Co-primary endpoint of PET2-guided BrECADD versus eBEACOPP in patients with advanced stage classical Hodgkin Lymphoma: results of GHSG phase III HD21 trial.

Peter Borchmann on behalf of the German Hodgkin Study Group

HD21 study rationale and objectives

- High efficacy of eBEACOPP allowed us to **individualize and reduce treatment intensity and duration for most patients** by early metabolic response assessment (PET) (HD15, HD18).[1,2,3]
- To further **improve the risk-to-benefit ratio of eBEACOPP** we modified the regimen with Brentuximab vedotin (BV, BrECADD).[4,5]
- The CD30 targeting ADC brentuximab vedotin (BV) has proven high efficacy and tolerability in cHL. We thus asked the question, **if treatment related morbidity (TRMB) of the established eBEACOPP regimen could be reduced by its modification with BV**.

➢ Here, we present the interim analysis of the **efficacy endpoint of the GHSG HD21 study** comparing PET2-guided eBEACOPP versus PET2-guided BrECADD for patients aged 18-60 yo with newly diagnosed advanced stage cHL.

[1]Diehl, V., et al., N Engl J Med, 2003. 348(24): p. 2386-95.
[2]Engert, A., et al., Lancet, 2012. 379(9828): p. 1791-9.
[3]Borchmann, P., et al., Lancet, 2018. 390(10114): p. 2790-2802.
[4]Borchmann, P., et al., Blood, 2013. 122(21): p. 4344.
[5]Borchmann, P., et al., ASH 2022

GHSG HD21 remodeling eBEACOPP with Brentuximab vedotin

Drug	Day	BEACOPP[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	1250	*1250*	
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*	

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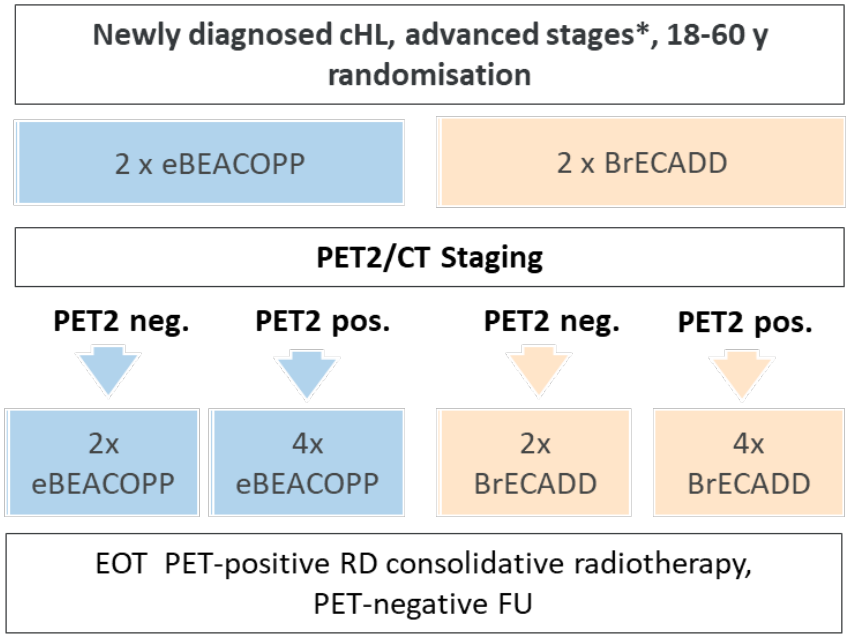
BrECADD, brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; eBEACOPP, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone

1. Diehl V, et al. N Engl J Med 2003;348:2386–95.

GHSG HD21 study design and primary endpoint



* Includes stage IIB with RF LMM or ED, and stage II and IV

Co-primary endpoint:

1. *superiority* for treatment related morbidity AND
2. *non-inferiority* for efficacy

1. *superiority* for treatment related morbidity (TRMB)

- Acute non-hematological organ toxicity of CTCAE grade 3 or 4
- Acute hematological toxicity: grade 4 anemia, grade 4 thrombocytopenia, and grade 4 infections
- during primary chemotherapy up to 12m

