Linfoma de Hodgkin- Estamos listos para iPD1 en 1L?

Talita Silveira, MD, PhD

AC Camargo Cancer Center

Santa Casa São Paulo

Faculdade Ciências Médicas Albert Einstein

Disclosure

No disclosure for this presentation

Reality

Expectation

Definition

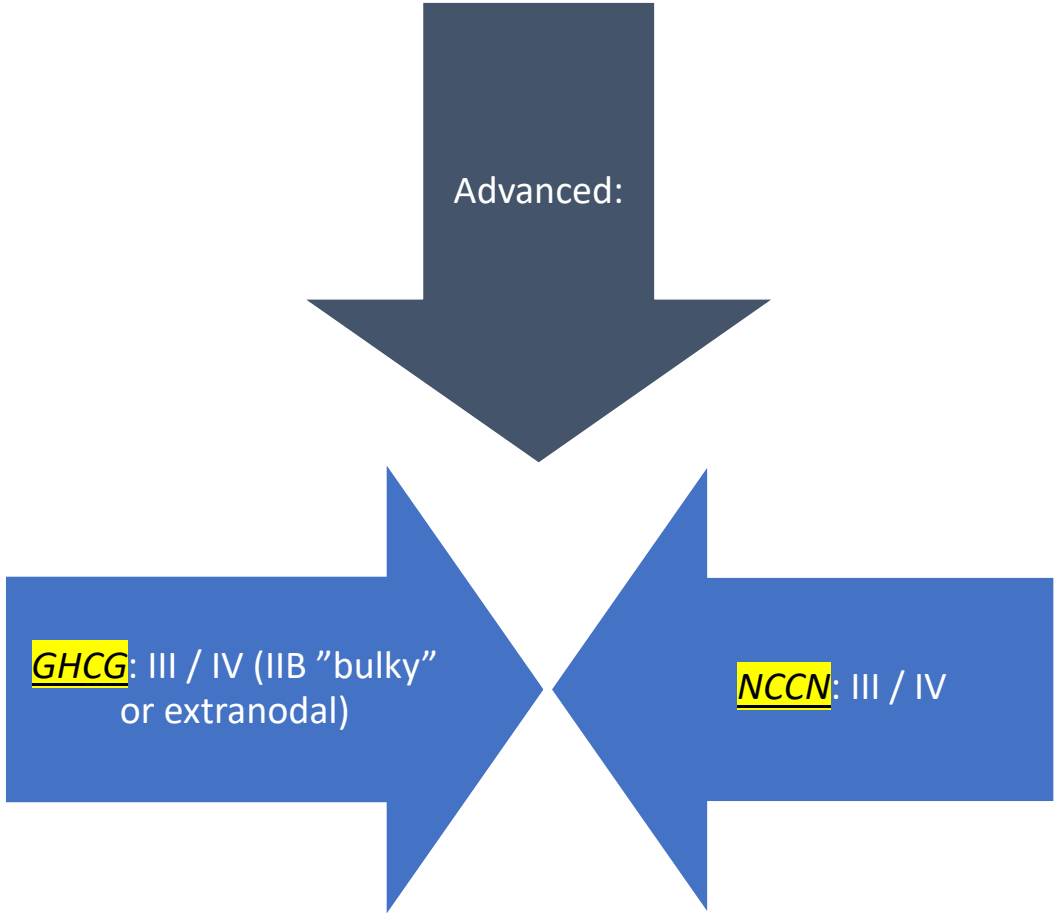


Table 2. Revised Staging System for Primary Nodal Lymphomas

Stage	Involvement	Extranodal (E) Status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky*	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

NOTE. Extent of disease is determined by positron emission tomography–computed tomography for avid lymphomas and computed tomography for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

*Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

NCCN VERSION 1.2017

Cheson BD. *J Clin Oncol*. 2014

IPS

International Prognostic Score (IPS) 1 point per factor (advanced disease)†

- Albumin <4 g/dL
- Hemoglobin <10.5 g/dL
- Male
- Age ≥45 years
- Stage IV disease
- Leukocytosis (white blood cell count at least 15,000/mm^3)
- Lymphocytopenia (lymphocyte count less than 8% of white blood cell count, and/or lymphocyte count less than 600/mm^3)

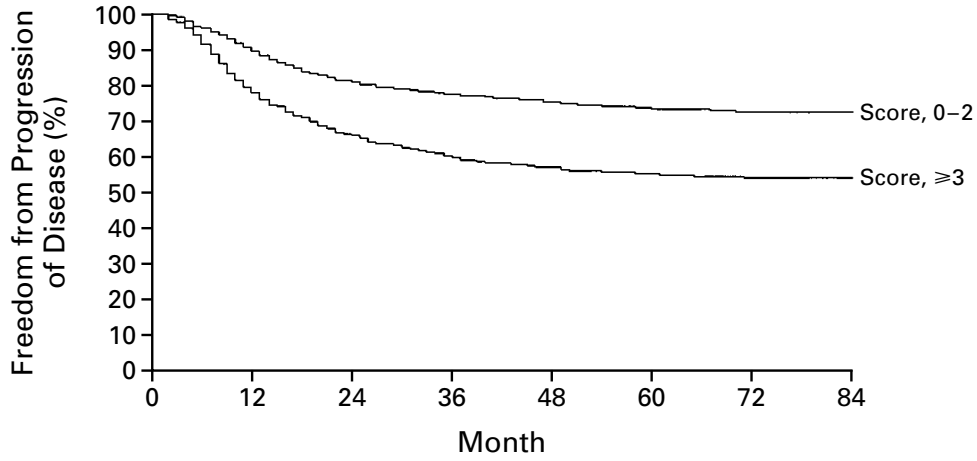


Figure 3. Freedom from Progression of Disease in 1618 Patients According to Whether the Prognostic Score Was 0 to 2 or 3 or Higher.

Diefenbach CS. *Br J Haematol.2015*
Hasenclever D. *N Engl J Med*. 1998

Treatment

ABVD

BEACOPPesc

Treatment

BV-AVD

ABVD

BEACOPPesc

Treatment

BV-AVD

ABVD

B(R)EACOPP(DD)esc

NIVO-AVD

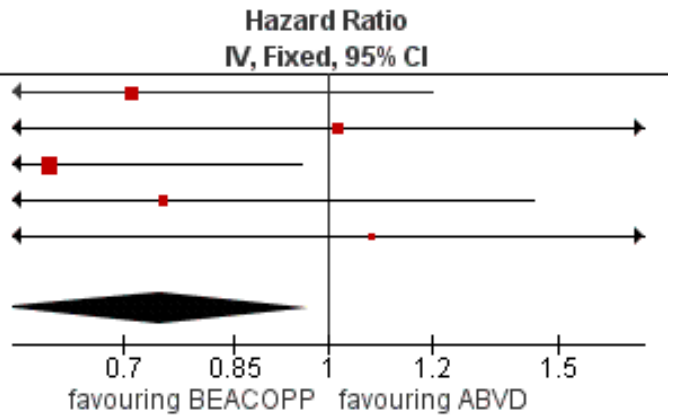
Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma (Review)

Skoetz N, Will A, Monsef I, Brillant C, Engert A, von Tresckow B

Figure 3. Forest plot of comparison: 1 Analysis of Overall Survival, outcome: 1.1 OS - all - same recruitment period between the 2 arms (HD9).

Study or Subgroup	log[Hazard Ratio]	SE	BEACOPP Total	ABVD Total	Weight	Hazard Ratio IV, Fixed, 95% CI
EORTC 20012	-0.3425	0.2679	274	275	24.9%	0.71 [0.42, 1.20]
GHSG HD14	0.02	0.32	805	818	17.4%	1.02 [0.54, 1.91]
GHSG HD9	-0.485	0.225	265	177	35.3%	0.62 [0.40, 0.96]
GSM-HD 2008	-0.287	0.331	163	168	16.3%	0.75 [0.39, 1.44]
HD 2000	0.077	0.538	98	99	6.2%	1.08 [0.38, 3.10]
Total (95% CI)			**1605**	**1537**	**100.0%**	**0.74 [0.57, 0.97]**

Heterogeneity: Chi² = 2.19, df = 4 (P = 0.70); I² = 0%
Test for overall effect: Z = 2.21 (P = 0.03)

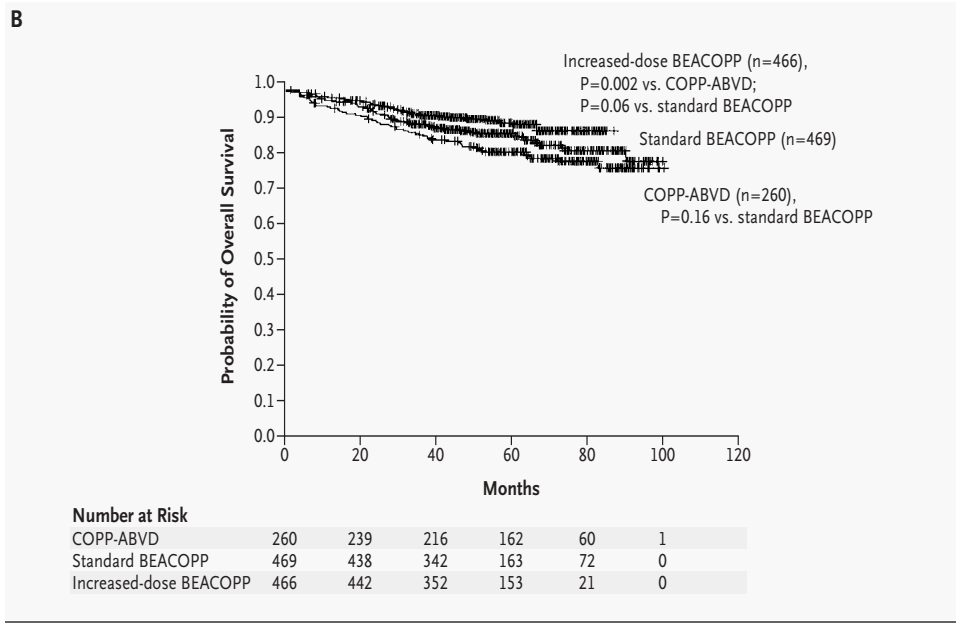


Treatment- HD9

Standard and Increased-Dose BEACOPP Chemotherapy Compared with COPP-ABVD for Advanced Hodgkin's Disease

Table 1. Planned Regimens of Cyclophosphamide, Vincristine, Procarbazine, Prednisone, Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine (COPP-ABVD) and Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, and Prednisone (BEACOPP).

