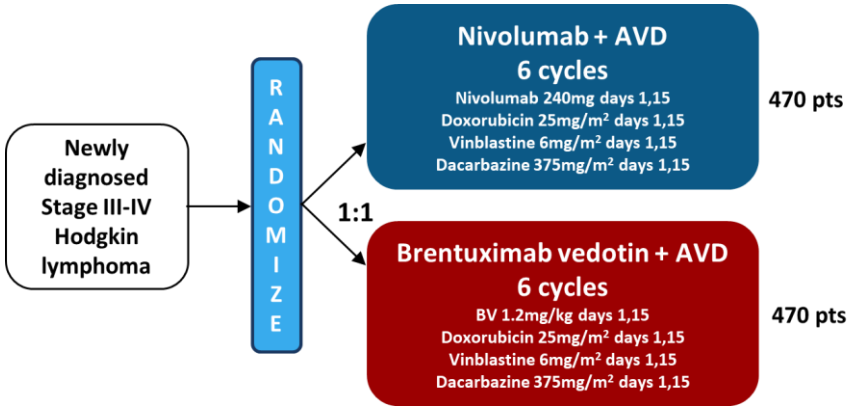
Actual scenario in frontline advanced stage

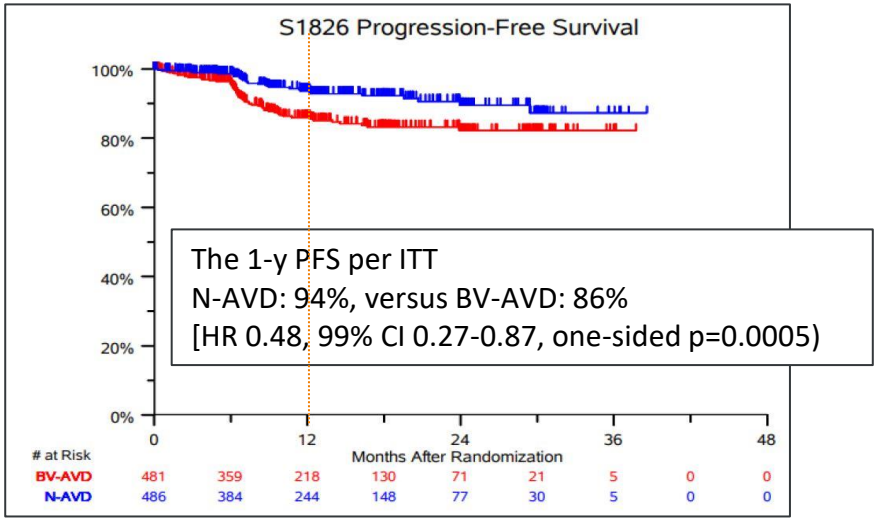
Peter Borchmann

on behalf of the German Hodgkin Study Group

University Hospital Cologne, Germany

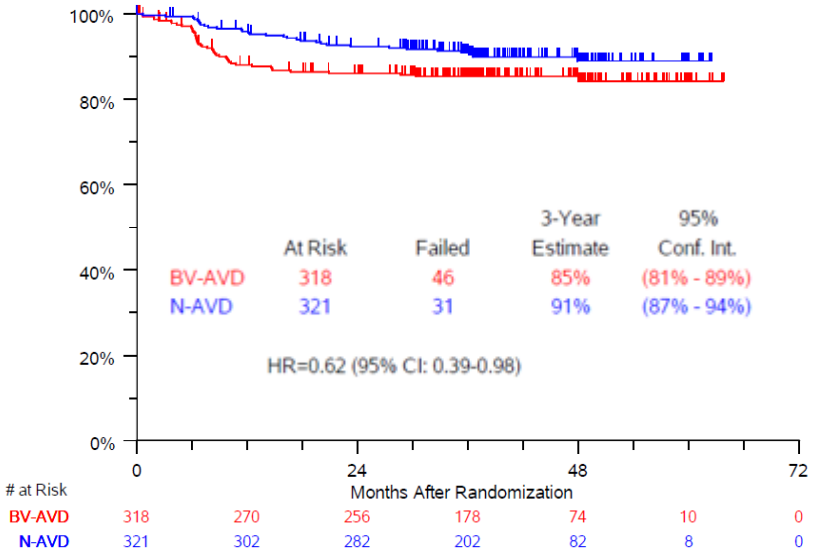
The SWOG S1826 study: ”one size for all” strategy



