BrECADD/HD21 and beyond

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COIs

Employment, management position	–
Advisory/expert activity	Takeda Oncology, BMS, Roche, Amgen, Novartis, Miltenyi Biotech, Gilead, MSD, Incyte, Beigene
Ownership (shares, stocks, funds)	–
Patent, copyright, sales license	–
Honoraria	Takeda Oncology, Novartis, BMS, Roche, MSD, Celgene, Miltenyi Biotech, Gilead, Abbvie
Funding scientific research	Takeda Oncology, MSD, Incyte, Amgen
Other financial relationships	–
Intangible conflicts of interest	–

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FROM INTENSIFICATION TO INDIVIDUALISATION

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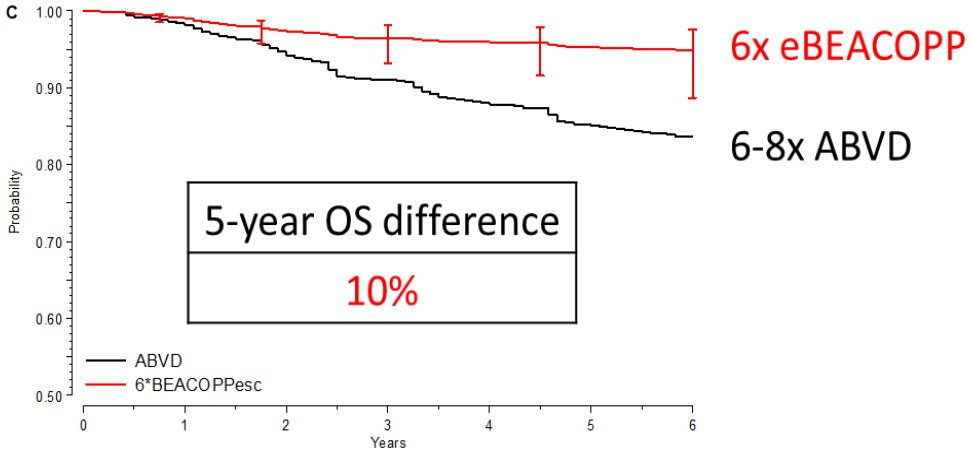
ABVD or BEACOPP? There is no reliable "*second shot*", but



Skoetz et al, Lancet Oncol, 2012

- Obvious OS benefit for eBEACOPP; however, about 60%-70% of the patients could have been primarily cured just with ABVD: those are "overtreated" with eBEACOPP.
- IPS can predict outcome with ABVD, but no longer with the eBEACOPP.

➢ **How can we de-escalate eBEACOPP?**

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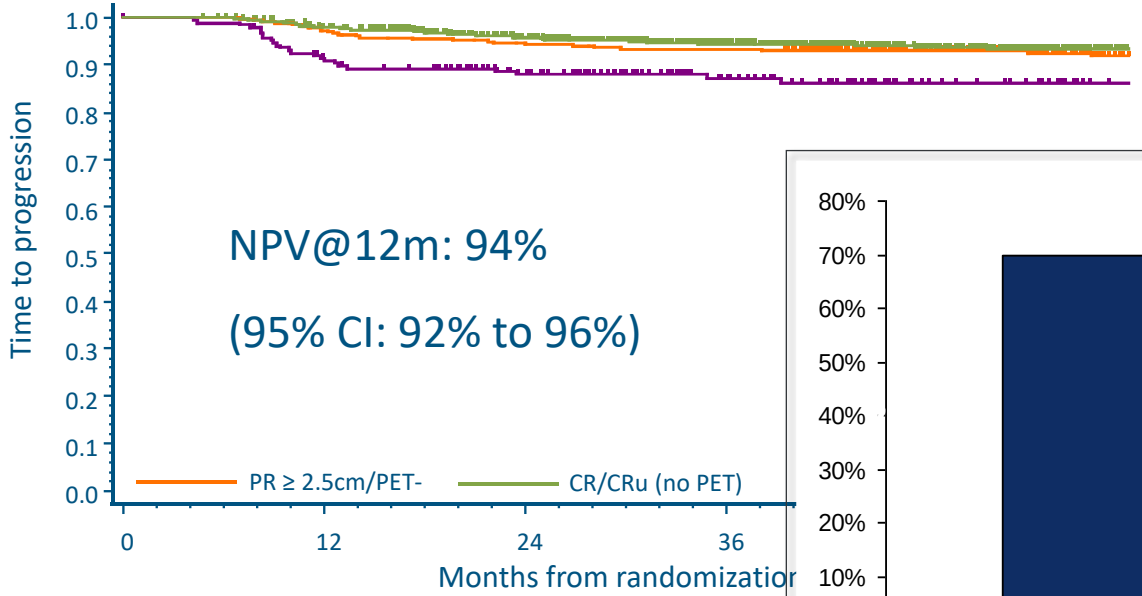
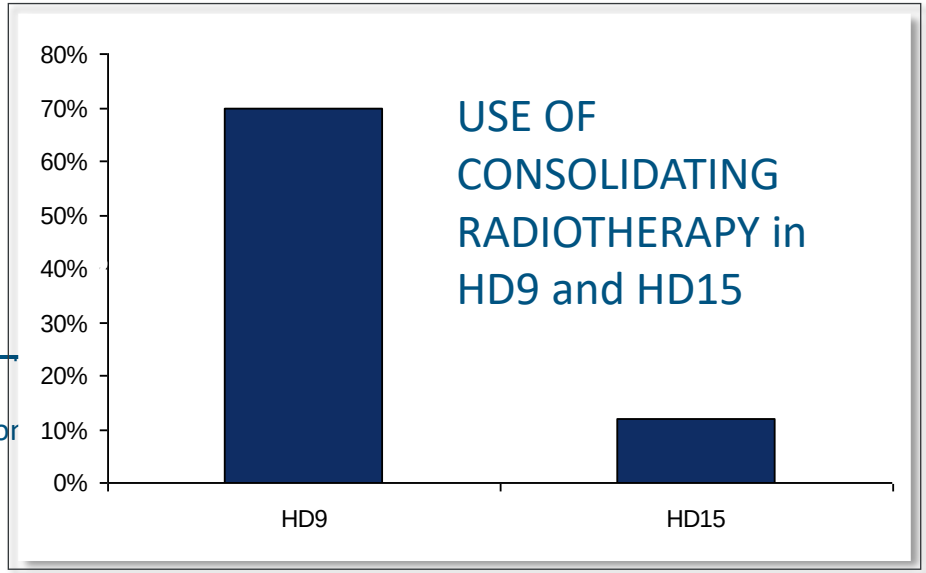
Metabolic response assessment: individualisation by PET-guided radiotherapy in HD15





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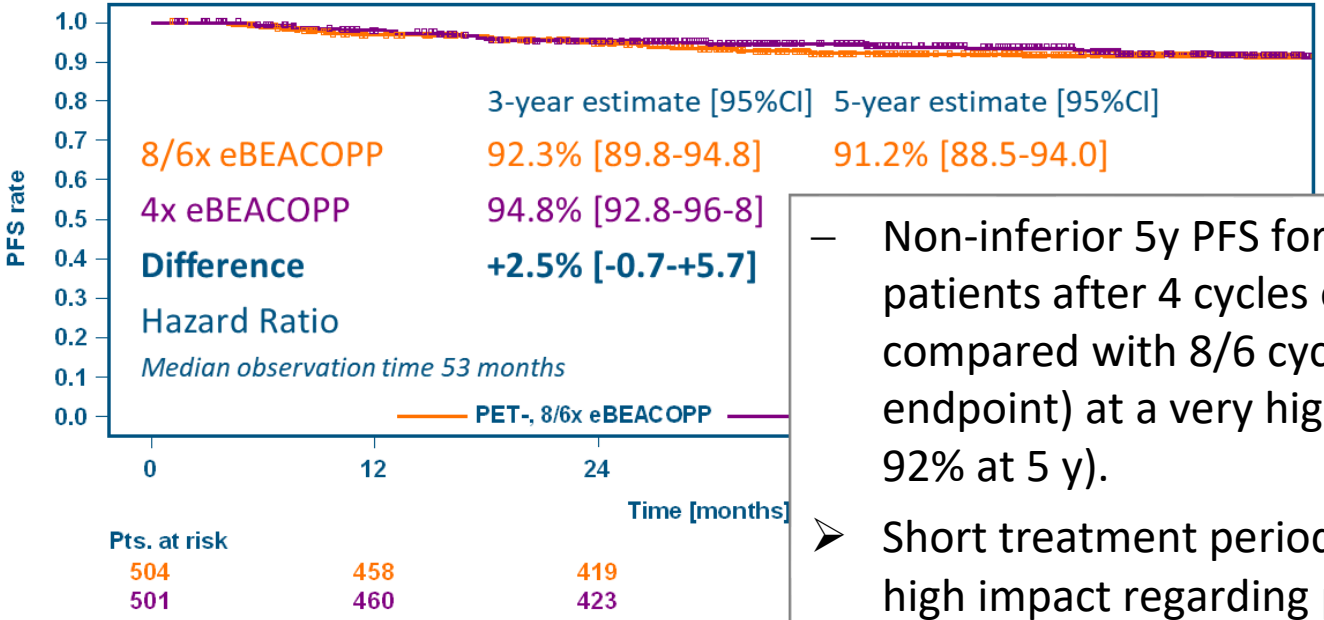
Engert et al, Lancet, , 2012

