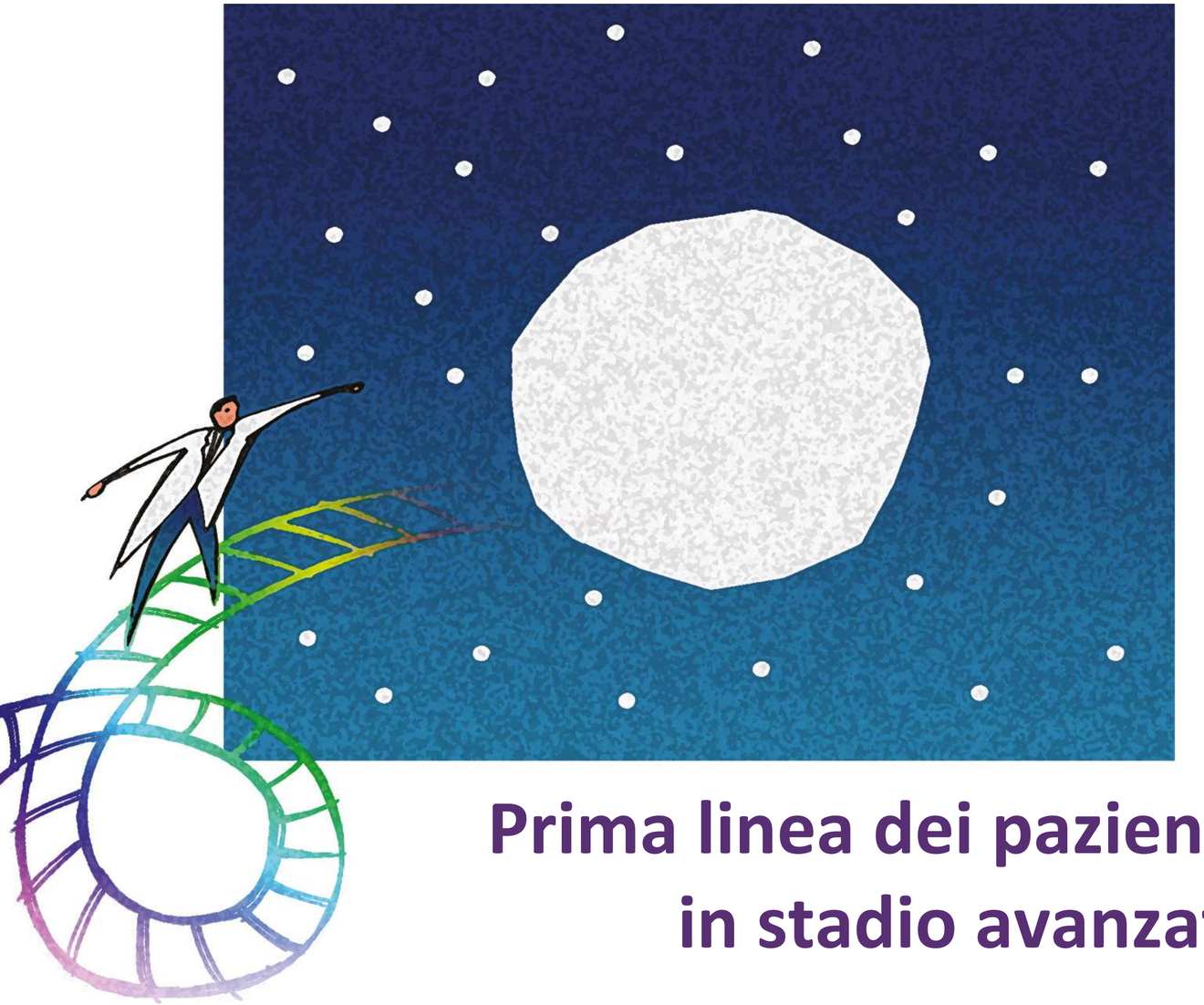

The young side of
LYMPHOMA

gli under 40 a confronto

Milano, 14-15 aprile 2023

Prima linea dei pazienti affetti da linfoma di Hodgkin in stadio avanzato: qualcosa è cambiato?

Annarosa Cuccaro

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Disclosures of Annarosa Cuccaro

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
No disclosures							

Il paziente

♀ **22 anni** (26.04.2000), PS ECOG: 1

Peso 66 kg, h 165 cm.

Non comorbidità di alcun tipo. Non allergie. Non abitudine tabagica.

Istologia 23.03.23: Linfoma di Hodgkin deplezione linfocitaria

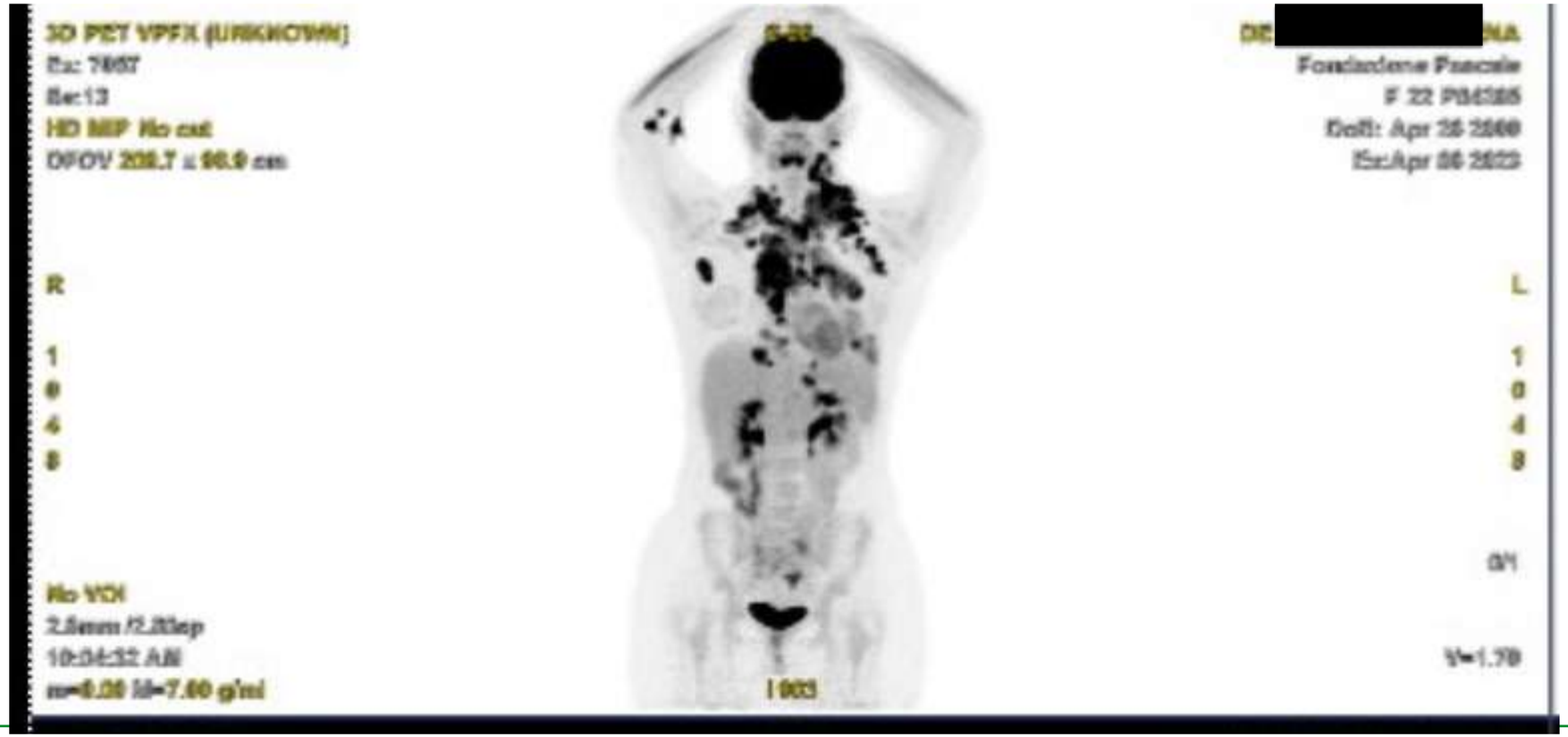
Exeresi linfonodale dopo una settimana dalla sospensione di cortisone.

