

Evolving Adv. Hodgkin Lymphoma Landscape: Optimizing Treatment Outcomes with Expert's Insights



Singapore Lymphoma Scientific Symposium
30th August 2025, Saturday
11.30am – 12.00pm

Dr. med. Justin Ferdinandus
Speaker
German Hodgkin Study Group

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Brentuximab vedotin is indicated for the treatment of adult patients with previously untreated CD30+ Stage III and IV Hodgkin lymphoma (HL), in combination with doxorubicin, vinblastine, and dacarbazine. Brentuximab vedotin has yet to be approved in Singapore for adult patients with previously untreated CD30+ Stage IIB with risk factors, Stage III or Stage IV HL in combination with etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone. Approval status may vary by country; please refer to your local approved prescribing information

Dr. Justin Ferdinandus is a Clinician Scientist based at the Department of Internal Medicine I at University Hospital Cologne in Germany. He is an integral member of the German Hodgkin Study Group (GHSg), where his research focuses on advanced-stage Hodgkin lymphoma, imaging biomarkers, and health-related quality of life. Prior to his current position, he spent time at Cancer Imaging Departments in Essen and Melbourne, gaining experience in both clinical practice and translational research.



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Updates on Frontline Hodgkin Lymphoma Treatment

Dr. med. Justin Ferdinandus

German Hodgkin Study Group

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Conflicts of Interest

Speaker fees: Takeda Oncology, DASA Oncology, Roche Pharma

Consultant: Pfizer

Non monetary: German Hodgkin Study Group



Focus today

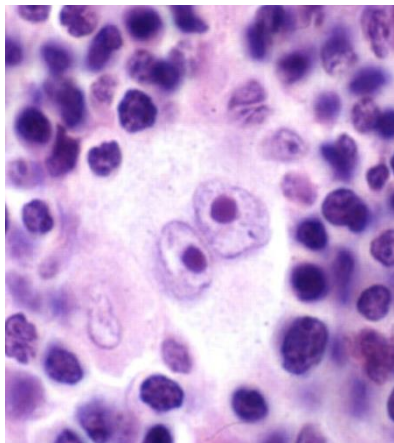
Thirty minutes of time today. So focus on:

- **Advanced stage classic Hodgkin Lymphoma**
- **German Hodgkin Study Group Concepts**

Many more relevant advancements not discussed today...



Hodgkin Lymphoma: GHSG clinical classification system

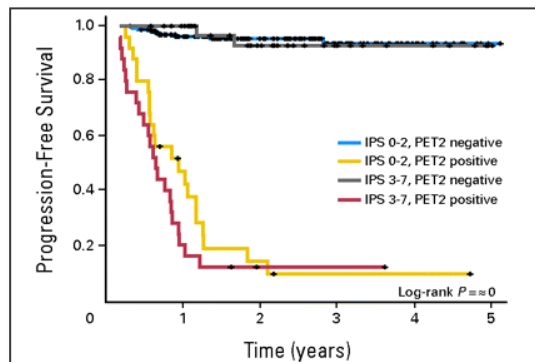


The definition of areas is based on x-rays using bones as landmarks, and the definition of the risk factors is based on clinical observations with very old protocols

How can we improve our approaches?

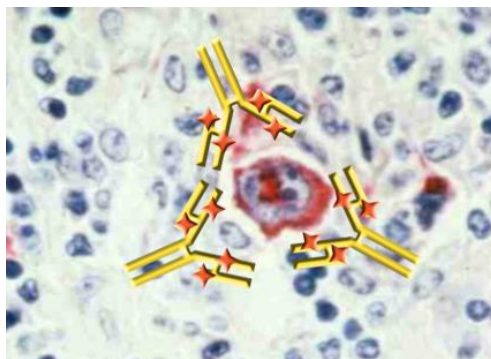
New technologies and/or new drugs might improve treatment

PET may guide treatment in cHL



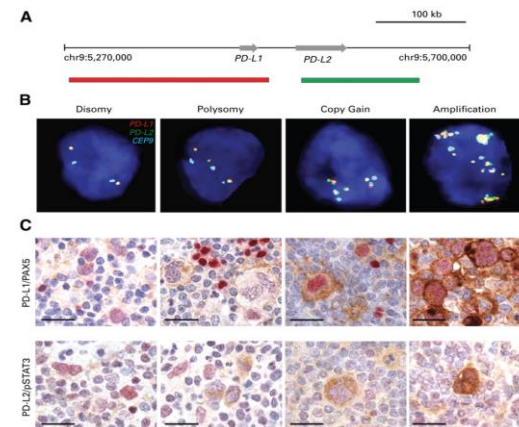
Gallamini et al., J Clin Oncol 2007
Hasenclever et al., NEJM, 1998

The ADC brentuximab vedotin is highly active in cHL



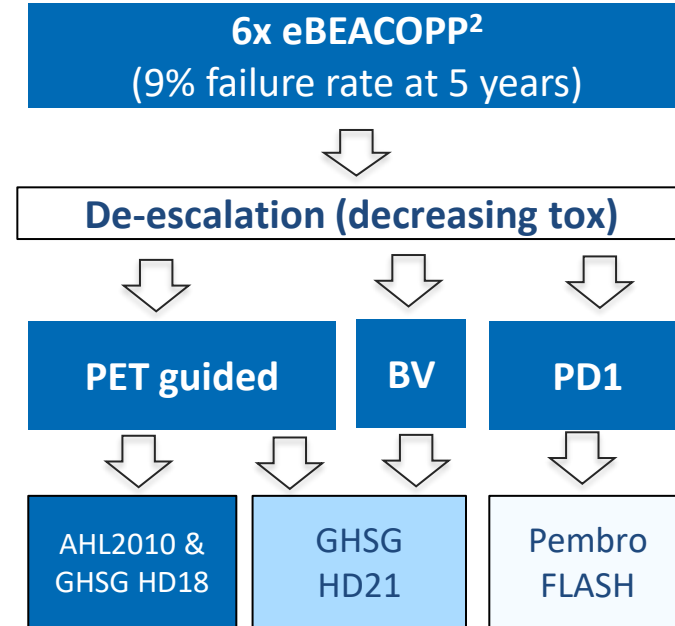
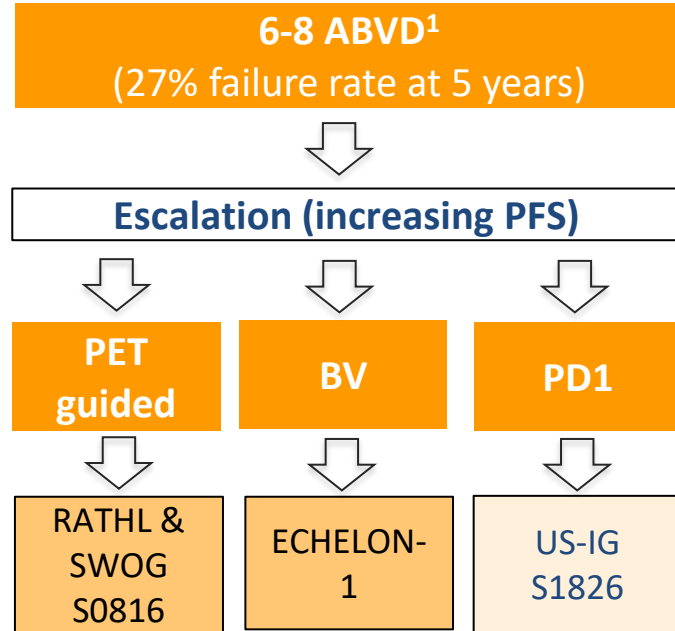
Younes A, et al. J Clin Oncol 2012;30:2183–9.

PD-L1 and PD-L2 Alterations and Associated Expression in cHL

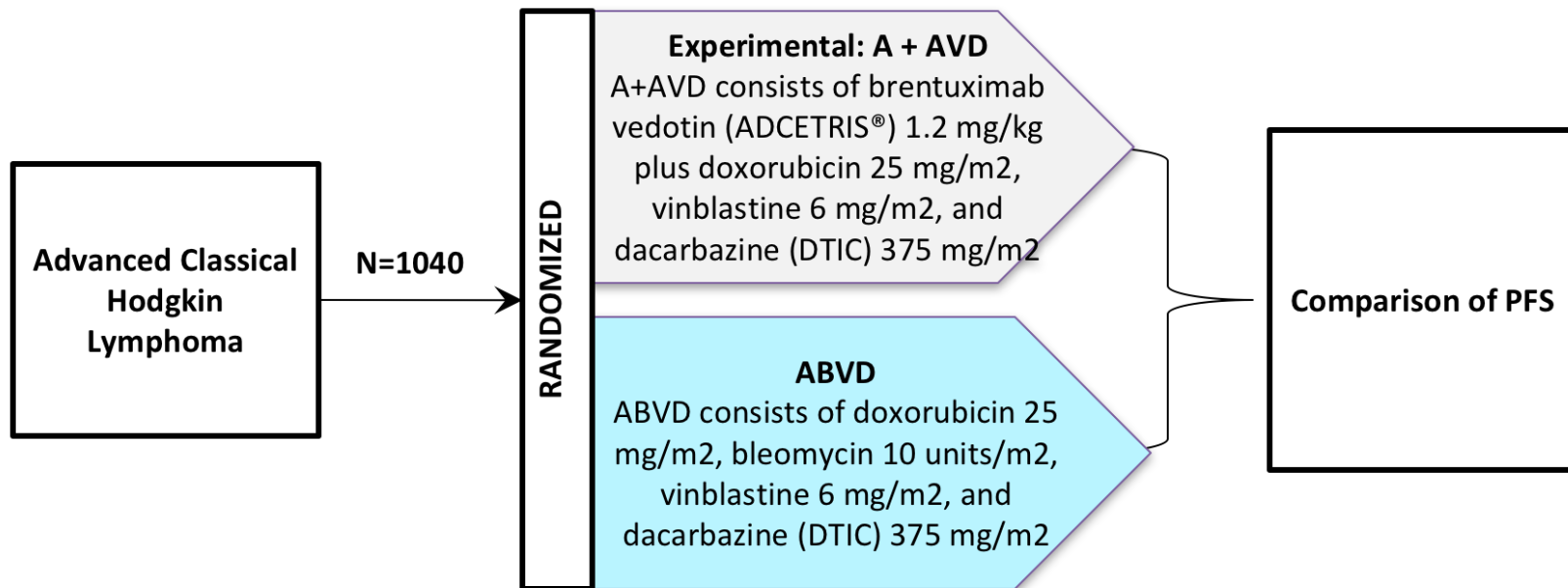


Roemer MG et al. J Clin Oncol. 2016;34:2690-2697.