Drug	COPP-ABVD		Standard BEACOPP		Increased-Dose BEACOPP	
	Single Dose	Days Given*	Single Dose	Days Given†	Single Dose	Days Given†
	mg/m²		*mg/m²*		*mg/m²*	
Bleomycin	10	29, 43	10	8	10	8
Etoposide	—	—	100	1–3	200	1–3
Doxorubicin	25	29, 43	25	1	35	1
Cyclophosphamide	650	1, 8	650	1	1200	1
Vincristine	1.4‡	1, 8	1.4‡	8	1.4‡	8
Procarbazine	100	1–14	100	1–7	100	1–7
Prednisone	40	1–14	40	1–14	40	1–14
Vinblastine	6	29, 43	—	—	—	—
Dacarbazine	375	29, 43	—	—	—	—



Diehl V. *N Engl J Med*. 2003

Treatment

Table 3. Acute Adverse Effects of Chemotherapy.*

Adverse Effect	COPP-ABVD	Standard BEACOPP	Increased-Dose BEACOPP
		percent	
Leukopenia			
Grade 3	52	36	8
Grade 4	19	37	90
Thrombocytopenia			
Grade 3	4	6	23
Grade 4	2	3	47
Anemia			
Grade 3	4	16	51
Grade 4	1	1	15
Infection			
Grade 3	2	13	14
Grade 4	1	3	8
Mucositis of grade 3 or 4	1	2	8
Respiratory tract effects of grade 3 or 4	2	5	4
Nausea of grade 3 or 4	20	12	20
Digestive tract effects of grade 3 or 4	3	2	4
Neurologic effects of grade 3 or 4	4	5	4
Skin effects of grade 3 or 4	1	1	3
Pain of grade 3 or 4	2	3	9
Hair loss of grade 3 or 4	36	75	79

Number of cycles
Age
Final radiotherapy

Diehl V. *N Engl J Med*. 2003

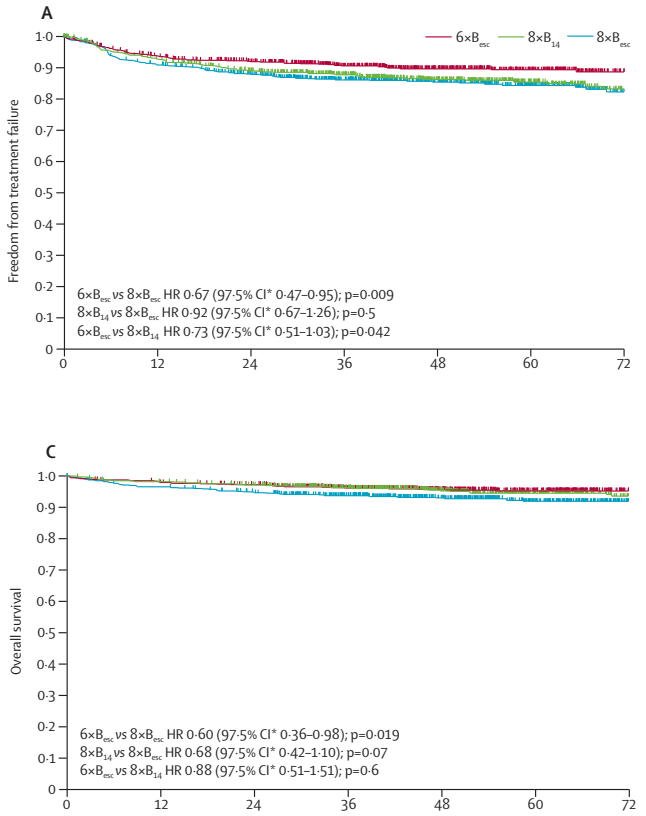
HD15

	8×BEACOPP$_{escalated}$ (N=705)	6×BEACOPP$_{escalated}$ (N=711)	8×BEACOPP$_{14}$ (N=710)
Acute toxicity (WHO grade 3 or 4)*			
At least one event	658/684 (96·2%)	671/696 (96·4%)	619/693 (89·3%)
Leucopenia	613/684 (89·6%)	619/696 (88·9%)	504/693 (72·7%)
Anaemia	425/684 (62·1%)	370/696 (53·2%)	385/693 (55·6%)
Thrombocytopenia	429/684 (62·7%)	372/696 (53·4%)	133/693 (19·2%)
Any haematological	632/684 (92·4%)	638/696 (91·7%)	552/693 (79·7%)
Alopecia	374/684 (54·7%)	368/696 (52·9%)	369/693 (53·2%)
Infection	169/684 (24·7%)	155/696 (22·3%)	143/693 (20·6%)
Nausea or vomiting	88/684 (12·9%)	77/696 (11·1%)	74/693 (10·7%)
Mucositis	83/684 (12·1%)	73/696 (10·5%)	55/693 (7·9%)
Pain	90/684 (13·2%)	64/696 (9·2%)	56/693 (8·1%)
Nervous system	52/684 (7·6%)	35/696 (5·0%)	88/693 (12·7%)
Respiratory tract	44/684 (6·4%)	26/696 (3·7%)	64/693 (9·2%)
Gastrointestinal tract	47/684 (6·9%)	44/696 (6·3%)	41/693 (5·9%)
Drug fever	30/684 (4·4%)	28/696 (4·0%)	31/693 (4·5%)
Secondary neoplasia			
Total	33 (4·7%)	17 (2·4%)	22 (3·1%)
sAML/MDS	19 (2·7%)	2 (0·3%)	8 (1·1%)
NHL	8 (1·1%)	6 (0·8%)	5 (0·7%)
Solid tumour	6 (0·9%)	9 (1·3%)	9 (1·3%)
Causes of death			
Total	53 (7·5%)	33 (4·6%)	37 (5·2%)
Hodgkin's lymphoma	13 (1·8%)	11 (1·5%)	15 (2·1%)
Treatment-related toxic effects	15 (2·1%)	6 (0·8%)	6 (0·8%)
Secondary neoplasia	13 (1·8%)	5 (0·7%)	8 (1·1%)
Toxic effects of salvage treatment	2 (0·3%)	2 (0·3%)	1 (0·1%)
Other†	6 (0·9%)	6 (0·8%)	4 (0·6%)
Unclear	4 (0·6%)	3 (0·4%)	3 (0·4%)

Data are number (%) or n/N (%). sAML=secondary acute myeloid leukaemia. MDS=myelodysplastic syndrome. NHL=non-Hodgkin's lymphoma. *Toxicities with an incidence of at least 3% only. †Suicide (n=3), cardiovascular (n=3), respiratory (n=2), accident (n=2), single reasons (n=6).

Table 2: **Adverse events by treatment group**

Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial



Engert A. *The Lancet*. 2012

PET adapted treatment - HD18

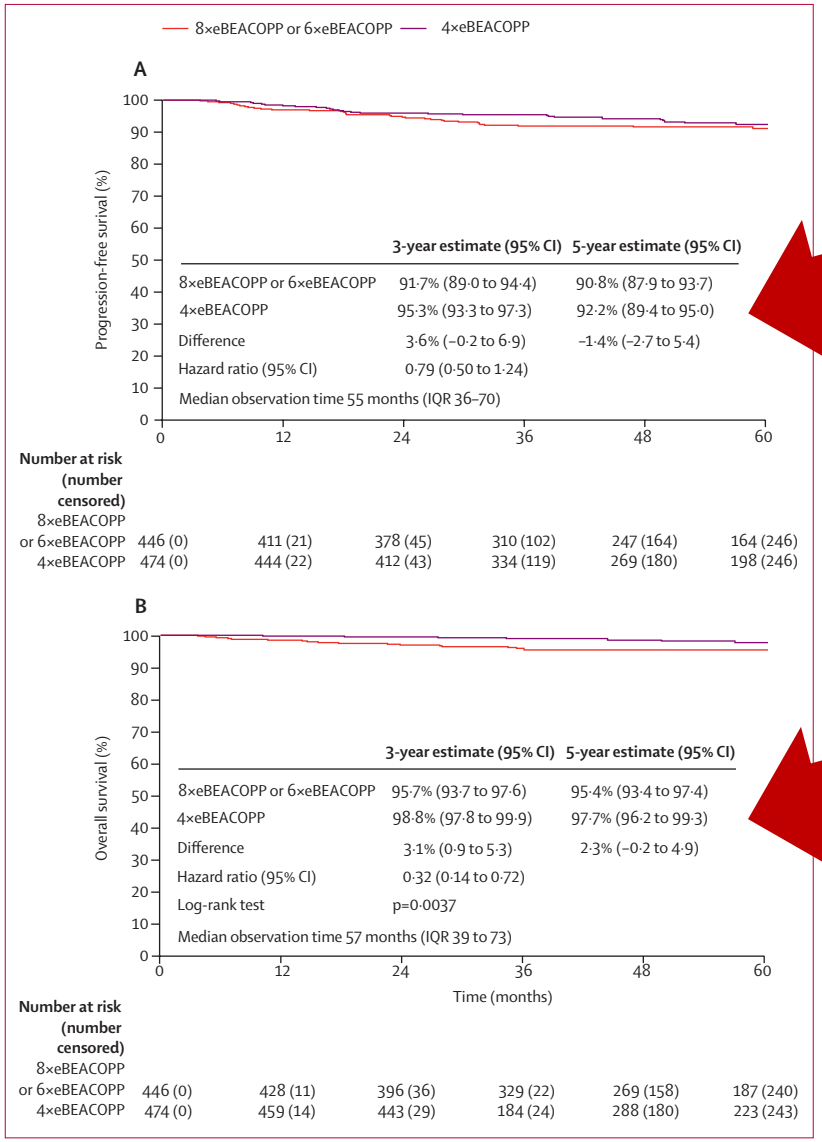


Figure 4: **Progression-free survival and overall survival for patients with negative PET-2**
Kaplan-Meier estimates of (A) progression-free survival and (B) overall survival for patients with negative PET-2, in the per-protocol set. PET-2=PET after two cycles of chemotherapy. eBEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine in escalated dose.

Borchmann P. *Lancet*. 2017

HD18

	8 × eBEACOPP (n=288)	6 × eBEACOPP (n=216)	4 × eBEACOPP (n=501)
Severe protocol deviations			
Discontinuation due to toxicity	11 (4%)	0	2 (<1%)
Patient withdraws from chemotherapy	18 (6%)	4 (2%)	1 (<1%)
Administration of more than target number of chemotherapy cycles	0	0	6 (1%)
Other or unknown*	7 (2%)	4 (2%)	7 (1%)
Toxicity and supportive measures†			
Anaemia	164 (57%)	110 (51%)	195 (39%)
Thrombopenia	212 (74%)	150 (70%)	286 (57%)
Leukopenia	268 (93%)	199 (93%)	438 (88%)
Anaemia, thrombopenia or leukopenia	274 (95%)	202 (94%)	447 (90%)
Infection	50 (17%)	25 (12%)	40 (8%)
Organ toxicities of CTCAE grade III or IV			
Nausea or vomiting	31 (11%)	18 (8%)	32 (6%)
Mucositis	26 (9%)	13 (6%)	28 (6%)
Gastrointestinal tract disorders	15 (5%)	14 (7%)	11 (2%)
Respiratory tract disorders	16 (6%)	4 (2%)	10 (2%)
Nervous system disorders	37 (13%)	15 (7%)	17 (3%)
Any organ toxicity‡	62 (22%)	29 (13%)	38 (8%)
Toxicities of CTCAE grade III or IV			
Treatment-related morbidity			
Any organ toxicity of CTCAE grade III or IV‡	62 (22%)	29 (13%)	38 (8%)
Anaemia, thrombopenia or infection of CTCAE grade IV	169 (59%)	115 (53%)	187 (38%)
Treatment-related morbidity	189 (66%)	132 (61%)	204 (41%)
Onset of treatment-related morbidity			
Cycles 5–6	30 (10%)	32 (15%)	NA
Cycles 7–8	24 (8%)	NA	NA
Febrile neutropenia			
Occurrence of febrile neutropenia	96 (33%)	49 (23%)	109 (22%)
Hospitalisation due to febrile neutropenia	71 (25%)	39 (18%)	90 (18%)
Onset of febrile neutropenia			
Cycles 1–4	69 (24%)	39 (18%)	109 (22%)
Cycles 5–6	16 (6%)	10 (5%)	NA
Cycles 7–8	11 (4%)	NA	NA
Supportive measures			
Use of G-CSF	286 (100%)	212 (99%)	495 (99%)
Platelet infusions	132 (46%)	72 (33%)	122 (24%)
Red blood cell transfusions	203 (71%)	129 (60%)	233 (47%)

Data are n (%). PET-2=positron emission tomography after two cycles of chemotherapy. eBEACOPP=bleomycin, CTCAE=Common Terminology Criteria for Adverse Events. G-CSF=granulocyte-colony stimulating factor. NA=not applicable. *Including patient refusal to continue with radiotherapy (n=1), no radiotherapy in spite of panel recommendation (n=1), radiotherapy without panel recommendation (n=4), violation of inclusion or exclusion criteria (n=3), lack of compliance (n=3), withdrawal of consent (n=2), treatment in non-participating centre (n=1), restaging not timely performed (n=1), unknown (n=2). †Documentation of chemotherapy missing in five (<1%) of 1005 patients; toxicity and supportive measures assessed in 287 patients in the 8 × eBEACOPP group, 215 patients in the 6 × eBEACOPP group, and 498 patients in the 4 × eBEACOPP group. ‡Also including urogenital tract, cardiac and skin disorders, drug fever, and allergy.

