Hodgkin Lymphom Erstlinientherapie:

PET-gesteuerte und altersabhängige Therapie

oder

BV-AVD für Alle?

Teresa Halbsguth

Offenlegung Interessenskonflikte

1. Anstellungsverhältnis oder Führungsposition

Nein

2. Beratungs- bzw. Gutachtertätigkeit

Nein

3. Besitz von Geschäftsanteilen, Aktien oder Fonds

Nein

4. Patent, Urheberrecht, Verkaufslizenz

Nein

5. Honorare

Nein

6. Finanzierung wissenschaftlicher Untersuchungen

Nein

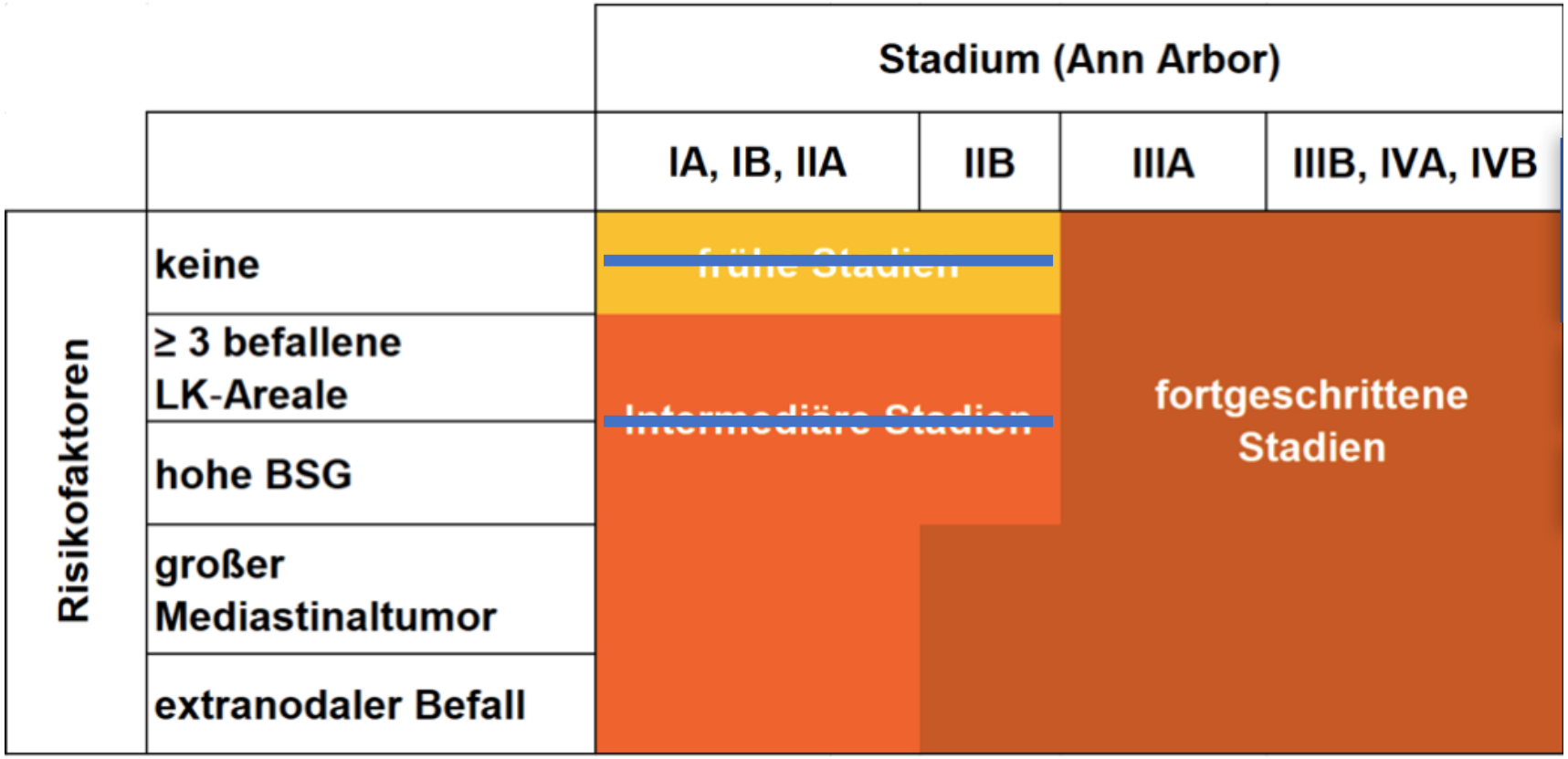
7. Andere finanzielle Beziehungen

Nein

8. Immaterielle Interessenkonflikte

Nein

GHSG Stadieneinteilung des Hodgkin Lymphoms



Risikofaktoren gemäß GHSG sind:

- Befall von 3 oder mehr Lymphknotenarealen (s. Abbildung 2)
- hohe BSG (in der ersten Stunde; ≥50mm ohne B-Symptome, ≥30mm mit B-Symptomen)
- großer Mediastinaltumor (≥1/3 des maximalen Thorax-Querdurchmessers in der konventionellen Röntgenaufnahme des Thorax)
- E-Befall

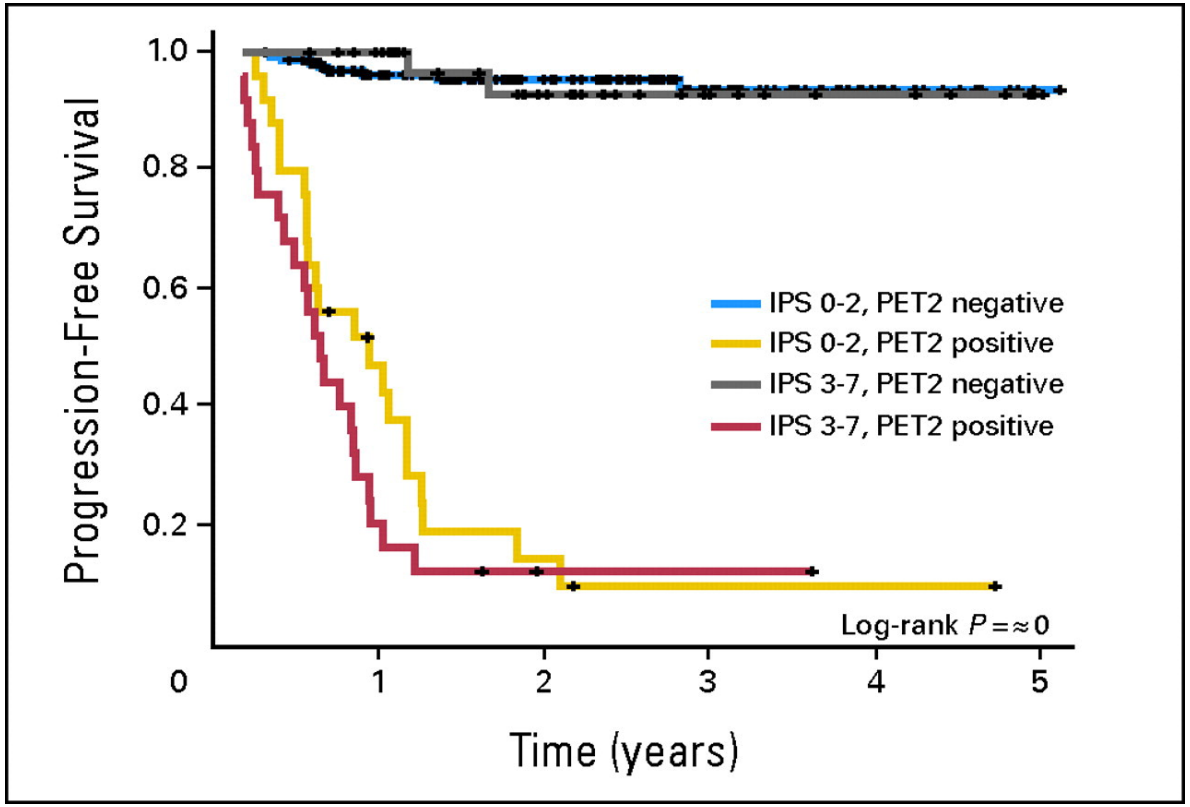
Quelle: Onkopedia Guideline Hodgkin Lymphom Mai 2023

BEACOPPesk oder BV-AVD?

Studien zur PET und altersbasierten Strategie

- GITIL/FIL HD 0607 (Gallamini et al JCO 2011, Gallamini et al JCO 2018)
- RATHL Trial (Johnson et al NEJM 2016, Russel et al Ann Hematol 2021)
- SWOG S0816 (Press et al JCO 2016, Stephens et al Blood 2019)
- HD18 (Borchmann et al Lancet 2017, Kreissl et al Lancet Haematol 2021)
- AHL2011 (Casasnovas et al Lancet Oncol 2019, Casasnovas JCO 2022)

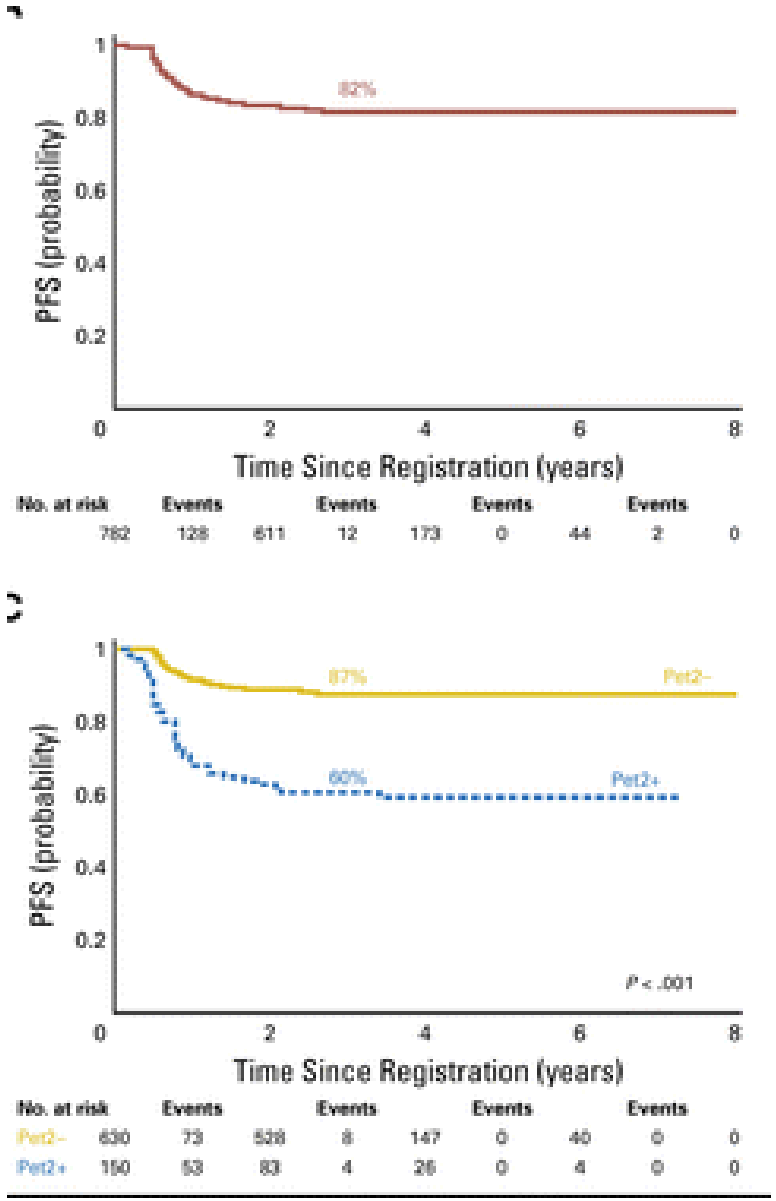
PFS für PET2 positive Patienten nach 2 Zyklen ABVD



Published in: Andrea Gallamini; Martin Hutchings; Luigi Rigacci; Lena Specht; Francesco Merli; Mads Hansen; Caterina Patti; Annika Loft; Francesco Di Raimondo; Francesco D'Amore; Alberto Biggi; Umberto Vitolo; Caterina Stelitano; Rosario Sancetta; Livio Trentin; Stefano Luminari; Emilio Iannitto; Simonetta Viviani; Ivana Pierri; Alessandro Levis; *Journal of Clinical Oncology* 2007 253746-3752.
DOI: 10.1200/JCO.2007.11.6525

GITIL/FIL HD0607

- N=782, 18-60 Jahre
- Beginn mit 2 Zyklen ABVD
- PET2 +: Eskalation auf 4 x BEACOPPesk + 4 x BEACOPPbasis +/- Rituximab
- PET2-: weiter 4 Zyklen ABVD
- Zusätzliche Radiotherapie bei PET negativem Abschluss-Staging
  - ➢ Verzicht auf Radiotherapie vs. Radiotherapie für initialen Befall > 5 cm

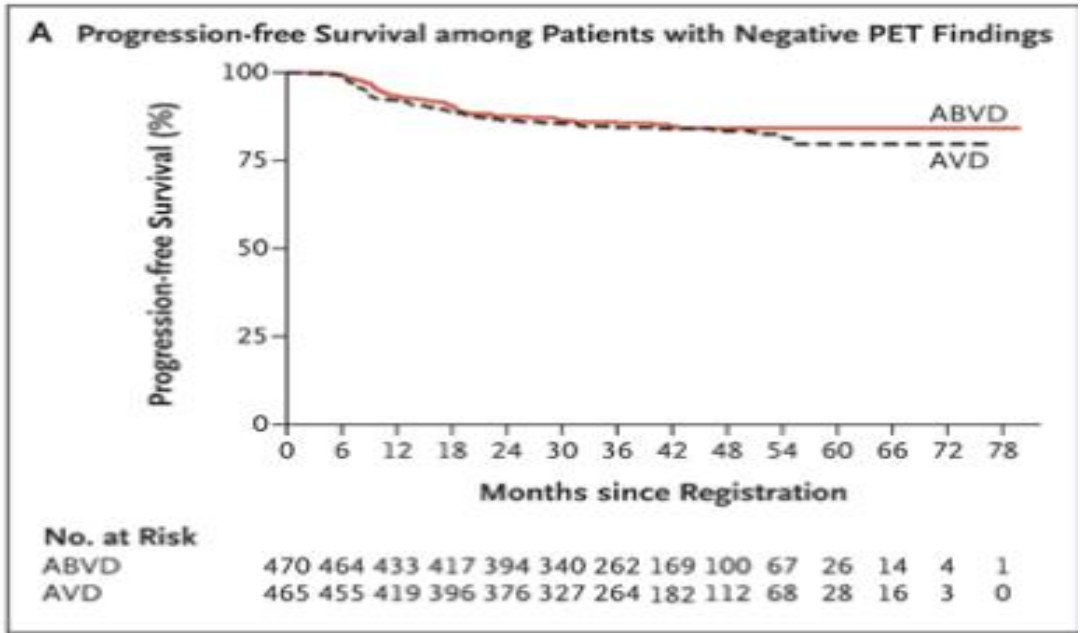


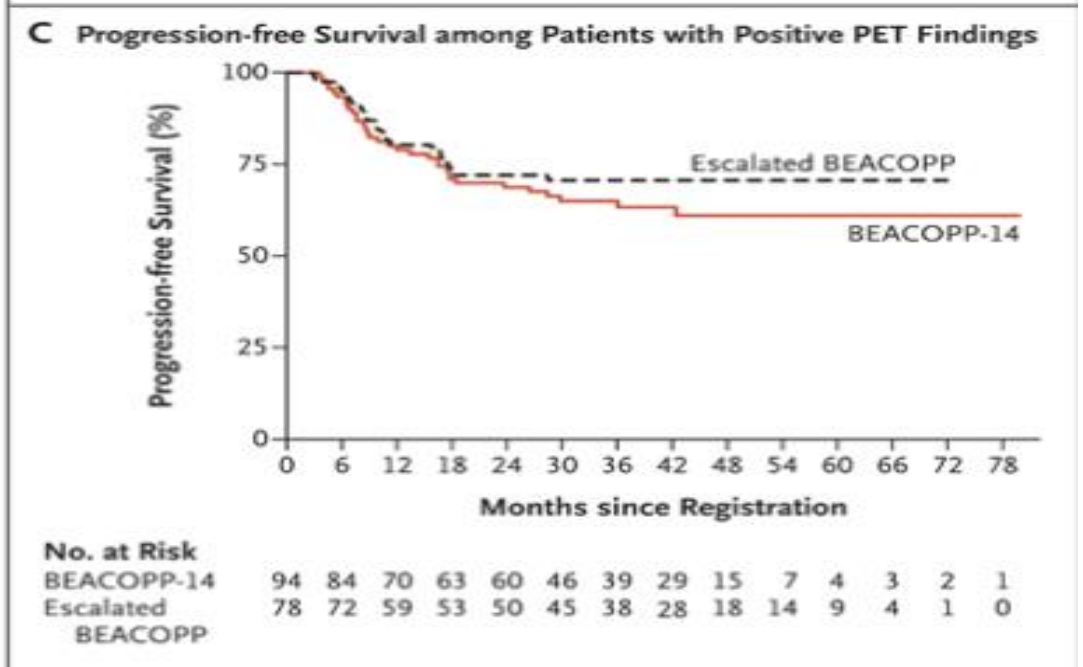
Gallamini et al JCO 2018 doi: 10.1200/JCO.2017.75.2543

RATHL

- N= 1119, 18 – 60 Jahre
- Beginn mit 2 Zyklen ABVD
- PET2 + (DS 4/5): 4xBEACOPP14 o. 3xBEACOPPesk, dann PET,
  - ➢wenn negativ dann 1 Zyklus des gewählten Regimes als Konsolidierung
  - ➢wenn positiv dann Salvagetherapie
- PET2 – (DS1-3) : Rando 4 x ABVD vs. 4xAVD ohne geplante Radiotherapie am Ende, diese war aber erlaubt

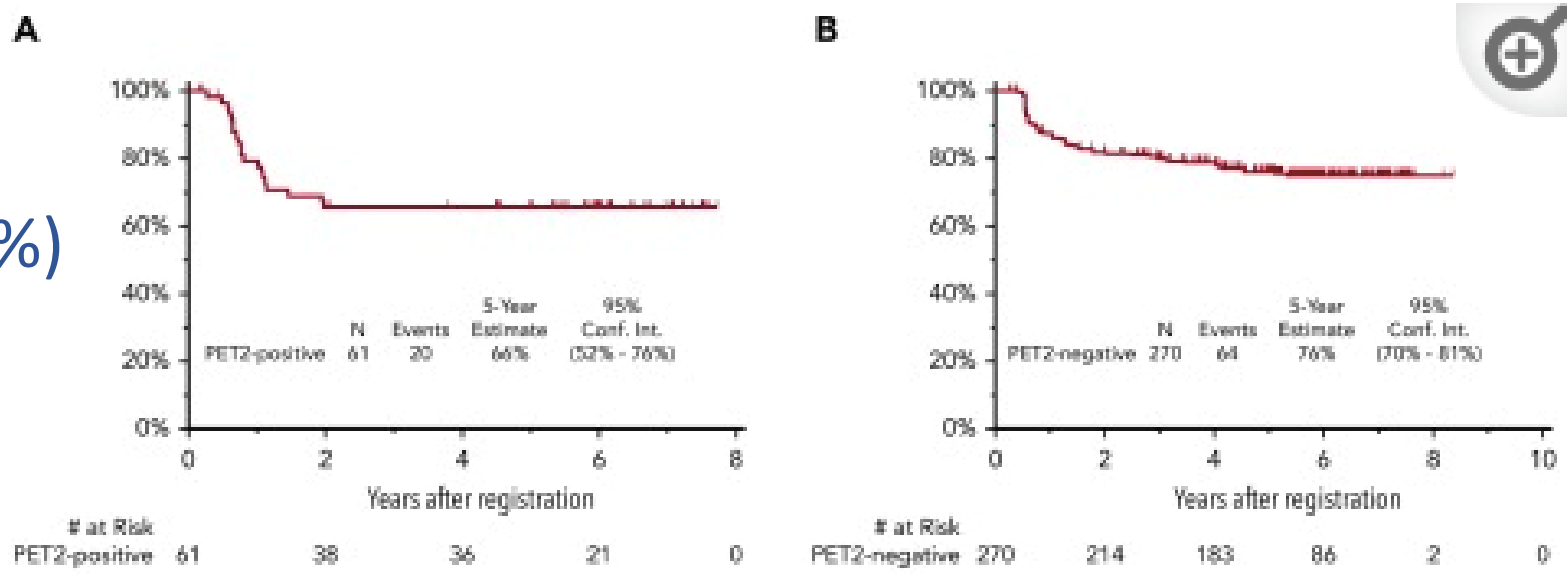
Johnson et al NEJM doi.10.1056/NEJMoa1510093





