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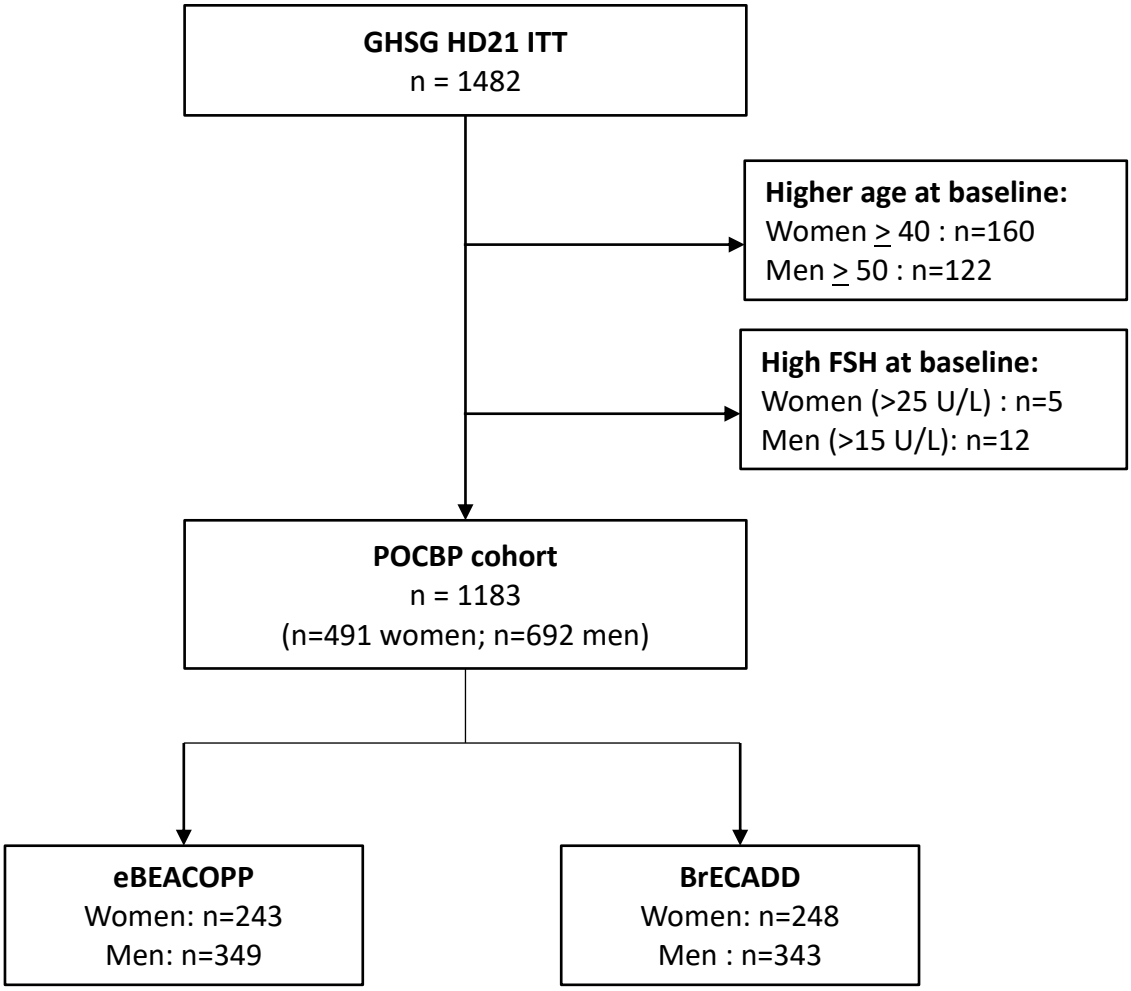
Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Ferdinandus J, Schneider G, Moccia A, et al. Fertility in patients with advanced-stage classic Hodgkin lymphoma treated with BrECADD versus eBEACOPP: a secondary analysis of the multicentre, randomised, parallel, open-label, phase 3 HD21 trial. *Lancet Oncol* 2025; published online July 10. https://doi.org/10.1016/S1470-2045(25)00262-1.

Gonadal function recovery and fertility in patients with advanced-stage classical Hodgkin Lymphoma: comparison of BrECADD and eBEACOPP in the phase 3 German Hodgkin Study Group HD21 trial – Supplementary Appendix

Trial profile



This CONSORT flow chart describes the POCBP cohort analyzed in this study. POCBP = person of childbearing potential, ITT = intention-to-treat, FSH = follicle-stimulating hormone, eBEACOPP = bleomycin, etoposide, doxorubicine, cyclophosphamide vincristine, procarbazine and prednisone, BrECADD = brentuximab vedotin, etoposide, cyclophosphamide, doxorubicine, dacarbazine, dexamethasone.

Supplementary Tables

	eBEACOPP (N=592)	BrECADD (n=591)	Total (n=1183)
Age – yr	28 (23-34)	28 (22-34)	28 (23-34)
Age categories			
18-19	66 (11%)	67 (11%)	133 (11%)
20-29	274 (46%)	271 (46%)	545 (46%)
30–39	184 (31%)	198 (34%)	382 (32%)
40–49	68 (12%)	55 (9%)	123 (10%)
Sex (%)			
Male	349 (59%)	343 (58%)	692 (58%)
Female	243 (41%)	248 (42%)	491 (42%)
Ann Arbor stage *			
IIB	99/591 (17%)	101 (17%)	200/1182 (17%)
IIIA	97/591 (16%)	99 (17%)	196/1182 (17%)
IIIB	125/591 (21%)	129 (22%)	254/1182 (21%)
IVA	99/591 (17%)	85 (14%)	184/1182 (16%)
IVB	171/591 (29%)	177 (30%)	348/1182 (29%)
ECOG performance status *			
0	419/588 (71%)	409/588 (70%)	828/1176 (70%)
1	156/588 (27%)	172/588 (29%)	328/1176 (28%)
2	13/588 (2%)	7/588 (1%)	20/1176 (2%)
Risk factors*			
Large mediastinal mass	204/588 (35%)	224/588 (38%)	428/1176 (36%)
Extranodal involvement	143/588 (24%)	164/588 (28%)	307/1176 (26%)
Involvement of 3 or more nodal areas	523/588 (89%)	528/588 (90%)	1051/1176 (89%)
High erythrocyte sedimentation rate	378/568 (67%)	384/564 (68%)	762/1132 (67%)
International Prognostic Score			
0–1	155 (26%)	175 (30%)	330 (28%)
2–3	316 (53%)	313 (53%)	629 (53%)
4–7	121 (20%)	103 (17%)	224 (19%)

Supplemental Table S1: Clinical characteristics of the patients in the POCB cohort Data are n (%), n/N (%), or median (inter quartile range). BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone. eBEACOPP=escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone. ECOG=Eastern Cooperative Oncology Group. POCBP= Patient of childbearing potential. *Data not available for all randomised patients.