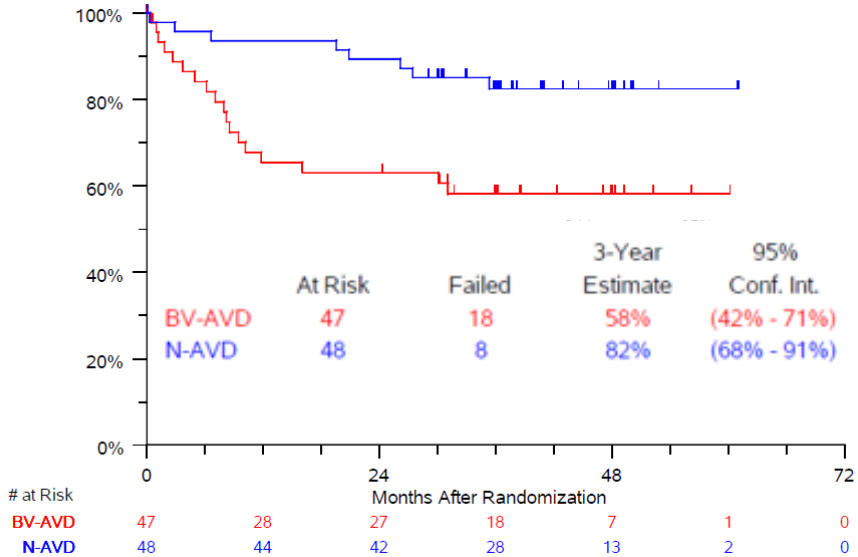


3y FU S1826: N-AVD improves efficacy over BV-AVD

3y PFS in pts 18-60 yo



3y PFS in pts > 60 yo

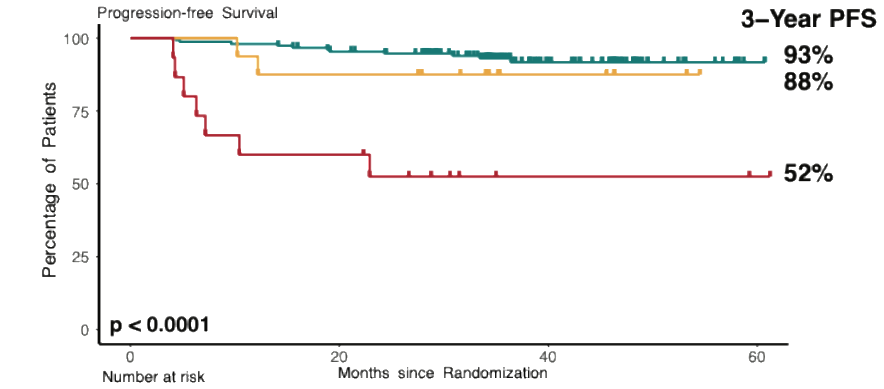


GHSG

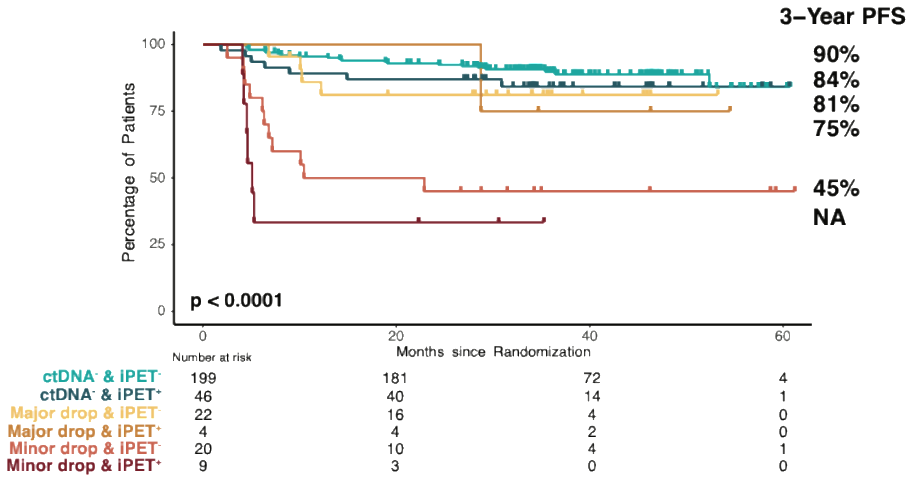
Herrera et al, BLOOD 2025; 146 abs 151.

