Immunochemotherapy-based strategies for sparing toxicity and improving efficacy in advanced-stage Hodgkin lymphoma: BEACOPP-based

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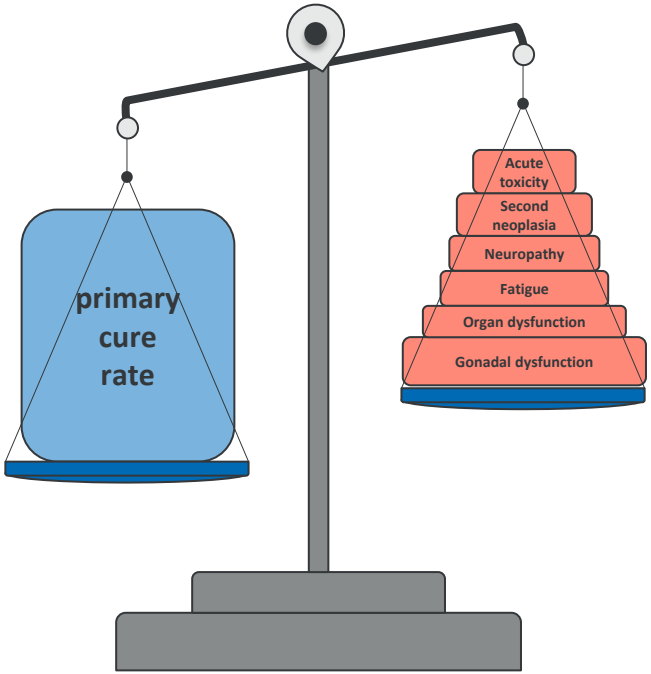
How can we optimize the risk-benefit ratio of 1L treatment for AS-cHL?



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

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

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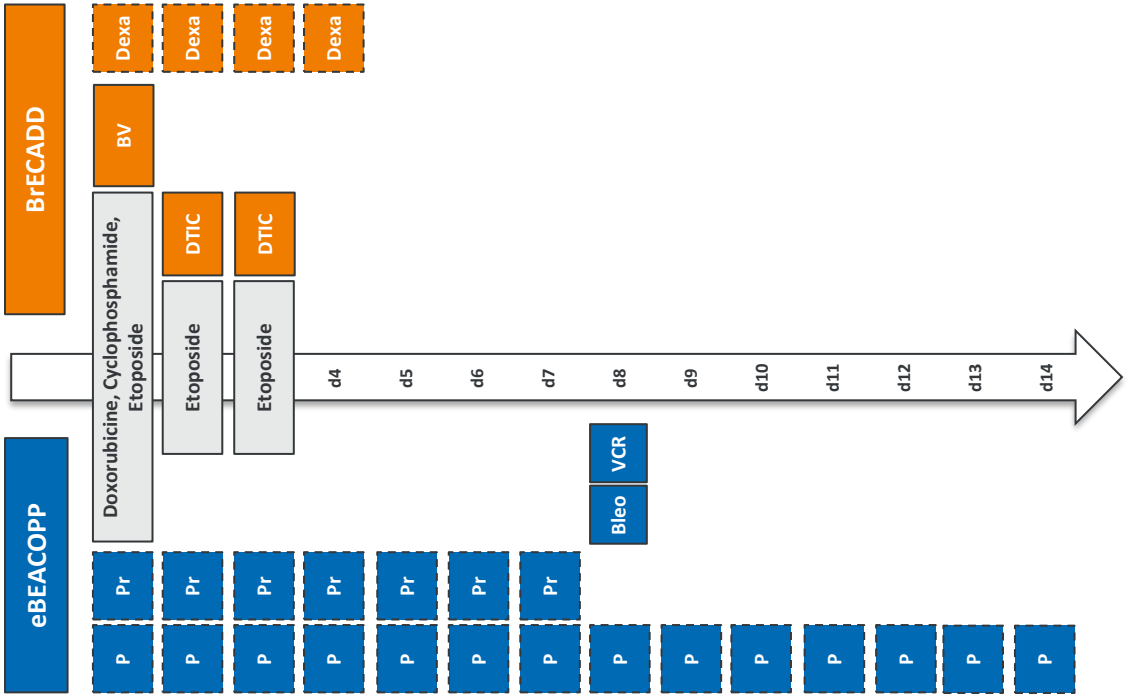
Primary cure beyond individualization: *eBEACOPP modification.*