SWOG S0816

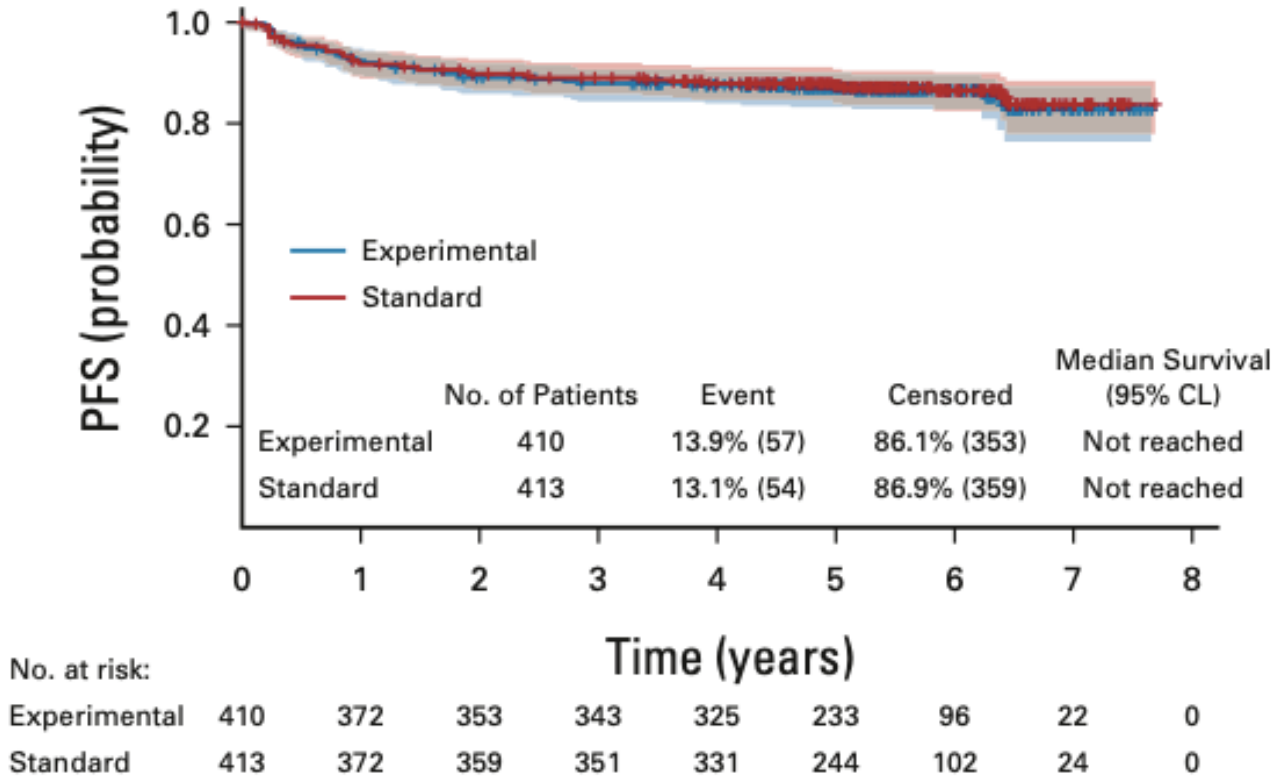
- N = 358 , 18 – 60 Jahre
- Nur Stadien Ann Arbor III/IV
- Beginn 2 x ABVD und PET2
  - ➢PET2 +: 6xBEACOPPesk (18%)
  - ➢PET2 - : 4 x ABVD (82%)
- Keine Radiotherapie am Ende erlaubt



Stephens et al Blood 2019 doi: 10.1182/blood.2019000719

AHL2011

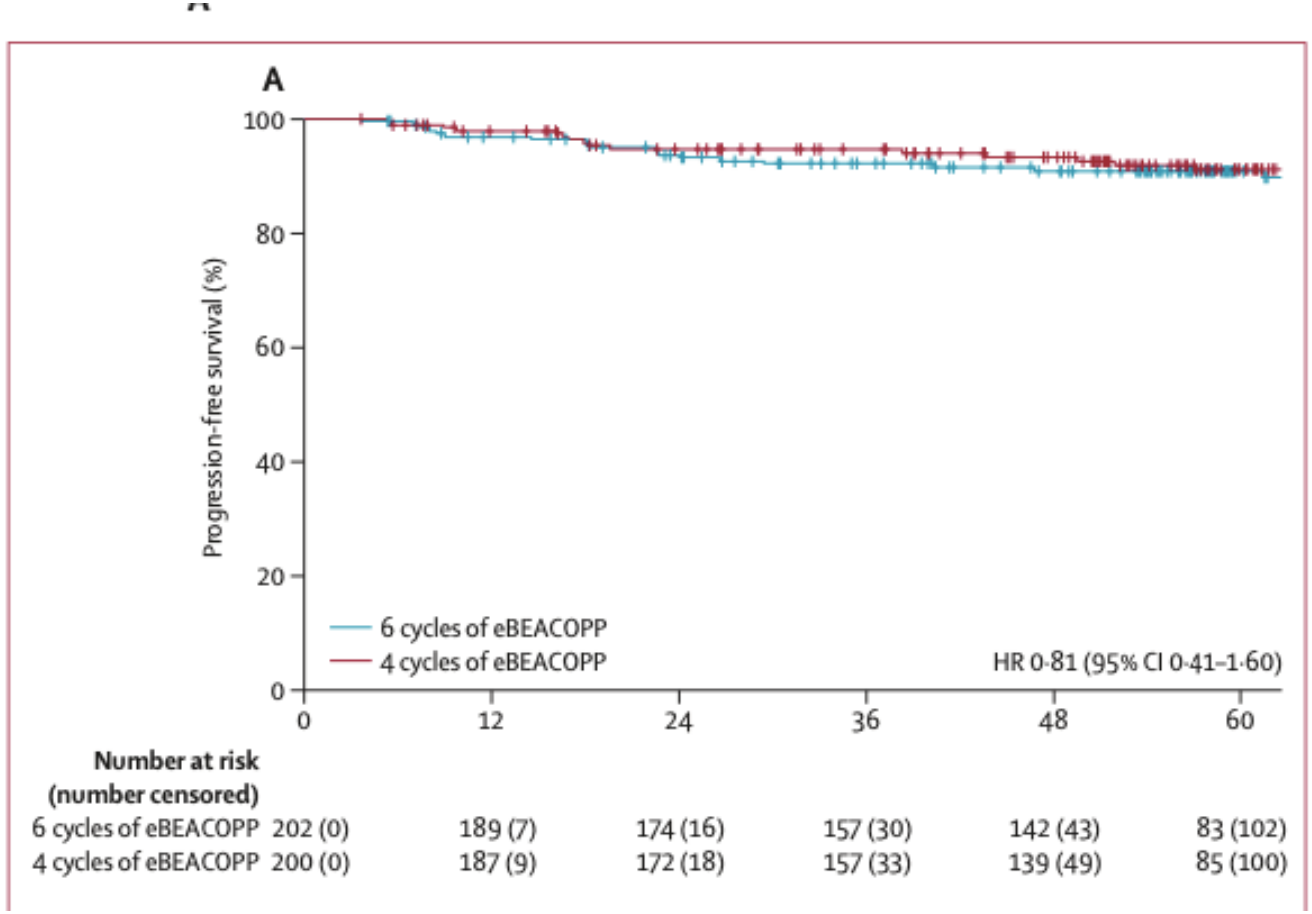
- N=823, 18 – 60 Jahre
- Rando. Standardarm vs. PET gesteuert
- In beiden Armen Beginn mit 2 x BEACOPPesk
- Im Standard Arm: 4 x BEACOPPesk
- Im Experimentellen Arm
  - ➢PET2 + : 4 x BEACOPPesk
  - ➢PET2 -: 4 x ABVD



Casanovas et al JCO doi: 10.1200/JCO.21.01777

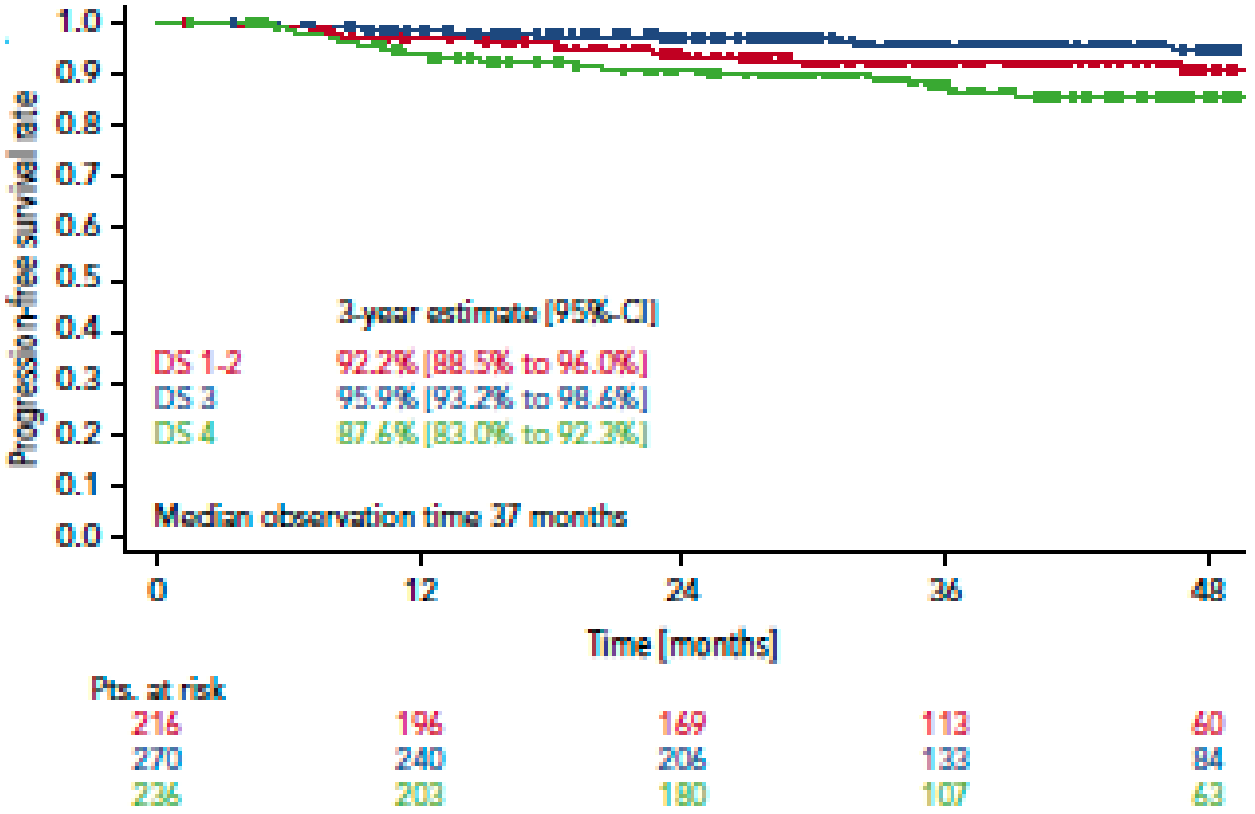
HD18

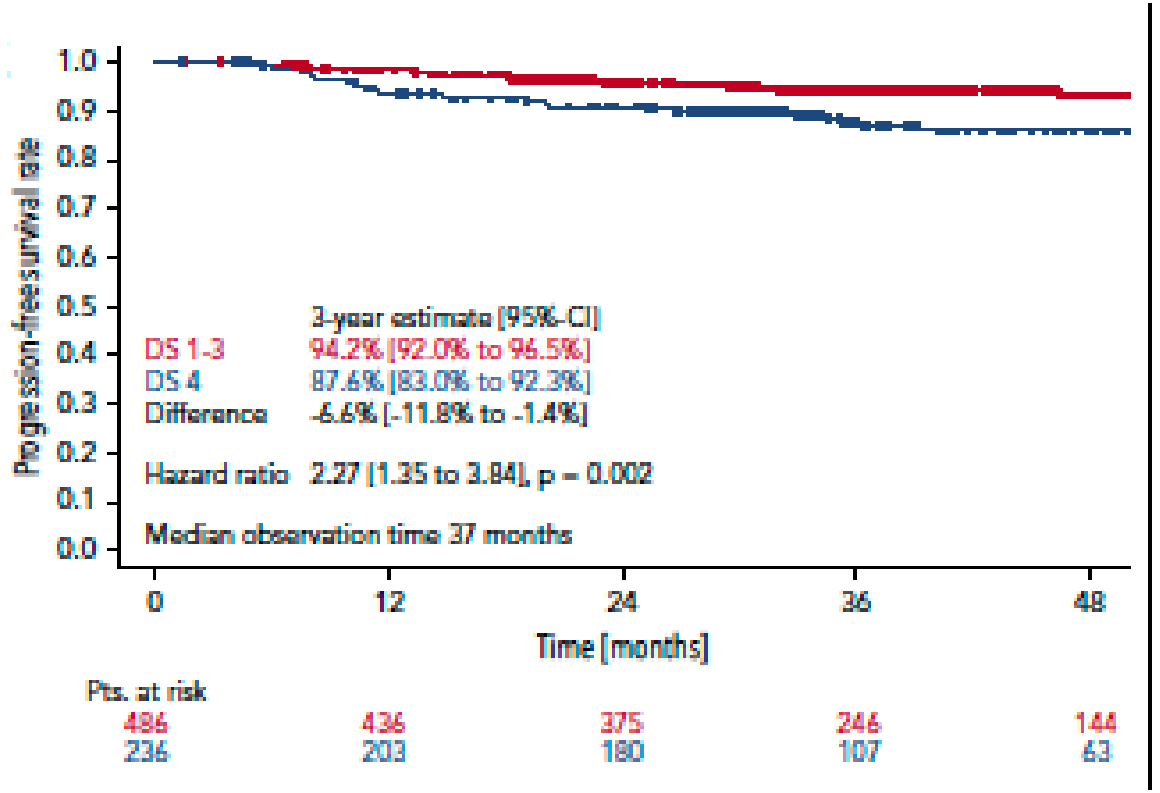
- N=2101, 18 – 60 Jahre
- Beginn mit 2 x BEACOPPesk
- PET2 + (DS3/4): Rando. 4 (6) x BEACOPPesk vs. 4(6) R-BEACOPPesk
  - ➢ wenn PET+ nach 6 (8) Zyklen + Radiatio
- PET2 - (DS1/2): Rando 2 x BEACOPPesk vs. 4 (6) BEACOPPesk



Borchmann et al Lancet 2017 DOI: 10.1016/S0140-6736(17)32134-7
Kreissl et al Lancet Haematol 2021 DOI: 10.1016/S2352-3026(21)00101-0

HD18: Wie sieht das PFS aus, wenn DS3 auch als negativ gewertet wird





Kobe et al Blood 2018 doi: DOI: 10.1182/blood-2018-05-852129

Vorbehalte BEACOPPeskaliert

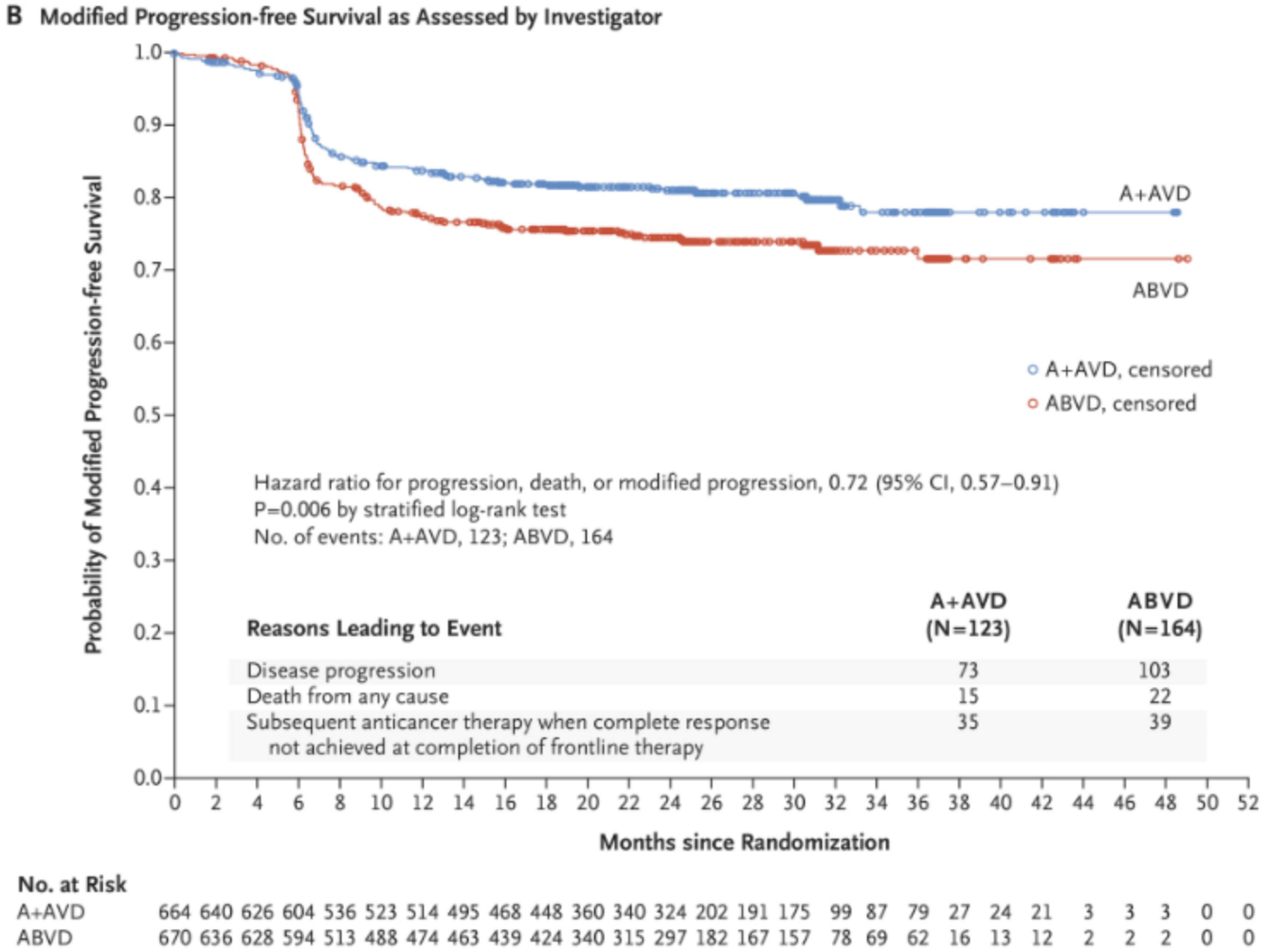
- Zu viel Toxizititität? CAVE Alter!
- Zu starke Beeinträchtigung der Fruchtbarkeit?
- Zu viele Zweittumorerkrankungen?
- Für viele Patienten Überbehandlung?

Studie zu BV-AVD: ECHELON-1

(Connors et al NEJM 2018, Straus et al Blood 2020,Straus et al Lancet Haemtaol 2021)

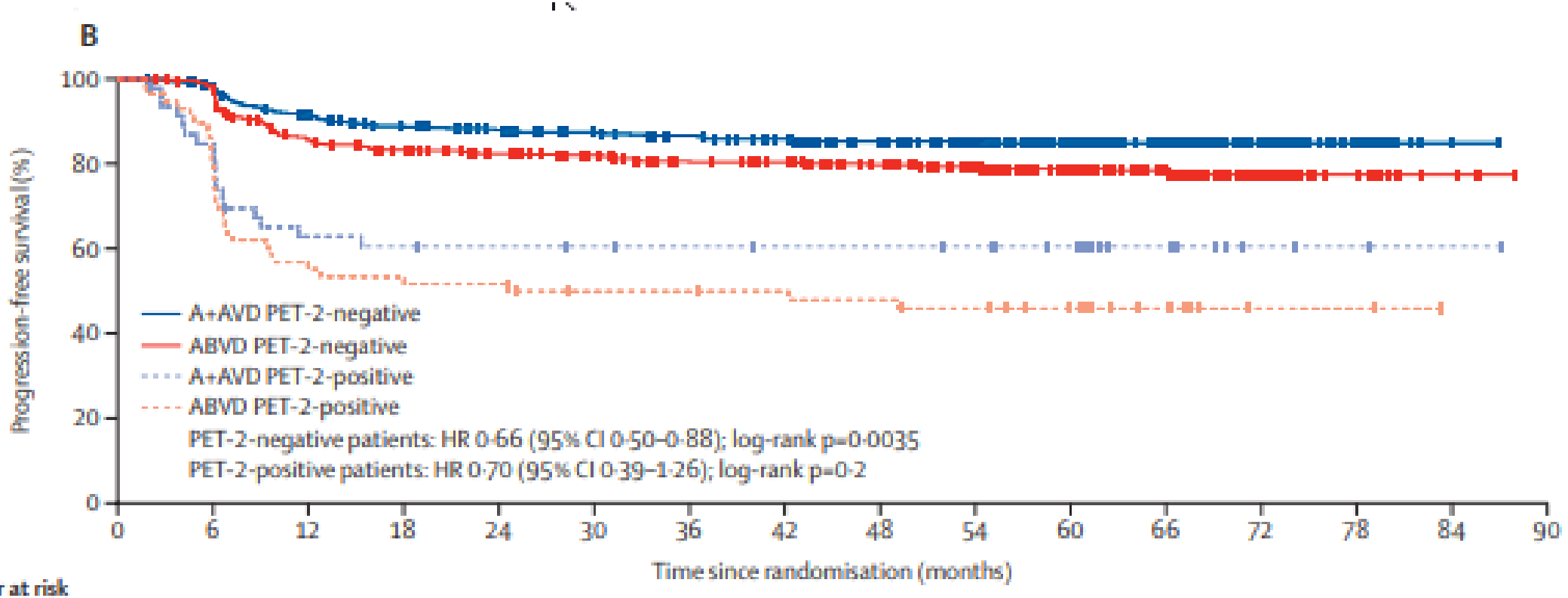
- N= 1334
- Hinzunahme von Brentuximab zu einem A(B)VD Backbone im Experimentellen Arm vs. ABVD im Standardarm
- Patienten ≥ 18 Jahre (also auch Patienten > 60 Jahre)
- PET nach 2 Zyklen – aber ohne Veränderung der Therapiestrategie
  - ➢ (bei Lugano/Deauville Score 5 war optional ein Therapieswitch erlaubt)
- Fixe Anzahl der Zyklen – insgesamt 6
- Verwendung von mPFS als Primärer Endpunkt