Al ricovero:

- Dispnea. SpO2 95% FC 117 bpm PA 110/70
- Segni sistemici B: sudorazione + febbre
- All'Emocromo: Hgb 10,1 g/dl piastrine 232.000/mmc Leucociti 14.300(mmc (cortisone), Linfociti 4,1% (totali 600/mmc)
- VES 1h 80
- ECG: tachicardia sinusale; Ecocardio FEV 65%
- Prove respiratory: DLCO: 66% predicted; FEV1: 64% predicted; FEF-25-75%: 73 % predicted
- Esami funzione renale nella norma: AST e ALT 3xUNL Albumina 3,2 LDH 258/220 U/L

06.04.2023: PET-scan

SUV max 17.4



Sedi di uptake patologico:
mediastino con aree fotopeniche contestuali, paratracheale superiore e inferiore, pre- e sottocarenale, FAP, laterocervicale bilaterale, sovra- e sottoclaveare, retropettorale, ascellare, mammaria interna e paravetebrale, fasci muscolari in regione dorsale superiore, nodale celiaca, localizzazione sacrale e 8.a e 9.a vertebra dorsale

La Malattia

04.04.2023: TAC TB

Cod. Paziente: **P84265** Richiesta N° **P1080580** Del: **04/04/2023**
Nome: [redacted]
Nato a: NAPOLI Il: 26/04/2000
Provenienza: **Interno** Reparto: **Ematologia**

ESAMI:	Classe di dose (*)
TC CEREBRALE (senza e con contrasto)	**II**
TC COLLO (senza e con contrasto)	**II**
TC ADDOME INF. (senza e con contrasto)	**IV**
TC ADDOME SUP. (senza e con contrasto)	**IV**
TC MASSICCIO FACCIALE (senza e con contrasto)	**II**
TC TORACE (senza e con contrasto)	**III**

T.S.R.M.: Concetta Raiano
C.P.S.I.:

(*) Classe di dose secondo l'art. 161 del D.Lgs 101/2020

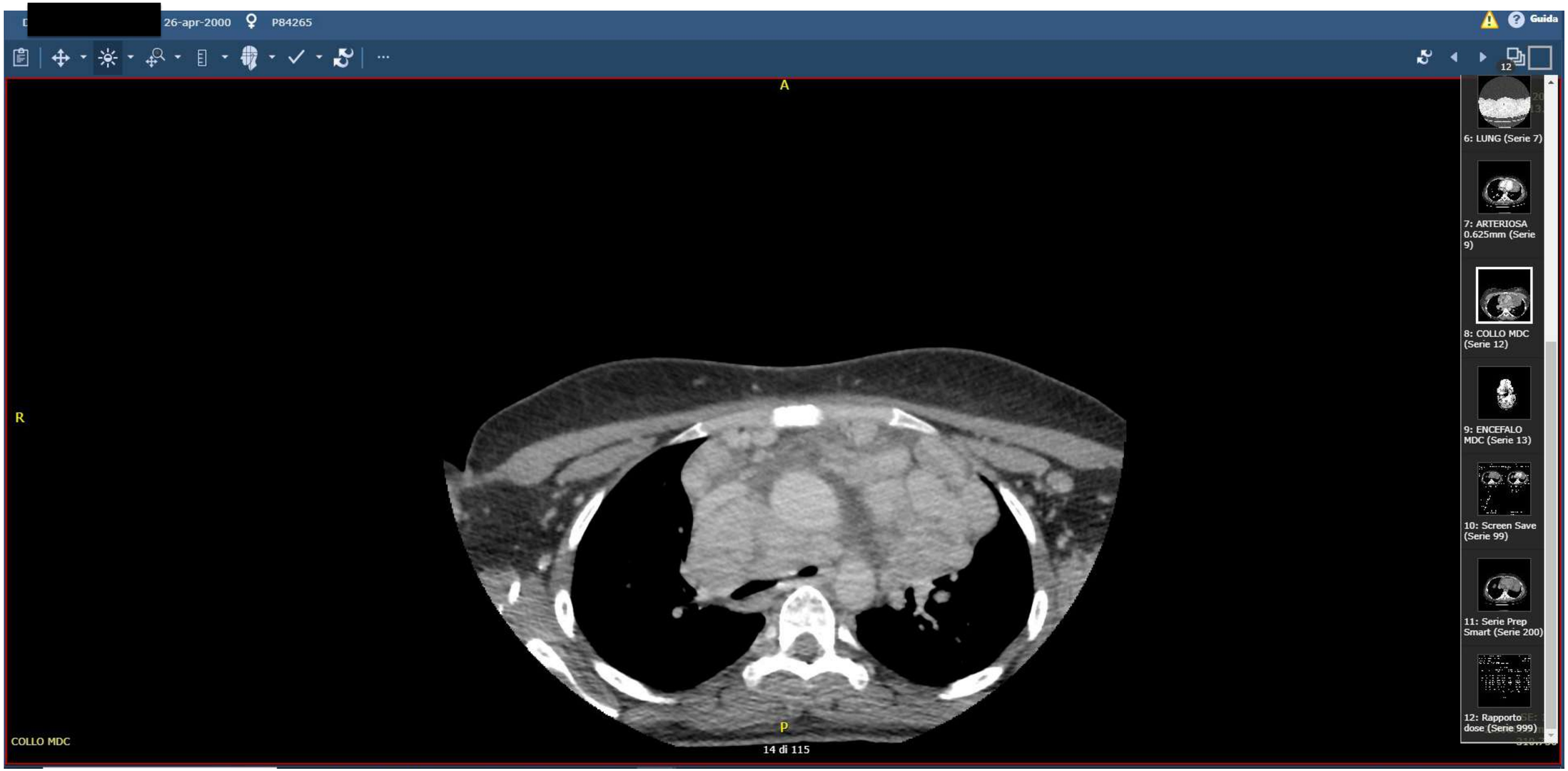
Testo del Referto:

L'indagine è stata eseguita senza somministrazione di mdc per os , prima e dopo perfusione di mdc ev. (xenetix 350mg)

TORACE Presenza di tumefazioni linfonodali a sede sovra e sottoclaveare bilateralmente (a sinistra il maggiore misura circa 60mm). A sede mediastinica si apprezzano tumefazioni linfonodali conglobati tra di loro; la massa avvolge le strutture vascolari, comprime la trachea e misura circa 92x56mm a destra mentre a sinistra circa 110x91.

La Malattia

04.04.2023: TAC TB



Clinical conundrum

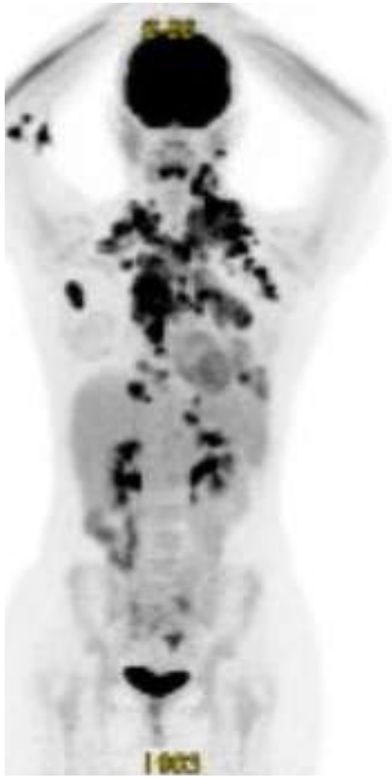
Linfoma in stadio Avanzato IVEXB e istologia Deplezione Linfocitaria
E-sites: osso (TAC – confirmed) e tessuti molli

Ridotta FEV 25-75 e DLCO

IPS 4 (Stadio, linfocitopenia, Hb, Albumina)
Projected 51% PFS e 61% OS

Bulky mediastinico
Un conglobato a dx 92x56 e uno a sinistra 110x91, M/T 0.49

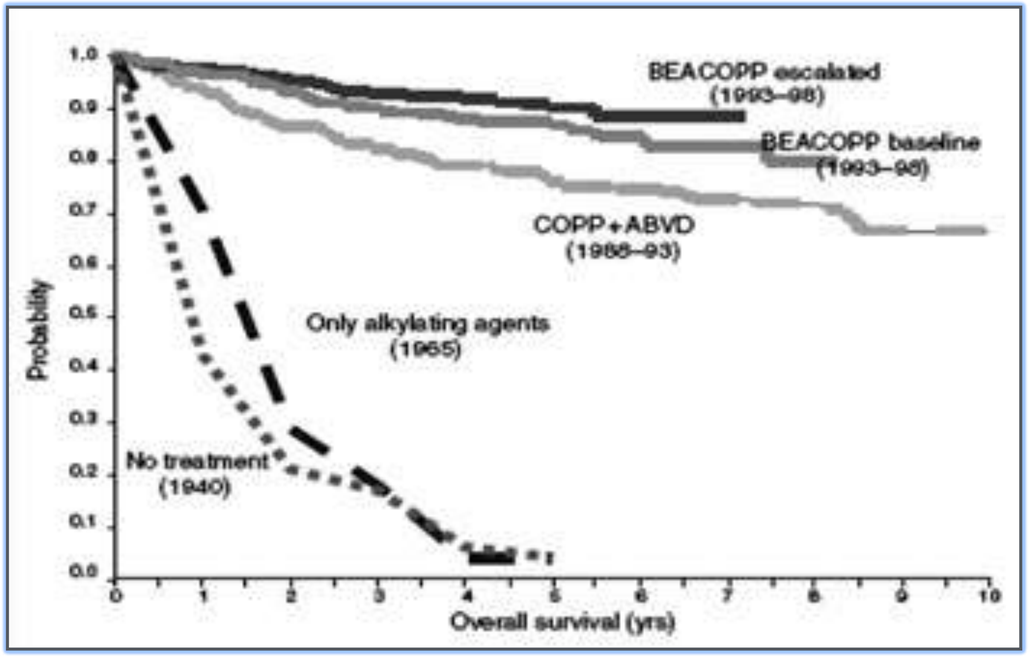
Quale schema Terapeutico ?