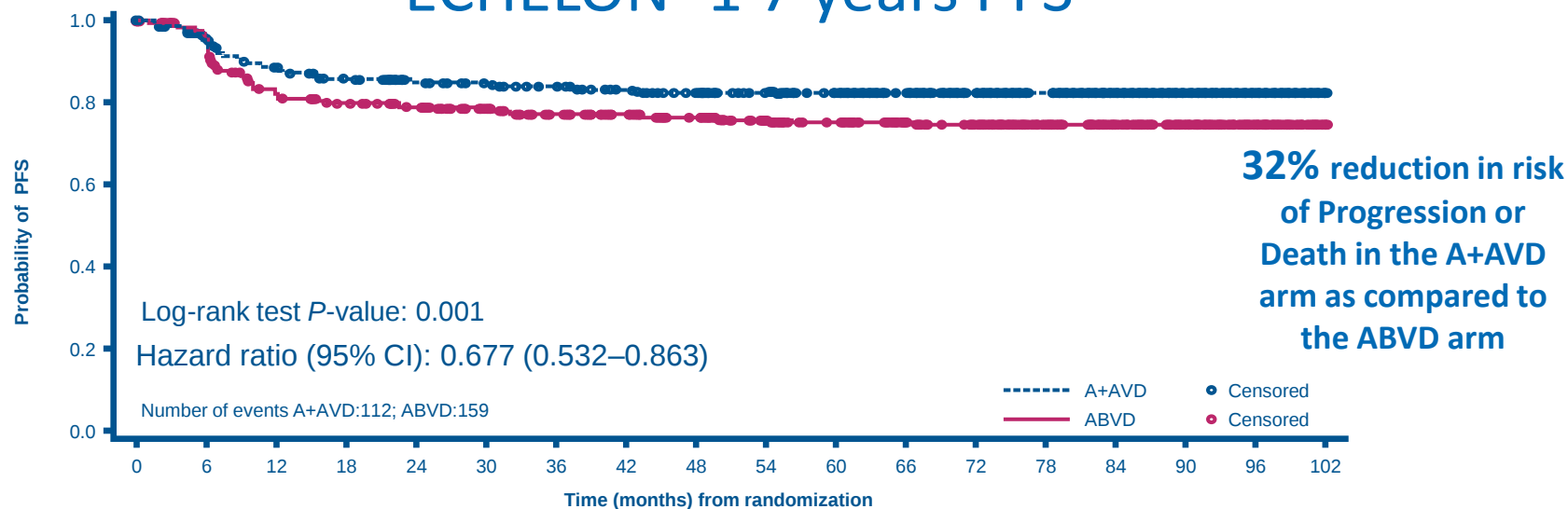
Treatment strategies for advanced stage HL



ECHELON-1



ECHELON -1 7 years PFS

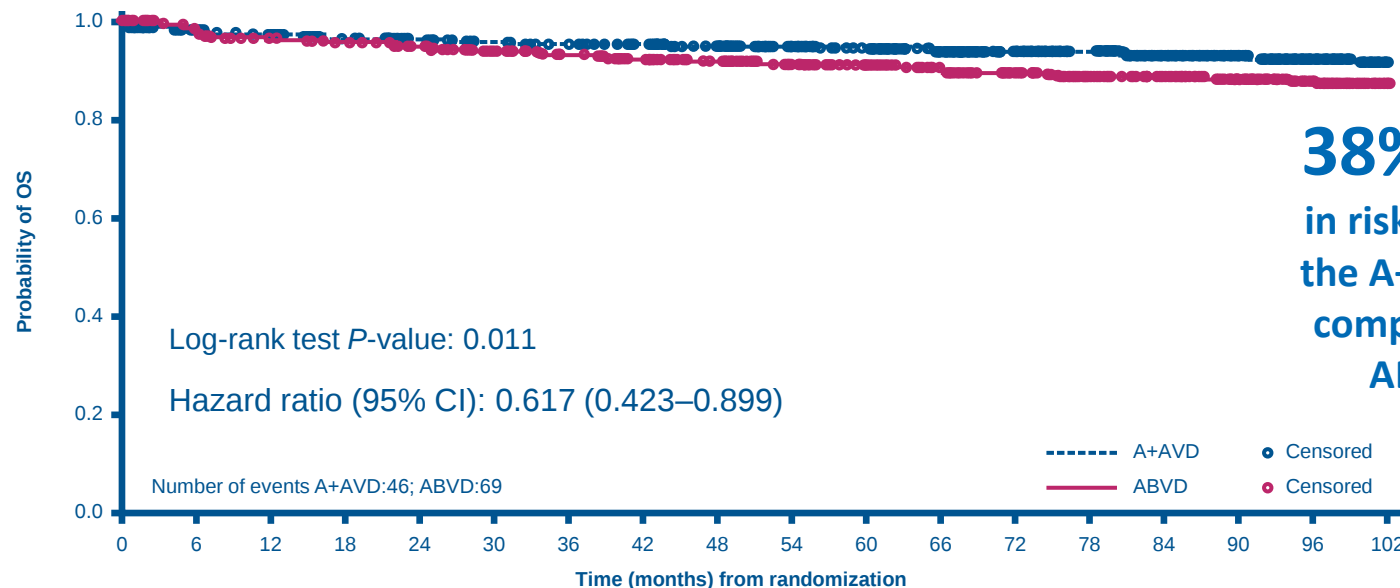


Number of patients at risk

A+AVD	664	619	563	537	520	508	496	480	463	446	426	405	384	362	332	273	177	101
ABVD	670	612	519	500	484	464	441	430	412	389	369	348	321	301	278	220	146	78

Consistent with previous PFS analysis in ECHELON-1, 7-year PFS with A+AVD vs ABVD were 82.3% vs 74.5%; HR 0.677 (95% CI: 0.532–0.863); $P=0.001$

ECHELON -1 7 years OS



Number of patients at risk

A+AVD	664	638	626	612	598	584	572	557	538	517	494	472	443	416	378	310	200	117
ABVD	670	634	614	604	587	567	545	527	505	479	455	426	398	372	340	268	178	97

↑ **7-year OS** with 6x BV-AVD vs 6x ABVD: 93.5% vs 88.8% (HR 0.617, 95%CI: 0.423–0.899)¹

Unmet needs: BV-AVD

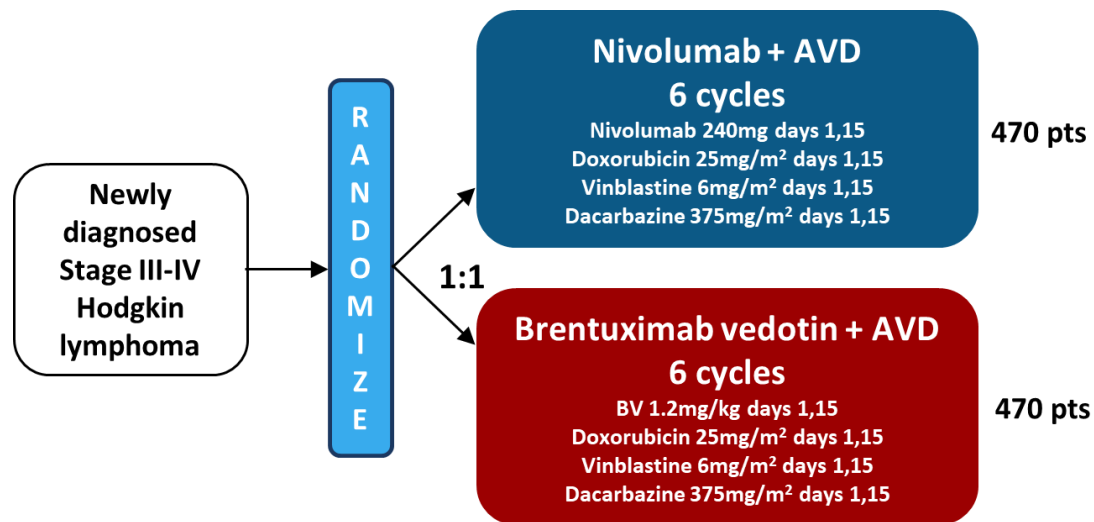
- **Cure rate:** With 82.2% 5y-PFS, treatment failure is approximately twice as likely as with eBEACOPP.¹
- **Long term toxicity:**
 - Combination of BV + Vinblastine leads to high rates of persisting peripheral neuropathy.
 - Cumulative anthracycline dose of 300 mg/m² is associated with elevated risk for breast cancer² and may cause cardiomyopathy.
- **Duration:**
 - Patients receive 6 months of treatment, irrespective of response or risk profile.