	Information missing		Private practice		Hospital		University Hospital		Total	
Total	Female (n=6)	Male (n=5)	Female (n=34)	Male (n=47)	Female (n=226)	Male (n=342)	Female (n=225)	Male (n=298)	Female (n=491)	Male (n=692)
Cryopreservation done	5 (83%)	5 (100%)	10 (29%)	21 (45%)	83 (37%)	185 (54%)	107 (48%)	184 (62%)	205 (42%)	395 (57%)
European countries	Female (n=6)	Male (n=5)	Female (n=34)	Male (n=47)	Female (n=182)	Male (n=284)	Female (n=225)	Male (n=298)	Female (n=447)	Male (n=634)
Cryopreservation done	5 (83%)	5 (100%)	10 (29%)	21 (45%)	63 (35%)	185 (54%)	107 (48%)	184 (62%)	185 (41%)	364 (57%)
Non-European countries	Female (n=0)	Male (n=0)	Female (n=0)	Male (n=0)	Female (n=44)	Male (n=58)	Female (n=0)	Male (n=0)	Female (n=44)	Male (n=58)
Cryopreservation done	0	0	0	0	20 (46%)	31 (53%)	0		20 (46%)	31 (53%)

Data are n (%). POCBP= Patient of childbearing potential. eBEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine in escalated doses. BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone.

Supplemental Table S2: Use of cryopreservation in POCBP cohort stratified by type of treatment center and country

		Female patients (n=491)		Male patients (n=692)	
		eBEACOPP (n=243)	BrECADD (n=248)	eBEACOPP (n=349)	BrECADD (n=343)
Missing FSH values		72 (30)	72 (29)	130 (37)	142 (41)
	<30y	50/158 (32)	39/157 (25)	70/182 (38)	81/181 (45)
	>30y	22/58 (38)	33/91 (36)	60/167 (36)	61/162 (38)
	4 cycles	41/148 (28)	44/151 (29)	73/196 (37)	78/199 (40)
	6 cycles	22/85 (26)	25/90 (28)	53/147 (36)	54/130 (42)
	Neither 4 nor 6 cycles	9/10 (90)	3/7 (43)	4/6 (67)	10/14 (70)
	GnRH used	44/149 (30)	45/151 (30)		
	GnRH not used	14/56 (25)	15/64 (23)		
	No information on GnRH	14/38 (37)	12/33 (36)		

Data are n/N (%) FSH = follicle-stimulating hormone. GnRH = contraceptive measures including gonadotropin-releasing hormone analogues..eBEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine in escalated doses. BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone.

Supplemental Table S3: Patients without available FSH values.

	Female (N=491)				Male (N=692)			
	eBEACOPP (n=243)		BrECADD (n=248)		eBEACOPP (n=349)		BrECADD (n=343)	
	N (%)	Mean (SD)	N (%)	Mean (SD)	N (%)	Mean (SD)	N (%)	Mean (SD)
Screening	*132 (54)*	5·2 (4·1)	*134 (54)*	4.7 (3.7)	183 (52)	4·9 (2·7)	176 (51)	4.8 (2.6)
Restaging	*97 (40)*	23·9 (32·3)	*77 (31)*	25·7 (37·4)	139 (40)	22·7 (9·8)	124 (36)	19·1 (8·3)
FU 6 months	*23 (10)*	45·7 (36·5)	*21 (9)*	23·1 (25·5)	19 (5)	25·0 (15·3)	24 (7)	19·5 (7·6)
FU 12 months	*113 (47)*	29·9 (37·7)	*114 (46)*	11·3 (20·4)	126 (36)	20·2 (9·0)	126 (37)	14·1 (9·0)
FU 18 months	*42 (17)*	28·6 (35·9)	*53 (21)*	16·5 (30·1)	63 (18)	21·0 (13·7)	57 (17)	12·3 (8·4)
FU 24 months	*112 (46)*	29·8 (39·8)	*94 (38)*	14·1 (29·5)	120 (34)	18·2 (8·6)	119 (35)	8·6 (7·7)
FU 30 months	*43 (18)*	23·4 (35·0)	*51 (21)*	11·7 (20·9)	58 (17)	18·6 (9·1)	47 (14)	7·3 (6·8)
FU 36 months	*43 (18)*	25·0 (31·7)	*47 (19)*	12·0 (15·5)	42 (12)	19·5 (10·1)	42 (12)	8·9 (8·7)

Data are n (%), or mean (standard deviation). eBEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine in escalated doses. BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone. POCBP= Patient of childbearing potential. FSH = follicle-stimulating hormone. Screening = baseline assessment, Restaging = At first response assessment after completion of chemotherapy, FU=follow-up starting from end of treatment

Supplemental Table 4: Mean FSH per timepoint POCBP cohort (%)

	eBEACOPP		BrECADD		HR (95% CI)
	N	4-year recovery % (95% CI)	N	4-year recovery % (95% CI)	
Female patients	**171**	**73·3 (66·9-80·4)**	**176**	**95·3 (92·0-98·8)**	**1·69 (1·34-2·14)**
4 cycles	107	79·0 (71·5-87·3)	107	97·5 (94·0-100·0)	1·64 (1·23-2·19)
6 cycles	63	63·5 (52·5-76·8)	65	92·6 (86·0-99·8)	1·89 (1·25-2·83)
<30 years	108	88·9 (83·0-95·2)	118	99·2 (97·1-100·0)	1·25 (0·96-1·64)
>30 years	63	46·4 (35·4-60·8)	58	86·2 (77·5-95·9)	2·92 (1·84-4·65)
GnRH used*	105	76·2 (68·4-84·9)	106	96·0 (91·8-100·0)	1·59 (1·19-2·13)
GnRH not used*	42	69·0 (56·1-85·0)	49	95·9 (89·8-100·0)	2·13 (1·31-3·44)
Male patients	**219**	**39·7 (33·6-46·9)**	**201**	**86·0 (81·1-91·1)**	**3·31 (2·53-4·33)**
4 cycles	123	41·9 (33·8-51·9)	121	92·0 (86·8-97·5)	3·60 (2·53-5·12)
6 cycles	94	37·9 (29·2-49·4)	76	75·1 (65·8-85·7)	2·75 (1·80-4·21)
<30 years	112	50·8 (42·2-61·2)	100	92·3 (86·9-98·0)	2·64 (1·88-3·70)
>30 years	107	28·0 (20·5-38·2)	101	78·7 (70·9-87·4)	4·56 (2·95-7·05)