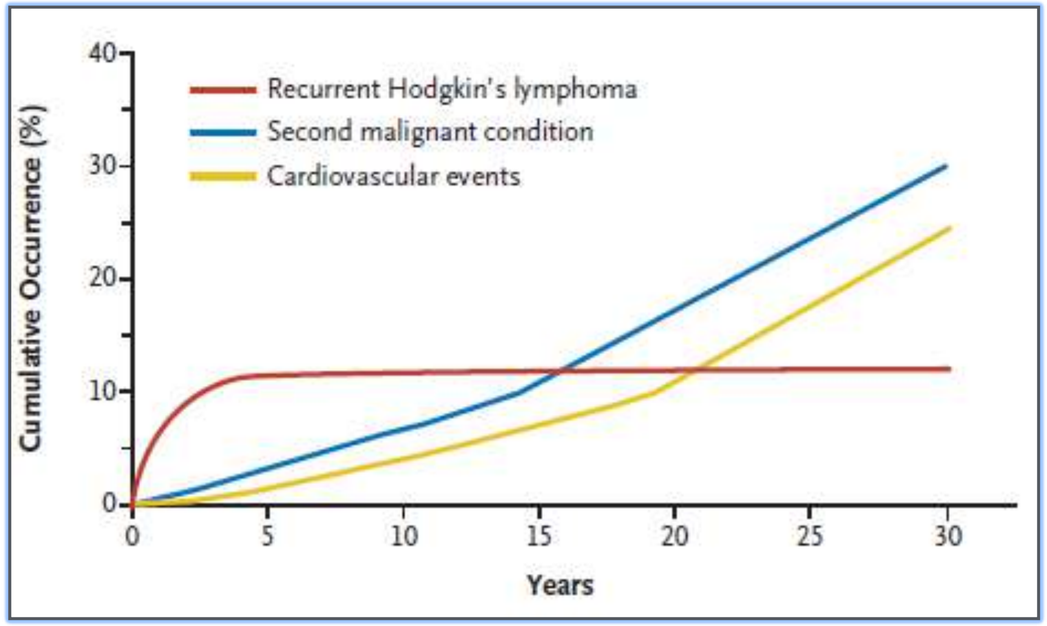
IVEXB var DL

- **ABVD PET-adapted**
- **A-AVD**
- **BEACOPP-esc**
- **DD-DI ABVD**

Hodgkin Lymphoma Dilemma



Diehl V et al, Lancet Oncol 2004



Armitage JO, N Engl J Med 2010

Efficacy *Tolerability*

Strategies

- **Risk adapted (Stage at presentation, clinical prognostic factors and comorbidities)**
- **Response adapted (Escalation/De-escalation)**
- **Non response adapted (Early intensification/Immunotherapy)**

EORTC/LYSA and GHSG HL risk group classification

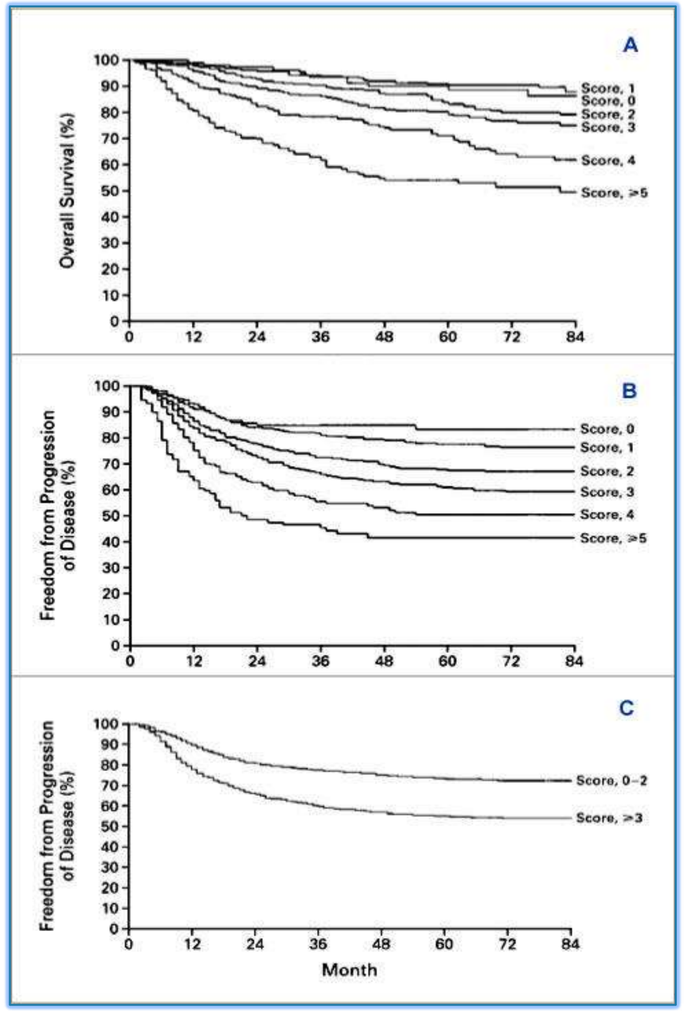
	EORTC/LYSA	GHSG
Risk factors	Mediastinum-to-thorax ratio ≥ 0.35	Mediastinal mass larger than 1/3 of the maximum thoracic width (A)
	Age ≥ 50 years	Extranodal disease (B)
	ESR > 50 mm/h without B symptoms or >30 mm/h with B symptoms	ESR > 50 mm/h without B symptoms or >30 mm/h with B symptoms (C)
	Involvement of ≥4 out of 5 supradiaphragmatic nodal areas	Involvement of ≥3 out of 11 nodal areas on both sides of the diaphragm (D)
Treatment group		
Earlystage	I–II without risk factors	I–II without risk factors
Intermediate stage	I–II ≥ 1 risk factors	I–IIA with ≥1 risk factors. IIB with risk factors C and/or D, but not A/B
Advanced stage	III–IV	IIB with risk factors A and/or B, III/IV

H. Vellemans & M. P. E. André. Cancers 2021, 13, 3745

Hasenclever Score

Factors	Value
Serum Albumin	< 4 g/dl
Hb	< 10.5 g/dl
Sex	male
Age	> 45 years
White blood cell count	≥ 15000/mm³
Absolute lymphocyte count	< 600/mm o < 8%