1 Straus DJ et al. Lancet Haematol. 2021

2 Neppelenbroek et al. JCO 2024

Comparing BV-AVD to Nivo-AVD:

The S1826 study



1. Using either concomitant nivolumab OR brentuximab vedotin to AVD as new SOC
2. Straight forward regimen. No personalized / PET-guided approach

¹ Herrera A et al. *NEJM* 2024

Toxicity of N-AVD vs. BV-AVD

Early Discontinuation: 8% vs 12%

Neutropenia $\geq$ G3: 47% vs 25% (but: 54% vs 98% G-CSF)

Anemia & Thrombocytopenia

- Comparable: 6% vs 9% and 2% vs 3%

PNP (sensory), of any degree

- 29% vs 55% (G3: 1% vs 8%)

Immune-related AE (irAE)

- 10% hypothyroidism with N-AVD

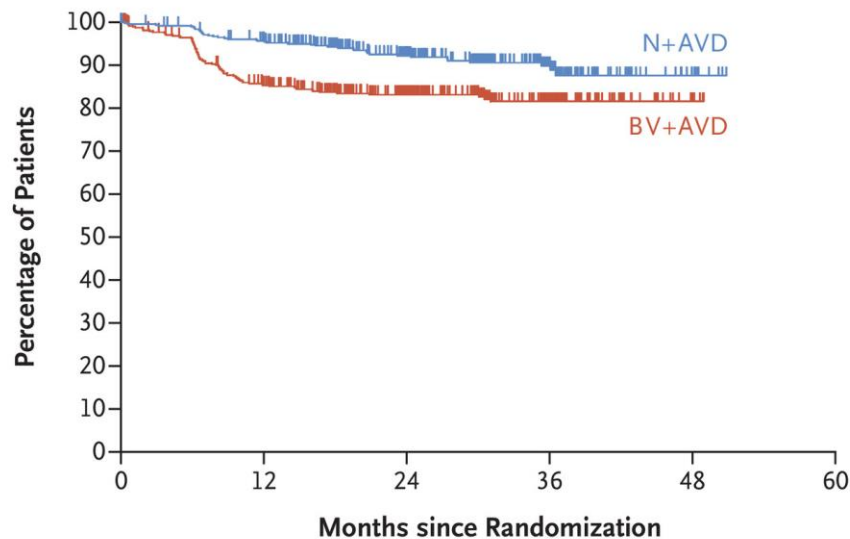
- Otherwise no differences, lower rates compared to phase 2 trials

➤ N-AVD appears better tolerable

➤ Surprisingly low irAE rate; long-term safety pending

High efficacy of N-AVD vs. BV-AVD

A Progression-free Survival



No. at Risk

N+AVD	487	450	281	101	9	0
BV+AVD	483	392	244	97	7	0

	Disease Progression or Death <i>no. of patients</i>	2-Year Estimate for Progression-free Survival (95% CI) <i>percent</i>
N+AVD	41	92 (89–94)
BV+AVD	81	83 (79–86)

Hazard ratio, 0.45 (95% CI, 0.30–0.65)

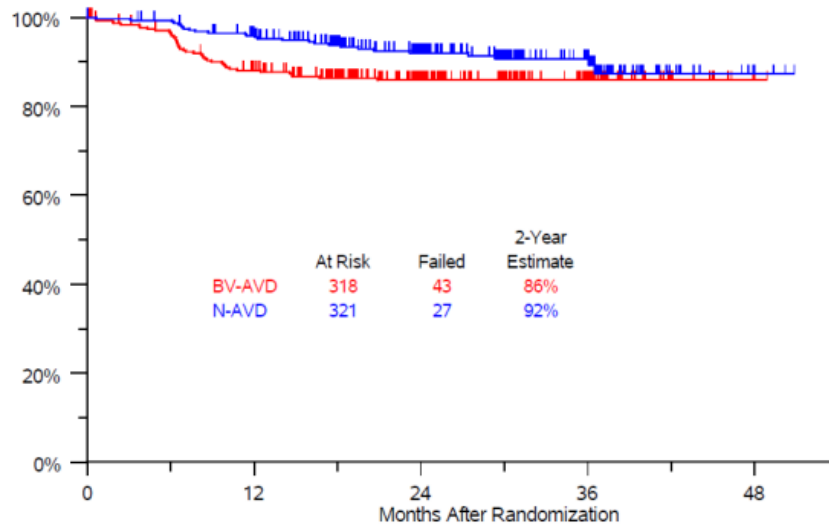
Striking results:

significance was reached early at a 99%-CI level due to interim analysis

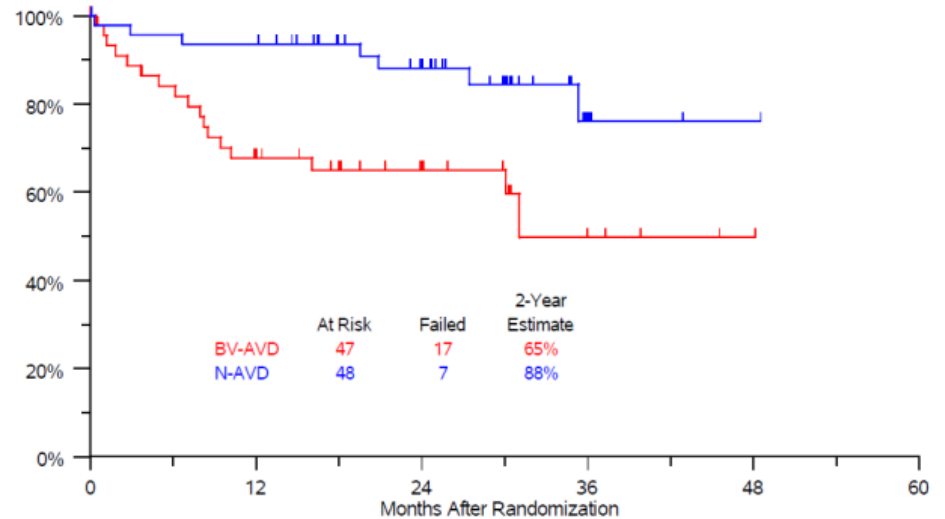
consolidating RT used only in very few patients

Subgroups

18-60 years



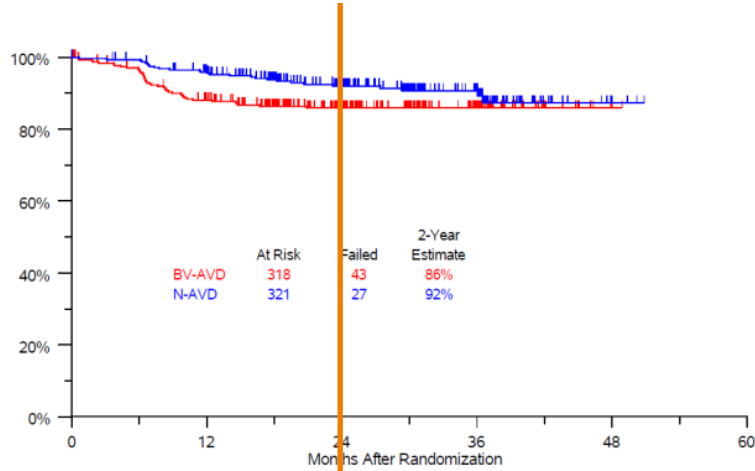
>60 years



➤ Largest improvement for elderly patients (and 12-17)

Shape of KM-curves and follow-up

18-60 years



- The KM curve for BV-AVD: PFS events occur within the first two years, after which the curve flattens out
- The KM curve for N-AVD steadily declines over time, and it is uncertain where it will stabilize.

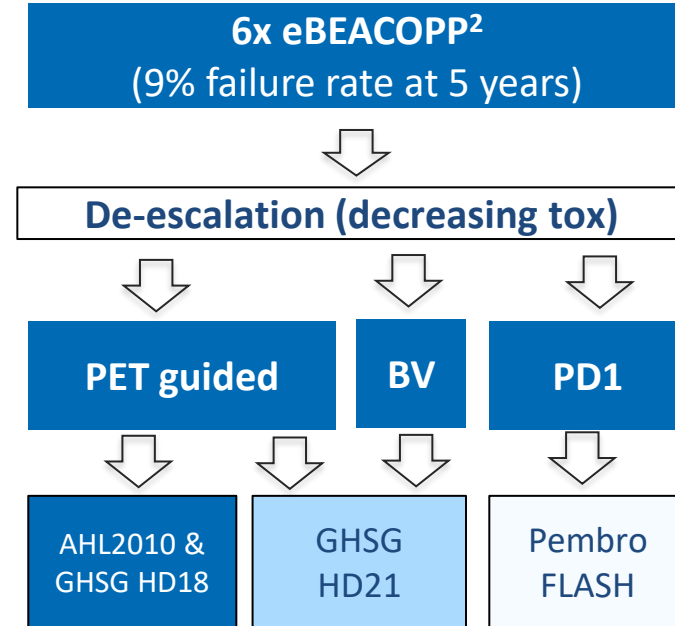
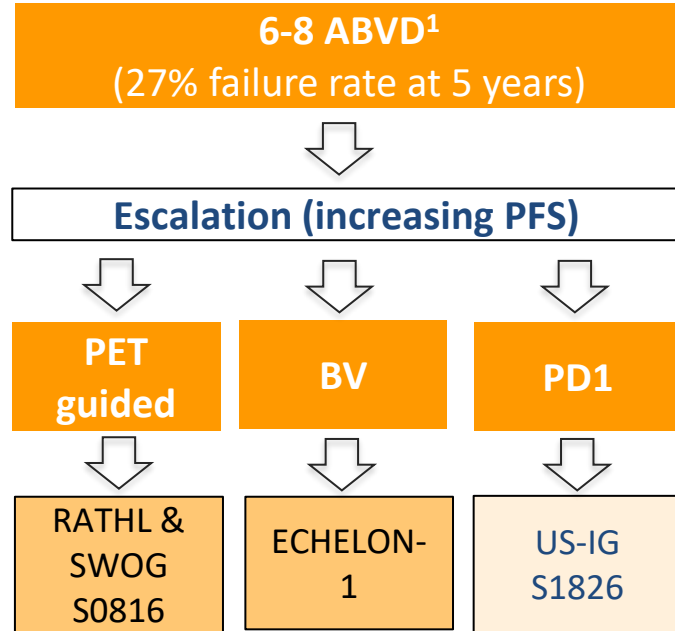
Is the 2y PFS benefit caused

- by *early responses* to PD1-blockade, which may not be durable, so relapses are just delayed, or
- by *synergism* of PD1 blockade and chemotherapy, resulting in deeper CRs and thus higher primary cure rates?

➤ PFS-benefit over BV-AVD is certain.