Table 3: **Therapy adherence, acute toxicities and supportive measures during chemotherapy of patients with negative PET-2, randomised intention-to-treat set**

Borchmann P. *Lancet*. 2017

AHL2011 trial

	Standard treatment group (n=413)		PET-driven treatment group (n=410)	
	Number of patients (%)	5-year progression-free survival (95% CI)	Number of patients (%)	5-year progression-free survival (95% CI)
PET after two induction cycles				
Reviewed	398 (96%)		397 (97%)	
Negative	349 (88%)	88·4% (83·3–92)	346 (87%)	89·4% (84·9–92·6)
Positive	49 (12%)	73·5% (58·7–83·6)	51 (13%)	68·2% (53·4–79·2)
PET after four induction cycles				
Reviewed	383 (93%)		376 (92%)	
Negative	356 (93%)	90·1% (85·3–93·3)	360 (96%)	89·2% (84·8–92·3)
Positive	27 (7%)	51·9% (31·9–58·5)	16 (4%)	37·5% (25·4–59·8)

Data are number (%) unless stated otherwise.

Table 2: **Metabolic response according to PET central review after two and four cycles of chemotherapy**

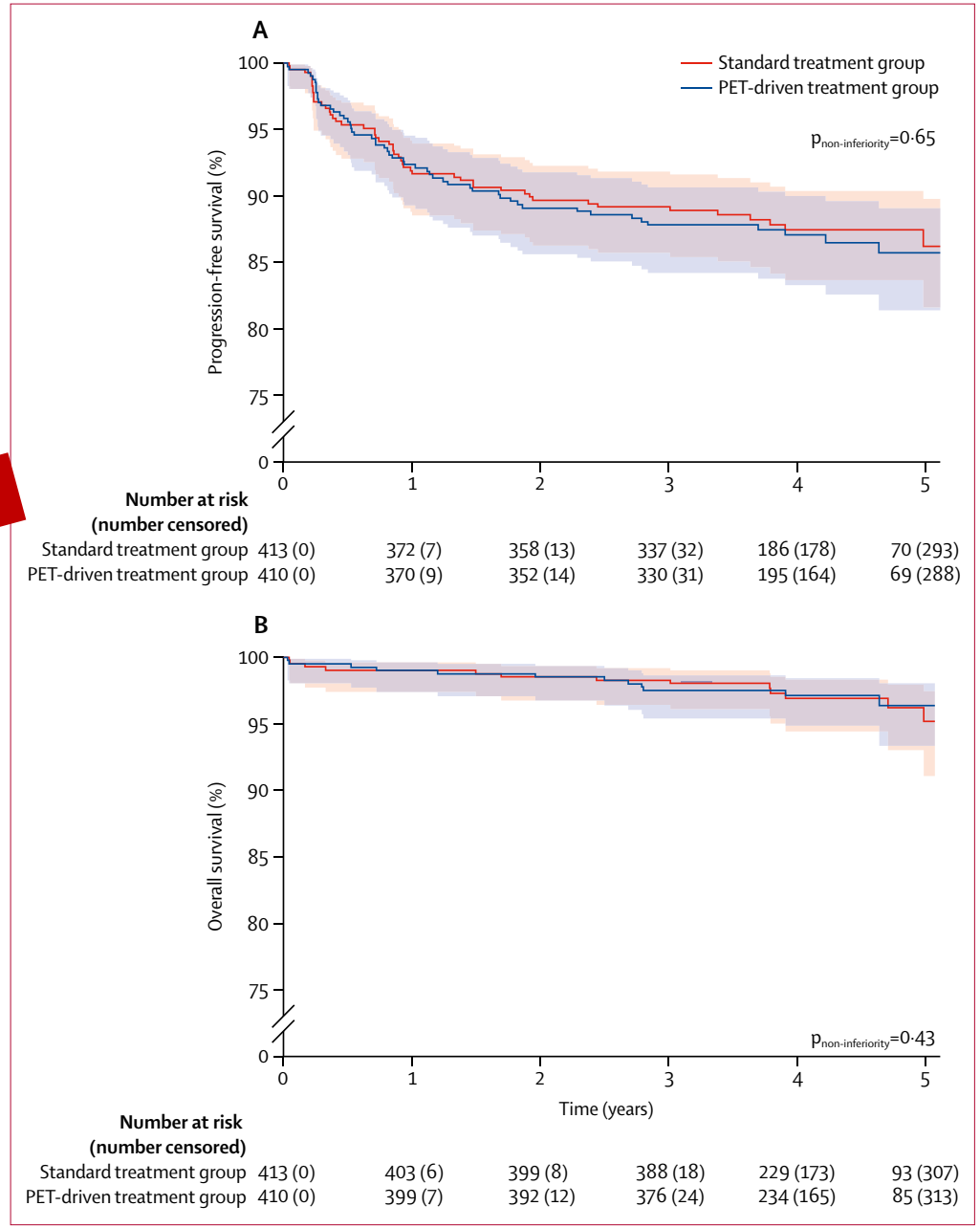
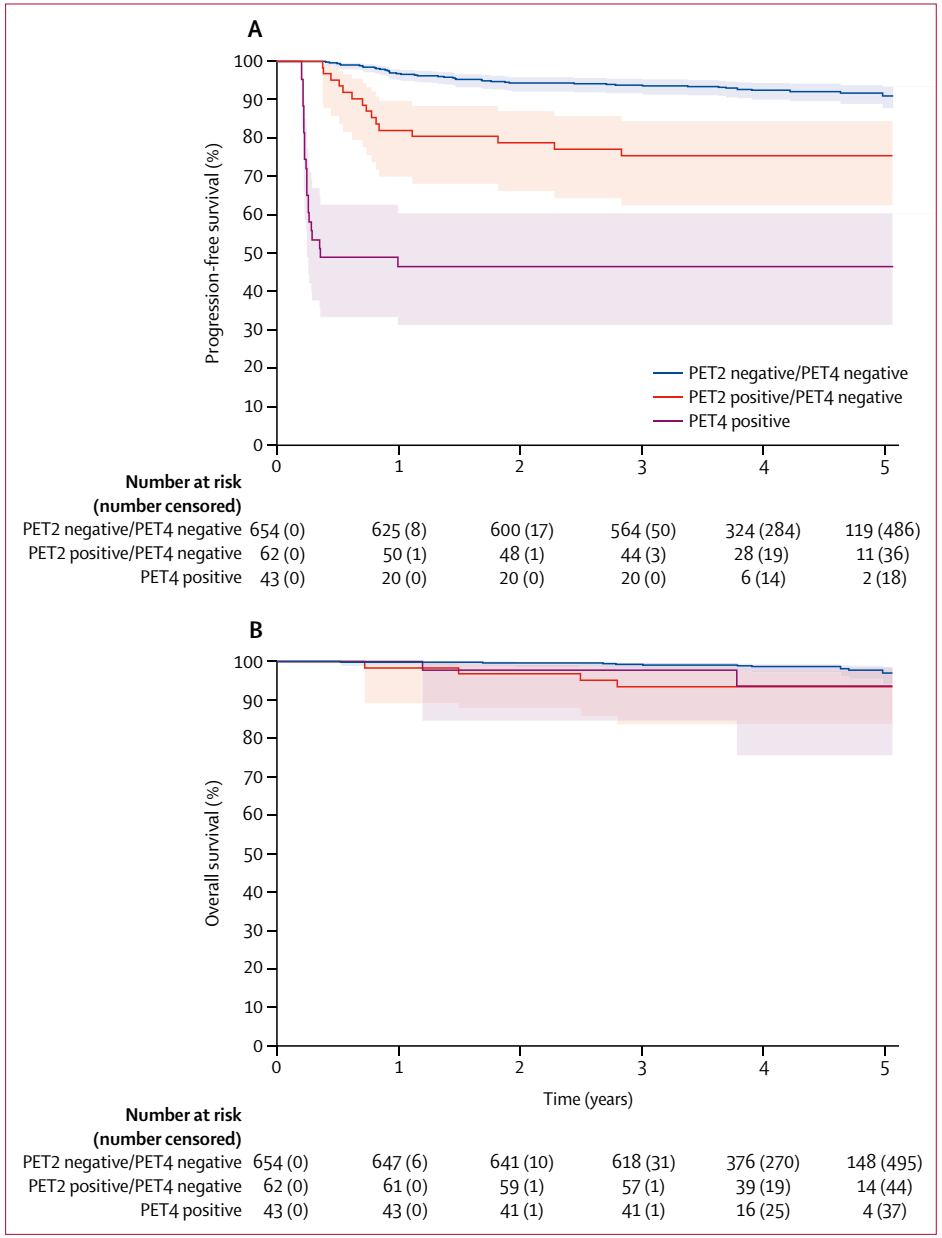


Figure 2: **Kaplan-Meier curves of survival outcomes by treatment group in the intention-to-treat population**
(A) Progression-free survival. (B) Overall survival. Data are survival estimates with 95% CIs.

Casanovas R. *TheLancet*. 2019



Casanovas R. *TheLancet*. 2019

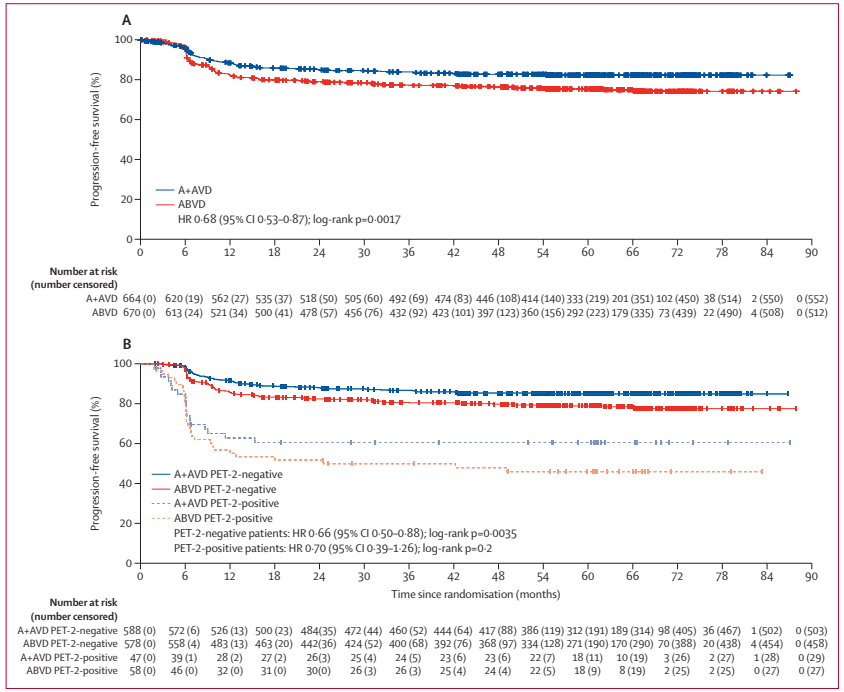
ECHELON-1

	A+AVD group (n=664)	ABVD group (n=670)	Total (n=1334)
Sex			
Female	286 (43%)	272 (41%)	558 (42%)
Male	378 (57%)	398 (59%)	776 (58%)
Median age, years	35 (26–51)	37 (27–53)	36 (26–52)
Age group, years			
<60	580 (87%)	568 (85%)	1148 (86%)
≥60	84 (13%)	102 (15%)	186 (14%)
Region			
Americas	261 (39%)	262 (39%)	523 (39%)
Europe	333 (50%)	336 (50%)	669 (50%)
Asia	70 (11%)	72 (11%)	142 (11%)
Ann Arbor stage at initial diagnosis			
Stage II*	1 (<1%)	0	1 (<1%)
Stage III	237 (36%)	246 (37%)	483 (36%)
Stage IV	425 (64%)	421 (63%)	846 (64%)
Not applicable, unknown, or missing	1 (<1%)	3 (<1%)	4 (<1%)
International Prognostic Score			
0–1	142 (21%)	141 (21%)	283 (21%)
2–3	355 (53%)	357 (53%)	712 (53%)
4–7	167 (25%)	172 (26%)	339 (25%)
ECOG performance status			
0	376 (57%)	378 (57%)	754 (57%)
1	260 (39%)	263 (39%)	523 (39%)
2	28 (4%)	27 (4%)	55 (4%)
Not obtained or missing	0	2 (<1%)	2 (<1%)
Extranodal involvement at diagnosis			
Yes	411 (62%)	416 (62%)	827 (62%)
1 extranodal site	217 (33%)	223 (33%)	440 (33%)
>1 extranodal site	194 (29%)	193 (29%)	387 (29%)
No	217 (33%)	228 (34%)	445 (33%)
Unknown or missing	36 (5%)	26 (4%)	62 (5%)
Patients with any B symptom	400 (60%)	381 (57%)	781 (59%)
PET-2 status			
Positive	47 (7%)	58 (9%)	105 (8%)
Negative	588 (89%)	578 (86%)	1166 (87%)
Unknown or unavailable	29 (4%)	34 (5%)	63 (5%)

Source: Connors et al, 2018.[7] Data are n (%) or median (IQR). A+AVD=brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine. ABVD=doxorubicin, bleomycin, vinblastine, and dacarbazine. ECOG=Eastern Cooperative Oncology Group. PET-2=PET scan done after two cycles of therapy. *Patients in this category had a major protocol violation.

