (8)
Peripheral motor neuropathy	20 (4)	1 (0)	35 (7)	6 (1)
Hematologic				
Neutropenia	268 (55)	227 (47)	152 (32)	118 (25)
Anemia	185 (38)	29 (6)	207 (44)	42 (9)
Thrombocytopenia	48 (10)	8 (2)	82 (17)	15 (3)
Received G-CSF	265 (54)		463 (95)	
Bone pain	39 (8)		94 (20)	
Infectious				
FN	26 (5)		32 (7)	
Sepsis	9 (2)		16 (3)	
Infections/infestations	22 (5)		36 (8)	

More neuropathy in BV+AVD arm

More neutropenia after N+AVD

More growth factor use, bone pain in BV+AVD arm

No increased infectious toxicity in N+AVD arm

AE, adverse event; BV+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; N+AVD, nivolumab, doxorubicin, vinblastine, dacarbazine; PN, peripheral neuropathy.

Herrera AF. Presented at the American Society for Clinical Oncology Annual Meeting, 2–6 June 2023, Chicago, IL: Oral presentation LBA4.

Immune-related AEs

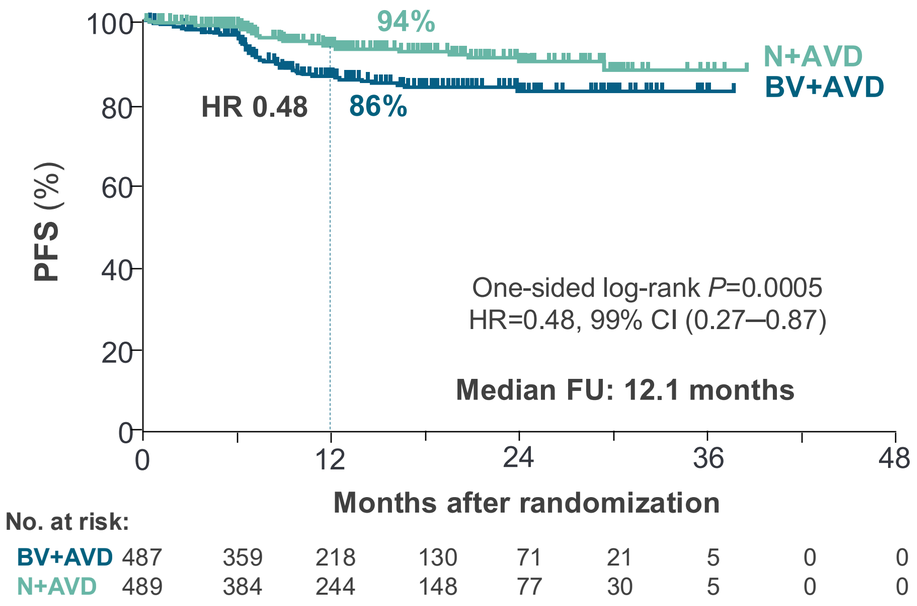
Toxicity	N+AVD n=483 N (%)		BV+AVD n=473 N (%)	
	Any grade N (%)	Grade ≥3 N (%)	Any grade N (%)	Grade ≥3 N (%)
ALT increased	156 (32)	22 (5)	194 (41)	22 (5)
AST increased	120 (25)	12 (2)	153 (32)	13 (3)
Rash maculopapular	51 (11)	4 (1)	58 (12)	0 (0)
Hypothyroidism	33 (7)	1 (0)	3 (1)	0 (0)
Rash acneiform	18 (4)	0 (0)	12 (3)	0 (0)
Pneumonitis	10 (2)	2 (0)	15 (3)	10 (2)
Gastritis	10 (2)	3 (1)	8 (2)	0 (0)
Hyperthyroidism	14 (3)	0 (0)	0 (0)	0 (0)
Colitis	5 (1)	1 (0)	6 (1)	4 (1)

Low rates of Grade ≥3 irAEs

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BV+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; irAE, immune-related AE; N+AVD, nivolumab, doxorubicin, vinblastine, dacarbazine.
Herrera AF. Presented at the American Society for Clinical Oncology Annual Meeting, 2–6 June 2023, Chicago, IL: Oral presentation LBA4.

SWOG 1826 trial: N+AVD improves PFS compared with BV+AVD

1-year PFS was 94% with N+AVD compared with 86% with BV+AVD

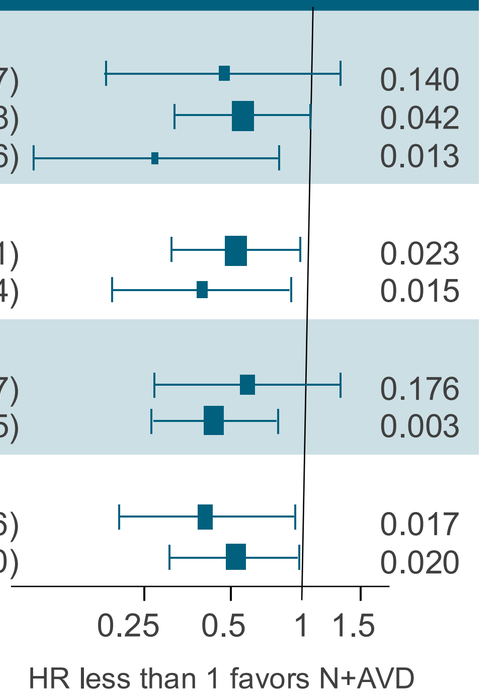


	N	Events	1-year estimate	95% CI
BV+AVD	487	58	86%	(82–90)
N+AVD	489	30	94%	(91–96)