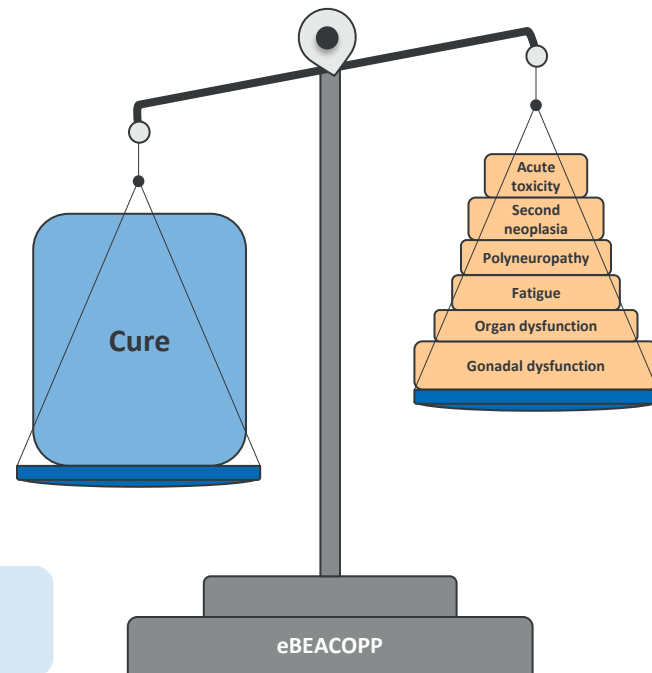
➤ More follow-up needed to determine cure rate

Treatment strategies for advanced stage HL



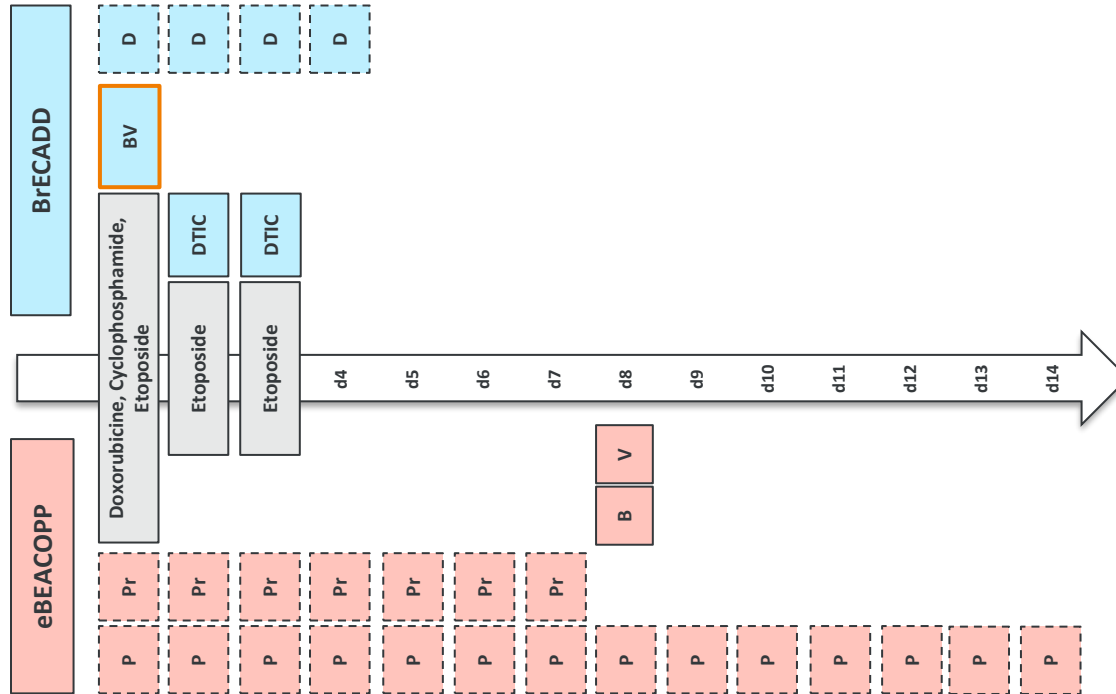
GHSG HD21: study rationale and objectives for AS-cHL

- Introduction of eBEACOPP (HD9) **improved progression-free survival (PFS) and subsequently overall survival (OS)**¹ as compared to less intensive approaches; however, at the cost of severe toxicities including infertility, sMDS/AML, and PNP
- Since then the goal was to **individualize and reduce treatment intensity**, e.g. by PET-guided omission of consolidative radiotherapy and reduction from 8 to 4 cycles eBEACOPP for most patients (HD15, HD18)^{2, 3}
- However, eBEACOPP remains a toxic and difficult to manage regimen



Aim in HD21: Optimize the risk-benefit ratio of 1L treatment for AS-cHL

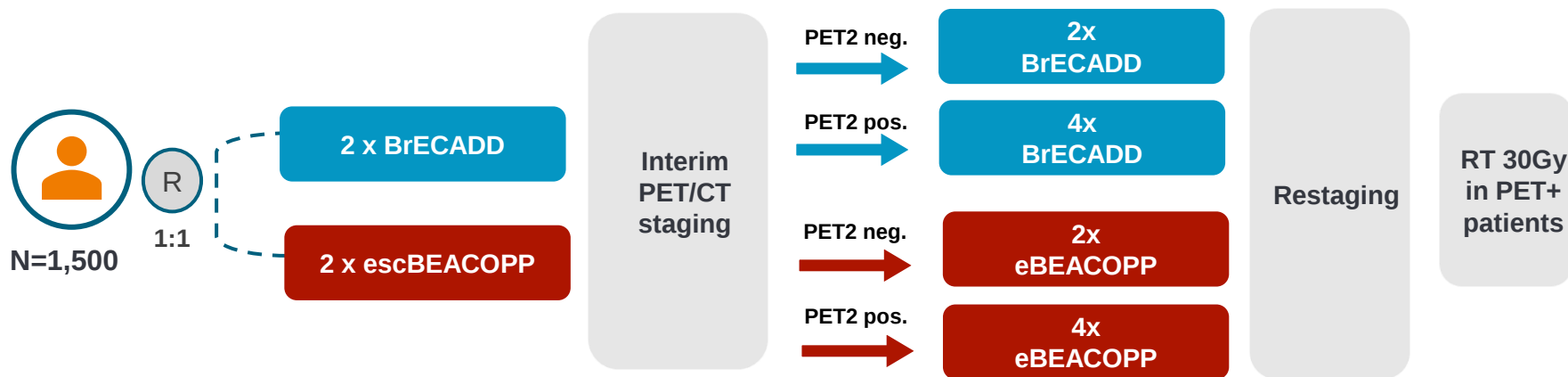
GHSG HD21 remodeling “eBEACOPP” to “BrECADD”



- The Kairos backbone **doxorubicin, cyclophosphamide, etoposide** was retained and *pre-defined dose de-escalation steps (DL 4, 3, 2, baseline)* 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)**

GHSG HD21 study design and primary endpoints

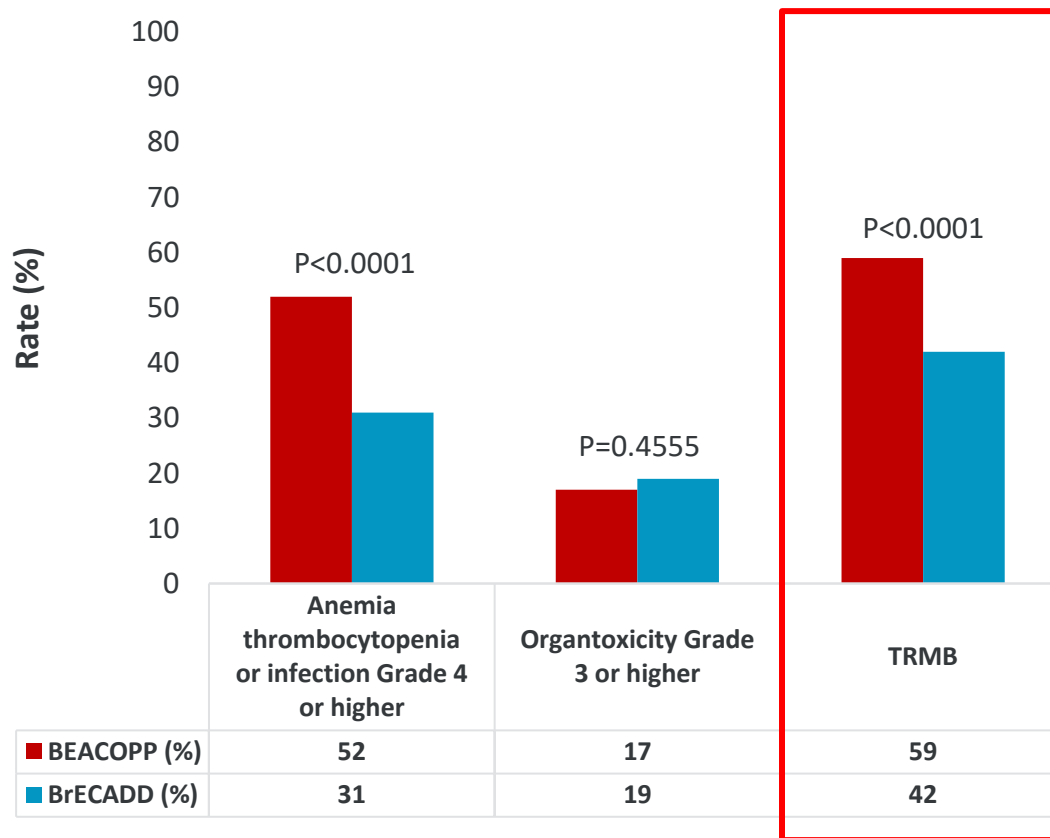
HD21 is an ongoing, randomized, open-label, Phase 3 study of BrECADD versus eBEACOPP in patients with previously untreated, advanced cHL



Co-primary objectives:

- Demonstrate reduced treatment-related morbidity (TRMB) with BrECADD.
- Demonstrate non-inferiority efficacy of 4-6 x BrECADD compared with 4-6 x BEACOPP in terms of PFS