3y FU S1826: Response assessment by ctDNA at C3D1 (iMRD/iPET)

PFS by ctDNA levels at C3D1 of NAVD



PFS by ctDNA levels and PET at C3D1



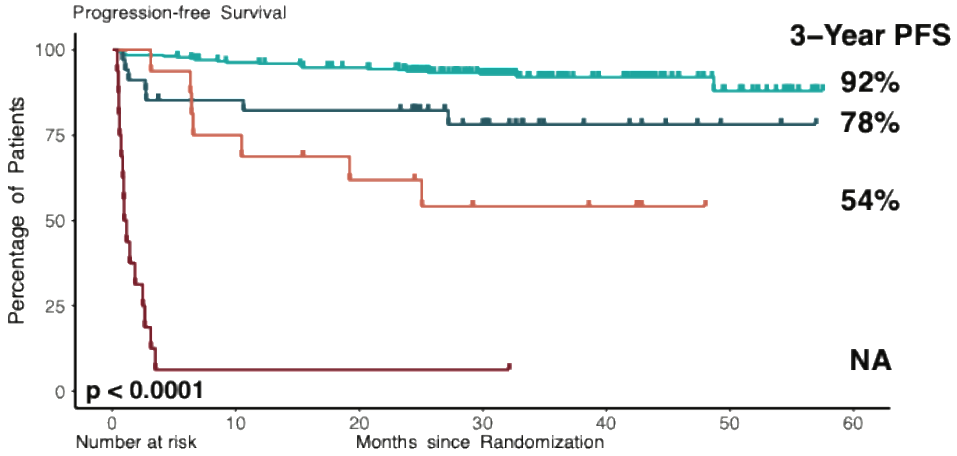
iMRDneg/iPETpos patients have a 3y PFS of 84%, double negative patients of 90%.

GHSG

Paczkowska et al, BLOOD 2025; 146 abs 351.

3y FU S1826: Response assessment by ctDNA and PET at EOT

PFS by ctDNA levels and PET at EOT



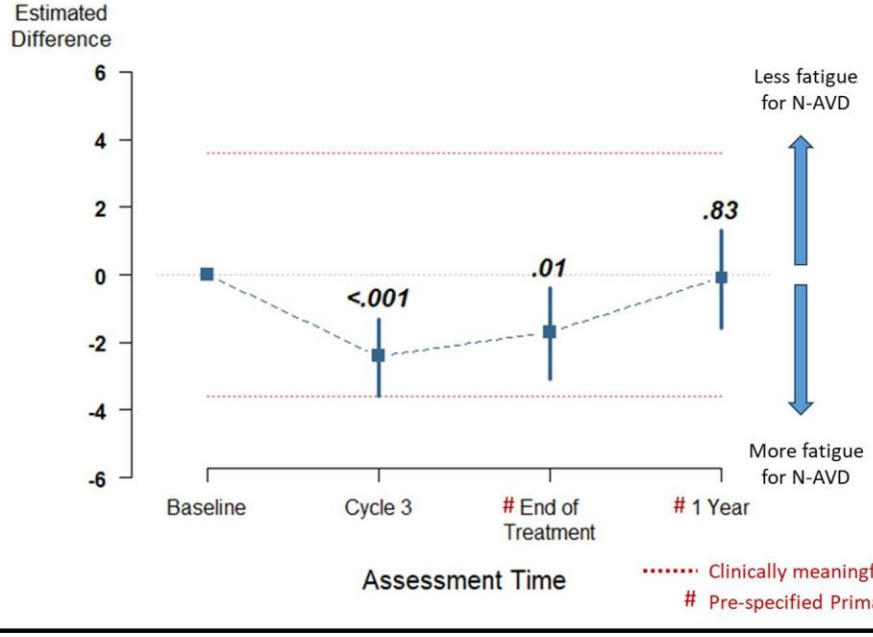
- EOTMRDneg/EOTPETpos patients have a 3y PFS of 78%, double negative patients of 92%
- ***PET and ctDNA seem to have complementary prognostic information***

GHSG

Paczkowska et al, BLOOD 2025; 146 abs 351.