*contraceptive measures including GnRH analogues. FSH = follicle-stimulating hormone. GnRH = Gonadotropin-releasing hormone.CI=confidence interval. HR=Hazard ratio

Supplemental Table S5: FSH recovery rates across relevant subgroups

Figure Ref.	Comparison	Population/Subgroup	HR from CIF (95% CI)	Adjusted HR from Cox-Regression (95% CI)
Hazard ratios for gonadal function recovery				
Figure 1A	BrECADD vs eBEACOPP	All Women	1·69 (1·34–2·14)	3·58 (2·17-5·92)
Figure 1B	BrECADD vs eBEACOPP	All Men	3·28 (2·51–4·30)	4·64 (3·04-7·08)
Figure 2A	BrECADD vs eBEACOPP	Women ≥ 30 years old	2·92 (1·84–4·65)	
Figure 2B	BrECADD vs eBEACOPP	Men ≥ 30 years old	4·56 (2·95–7·05)	
Figure 3A	BrECADD vs eBEACOPP	Women, 6 Cycles	1·89 (1·25–2·83)	
Figure 3B	BrECADD vs eBEACOPP	Men, 4 Cycles	3·60 (2·53–5·12)	
		Interaction term: Treatment x Age (Women)		0·28 (0·17-0·46)
		Interaction term: Treatment x Age (Men)		0·53 (0·31-0·91)
Hazard ratios for parenthood				
Figure 4A	BrECADD vs eBEACOPP	All Women	1·17 (0·72-1·89)	
Figure 4B	BrECADD vs eBEACOPP	All Men	2·46 (1·18-5·12)	

Abbreviations: HR = Hazard Ratio; CI = Confidence Interval; CIF = Cumulative Incidence Function. Endpoints include FSH recovery and live birth. Unadjusted HRs are based on CIF models estimated using Efron method. Adjusted HRs are from multivariable Cox proportional hazards models including treatment arm, age, and number of cycles.

Supplemental Table S6: Hazard ratios for gonadal function recovery (unadjusted HR from CIF and adjusted HR from Cox regression analysis) and parenthood

		Second year of FU		Third year of FU		Fourth year of FU	
Age group (y)	Birth rate per 1000 women in Germany in 2022*	Women	Expected births	Women	Expected births	Women in FU	Expected births
18	6.1	0	0.0	0	0.0	0	0.0
19	11.1	11	0.1	0	0.0	0	0.0
20	16.1	37	0.6	11	0.2	0	0.0
21	21.7	28	0.6	36	0.8	8	0.2
22	26.7	21	0.6	26	0.7	31	0.8
23	32.2	27	0.9	20	0.6	23	0.7
24	39.7	26	1.0	27	1.1	19	0.8
25	49	29	1.4	26	1.3	24	1.2
26	60.7	30	1.8	28	1.7	26	1.6
27	70	22	1.5	29	2.0	23	1.6
28	82.1	21	1.7	20	1.6	29	2.4
29	93.2	28	2.6	21	2.0	19	1.8
30	104.2	18	1.9	26	2.7	17	1.8
31	109.2	21	2.3	18	2.0	23	2.5
32	110.5	15	1.7	21	2.3	15	1.7
33	104.5	30	3.1	15	1.6	16	1.7
34	98.5	14	1.4	28	2.8	13	1.3
35	89.2	12	1.1	14	1.2	22	2.0
36	78	19	1.5	12	0.9	12	0.9
37	64.9	12	0.8	19	1.2	10	0.6
38	52.6	22	1.2	11	0.6	18	0.9
39	41.9	16	0.7	22	0.9	10	0.4
40	32	7	0.2	16	0.5	21	0.7
41	22.5	6	0.1	7	0.2	16	0.4
42	14.1	0	0.0	6	0.1	7	0.1
43	8.6	0	0.0	0	0.0	6	0.1
	Total:	472	28.8	459	29.0	408	26.0
	Expected Birth rate	6.1		6.3		6.4	

Supplemental Table S7: Comparison of birth rates in POCB cohort of HD21 with German populational data. FU = Follow-up *data obtained from https://www-genesis.destatis.de/genesis/online?sequenz=tabelleErgebnis&selectionname=12612-0008#abreadcrumb (accessed on 11 of July 2024)

	N	BrECADD	N	eBEACOPP	N	Total
First year of FU	248	0	241	0	489	0
Second year of FU	240	10 (4)	232	4 (2)	472	14 (3)
Third year of FU	232	11 (5)	227	13 (6)	459	24 (5)
Fourth year of FU	207	11 (5)	201	12 (6)	408	23 (6)

Data are n (%). ITT= intention-to-treat. EOT= end of therapy. FU=follow-up. only patients with EOT date included. eBEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine in escalated doses. BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone.

Supplemental Table S8: Live birth rates per year after EOT in the female ITT cohort of HD21 under 40 years of age

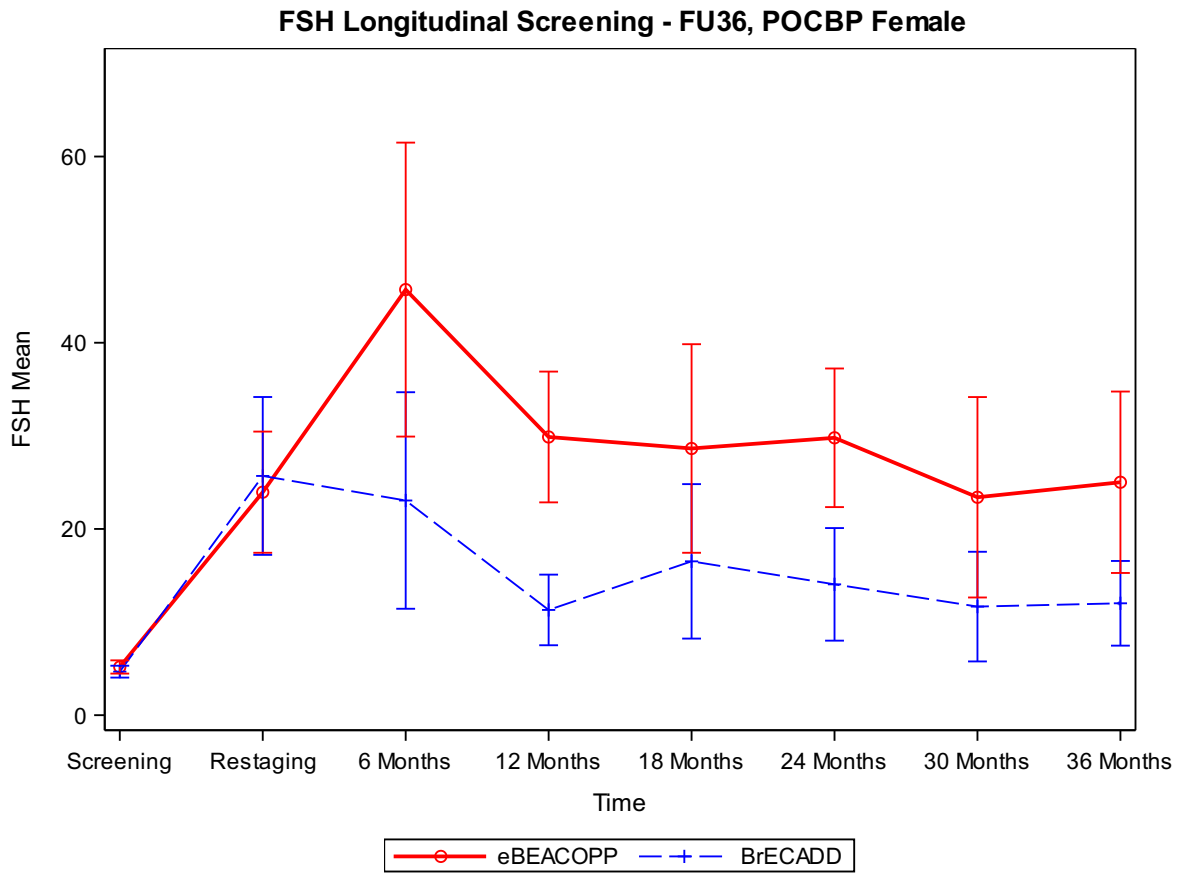
	N	BrECADD	N	eBEACOPP	N	Total
First year of FU	347	1 (<1)	355	2 (1)	702	3 (<1)
Second year of FU	335	4 (1)	339	2 (1)	674	6 (1)
Third year of FU	320	10 (3)	328	2 (1)	648	12 (2)
Fourth year of FU	276	7 (3)	279	4 (1)	555	11 (2)