92% vs 83% @ 23 months

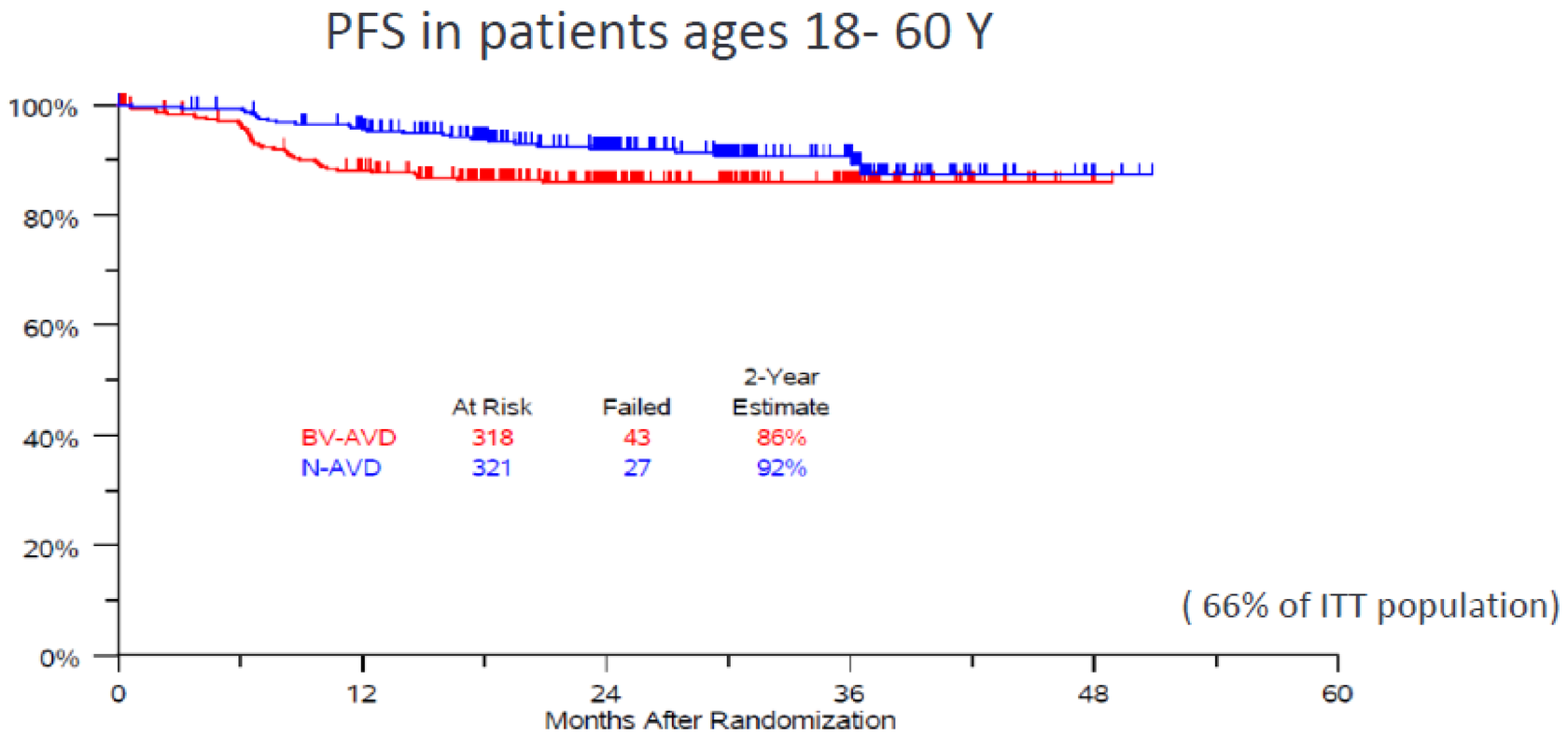
PFS benefit consistent across subgroups

Subgroup	N+AVD Events/N (%)	BV+AVD Events/N (%)	HR (95% CI)	*P*-value
Age, years				
12–17	6/120 (5.0)	12/117 (10.3)	0.48 (0.18–1.27)	0.140
18–60	19/323 (5.9)	32/323 (9.9)	0.56 (0.32–0.98)	0.042
>60	5/46 (10.9)	14/47 (29.8)	0.27 (0.10–0.76)	0.013
IPS				
0–3	20/331 (6.0)	36/330 (10.9)	0.53 (0.31–0.91)	0.023
4–7	10/158 (6.3)	22/157 (14.0)	0.40 (0.19–0.84)	0.015
Stage				
III	11/187 (5.9)	15/167 (9.0)	0.58 (0.27–1.27)	0.176
IV	19/301 (6.3)	43/317 (13.6)	0.44 (0.26–0.75)	0.003
Symptoms				
A	10/202 (5.0)	24/210 (11.4)	0.41 (0.20, 0.86)	0.017
B	20/286 (7.0)	34/274 (12.4)	0.52 (0.30, 0.90)	0.020