Modified PFS in ECHELON-1



Connors et al NEJM 2018
Doi 10.1056/NEJMoa1708984

Studie zu BV-AVD: ECHELON-1



Number at risk (number censored)																
A+AVD PET-2-negative	588 (0)	572 (6)	526 (13)	500 (23)	484(35)	472 (44)	460 (52)	444 (64)	417 (88)	386 (119)	312 (191)	189 (314)	98 (405)	36 (467)	1 (502)	0 (503)
ABVD PET-2-negative	578 (0)	558 (4)	483 (13)	463 (20)	442(36)	424 (52)	400 (68)	392 (76)	368 (97)	334 (128)	271 (190)	170 (290)	70 (388)	20 (438)	4 (454)	0 (458)
A+AVD PET-2-positive	47 (0)	39 (1)	28 (2)	27 (2)	26(3)	25 (4)	24 (5)	23 (6)	23 (6)	22 (7)	18 (11)	10 (19)	3 (26)	2 (27)	1 (28)	0 (29)
ABVD PET-2-positive	58 (0)	46 (0)	32 (0)	31 (0)	30(0)	26 (3)	26 (3)	25 (4)	24 (4)	22 (5)	18 (9)	8 (19)	2 (25)	2 (25)	0 (27)	0 (27)

Straus et al Lancet Haemtaol 2021

PFS für PET2+ Patienten im Vergleich

	N	3 Jahres PFS	5 Jahres PFS
GITL/FL HD0607 BEACOPPesc	76	57.0% (95%CI 45.0% - 68.0%)	
R-BEACOPPesc	72	63.0% (95%CI 50.0% - 74.0%	
RATHL 2xABVD + BEACOPPesc	172	67.5% (95%CI 59.7 – 72.9)	
SWOG S0816 2xABVD+	61 (49)	NA	66.0% (95%CI 52.0 – 76.0)
AHL2011. Standardarm	49	NA	73.5% (95%CI 58.7 – 83.6)
PET-guided-Arm	51	NA	68.2% (95%CI 53.4 – 79.2)
HD18 8xBEACOPPesc	217	91.4% (CI95% 87.0 - 95.7)	89.9% (95%CI 85.7 – 94.1)
8x-R-BEACOPPesc	217	93.0% (CI95% 89.4– 96.6)	87.7% (95%CI 83.1 – 92.4)
	506	NA	90.1% (95%CI 87.2 – 92.9)
6xBEACOPPesc	115	90.5% (CI95% 84.4 – 96.6)	NA
8x BEACOPPesc (DS4)	120	91.0% (CI95% 85.7 – 96.4)	NA
8x R-BEAFCOPPesc (DS4)	236	87.6% (CI95% 83.0 – 93.3)	85.6% (95%CI 80.8 – 90.5)
6x BEACOPPesc (DS4)			
ECHELON-1. A-AVD	47	67.7% (CI95% 53.8 – 78.3)	60,6% (95%CI 46.4 – 75.9)
ABVD	58	51.5% (CI95% 38.2 – 63.4)	45.9% (95%CI 32.7 – 58.2)

ECHELON-1:
PFS im Subgruppenvergleich

	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**

Straus et al Lancet Haemtaol 2021

BV-AVD und ABVD beim älteren Patienten

Patients' Characteristics and Outcomes	BV-AVD (Sequential Regimen) [94]	BV-AVD (Concomitant Regimen) [93]	ABVD Comparator [93]
Patients (N)	48	84	102
Age [years, median (range)]	69 (60–88)	68 (60–82)	66 (60–83)
ECOG PS $\geq$ 2	19%	12%	10%
Ann Arbor Stage			
II	19%	0%	0%
III	37%	37%	34%
IV	44%	61%	66%
Efficacy			
Response to BV × 2 [ORR (CR)]	82% (36%)	NA	NA
Interim PET positive	24% (10/42 pts)	20%	18%
EoT PET-negative	90% (38/42 pts)	71%	74%
2-year PFS	84%	70.3% *	71.4% *
5-year PFS	NA	67.1%	61.6%
2-year OS	93%	NA	NA
Toxicity			
TRM	2%	3.6%	5.1%
Neutropenia, grade $\geq$ 3	44%	70%	59%
Febrile neutropenia, grade $\geq$ 3	8%	37%	17%
Peripheral neuropathy			
any grade	NA	65%	43%
grade $\geq$ 3	4%	18%	3%
grade 2	27%	37%	16%
resolution	69%	80%	83%
Pulmonary toxicity, any grade	NA	2%	13%

ECOG: Eastern Cooperative Oncology Group, BV: Brentuximab Vedotin, PET: positron emission tomography, PFS: progression-free survival, OS: overall survival, TRM: treatment-related mortality, ORR: overall response rate, CR: complete response, EoT: end of treatment, NA: not available, ABVD: Doxorubicin, Bleomycin, Vinblastine, Dacarbazine AVD: Doxorubicin, Vinblastine, Dacarbazine. * modified progression-free survival (modified PFS).

Vassilakopoulos et al Int J Mol Sci 2023 DOI: 10.3390/ijms241713187

		N	3-Year PFS All, %	3-Year PFS Stage III/IV, %	3-Year OS All, %	3-Year OS Stage III/IV, %	3-Year Cum. Incidence SN, %	TRM, %	Grade III/IV AEs, %
HD18	PET-positive, 6× eBEACOPP	506	92.0	92.2	98.0	98.0	4.1	0	95.2
	PET-negative, 4× eBEACOPP	501	94.8	94.6	98.7	98.5	1.6	0	91.4
	All (full ITT, 4–8× eBEACOPP)[a]	2073	92.3	92.2	96.9	96.8	2.8	0.8	94.5

		N	3-Year PFS All, %	3-Year PFS Stage III/IV, %	3-Year OS All, %	3-Year OS Stage III/IV, %	SN After 41 Months MOT, %	TRM, %	Grade III/IV AEs, %
RATHL	PET-positive, 2× ABVD + 4× eBEACOPP or +6× BEACOPP-14	172	67.5	63.9	87.8	87.8	1.7	2.3[b]	≥80–83 (information for cycles 3–8 only)
	PET-negative, 2× ABVD + 4× AVD	465	84.4	82.1	97.6	97.8	2.4	0	≥65 (information for cycles 3–6 only)
	All eligible patients (2× ABVD + 4× ABVD, AVD, eBEACOPP, or 6× BEACOPP-14, respectively)	1203	82.6	79.8	95.8	94.6	2.4	0.7[b]	≥64 (information for cycles 1–2 only)

		N	2-Year mPFS Stage III/IV, %	2-Year OS Stage III/IV, %	6 J. cum. Inzdienz SN%	TRM, %	Grade III/IV AEs, %
E-1[c]	BV + AVD	664	82.1[d]	96.6	3,6	1.2[b]	83
	ABVD	670	77.2[d]	94.9	4,6	1.0[b]	66

ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine, AE = adverse event, AVD = doxorubicin, vinblastine, and dacarbazine, BV = brentuximab vedotin, HL = Hodgkin lymphoma, ITT = intention-to-treat, mPFS = modified progression-free survival, OS = overall survival, PET = positron emission tomography, PFS = progression-free survival, TRM = treatment-related mortality.

[a] Includes patients treated with 8× (Rituximab +)eBEACOPP.

[b] Includes pts > 60 years.

[c] Only 2-year data available.

[d] mPFS includes additional failure events as compared with PFS.

Borchmann et al 2018 HemaSphere2(3):e52,.

Sekundäre Neoplasien in HD18 im 5 Jahres Update PET negative Gruppe

	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 eBEACOPP (n=216)	8 or 6 cycles of eBEACOPP (n=504)	4 cycles of eBEACOPP (n=501)
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).

Kreissl et al Lancet Haematol 2021 DOI: 10.1016/S2352-3026(21)00101-0

Sekundäre Neoplasien in HD18 im 5 Jahres Update PET positive Gruppe

	PET-2-positive cohort pre-amendment		PET-2-positive cohort post-amendment
	8 cycles of eBEACOPP (n=217)	8 cycles of rituximab plus eBEACOPP (n=217)	6 cycles of eBEACOPP (n=506)
Second primary malignant neoplasms			
Any event	12 (6%)	8 (4%)	22 (4%)
Acute myeloid leukaemia or myelodysplastic syndrome	5 (2%)	4 (2%)	5 (1%)
Non-Hodgkin lymphoma	3 (1%)	2 (1%)	8 (2%)
Solid tumour	6 (3%)	2 (1%)	9 (2%)

Kreissl et al Lancet Haematol 2021 DOI: 10.1016/S2352-3026(21)00101-0

PNP in ECHELON-1

Table S11. Summary of Outcomes in Patients with Treatment-Emergent Peripheral Neuropathy (Safety Population)

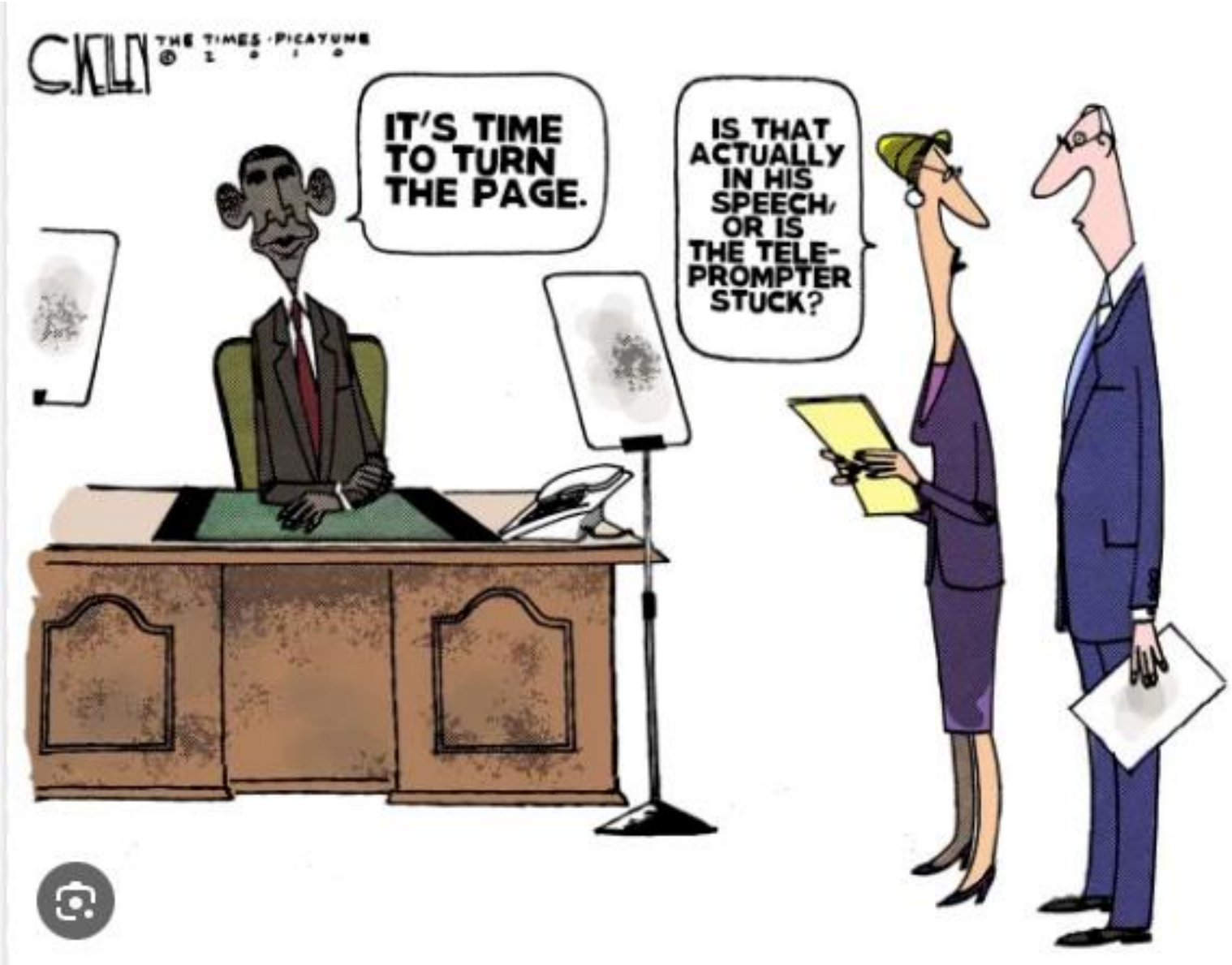
Patients with treatment-emergent PN	**A+AVD (n=443)**	**ABVD (n=286)**
Patients with resolution/improvement of PN events at last follow-up — n (%)	379 (85.6)	249 (87.1)
Resolution*	318 (71.8)	227 (79.4)
Improvement†	61 (13.8)	22 (7.7)
Median time to resolution of PN events (range) — weeks	16.0 (0 to 283)	10.0 (0 to 343)
Median time to improvement of PN events (range) — weeks	42.0 (2 to 182)	72.5 (15 to 142)
Safety population	**A+AVD (n=662)**	**ABVD (n=659)**
Patients with ongoing PN events at last follow-up — n (%)	125 (18.9)	59 (9.0)
Grade 1	71 (10.7)	39 (5.9)
Grade 2	38 (5.7)	16 (2.4)
Grade 3‡	15 (2.3)	4 (0.6)
Grade 4‡	1 (0.2)	0

*Resolution was defined as resolved/recovered with or without sequelae; or return to baseline or lower severity as of the latest assessment for pre-existing events.

†Improvement was defined as resolution or a decrease by at least one grade from the worst grade with no higher grade thereafter. Time to improvement was defined from the onset date of the maximum grade to the first onset date that the toxicity grade was below maximum grade with no higher grade thereafter.

Ansell et al NEJM 2022 DOI: 10.1056/NEJMoa2206125

Aber Zeit ändern sich……

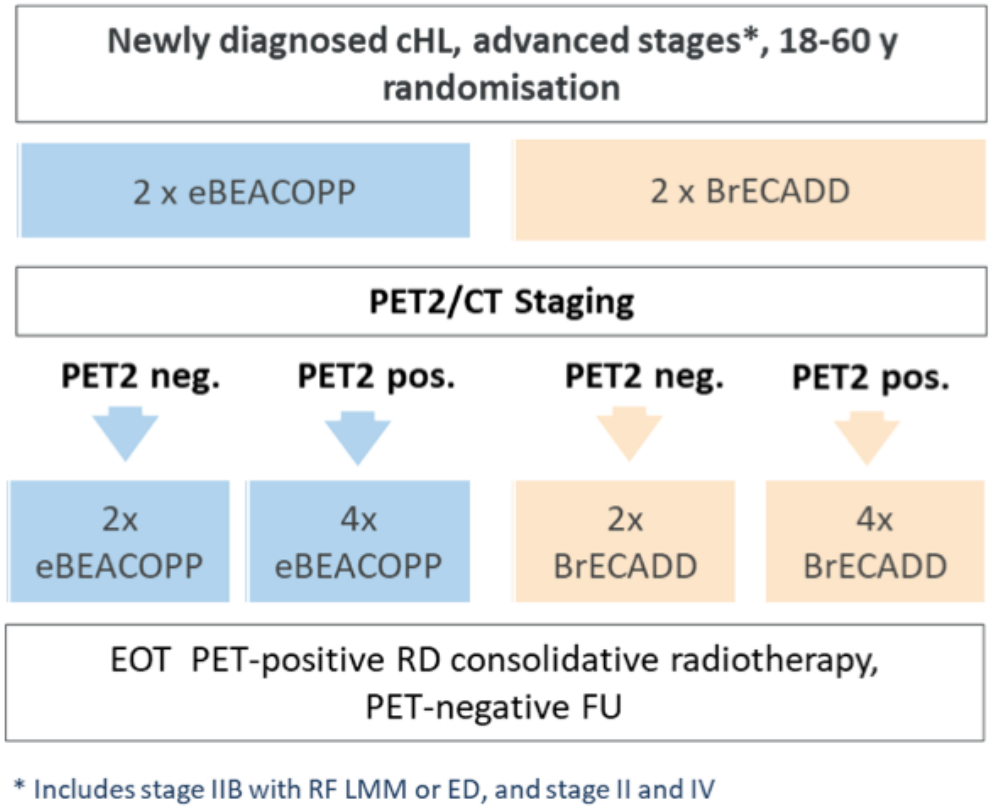


HD21 BrECADD

Drug	Day	BEACOPP[1] Dose (mg/m²)	BrECADD Dose (mg/m²)	*Potential* improvement
Bleomycin	8	10	-	lung tox
Etoposide	1–3	200	*150*	hem tox, transfusion frequency
Doxorubicin	1	35	*40*	
Cyclophosphamide	1	1250	*1250*	
Vincristine	8	1.4	-	neuropathy
Brentuximab vedotin	1	-	*1.8 mg/kg*	
Procarbazine	1–7	100	-	gonadal tox, sAML/MDS
Prednisone	1–14	40	-	weight, bone, infections
Dacarbazine	2–3	-	*250*	
Dexamethasone	1–4	-	*40*	

Borchmann et al Hematological Oncology, 41: 881-882. Lugano 2023

GHSG HD21 study design and primary endpoint



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

Co-primary endpoint:

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

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

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

Borchmann et al Hematological Oncology, 41: 881-882. Lugano 2023

GHSG HD21 demographics and patient characteristics (ITT-PFS)

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

eBEACOPP and BrECADD cohorts were also well balanced for:

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

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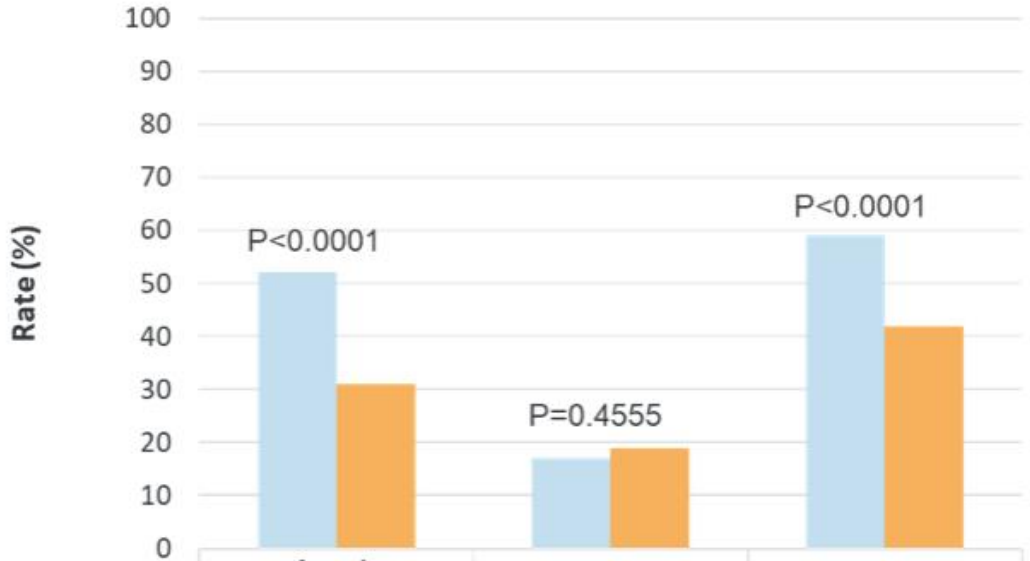
GHSG HD21 primary safety endpoint TRMB analyses results



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

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

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

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

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

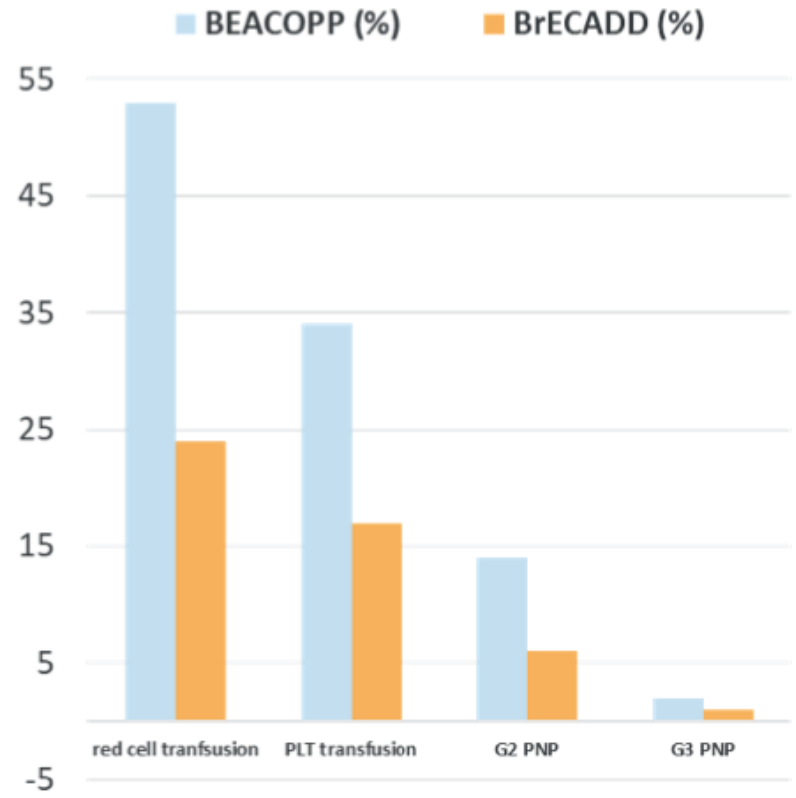
GHSG HD21 clinical implications of observed differences

