# New frontline regimens in advanced stage: a head-on collision or the possibility of diversification based on patient type?

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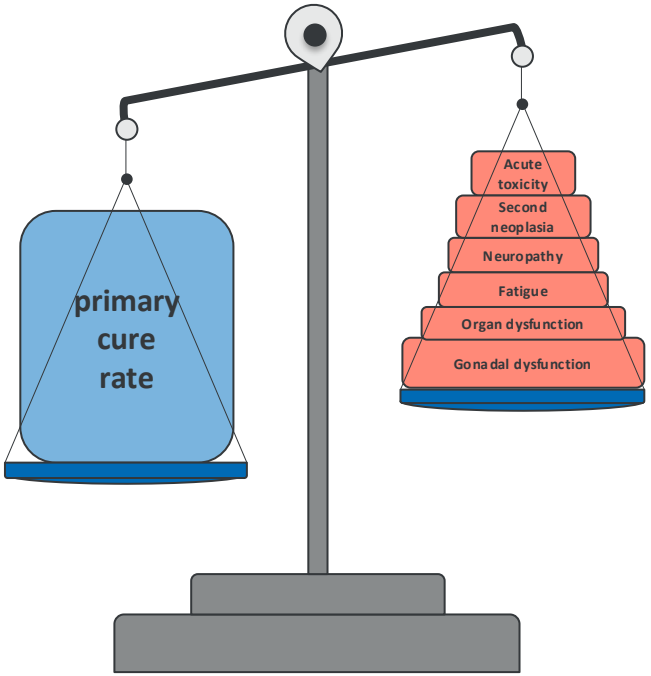
# How can we optimize the risk-benefit ratio of 1L treatment for AS-cHL?




To improve the risk/benefit ratio of the eBEACOPP regimen the GHSG has focussed on

1. ***treatment individualization by metabolic response assessment,***
2. ***modification of eBEACOPP with the CD30 targeting ADC Brentuximab vedotin***

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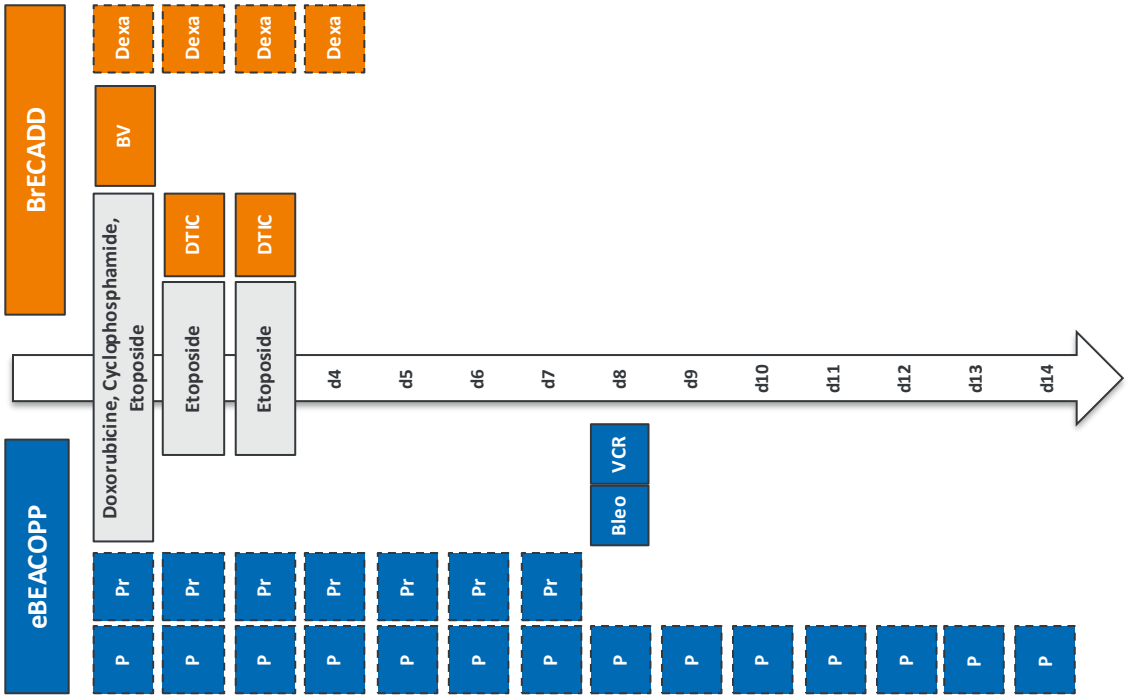
# Primary cure beyond individualization: *eBEACOPP modification.*




The Kairos backbone with **doxorubicin, cyclophosphamide, etoposide** was retained and **brentuximab vedotin** added.