GHSG HD21 primary safety endpoint TRMB analyses results



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

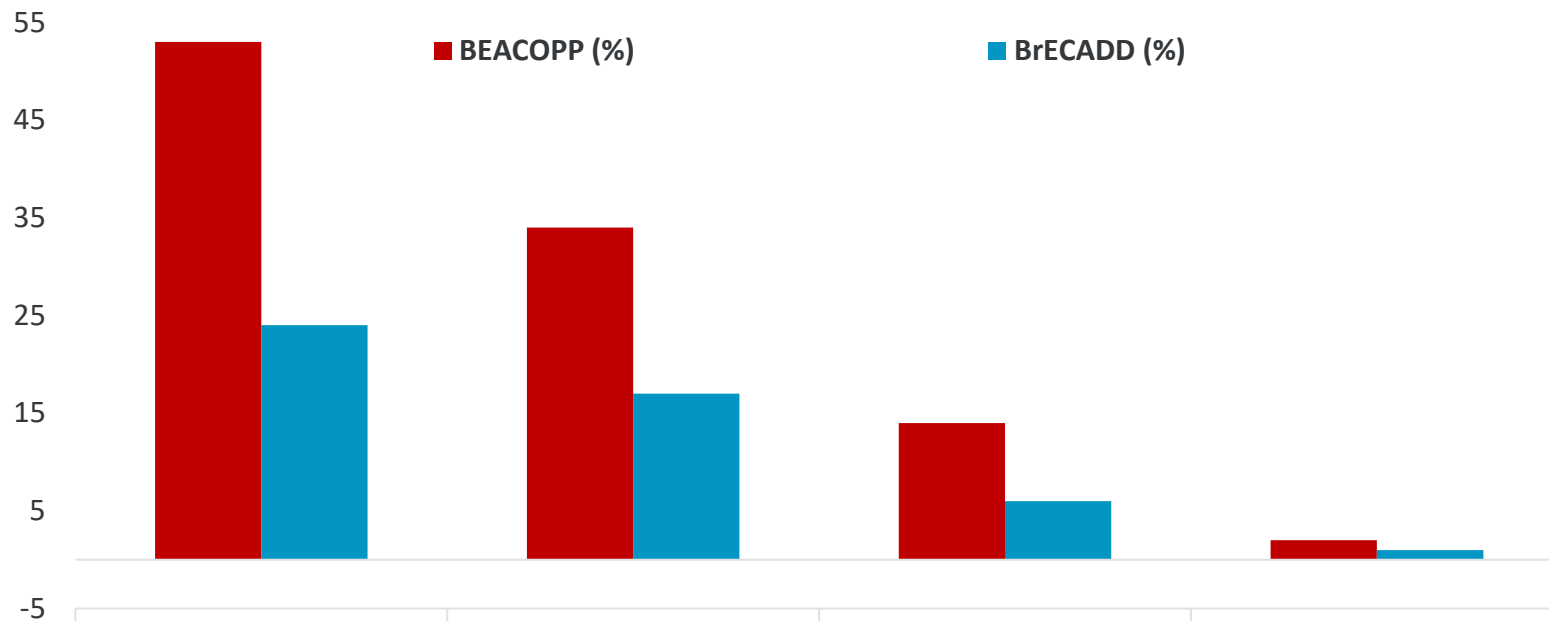
ITT-analysis of „explicitly treatment related“ TRMB*, C-Rel-Risk of BrECADD =
0.71; 95%-CI = **0.64 – 0.80**; $p < 0.0001$

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)

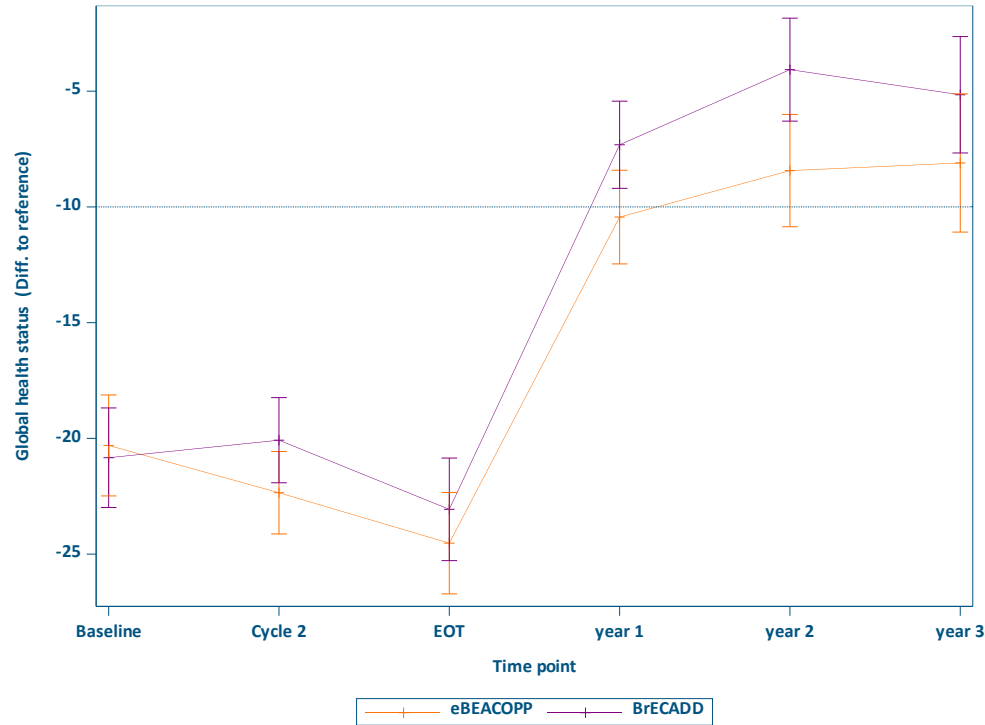
° TRMB-Incidence: ITT-TRMB: 50.5%; ITT-TRMB2: 48.4%; PP-TRMB: 50.8%

GHSB HD21 clinical implications of lower TRMB



■ BEACOPP (%)	53	34	14	2
■ BrECADD (%)	24	17	6	1

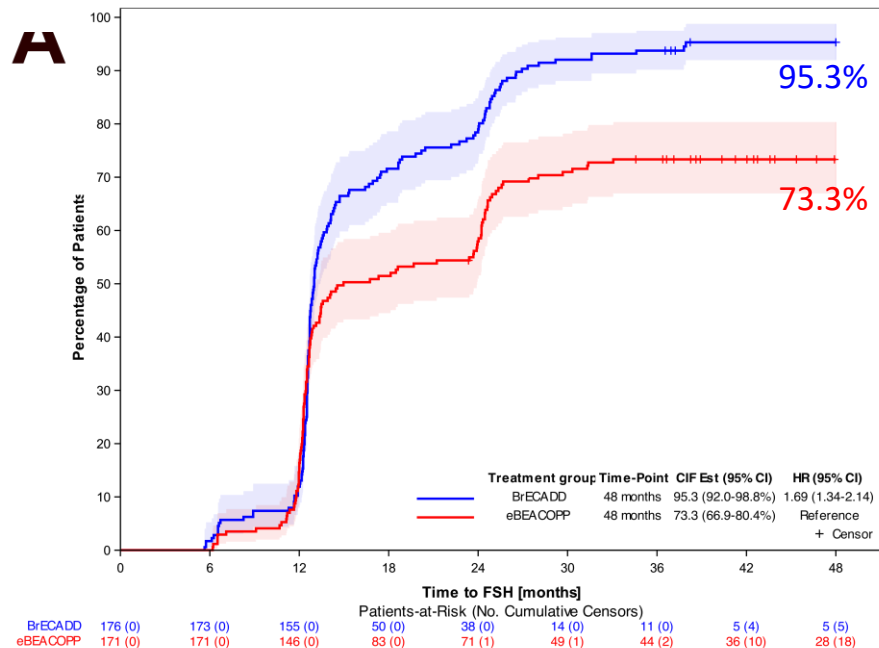
GHSG HD21 Health-related Quality of Life



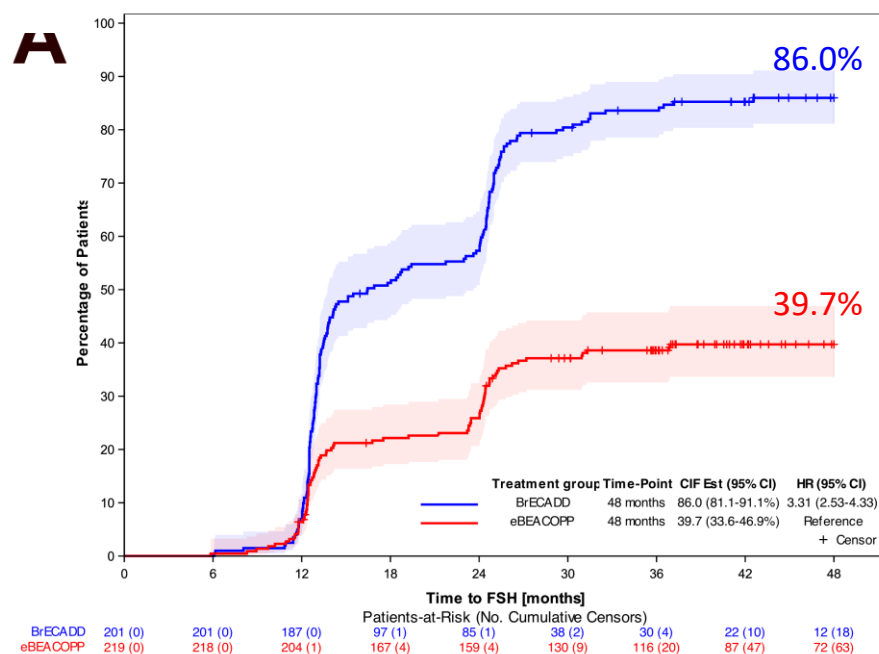
Global Health status in the BrECADD and eBEACOPP group: mean deviations from population reference values over time

GHSB HD21 gonadal function (FSH-recovery)