Table 1: **Key characteristics of the intention-to-treat population**

Connors JM. *N Eng J Med*. 2018
Ansell S. *NEJM*. 2022



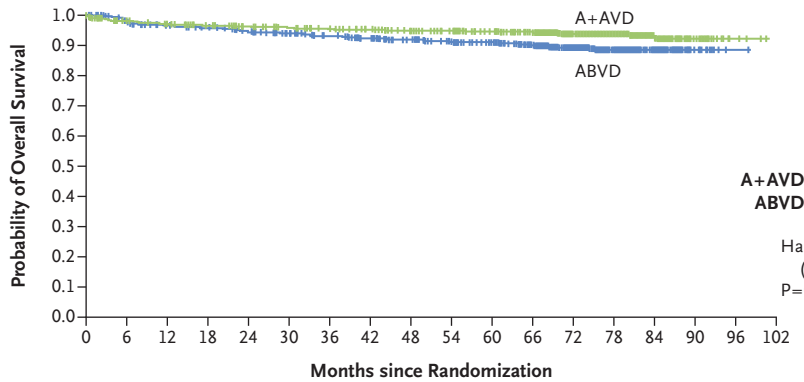


Figure 1. Overall Survival (Intention-to-Treat Population).

The intention-to-treat population included all the patients who underwent randomization. Tick marks indicate censored data. A+AVD denotes brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; and ABVD doxorubicin, bleomycin, vinblastine, and dacarbazine.

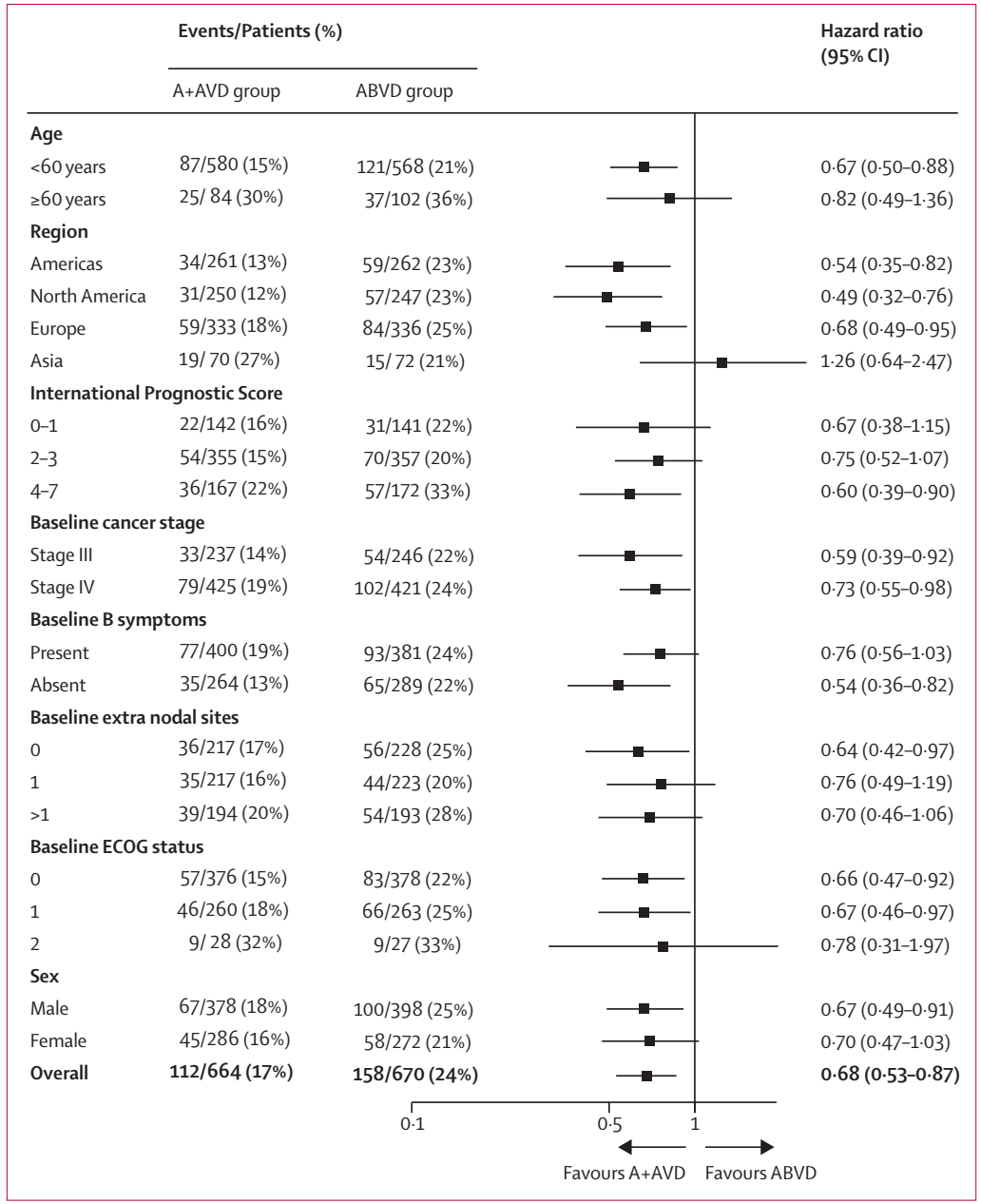
Ansell S. *NEJM*. 2022

	A+AVD group		ABVD group		HR (95% CI)	p value
	Number of patients	Progression-free survival (95% CI)	Number of patients	Progression-free survival (95% CI)		
All-patient analyses						
All patients	664	82·2% (79·0–85·0)	670	75·3% (71·7–78·5)	0·68 (0·53–0·87)	0·0017
PET-2-negative patients	588	84·9% (81·7–87·6)	578	78·9% (75·2–82·1)	0·66 (0·50–0·88)	0·0035
PET-2-positive patients	47	60·6% (45·0–73·1)	58	45·9% (32·7–58·2)	0·70 (0·39–1·26)	0·23
Patients <60 years						
All patients	580	84·3% (81·0–87·1)	568	77·8% (74·0–81·1)	0·67 (0·51–0·88)	0·0034
PET-2-negative patients	521	86·6% (83·3–89·3)	493	81·5% (77·7–84·7)	0·68 (0·49–0·93)	0·014
PET-2-positive patients	42	63·1% (46·4–75·9)	50	49·3% (34·7–62·3)	0·70 (0·37–1·33)	0·27
Patients ≥60 years						
All patients	84	67·1% (55·1–76·5)	102	61·6% (50·9–70·7)	0·82 (0·49–1·36)	0·44
PET-2-negative patients	67	71·9% (59·0–81·3)	85	64·9% (53·5–74·2)	0·72 (0·40–1·29)	0·27
PET-2-positive patients	5	40·0% (5·2–75·3)	8	25·0% (3·7–55·8)	0·92 (0·23–3·72)	0·91

p values were calculated with a log-rank test to compare progression-free survival between the two treatment groups. HRs (A+AVD *vs* ABVD) and 95% CIs were based on a Cox's proportional hazard regression model with treatment as the explanatory variable in the model. The all-patient analyses were stratified by region and IPS risk group; subgroup analyses were unstratified. A+AVD=brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine. ABVD=doxorubicin, bleomycin, vinblastine, and dacarbazine. HR=hazard ratio. PET-2=PET scan after two cycles of therapy. IPS=International Prognostic Score.

Table 2: **Progression-free survival per investigator assessment at 5 years by PET-2 status and age in the intention-to-treat population**

Ansell S. *NEJM*. 2022



Ansell S. *NEJM*. 2022

Table S5. Summary of Second Malignancies Recorded as Cause of Death by Treatment Arm

Treatment arm	Second Malignancy Category (Number of Patients)
A+AVD	Solid tumors (n=1) Prostate* (n=1)
ABVD	Solid tumors (n=4) Gastrointestinal (n=2) Gallbladder (n=1) Prostate (n=1)
	Hematological malignancies (n=7) Diffuse large B-cell lymphoma NOS (n=1) Precursor B-acute lymphoblastic leukemia/lymphoblastic lymphoma (n=1) Acute promyelocytic leukemia (n=1) Acute myeloid leukemia or related precursor neoplasm (n=1) Myelodysplastic syndrome (n=1) Peripheral T-cell lymphoma, NOS (n=1) Angioimmunoblastic T-cell lymphoma (n=1)

*Cause of death was likely due to pneumonia following diagnosis and treatment for metastatic prostate cancer.

A+AVD, brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; NOS, not otherwise specified.

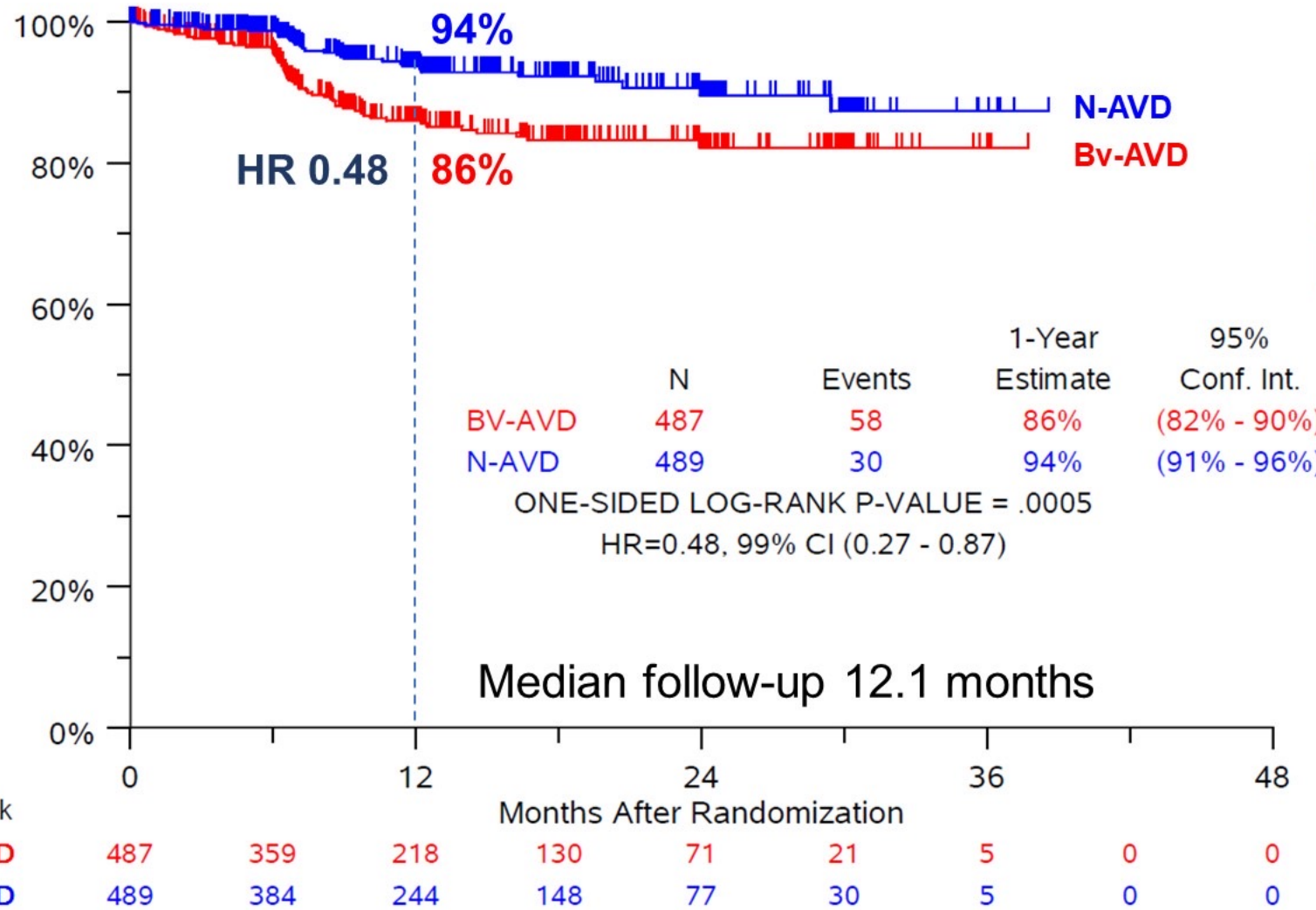
Table S6. Causes of On-Treatment Treatment-Related Deaths by Treatment Arm (Safety Population)[2]

A+AVD (n=8)	ABVD (n=7)
Cardio-respiratory arrest (n=1)	Pneumocystis jirovecii pneumonia (n=1)
Histiocytosis hematophagic (n=1)	Pneumonia (n=2)
Respiratory failure (n=1)	Cardiac arrest (n=1)
Unknown (n=1)	Pulmonary toxicity (n=1)
Multiple organ dysfunction syndrome (n=1)	Pneumonitis (n=1)
Myocardial infarction (n=1)	Respiratory disorder (n=1)
Neutropenic sepsis (n=1)	
Septic shock (n=1)	

Causes are listed as MedDRA Preferred Term.