Problematic drugs were removed with the aim to improve acute and long-term tolerability:

- **Bleomycin** (pulmonary toxicity)
- **Vincristine** (neurotoxicity)
- **Procarbazine** (gonadal and genotoxicity)
- **14 days of Prednisone**

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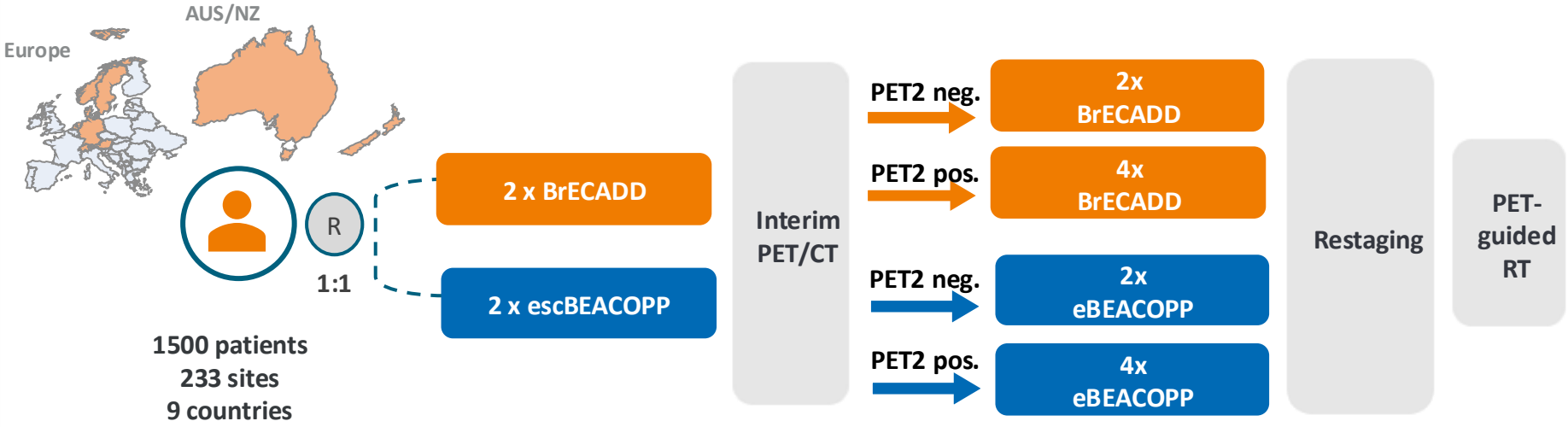
Borchmann et al, Lancet, 2024
BV administration on d0 as recommend by GHSG

# GHSG HD21 study design and primary endpoints

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




**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

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# GHSG HD21: feasibility of PET-guided BrECADD

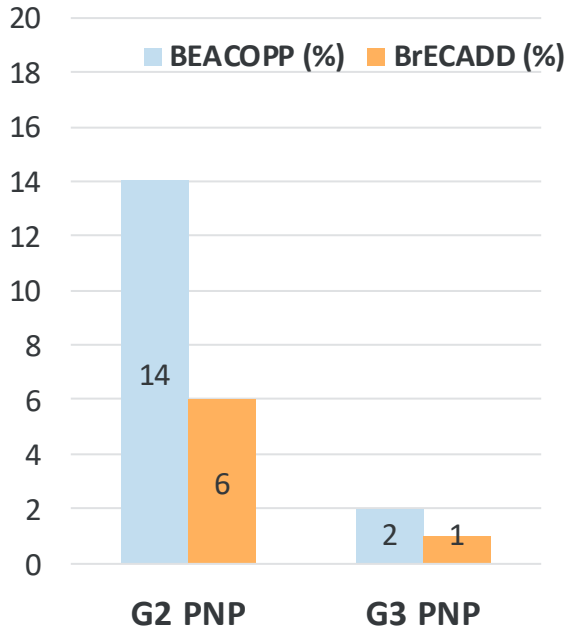
| | BEACOPP N=740 (%) | BrECADD n=742 (%) |
|---|---|---|
| **Response at PET/CT2** | | |
| Central PET2 review (post-amendment) | 669 (90) | 677 (91) |
| **CMR (DS1-3) PET/CT2** | **430/669 (64)** | **430/677 (64)** |
| **Response at EOT** | | |
| RTx recommended (i.e. no mCR, DS 4,5) | 127 (17) | 125 (17) |
| **RTx documented** | **112 (15)** | **104 (14)** |