N. of risk factors[2]	% of total	5-yr FFP %
0	7	84
1	22	77
2	29	67
3	23	60
4	12	51
≥5	7	42

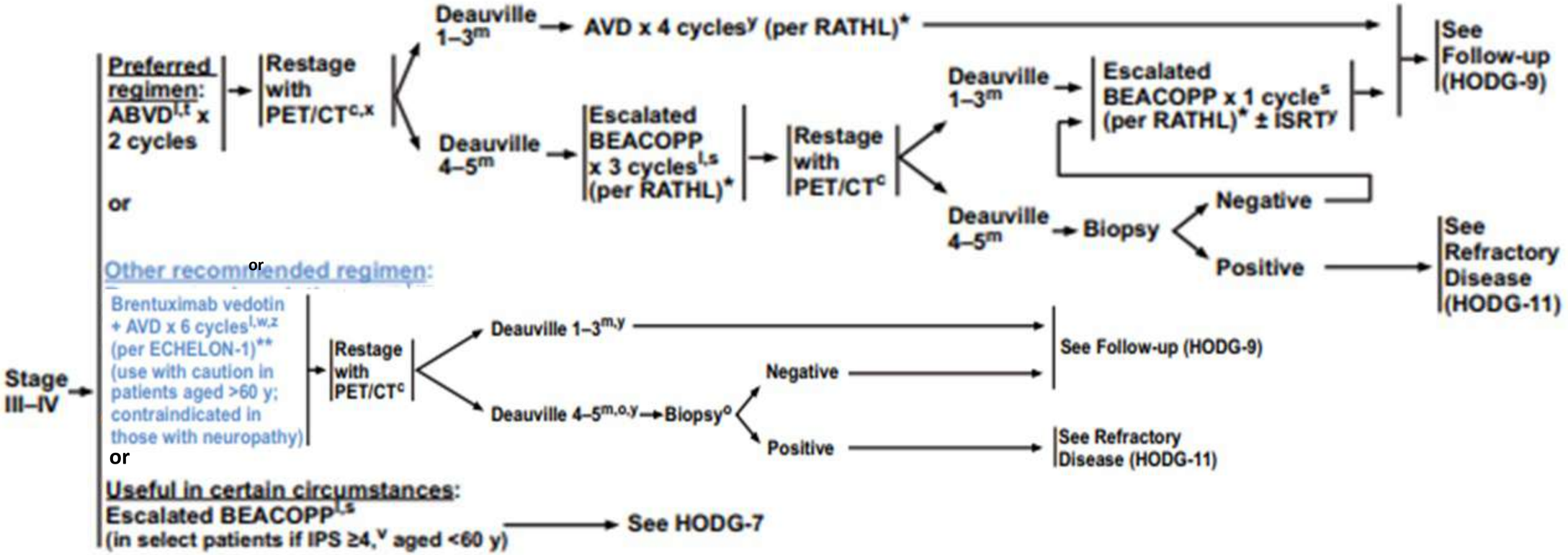


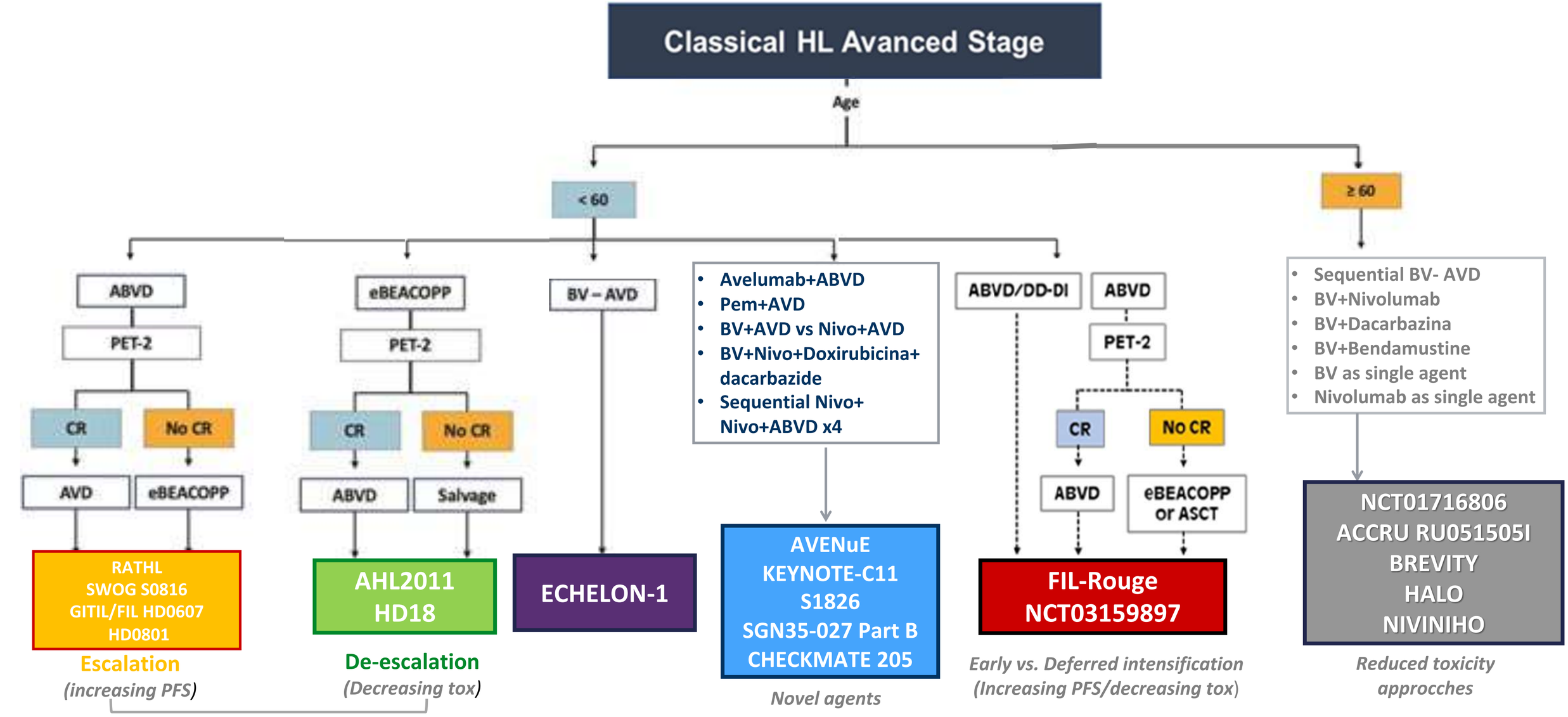
Hasenclever et al, N Engl J Med, 1998; 339, 1506

Hodgkin Lymphoma, Version 2.2022 NCCN GUIDELINES® INSIGHTS CE

CLINICAL PRESENTATION:
Stage III–IV Classic Hodgkin Lymphoma[k]

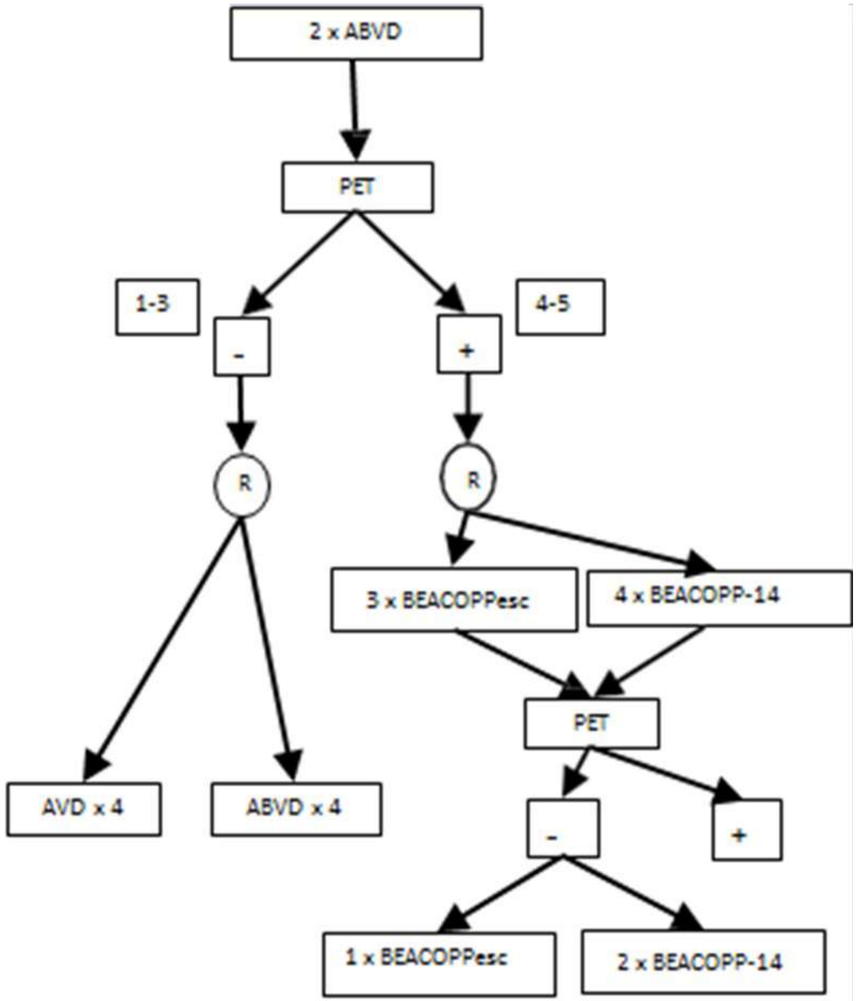
PRIMARY TREATMENT[k]




Classical HL Avanced Stage
Age
< 60
≥ 60
ABVD
PET-2
CR
No CR
AVD
eBEACOPP
RATHL
SWOG S0816
GITIL/FIL HD0607
HD0801
Escalation
(increasing PFS)
eBEACOPP
PET-2
CR
No CR
ABVD
Salvage
AHL2011
HD18
De-escalation
(Decreasing tox)
BV – AVD
ECHELON-1
Non PET-adapted
Avelumab+ABVD
Pem+AVD
BV+AVD vs Nivo+AVD
BV+Nivo+Doxirubicina+ dacarbazide
Sequential Nivo+ Nivo+ABVD x4
AVENuE
KEYNOTE-C11
S1826
SGN35-027 Part B
CHECKMATE 205
Novel agents
ABVD/DD-DI
ABVD
PET-2
CR
No CR
ABVD
eBEACOPP or ASCT
FIL-Rouge
NCT03159897
Early vs. Deferred intensification
(Increasing PFS/decreasing tox)
Non PET-adapted vs. PET-adapted
Sequential BV- AVD
BV+Nivolumab
BV+Dacarbazina
BV+Bendamustine
BV as single agent
Nivolumab as single agent
NCT01716806
ACCRU RU051505I
BREVITY
HALO
NIVINIHO
Reduced toxicity
approcches
Non PET-adapted
PET-adapted