Data are n (%). ITT= intention-to-treat. EOT= end of therapy. FU=follow-up. only patients with EOT date included eBEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine in escalated doses. BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone.

Supplemental Table S9: Live birth rates per year after EOT in the male ITT cohort of HD21 under 50 years of age

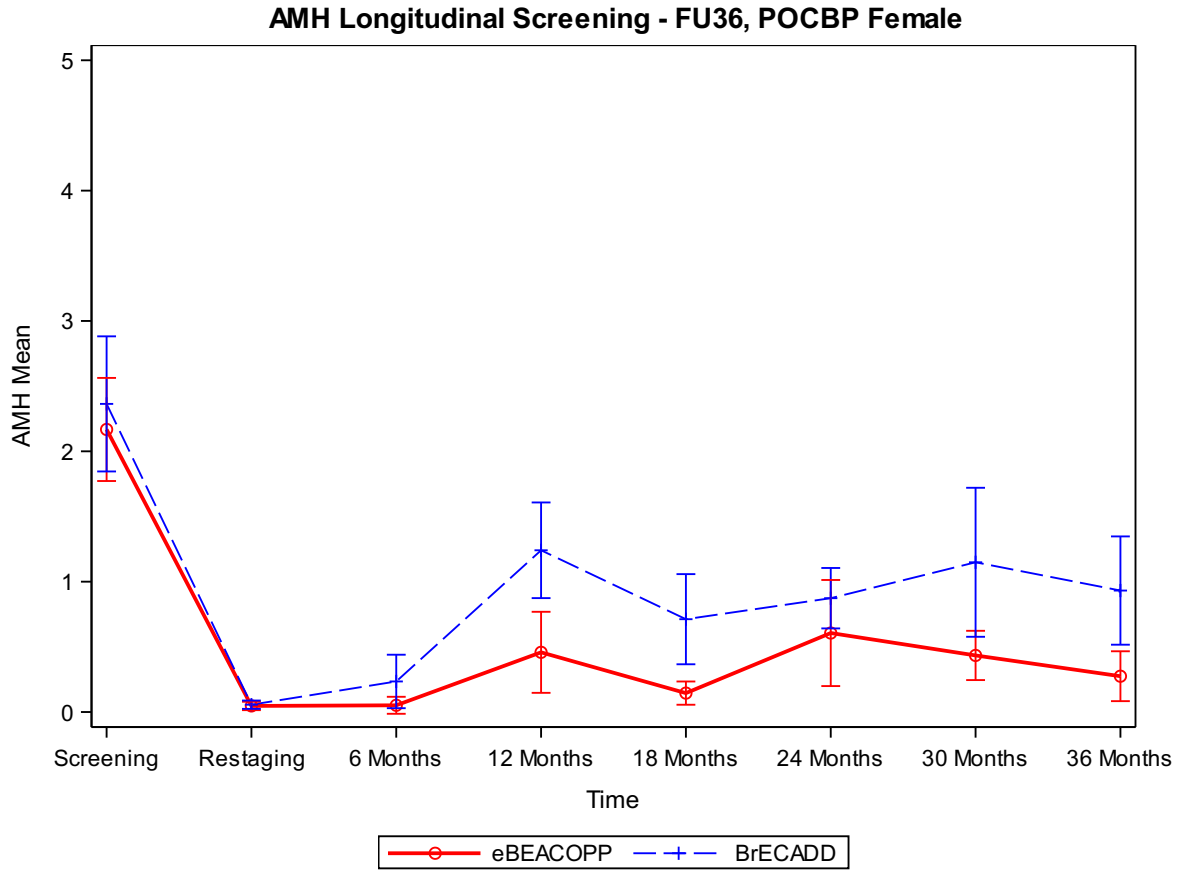
Supplementary Figures

Supplementary Figure S1: FSH mean values among female patients in the POCBP cohort over time