| ITT-PFS | BEACOPP N=740 | | BrECADD N=742 | |
|---|---|---|---|---|
| **Number of cycles started/expected** | N | % | N | % |
| **4/4** | 427 | **57.7** | 4225 | **57.3** |
| 5/4 | - | - | 2 | 0.3 |
| 6/4 | 2 | 0.3 | | |
| | | | | |
| 4/6 | 8 | 1.1 | 7 | 0.9 |
| 5/6 | 5 | 0.7 | 3 | 0.4 |
| **6/6** | 278 | **37.6** | 284 | **38.3** |

**99 % of all patients received the scheduled number and dose of treatment cycles with BrECADD in HD21.**

**Only 92 % completed treatment with NAVD in S1826.**

# GHSG HD21: sensory polyneuropathy with BV in BrECADD




| | eBEACOPP N = 734 | BrECADD N = 739 |
|---|---|---|
| **Any PNP during treatment** | 368 (50%) | 294 (36%) |
| No PNP at EOT | 452 (62%) | 540 (73%) |
| No PNP or resolved at final analysis | 724 (99%) | 724 (98%) |
| Resolved to ≤G1 | 733 (100%) | 735 (100%) |

**Early termination rate of BV in BrECADD: 2.4 %**

**Early termination rate of Nivo in NAVD: 9.4 %**

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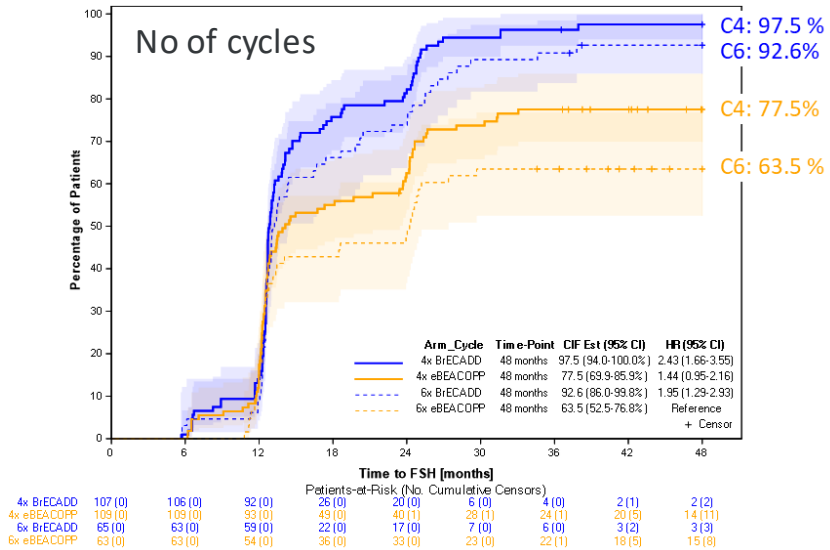
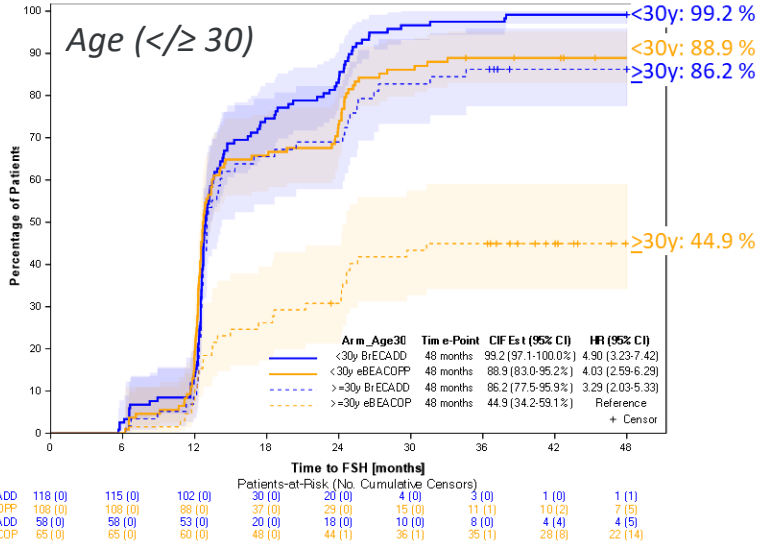
# GHSG HD21: Gonadal function of BrECADD treated women




Impact of No of cycles on recovery is neglectable

Gonadal function recovery occurred in all women below 30y following BrECADD.