Early interim PET-guided individualised chemotherapy: GHSG HD18



- Non-inferior 5y PFS for PET-2-negative patients after 4 cycles of eBEACOPP compared with 8/6 cycles (primary endpoint) at a very high level (95% at 3y, 92% at 5 y).

➢ Short treatment period of 3 months with high impact regarding patients´ safety, PROs and social re-integration, but

➢ eBEACOPP, still.

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Borchmann et al, The Lancet, 2018

FROM BEACOPP TO BRECADD

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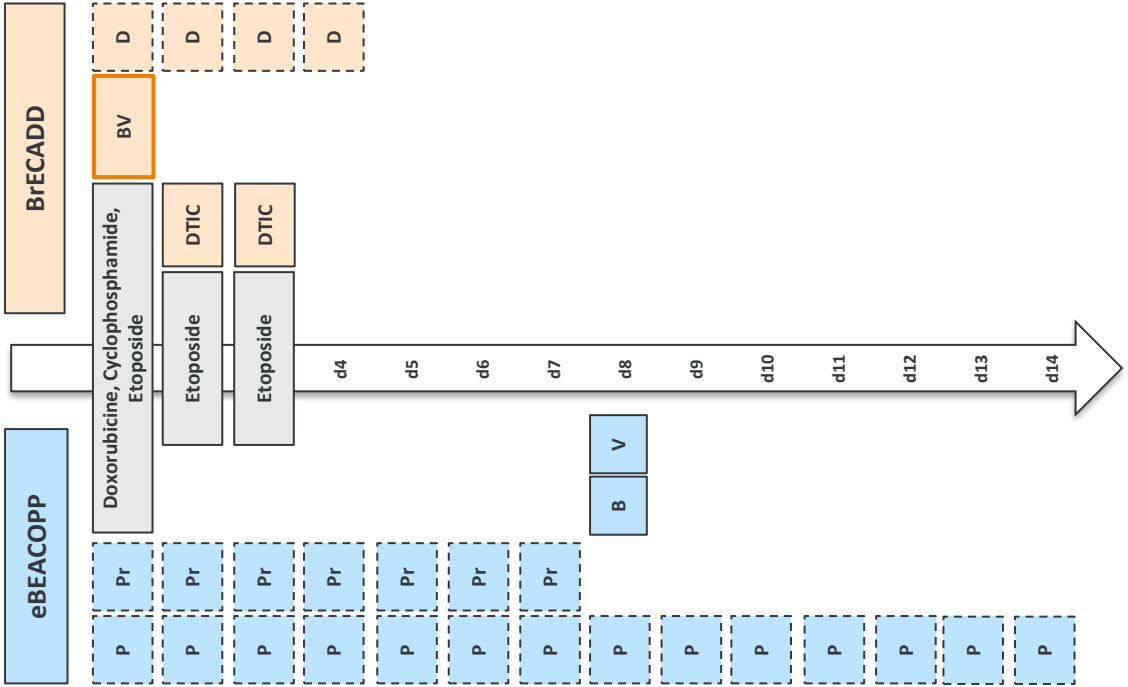
GHSG HD21: eBEACOPP optimization with Brentuximab vedotin



- The Kairos backbone **doxorubicin, cyclophosphamide, etoposide** was retained and *pre-defined dose de-escalation steps (DL 4, 3, 2, 1, BL) were identical in both groups*
- Introducing **Brentuximab Vedotin** (BV), **therefore omitting Bleomycin** (B, **pulmonary toxicity**) **and Vincristin** (V, **neuropathy**)
- Replacing **Procarbazine** (Pr) with the **less geno- and gonadotoxic Dacarbazine** (DTIC)
- Replacing 14 days of **Prednisone** (P) to 4 days of **Dexamethasone** (D)

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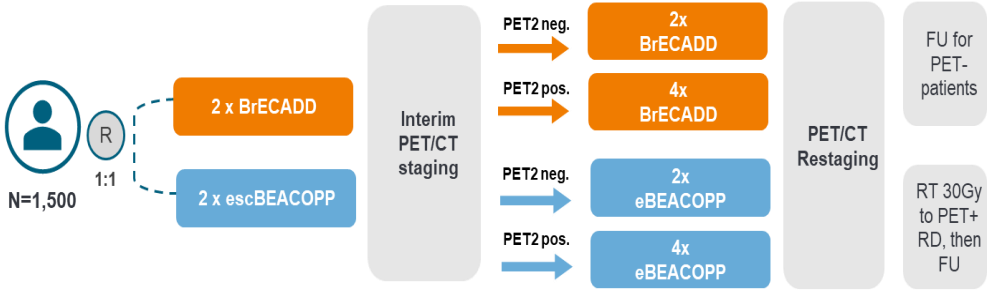
Borchmann et al., Lancet. 2024 Mar;35(3):276-284

GHSG HD21 study design and patient flow

HD21 is an international randomized, open-label, phase 3 study of BrECADD versus eBEACOPP in adult patients < 60 yo with previously untreated, AS-cHL



1482/1500 patients recruited in nine countries and 233 study sites are available for analysis

Co-primary objectives:

- Demonstrate **superior tolerability** defined by treatment-related morbidity (TRMB) with BrECADD.
- Demonstrate **non-inferior efficacy** of 4-6 x BrECADD compared with 4-6 x BEACOPP determined by PFS (NI margin 6%, HR to be excluded 1.69)

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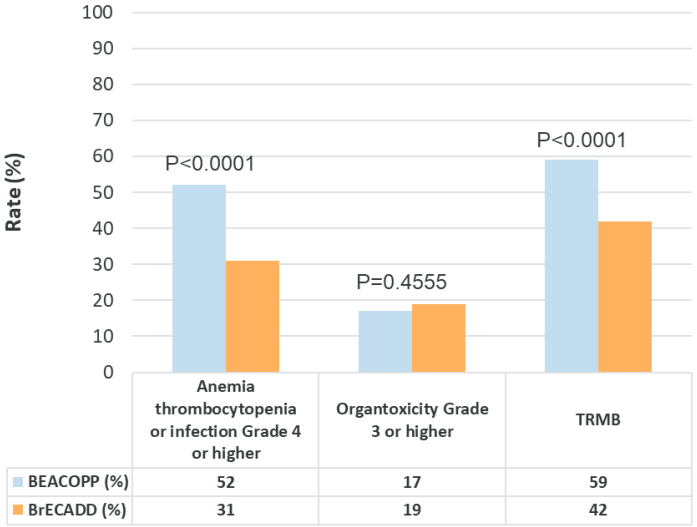
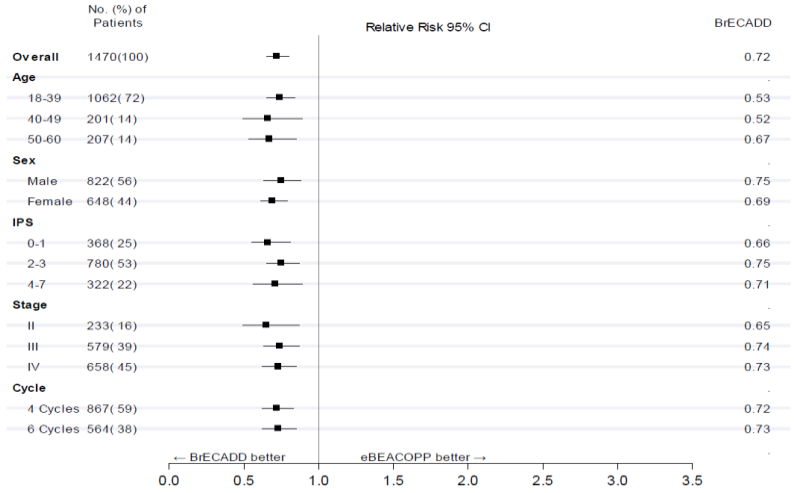
Borchmann et al., Lancet. 2024 Mar;35(3):276-284