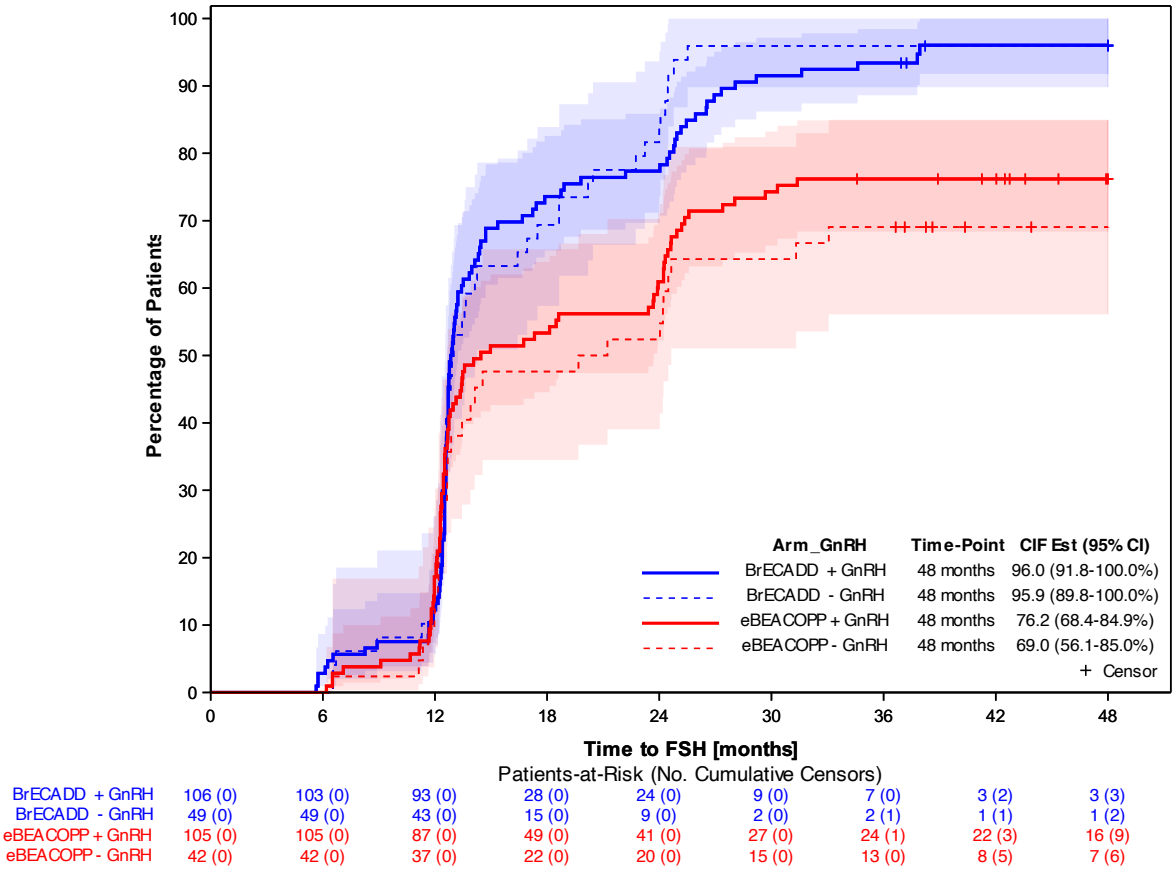
FSH = follicle stimulating hormone, POCBP = Patient of childbearing potential, eBEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine in escalated doses. BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone.

Supplementary Figure S2: AMH mean values among female patients in the POCBP cohort over time



AMH= anti-muellerian hormone. POCBP = Patient of childbearing potential, eBEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine in escalated doses. BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone.

Supplementary Figure S3: FSH-recovery in the POCBP cohort stratifed by contraceptive use (including GnRH-a)

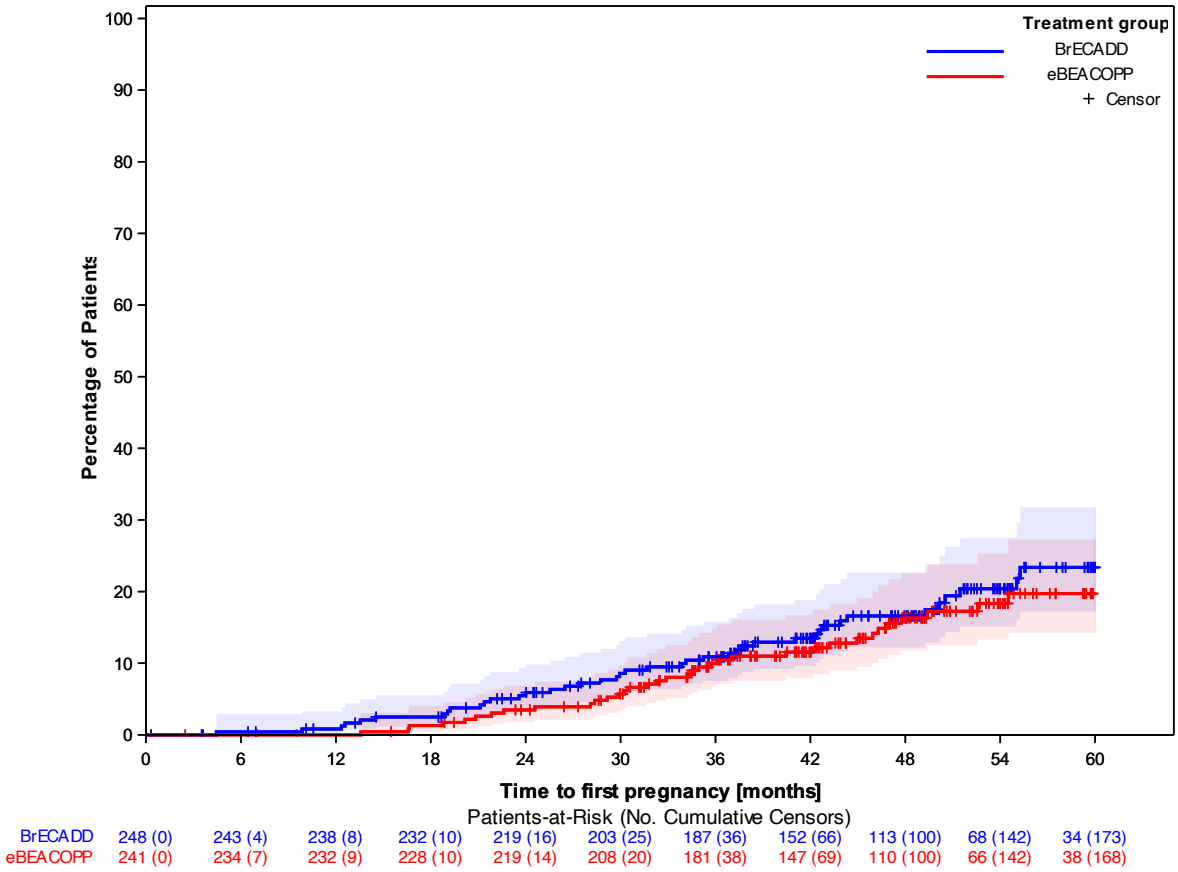


Patients-at-Risk (No. Cumulative Censors)

BrECADD + GnRH	106 (0)	103 (0)	93 (0)	28 (0)	24 (0)	9 (0)	7 (0)	3 (2)	3 (3)
BrECADD - GnRH	49 (0)	49 (0)	43 (0)	15 (0)	9 (0)	2 (0)	2 (1)	1 (1)	1 (2)
eBEACOPP + GnRH	105 (0)	105 (0)	87 (0)	49 (0)	41 (0)	27 (0)	24 (1)	22 (3)	16 (9)
eBEACOPP - GnRH	42 (0)	42 (0)	37 (0)	22 (0)	20 (0)	15 (0)	13 (0)	8 (5)	7 (6)