3y FU S1826: patient reported outcomes with N-AVD or BV-AVD

Figure 4. PROMIS-Fatigue Regression Model Results Over Time

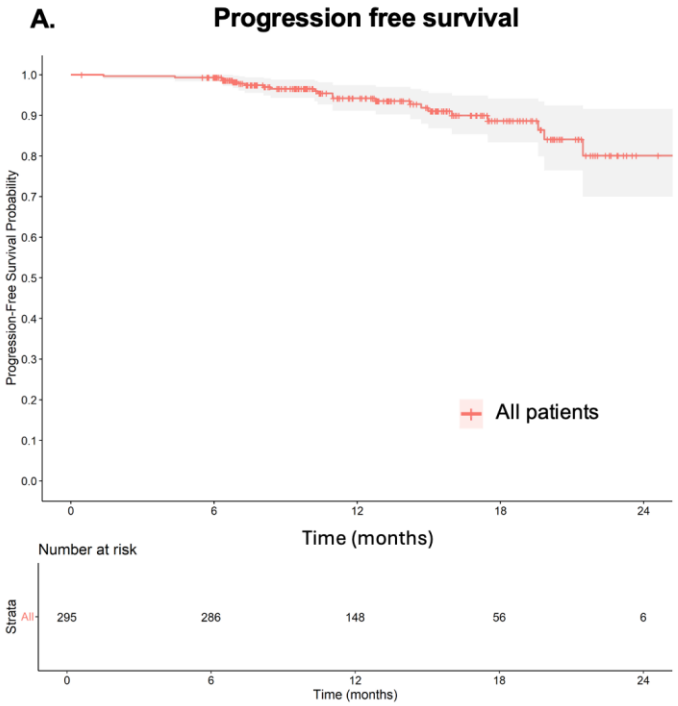


- Fatigue for patients on N-AVD arm statistically significantly worse at Cycle 3, but…
- This difference did NOT meet clinically meaningful difference vs BV-AVD

GHSG

Davison et al, BLOOD 2025; 146 abs 2738.

A real-world analysis of safety and outcomes with first line N-AVD in patients with classic Hodgkin lymphoma (cHL) – a multicenter cohort study.



Immune related adverse events (all pts, n=332)

Immune related adverse events (irAE)(n=329)[1]	
Grade 1-2 irAE (n=329)	
Hypothyroidism	31 (9%)
Rash	11 (3%)
Inflammatory arthritis[2]	10 (3%)
Hepatotoxicity	8 (2%)
Pneumonitis	2 (1%)
Thyroiditis	3 (1%)
Colitis	3 (1%)
Adrenal insufficiency	2 (0.6%)
Pericarditis	2 (0.6%)
Other[3]	8 (2%)
Grade ≥ 3 irAE[4] (n=329)	
Hepatotoxicity	14 (4%)
Inflammatory arthritis	3 (1%)
Colitis	3 (1%)
Adrenal insufficiency	2 (0.6%)
Type 1 diabetes mellitus	1 (0.3%)
Pneumonitis	2 (0.3%)
HLH in setting of baseline CVID	1 (0.3%)
AKI/ATN requiring HD	1 (0.3%)
Myocarditis	1 (0.3%)
Thyrotoxicosis	1 (0.3%)
Pancreatitis	1 (0.3%)
DRESS	1 (0.3%)

Grade 1 or 2
23.2%

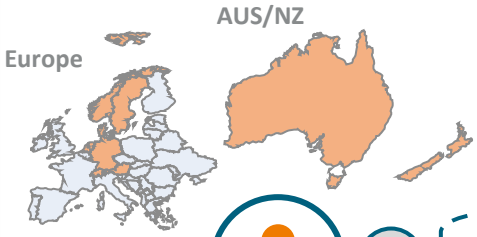
Grade 3 or 4
9% (7.5% of pts)

GHSG

Allison Bock et al., Salt Lake City, USA *et al, BLOOD 2025; 146 abs 1841.*

GHSG HD21: individualized targeted therapy for AScHL

Randomized, open-label, Phase 3 trial of BrECADD versus eBEACOPP in patients with newly diagnosed AS-cHL