Herrera AF et al, NEJM 2024

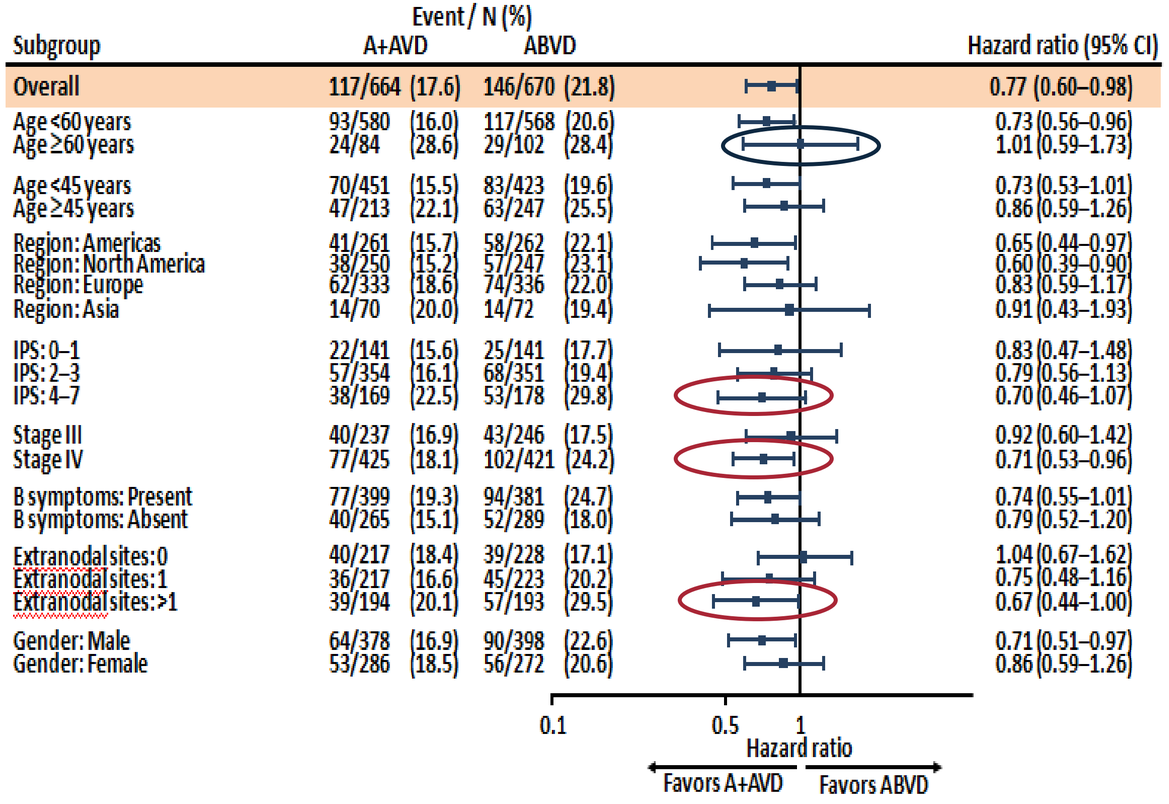
Nivo-AVD vs BV-AVD: the adults



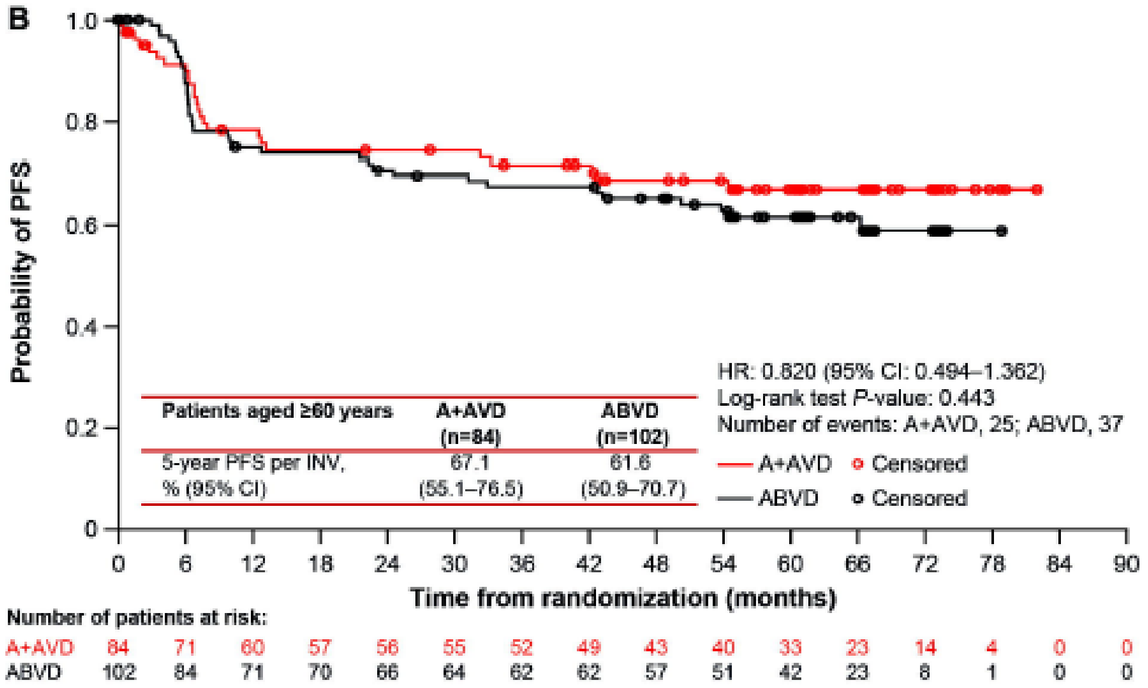
SWOG1826 and adults: no survival differences, waiting for longer follow-up?