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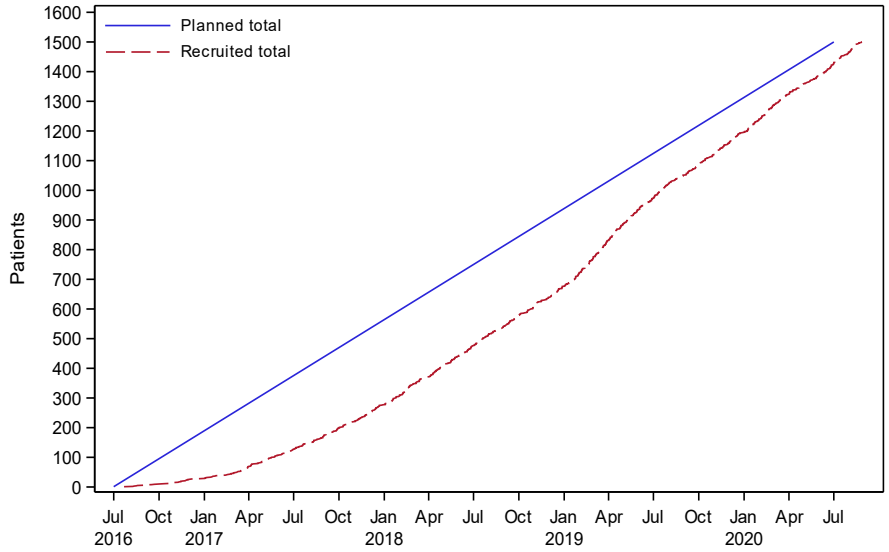
GHSG 21 consort diagram

1,500 patients from 9 countries and 233 trial sites between July 2016 and August 2020



TRMB analysis set

	BEACOPP N=749	Random. N=1500	**BrECADD N=751**	
excluded N=17	**ITT-TRMB N=732**	ITT-TRMB N=1470	**ITT-TRMB N=738**	excluded N=13

PFS analysis set

	eBEACOPP N=749	Random. N=1500	**BrECADD N=751**	
Excluded N=9	**ITT-PFS N=740**	ITT-PFS N=1482	**ITT-PFS N=742**	Excluded N=9

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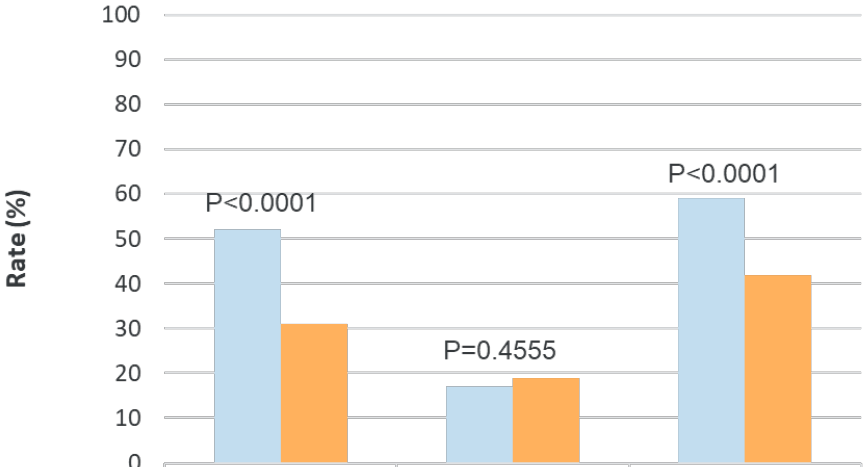
GHSG HD21 demographics and patient characteristics (ITT-PFS)

ITT-PFS Stratification factors for randomization	eBEACOPP N=740	BrECADD N=742
	N [%]	NN [%]
Location of recruitment		
Europe	682 **(92)**	684 **(92)**
AU, NZ	58 **(8)**	58 **(8)**
Sex female	326 **(44)**	330 **(44)**
male	414 **(56)**	412 **(56)**
Age < 45	577 **(78)**	587 **(79)**
>= 45	163 **(22)**	155 **(21)**
IPS < 3	399 **(54)**	391 **(53)**
>= 3	341 **(46)**	351 **(47)**

eBEACOPP and BrECADD cohorts were also well balanced for:

- Median age: 34 y [18-61] vs 34 y [18-61]
- ECOG PS 0: 70% vs 68%
- B-Symptoms: 67% vs 68%
- Ann-Arbor stage: IIB 16% and III/IV 84% each
- Histology: 48% vs 53% with subtype nodular sclerosis