R

1:1

2 x BrECADD

2 x escBEACOPP

1500 patients
233 sites
9 countries

Interim PET/CT

PET2 neg. → **2x BrECADD**

PET2 pos. → **4x BrECADD**

PET2 neg. → **2x eBEACOPP**

PET2 pos. → **4x eBEACOPP**

Restaging

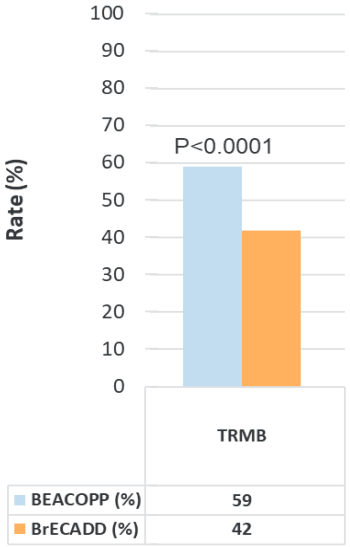
PET-guided RT

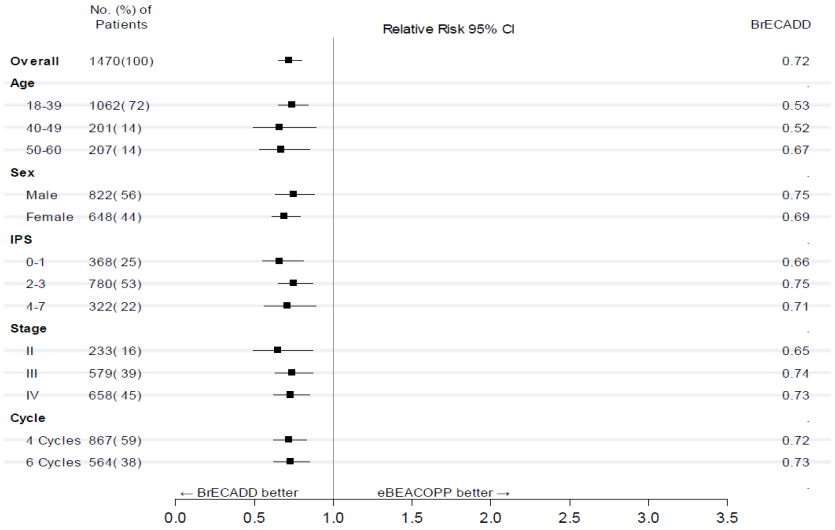
Co-primary objectives:

- **Demonstrate better acute tolerability**, i.e. reduced treatment-related morbidity (TRMB) with BrECADD
- **Demonstrate non-inferior efficacy** of BrECADD in terms of PFS

GHSG

GHSG HD21 primary safety endpoint TRMB analyses results





TRMB C-Rel-Risk of BrECADD = **0.70;**
95%-CI = **0.63 – 0.78;** p **< 0.0001**

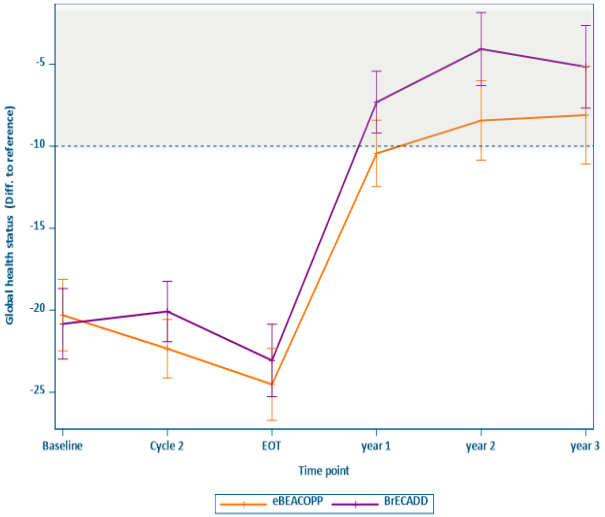
Benefit treatment with BrECADD for TRMB consistent over subgroups

BrECADD: some key aspects of optimization on tolerability

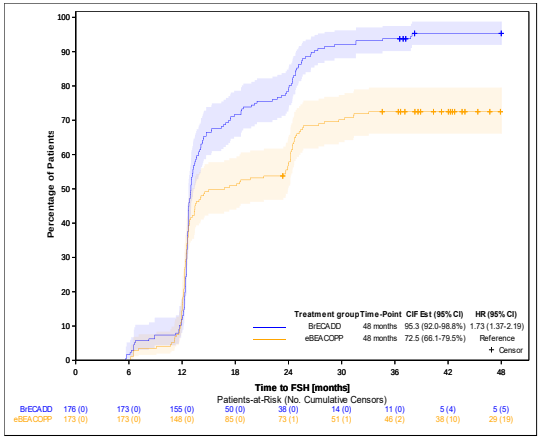
Full resolution adverse events at 12 months FU in 675/677 patients (> 99%)

Treatment related morbidity	BrECADD (n=677)
Anemia, thrombocytopenia, or infection of CTCAE grade 4	0 (0)
Organ toxicity of CTCAE grade 3-4	2 (<1)
Treatment related morbidity	2 (<1)

Normalized global health status with BrECADD starting at 12 months



Recovery of gonadal function and normalized birth rate (compared to healthy control)