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**



Relative risk for treatment-related morbidity in subgroups

GHSG HD21 clinical implications of lower TRMB

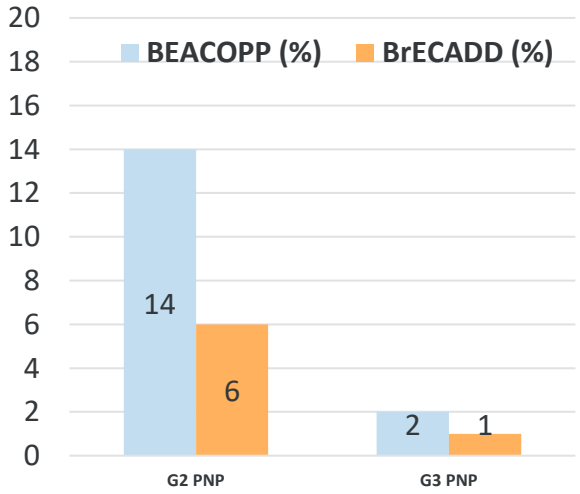
Transfusion frequencies

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

	Red blood cell transfusions		Platelet transfusions	
Total Number of Transfusions	eBEACOPP	BrECADD	eBEACOPP	BrECADD
	1670	**647**	**637**	**277**

*pts with at least one transfusion

Sensory polyneuropathy



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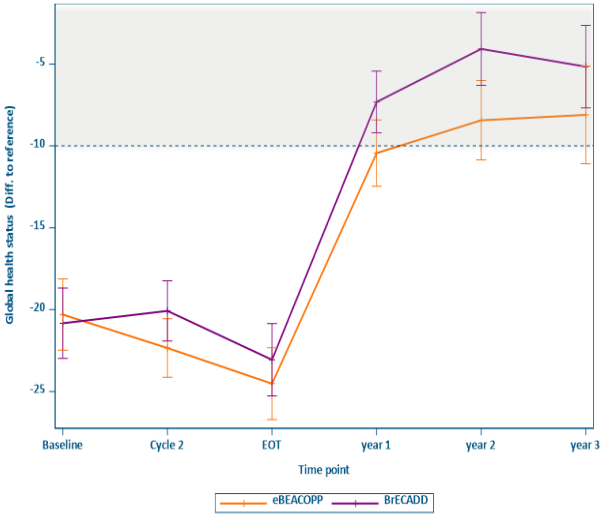
BrECADD: some key aspects of optimization on tolerability

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

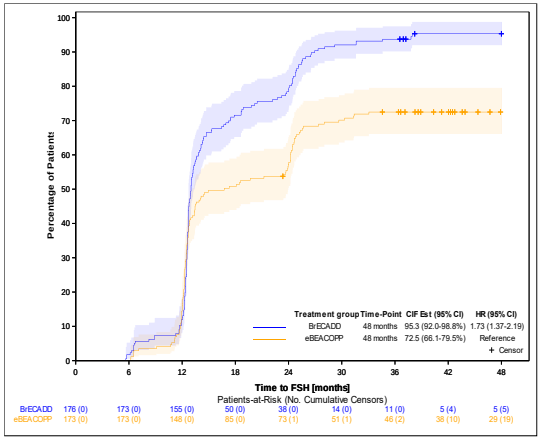
Treatment related morbidity	BrECADD (n=677)
Anemia, thrombocytopenia, or infection of CTCAE grade 4	0 (0)
Organ toxicity of CTCAE grade 3-4	2 (<1)
Treatment related morbidity	2 (<1)

- 2/742 sAML/MDS (0.27%)
- no Tx-related mortality

Normalized global health status with BrECADD starting at 12 months



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



- FSH recovery in women 96%, men 86%
- Normal birth rate in women

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HD21 PET-assessment and treatment exposure

	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**	425	**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**

98% of all patients received the scheduled number of treatment cycles

HD21 PFS endpoint at **interim analysis** (40 months mFU)

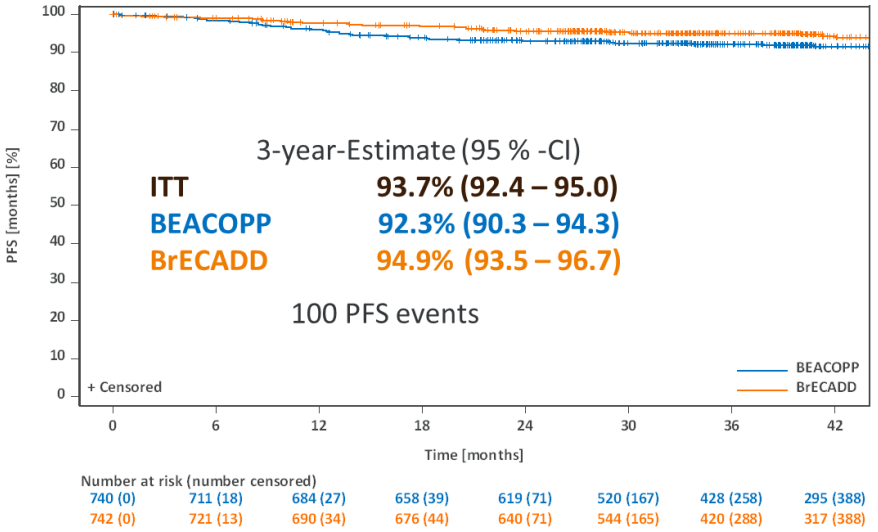
PFS events at interim analysis

	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 PRO or REL	6	0.9	7	0.9
PFS events, total	61	8.4	39	5.3

Reduction of early PFS events with BrECADD

- **KAIROS principle**

PFS at interim analysis



With a HR of 0.63 (99%-CI: 0.37 – 1.07) **non-inferiority of BrECADD was fully established at IA.**

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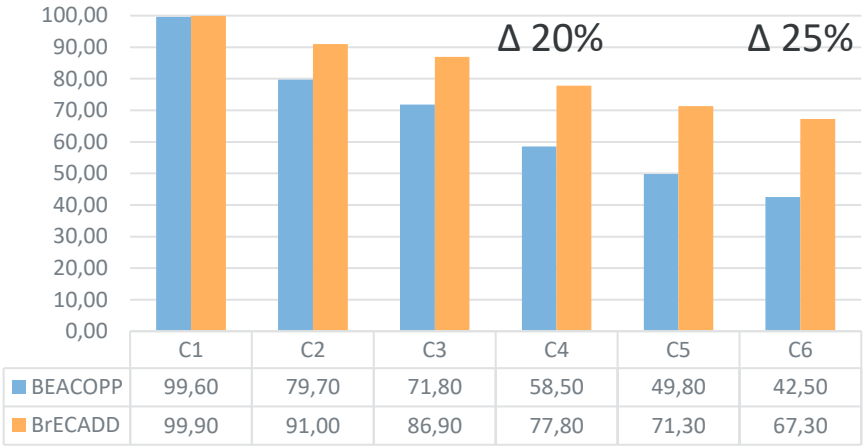
HD21: impact of tolerability on feasibility and efficacy?