GHSG HD21 primary safety endpoint TRMB analyses results



	Anemia thrombocytopenia or infection Grade 4 or higher	Organtoxicity Grade 3 or higher	TRMB
BEACOPP (%)	52	17	59
BrECADD (%)	31	19	42

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

ITT-analysis of „explicitly treatment related“ TRMB*°, C-Rel-Risk of BrECADD = **0.71**; 95%-CI = **0.64 – 0.80**; p **< 0.0001**

ITT-analysis of TRMB°
C-Rel-Risk of BrECADD =
0.72; 95%-CI = **0.65 – 0.79;** p **< 0.0001**

*Events excluded if not at least „possibly related“ to study treatment (local investigator)
° TRMB-Incidence: ITT-TRMB: 50.5%; ITT-TRMB2: 48.4%; PP-TRMB: 50.8%

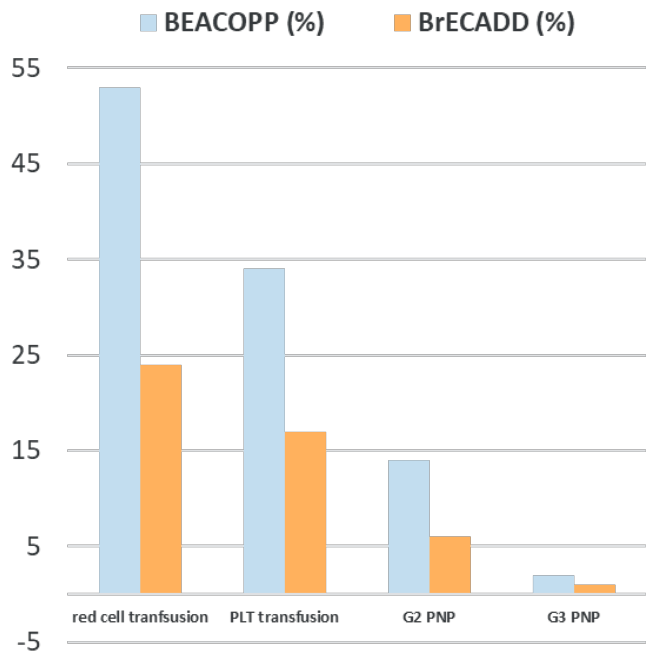
GHSG HD21 clinical implications of observed differences

Toxicity	eBEACOPP (%)	BrECADD (%)
red cell transfusion*	53	24
platelet transfusion*	34	17

	eBEACOPP (%)	BrECADD (%)
Sensory PNP		
All grades	49	38
Grade 2	14	6
Grade 3	2	1

	eBEACOPP (%)	BrECADD (%)
Treatment related mortality	< 1%	0%

*pts with at least one transfusion



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GHSG HD21 gonadal dysfunction determined by FSH (U/l)

female patients (18-39) per arm

	BEACOPP (N=326)		BrECADD (N=331)	
	N	Mean	N	Mean
N (min FU12 m)	145	**27,2** U/l	149	**13,4** U/l

- FSH normal values (cycle dependent): 1,7 – 21,5 U/l
- FSH documented in: 58 % in BEACOPP and 57 % in BrECADD

male patients (18-49) per arm

	BEACOPP (N=418)		BrECADD (N=417)	
	N	Mean	N	Mean
N (min FU12 m)	189	**20,5** U/l	178	**11,9** U/l

- FSH normal values: FSH: 1.5 – 12.4 U/l
- FSH was documented in: 45 % in BEACOPP and 45 % in BrECADD

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GHSG HD21 TRMB of BrECADD versus eBEACOPP