PET-Adapted Treatment- *Escalation*

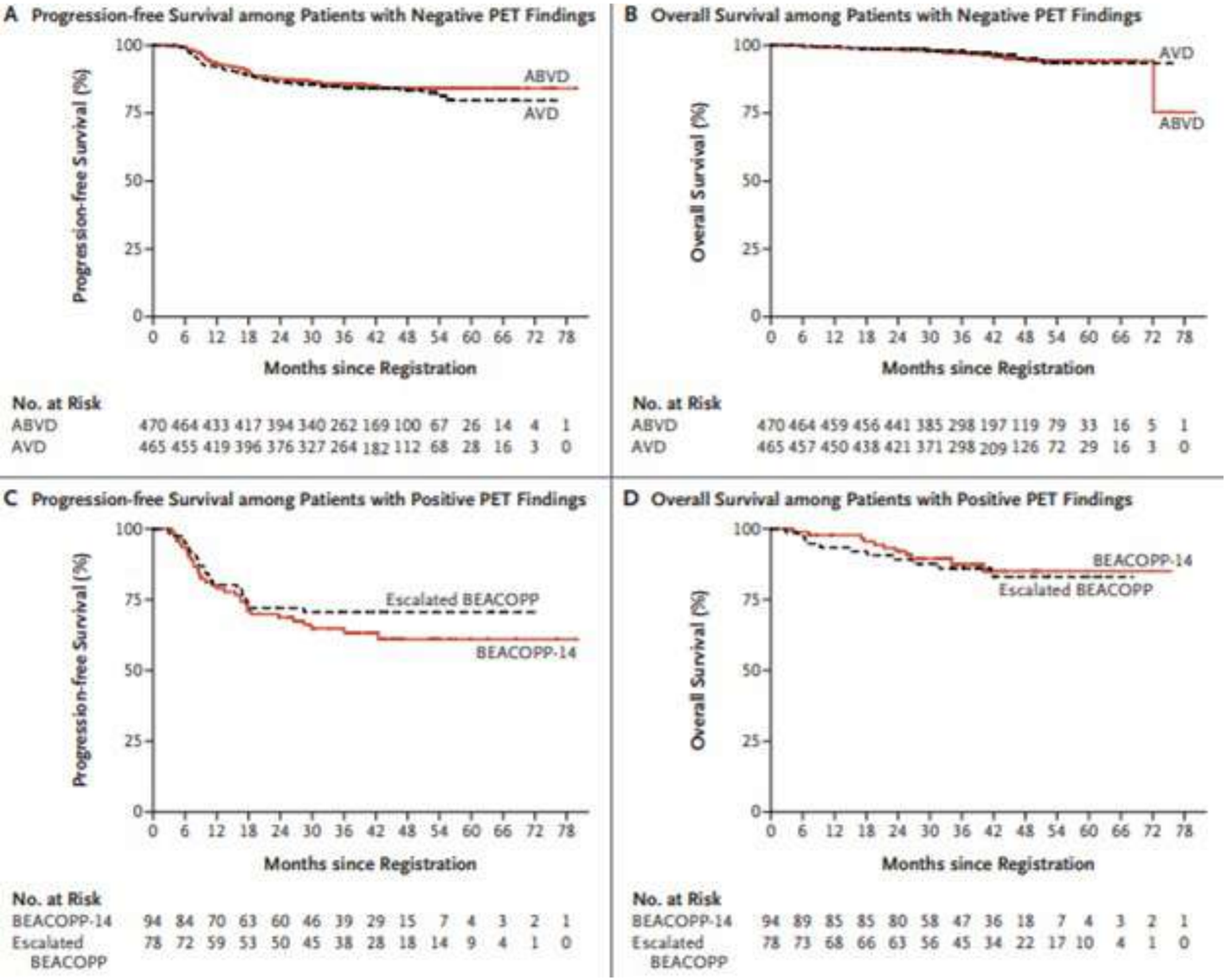
RATHL Trial



Patients Characteristics

Caracteristic	PET neg ABVD (N 470)	PET neg AVD (N 465)	PET pos BEACOPP (N 172)	Total Patients (N 1203)
Age at registration — yr				
Median	32	33	32	33
Range	18–79	18–76	18–70	18–79
Age — no. (%)				
18–24 yr	121 (25.7)	117 (25.2)	47 (27.3)	299 (24.9)
25–44 yr	231 (49.1)	223 (48.0)	75 (43.6)	576 (47.9)
45–59 yr	80 (17.0)	81 (17.4)	32 (18.6)	213 (17.7)
≥60 yr	38 (8.1)	44 (9.5)	18 (10.5)	115 (9.6)
Male sex — no. (%)	261 (55.5)	252 (54.2)	92 (53.5)	656 (54.5)
Ann Arbor Stage — no. (%)				
II	195 (41.5)	197 (42.4)	73 (42.4)	500 (41.6)
III	157 (33.4)	140 (30.1)	34 (19.8)	363 (30.2)
IV	118 (25.1)	128 (27.5)	65 (37.8)	340 (28.3)
B symptoms — no. (%)	287 (61.1)	277 (59.6)	121 (70.3)	738 (61.3)
Bulky disease — no. (%)	133 (28.3)	150 (32.3)	79 (45.9)	386 (32.1)
IPS				
0 or 1	170 (36.2)	172 (37.0)	34 (19.8)	404 (33.6)
2 or 3	219 (46.6)	224 (48.2)	84 (48.8)	579 (48.1)
≥4	75 (16.0)	67 (14.4)	52 (30.2)	209 (17.4)

Johnson P. et al; N engl j med 374;25 June 23, 2016



Toxicity

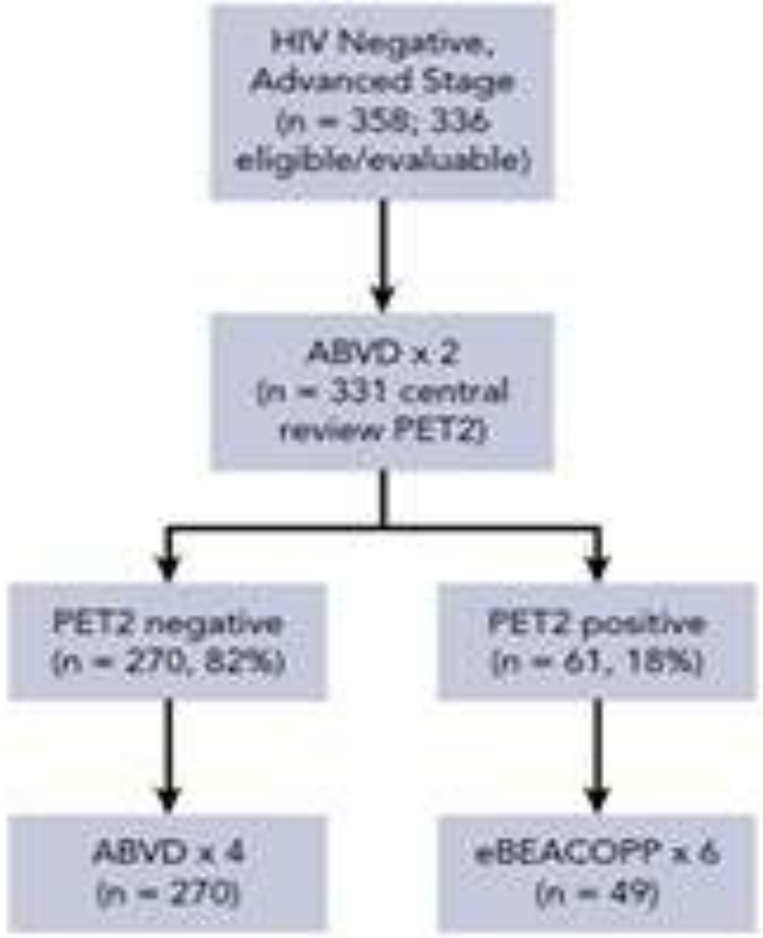
Grade 3 or 4 Adverse Events among Patients with Negative PET Findings Who Started Their Assigned Treatment.

Event	ABVD, Cycles 1 and 2 (N = 1203)	ABVD, Cycles 3–6 (N = 468)	AVD, Cycles 3–6 (N = 457)	BEACOPP14 P-14 (N = 94)	Escalated BEACOPP (N = 78)
Any blood or bone marrow event	711 (59)	280 (60)	273 (60)	68 (72)	58 (74)
Neutropenia	694 (58)	275 (59)	269 (59)	59 (63)	52 (67)
Thrombocytopenia	16 (1)	6 (1)	15 (3)	18 (19)	33 (42)
Any cardiac event	9 (1)	6 (1)	2 (<0.5)	1 (1)	0
Any constitutional symptom	36 (3)	18 (4)	13 (3)	11 (12)	11 (14)
Fatigue	14 (1)	14 (3)	5 (1)	8 (9)	3 (4)
Fever	16 (1)	4 (1)	7 (2)	2 (2)	9 (12)
Any infection	76 (6)	68 (15)	47 (10)	35 (37)	33 (42)
Febrile neutropenia	24 (2)	22 (5)	10 (2)	10 (11)	20 (26)
Any neurologic event	20 (2)	23 (5)	14 (3)	9 (10)	3 (4)
Any pulmonary event	8 (1)	15 (3)	3 (1)	4 (4)	4 (5)
Dyspnea	5 (<0.5)	9 (2)	1 (<0.5)	2 (2)	2 (3)
Pneumonitis	0	5 (1)	1 (<0.5)	0	2 (3)
Any vascular event	18 (1)	23 (5)	12 (3)	8 (9)	2 (3)
Any clinical adverse event	188 (16)	143 (31)	96 (21)	52 (55)	47 (60)
Any grade 3 or 4 adverse event	771 (64)	322 (69)	299 (65)	75 (80)	65 (83)