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

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

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

*pts with at least one transfusion



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

female patients (18-39) per arm

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

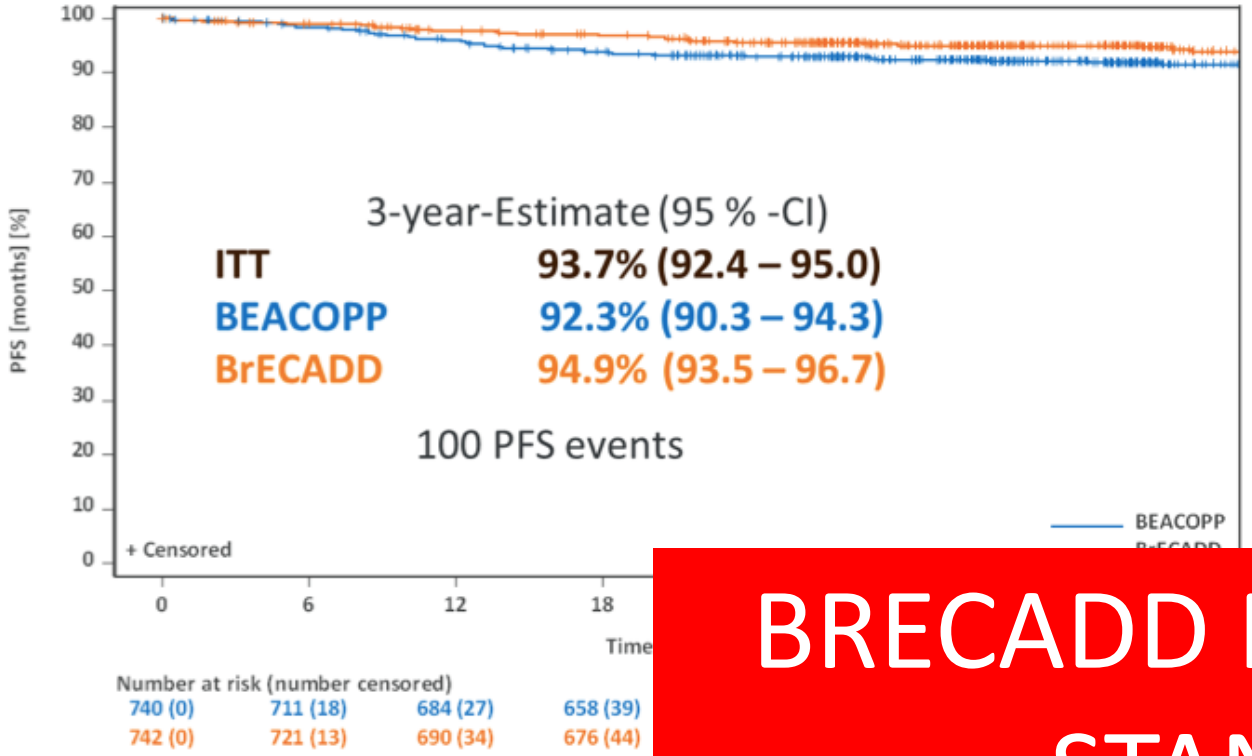
- FSH normal values (cycle dependent): 1,7 – 21,5 U/l
- FSH documented in: 58 % in BEACOPP and 57 % in BrECADD

male patients (18-49) per arm

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

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

HD21 PFS events and Kaplan Meyer analysis



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

BRECADD NEUER GHSG STANDARD

Borchmann et al Hematological Oncology, 41: 881-882. Lugano 2023

2023 ASCO ANNUAL MEETING

SWOG S1826, a Randomized Study of Nivolumab(N)-AVD Versus Brentuximab Vedotin(Bv)-AVD in Advanced Stage Classic Hodgkin Lymphoma (cHL)

Alex F. Herrera, MD[1], *Michael L. LeBlanc, PhD*[2], *Sharon M. Castellino, MD, MSc*[3], *Hongli Li, MS*[2], *Sarah C. Rutherford, MD*[4], *Andrew M Evens, DO, MSc*[5], *Kelly Davison, MD*[6], *Angela Punnett, MD*[7], *David C. Hodgson, MD, MPH, FRCPC*[8], *Susan K Parsons, MD, MRP*[9], *Sairah Ahmed, MD*[10], *Carla Casulo, MD*[11], *Nancy L. Bartlett, MD*[12], *Joo Y. Song, MD*[13], *Richard F. Little*[14], *Brad S. Kahl, MD*[12], *John P. Leonard, MD*[4], *Sonali M. Smith, MD*[15], *Kara M. Kelly, MD*[16], *and Jonathan W. Friedberg, MD, MSSc*[11]

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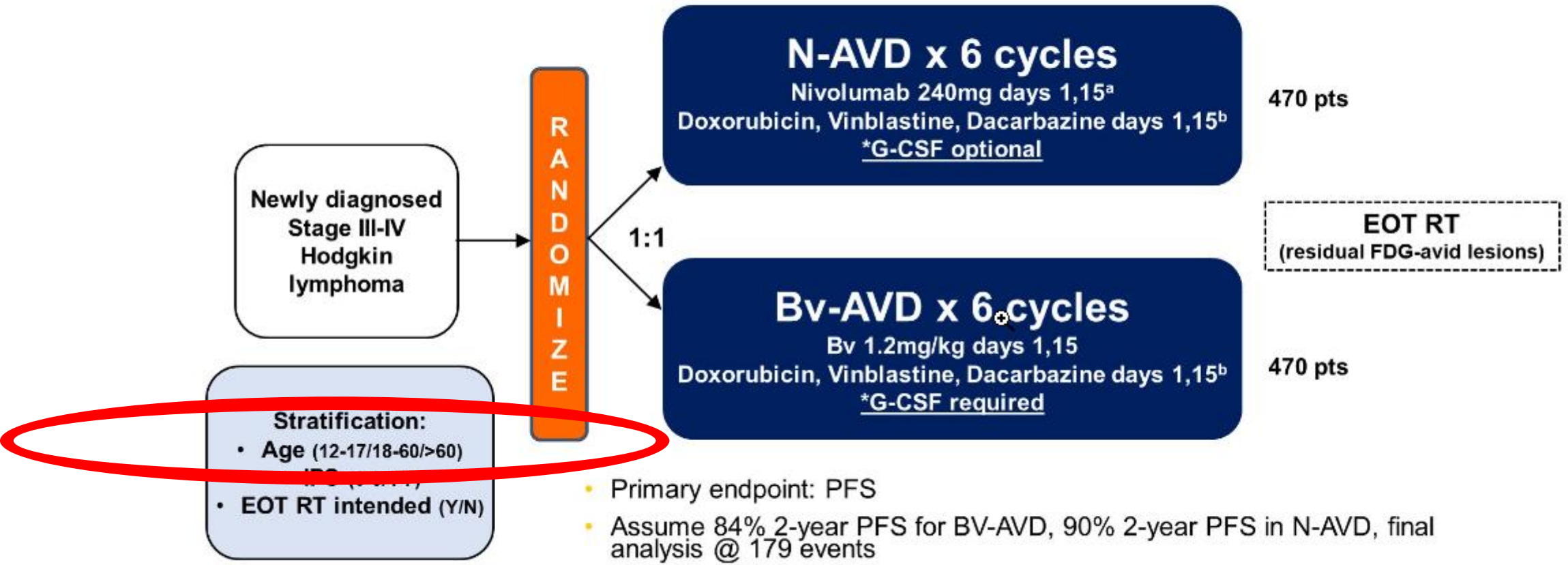
S1826 Study Design



- Primary endpoint: PFS
- Assume 84% 2-year PFS for BV-AVD, 90% 2-year PFS in N-AVD, final analysis @ 179 events

PRESENTED BY: Alex F. Herrera, MD

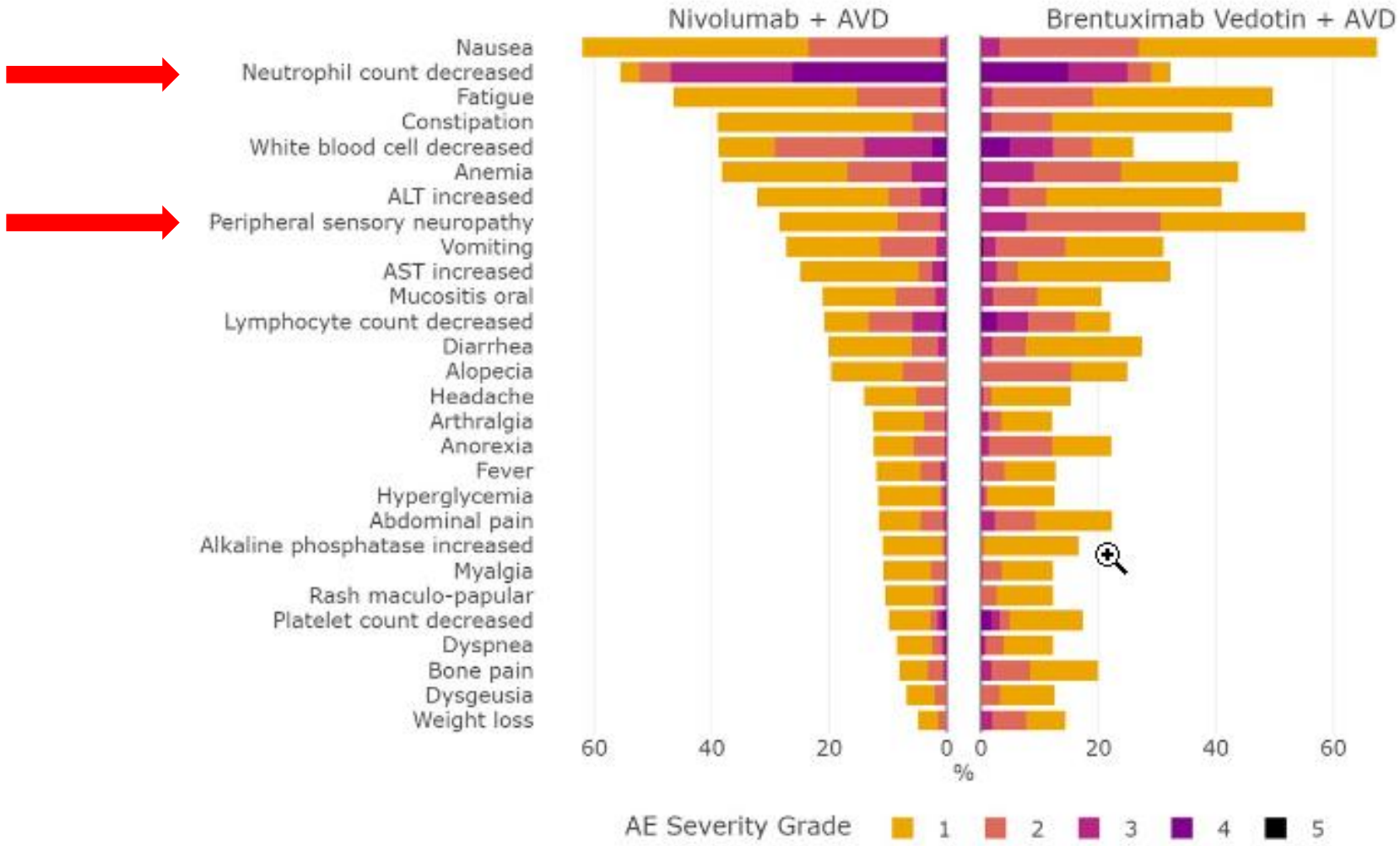
[a] Nivolumab 3mg/kg for ages ≤ 17, max 240mg
[b] Conventional doses of AVD: Stephens DM et al Blood 2019, Ansell SM et al NEJM 2022

S1826 Baseline Characteristics

Baseline characteristics	N-AVD n=489 N (%)	Bv-AVD n=487 N (%)
Age, median (range)	27 (12-83)	26 (12-81)
12-17 years	120 (25%)	117 (24%)
18-60 years	323 (66%)	323 (66%)
≥ 61 years	46 (9%)	47 (10%)
Female Sex	218 (45%)	213 (44%)
Race		
White	375 (77%)	364 (75%)
Black	57 (12%)	56 (11%)
Asian	11 (2%)	17 (3%)
Other/Unknown	46 (9%)	50 (10%)
Hispanic	68 (14%)	59 (12%)

Baseline characteristics	N-AVD n=489 N (%)	Bv-AVD n=487 N (%)
Stage		
III	187 (38%)	167 (34%)
IV	301 (62%)	317 (65%)
Not reported	1 (0.2%)	3 (1%)
B symptoms present	286 (58%)	274 (56%)
IPS Score		
0-3	331 (68%)	330 (68%)
4-7	158 (32%)	157 (32%)
Bulky disease > 10cm	155 (32%)	131 (27%)
HIV+	10 (2%)	5 (1%)

Adverse Events in ≥ 10% patients by Arm

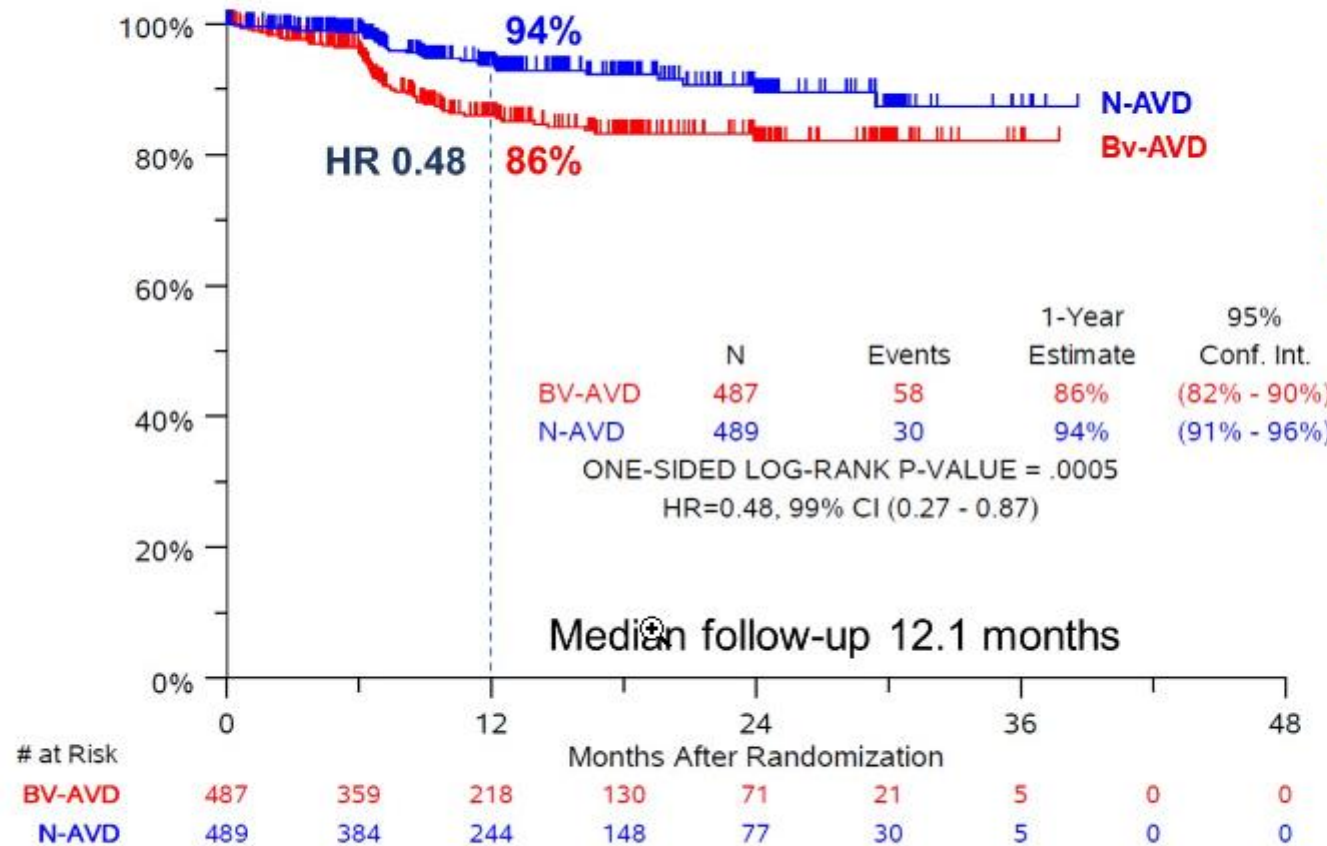


AEs of Interest: Immune/Other

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

N-AVD improves PFS compared to Bv-AVD

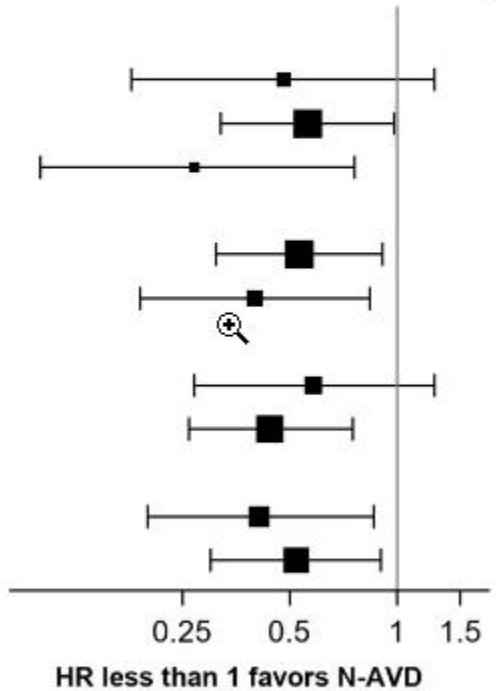


1-year PFS
N-AVD 94%
Bv-AVD 86%

PRESENTED BY: Alex F. Herrera, MD

PFS benefit consistent across subgroups

Subgroup	N + AVD Events/N (%)	BV + AVD Events/N (%)	HR (95% CI)	P Value
Age				
12 - 17 y	6/120 (5.0)	12/117 (10.3)	0.48 (0.18, 1.27)	0.140
18 - 60 y	19/323 (5.9)	32/323 (9.9)	0.56 (0.32, 0.98)	0.042
> 60 y	5/46 (10.9)	14/47 (29.8)	0.27 (0.10, 0.76)	0.013
IPS				
0 - 3	20/331 (6.0)	36/330 (10.9)	0.53 (0.31, 0.91)	0.023
4 - 7	10/158 (6.3)	22/157 (14.0)	0.40 (0.19, 0.84)	0.015
Stage				
III	11/187 (5.9)	15/167 (9.0)	0.58 (0.27, 1.27)	0.176
IV	19/301 (6.3)	43/317 (13.6)	0.44 (0.26, 0.75)	0.003
Symptoms				
A	10/202 (5.0)	24/210 (11.4)	0.41 (0.20, 0.86)	0.017
B	20/286 (7.0)	34/274 (12.4)	0.52 (0.30, 0.90)	0.020



Zusammenfassung

- BrECADD neuer Therapiestandard in Deutschland für fortgeschrittene Stadien
  - Sehr gute Effektivitä und sicherer Ausschluss der Unterlegenheit
  - weniger Therapie bedingte Morbidität
  - 57,5 % behandelt mit nur 4 Zyklen BrECADD

- NV-AVD verbessert PFS und EFS im Vergleich zu BV-AVD
  - < 1% Bestrahlung in NV-AVD
  - Aber alle Patienten behandelt mit 6 Zyklen NV-AVD

Vielen Dank für die Aufmerksamkeit

AEs of Interest: Peripheral Neuropathy

Toxicity	N-AVD n = 483		Bv-AVD n = 473	
	Any Gr N (%)	Gr ≥ 3 N (%)	Any Gr N (%)	Gr ≥ 3 N (%)
Peripheral sensory neuropathy	138 (29%)	6 (1%)	262 (55%)	37 (8%)
Peripheral motor neuropathy	20 (4%)	1 (0%)	35 (7%)	6 (1%)

More neuropathy in Bv-AVD arm

Treatment Discontinuation and Deaths

Disposition	N-AVD (n=489) N (%)	Bv-AVD (n=487) N (%)
Treatment ongoing	22	30
Completed treatment	428	400
Discontinued all treatment early	**39 (8%)**	**57 (12%)**
Adverse event	22 (4%)	18 (4%)
Refusal unrelated to AE	10	14
Progression/relapse	**0 (0%)**	**7 (1.4%)**
Death on treatment	**2 (0.4%)**	**8 (1.6%)**
Other – not protocol specified	5	10
Discontinued Bv or Nivolumab	**53 (11%)**	**109 (22%)**
Received radiotherapy	**2 (0.4%)**	**4 (0.8%)**

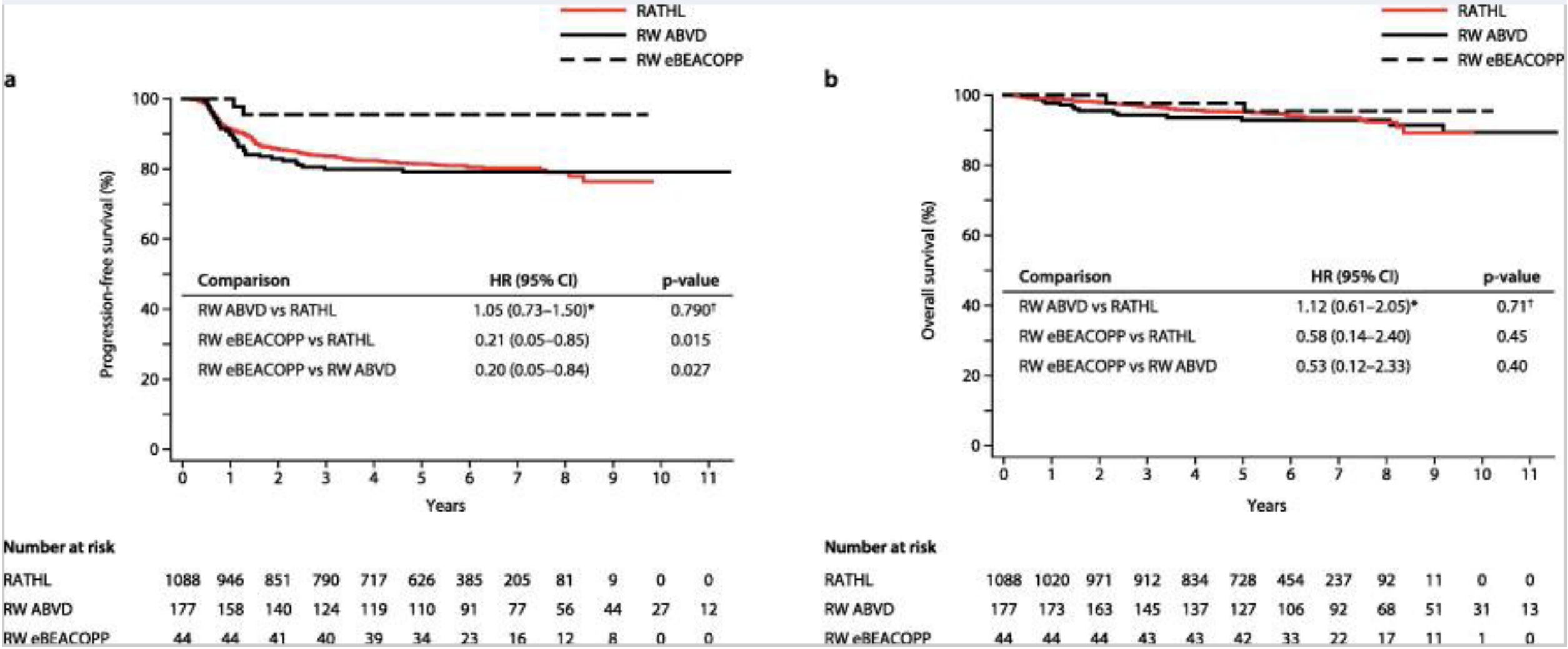
S1826 Conclusions

- **N-AVD improved PFS compared to Bv-AVD in advanced stage cHL**
  - N-AVD improved EFS versus Bv-AVD
- N-AVD was well-tolerated
  - Few immune-related adverse events
- < 1% of patients received consolidative RT
  - May reduce late effects
- Follow-up ongoing to confirm durability of PFS, assess long-term safety, OS, and PROs
- Key step towards harmonizing pediatric and adult therapy of cHL
- **N-AVD is poised to be a new standard therapy for advanced stage cHL**