A+AVD, brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; MedDRA, Medical Dictionary of Regulatory Activities.

N-AVD improves PFS compared to Bv-AVD



1-year PFS
N-AVD 94%
Bv-AVD 86%

Adverse events – eBEACOPP x NivoAVD

	PET-2-negative cohort, pre-amendment		PET-2-negative cohort, post-amendment		PET-2-negative cohort, combined	
	8 cycles of eBEACOPP (n=288)	4 cycles of eBEACOPP (n=285)	6 cycles of eBEACOPP (n=216)	4 cycles of eBEACO (n=216)	8 or 6 cycles of eBEACOPP (n=504)	4 cycles of eBEACOPP (n=501)
Follow-up						
Follow-up for disease status, months	76 (61–96)	75 (60–97)	59 (47–70)	57 (43–64)	66 (54–86)	64 (51–84)
Follow-up for survival status, months	83 (64–101)	78 (63–101)	60 (52–75)	61 (50–69)	69 (56–90)	66 (54–88)
Tumour events						
Any tumour event	16 (6%)	19 (7%)	13 (6%)	15 (7%)	29 (6%)	34 (7%)
Progression	1 (<1%)	0	0	3 (1%)	1 (<1%)	3 (1%)
Early relapse (within 1 year after end of treatment)	3 (1%)	7 (2%)	4 (2%)	5 (2%)	7 (1%)	12 (2%)
Late relapse	12 (4%)	12 (4%)	9 (4%)	7 (3%)	21 (4%)	19 (4%)
Number of tumour events						
1	15 (5%)	18 (6%)	11 (5%)	12 (6%)	26 (5%)	30 (6%)
2	1 (<1%)	1 (<1%)	1 (<1%)	3 (1%)	2 (<1%)	4 (1%)
3	0	0	1 (<1%)	0	1 (<1%)	0
Second-line therapy						
High-dose chemotherapy and autologous HSCT	9 (3%)	8 (3%)	7 (3%)	10 (5%)	16 (3%)	18 (4%)
Allogeneic HSCT	0	1 (<1%)	0	0	0	1 (<1%)
Salvage chemotherapy without documented HSCT	3 (1%)	3 (1%)	2 (1%)	1 (<1%)	5 (1%)	4 (1%)
Other chemotherapy	2 (1%)	2 (1%)	1 (<1%)	1 (<1%)	3 (1%)	3 (1%)
Radiotherapy only	1 (<1%)	1 (<1%)	0	0	1 (<1%)	1 (<1%)
Antibody therapy	1 (<1%)	0	0	1 (<1%)	1 (<1%)	1 (<1%)
Unknown	0	4 (1%)	3 (1%)	2 (1%)	3 (1%)	6 (1%)
Cause of death						
Any event	19 (7%)	6 (2%)	9 (4%)	5 (2%)	28 (6%)	11 (2%)
Hodgkin lymphoma	2 (1%)	3 (1%)	2 (1%)	2 (1%)	4 (1%)	5 (1%)
Toxicity of study treatment	4 (1%)	0	2 (1%)	0	6 (1%)	0
Toxicity of salvage therapy	2 (1%)	1 (<1%)	0	1 (<1%)	2 (<1%)	2 (<1%)
Second primary malignant neoplasms	8 (3%)	1 (<1%)	5 (2%)	1 (<1%)	13 (3%)	2 (<1%)
Other disease*	1 (<1%)	0	0	1 (<1%)	1 (<1%)	1 (<1%)
Accident or suicide	0	1 (<1%)	0	0	0	1 (<1%)
Unclear	2 (1%)	0	0	0	2 (<1%)	0
Second primary malignant neoplasms						
Any event	14 (5%)	12 (4%)	7 (3%)	6 (3%)	21 (4%)	18 (4%)
Acute myeloid leukaemia or myelodysplastic syndrome	7 (2%)	1 (<1%)	2 (1%)	1 (<1%)	9 (2%)	2 (<1%)
Non-Hodgkin lymphoma	3 (1%)	6 (2%)	2 (1%)	2 (1%)	5 (1%)	8 (2%)
Solid tumour	5 (2%)	5 (2%)	3 (1%)	3 (1%)	8 (2%)	8 (2%)

Data are median (IQR) or n (%). PET-2=PET scan after two cycles of chemotherapy. eBEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated doses. HSCT=haematopoietic stem-cell transplantation. *Including diarrhoea (n=1) and non-treatment-related infection (n=1).

Table 2: **Outcomes of the PET-2-negative cohort**

Kreisse S. *Lancet Haematol*. 2021

Adverse events – eBEACOPP x NivoAVD

Cause of death						
Any event	19 (7%)	6 (2%)	9 (4%)	5 (2%)	28 (6%)	11 (2%)
Hodgkin lymphoma	2 (1%)	3 (1%)	2 (1%)	2 (1%)	4 (1%)	5 (1%)
Toxicity of study treatment	4 (1%)	0	2 (1%)	0	6 (1%)	0
Toxicity of salvage therapy	2 (1%)	1 (<1%)	0	1 (<1%)	2 (<1%)	2 (<1%)
Second primary malignant neoplasms	8 (3%)	1 (<1%)	5 (2%)	1 (<1%)	13 (3%)	2 (<1%)
Other disease*	1 (<1%)	0	0	1 (<1%)	1 (<1%)	1 (<1%)
Accident or suicide	0	1 (<1%)	0	0	0	1 (<1%)
Unclear	2 (1%)	0	0	0	2 (<1%)	0

Kreisse S. *Lancet Haematol*. 2021

Adverse events – eBEACOPP x NivoAVD

	8 cycles of eBEACOPP or 8 cycles of rituximab plus eBEACOPP		6 cycles of eBEACOPP		4 cycles of eBEACOPP		Total	
	Number of participants	Mean (SD)	Number of participants	Mean (SD)	Number of participants	Mean (SD)	Number of participants	Mean (SD)
Female patients								
Cardiac function								
LVEF (baseline), all available data	210	64·7% (8·6)	211	63·5% (7·7)	156	65·2% (8·4)	577	64·4% (8·2)
LVEF (baseline), only patients with follow-up data	35	64·5% (8·9)	32	62·5% (6·1)	26	65·4% (9·3)	93	64·1% (8·2)
LVEF (5-year follow-up)	35	62·8% (10·2)	32	62·3% (6·0)	26	62·3% (6·5)	93	62·5% (7·9)
Lung function								
DLCO (baseline), all available data	142	75·9% (15·9)	166	78·4% (19·8)	101	80·6% (17·8)	409	78·1% (18·1)
DLCO (baseline), only patients with follow-up data	14	73·2% (15·2)	15	79·2% (25·5)	4	78·2% (40·7)	33	76·5% (23·3)
DLCO (5-year follow-up)	14	78·1% (9·7)	15	70·1% (27·1)	4	84·1% (17·2)	33	75·2% (20·3)
Male patients								
Cardiac function								
LVEF (baseline), all available data	313	63·5% (7·1)	351	63·4% (6·8)	246	63·8% (7·1)	910	63·5% (7·0)
LVEF (baseline), only patients with follow-up data	55	64·4% (6·9)	61	64·0% (6·6)	41	63·7% (6·8)	157	64·1% (6·7)
LVEF (5-year follow-up)	55	61·3% (8·5)	61	61·5% (5·4)	41	60·3% (5·9)	157	61·1% (6·7)
Lung function								
DLCO (baseline), all available data	232	82·6% (19·7)	243	81·2% (24·4)	172	81·3% (21·6)	647	81·8% (22·1)
DLCO (baseline), only patients with follow-up data	15	79·5% (17·1)	14	89·5% (10·9)	8	90·1% (13·4)	37	85·6% (14·8)
DLCO (5-year follow-up)	15	84·7% (12·1)	14	82·5% (24·7)	8	87·4% (17·5)	37	84·5% (18·4)

Data are n or mean (SD). eBEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone [illegible] escalated doses. LVEF=left ventr[illegible]ular ejection fraction. DLCO=diffusion capacity of the lung.

Table 3: **Secondary outcomes of cardiac and lung toxicities**

Kreisse S. *Lancet Haematol*. 2021

Adverse events – eBEACOPP x NivoAVD

Table 2. Adverse Events in Trial Participants

	Therapy, No. (%)			
	Concomitant (n = 55)		Sequential (n = 54)	
Adverse event	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Hematological				
Anemia	49 (89)	2 (4)	45 (83)	1 (2)
Thrombocytopenia	11 (20)	0	11 (20)	1 (2)
Leukopenia	49 (89)	39 (71)	46 (85)	34 (63)
Infection	25 (45)	3 (5)	23 (43)	1 (2)
Organ				
Mucositis	14 (25)	0	18 (33)	3 (6)
Gastrointestinal tract disorders	28 (51)	3 (5)	19 (35)	4 (7)
Urogenital tract disorders	4 (7)	0	4 (7)	0
Respiratory tract disorders	12 (22)	0	13 (24)	1 (2)
Cardiac disorders	1 (2)	0	2 (4)	0
Skin disorders	23 (42)	3 (5)	31 (57)	4 (7)
Hepatobiliary/pancreatic disorders	27 (49)	7 (13)	28 (52)	5 (9)
Kidney/genitourinary disorders	4 (7)	0	2 (4)	0
Nervous system disorders	23 (42)	2 (4)	18 (33)	2 (4)
Other				
Nausea or vomiting	41 (74)	1 (2)	37 (69)	4 (7)
Drug fever	6 (11)	1 (2)	11 (20)	3 (6)
Allergy or infusion reaction	1 (2)	1 (2)	2 (4)	0
All	54 (98)	42 (76)	53 (98)	43 (80)
Treatment-related morbidity	10 (18)		12 (22)	
Anemia, thrombocytopenia or infection of CTCAE grade IV	0		0	
Any organ toxic effect of CTCAE grade III or IV[a]	10 (18)		12 (22)	
Onset of treatment-related morbidity				
During first 4 therapy applications	10 (18)		10 (19)	
During further N-AVD cycles	0		2 (4)	
Any serious adverse event	21 (38)		15 (28)	

Table 3. Supportive Measures

	Therapy, No. (%)	
Prophylactic treatments	Concomitant (n=55)	Sequential (n=54)
Corticosteroid prophylaxis	46 (84)	44 (81)
At first dose of study therapy	40 (73)	34 (63)
Antihistamine prophylaxis	14 (25)	15 (28)
Antibiotic prophylaxis	19 (35)	16 (30)
Antiviral prophylaxis	10 (18)	9 (17)
Antiemetic prophylaxis	41 (75)	34 (63)
Granulocyte-colony stimulating factor prophylaxis	32 (58)	31 (57)