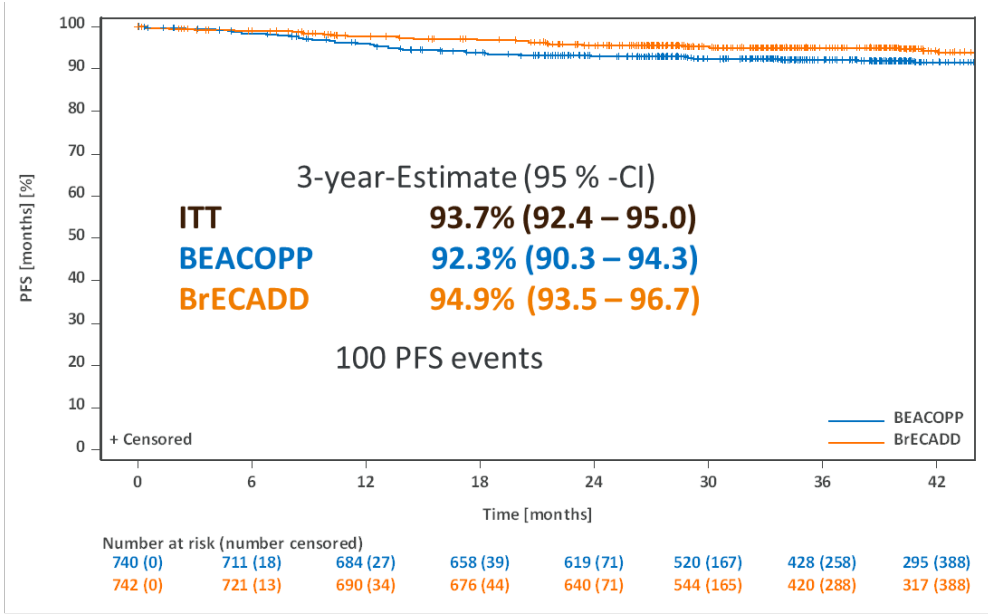
- The first part of the combined primary endpoint in HD21 shows a **significant reduction of acute treatment related morbidity with BrECADD compared to the SOC eBEACOPP**

- **The reduction in TRMB is clinically meaningful** with a relevant reduction of
  - transfusion frequency for red blood cells and platelets, and
  - peripheral neuropathy, and
  - FSH levels within the normal range indicating normal gonadal function

➢ Observed differences are significant and relevant, but need to be accompanied by non-inferiority in terms of efficacy

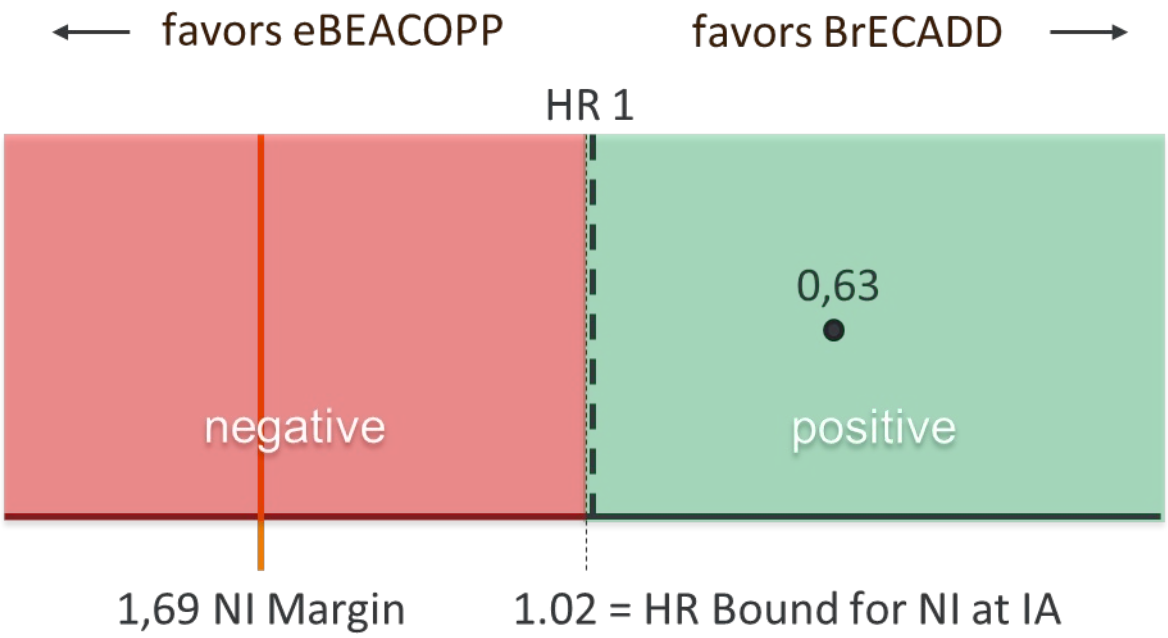
➢ Non-inferiority for efficacy (PFS, controlled by blinded central review) was assessed by interim analysis with estimated 36 months of median follow-up: a point estimate of Hazard Ratio bound < 1,02 would show statistical significance of non-inferiority with termination of the trial for efficacy