PRESENTED BY: Alex F. Herrera, MD

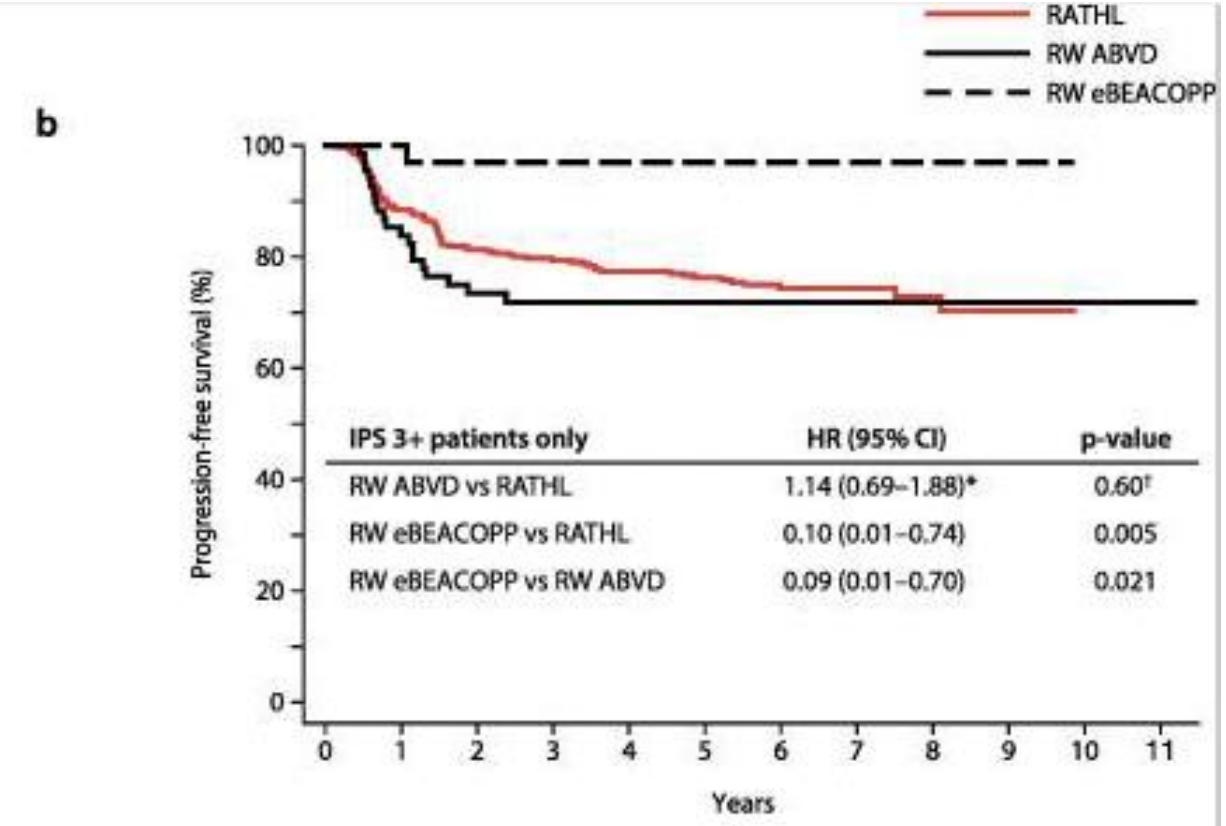
RATHL vs. REAL World

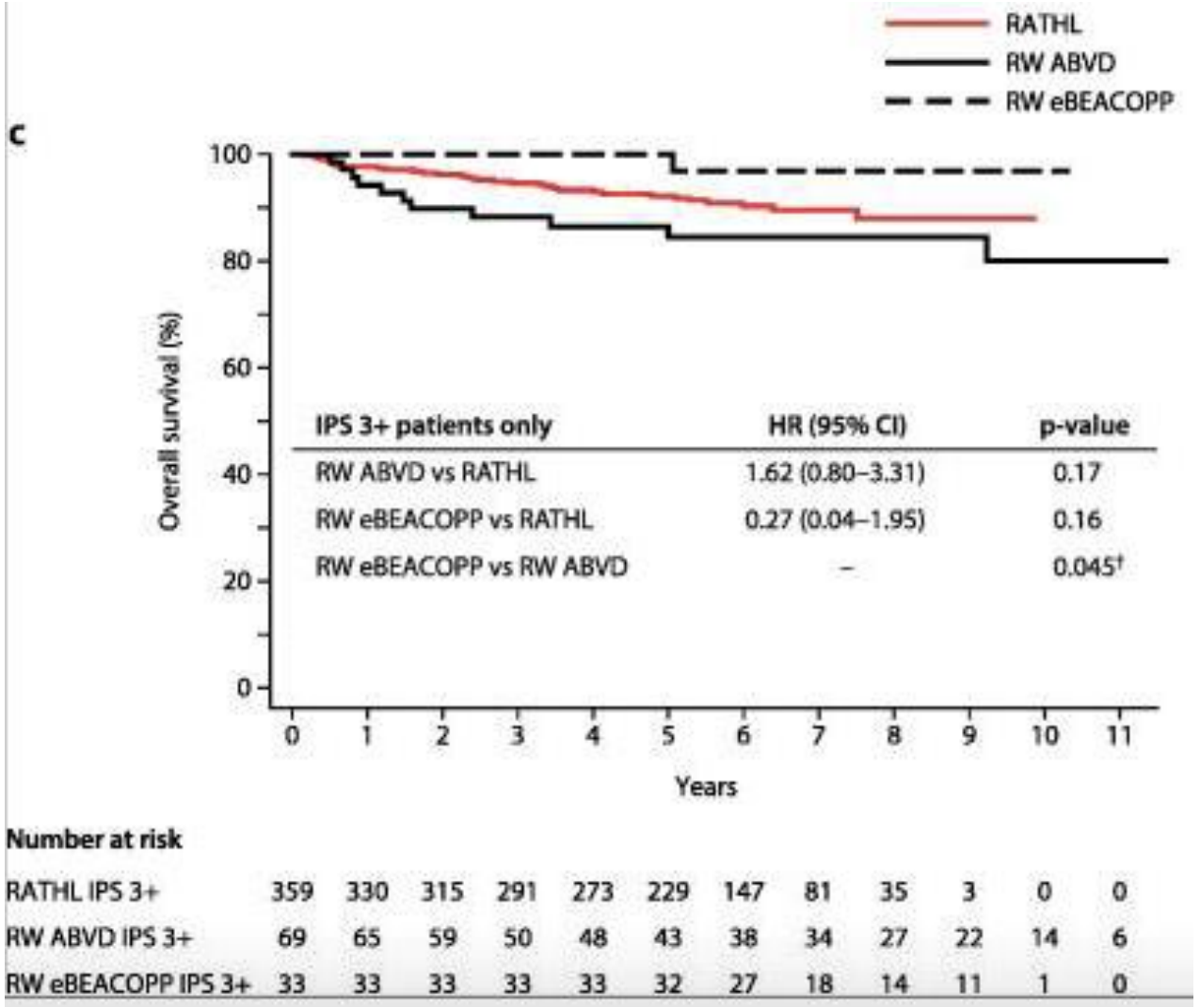
Russel et al Annals of Hematol 2021 doi 10.1007/s00277-021-04460-9



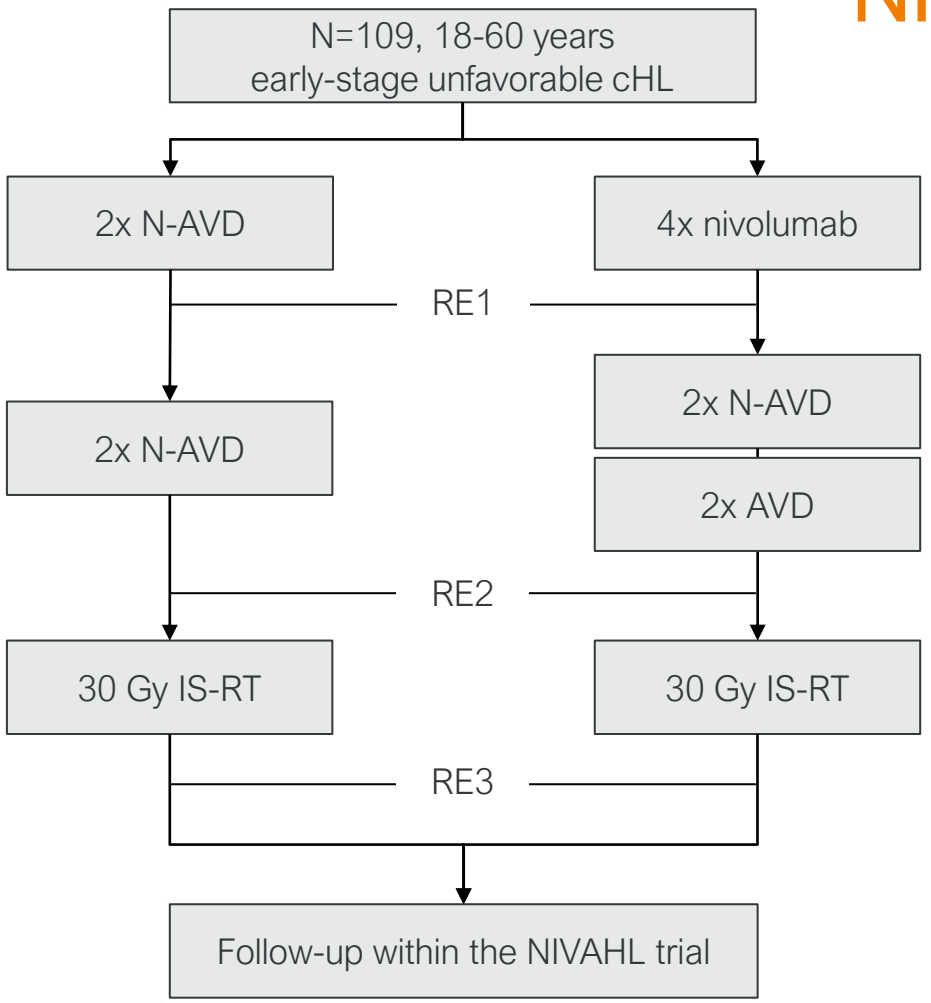
RATHL vs. REAL World

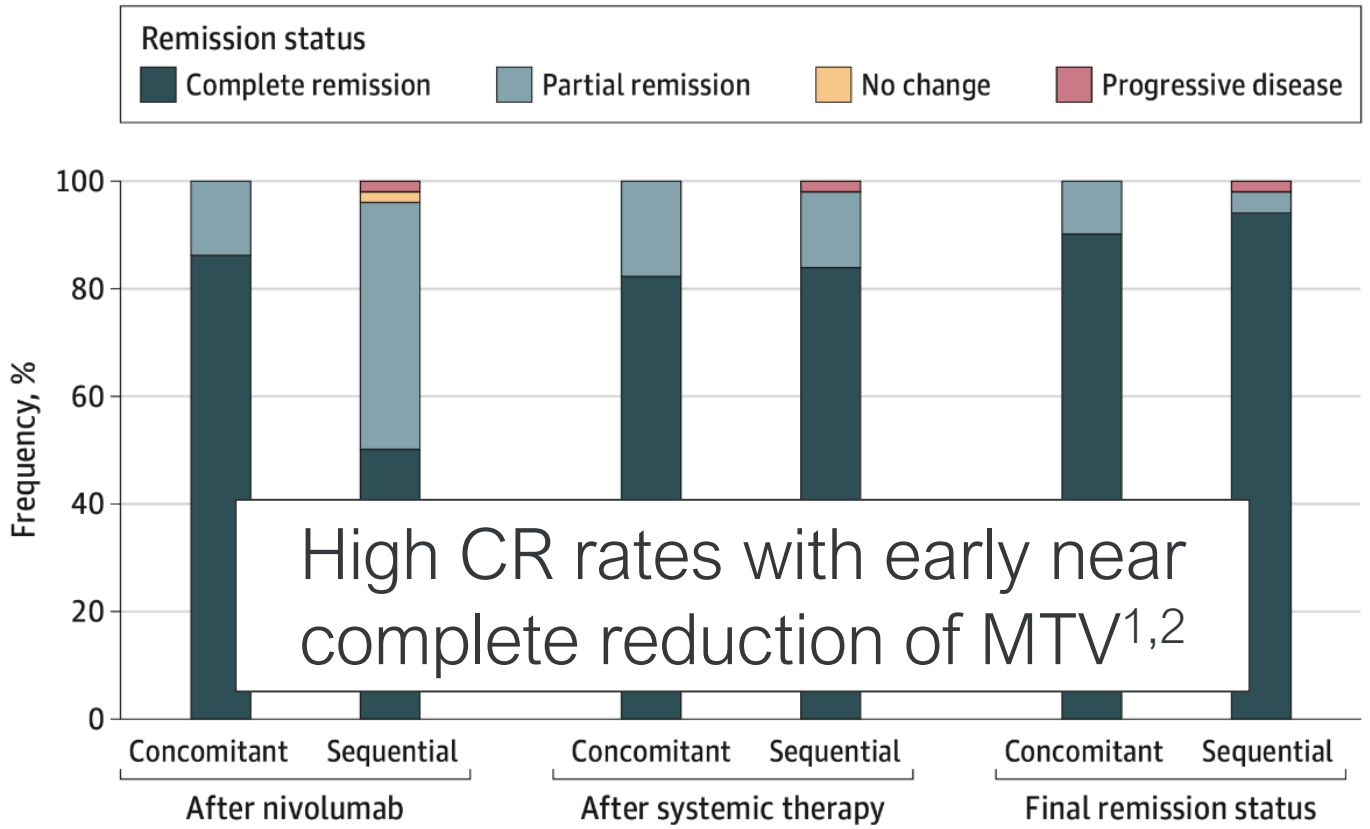
Russel et al Annals of Hematol 2021 doi 10.1007/s00277-021-04460-9





NIVAHL Background

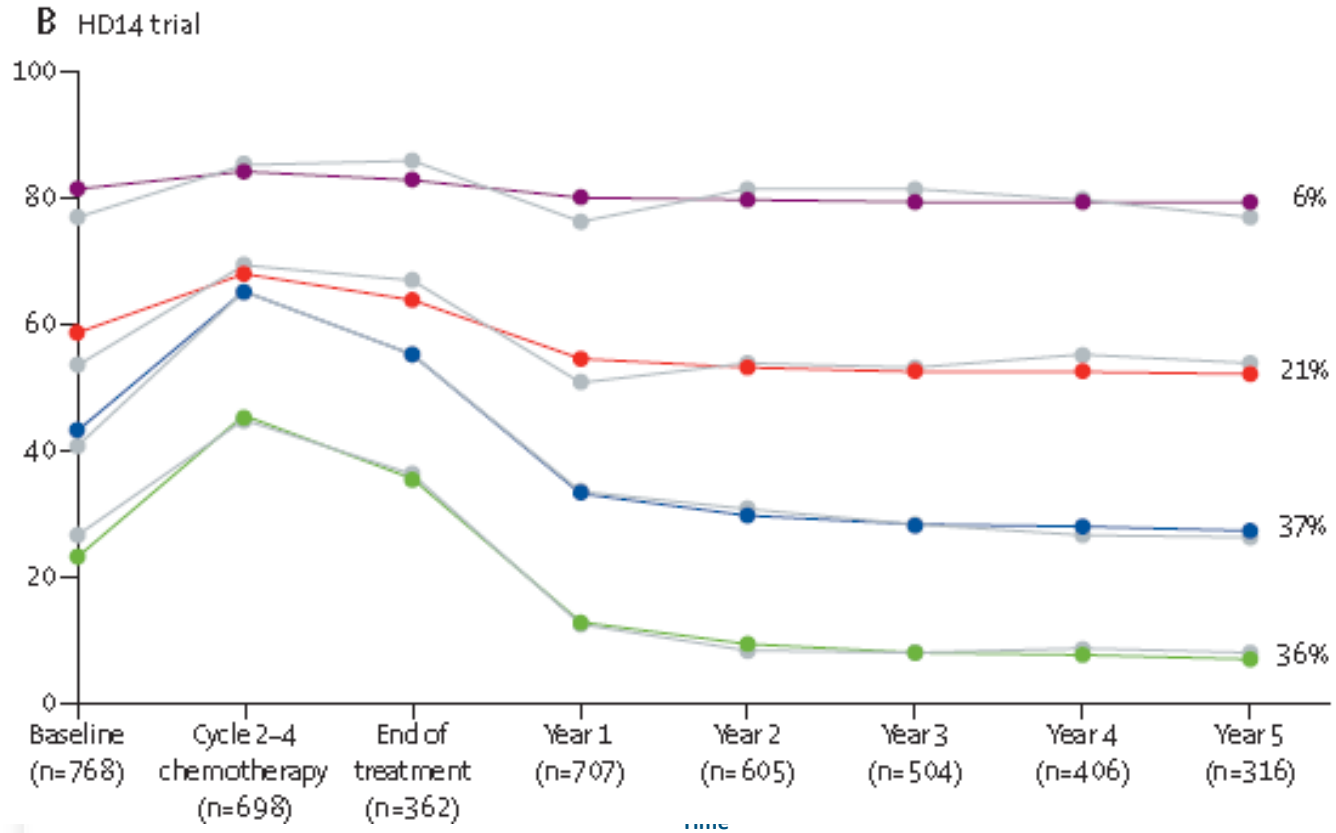


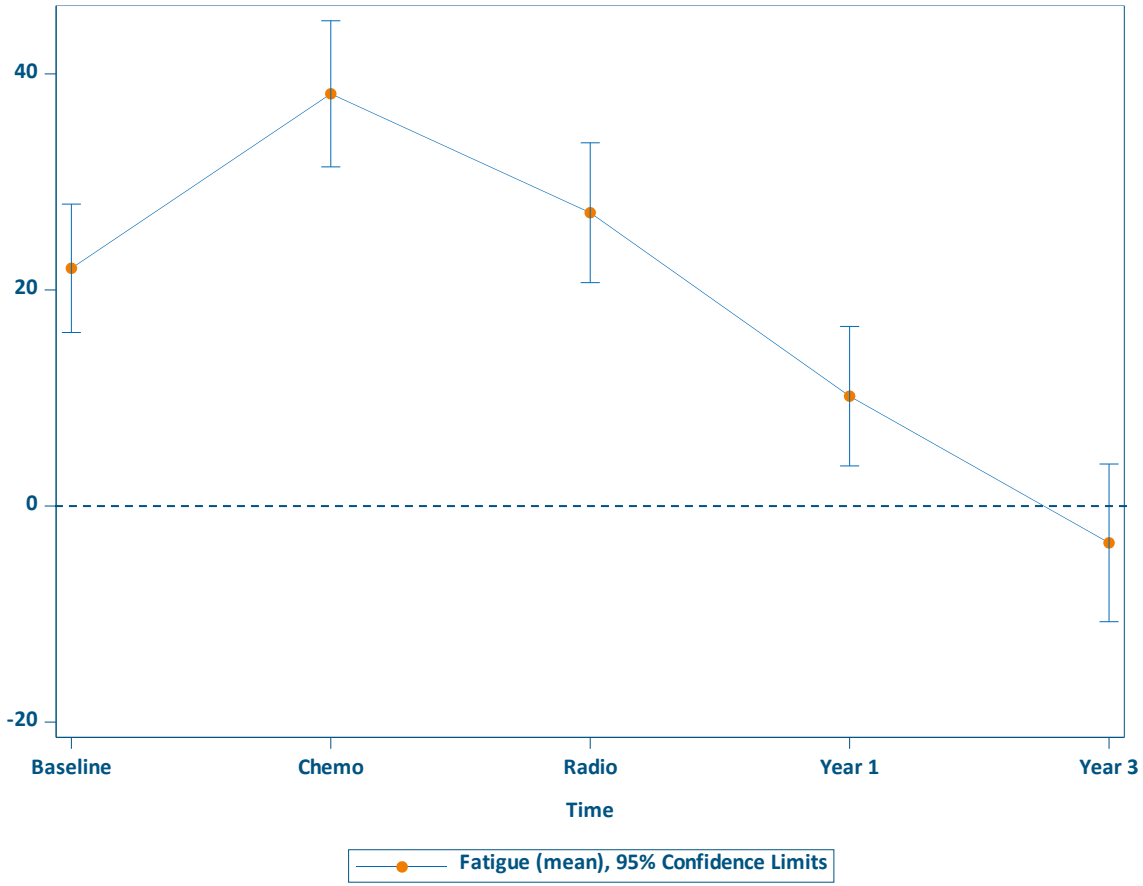


Very early histologic CR[3] and reversion of exhausted lymphocyte phenotypes[4]