Brockelmann P. *JAMA Oncol.* 2020

AEs of Interest: Immune/Other

Toxicity	N-AVD n = 483		Bv-AVD n = 473	
	Any Grade No (%)	Grade ≥ 3 No (%)	Any Grade No (%)	Grade ≥ 3 No (%)
ALT increased	**156 (32%)**	**22 (5%)**	**194 (41%)**	**22 (5%)**
AST increased	**120 (25%)**	**12 (2%)**	**153 (32%)**	**13 (3%)**
Rash maculo-papular	51 (11%)	4 (1%)	58 (12%)	0 (0)
Hypothyroidism	**33 (7%)**	**1 (0%)**	**3 (1%)**	**0 (0)**
Rash acneiform	18 (4%)	0 (0)	12 (3%)	0 (0)
Pneumonitis	10 (2%)	2 (0%)	15 (3%)	10 (2%)
Gastritis	10 (2%)	3 (1%)	8 (2%)	0 (0)
Hyperthyroidism	**14 (3%)**	**0 (0)**	**0 (0)**	**0 (0)**
Colitis	5 (1%)	1 (0%)	6 (1%)	4 (1%)

Low rates of immune-related adverse events

My personal experience

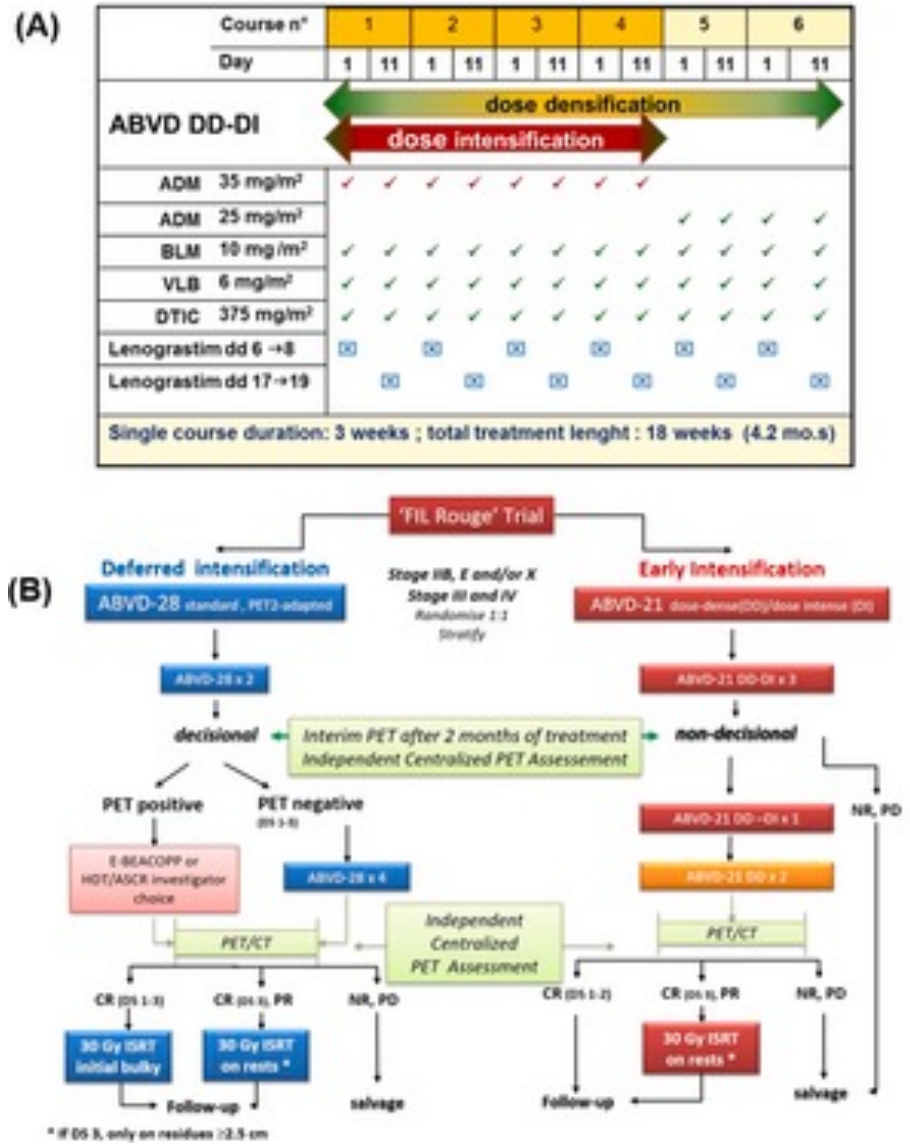
3 colitis GRADE 4

2 arthritis soronegatives in cronic treatment

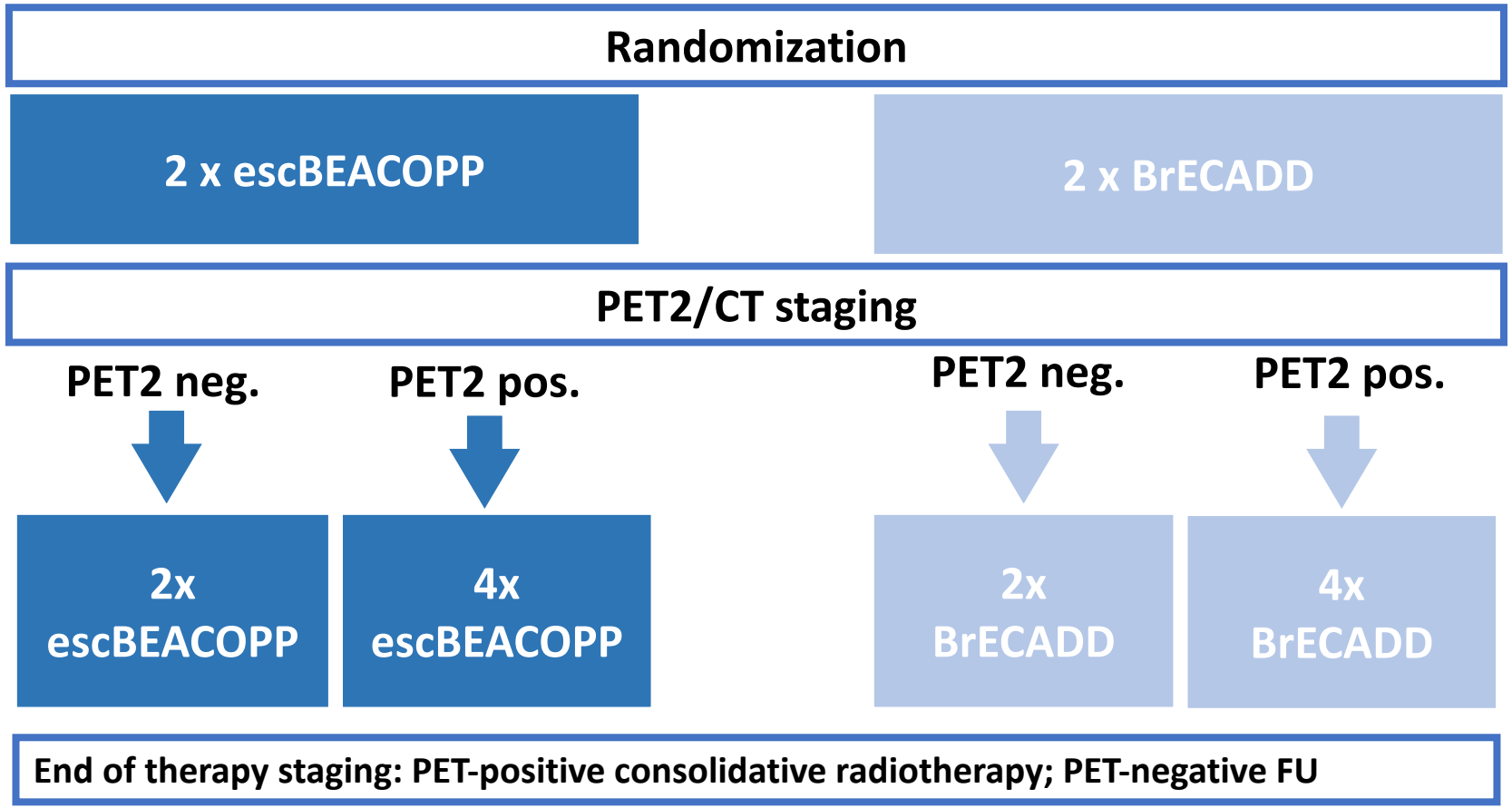
1 recently fatal death from fulminant hepatitis

FRONTLINE INTENSIFIED ABVD DEMONSTRATES SUPERIOR EFFICACY THAN PET-ADAPTED ABVD IN ADVANCED HODGKIN LYMPHOMA: THE FIL-ROUGE PHASE 3 TRIAL BY THE FONDAZIONE ITALIANA LINFOMI

Figure 1



Study design and primary safety endpoint TRMB



Primary Safety Endpoint: 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 12 months

17ISHL- Lugano

BrECADD, brentuximab vedotin + etoposide + cyclophosphamide + doxorubicin + dacarbazine + dexamethasone; escBEACOPP, escalated BEACOPP (bleomycin + etoposide + doxorubicin + cyclophosphamide + vincristine + procarbazine + prednisone); CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; FU, follow-up; neg., negative; PET(2), positron emission tomography (after 2 cycles); pos., positive; RD, radiotherapy; TRMB, treatment-related morbidity.

Borchmann P et al. Oral presentation 317. Presented at the 64th American Society of Hematology Annual Meeting, December 10–13, 2022.

ONCOLOGY

Remodeling escBEACOPP with brentuximab vedotin

Drug	Day	escBEACOPP[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	**1,250**	***1,250***	
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***	

BrECADD, brentuximab vedotin + etoposide + cyclophosphamide + doxorubicin + dacarbazine + dexamethasone; escBEACOPP, escalated BEACOPP (bleomycin + etoposide + doxorubicin + cyclophosphamide + vincristine + procarbazine + prednisone); hem, hematologic; MDS, myelodysplasia; sAML, secondary acute myeloid leukemia; tox, toxicity.

1. Diehl V et al. *N Engl J Med* 2003;348:2386–9.

Borchmann P et al. Oral presentation 317. Presented at the 64th American Society of Hematology Annual Meeting, December 10–13, 2022

Demographics and patient characteristics

ITT-TRMB	escBEACOPP N=732		BrECADD N=738	
	N	%	N	%
Location of recruitment*				
Europe	676	92	680	92
AU, NZ	56	8	58	8
Sex*				
Female	320	43	328	44
Male	412	56	410	56
Age*				
<45	571	78	584	79
≥45	161	22	154	21
IPS*				
<3	396	54	390	53
≥3	336	46	348	47

ITT-TRMB	escBEACOPP N=732		BrECADD N=738	
	N	%	N	%
ECOG PS				
0	515	70	507	69
1	199	27	220	30
2	18	3	11	2
B symptoms	490	67	506	69
Ann Arbor stage*				
IIA†			2	<1
IIB	116	16	117	16
IIIA	131	18	129	18
IIIB	156	21	161	22
IVA	111	15	101	14
IVB	218	30	227	31

*Stratification factors for randomization, also used for test of TRMB; †excluded from ITT-TRMB.

AU, Australia; BrECADD, brentuximab vedotin + etoposide + cyclophosphamide + doxorubicin + dacarbazine + dexamethasone; escBEACOPP, escalated BEACOPP (bleomycin + etoposide + doxorubicin + cyclophosphamide + vincristine + procarbazine + prednisone); ECOG PS, Eastern Cooperative Oncology Group Performance Status; IPS, International Prognostic Score; ITT, intent-to-treat; NZ, New Zealand; TRMB, treatment-related morbidity.