Patients treated with *full dose* (cyclo, etoposide, doxo) *per cycle* (%)



	C1	C2	C3	C4	C5	C6
BEACOPP	99,60	79,70	71,80	58,50	49,80	42,50
BrECADD	99,90	91,00	86,90	77,80	71,30	67,30

Early termination of the tubulin inhibitors VCR and BV

BV in BrECADD:
18/738 patients, 2·4%

VCR in eBEACOPP:
132/732 patients, 18·0%

Δ 15.6%

The unexpected and positive effect of BrECADD on efficacy might be explained by both

- use of the targeted agent BV, and
- maintenance of higher dose-levels in more patients with BrECADD

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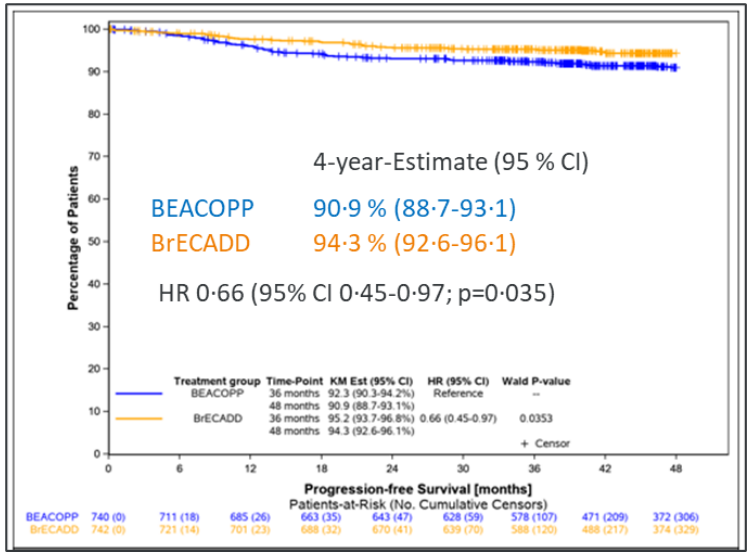
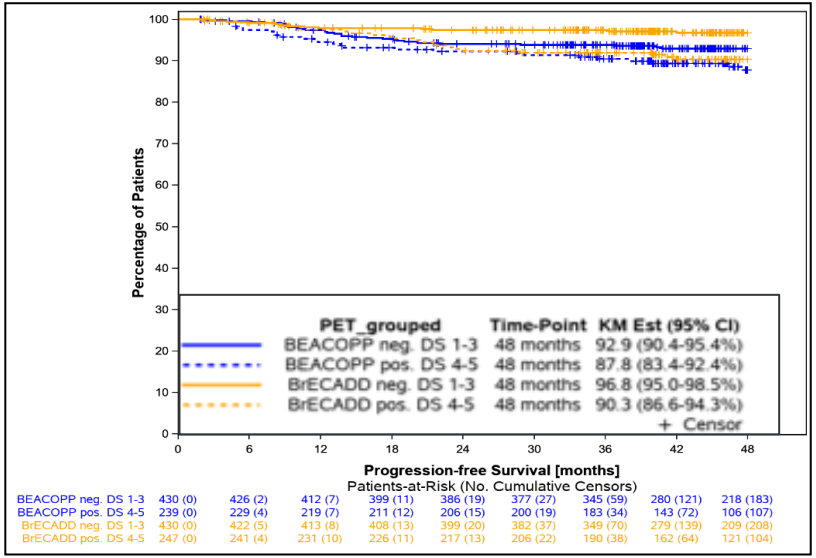
HD21 final analysis: BrECADD is superior to eBEACOPP (mFU 48 m)

[1] Amendment for test on superiority was initiated by study investigators request and approved by the regulatory authority (PEI) to ensure study integrity.

Progression-free survival



PFS by risk factor PET2-status



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GHSG HD21 summary and conclusion

BrECADD is significantly better tolerated than eBEACOPP and

- recovery of TRMB after 12 months in > 99% of patients, normalization of QoL (!), no relevant impact on gonadal function, no TRM, very low sMDS/AML rate (2/742, 0.27%), although
- relative dose intensity was higher with BrECADD due to improved feasibility (up to 25% higher rate of full dose Tx), and only 2% early termination of the tubulin inhibitor MMAE.

Efficacy of BrECADD is superior to eBEACOPP reaching an unprecedented **PFS of 94.3%** with *mature* FU of 4-years, although

- most patients (64%) receive only 4 cycles (i.e. 12 weeks) of therapy, and
- cumulative doses of cytotoxic drugs below critical thresholds (e.g. doxorubicin at 160 mg/m² for 2/3 of patients)

➢ **Overall, we thus feel very safe to recommend BrECADD as standard therapy based on these mature data.**

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1 Anderson et al, Lancet Oncol 2018; 19: 1328–37

Advanced Hodgkin lymphoma: beyond S1826 and HD21

1. ***Response assessment for treatment individualization***:
   - We need to improve our test-method aiming at less false positive findings. MTV seems to be superior to DS. MRD should be evaluated.
   - Having a better tool than DS, more patients will need only a reduced treatment intensity with low cumulative doses of cytotoxic drugs and without cons. RT.

2. ***Re-evaluating chemotherapy intensity in combination with PD1 inhibition***:
   - AVD might not be enough, BrECADD might be more than enough.

3. ***Baseline risk assessment for treatment individualization***:
   - We need to identify patients highly susceptible to PD1 blockade upfront

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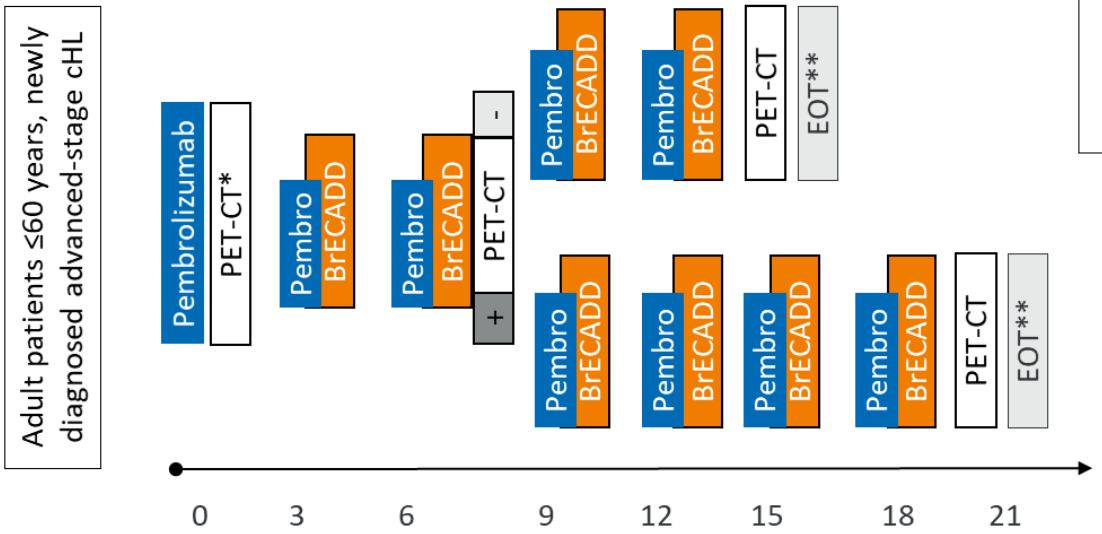
Individualized immuno-chemotherapy for newly diagnosed advanced stage cHL patients: Pembro-FLASH pilot.



Can we cure more than 64% of patients with only 4 cycles of BrECADD?

START Q2 2025

* For scientific purpose

** RT to PET pos RD

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Thank you very much for your attention!