[1] Bröckelmann PJ et al. *JAMA Oncol* 2020, [2] Voltin CA (…) Bröckelmann PJ *Clin Cancer Res* 2020, [3] Reinke S* & Bröckelmann PJ* et al. *Blood* 2020, [4] Garcia-Marquez MA (…) Bröckelmann PJ* & Schlösser HA* *Leukemia* 2021

NIVAHL QoL & Fatigue

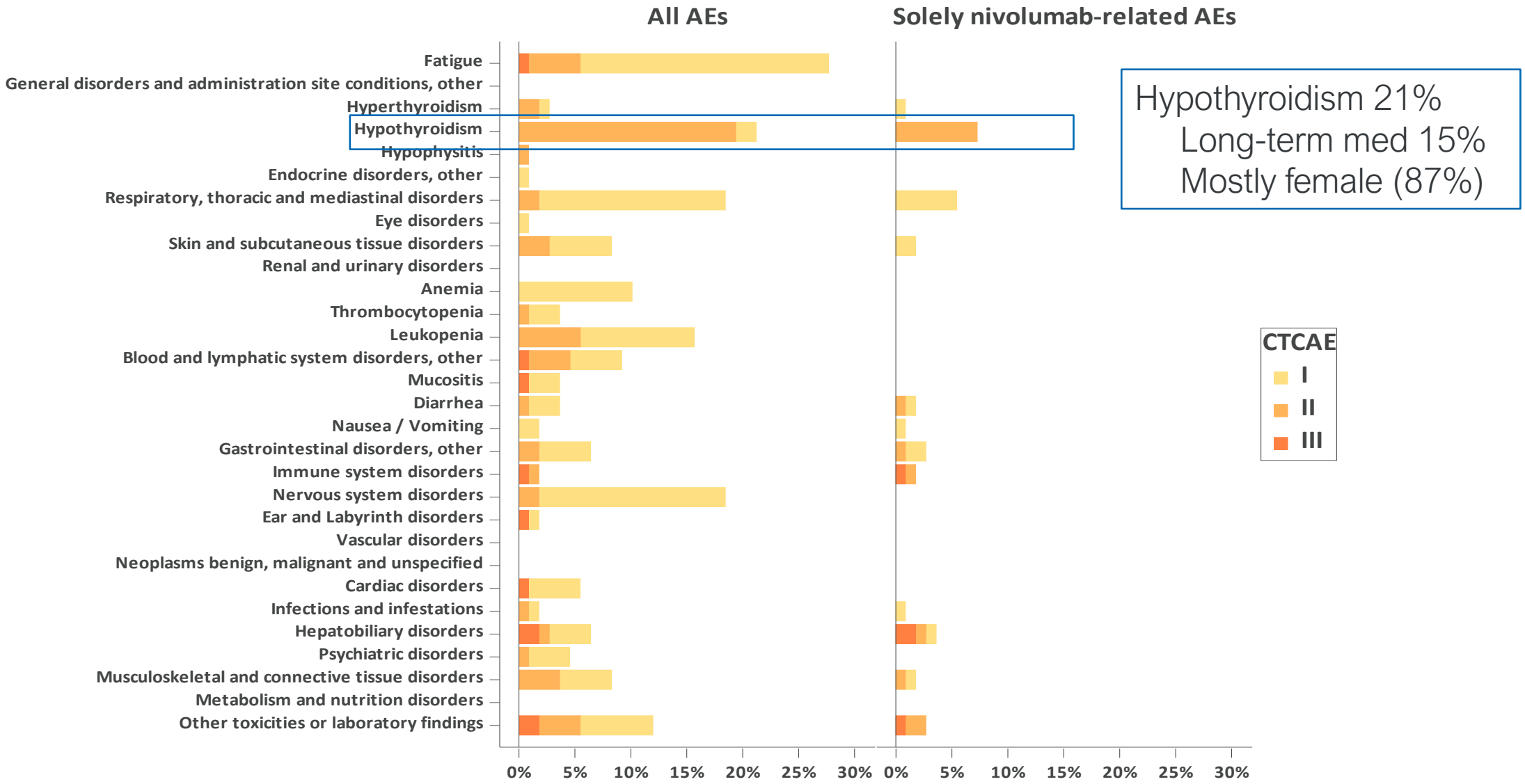




Improvement of age- and sex-adjusted global QoL and fatigue levels vs pre-treatment

Measured by EORTC QLQ-C30 questionnaire. Abbreviations: QoL: quality of life
S. Kreissel Lancet Oncol 2016

NIVAHL Toxicities during FU



Hypothyroidism 21%
Long-term med 15%
Mostly female (87%)

Bröckelmann et al J Clin Oncol 2022 41:1193-1199

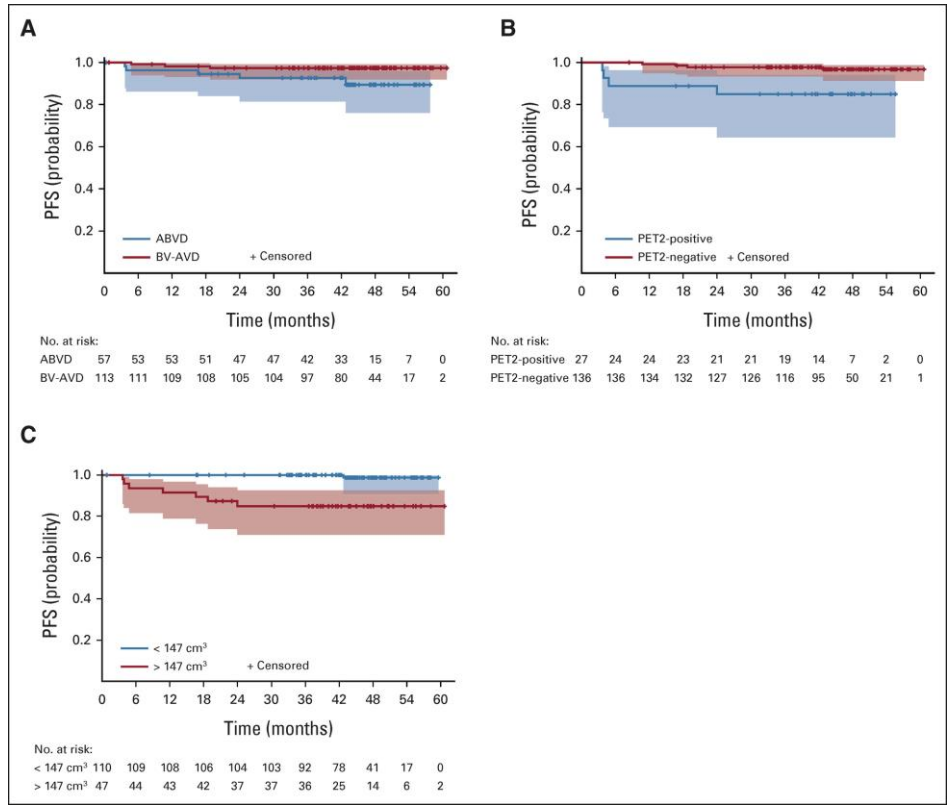


FIG 2. Kaplan-Meier curves of progression-free survival (A) by treatment arm, (B) by PET status after two cycles, and (C) by baseline TMTV. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BV-AVD, brentuximab vedotin plus doxorubicin, vincristine, and dacarbazine; FAS, full analysis set; PET, positron emission tomography; TMTV, total metabolic tumor volume.

Published in: Luc-Matthieu Fornecker; Julien Lazarovici; Igor Aurer; René-Olivier Casasnovas; Anne-Claire Gac; Christophe Bonnet; Krimo Bouabdallah; Pierre Feugier; Lena Specht; Lysiane Molina; Mohamed Touati; Cécile Borel; Aspasia Stamatoullas; Emmanuelle Nicolas-Virelizier; Laurent Pascal; Pieternella Lugtenburg; Nicola Di Renzo; Thierry Vander Borght; Alexandra Traverse-Glehen; Peggy Dartigues; Martin Hutchings; Annibale Versari; Michel Meignan; Massimo Federico; Marc André; *Journal of Clinical Oncology* 2023 41327-335.
DOI: 10.1200/JCO.21.01281

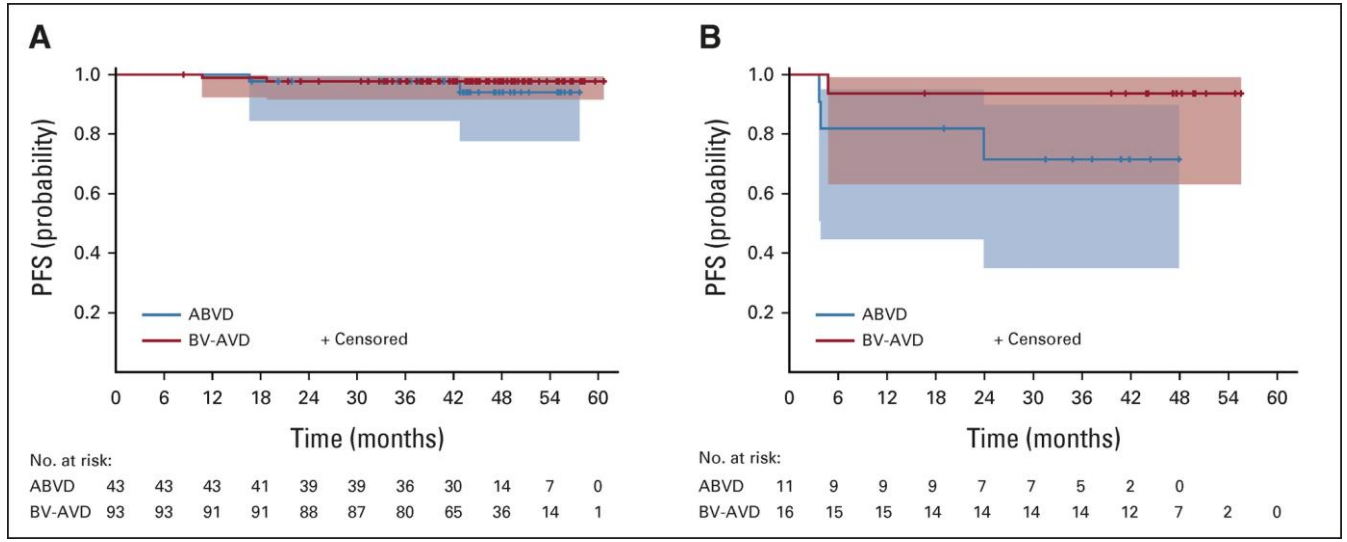


FIG A1. PFS according to the treatment arm and PET2 results. Patients with (A) negative PET2 and (B) positive PET2. ABVD, doxorubicin, bleomycin, vincristine, and dacarbazine; BV-AVD, brentuximab plus doxorubicin, vincristine, and dacarbazine; FAS, full analysis set; PET2, positron emission tomography after 2 cycles; PFS, progression-free survival.

Published in: Luc-Matthieu Fornecker; Julien Lazarovici; Igor Aurer; René-Olivier Casasnovas; Anne-Claire Gac; Christophe Bonnet; Krimo Bouabdallah; Pierre Feugier; Lena Specht; Lysiane Molina; Mohamed Touati; Cécile Borel; Aspasia Stamatoullas; Emmanuelle Nicolas-Virelizier; Laurent Pascal; Pieternella Lugtenburg; Nicola Di Renzo; Thierry Vander Borght; Alexandra Traverse-Glehen; Peggy Dartigues; Martin Hutchings; Annibale Versari; Michel Meignan; Massimo Federico; Marc André; *Journal of Clinical Oncology* 2023 41327-335.
DOI: 10.1200/JCO.21.01281

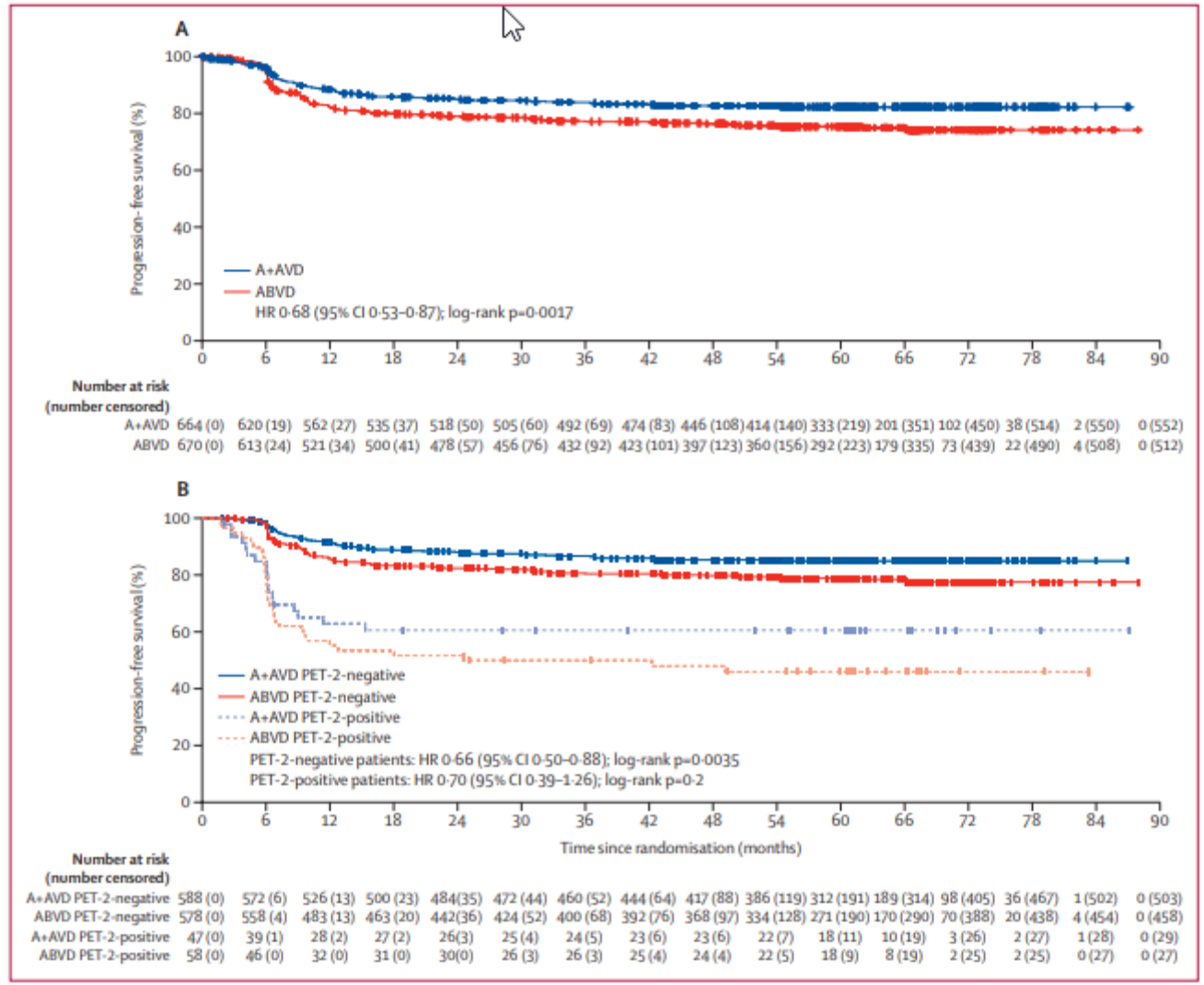


Figure 2: **Progression-free survival per investigator assessment in the intention-to-treat population**

(A) Patients treated with A+AVD or ABVD. A+AVD group: 16 deaths and 96 progressive disease events. ABVD group: 30 deaths and 128 progressive disease events. (B) Patients receiving A+AVD or ABVD by PET-2 status (positive or negative for active disease by PET scan after two cycles of therapy). A+AVD PET-2-negative subgroup: nine deaths and 76 progressive disease events. ABVD PET-2-negative subgroup: 26 deaths and 94 progressive disease events. A+AVD PET-2-positive subgroup: no deaths and 18 progressive disease events. ABVD PET-2-positive subgroup: three deaths and 28 progressive disease events. Tick marks indicate censored data. A+AVD=brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine. ABVD=doxorubicin, bleomycin, vinblastine, and dacarbazine. HR=hazard ratio.

ECHELON-1

Table 3. Summary of Responses in the Intention-to-Treat Population.

Measure	A+AVD (N=664)	ABVD (N=670)	Difference (95% CI)*
	no. (%)		%
Complete response at end of randomized regimen†	488 (73)	472 (70)	3.0 (−2.3 to 8.4)
Overall response at end of randomized regimen‡	569 (86)	553 (83)	3.2 (−2.2 to 8.6)
Complete response at end of frontline therapy§	488 (73)	474 (71)	2.7 (−2.6 to 8.1)
Deauville score¶			
≤3 After completion of frontline therapy	570 (86)	551 (82)	3.6 (−1.8 to 9.0)
≤2 After completion of frontline therapy	563 (85)	537 (80)	4.6 (−0.8 to 10.0)
Summary at cycle 2			
1	435 (66)	414 (62)	
2	131 (20)	133 (20)	
3	22 (3)	30 (4)	
4	26 (4)	28 (4)	
5	21 (3)	30 (4)	
Unavailable	29 (4)	35 (5)	
Summary after completion of primary chemotherapy			
1	444 (67)	425 (63)	
2	119 (18)	112 (17)	
3	7 (1)	14 (2)	
4	12 (2)	20 (3)	
5	46 (7)	45 (7)	
Unavailable	36 (5)	54 (8)	

Connors et al Engl J Med 2018 Jan 25;378(4):331-344.
doi: 10.1056/NEJMoa1708984

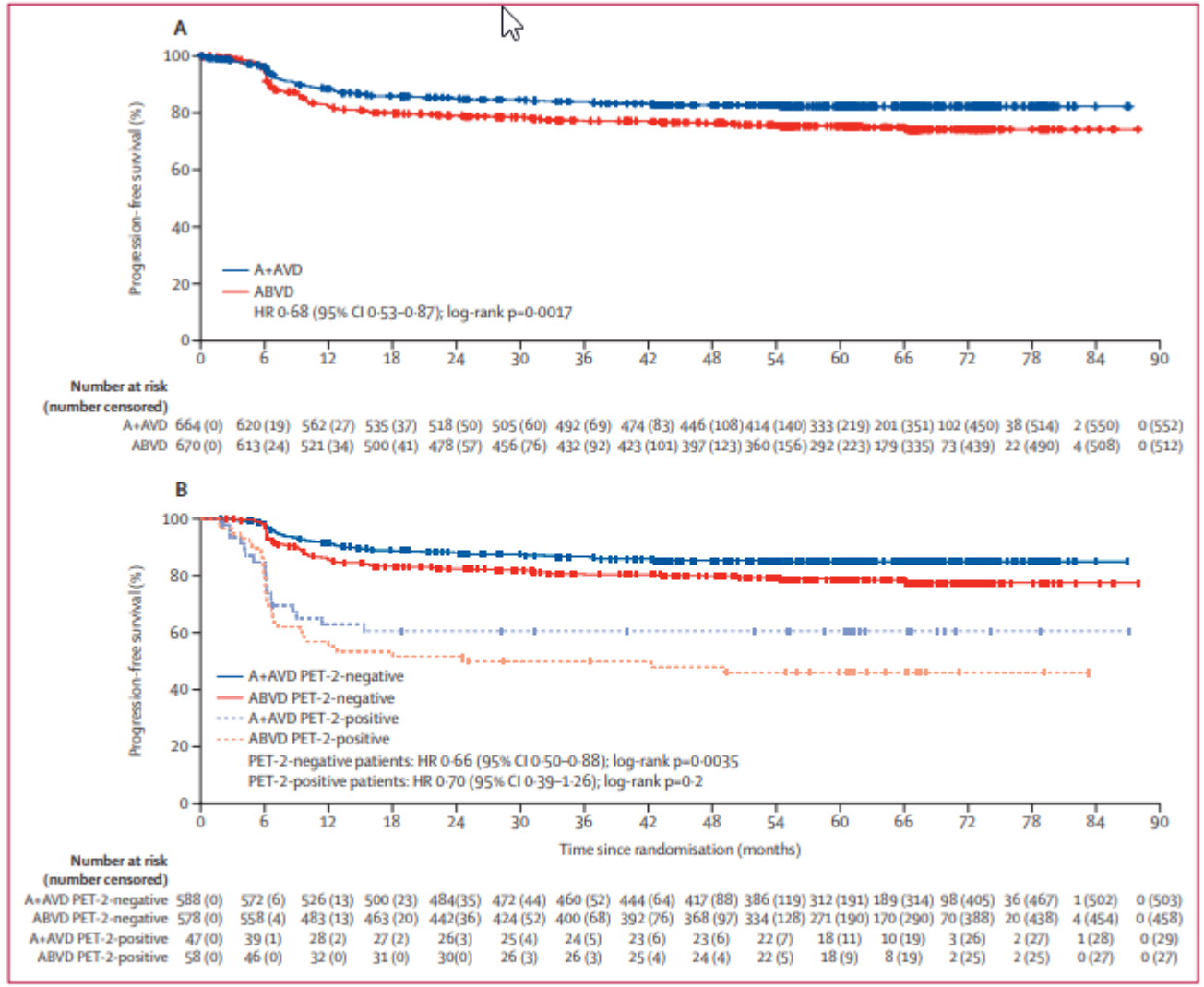


***Figure 2*: Progression-free survival per investigator assessment in the intention-to-treat population**
(A) Patients treated with A+AVD or ABVD. A+AVD group: 16 deaths and 96 progressive disease events. ABVD group: 30 deaths and 128 progressive disease events. (B) Patients receiving A+AVD or ABVD by PET-2 status (positive or negative for active disease by PET scan after two cycles of therapy). A+AVD PET-2-negative subgroup: nine deaths and 76 progressive disease events. ABVD PET-2-negative subgroup: 26 deaths and 94 progressive disease events. A+AVD PET-2-positive subgroup: no deaths and 18 progressive disease events. ABVD PET-2-positive subgroup: three deaths and 28 progressive disease events. Tick marks indicate censored data. A+AVD=brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine. ABVD=doxorubicin, bleomycin, vinblastine, and dacarbazine. HR=hazard ratio.