Women > 30y derived the highest relative benefit from BrECADD (HR 3.23, CI95: 2.03-5.33).

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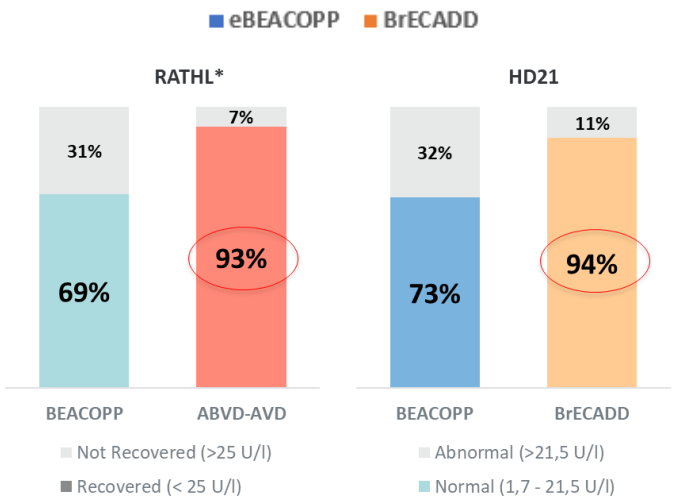
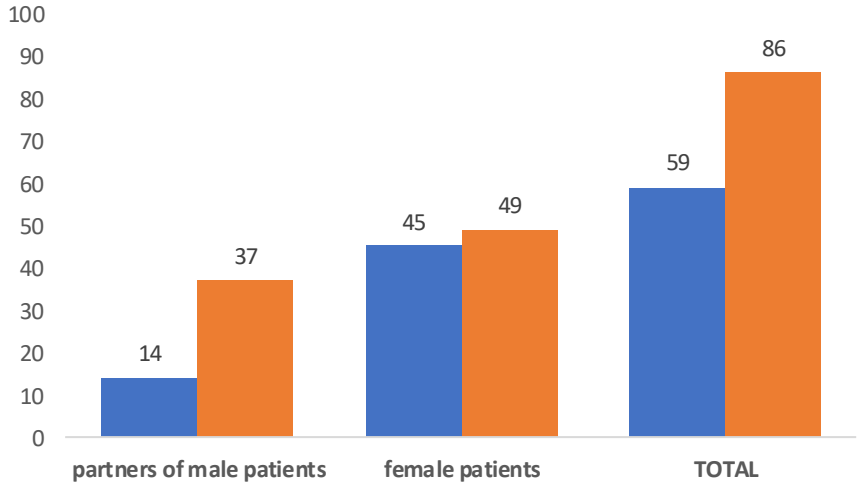
# GHSG HD21: ovarian function and fertility with BrECADD at 5y mFU

## Ovarian function in HD21 and RATHL




## Parenthood in HD21




***gonadal function equal to A(B)VD*** treated female patients in RATHL, and motherhood rate with ***BrECADD is equal to German healthy control*** from 3 years onwards

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**Numbers for NAVD?**


Ferdinandus et al., BLOOD 2025; 146 abs 152

Anderson et al., Lancet Oncol 2018

# 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*

**Numbers for NAVD?**

Ferdinandus et al., BLOOD 2025; 146 abs 152

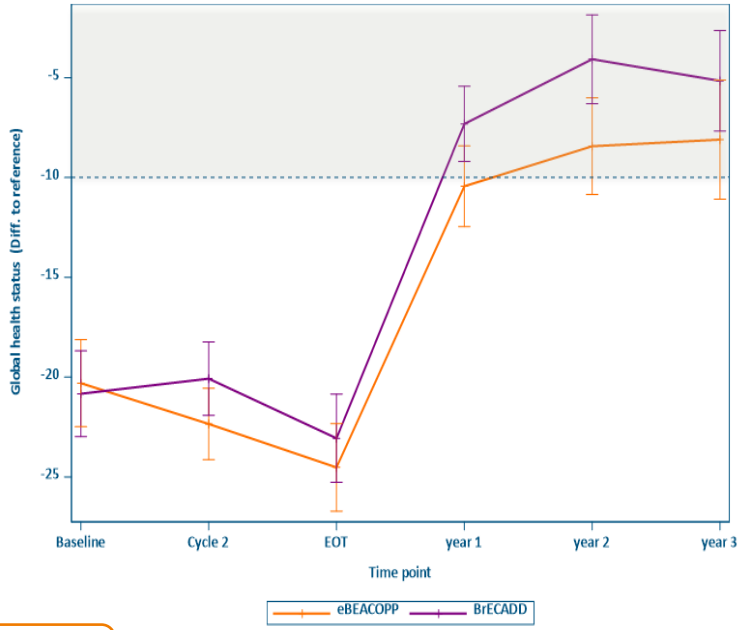
# GHSG HD21: some more key aspects of ***tolerability of BrECADD***.