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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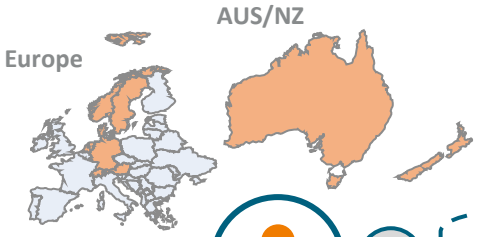
Borchmann et al, Lancet, 2024

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



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

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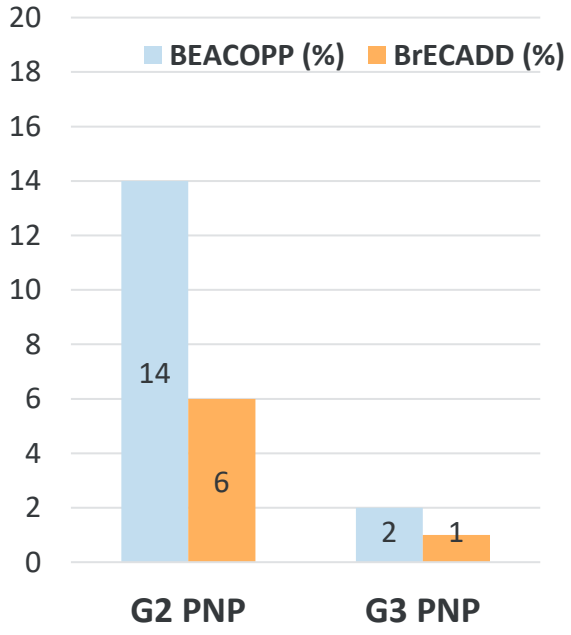
GHSG HD21: sensory polyneuropathy with BV in BrECADD



	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 %

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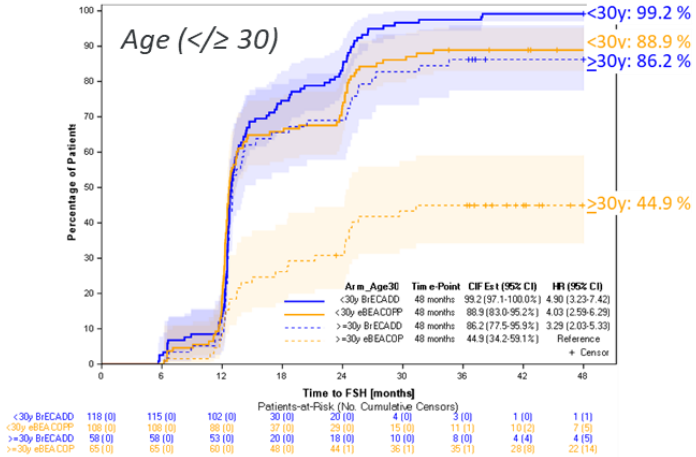
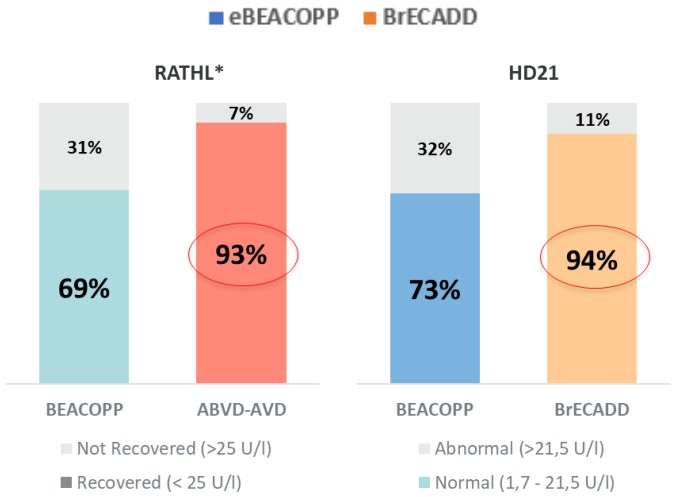
GHSG HD21: Gonadal function of BrECADD treated women



- Gonadal function recovery occurred in all women < 30y following BrECADD.
- Women > 30y derived the highest relative benefit from BrECADD (HR 3.23, CI95: 2.03-5.33).