Echelon Update Lancet 2021

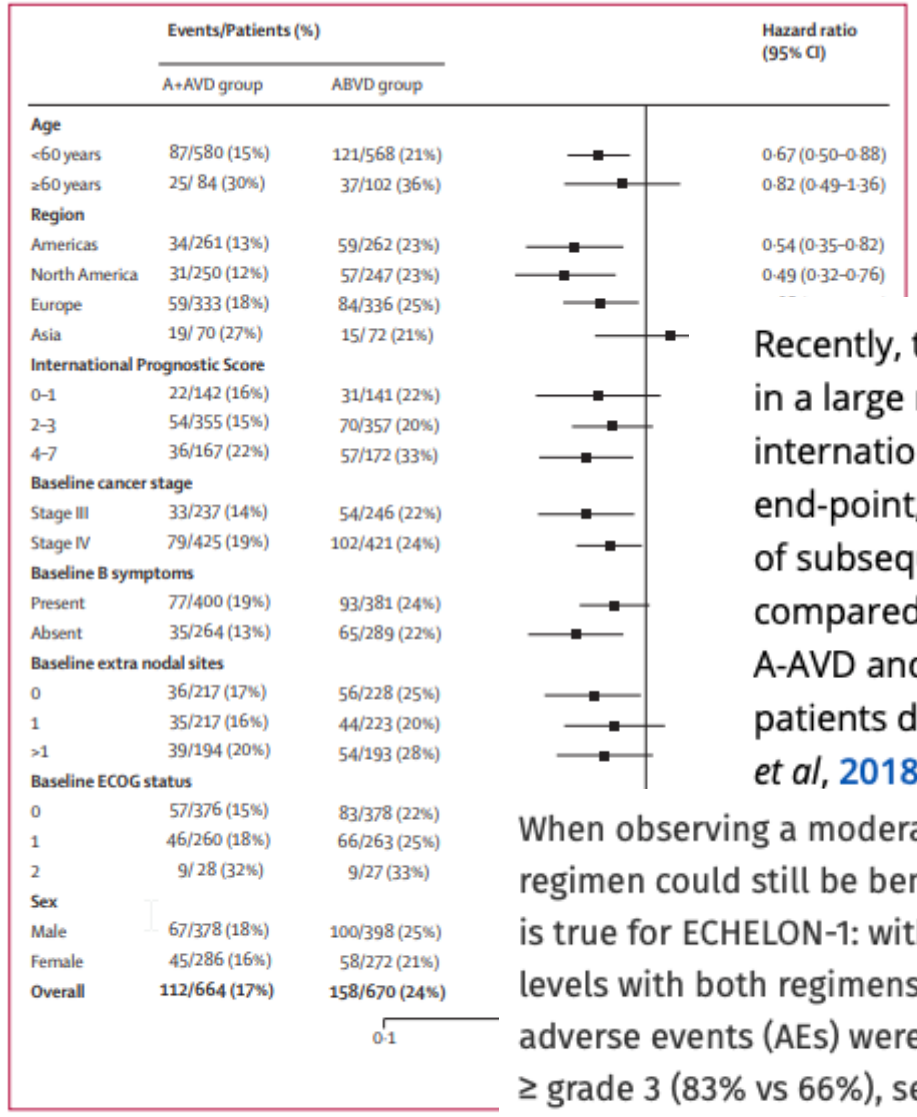
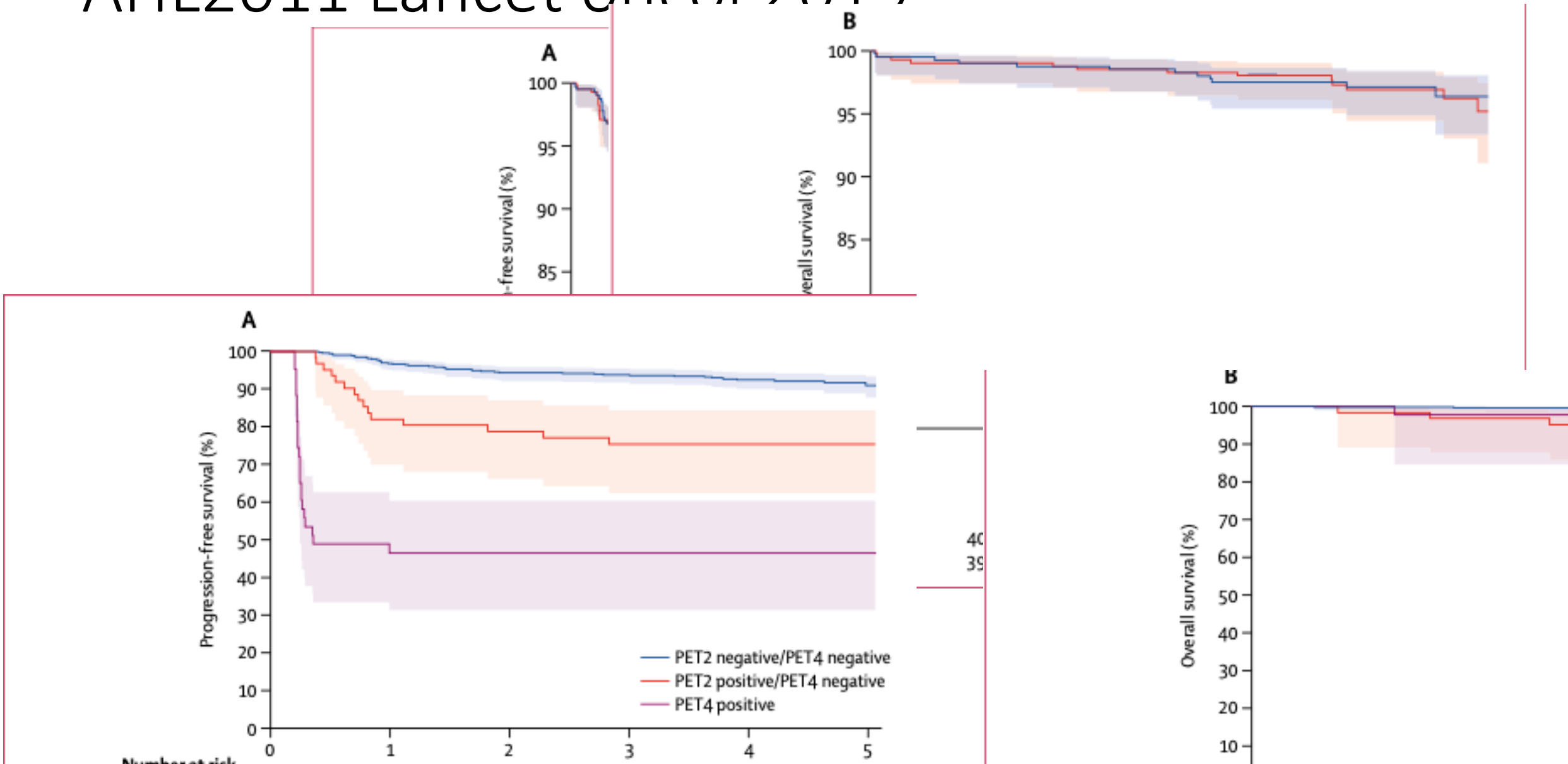


Figure 3: Subgroup analysis of progression-free survival per i
Hazard ratios (A+AVD *vs* ABVD) and 95% CIs were based on a str
A+AVD=brentuximab vedotin in combination with doxorubicin,
bleomycin, vinblastine, and dacarbazine. ECOG=Eastern Coopera

Recently, the combination of brentuximab vedotin with AVD (
in a large randomized trial in an attempt to gain the highest p
international randomized phase-III ECHOLON-1 study (Conno
end-point, modified PFS (mPFS; time to progression, death or
of subsequent anticancer therapy) after 2 years, was significa
compared to the ABVD group with mPFS of 82% (95% CI: 79–8
A-AVD and ABVD, respectively. However, the mPFS showed th
patients did not benefit from A-AVD [hazard ratio (A-AVD vs. A
et al, 2018). In addition, A-AVD caused increased severe toxici

When observing a moderate benefit for a vulnerable primary endpoint, the expe
regimen could still be beneficial for the patient if it was better tolerated. Howev
is true for ECHELON-1: with the exception of severe lung toxicity, which occurred
levels with both regimens (<1% vs 3% for BV + AVD vs ABVD, respectively); all oth
adverse events (AEs) were clearly more frequent with BV + AVD. This is true for s
≥ grade 3 (83% vs 66%), serious AEs (43% vs 27%), hospitalizations (37% vs 28%),
particular, severe neutropenia and severe neuropathy occurred more often with
containing 2 microtubule inhibitors. This raises doubts on the usefulness of the
regimen. Grade 2 or higher peripheral neuropathy can be a disabling AE, which s
particularly avoided in these young HL patients. Overall, 30% of BV + AVD-treate

AHL2011 Lancet oncol 2019



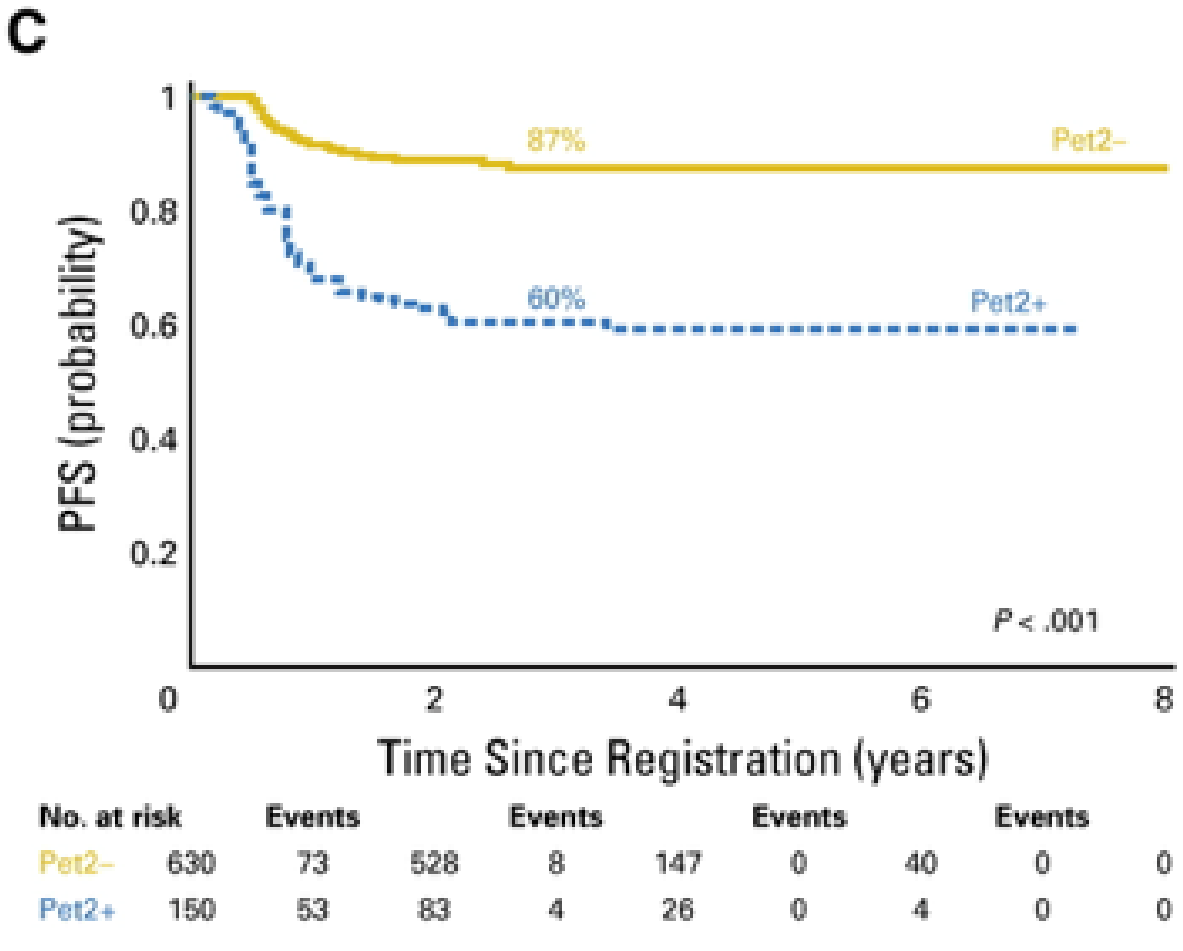
AHL 2011 JCO 2022

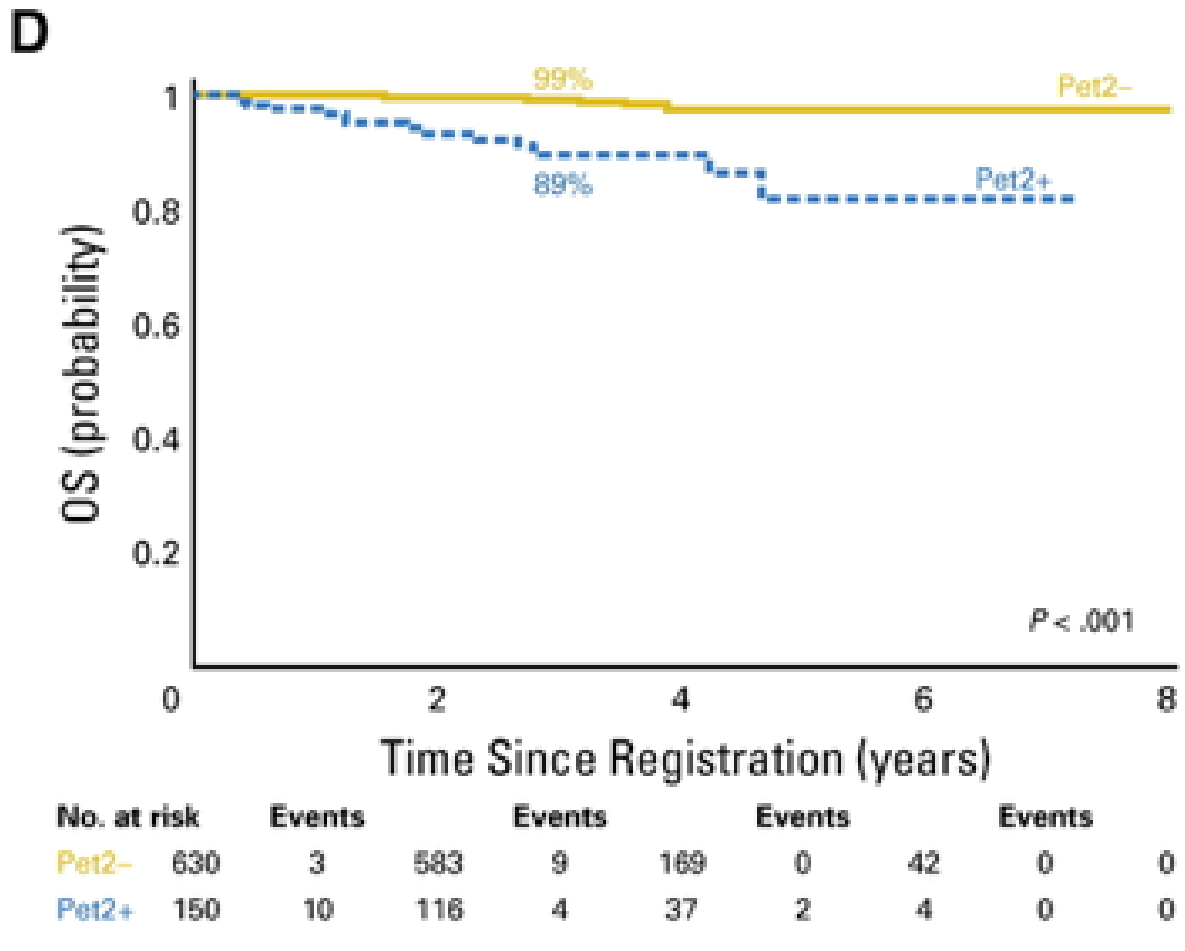
Results: In total, 823 patients were enrolled including 413 in the standard arm and 410 in the PET-driven arm. With a 67.2-month median follow-up, 5-year PFS (87.5% *v* 86.7%; hazard ratio [HR] = 1.07; 95% CI, 0.74 to 1.57; *P* = .67) and OS (97.7% in both arms; HR = 1.012; 95% CI, 0.50 to 2.10; *P* = .53) were similar in both randomization arms. In the whole cohort, full interim PET assessment predicted patients' 5-year PFS (92.3% in PET2-/PET4-, 75.4% [HR = 3.26; 95% CI, 18.3 to 5.77] in PET2+/PET4- and 46.5% [HR = 12.4; 95% CI, 7.31 to 19.51] in PET4+ patients, respectively; *P* < .0001) independent of international prognosis score. Five-year OS was also affected by interim PET results, and PET2+/PET4- patients (93.5%; HR = 3.3; 95% CI, 1.07 to 10.1; *P* = .036) and PET4+ patients (91.9%; HR = 3.756; 95% CI, 1.07 to 13.18; *P* = .038) had a significant lower OS than PET2-/PET4- patients (98.2%). Twenty-two patients (2.7%) developed a second primary malignancy, 13 (3.2%) and 9 (2.2%) in the standard and experimental arms, respectively.

Conclusion: The extended follow-up confirms the continued efficacy and favorable safety of AHL2011 PET-driven strategy, which is noninferior to standard six cycles of BEACOPP. PET4 provides additional prognostic information to PET2 and allows identifying patients with particularly poor prognosis.