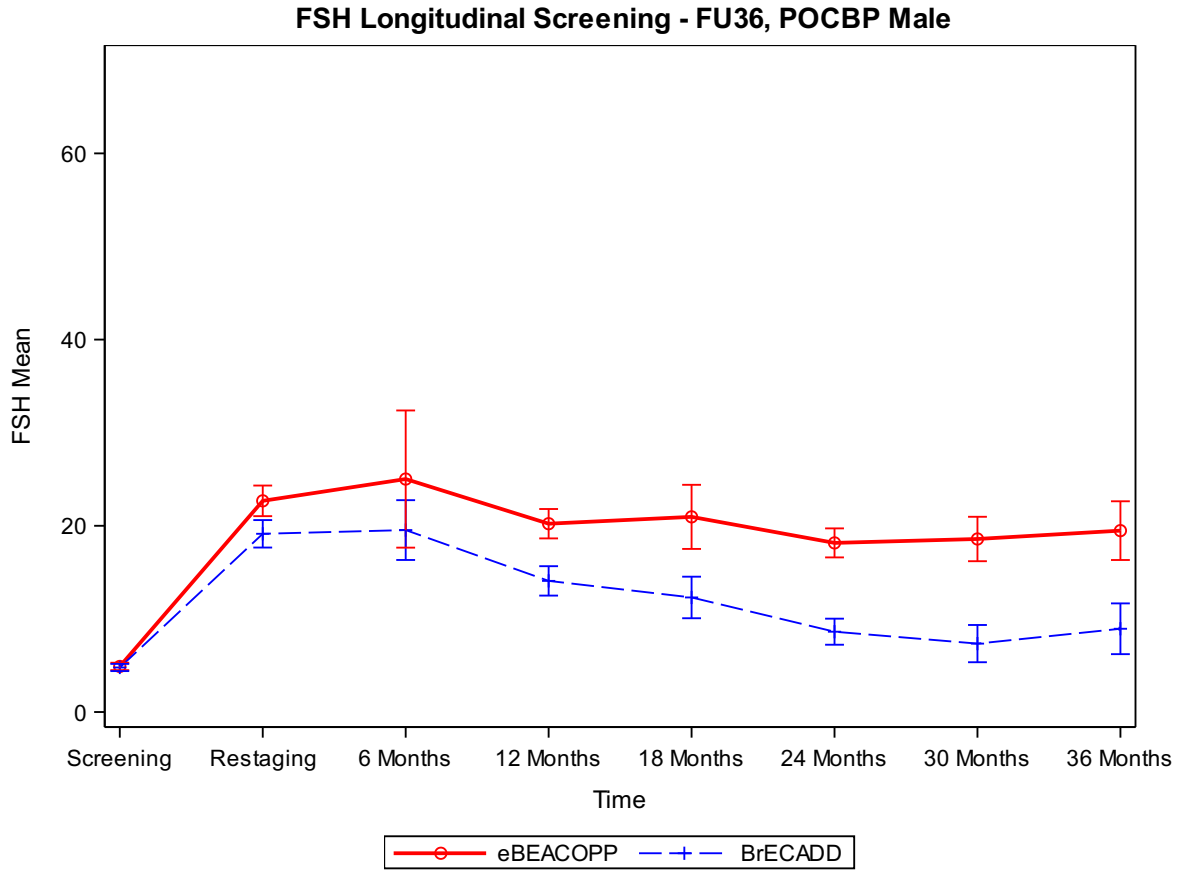
FSH = follicle-stimulating hormone. GnRH = contraceptive measures including gonadotropin-releasing hormone analogues. POCBP = Patient of childbearing potential, eBEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine in escalated doses. BrECADD = brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone.

Supplementary Figure S4: Cumulative incidence of first pregnancy after treatment among female patients in the ITT cohort of HD21 under 40 years of age



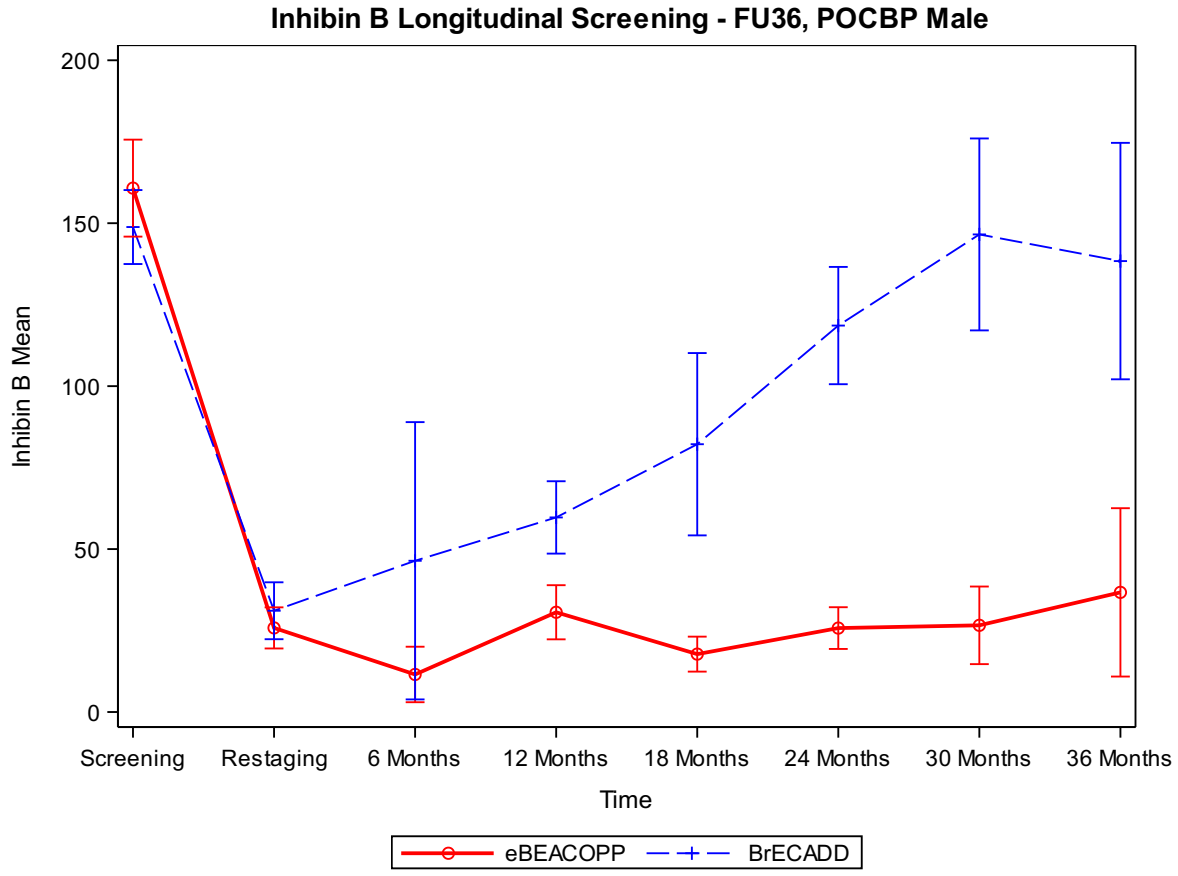
eBEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine in escalated doses. BrECADD = brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone.