Ovarian function in HD21 and RATHL



- 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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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

Ferdinandus et al., BLOOD 2025; 146 abs 152

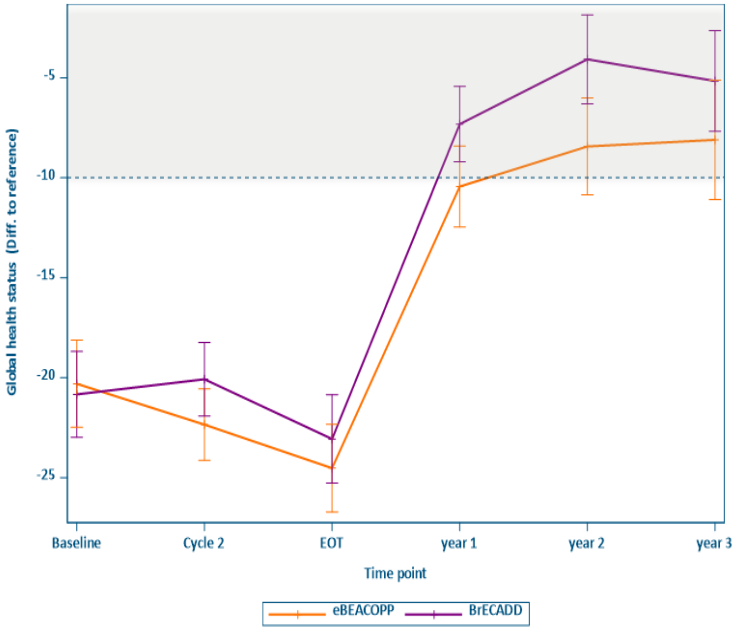
GHSG HD21: some more key aspects of ***tolerability of BrECADD***.

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



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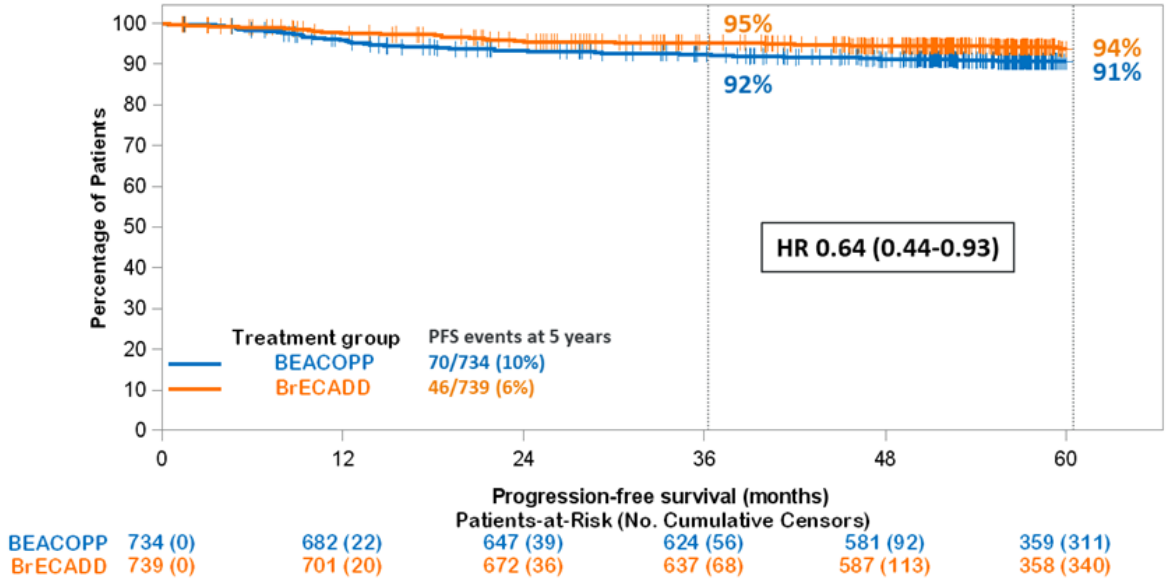
HD21: BrECADD is the most effective regimen for AS-cHL ever reported

Progression free survival

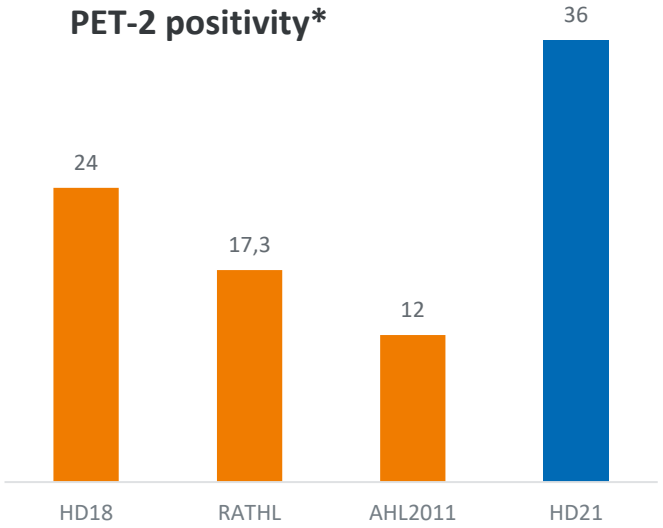


Only ***one additional PFS-event*** since publication in BrECADD arm (vs. 4 in eBEACOPP):

PFS of 94% at 5 y mFU

- Risk-benefit ratio for BrECADD is exceptional, if acute hem-tox can be safely managed.