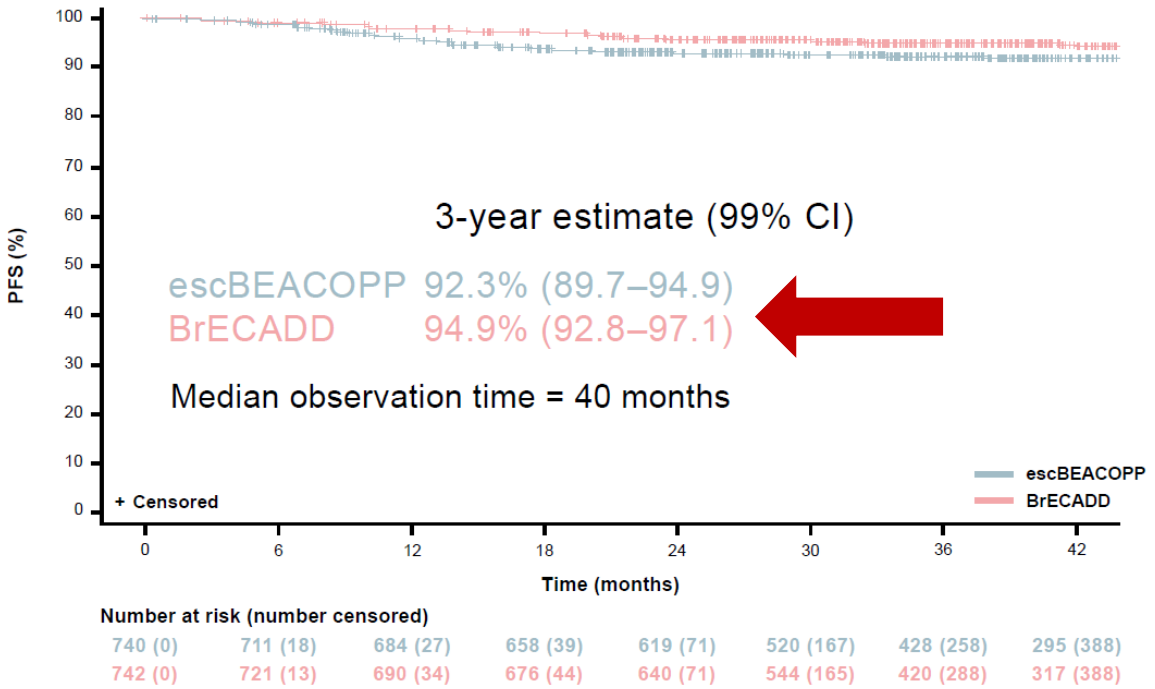
Borchmann P et al. Oral presentation 317. Presented at the 64th American Society of Hematology Annual Meeting, December 10–13, 2022.

PFS in the ITT population

PFS events at a median follow-up of 40 months

	escBEACOPP (N=740)		BrECADD (N=742)	
	n	%	n	%
Progression/relapse	55	7.4	32	4.3
Progression	14	1.9	5	0.7
Early relapse, follow-up ≤1 year	23	3.1	11	1.5
Late relapse, follow-up >1 year	18	2.4	16	2.2
Death without previous progression or relapse	6	0.9	7	0.9
Total PFS events	**61**	**8.4**	**39**	**5.3**

3-year PFS in the ITT population



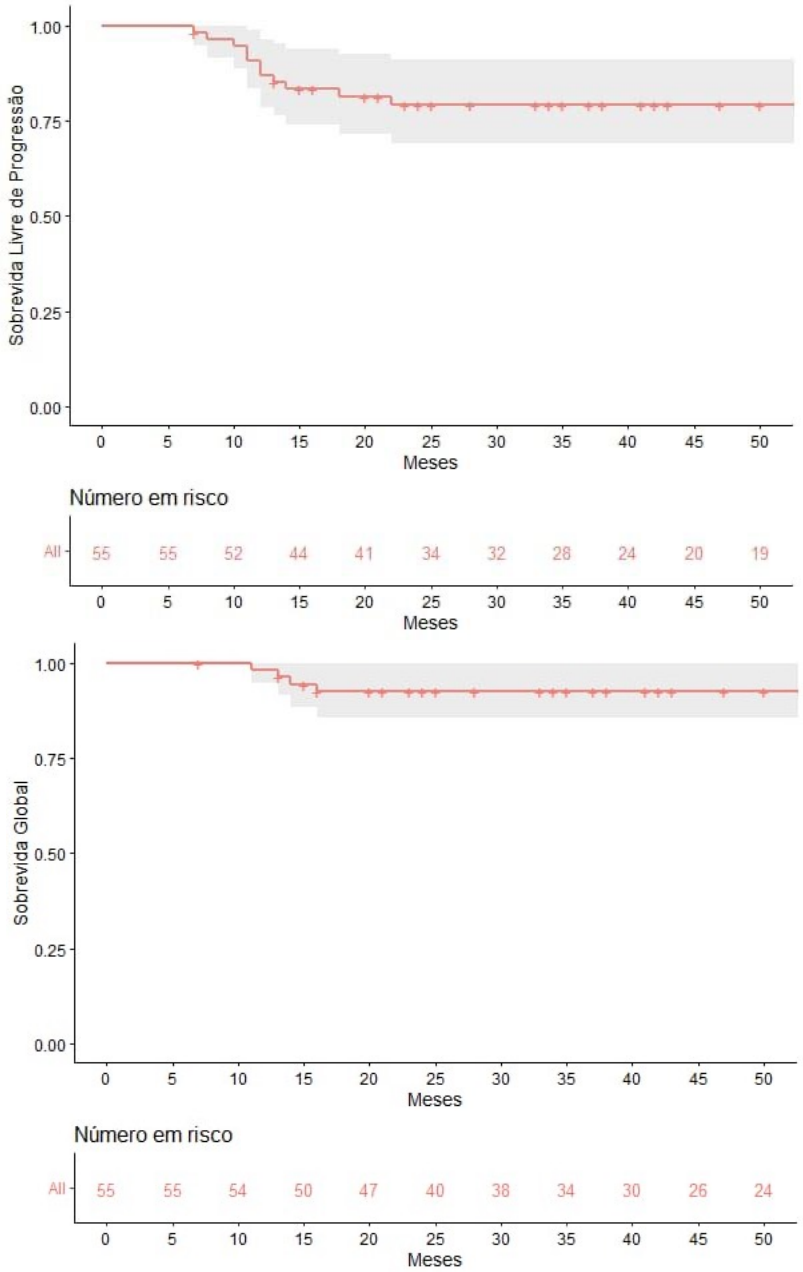
With an HR of 0.63 for PFS (in favor of BrECADD), the HR bound of 1.02 is excluded and non-inferiority of BrECADD established vs escBEACOPP. The 99% CI for the HR (1.07–0.37) indicates a trend towards superiority (to be determined at final analysis with 95% CI)

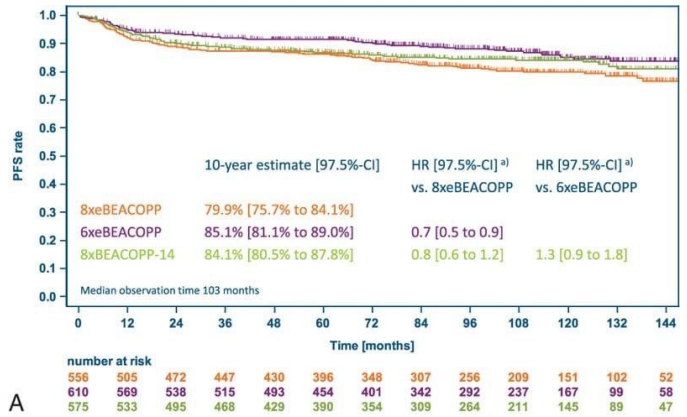
BrECADD, brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; CI, confidence interval; escBEACOPP, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; HR, hazard ratio; ITT, intention-to-treat; PFS, progression-free survival.

Borchmann P et al. Oral presentation LBA4. Presented at the 17th International Conference on Malignant Lymphoma, June 13–17, 2023.

BEACODD in Brazil (Santa Casa São Paulo- public center)

- 56 patients
- IPS >2
- FU 47 months
- OS 92,5%
- PFS 79,2% IC 68,9- 91%





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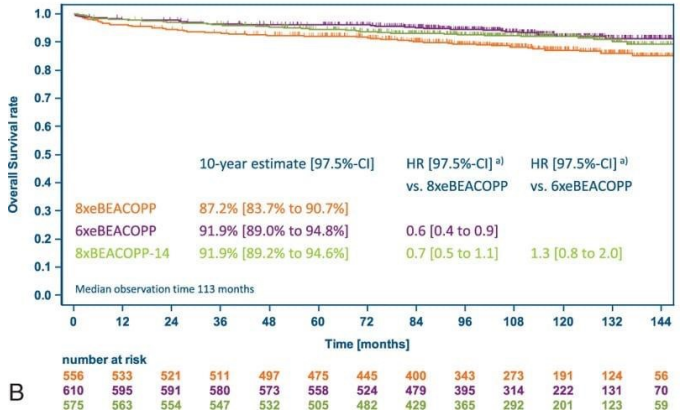


B

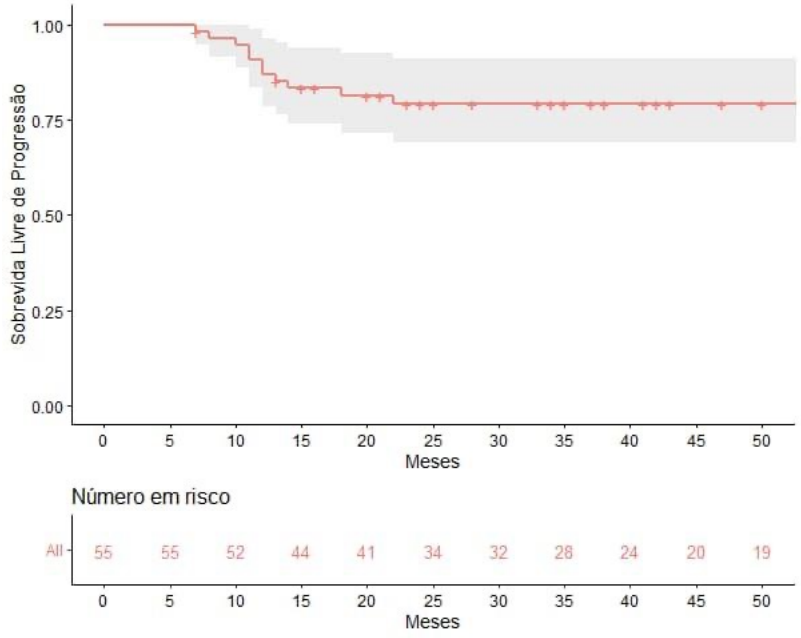
Santa Casa São Paulo

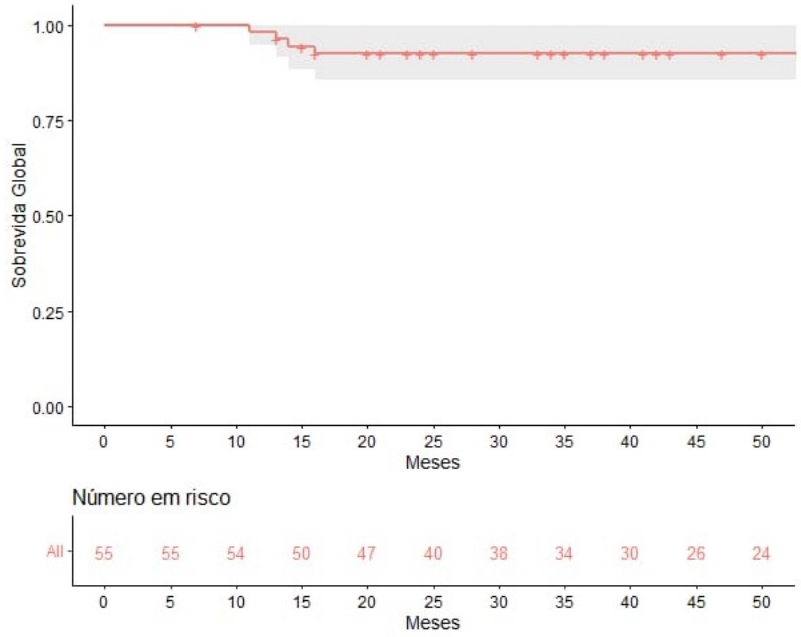
Engert A. *The Lancet*. 2012

BEACODD in Brazil (Santa Casa São Paulo- public center)