GHSG

GHSG HD21 ***reducing genotoxicity:*** incidence of sMDS/AML at 5y mFU

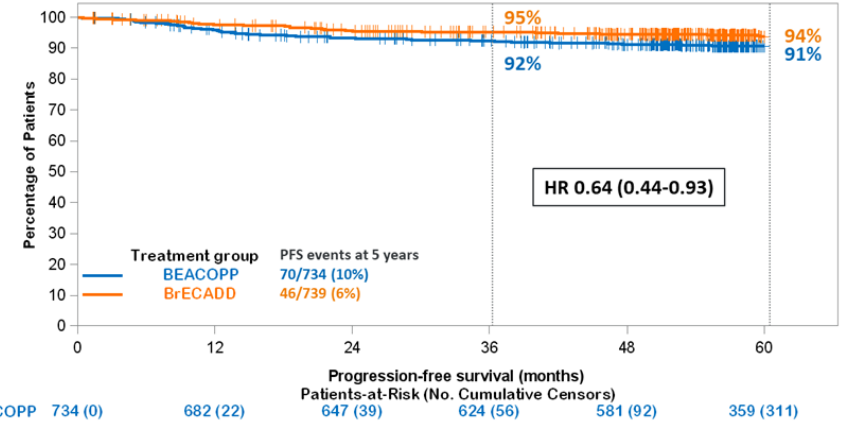
		eBEACOPP N=734	**BrECADD** N=739	**ITT** N=1473
Second malignancies		19 (3%)	21 (3%)	40 (3%)
Type of malignancy	**AML/MDS**	**6 (1%)**	**1 (<1%)**	7 (<1%)
	NHL	**2 (<1%)**	**8 (1%)**	10 (1%)
	Solid tumor	9 (1%)	11 (1%)	20 (1%)
	Other hematological malignancy	2 (<1%)	1 (<1%)	3 (<1%)
Year of event	2016-2023 (pre-publication)	16/19 (84%)	21/21 (100%)	37/40 (93%)
	2024	**3/19 (16%)**	**0/21 (0%)**	3/40 (8%)

Overall low rate of second primary malignancies and very low incidence of sAML/MDS

Ferdinandus et al., BLOOD 2025; 146 abs 152

GHSG HD21: primary cure rate at 5y mFU is very high

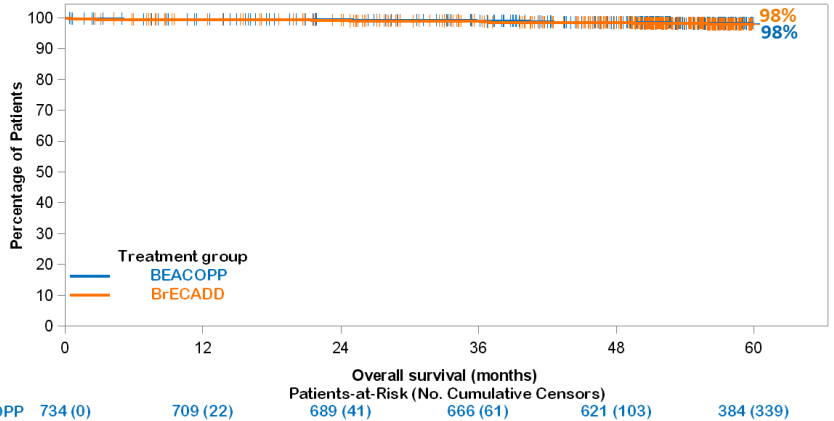
Progression free survival



Patients-at-Risk (No. Cumulative Censors)

BEACOPP	734 (0)	682 (22)	647 (39)	624 (56)	581 (92)	359 (311)
BrECADD	739 (0)	701 (20)	672 (36)	637 (68)	587 (113)	358 (340)

Overall survival



Patients-at-Risk (No. Cumulative Censors)

BEACOPP	734 (0)	709 (22)	689 (41)	666 (61)	621 (103)	384 (339)
BrECADD	739 (0)	718 (17)	703 (32)	663 (68)	615 (113)	383 (345)

Only ***one additional PFS-event*** since publication in BrECADD arm (vs. 4 in eBEACOPP): primary cure rate of 94% at 5 y mFU

Balancing available options: patients´ perspective[1]

1. Primary cure rate

- Determined by PFS

2. Long-term consequences

- persisting or late occurring toxicities
- Organ dysfunction
- Second primary malignancies

3. Acute toxicties

- TRMB rate
- Rate of unplanned hospitalization, e.g. due to febrile neutropenia

4. Treatment duration

5. Fertility

	BrECADD	NAVD
3y PFS 18 – 60 yo	95%	91 %
2y PFS ≥ 60 yo	92%	89%[4]
Cum. doxorubicin dose	160 / 240 mg/m²	300 mg/m²
Persisting toxicities at 1y	0.27 %	> 10% IRAEs?
unplanned hospitalization	~25 %	~20 % ?[3]
TRM (inv. assessed)	0/742	4/487
Treatment duration	12 / 18 weeks	24 weeks
Gonadal function at 3 y FU	Normal	?

GHSG

[1] GHSG patient representatives Survey-Monkey; GHSG data on file; [2] Herrera et al., NEJM; 2024; [3] Bock et al., BLOOD 2025; 146 abs 1841.; Rutherford et al., 2025 Sep 0;43(27):2968-2973 ; Ferdinandus et al., J Clin Oncol. 2025 Sep 20;43(27):2974-2985

What else could be important when balancing options?