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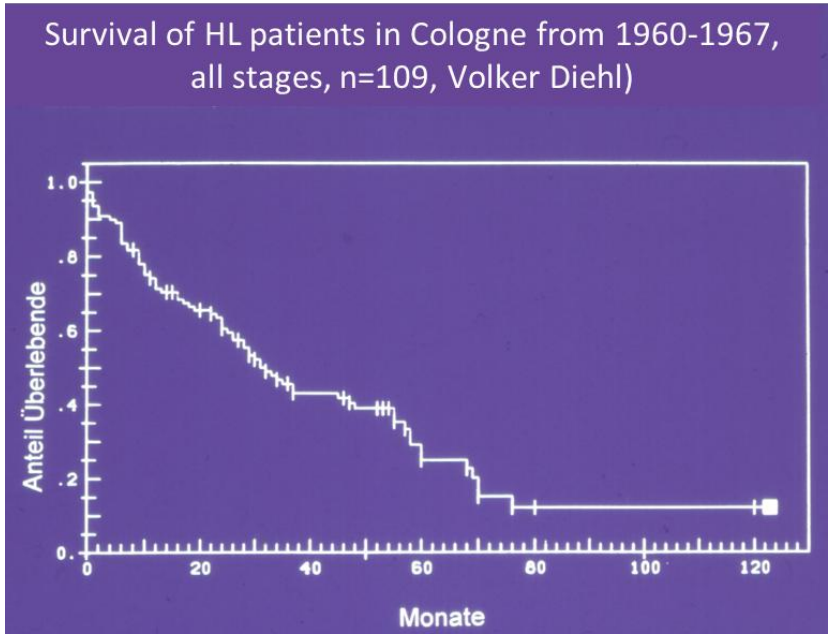
Hodgkin Lymphoma: a miraculous and fatal disease of young adults



Volker Diehl with doctors and patients at ISHL12 (2022)

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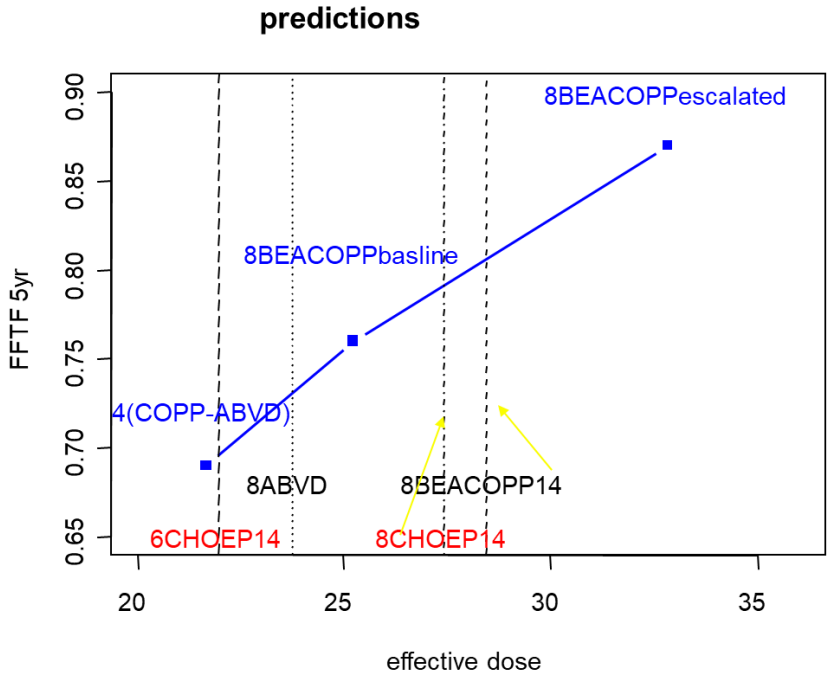
How eBEACOPP has been developed: the “Kairos Principle” and the “Hasenclever model”

The change of COPP/ABVD to BEACOPP

A Adriamycin		B Bleomycin
B Bleomycin		E Etoposide
V Vinblastin		A Adriamycin
D Dacarbazin	C Cyclophosphamid	C Cyclophosphamid
d 15	O Vincristin	O Vincristin
	P Procarbazin	P Procarbazin
	P Prednison	P Prednison
restart: d 28	d 1	Restart d 21

Aim: To optimize the schedule ⟹ 1. Incorporate active drugs
2. Shorten intervals
3. Intensify dose



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The prognostic value of the IPS using a more effective treatment than ABVD

IPS	COPP/ABVD (%)	bBEACOPP (%)	eBEACOPP (%)
	Early progression		
Good (0–1)	10	6	2
Fair (2–3)	11	9	2
Poor (4–7)	18	9	3

GHSG HD9 study[1]

Study	Group	n	5-year PFS (%)	5-year OS (%)
EORTC IG 20012[2] **IPS 3–7**	ABVD	275	69	86.7
	BEACOPP (4 esc + 4 std)	274	84	90.3
LYSA H34[3] **IPS 0–2**	ABVD	77	75	92
	BEACOPP (4 esc + 4 std)	68	93	99

- eBEACOPP improves survival and reduces the risk of refractoriness and early progression for all patients ad regardless of the IPS!
- But many patients are being overtreated to achieve good outcomes for all patients.

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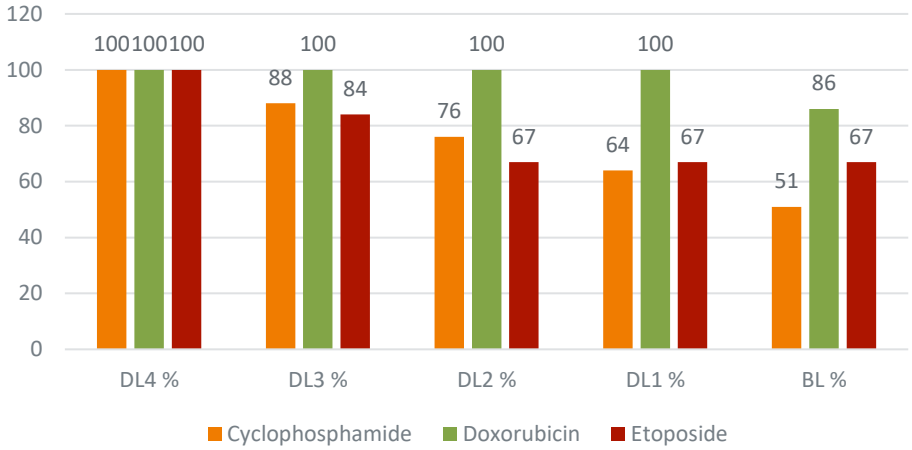
1. Diehl V, et al. N Engl J Med 2003;348:2386–95, 2. Carde P, et al. J Clin Oncol 2016;34:2028–36. 3. Mounier N, et al. Ann Oncol 2014;25:1622–8.

Tailoring therapy: individualized eBEACOPP dosing since 1994

- leukopenia for more than 4 days (leukocytes < 1000/mm3)
- thrombocytopenia < 25.000/mm3 on one or more days
- Infection CTCAE grade 4
- Other CTCAE grade 4 toxicities, e.g. mucositis
- Treatment delay of more than 2 weeks due to inadequate recovery of blood values
- **If one or more toxic events occur in a given cycle, the dose in all following cycles has to be reduced by one dose level.**
- **If toxicity events occur in two successive cycles, the doses are reduced to baseline level.**

GHSG guidlines for dose reduction of Cyclo, Doxo, and Eto with BrECADD



	DL4	DL3	DL2	DL1	BL
Cyclophosphamide mg/m²	1250	1100	950	800	635
Doxorubicin mg/m²	40	40	40	40	35
Etoposide mg/m²	150	125	100	100	100

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Borchmann, P., et al.,. Lancet, 2018. 390(10114): p. 2790-2802.