The elderly and the ECHELON-1

186 pts (14%) age ≥ 60 ys

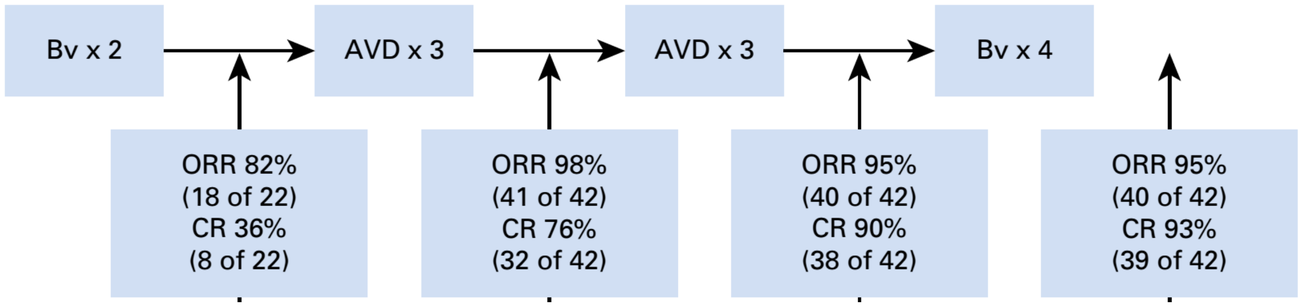


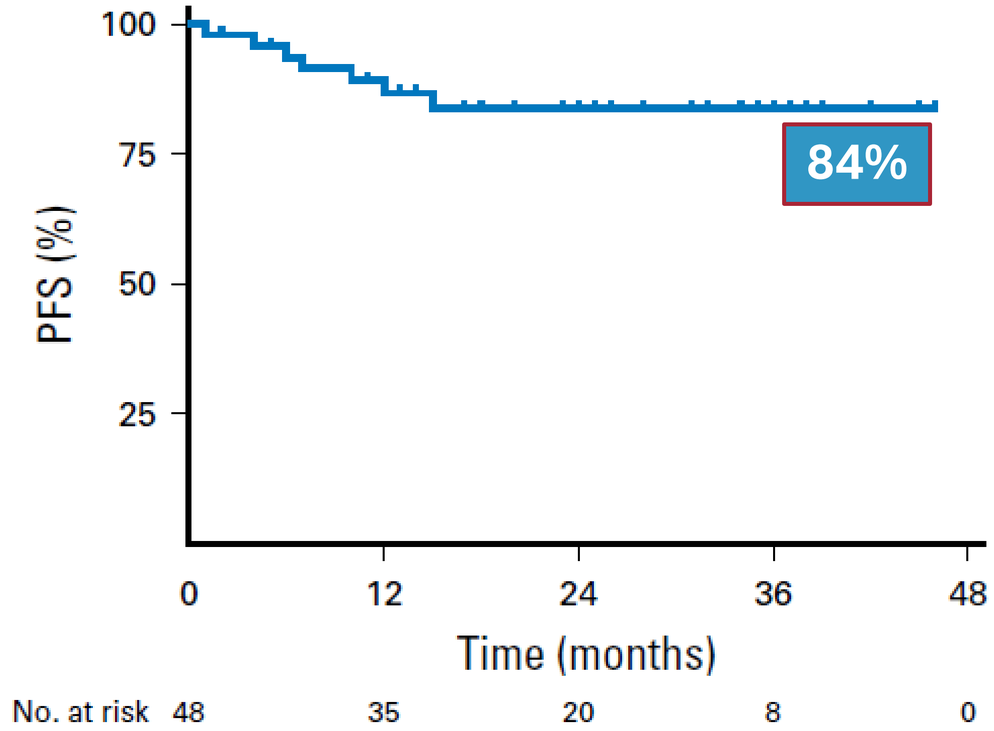
Connors JM et al, NEJM 2017

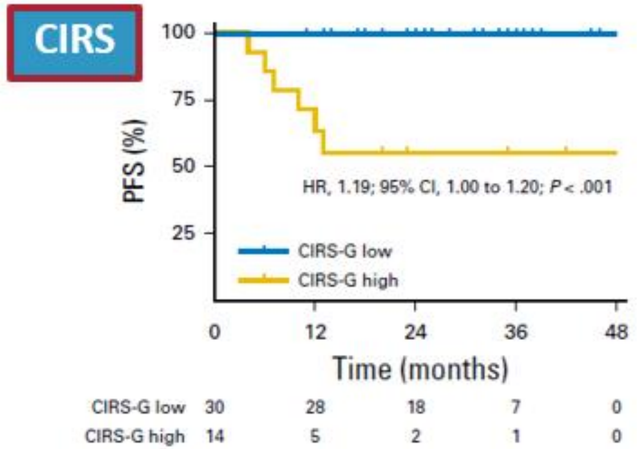


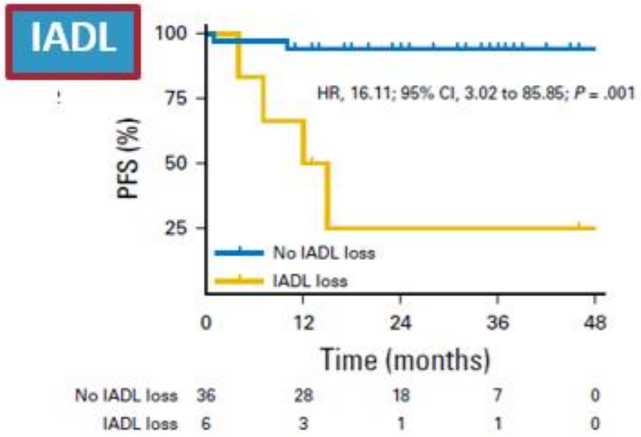
Evens A et al, Haematologica 2021

BREVITY trial



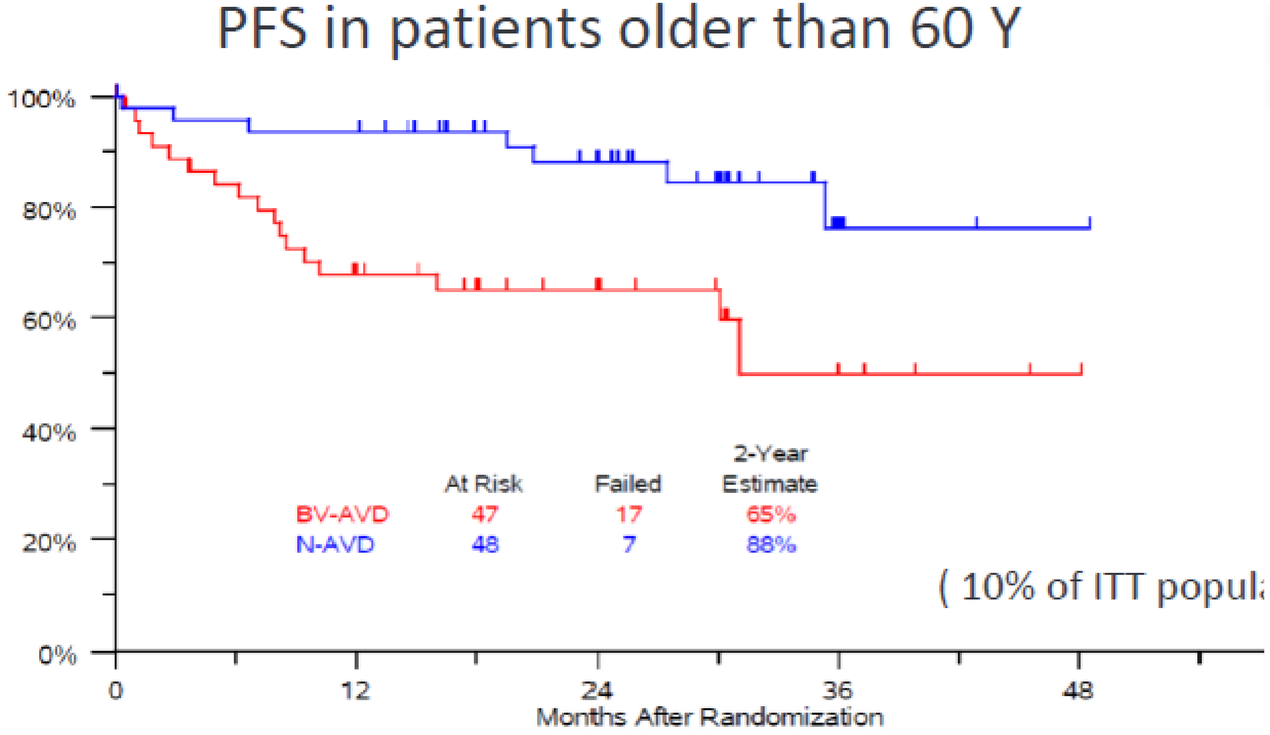


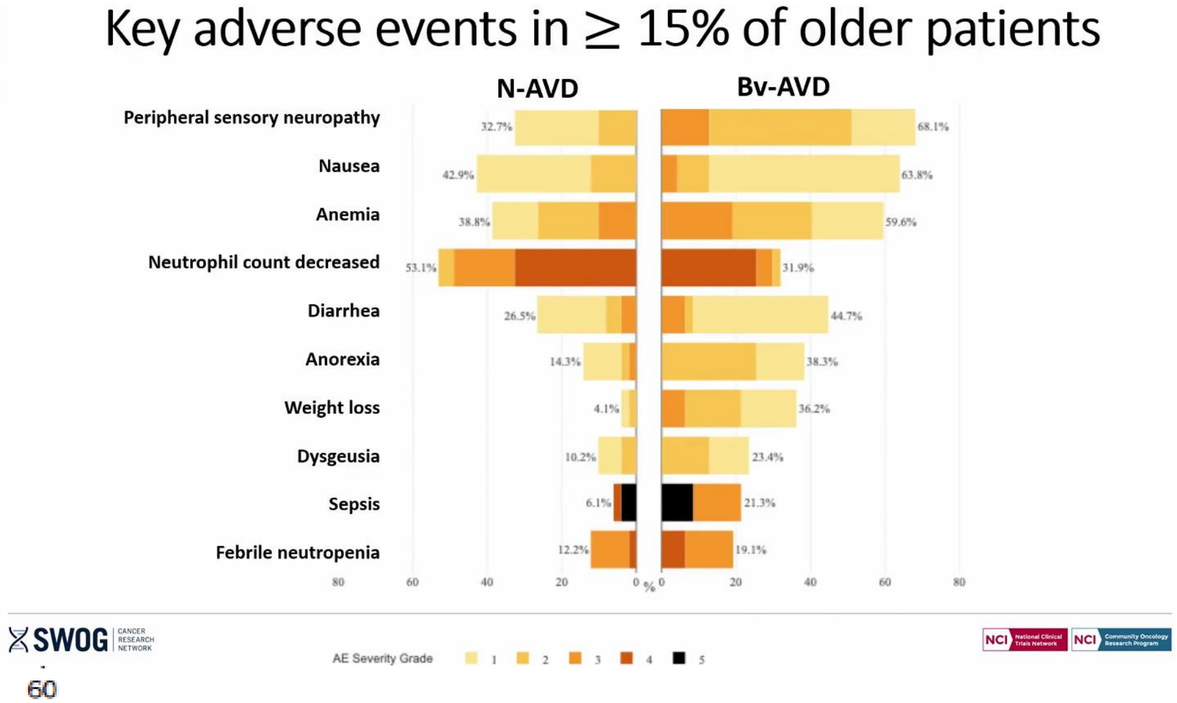




Sequential Bv-AVD: well tolerated and effective; geriatric based measures are strongly associated with survival

Evens AM et al, JCO 2018