Optimizing the risk-benefit ratio of 1L treatment for AS-cHL: mission completed or do we have an unmet medical need still?



NAVD in S1826: 15% (22%)**

How to increase the number of patients needing only 4 cycles?

- *Improving treatment individualization by modification of response assessment*

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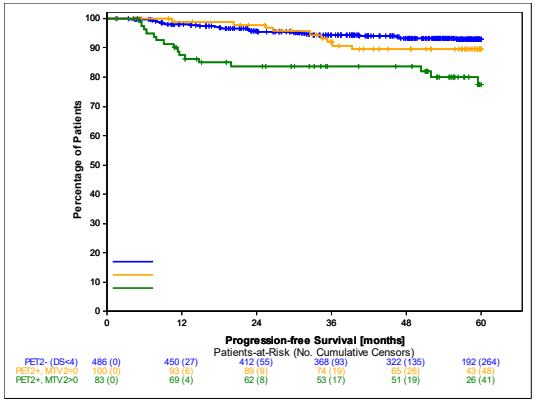
*as reported. Varying criteria in AHL2011.
**Bartlett et al. et al, BLOOD 2025; 146 abs 1851

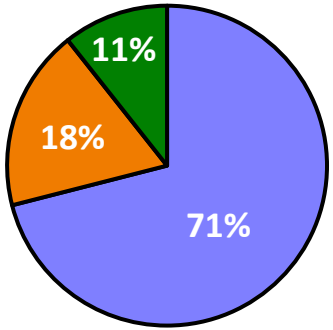
Improving treatment individualization by modification of response assessment: MTV-2

C6 Cohort HD18 (n=645)



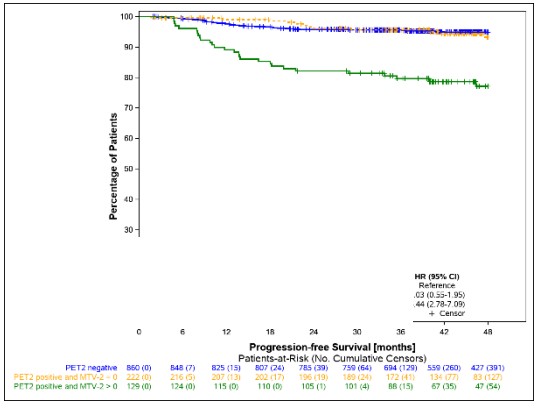
	5y-PFS	HR
DS1-3	**92.9%** (90.5-95.4)	Reference
DS4-5 & MTV = 0	**89.5%** (83.2-96.3)	**1.5** (0.74-3.05)
MTV>0	**77.5%** (67.9-88.4)	**3.29** (1.81-6.01)

HD21 ITT (n=1211)



Proportions of **PET-negative**, **PET-positive & MTV = 0** and **patients with remaining MTV-2**