How BrECADD has been developed using the “Hasenclever model”

regimens

	ABVD	B basis	B14	B esc		neues Schem	neues Schema 02.08.10	B esc, weniger Cyclo
Zyklusdauer (Wochen)	**4**	**3**	**2**	**3**		3	3	3
Drug								
Bleomycin	20	10	10	10		0	0	10
Cyclophosphamid		650	650	1250		1250	1250	750
DTIC	750					500	500	
Doxorubicin	50	25	25	35		40	40	35
Epi						0	0	
Etoposide		300	300	600		450	450	600
Prednison		560	560	560		560	560	560
Procarbazin		700	700	700		0	0	700
Vinblastin	12					0	0	
Vincr		1,2	1,2	1,2	BV	1,2	4	1,2

dosing and schedule

Effektive Dosis								
Zyklen	2	8,6	8,4	8,8	11,0	8,9	10,9	10,4
	3	12,0	12,0	12,7	15,6	12,7	15,5	14,7
	4	15,0	15,2	16,3	19,8	16,1	19,7	18,6
	5	17,7	18,1	19,6	23,5	19,1	23,4	22,2
	6	20,0	20,7	22,8	26,9	21,9	26,8	25,4
	7	22,1	23,0	25,7	29,9	24,4	29,9	28,3
	8	24,0	25,2	28,4	32,8	26,7	32,7	31,0

Effective dose

*) max 2mg pro Zyklus, daher werden für einen durchschnittlichen Erwachsenen nur 1,2mg/m² gerechnet

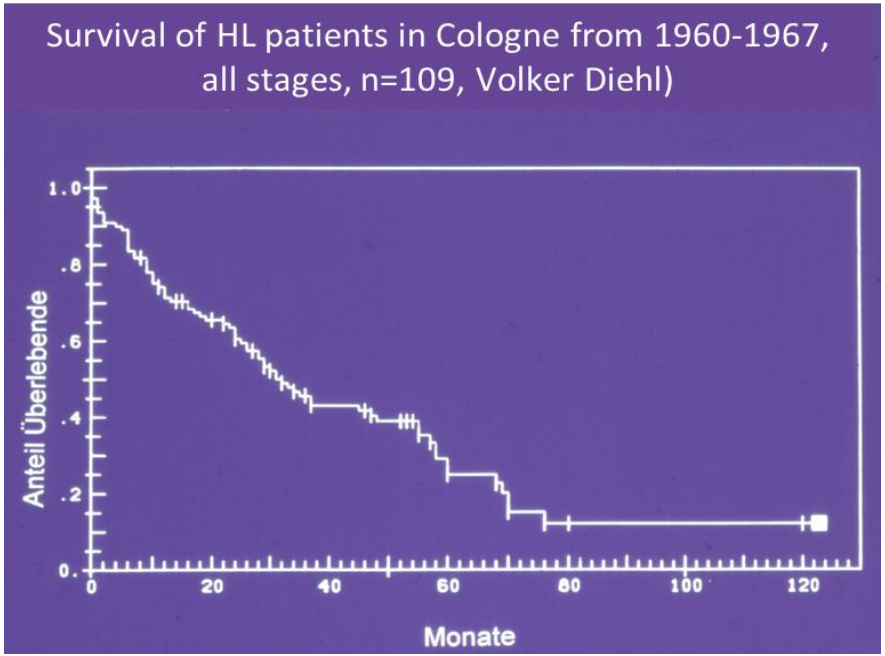
$) 500mg feste Dosis, daher analog Vincristin auf Dosis/m² umgerechnet, von Dirk Hasenclever in 4/06 nicht berücksichtigt

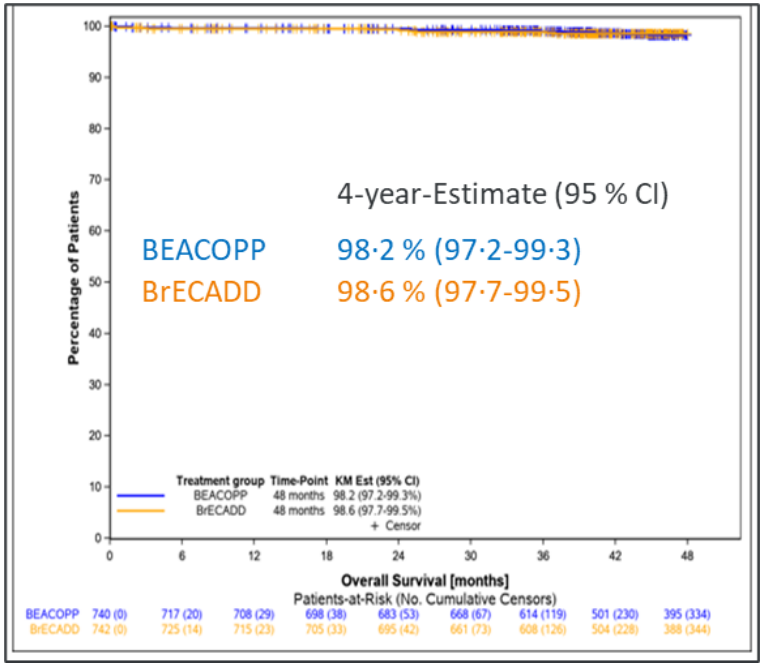
Berechnungsteil:

Drug	**Weight (old)**	**Weight (4/06)**						
Bleomycin	18	18	1,1111	0,555556	0,55556	0,5556	0	0	0,5556
Cyclophosphamid	1238	1408	0	0,461648	0,46165	0,8878	0,88778409	0,88778409	0,5327
DTIC	7708	7708	0,0973	0	0	0	0,06486767	0,06486767	0
Doxorubicin	25	25	2	1	1	1,4	1,6	1,6	1,4
Etoposide	491	491,5	0	0,610376	0,61038	1,2208	0,9155646	0,9155646	1,2208
Prednison	574	517	0	1,083172	1,08317	1,0832	1,08317215	1,08317215	1,0832
Procarbazin	1235	1235	0	0,566802	0,5668	0,5668	0	0	0,5668
Vinblastin	9,3	6,55	1,8321	0	0	0	0	0	0
Vincr	3,65	2,47	0	0,48583	0,48583	0,4858	0,48582996	1,6194332	0,4858

weight of specific drugs

The role of chemotherapy in HL, a chemo-sensitive disease





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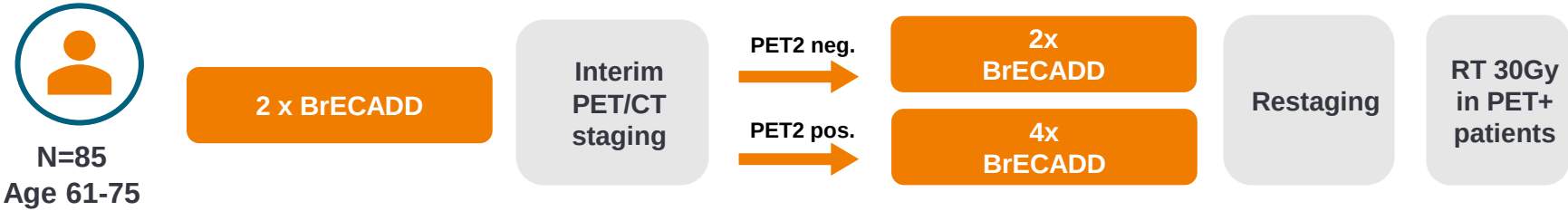
Borchmann et al., The Lancet, 2024

GHSG HD21 Older Cohort: Study Design

Prospective, international, multicenter, single-arm add-on cohort to the HD21 trial



Trial objectives

- Primary: Estimate efficacy of PET-guided BrECADD defined as CR rate after chemotherapy (primary endpoint).
- Secondary: Further explore efficacy, safety and feasibility of PET-guided BrECADD in older patients.