Supplementary Figure S5: FSH mean values among male patients in the POCBP cohort over time



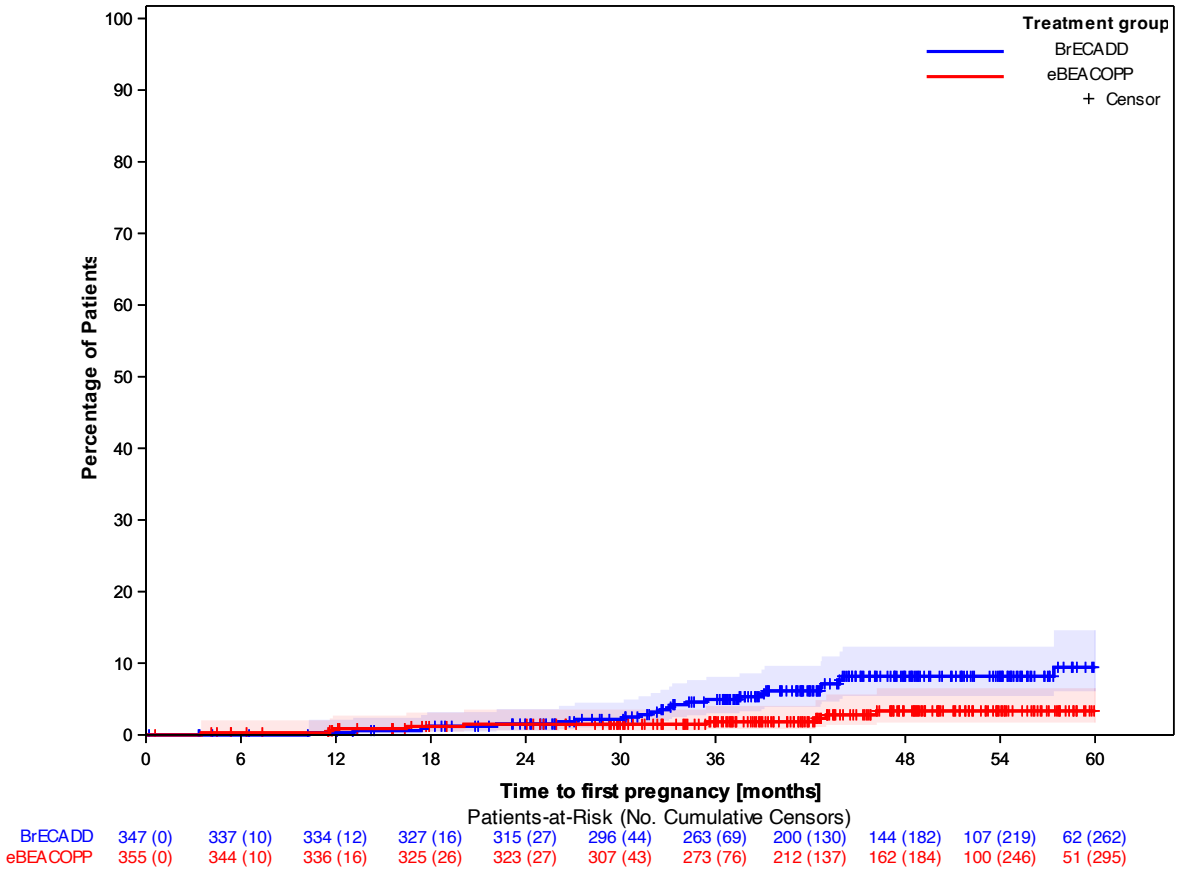
FSH = follicle stimulating hormone. POCBP = Patient of childbearing potential, eBEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine in escalated doses. BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone.

Supplementary Figure S6: Inhibin B mean values among male patients in the POCBP cohort over time



POCBP = Patient of childbearing potential, eBEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine in escalated doses. BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone.

Supplementary Figure S7: Cumulative incidence of first pregnancy after treatment among partners of male patients in the ITT cohort of HD21 under 50 years of age



eBEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine in escalated doses. BrECADD = brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone.

List of participating trial centres and patients enrolled in this study

Principle investigator	Country	Institution	Department	Patients enrolled
Prof Dr. med. Peter Borchmann	DE	Universitätsklinik Köln	Klinik I für Innere Medizin / Studienzentrum	46
Dr. med. Valdete Schaub	DE	Eberhard-Karls-Universität - Universitätsklinik Tübingen	GCP-Studienzentrale der Innere Medizin II	38
PD Dr. med. Andreas Hüttmann	DE	Universitätsklinik Essen	Klinik für Hämatologie / WTZ Ambulanz	21
PD Dr. med. Mathias Hänel	DE	Klinikum Chemnitz, Krankenhaus Küchwald	Klinik für Innere Medizin III / Studiensekretariat	19
Prim. Prof. Dr. Felix Keil	AT	Hanusch Krankenhaus Wien	3. Medizinische Abteilung (Hämatologie und Onkologie)	19
Prof. Dr. med. Urban Novak	CH	Inselspital, Universitätsspital Bern	Universitätsklinik für Medizinische Onkologie	18
Prof. Dr. med. Judith Dierlamm	DE	Universitätsklinikum Hamburg-Eppendorf	Onkologisches Zentrum, Abt. Hämatologie / Onkologie	17
Prim. Prof. Dr. Richard Greil	AT	Uniklinikum Salzburg, Landeskrankenhaus	Universitätsklinik für Innere Medizin III	16
Dr. med. Julia Meissner	DE	Universitätsklinikum Heidelberg	Medizinische Klinik und Poliklinik V	16
Prof. Dr. med. Martin Dreyling	DE	Klinikum Großhadern	Med. Klinik III für Hämatologie / Onkologie	16
Prof. Dr. med. Michaela Feuring-Buske	DE	Universitätsklinikum Ulm	Innere Abteilung III	16
Prof. Dr. Josée M. Zijlstra	NL	Amsterdam UMC - location VU University Medical Center	Dept. of Hematology	16
Prof. Dr. med. Bernd Hertenstein	DE	Klinikum Bremen Mitte gGmbH	Med. Klinik I, Abt. Hämatologie/ Onkologie	15
Prof. Dr. med. Dietger Niederwieser	DE	Universitätsklinik Leipzig	Medizinische Klinik II, Hämatologie	15
Dr. Pratush Giri	AU	Royal Adelaide Hospital	Haematology Clinical Trials	14
Prof. Dr. med. Christian Meyer zum Büschenfelde	DE	Vincentius-Diakonissen-Kliniken gAG	Medizinische Klinik, Abt. II Hämatologie / Onkologie	14
Ellen Ritter	DE	Universitätsklinikum Jena	Hämatologie u. Internistische Onkologie	14
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Deutsche Hodgkin Studiengruppe