	4-6x BrECADD 4y PFS		6x NAVD 3y PFS	
IPS 0-2 vs 3-7 (1:1 in HD21)	97%	92%		
IPS 0-3 vs 4-7 (2:1 in S1826)			92 %	87%
Std III/IV	95%	93%	93%	88%
PET2 neg /pos (65:35 vs 85:15)	97%	90%	93%	84%
PET_{EOT} neg /pos (83:17 vs 89:11)	95%	90%	94%	68%

- The IPS does not identify subgroups, for which there would be an obviously greater/smaller benefit for one over the other than for all patients.
- The PET comparison between study results is hampered by different time points and different rates of negativity/positivity; however, there seems to be a relevant disadvantage for PET-pos patients after treatment with NAVD

GHSG

AScHL 2026: reasonable aims for further development?

For NAVD, aims may include

- Tx de-escalation aiming at reduction of cumulative doxorubicin and nivolumab doses (reducing risk of second primary malignancies, congestive heart failure and persisting or late occurring IRAEs), and
- Tx escalation for patients at increased risk for treatment failure (improving PFS)?

For BrECADD, aims include

- decreasing the rate of “false” PET2-positive patients, thereby increasing number of patients with 4 cycles only, and
- minimizing the first-cycle effect and thereby reducing unplanned hospitalization?

Accordingly, key challenges for both approaches include

- For response adapted therapies: improving assessment methods over the qualitative DS system, e.g. by using MTV, ctDNA, and/or combinations
- For personalized approaches: Identification of baseline characteristics for upfront treatment-allocation for therapies with optimal risk/benefit ratio

GHSG

Thank you very much for your attention!

Chairman: P. Borchmann

Former-Chairman: A. Engert

Honorary Chairman: V. Diehl

Pathology: F. Fend, S. Hartmann, W. Klapper, G. Ott, A. Rosenwald

Radiotherapy: C. Baues, H. T. Eich

Nuclear Medicine: M. Dietlein, C. Kobe

Laboratory: S. Borchmann

Physicians: K. Behringer, B. Böll, P. Bröckelmann, D. Eichenauer, J. Ferdinandus, S. Gillessen, A.S. Robertz, H. Tharmaseelan, B. v. Tresckow, J. Welters

TRIAL COORDINATION CENTER

Head: M. Fuchs

Trial physicians: C. Jaworek

Data Management: B. Andrulevicius, B. Koch, S. Ladewig, B. van den Hoonaard

Project Management: L. Klemm, L.C. Klostermann. S. Kreitz, N. Moroz, I. Oosterhaar, S. Sevimli-Abdis, M. Weber

Quality Management: I. Oosterhaar

Database / IT: O.W. Abudu, L. Ganß, T. Schober, N. Schulze

Statistics: I. Bühnen, J. Jablonski, H. Kaul, M. Supprian

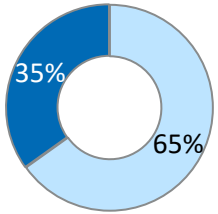
Assistant / Secretary: K. Rust, M. Schumacher, K. Tittmann

GHSG HD21 Progression-free survival

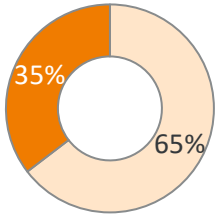
By treatment group and PET-2 result (Deauville Score)