HD21 PFS events and Kaplan Meyer analysis



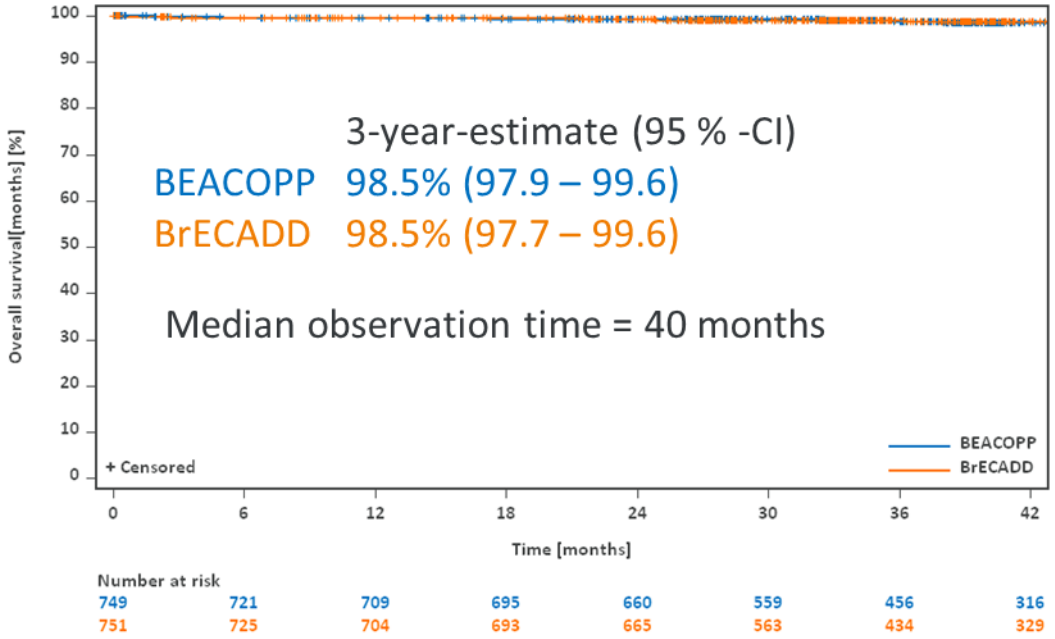
	eBEACOPP N=740		BrECADD N=742	
	n	%	n	%
Progression/Relapse	55	**7.4**	32	**4.3**
Progression	14	**1.9**	5	**0.7**
Early Relapse, FU <= 1 year	23	**3.1**	11	**1.5**
Late Relapse, FU > 1 year	18	2.4	16	2.2
Death without previous PRO or REL	6	0.9	7	0.9
PFS events, total	**61**	**8.4**	**39**	**5.3**

HD21 Test of non-inferiority



- HR bound of 1,02 is excluded and *non-inferiority of BrECADD thus fully established*

HD21 Overall Survival – ITT



mFU= **40 months** (95%-CI: 39-40) **Causes of death**	BEACOPP N=740 n	BrECADD N=742 n
Hodgkin lymphoma	**1**	**2**
TRM	**3**	**.**
sTRM (allogenic SCT)	1	.
Second neoplasia	1	.
Suicide	.	1
Other disease	2	6
Unclear	2	2
Total	**10**	**11**

HD21 summary and conclusions

- The relevant reduction in early PFS events with BrECADD resulted in *a 1-year PFS rate of 97.5* (99% CI 96.0-99.0), and a *3-years PFS for BrECADD of 94.9%* (99% CI 92.8% – 97.1%)
- This interim analysis at 40 months median follow-up **fully establishes non-inferiority of BrECADD compared to eBEACOPP with a HR of 0.63** (HR bound 1.02)

➢ These mature survival results demonstrate that individualized treatment with PET2-guided BrECADD is the most effective therapy currently available for AS-cHL. HD21 thus **sets a new benchmark for the primary cure rate in AS cHL.**

➢ **The excellent risk-benefit ratio observed for BrECADD in the HD21 trial defines a new SOC within the GHSG for adult patients with newly diagnosed AS cHL**

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Our patients, their friends and families

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