SWOG1826 and the elderly (fit and satisfying inclusion criteria): superior PFS and OS mainly due to higher toxicity and non-relapse mortality in the standard arm → nivo-AVD as the potential new standard in this population

Herrera AF et al, NEJM 2024
Rutherford SC et al, ISHL 2024

Advanced stage cHL beyond ABVD

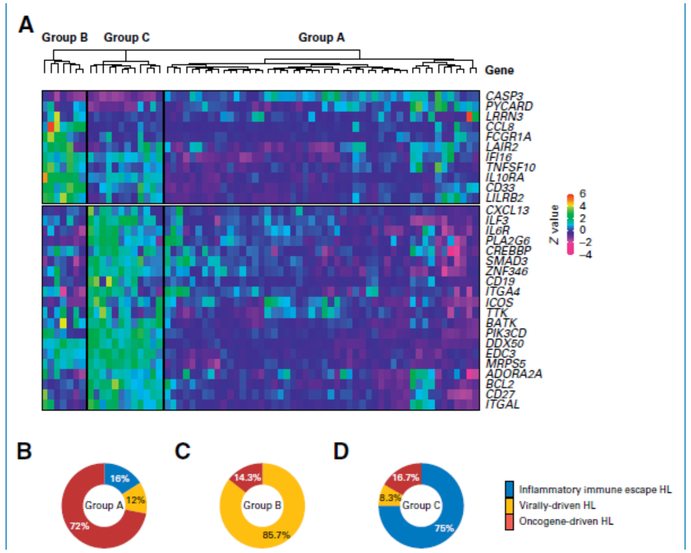
- 18-60 years:
  - stage III (and IIB) ABVD iPET adapted (RATHL)
  - Stage IV ineligible to bleomycine: BV-AVD (ECHELON-1)

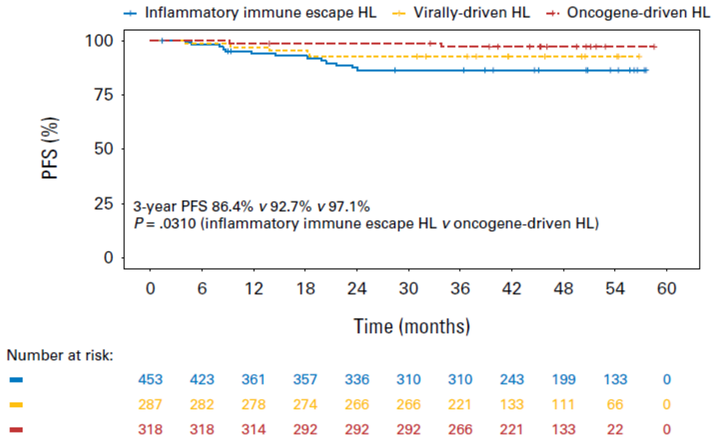
  Waiting for BrECADD!