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Ferdinandus et al., ASH 2024

Baseline Characteristics

ITT population (n=83)

Characteristic		No. (%)
Age	Median (IQR, range)	67 (63 – 70, 61 – 75)
Sex	Female	32 (39)
	Male	51 (61)
CIRS-G Sum Score	Mean (SD)	3.7 (2.7)
	Median (range)	3 (0 – 10)
Comorbidities	Absent	11 (13)
	Present	72 (87)
ECOG	0	39 (47)
	1	29 (35)
	2	15 (18)
Frailty[1]	0 (fit)	43 (52%)
	1-2 (unfit)	38 (46%)
	3 (frail)	2 (2%)
Ann Arbor Stage	II	3 (4)
	III	35 (42)
	IV	45 (54)
IPS	0-2	22 (27)
	3-7	61 (73)

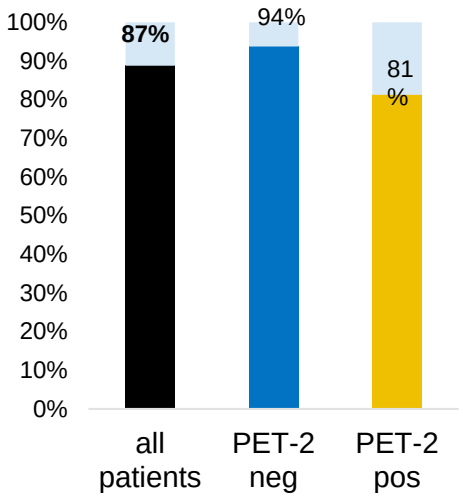
Summary

- 83 patients included in the ITT cohort.
- Median age: 67 years (range: 61-75)
- A majority had IPS ≥3 (73%)
- Almost all presented with comorbidities (87%).
- Mean Cumulative Illness Rating Scale-Geriatric (CIRS-G) score of 3.7 (SD 2.6).
- Approx. half of the cohort unfit or frail.[1]

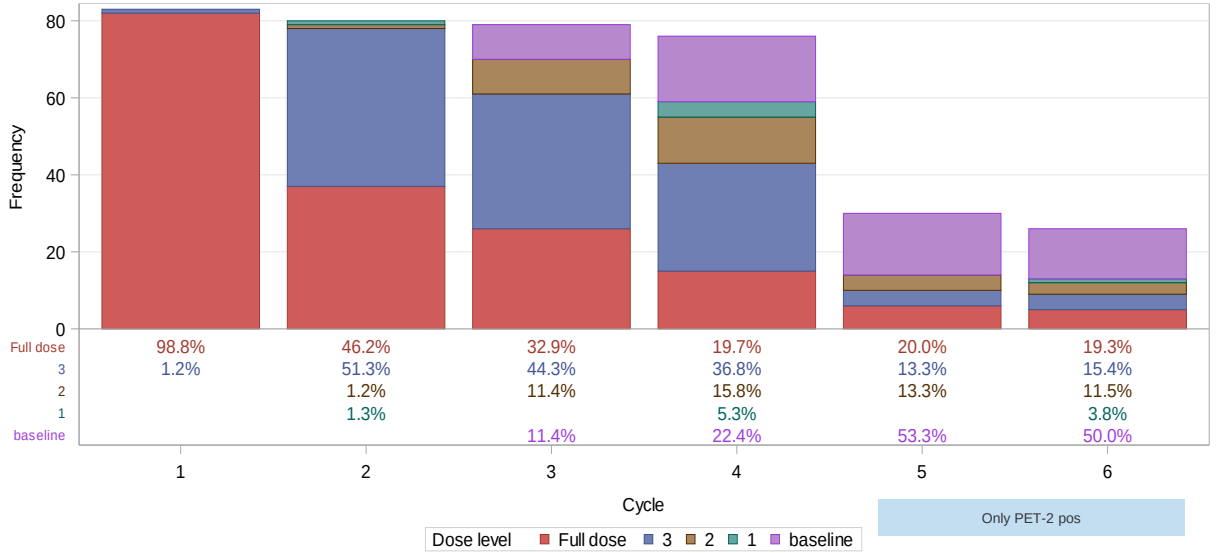
1 Lia K et al, @ISHL13

Treatment completion and dose levels

Treatment completion rate



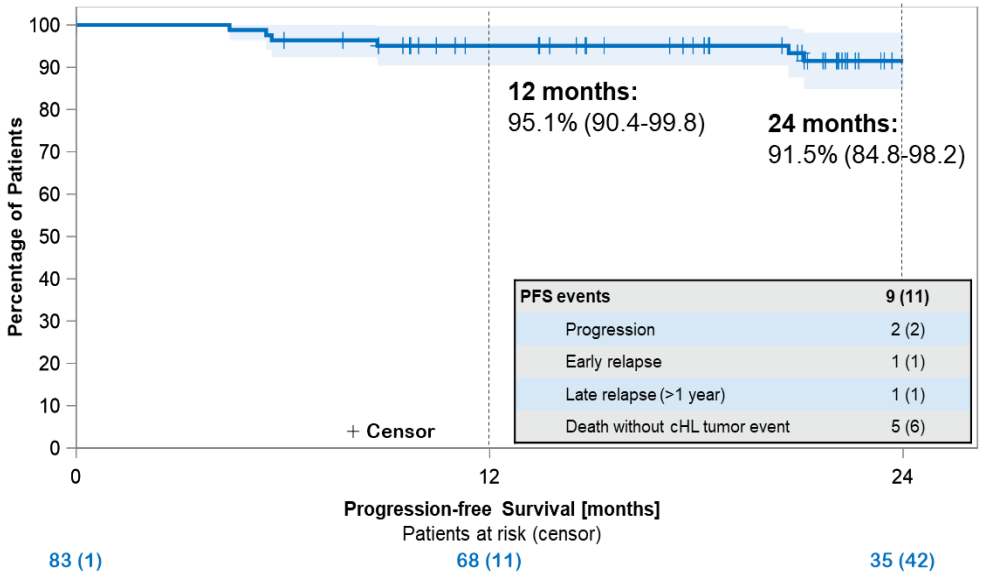
Dose levels



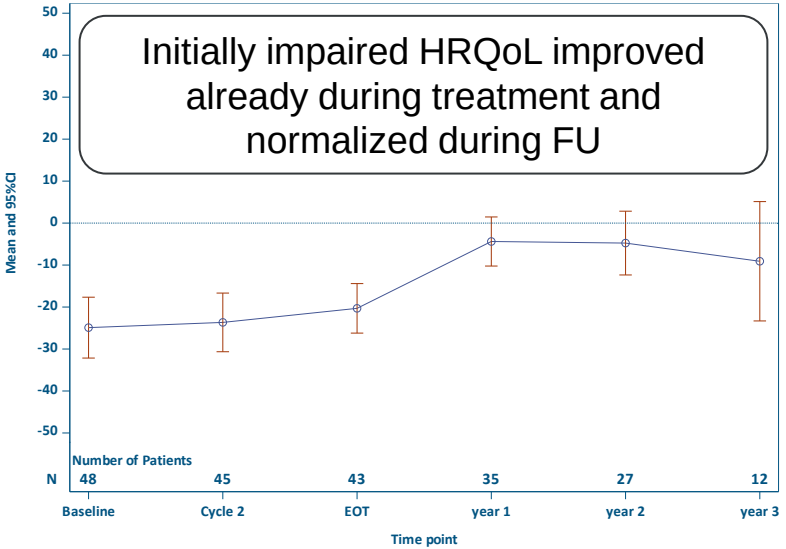
- **High treatment completion rate: 87% of entire cohort**
- **Supported by pre-defined, per-protocol dose reductions**

GHSG HD21 Older Cohort: Progression-free survival

Progression-free survival, mFU 23 m



HRQoL (QLQC30)

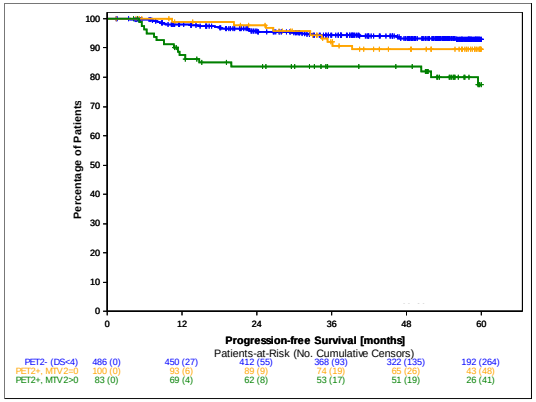


➢ BrECADD is very effective and safe (no TRM!) also in older patients

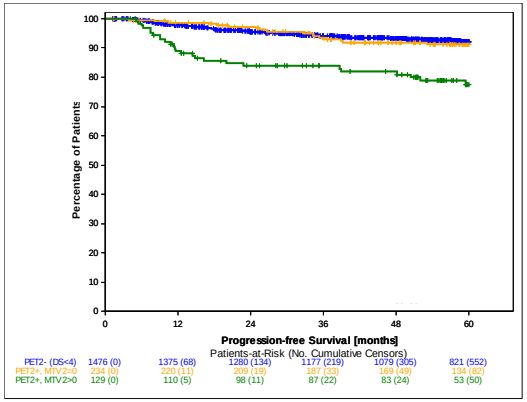
Ferdinandus et al., ASH 2024

Prognostic relevance of MTV-2

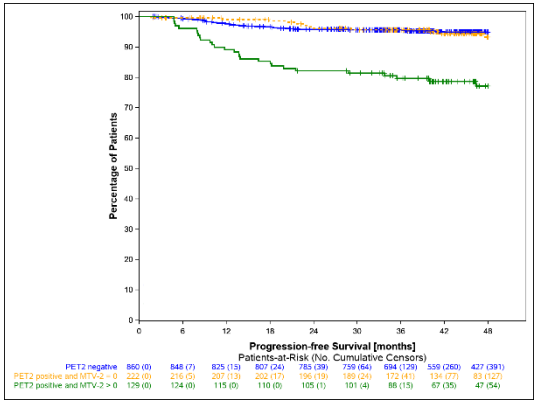
C6 Cohort (n=645)