Women up to 40

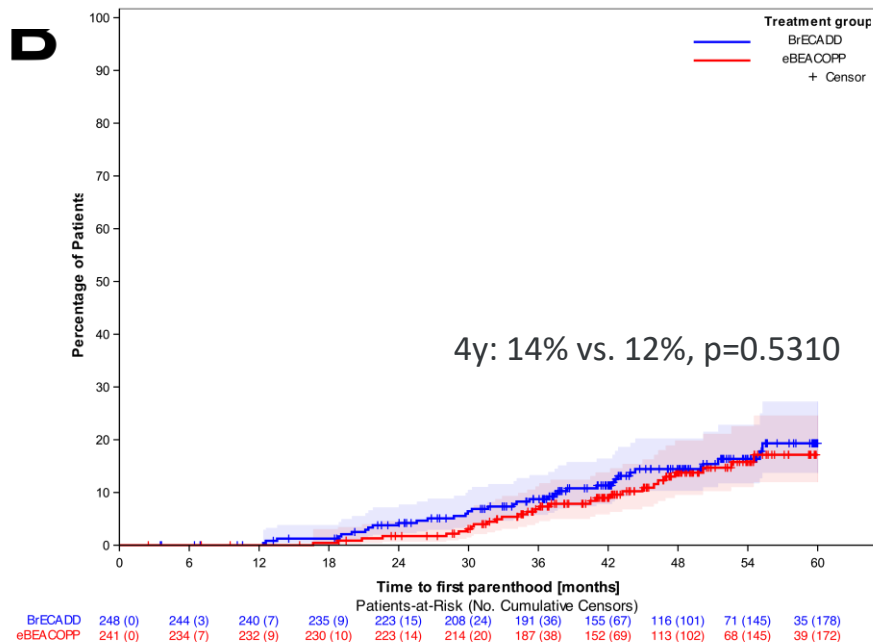


Men up to 50

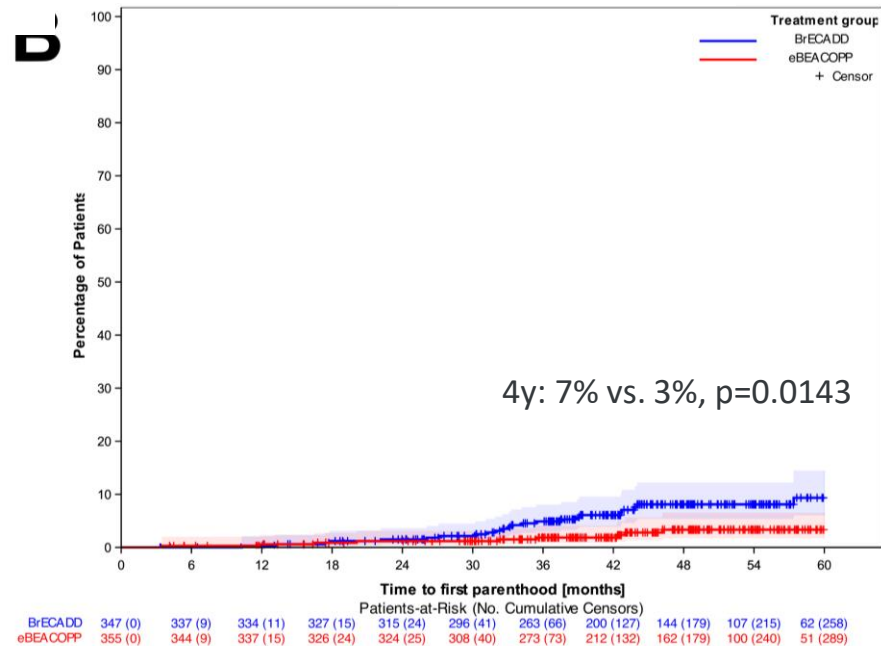


GHSg HD21 gonadal function (FSH-recovery)

Women up to 40

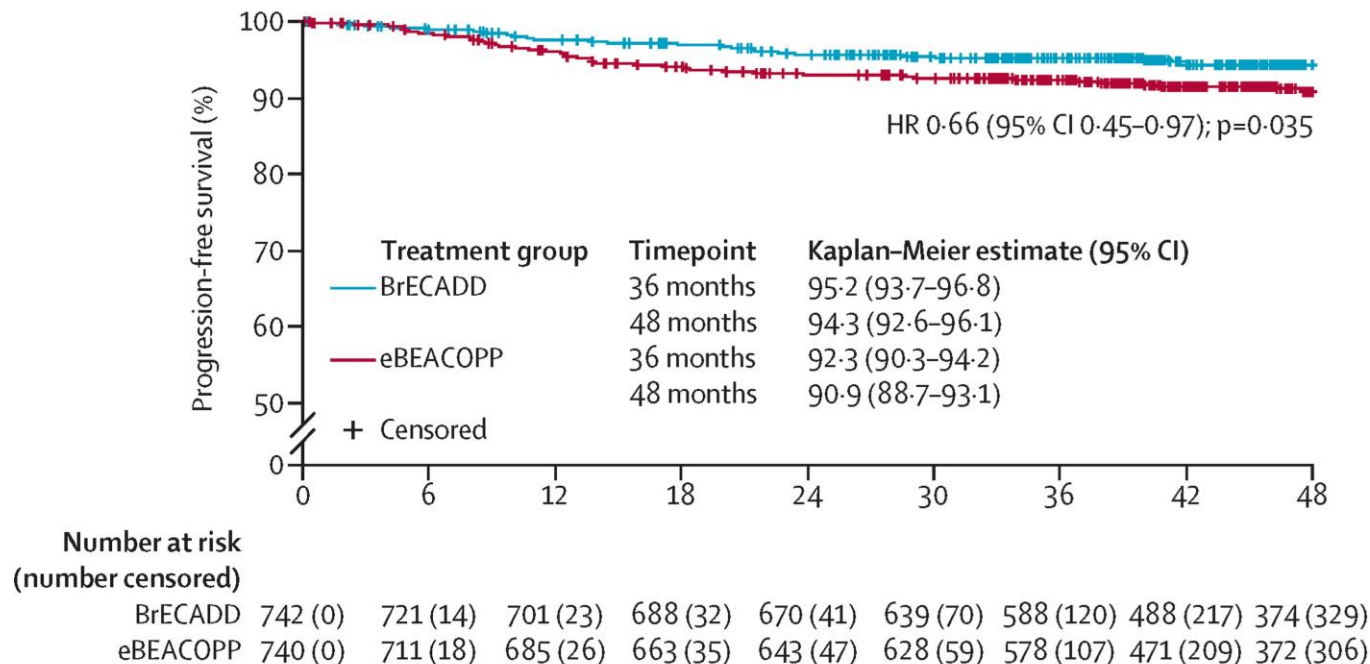


Men up to 50



HD21 final analysis (4y-FU): Efficacy of BrECADD is superior to eBEACOPP

Progression-free survival



GHSB HD21: Summary and Conclusions

Higher cure rate:

Efficacy of BrECADD is superior to eBEACOPP reaching an unprecedented PFS of 94.3%.

The high efficacy seems to be a direct consequence of improved deliverability.

Better tolerability:

BrECADD caused less acute side effects and addresses concerns with eBEACOPP:

Feasibility: Less complex

Brevity: Most patients receive only 4 cycles

Fertility: Improved gonadal function recovery. High rates of pregnancy and childbirth.

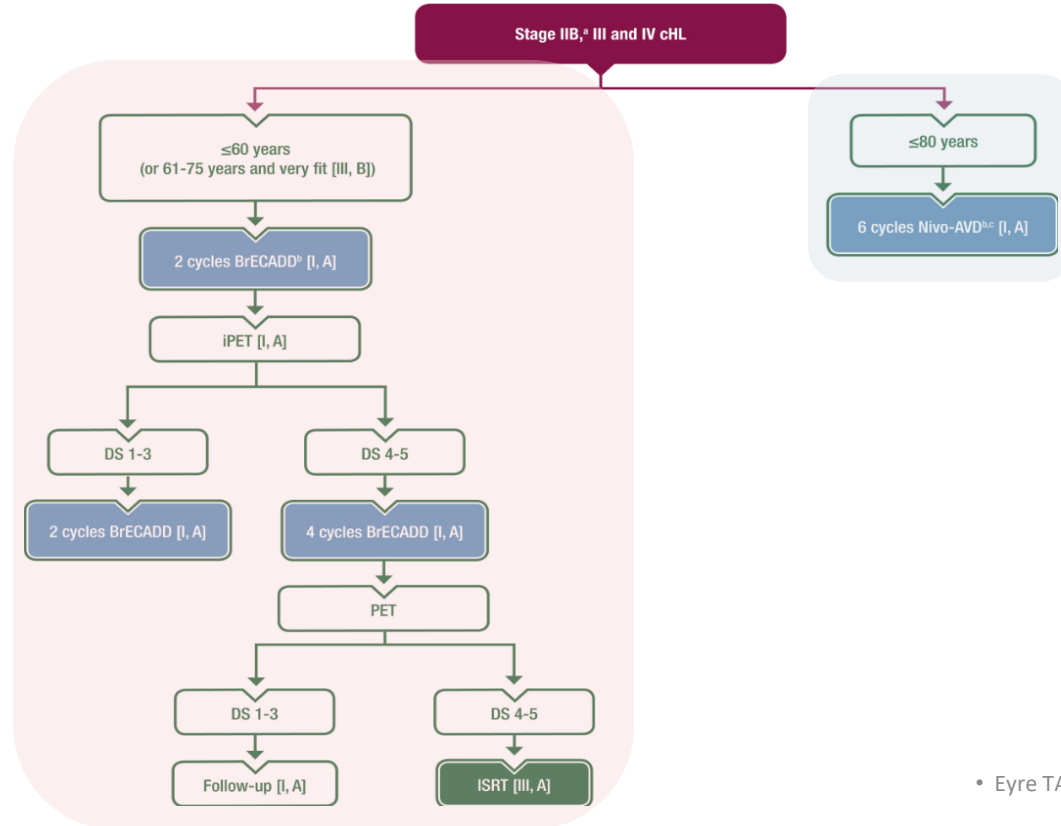
Long term toxicity: Omission of neuro- geno- and pneumotoxic agents with low rates of polyneuropathy and organ dysfunction.