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

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

***no Tx-related mortality in a global study!***

**Normalized global health status with BrECADD** starting at 12 months




**Numbers for NAVD?**

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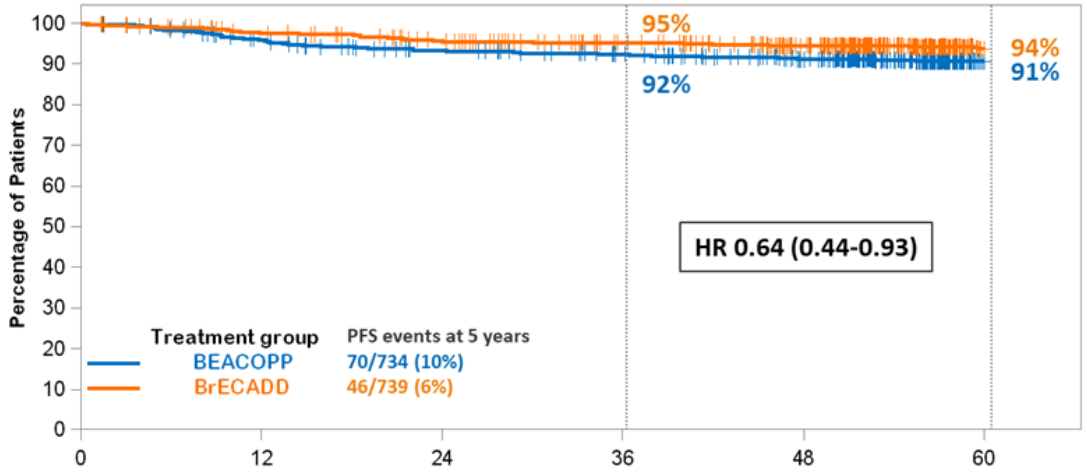
# GHSG HD21: unprecedent 5y progression free survival

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) |

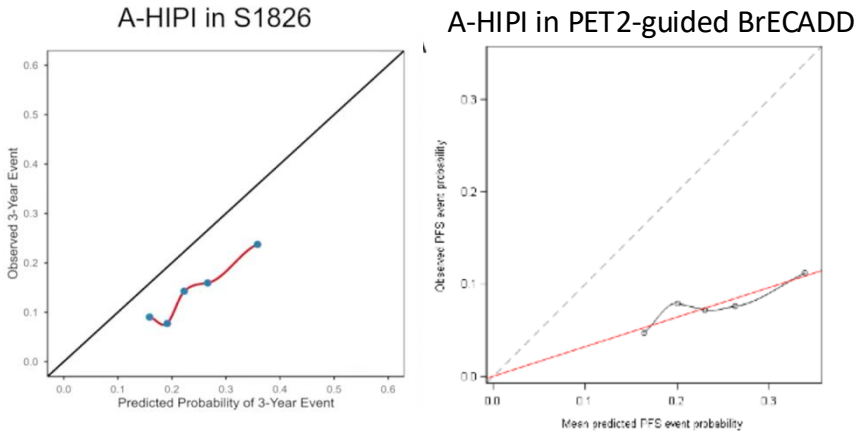
Only ***one additional PFS-event*** since publication in BrECADD arm (vs. 4 in eBEACOPP):

***PFS of 94% at 5 y mFU***

**Numbers for NAVD at 5y FU?**

# Efficacy of the available options BrECADD and NAVD

## A-HIPI and survival outcomes




***ABVD-based aHIPI baseline risk assessment allows outcome prediction for N-AVD, but not for effective regimens***

## PET-status and survival outcomes

| | BrECADD 5y PFS [%] | NAVD 3y PFS [%] |
|---|---|---|
| PET-2 pos | **91** | **84** |
| PET-EOT pos | **90** | **68** |
| PET-2 neg | **96** | **93** |
| PET-EOT neg | **95** | **94** |