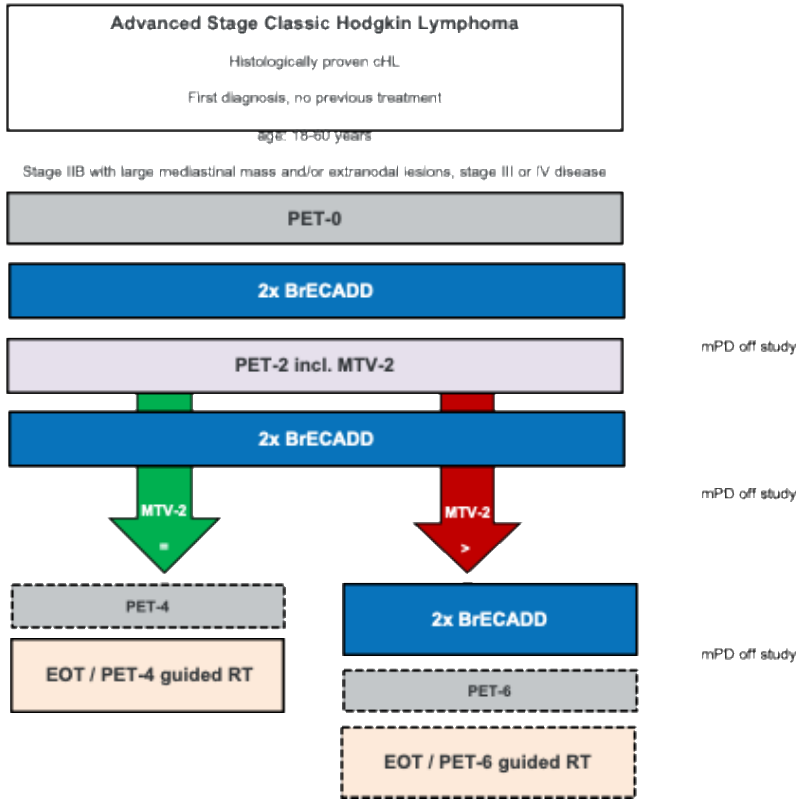
HD21 ITT (n=1211)



	4y-PFS	HR
DS1-3	**94.8%** (93.3-96.4)	Reference
DS4-5 & MTV = 0	**93.2%** (89.4-97.2)	**1.03** (0.55-1.95)
MTV>0	**77.1%** (69.9-85.1)	**4.44** (2.78-7.09)

GHSG QUANTIFY: A Low-Intervention Phase II Trial of Quantitative Imaging for Individualized Treatment of Advanced-Stage Classic Hodgkin Lymphoma

PHASE OF DEVELOPMENT	II	
INTERVENTION MODEL	Low-intervention single-group trial	
PRIMARY ENDPOINT	1y-PFS	
NUMBER OF PARTICIPANTS	300	
TRIAL SITES	50 sites in Germany	
SCHEDULE	First patient in (FPI)	approval date + approx. 2 months
	Last patient in (LPI)	FPI + 24 months
	End of Study (EoS)	LPI + 18 months
	Final analysis	Within 6 months after EoS



Main responsible persons:

- Dr. Justin Ferdinandus (PI)
- Prof. Dr. Carsten Kobe (Reference Nuclear Medicine)
- PD Dr. Dr. Sven Borchmann (GHSG Laboratory)
- Max Büttner, M.Sc. (Patient representative)

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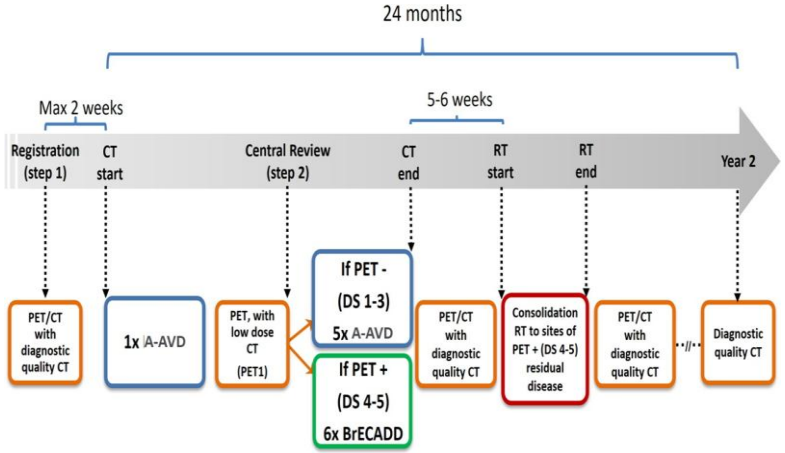
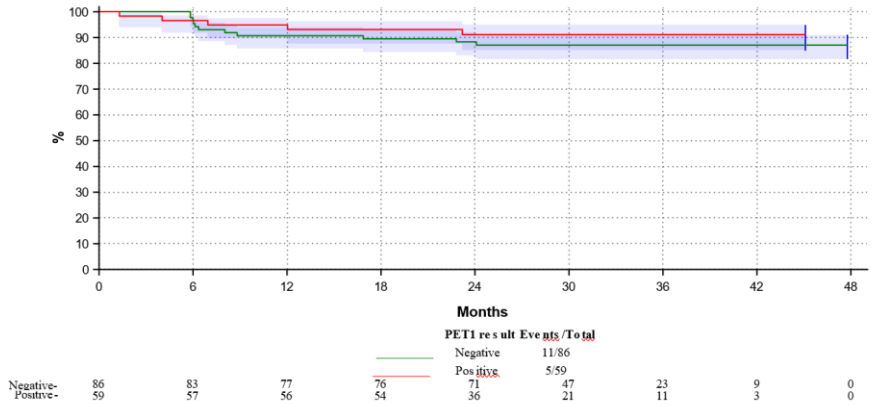
Is BrECADD effective enough to overcome the poor outcome of ABVD-based early iPET-positive patients? The EORTC COBRA trial challenges the Kairos principle.