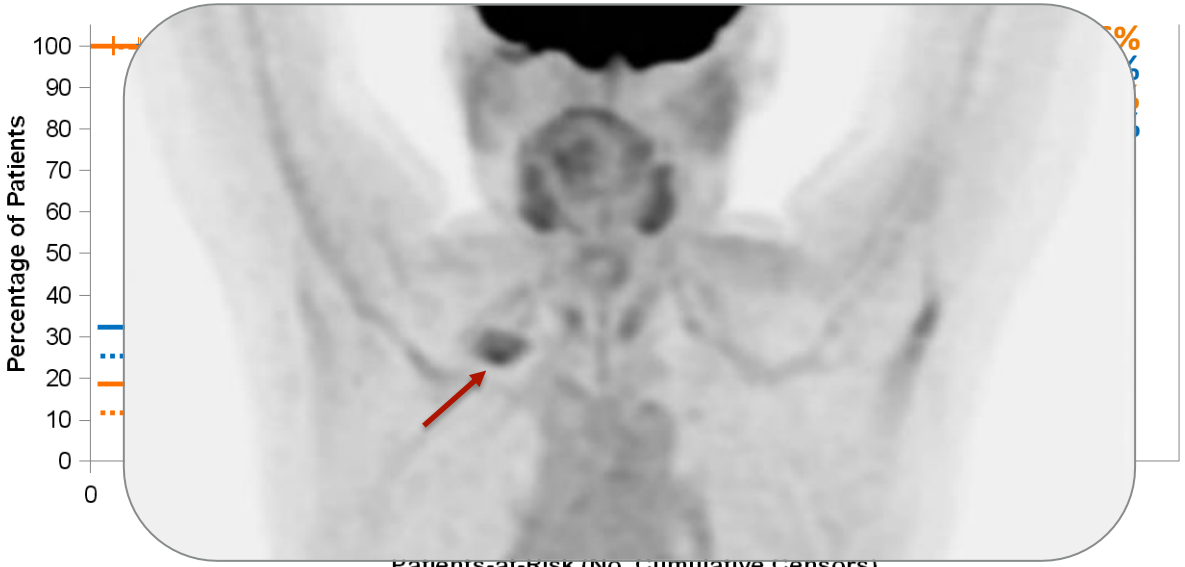
DS4-5 positivity rates

BEACOPP



BrECADD



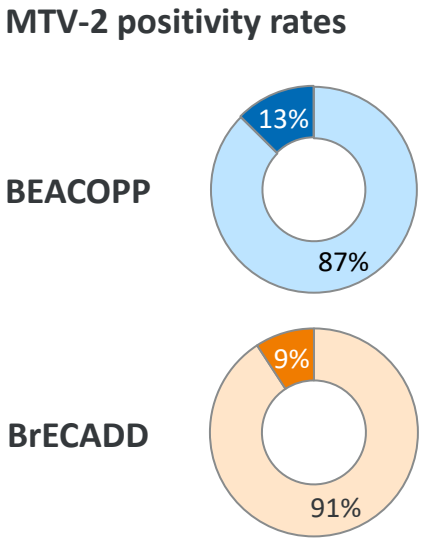


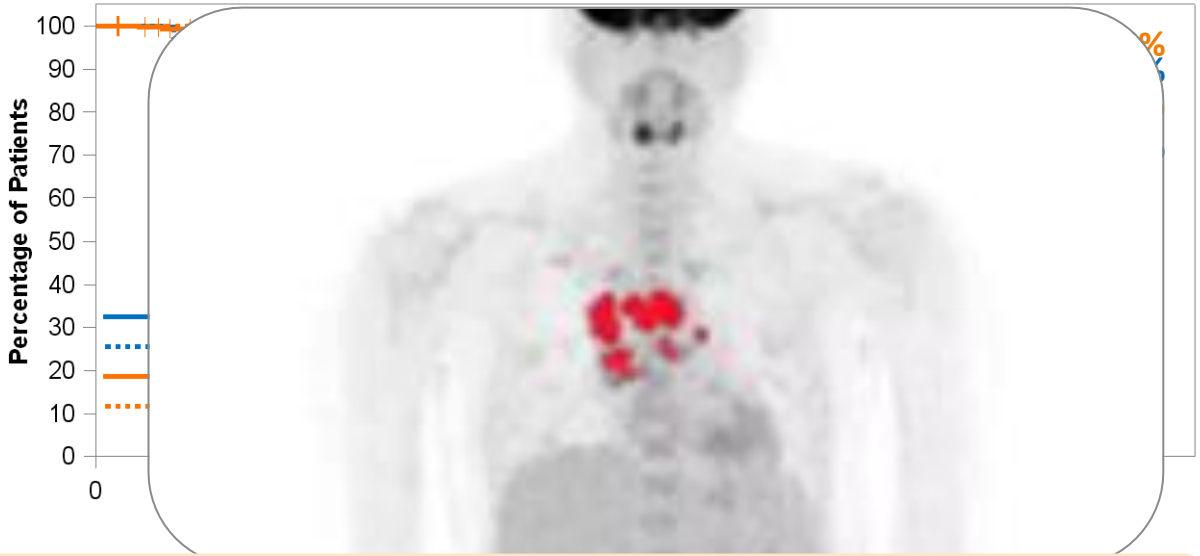
Patients-at-Risk (No. Cumulative Censors)

BEACOPP DS 1-3	428 (0)	410 (6)	388 (16)	376 (26)	349 (50)	208 (189)
BEACOPP DS 4-5	229 (0)	211 (5)	200 (12)	191 (17)	177 (28)	105 (99)
BrECADD DS 1-3	429 (0)	412 (8)	400 (18)	381 (37)	350 (66)	201 (215)
BrECADD DS 4-5	235 (0)	221 (8)	208 (11)	199 (19)	185 (30)	117 (97)

GHSG HD21 Progression-free survival

By treatment group and MTV-2 result (SUV4-Method)





Residual MTV after two cycles (MTV-2) is a better risk marker than DS4-5.