***6x N-AVD is sufficiently effective in low-risk patients, but insufficient for PET2/EOT positive patients***

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Ferdinandus et al., BLOOD 2025; 146 abs 152
Herrera, et al., *BLOOD 2025; 146 abs* 151
Bartlett et al. *et al, BLOOD 2025; 146 abs* 1851

# What is important when balancing options? Ask the patient![1]

**1. Primary cure**

- Determined by PFS

**2. No late or persisting toxicity**

- Any organ dysfunction
- Second primary malignancies
- QoL/PROs

**3. Low acute toxicities**

- TRM
- Unplanned hospitalization,

| | BrECADD | NAVD |
|---|---|---|
| 3y PFS 18 – 60 yo | 95% | 91 % |
| 2y PFS ≥ 60 yo | 92%[5] | 89%[4] |
| Cumulative doxorubicin dose | 160 / 240 mg/m² | 300 mg/m² |
| Persisting severe toxicities | 0.27% (all organ systems) | > 10 % (IRAEs)[2] |
| Septic death on trial | 0/742 | 4/487 |
| unplanned hospitalization | ~25 % | ~20 %[3] |

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[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 ; [5]Ferdinandus et al., J Clin Oncol. 2025 Sep 20;43(27):2974-2985

# Advanced stage cHL in 2026: balancing options.

**Compared to 6x NAVD, PET2-guided 4-6x BrECADD**

- is ***more effective for all patients,*** including patients at high individual risk
- with ***more, but safely manageable hem-tox*** during treatment, and
- at the same time with ***more patients fully recovering*** from treatment,
- and ***normalized PROs and QoL*** (age and gender matched healthy control)

- 6x NAVD is a valuable option for healthcare systems and patients who are not prepared for or fit enough to manage or tolerate acute hem-tox episodes of around four days/cycle. However, as long as we cannot predict individual outcome at baseline
- the superior efficacy and long-term tolerability makes individualized ***PET2-guided 4-6x BrECADD my preferred treatment option*** for patients aged 18-60 with AScHL.

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The GHSG's mission is to cure Hodgkin lymphoma in all patients,

every single one!

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# Thank you very much for your attention!

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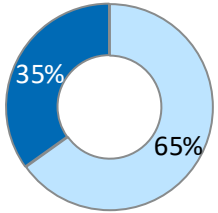
# GHSG HD21 Progression-free survival

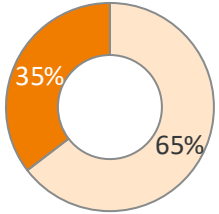
## By treatment group and PET-2 result (Deauville Score)