2y PFS

PET1-negative (60%, 6x BV-AVD)	88.3%
PET1-positive (40%, 1x BV-AVD, 6x BrECADD)	91.3%

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Hutchings et al., The Lancet preprint: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=5781033

Any new development must include the patients´ perspectives on the relevance of its endpoints!

1. Primary cure

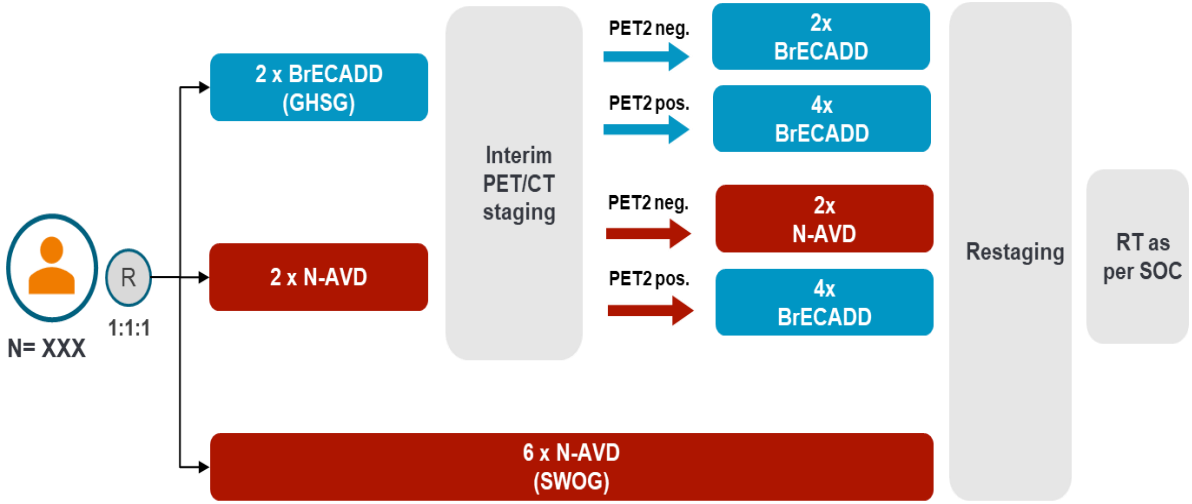
- Determined by PFS

2. No late or persisting toxicity

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

3. Low acute toxicities

- TRM
- Unplanned hospitalization



- *Increasing benefit of NAVD by interim PET/ctDNA guided treatment duration in good responders?*
- *Is N-AVD associated with less acute and severe toxicities or do IRAEs outweigh neutropenic fever? LT-Tox? PROs?*

[1] GHSG patient representatives Survey-Monkey; GHSG data on file;

Thank you very much for your attention!

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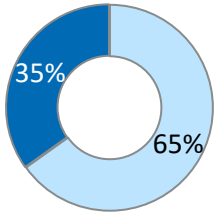
GHSG HD21 Progression-free survival

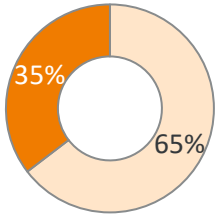
By treatment group and PET-2 result (Deauville Score)