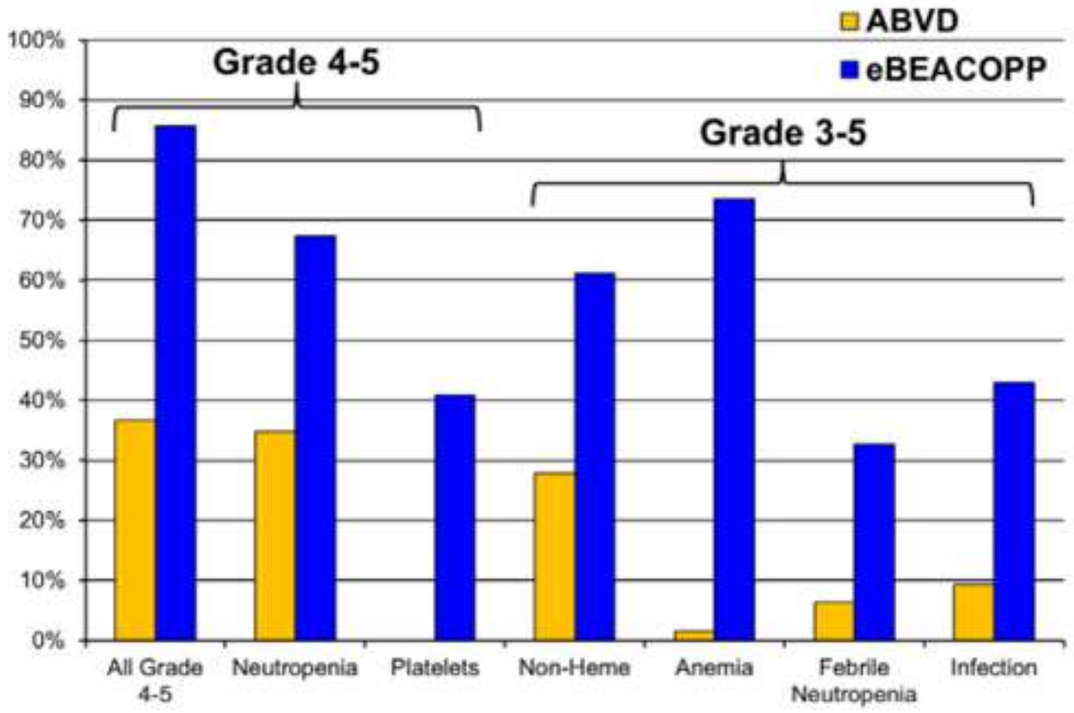
Johnson P. et al; N engl j med 374;25 June 23, 2016

PET-Adapted Treatment- *Escalation*

SWOG Trial



Toxicity

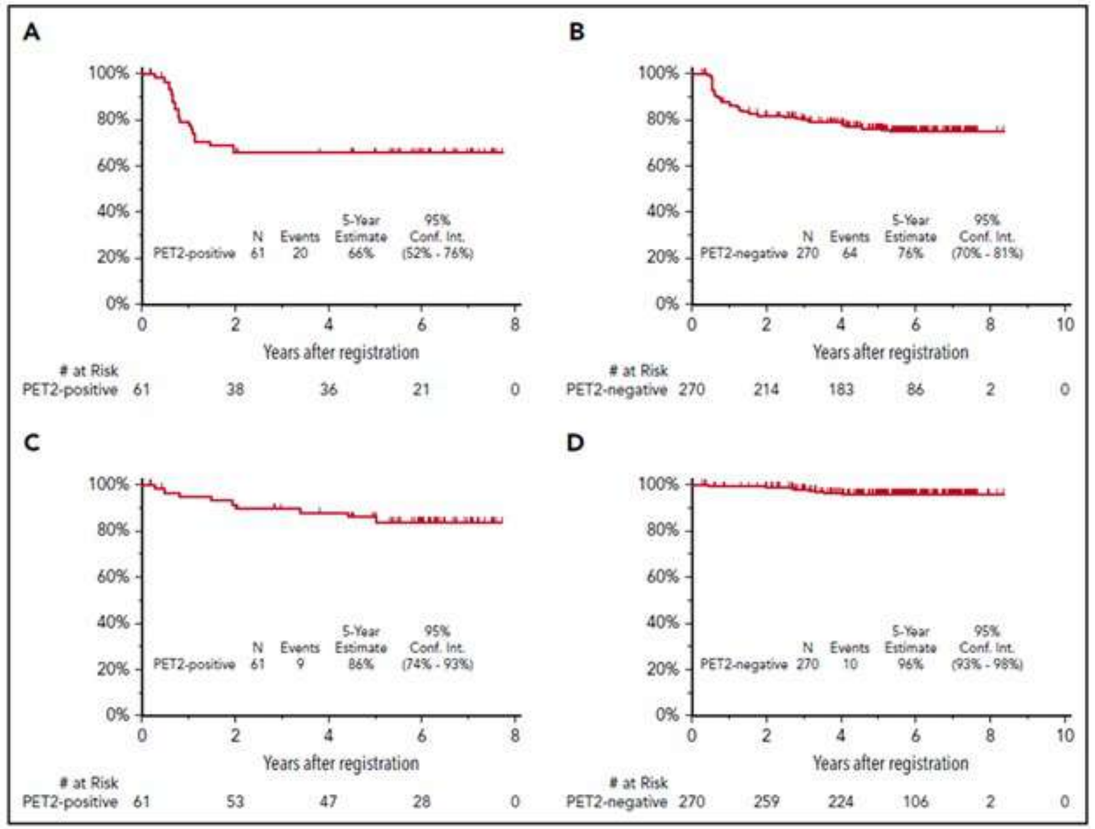


Press W.O. et al J Clin Oncol 34:2020-2027

PET-Adapted Treatment- *Escalation*

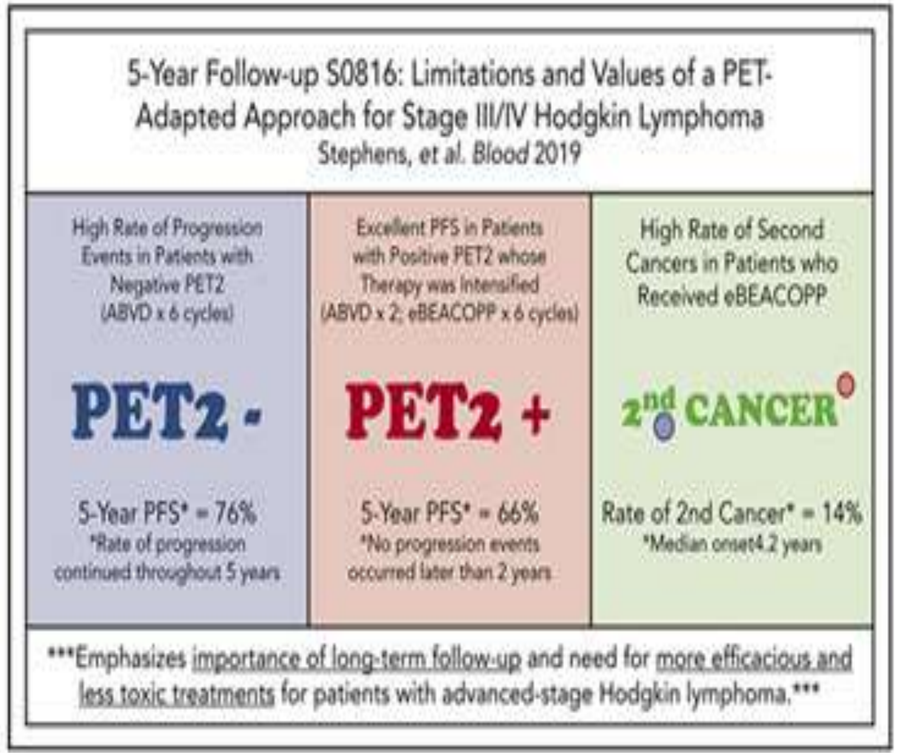
Five-year follow-up of SWOG S0816: limitations and values of a PET-adapted approach with stage III/IV Hodgkin lymphoma

Deborah M. Stephens,[1] Hongli Li,[2] Heiko Schöder,[3] David J. Straus,[3] Craig H. Moskowitz,[3] Michael LeBlanc,[2] Lisa M. Rimsza,[4] Nancy L. Bartlett,[5] Andrew M. Evens,[6] Ann S. LaCasce,[7] Paul M. Barr,[8] Michael V. Knopp,[9] Eric D. Hsi,[10] John P. Leonard,[11] Brad S. Kahl,[5] Sonali M. Smith,[12] and Jonathan W. Friedberg[8]