- 56 patients
- IPS >2
- FU 47 months
- OS 92,5%

- PFS 79,2% IC 68,9- 91%





Brazilian Registry

PFS 5 years: 62%
OS 5 Years: 80%

Santa Casa São Paulo

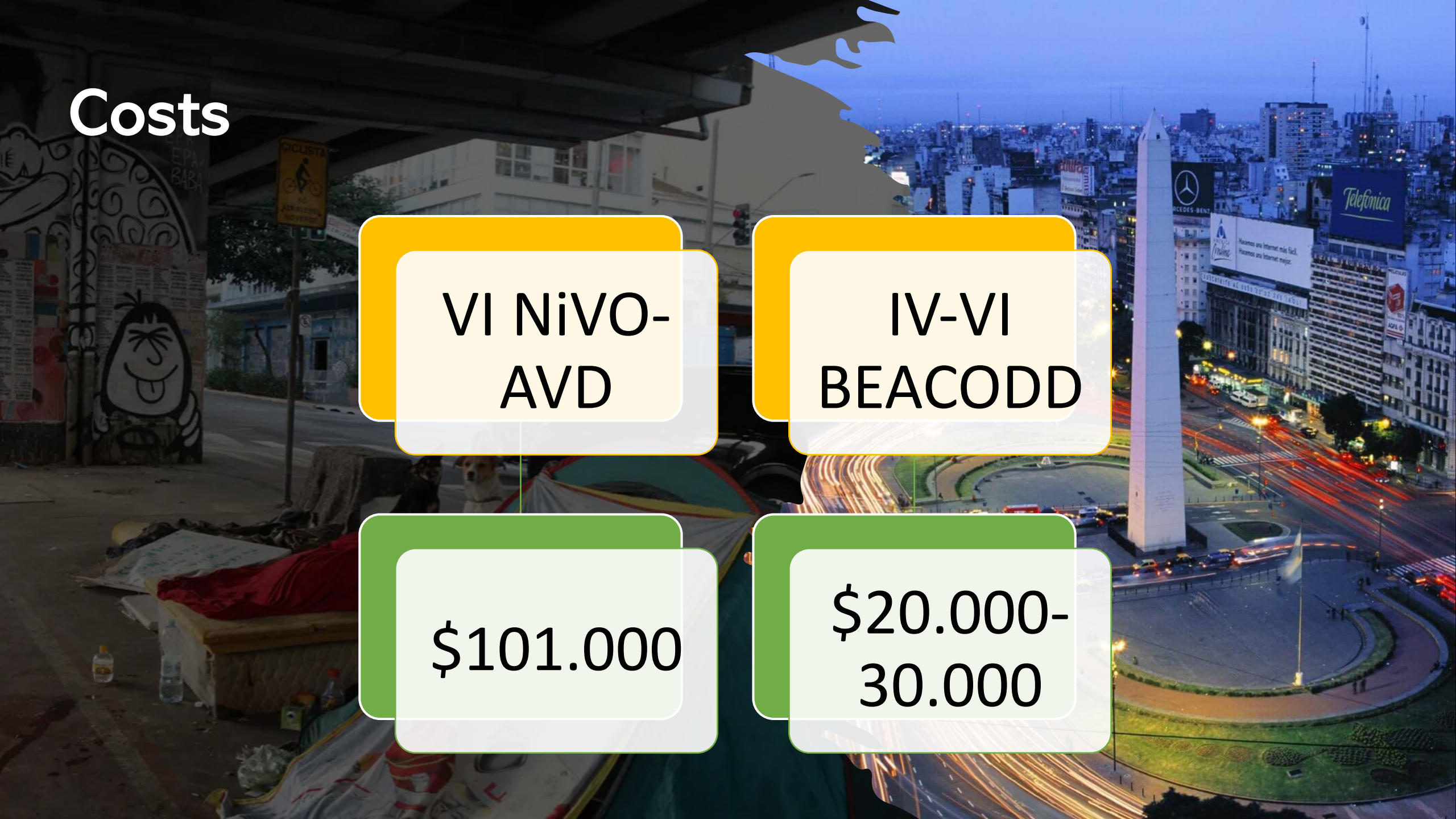
Accepted article, in press

BEACODD in Brazil (Santa Casa São Paulo- public center)

	All patients n=31	500mg/m² n=17	375mg/m² n=14	p value
De-escalation to ABVD, n (%):				0.003
No	23 (74.2)	9 (52.9)	14 (100)	
Yes	8 (25.8)	8 (47.1)	0 (0)	
First line response, n (%):				>0.99
No information	5 (16.1)	3 (17.6)	2 (14.3)	
Complete remission	23 (74.2)	13 (76.5)	10 (71.4)	
Refractory disease	3 (9.7)	1 (5.9)	2 (14.3)	
Relapse or Progression, n (%):				>0.99
No	27 (87.1)	15 (88.2)	12 (85.7)	
Yes	4 (12.9)	2 (11.8)	2 (14.3)	
Febrile Neutropenia, n (%):				>0.99
No	17 (54.8)	9 (52.9)	8 (57.1)	
Yes	14 (45.2)	8 (47.1)	6 (42.9)	
Hospitalization for Febrile Neutropenia, n (%):				0.786
No	18 (58.1)	9 (52.9)	9 (64.3)	
Yes	13 (41.9)	8 (47.1)	5 (35.7)	
Number of cycles with diagnose of febrile neutropenia, n (%):	19 (11.8)	14 (17.9)	5 (6.1)	0.004

Accepted article. In press

Costs



VI NiVO-AVD	IV-VI BEACODD
$101.000	$20.000-30.000

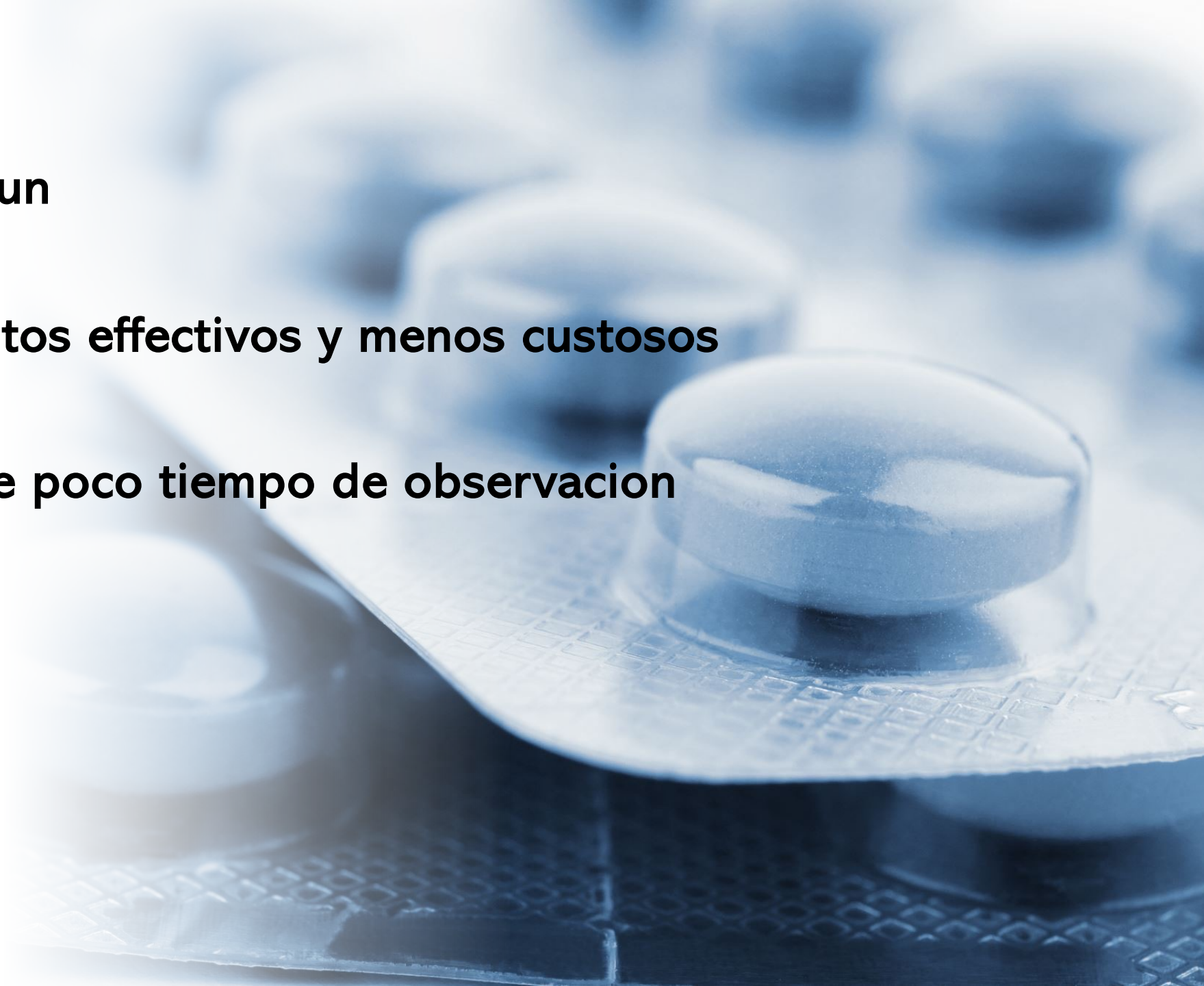
Linfoma de Hodgkin- Estamos listos para iPD1 en 1L?

Claro que si- siempre listos

No necessitamos aun

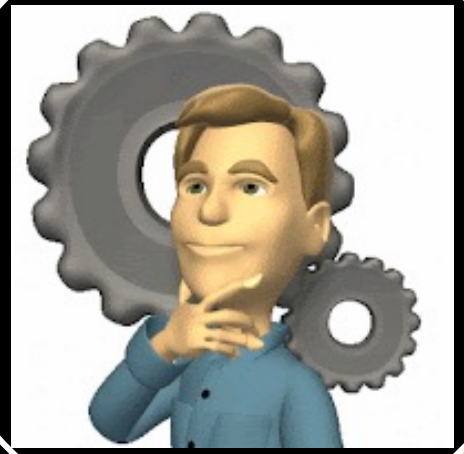
Tenemos tratamientos effectivos y menos custosos

Nivo-AVD aun tiene poco tiempo de observacion



“Espere um poco más”

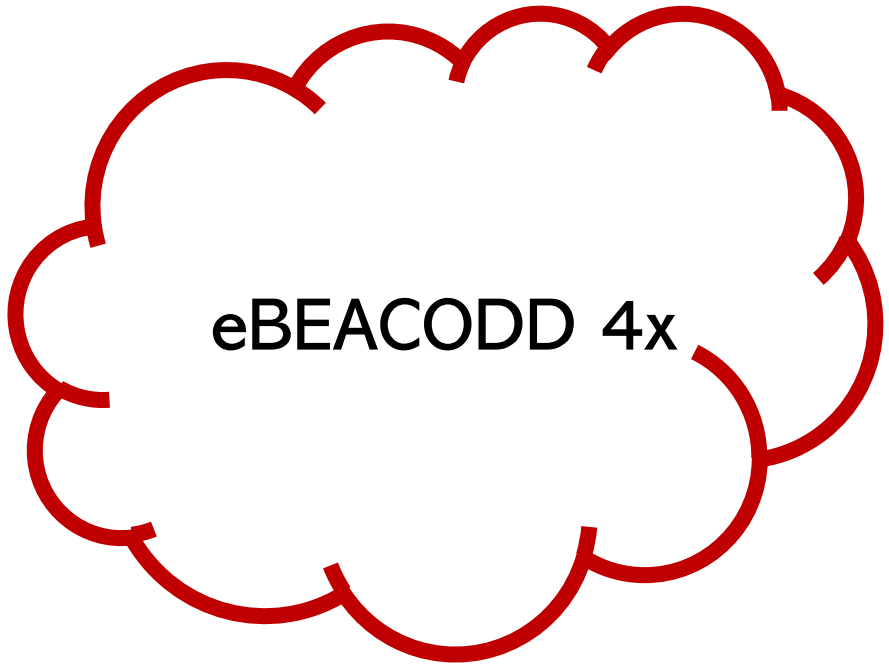
“Respire y refleja”



“No tenga miedo”
BEACODD/iABVD son eficazes, menos costoso, solo requieren coraje

Case

Hombre, 33 años, com LH clássico con sudoración nocturna. Hb 11,5, albumina 3,8, leuco 10.000 e linfócitos 800. PET com etapa IV



Muchas Gracias

tasilveira6@yahoo.com.br