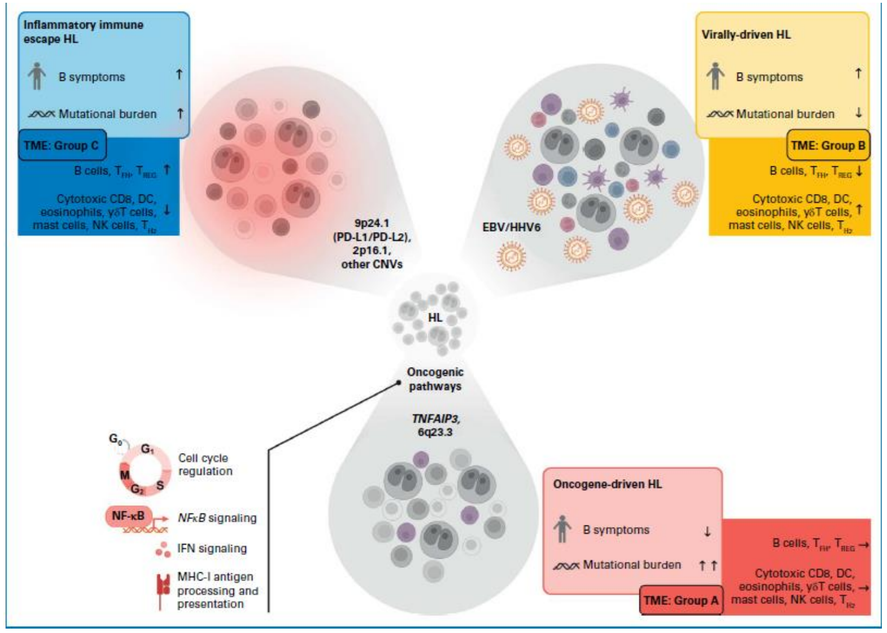
  Waiting for nivo-AVD?
- Elderly > 60 years and FIT:
  - stage III (and IIB) A(B)VD
  - Stage IV ineligible to bleomycine: BV-AVD sequential (Brevity Trial)

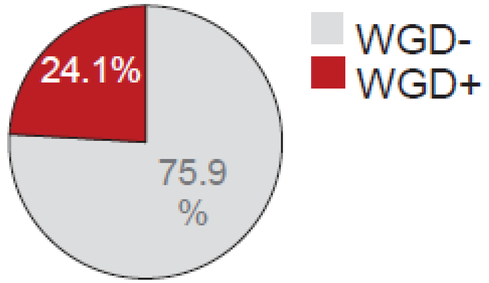
  Waiting for nivo-AVD!
- Frail patients:
  - Unmet need, polychemotherapy whenever possibile at personalized dose

Optimizing tools for treatment personalization: non-invasive genomic profiling of classical HL