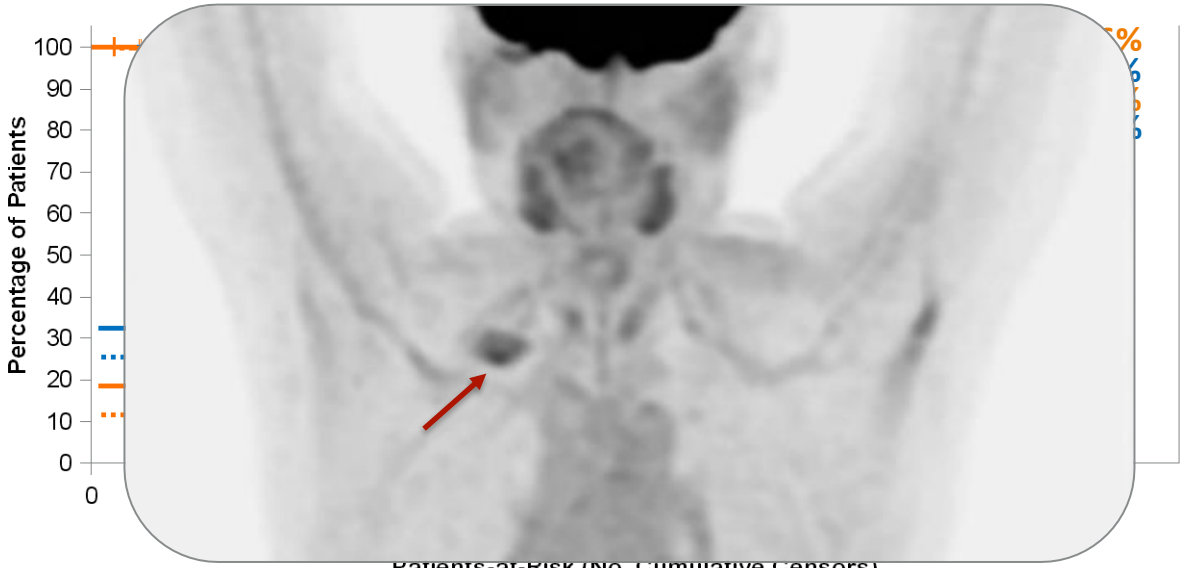
**DS4-5 positivity rates**

**BEACOPP**




**BrECADD**



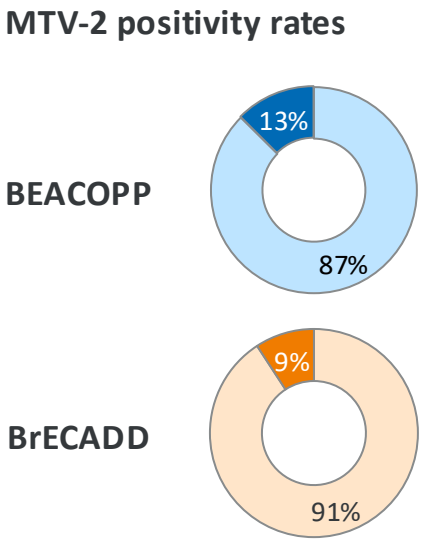



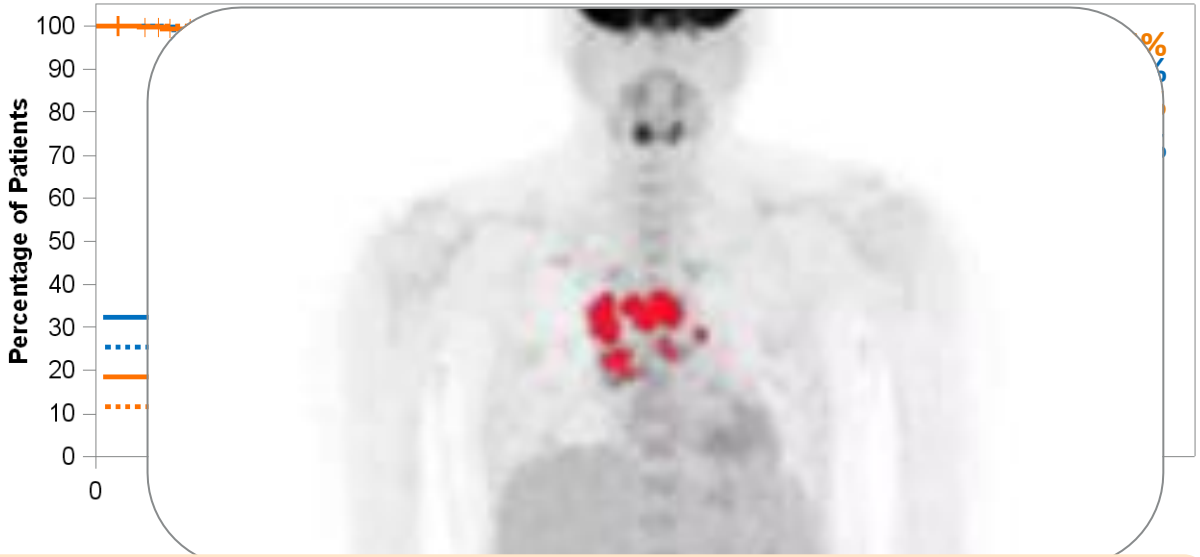

Patients-at-Risk (No. Cumulative Censors)

| | | | | | | |
|---|---|---|---|---|---|---|
| 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

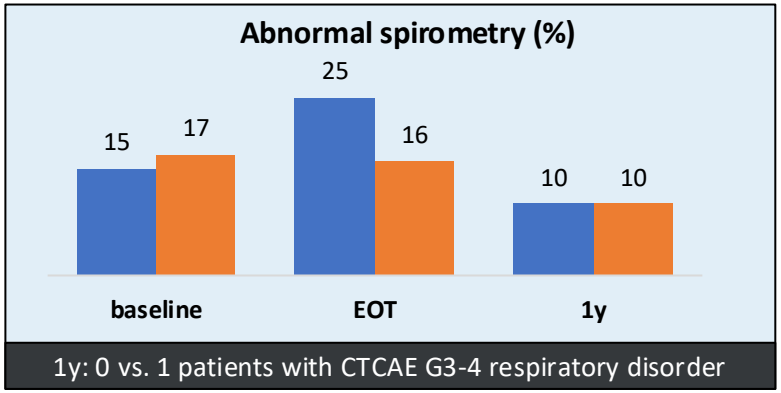
## By treatment group and MTV-2 result (SUV4-Method)