KEY POINTS

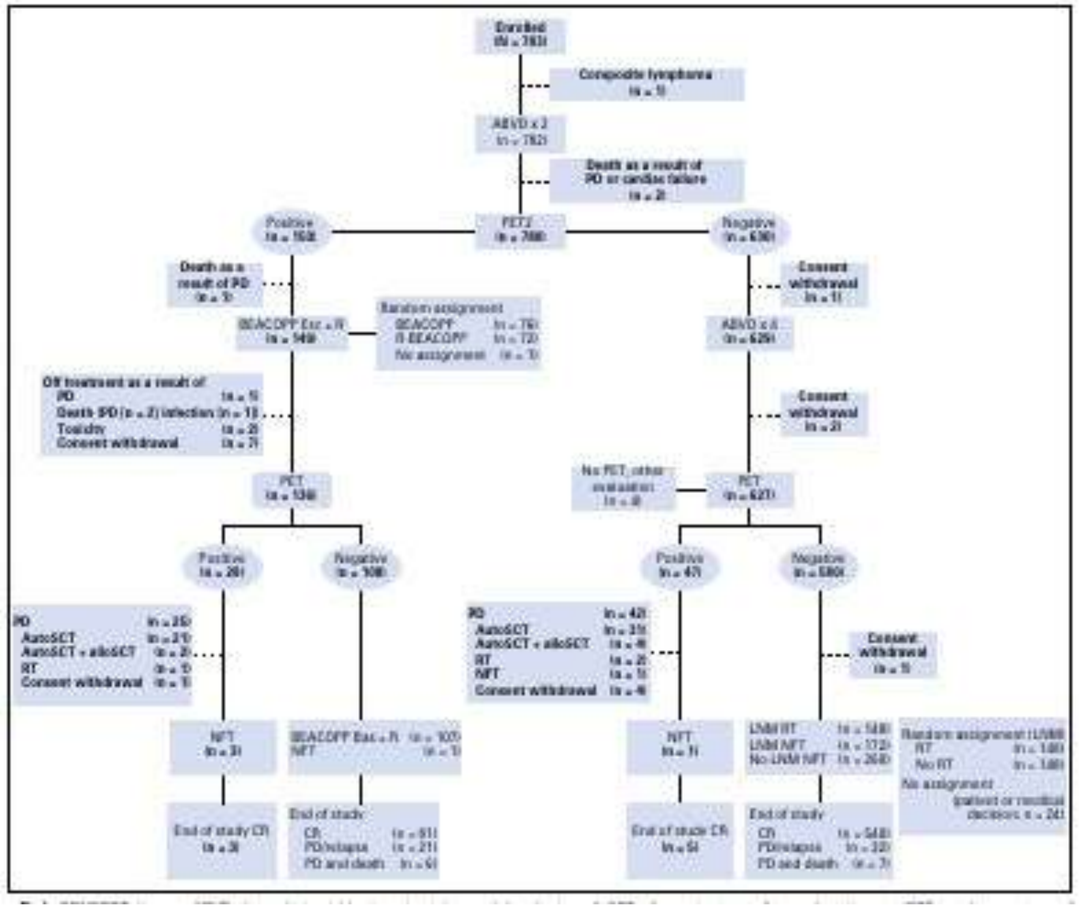
- **Nearly 25% of PET2⁻ patients relapsed, demonstrating limitations of frontline ABVD and low negative predictive value of PET2.**
- **In patients with a positive PET2 who received eBEACOPP, PFS was favorable, but was associated with a high rate of second cancers.**



Authors'conclusion: PFS in PET2-negative patients is too low. PET2 is NOT suited to guide treatment

PET-Adapted Treatment- *Escalation*

GITIL/FIL HD0607 Trial



Patients Characteristics

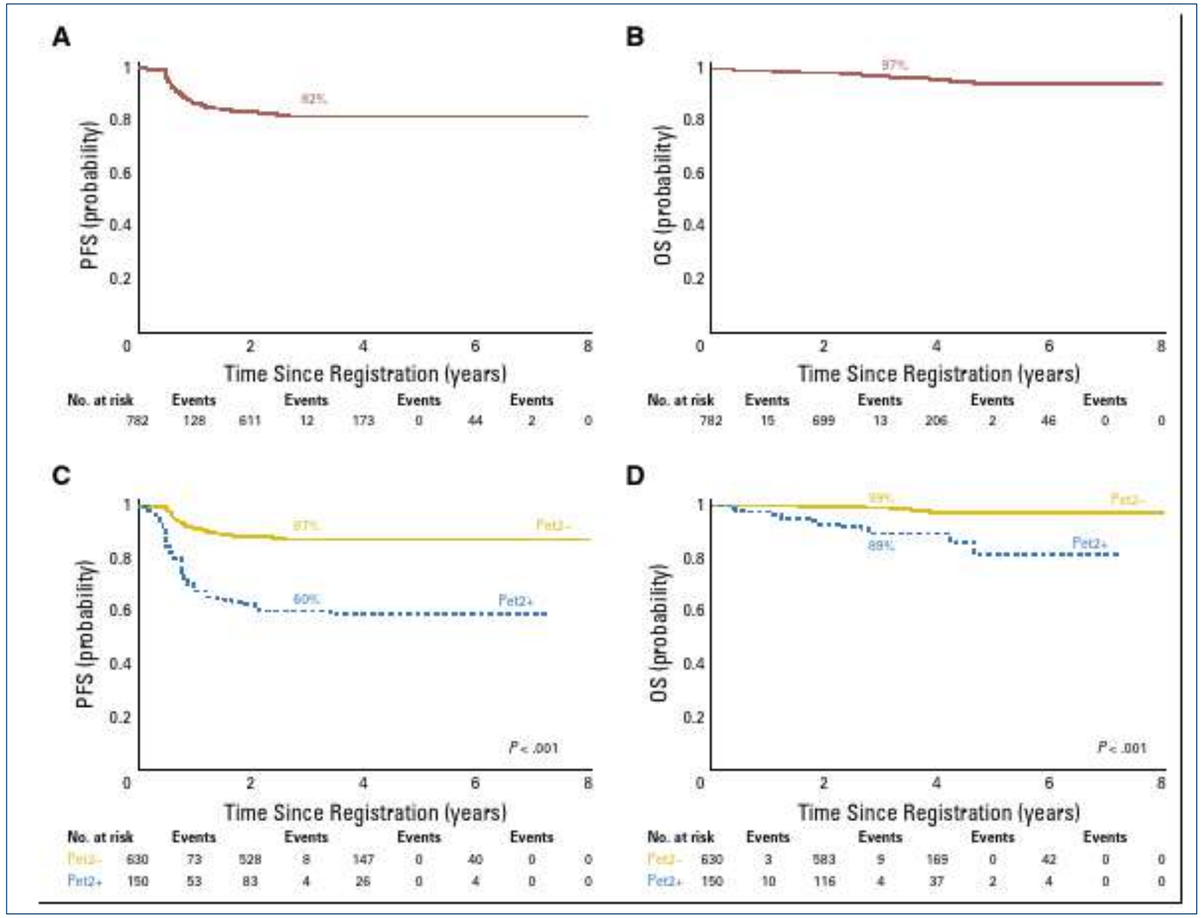
Table 1. Baseline Characteristics of Patients Included in the Study According to PET2 Results

Characteristic	All Patients*	PET2 Negative	PET2 Positive	*P*
No. of patients	782	630	150	
Median age (range), years	31 (14-60)	31 (14-60)	30.5 (18-60)	.385
≥ 50	79 (10.1)	61 (26.5)	17 (11.3)	.545
Sex				.036
Male	382 (48.9)	297 (47.1)	85 (56.7)	
Female	400 (51.1)	333 (52.9)	65 (43.3)	
WHO activity index				.122
0-1	707 (90.4)	576 (91.4)	131 (87.3)	
> 1	73 (9.3)	54 (8.6)	19 (12.7)	
Ann Arbor stage				.284
II	279 (35.7)	229 (36.3)	50 (33.3)	
III	252 (32.2)	208 (33.0)	44 (29.3)	
IV	251 (32.1)	193 (30.6)	56 (37.3)	
IPS				< .001
0-1	286 (36.6)	251 (39.8)	35 (23.3)	
2-3	398 (50.9)	311 (49.4)	87 (58.0)	
> 3	98 (12.5)	68 (10.8)	28 (18.7)	
Large nodal mass, cm				< .001
< 5	328 (41.9)	277 (44.0)	49 (32.7)	
5-7	140 (17.9)	123 (19.5)	17 (11.3)	
8-10	159 (20.3)	117 (18.6)	42 (28.0)	
> 10	155 (19.8)	113 (17.9)	42 (28.0)	
B symptoms	634 (81.1)	511 (81.1)	121 (80.7)	.901

Gallamini A.et alJ Clin Oncol 38:3905-3913

PET-Adapted Treatment- *Escalation*

GITIL/FIL HD0607 Trial



Toxicity

Table 2. Toxicities Assessed by National Cancer Institute Common Terminology Criteria for Adverse Events (Version 3.0)