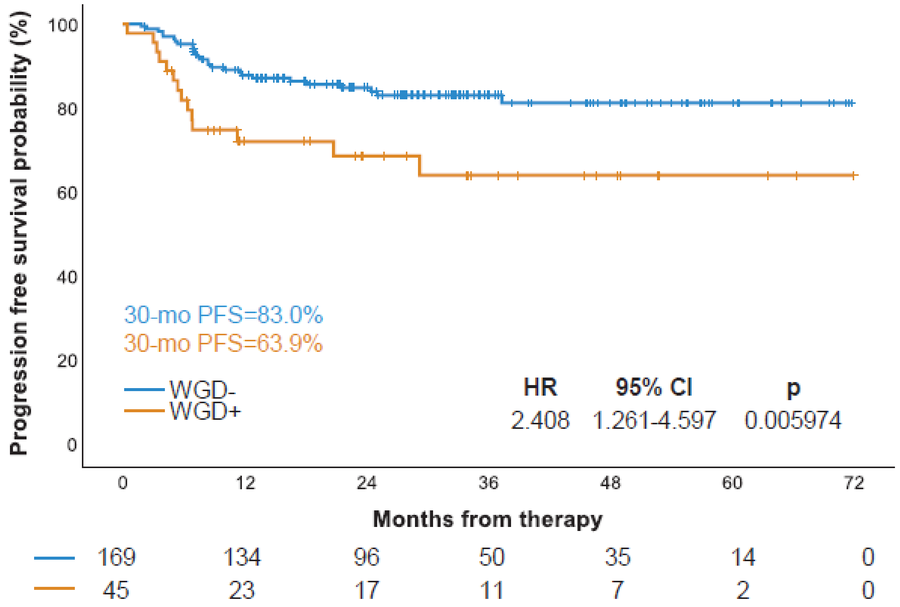






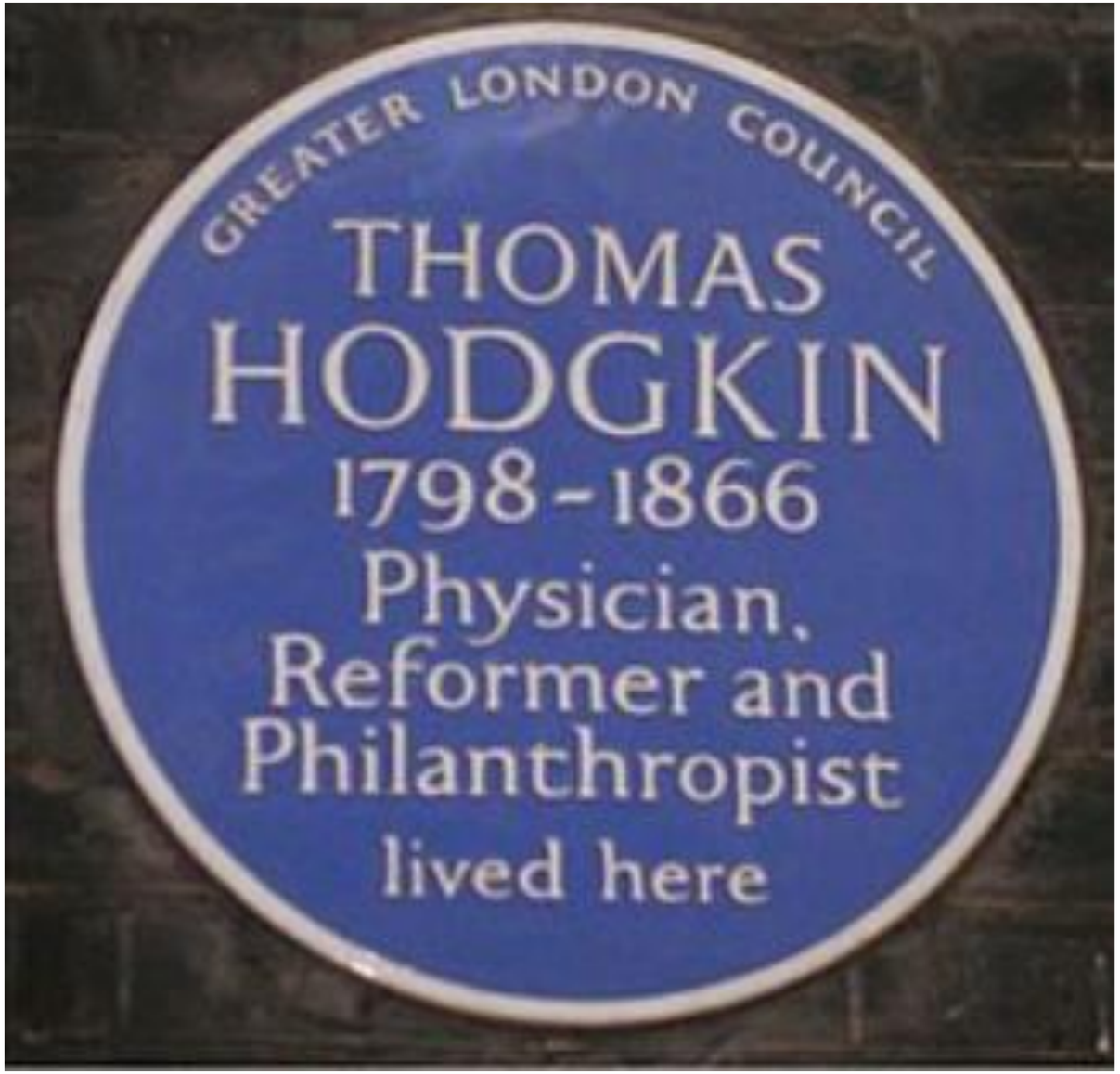


cHL



Heger JM et al, JCO 2024

Pirosa MC et al, Blood 2025



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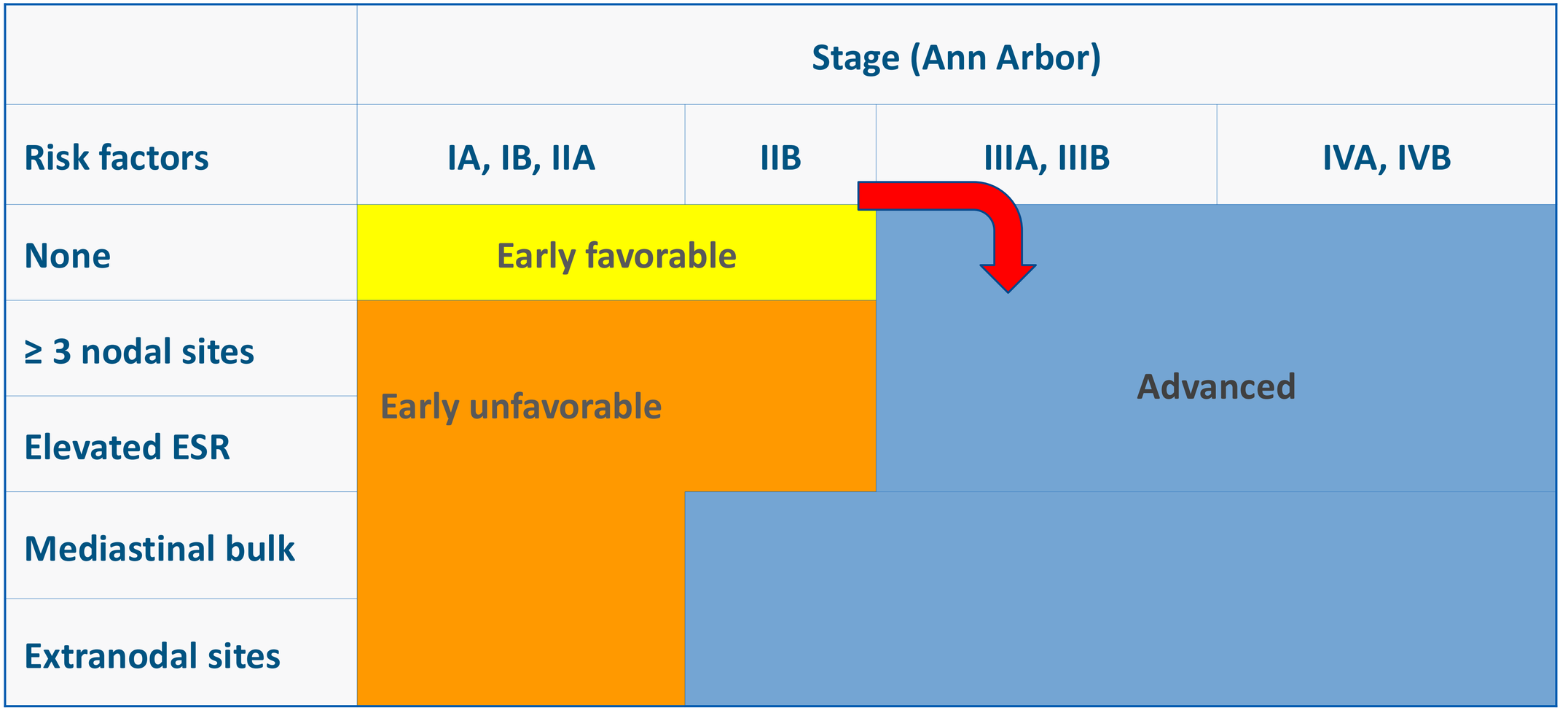
FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

Thanks for your attention!