GHSG
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Clinical trials for adults

HD21 for advanced stages

(Recruitment for randomized study: 13th January 2016 – 21st August 2021)

Statistical Analysis Plan on

the analysis of fertility

in the HD21 trial

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Statistical analysis plan

on the analysis of fertility

Version 1.0

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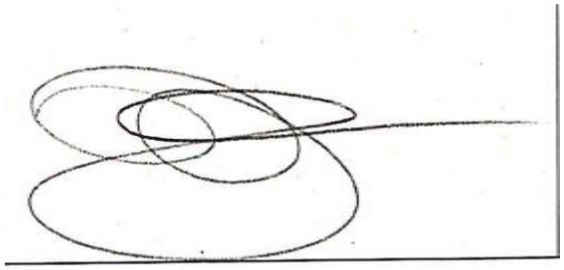
Prof. P. Borchmann		05 MAR 2024

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1. Overview

Gonadal function and fertility are important complementary data to the clinical results of the HD21 trial. In the prospective, multicenter, randomized and open-label trial, patients were randomly assigned to PET-guided 4 or 6 cycles of either escalated BEACOPP (eBEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) in the standard group or BrECADD (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone) in the experimental group. Patients with a complete metabolic response after 2 cycles (PET-2 negative) received 4 cycles of chemotherapy, PET-2 positive patients received 6 cycles. In both groups, patients with PET positive residual tumor masses at the end of chemotherapy according to PET-4 or PET-6 are subjected to local irradiation with 30 Gy. Recording late effects, especially toxicities that impair fertility is also an important aim of this trial.

Survivors of Hodgkin lymphoma have a decreased parenthood rate after chemotherapy and fertility can be severely affected for many years. For this reason gonadal function, fertility and parenthood are analyzed within the HD21 trial. Further information about the HD21 study, in particular the randomization and treatment procedures, can be found in the protocol and the main statistical analysis plan.

2. Endpoints

The primary endpoints of the fertility analysis will be measured by follicle-stimulating hormone (FSH) serum level. Impairment of gonadal function will be defined as a follicle-stimulating hormone (FSH) serum level >25 U/L in women and >15 U/L in men. Time to recovery is the time from the end of treatment until the first measurement of an FSH level below the aforementioned threshold or, if this is not reached, censored until the last FSH measurement. Gonadal function assessment is strongly recommended for patients not older than 60 years during follow-up at 12 months, 24 months and 60 months after end of chemotherapy.

To examine pregnancies and births, both are collected during the trial and the follow-up examination. The time to first parenthood after therapy is defined as the time from the end of treatment to the first birth or, if this has not occurred, to the last available date from the end date of progression-free survival, the date of last follow-up or the date of death. Desire to have children will be assessed on the HRQoL questionnaires.

This applies exclusively to German speaking patients. The analysis strategy for HRQoL data is dealt with in a separate SAP.

3. Populations for analysis

The patient sets used for the analyses of fertility endpoints are listed below.

The **intention-to-treat (ITT) analysis set** includes all patients from the FAS who have not withdrawn consent before start of randomized study therapy and whose initial diagnosis of HL has not been revoked by the reference pathology panel. Patients originally considered as having cHL but considered NLPHL after reference pathology review remain in the ITT set.

The **pregnancy analysis set** consists of all ITT set patients with the restriction of women under 40 and men under 50 years of age at enrollment.

The **patients of childbearing potential (POCBP)** cohort is an analysis set including all ITT set patients with the restriction of female patients below 40 years of age at enrollment with baseline FSH ≤ 25 U/L and male patients below 50 years of age at enrollment with baseline FSH ≤ 15 U/L.

Unless otherwise specified, analyses will be performed according to the POCBP analysis set with available data regarding the outcome analysed.

4. Statistical methods

For continuous variables, descriptive statistics will include the following: the number of patients reflected in the calculation (n), mean, median, standard deviation, minimum, and maximum. For categorical or ordinal data, frequencies and percentages will be displayed for each category.

Comparisons between the standard eBEACOPP arm and the experimental BrECADD arm will be performed seperately for women and men of the POCBP cohort, unless specified otherwise. For the analysis of pregnancies and childbirths the pregnancy ananlysis set will be used. Descriptive subgroup analyses of the FSH recovery endpoint will include presentation of effect by age group (<30 vs. ≥ 30 years), PET-2 result and additionally for female patients by use of contraceptive measures including GnRH analogues. Unless otherwise specified, there will be no imputation of any missing data within this trial. The number of available data will be reported for each

variable. The level of significance will be set to alpha < 0.05 without any correction for multiple testing.

Gonadal function recovery

The cumulative incidence of recovery of FSH will be analysed per treatment group according to Kaplan-Meier. Hazard ratios and corresponding 95% confidence intervals (CI) will be reported.

If sufficient measurements are available, further sexual hormones will be compared by treatment group. Means and corresponding 95% CIs will be calculated for each time point of measurement.

Pregnancies and childbirths

Frequencies of pregnancies and live births in the overall study, per treatment arm and per Follow-up year as well as the number of pregnancies achieved by use of cryopreserved material will be reported. The frequency of patients reporting at least one childbirth after treatment will be reported per treatment group and for patients with reported desire to have children. The cumulative incidence of first parenthood after therapy will be analysed per treatment group and sex according to Kaplan-Meier and compared by using Gray's test.

5. Variables for Analysis

Hormone measurements are captured in the eCRF events "Gonadal function" and "Pregnancy Report". All variables that were used for the analysis of the HD21 Trial and are also used in the analysis of the fertility are listed in main SAP (HD21_SAP_V1.3_2024_03_05). Variables that will be used in particular for the analysis of fertility are listed below and will be extracted from the specified item groups.

- Hormonal contraception (incl. GnRH-analogues)
- Hormone measurements taken
- FSH
- Anti-Müllerian hormone
- Inhibin B
- Date of birth/abortion

- Reason pregnancy ended
- Cryoconservate used