HD21 has met both co-primary endpoints and thus established PET-2 guided BrECADD as standard option in AS-cHL

Unmet needs: BV-AVD vs. BrECADD

- **Cure rate:** 82.2% 5y-PFS vs. 94.3% 4y-PFS
- **Long term toxicity:**
 - PNP: 67% G1 and 4% G3-4 vs. 39% G1 and 1% G3-4
 - Doxorubicine: 300 mg/m² vs. 140-210 mg/m²
- **Duration:**
 - 6 months vs. 3-4.5 months

2025 ESMO Guidelines: Advanced-Stage HL



Older patients

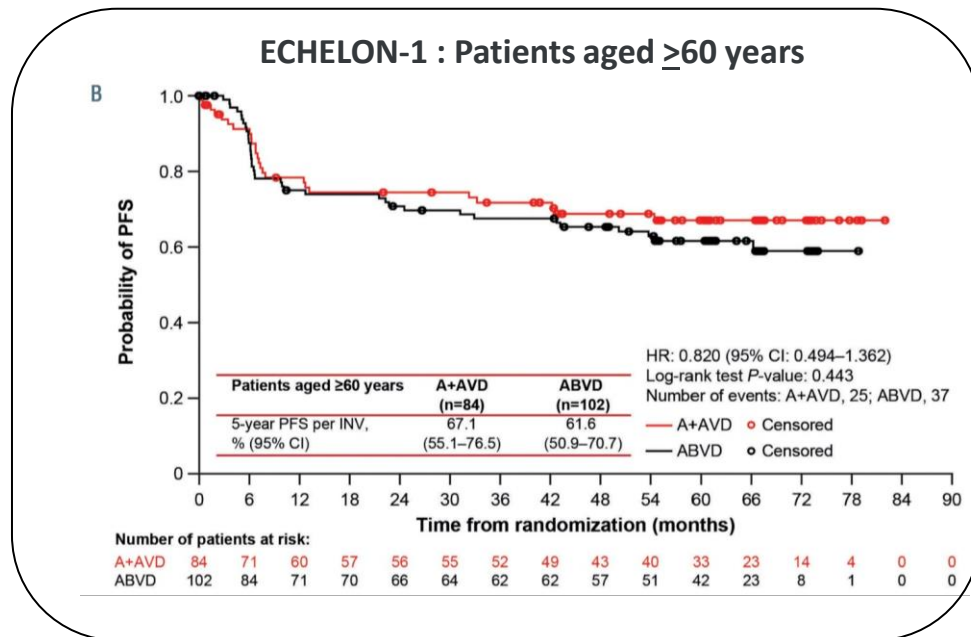
Area of high unmet need...

Background and objective in older patients with AS-cHL

Older patients with advanced-stage Hodgkin Lymphoma (AS-cHL) have inferior outcomes and fewer treatment options.

- eBEACOPP is not feasible with a treatment-related mortality of approx. 15%.²

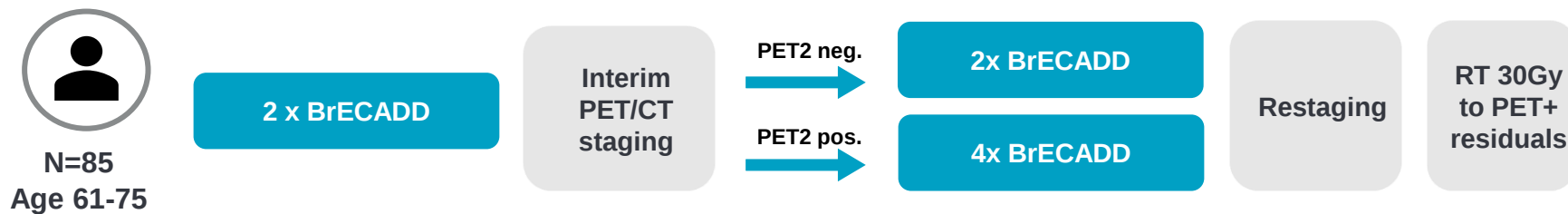
- 5y-PFS of BV-AVD (67%) and ABVD (62%) is insufficient.¹



➤ High unmet need for effective treatment options in patients with AS-cHL older than 60 years.

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 with AS-cHL

Baseline Characteristics

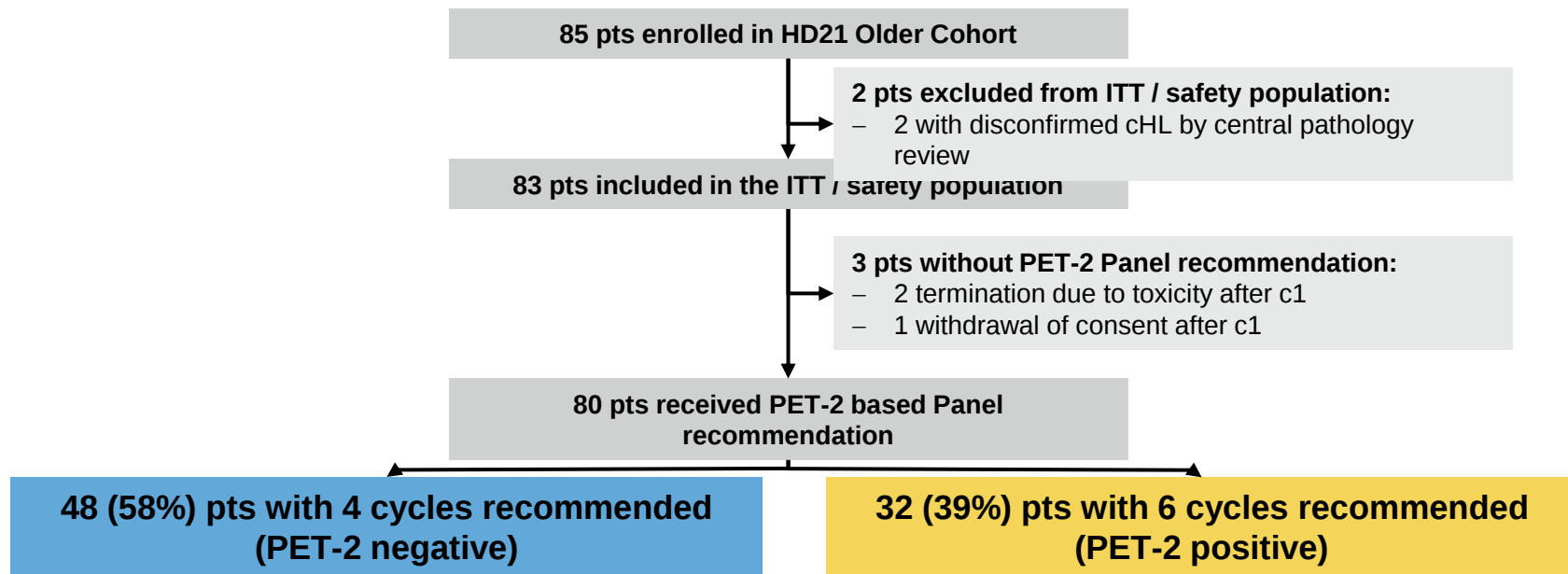
ITT population (n=83)

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

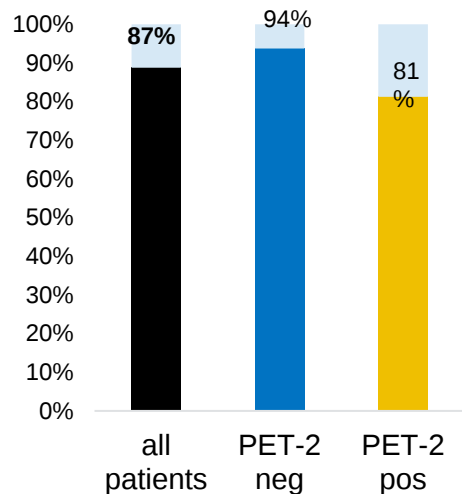
Trial flowchart



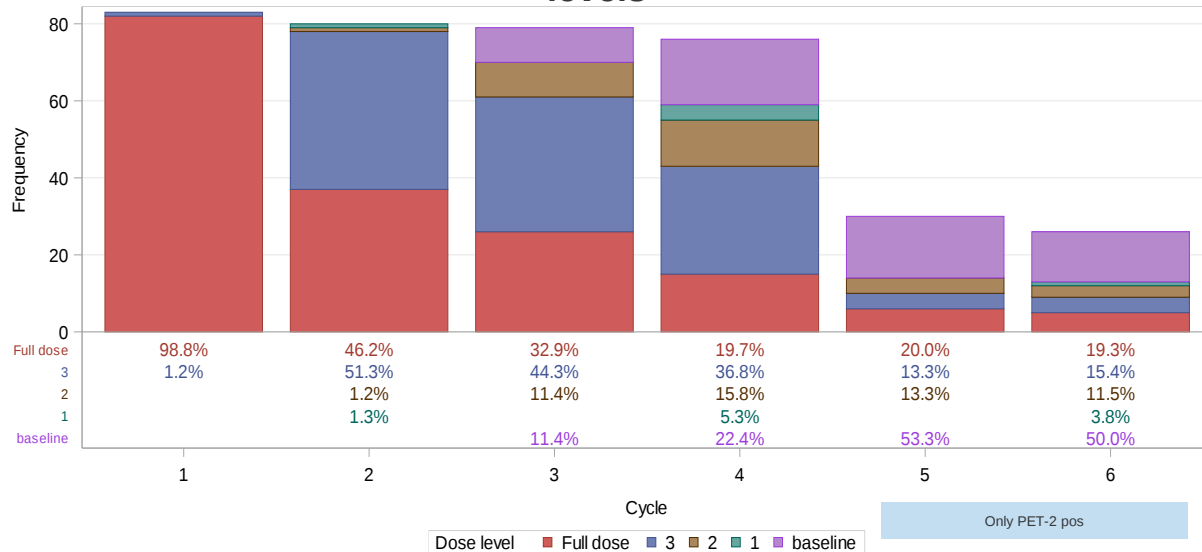
➤ A majority of patients achieved CR in PET2 and was scheduled for 4 cycles of BrECADD.