Backup slides

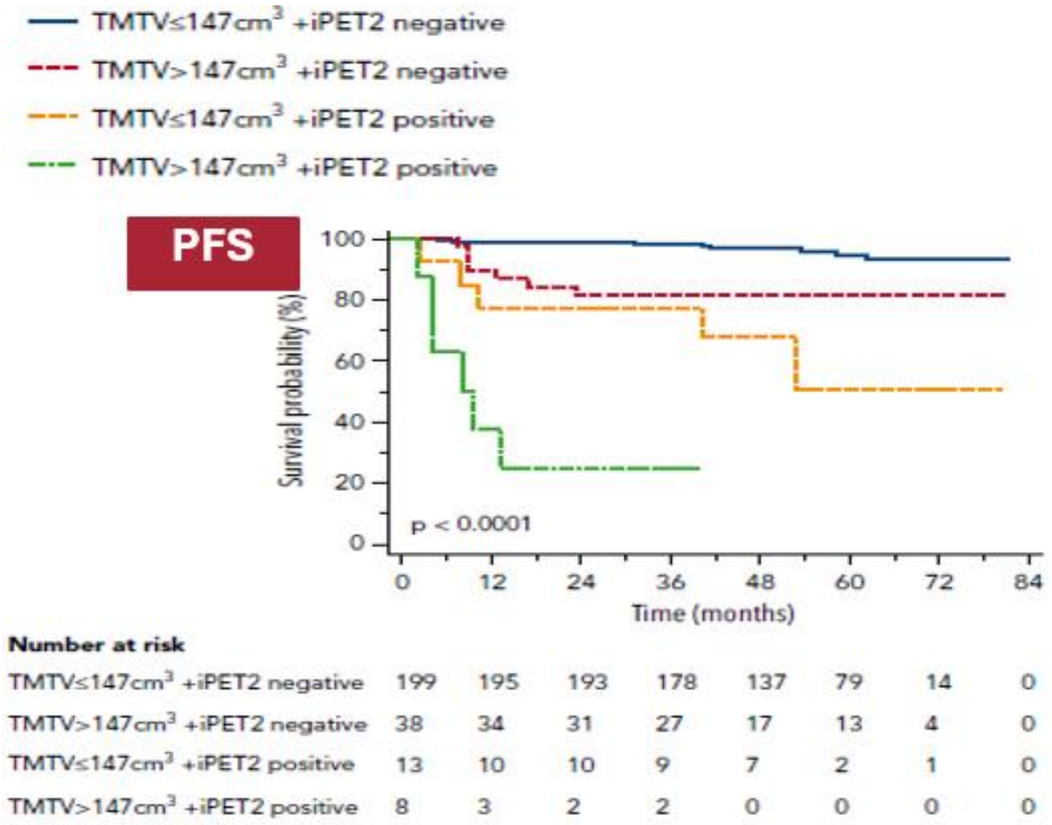
What do we call “advanced stage”?



Engert A, ISHL 2017

Beyond Hasenclever score

Total metabolic tumor volume

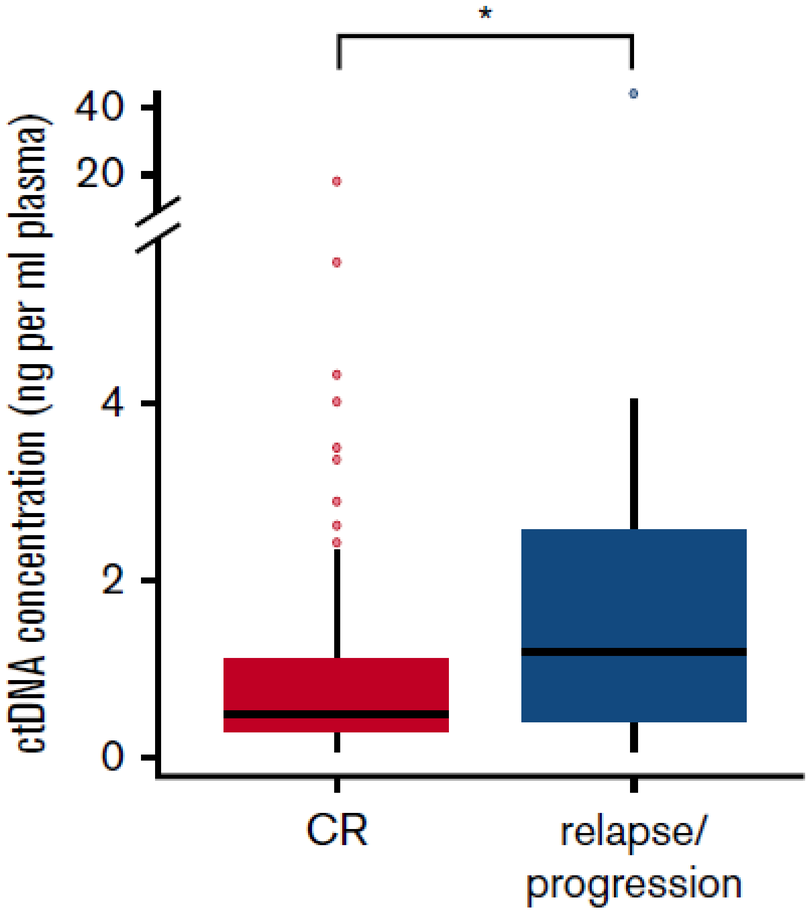


Number at risk

TMTV≤147cm^3 +iPET2 negative	199	195	193	178	137	79	14	0
TMTV>147cm^3 +iPET2 negative	38	34	31	27	17	13	4	0
TMTV≤147cm^3 +iPET2 positive	13	10	10	9	7	2	1	0
TMTV>147cm^3 +iPET2 positive	8	3	2	2	0	0	0	0

Cottereau AS et al, Blood 2018

Circulating tumor DNA



Buedts L et al, Blood Adv 2021