HD18 ITT (n=1756)



HD21 ITT (n=1211)



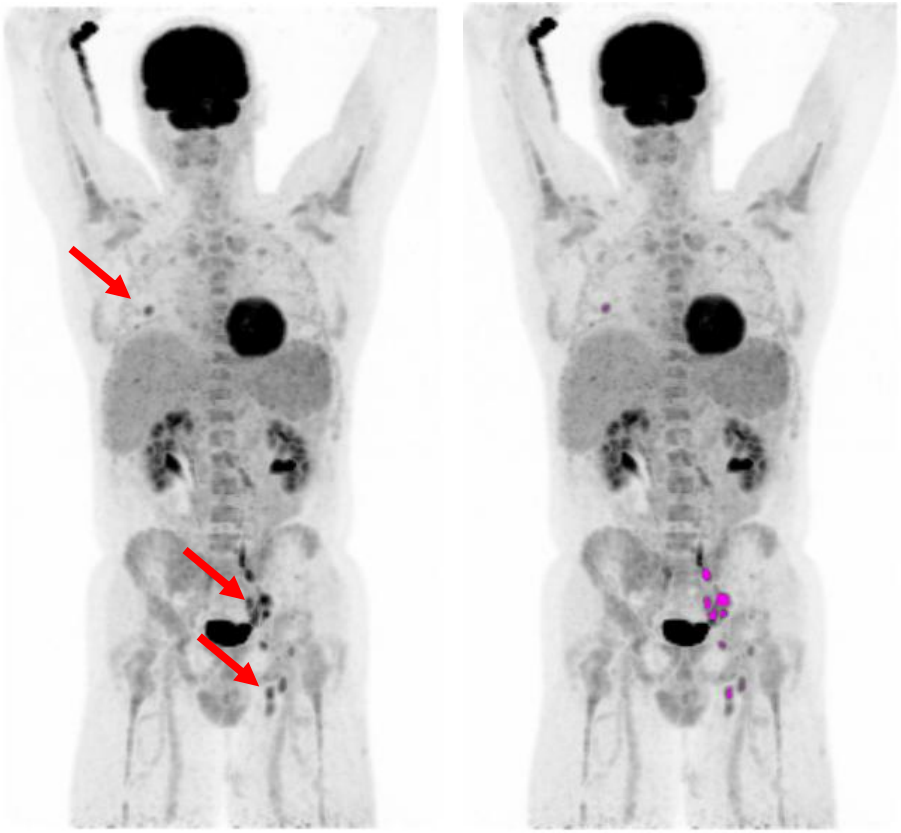
Similar PFS among **PET-negative** and **PET-positive & MTV = 0** groups.

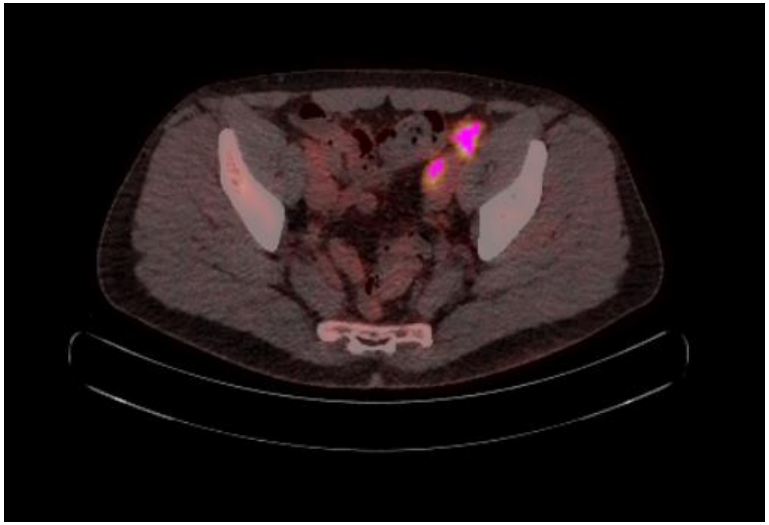
High risk of early progression with low PFS in **patients with remaining MTV-2**

GHSG

Ferdinandus, ASH24

Can we improve on response assessment by Deauville Score?
MTV-2 Measurement



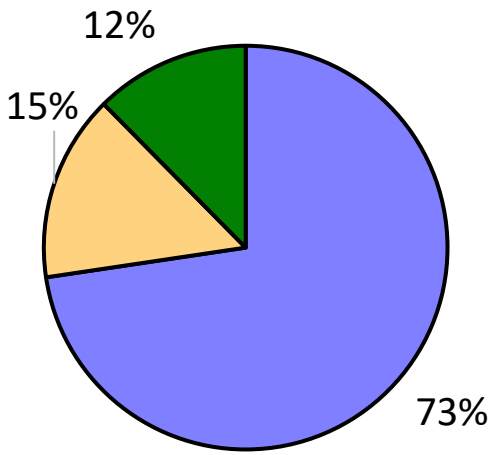


Lung lesion and right inguinal and iliacal nodes with SUV > 4:

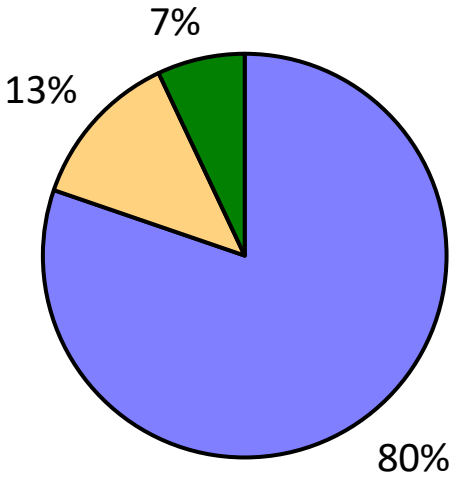
MTV-2 = 7.6 ml

Deauville score and MTV-2

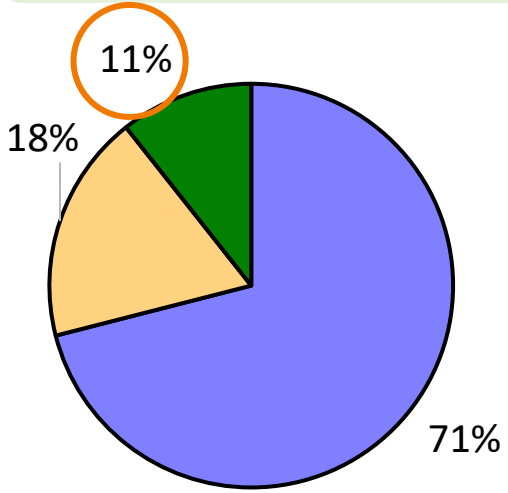
C6 Cohort (n=645)



HD18 ITT (n=1756)



HD21 ITT (n=1211)



Proportions of **PET-negative**, **PET-positive & MTV = 0** and **patients with remaining MTV-2** are comparable between cohorts, but slight variance is noted.

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