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

Adverse Events

Summary

- Most common higher grade toxicities were hematologic, incl. anemia (69%) and thrombocytopenia (86%).
- Neutropenic fever occurred in 46 (55%) patients.
- Grade 2 sensory PN occurred in 9 (11%); one (1%) patient had G3.
- No Grade 5 toxicity

Adverse event*	Any Grade (%)	Grade ≥ 3 (%)
Anemia	81 (98)	57 (69)
Thrombocytopenia	78 (94)	71 (86)
Leukopenia	81 (98)	80 (96)
Neutropenic fever	46 (55)	46 (55)
Infection	55 (65)	39 (47)
Cardiac disorders	23 (28)	2 (2)
Gastrointestinal disorders	60 (72)	19 (23)
Nausea	30 (36)	4 (5)
Mucositis	47 (57)	14 (17)
Peripheral sensory neuropathy**	33 (40)	1 (1)
Nervous system disorder (other than neuropathy)	24 (29)	3 (4)
Renal and urinary disorders	12 (15)	3 (4)
Respiratory, thoracic and mediastinal disorders	37 (45)	5 (6)
Skin and subcutaneous tissue disorders	35 (42)	1 (1)
Hematological TRMB¹ event (%)	60 (72)	
Organ TRMB¹ event (%)	28 (34)	
Any TRMB¹ event (%)	66 (80)	

* Frequency ≥10%, ** PNP G2 or higher in 11 (12%) pts. TRMB = Treatment-related morbidity

Ferdinandus J, JCO 2025

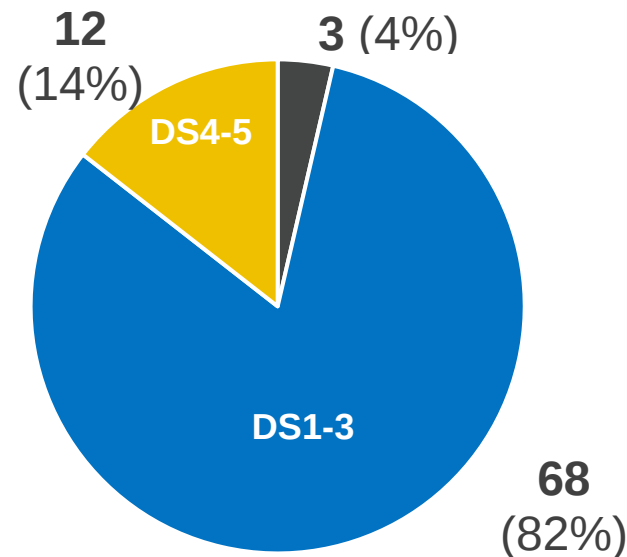
Primary Endpoint: CR Rate after Chemotherapy

CR rate after Chemotherapy: 68/83 patients (82%; 95%CI 72 – 90)

- 4 cycles: 45/48 patients (94%; 95%CI 83 – 99)
- 6 cycles: 23/32 patients (72%; 95%CI 53 – 86)

Non-CR due to:

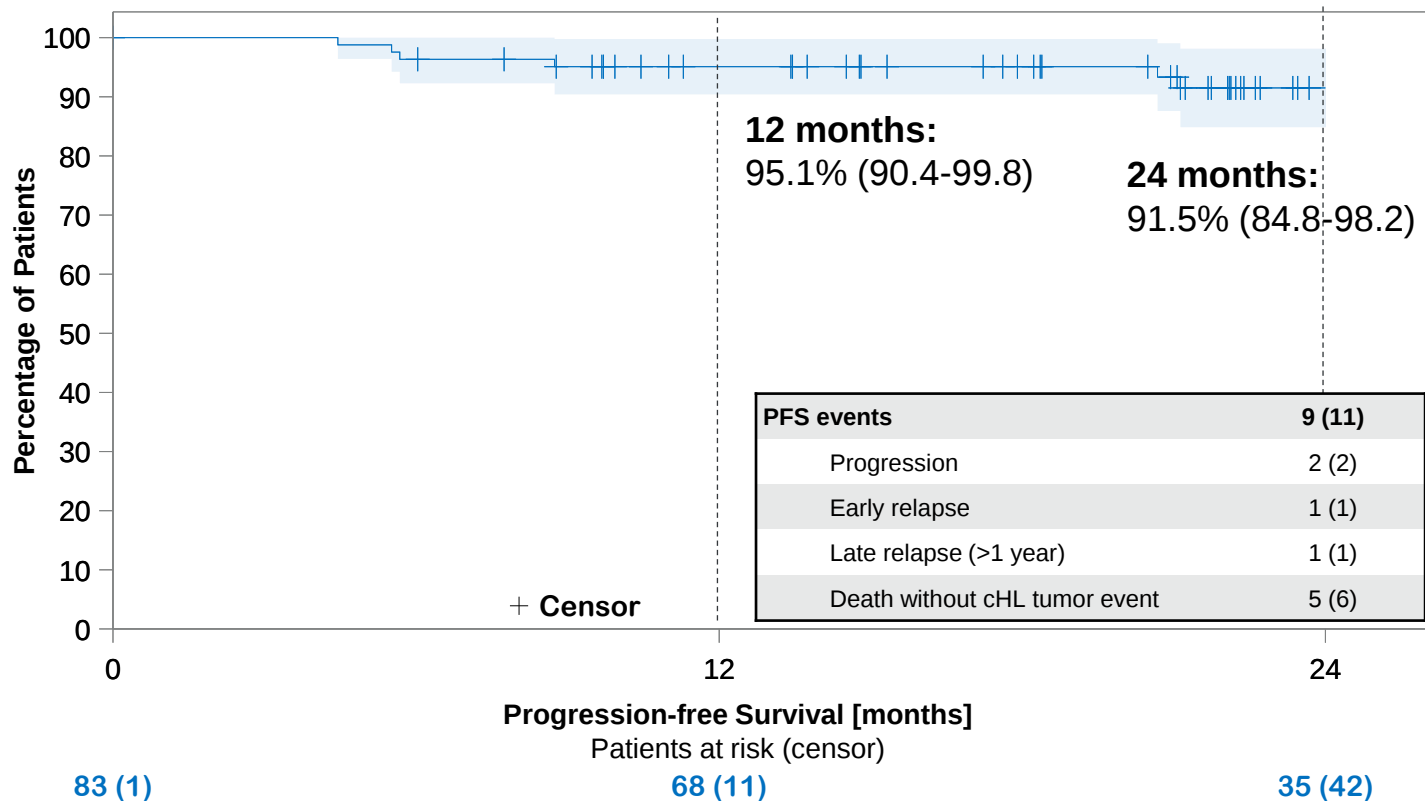
- Non-CR (DS4-5) at EOT by central review (N=12)
- No response assessment available (N=3)



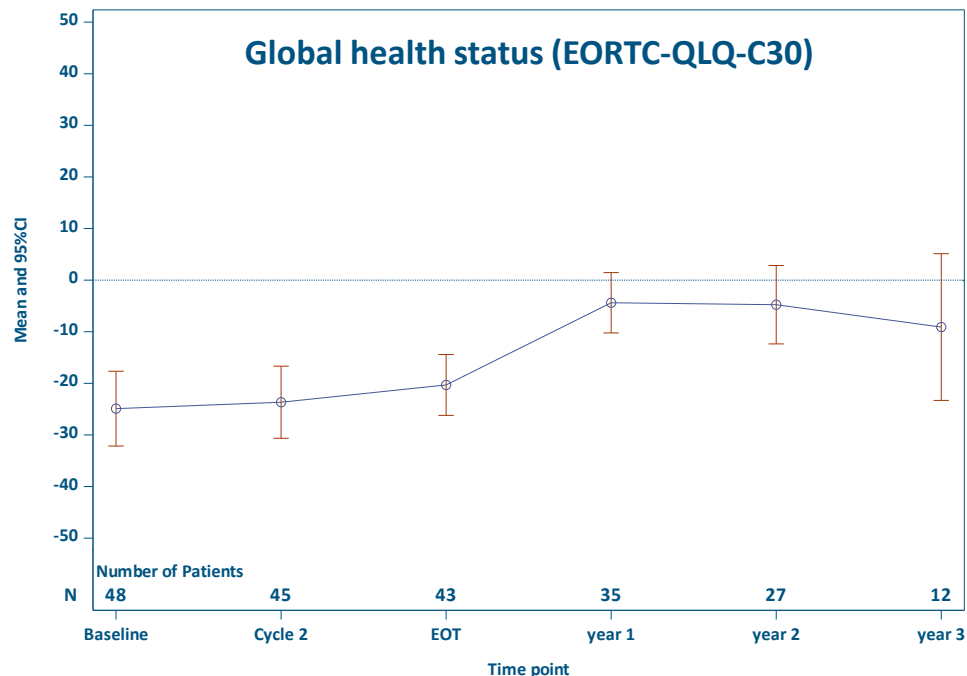
Most patients (82%) were in CR after receiving PET-guided BrECADD.

Progression-free survival

mFU 23 months



Health-related Quality of Life



Dedicated analysis of patient reported outcomes in patients providing separate consent to identify impact on health-related quality of life.

EORTC questionnaires (QLQ-C30, CIPN-20, FA12)

Sex- and age- adjusted differences to reference population of general health status by QLQ-C30:

Improvement after treatment

Similar improvements in terms of symptom- and functioning scales.

Initially impaired HRQoL improved already during treatment and normalized during follow-up

Summary of my recommendations for patients > 60 years

Strategy	PFS (%)	OS (%)	Pros	Cons	My considerations
6x A(B)VD (Evens, Br J Haematol, 2013)	FFS: 48% @ 5y	58% @ 5y	Safe	Low efficacy	My former SOC
6x BV-AVD (Echelon1)	81% @ 2y	96% @ 2y	No better survival outcome than with ABVD	More neurotoxicity and neutropenia than ABVD	
2xBV+ 6xAVD+ 4xBV (Evens, J Clin Oncol, 2018)	PFS: 84% @ 2y	93% @ 2y	Better tolerability than 6x A(B)VD	Only Ph II data	Unfit?
CHOP-21 (Kolstad, Leuk Lymphoma, 2007)	PFS: 76% @ 3y	79% @ 3y	Safe and feasible also in elderly patients	Low evidence	Unfit!*
6x N-AVD (S1826)	PFS: 88% @ 2y	96% @ 2y	OS Benefit compared to BV-AVD	Short FU until now	New SOC?
4-6x BrECADD (HD21)	PFS: 91.5% @ 2y	91% @ 2y	Highest efficacy reported, PD1 reserved for 2L	More acute side effects (hematotoxicity, FN, infections), Only Ph II data	fit

Many thanks for your attention... and Greetings from Cologne!



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