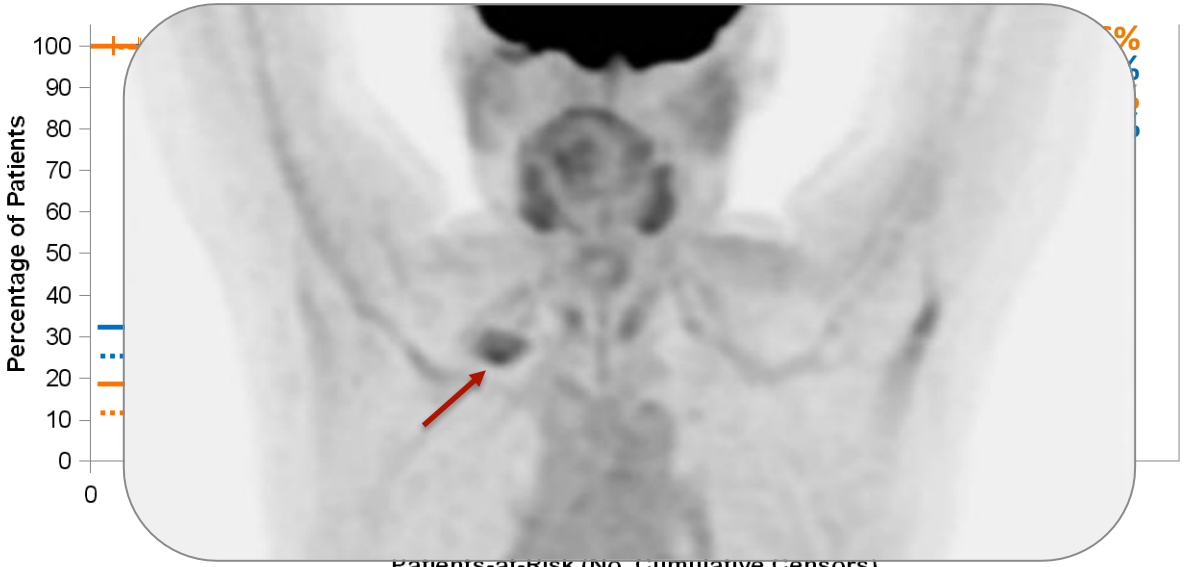
DS4-5 positivity rates

BEACOPP



BrECADD



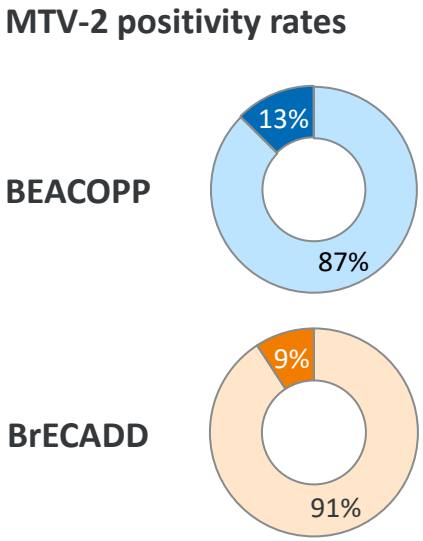


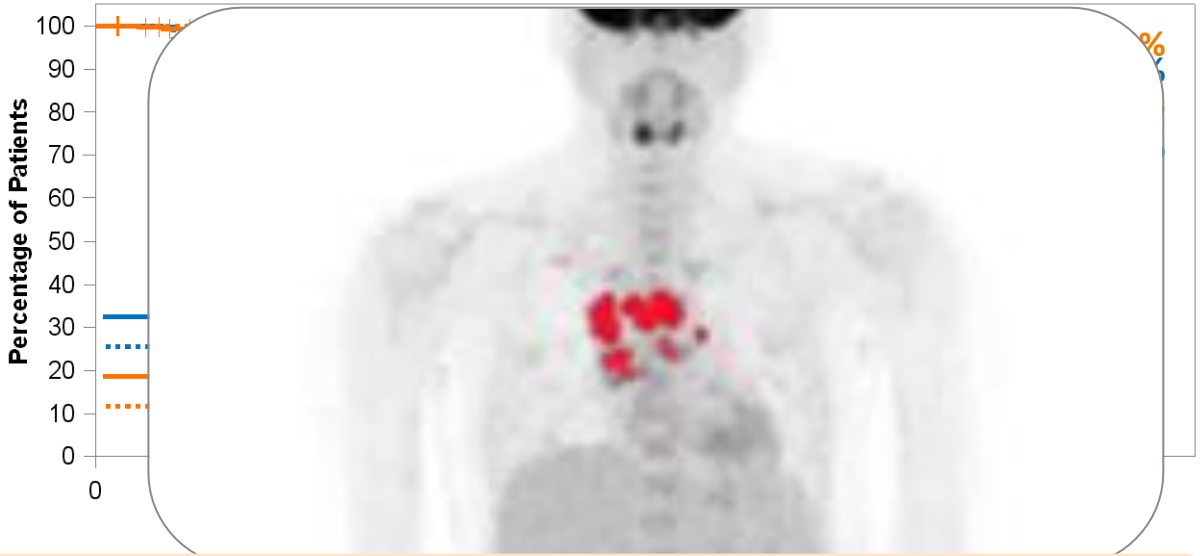
Patients-at-Risk (No. Cumulative Censors)