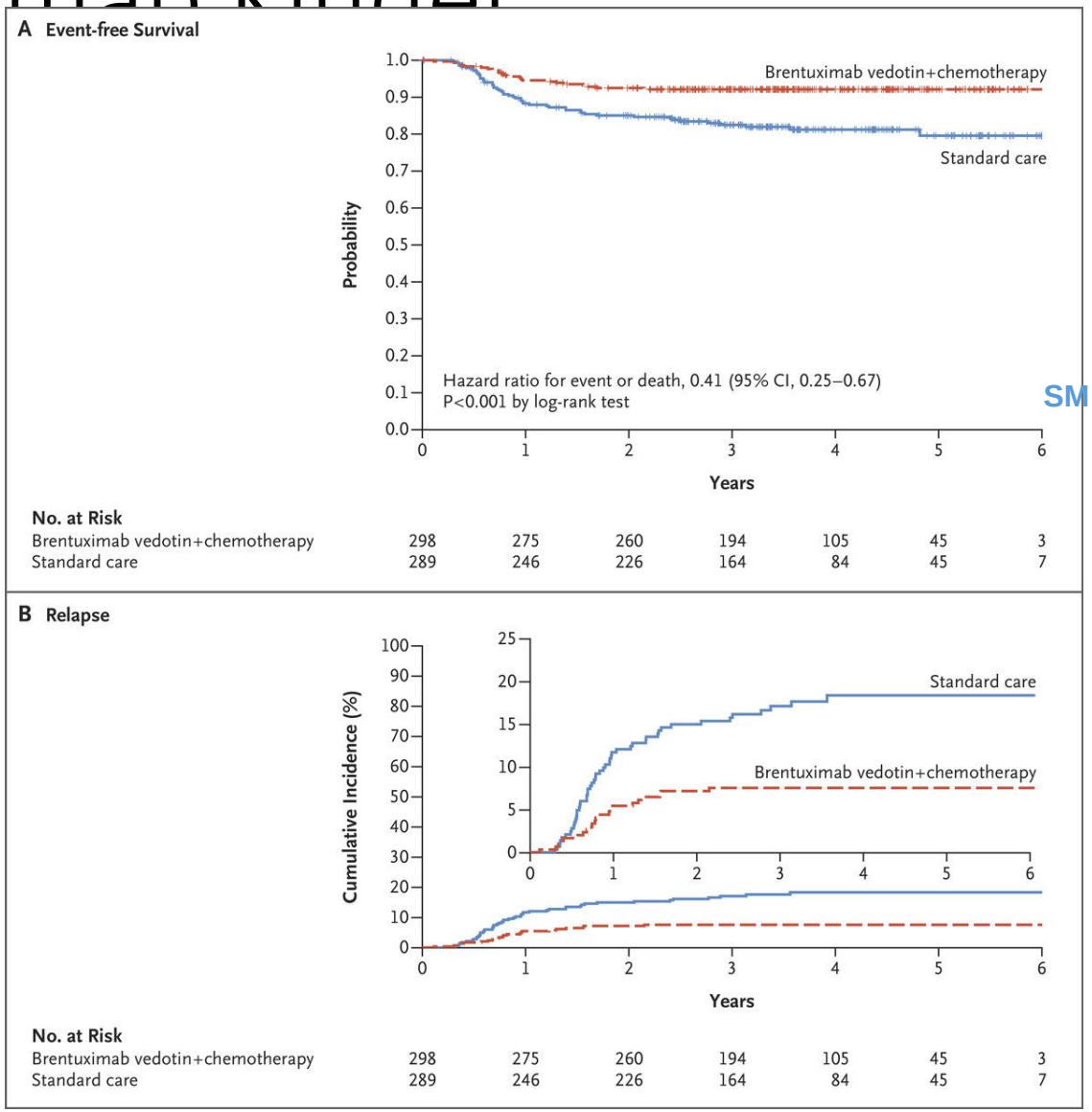
GITIL/FIL HD0607

13% ABVD treatment failure bei negativer PET



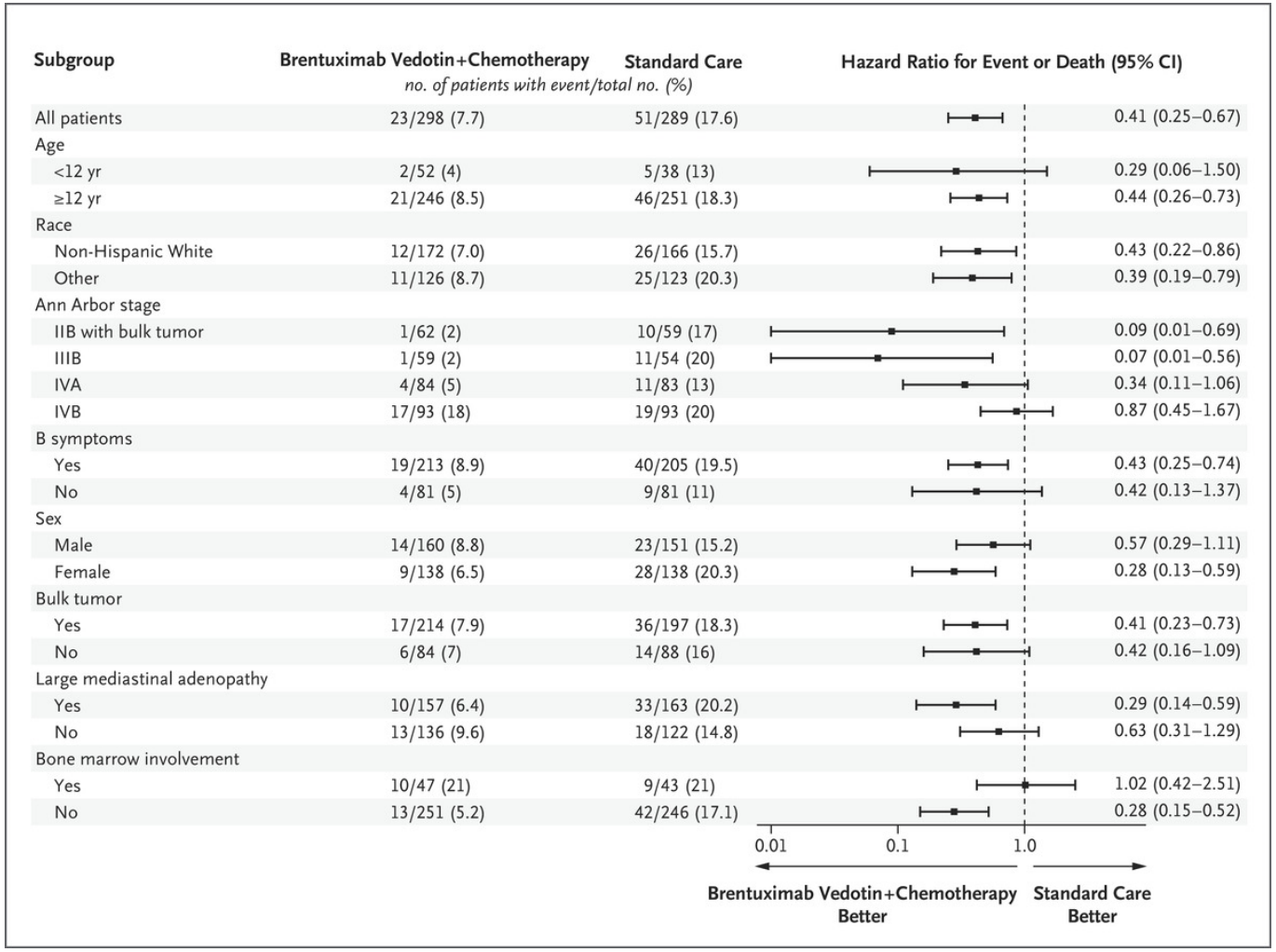


Brentuximab Kinder



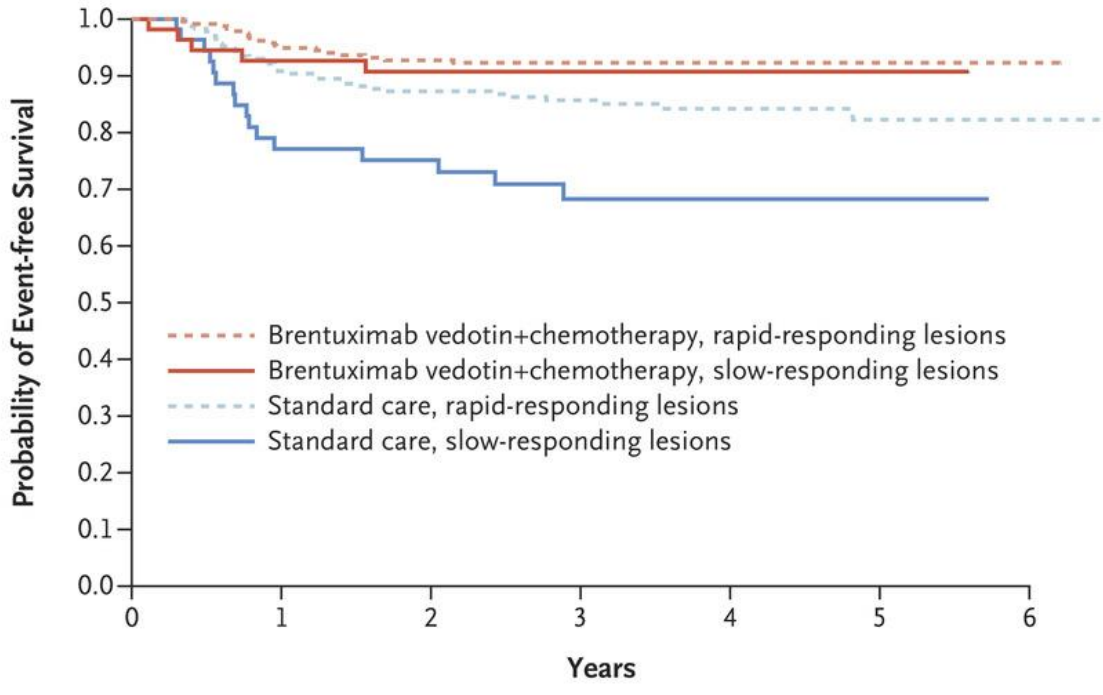
SM Castellino et al. N Engl J Med 2022;387:1649-1660.

Subgroup Analysis of Event-free Survival.



SM Castellino et al. N Engl J Med 2022;387:1649-1660.

Event-free Survival According to Results on Interim Positron-Emission Tomographic (PET) Assessment.



No. at Risk							
Brentuximab vedotin+chemotherapy, rapid-responding lesions	237	222	209	159	86	40	3
Brentuximab vedotin+chemotherapy, slow-responding lesions	55	49	47	33	18	5	0
Standard care, rapid-responding lesions	230	206	190	140	76	40	6
Standard care, slow-responding lesions	55	39	36	24	8	5	1

SM Castellino et al. N Engl J Med 2022;387:1649-1660.

Key Adverse Events.*

Table 2. Key Adverse Events.*

Event	Brentuximab Vedotin+ Chemotherapy (N=298)	Standard Care (N=289)	Overall (N=587)
Any adverse event of grade ≥3	219 (73.5)	197 (68.2)	416 (70.9)
Febrile neutropenia	92 (30.9)	94 (32.5)	186 (31.7)
Sepsis	8 (2.7)	12 (4.2)	20 (3.4)
Mucositis or oral adverse event	31 (10.4)	21 (7.3)	52 (8.9)
Enterocolitis or typhlitis	13 (4.4)	5 (1.7)	18 (3.1)
Allergic reaction or anaphylaxis	12 (4.0)	15 (5.2)	27 (4.6)
Infusion-related reaction	0	4 (1.4)	4 (0.7)
Vascular-access complication	3 (1.0)	4 (1.4)	7 (1.2)
Elevated alanine aminotransferase level	12 (4.0)	9 (3.1)	21 (3.6)
Any peripheral neuropathy†			
Grade ≥2	56 (18.8)	56 (19.4)	112 (19.1)
Grade ≥3	20 (6.7)	16 (5.5)	36 (6.1)
Thromboembolic event	11 (3.7)	5 (1.7)	16 (2.7)
Pancreatitis	4 (1.3)	2 (0.7)	6 (1.0)
Pneumonitis	0	1 (0.3)	1 (0.2)
Constipation	2 (0.7)	1 (0.3)	3 (0.5)

* Clinically significant adverse events were defined as events of grade 3 or higher according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.0 (through 2019), and version 5.0 thereafter (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_40).

† The reporting of peripheral neuropathy of higher than grade 2 on the Balis Pediatric Scale of Peripheral Neuropathy was required by the protocol; this scale includes indicators of activities of daily living specific to children and indicators of use of medication to manage symptoms (see the protocol).[15] Grades range from 1 to 4, with higher scores indicating greater severity. Grade 2 indicates pain leading to the use of nonnarcotic medications for symptoms not interfering with function. Grade 3 includes pain leading to the use of narcotic medications and motor disruption leading to assistance with activities of daily living.

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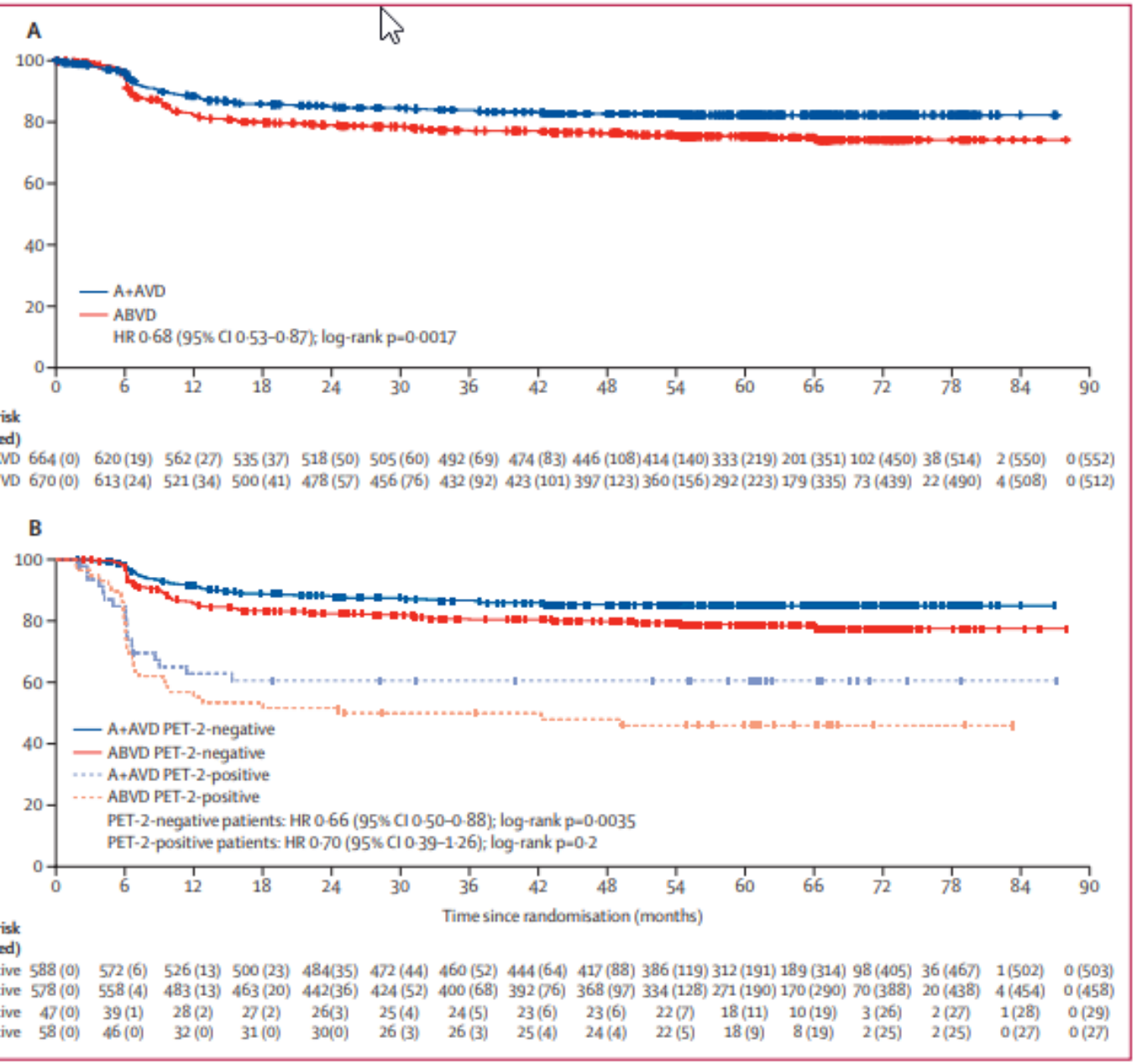


on-free survival per investigator assessment in the intention-to-treat population

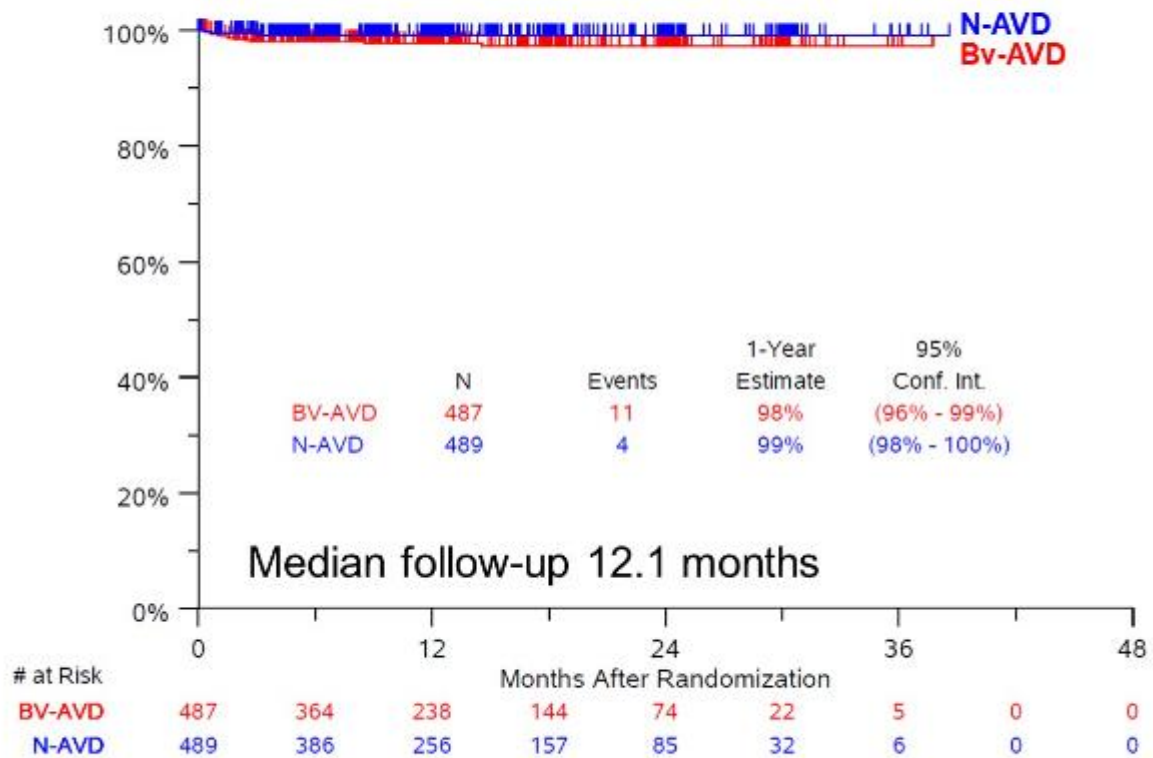
with A+AVD or ABVD. A+AVD group: 16 deaths and 96 progressive disease events. ABVD group: 30 deaths and 128 progressive disease events.

the post-amendment cohort. In the PET-2-positive cohort, 5-year progression-free survival was 90·1% (95% CI 87·2–92·9), estimated 5-year overall survival was 96·7% (95% CI 94·9–98·4), and the cumulative incidence of secondary primary malignant neoplasms at 5 years was 4·6% (95% CI 2·6–6·7). In the PET-2-negative cohort, 5-year progression-free survival was 90·9% (95% CI 86·8–95·1), 5-year overall survival was 96·3% (95% CI 93·7–99·0), and the cumulative incidence of secondary primary malignant neoplasms at 5 years was 3·1% (95% CI 0·6–5·6) in patients who received six cycles of eBEACOPP in total, while 5-year progression-free survival was 90·9% (86·8–95·1), 5-year overall survival was 97·5% (95·0–100·0), and the cumulative incidence of secondary primary malignant neoplasms at 5 years was 2·9% (0·3–5·5) in patients who received four cycles of eBEACOPP. These data show that giving six cycles

	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 eBEACOPP (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).

Overall Survival



Cause of death	N-AVD	Bv-AVD
Infection	2	4
Sepsis	1	2*
Cardiac arrest	0	1
Pneumonitis	0	1
Dehydration, vomiting, cHL	0	1
cHL	1**	0
Unknown	1	2
Total OS events	**4**	**11**

* 1 death from COVID-19/sepsis
** never received treatment, ineligible on C1D1

RATHL vs. REAL World

Russel et al Annals of Hematol 2021 doi 10.1007/s00277-021-04460-9

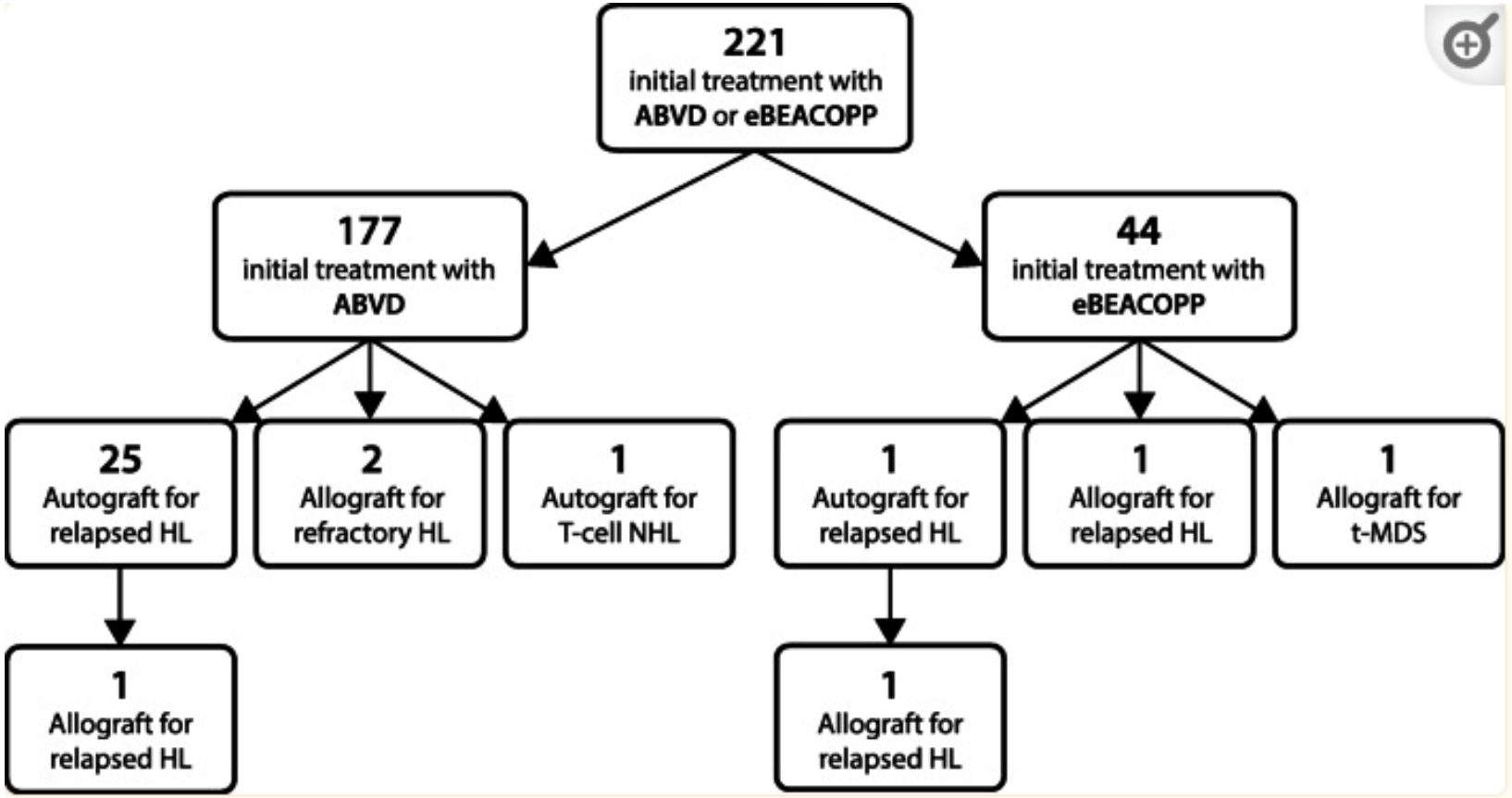


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Table 2: Outcomes of the PET-2-negative cohort