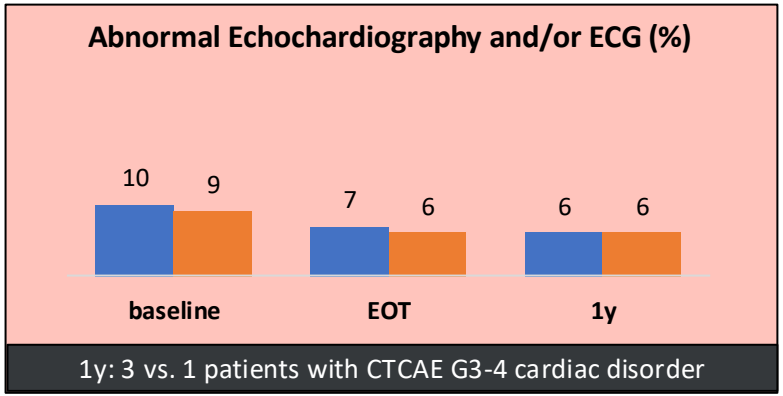




**Residual MTV after two cycles (MTV-2) is a better risk marker than DS4-5.**

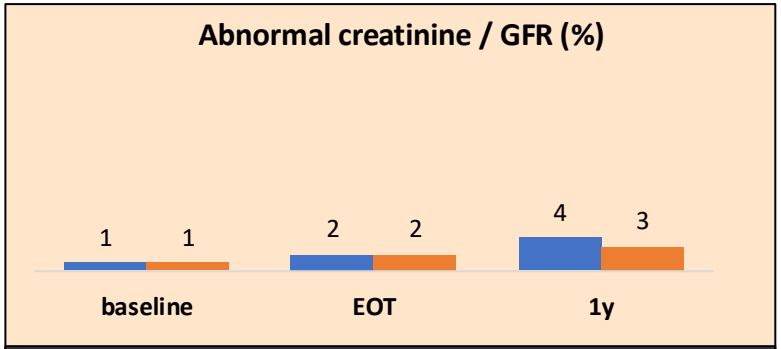
# GHSG HD21 eBEACOPP vs. BrECADD Organ function over time



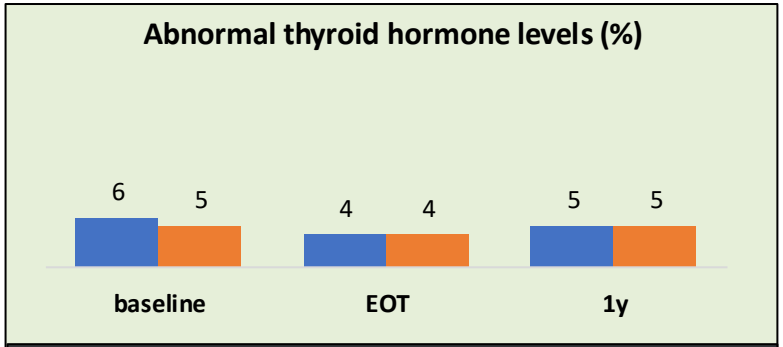

1y: 0 vs. 1 patients with CTCAE G3-4 respiratory disorder




1y: 3 vs. 1 patients with CTCAE G3-4 cardiac disorder




1y: No patients with CTCAE G3-4 renal disorder




1y: No patients with CTCAE G3-4 endocrine disorders

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# GHSG HD21 Final Analysis (5y mFU): Summary and Conclusions

**Very high primary cure rate with BrECADD**

5y PFS 94% for all patients

PET-2 guided approach:

- Allows short treatment for most patients with 5y-PFS 96% after 4 cycles
- Negates risk from higher lymphoma burden with 5y-PFS 90% after 6 cycles

**Low rate of long-term side effects with BrECADD**

Omission of problematic drugs led to

- improvements in organ function
- very low AML/MDS rate
- high childbirth rate

Almost all patients recovered from peripheral neuropathy and any other toxicity during FU

**Individualized BrECADD sets a new benchmark for the primary cure rate of AS-cHL with minimal long-term side effects**

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