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

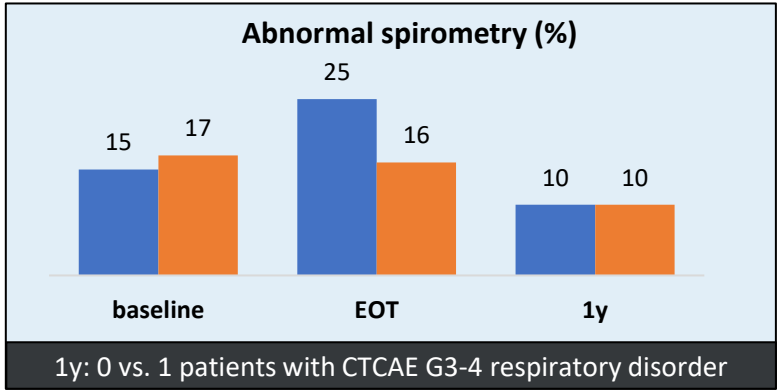
By treatment group and MTV-2 result (SUV4-Method)



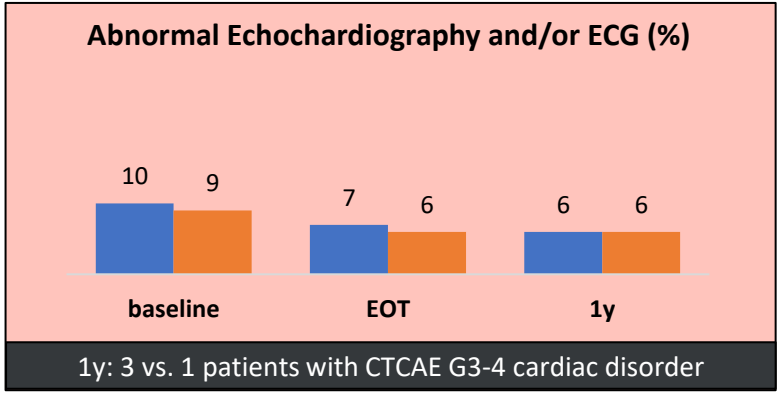


Residual MTV after two cycles (MTV-2) is a better risk marker than DS4-5.

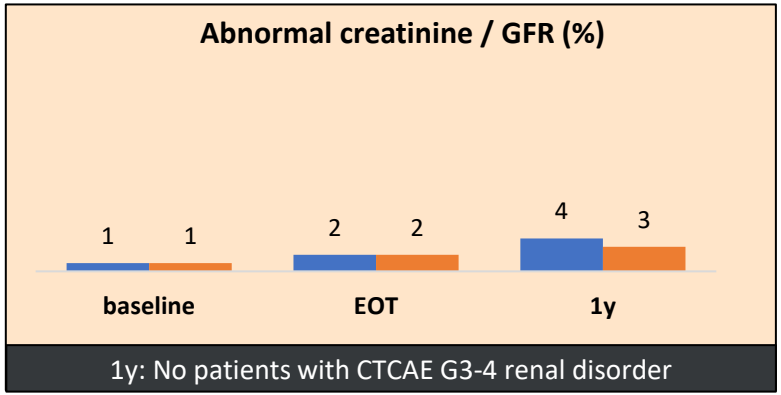
GHSG HD21 eBEACOPP vs. BrECADD Organ function over time



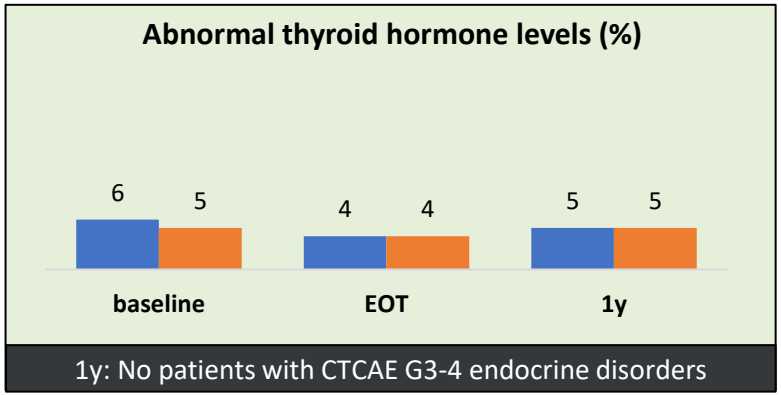
1y: 0 vs. 1 patients with CTCAE G3-4 respiratory disorder



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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