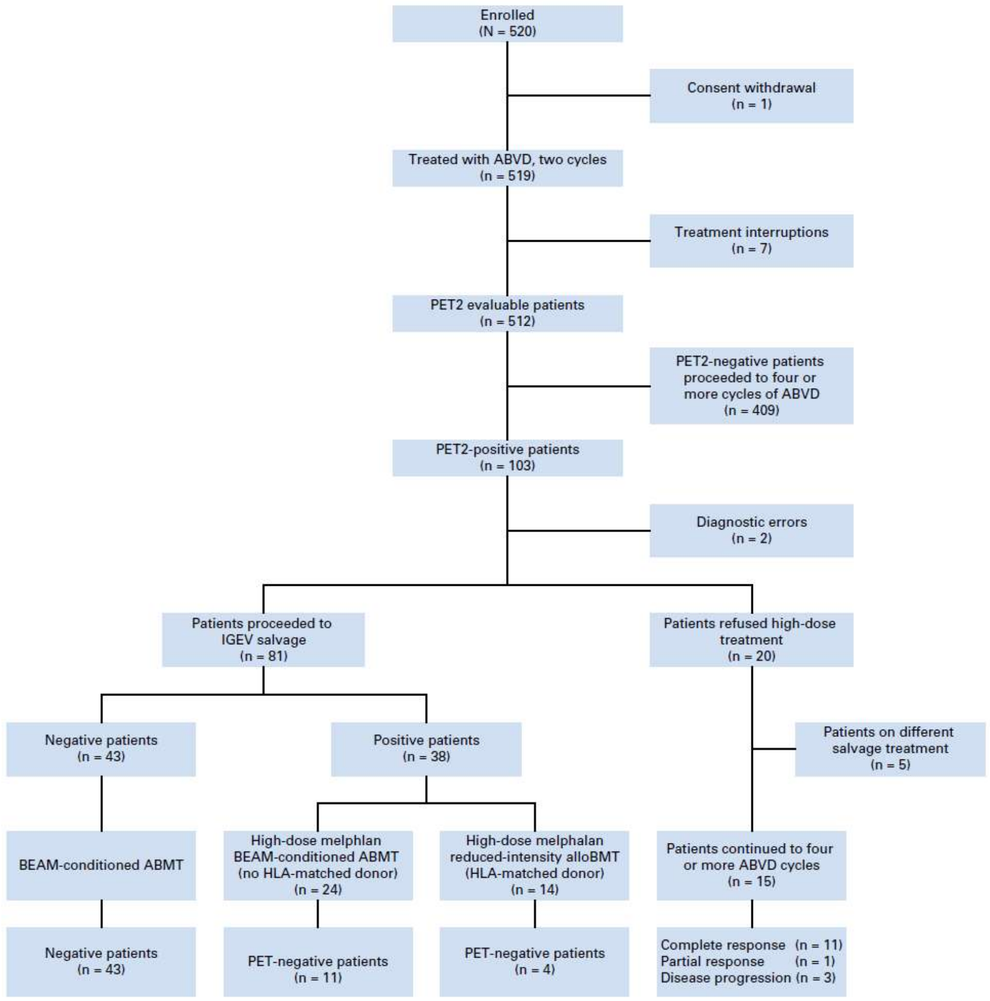
	Highest Grade, No. (%)					
	Pre-PET2 (n = 782)		PET2 Negative (n = 630)		PET2 Positive (n = 150)	
Adverse Event	1-2	3-4	1-2	3-4	1-2	3-4
Blood/bone marrow	105 (13)	323 (41)	109 (17)	189 (30)	4 (3)	114 (76)
GI	48 (6)	6 (1)	38 (6)	6 (1)	17 (11)	0 (0)
Infection	17 (2)	5 (1)	33 (5)	5 (1)	12 (8)	16 (10)
Pulmonary/upper respiratory	6 (1)	2 (< 1)	30 (5)	11 (2)	9 (6)	1 (1)
Constitutional symptoms	4 (1)	0 (0)	18 (3)	1 (< 1)	15 (10)	2 (1)
Vascular	8 (1)	0 (0)	14 (2)	2 (< 1)	10 (7)	2 (1)
Neurology	5 (1)	0 (0)	11 (2)	1 (< 1)	13 (9)	2 (1)
Pain	6 (1)	0 (0)	8 (1)	0 (0)	6 (4)	1 (1)
Dermatology/skin	3 (< 1)	0 (0)	11 (2)	0 (0)	5 (3)	1 (1)
Metabolic/laboratory	5 (1)	6 (1)	1 (< 1)	0 (0)	4 (3)	0 (0)
Cardiac arrhythmia/cardiac general	3 (< 1)	1 (< 1)	4 (1)	2 (< 1)	4 (3)	3 (2)
Musculoskeletal/soft tissue	2 (< 1)	0 (0)	2 (< 1)	3 (< 1)	2 (1)	3 (2)
Allergy/immunology	4 (1)	1 (< 1)	0 (0)	0 (0)	0 (0)	0 (0)
Hepatobiliary/pancreas	0 (0)	3 (< 1)	1 (< 1)	0 (0)	0 (0)	0 (0)
Coagulation	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)

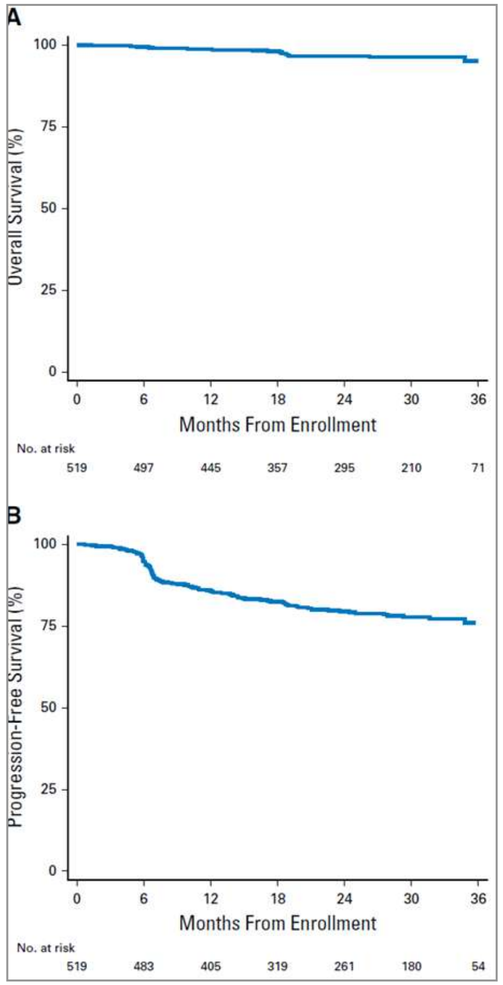
Abbreviation: PET2, ^{18}F-Fluoro-deoxy-d-glucose positron emission tomography performed after two doxorubicin, vinblastine, vincristine, and dacarbazine cycles.

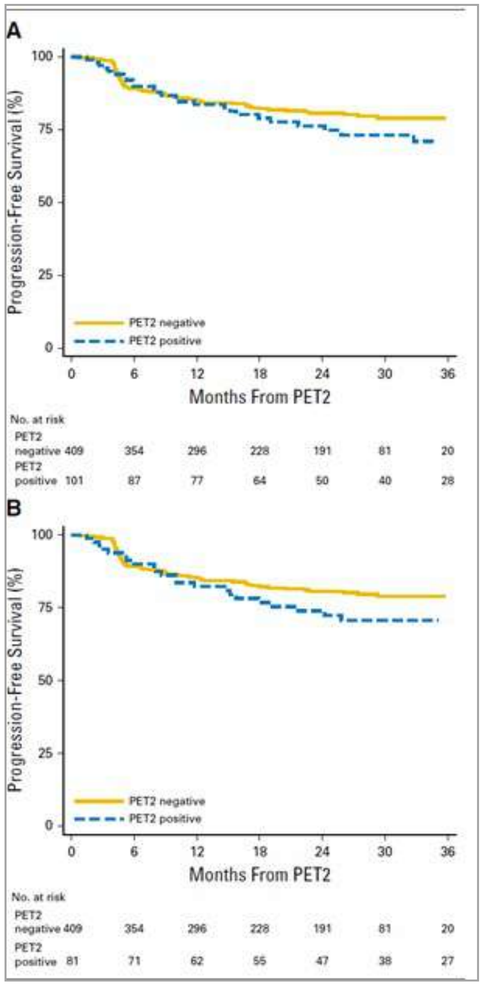
Gallamini A.et alJ Clin Oncol 38:3905-3913

PET-Adapted Treatment- *Escalation*

HD0801 Trial







J Clin Oncol 34:1376-1385. © 2016

PET-Adapted Treatment- *De-Escalation*

AHL2011 Trial

Positron Emission Tomography–Driven Strategy in Advanced Hodgkin Lymphoma: Prolonged Follow-Up of the AHL2011 Phase III Lymphoma Study Association Study

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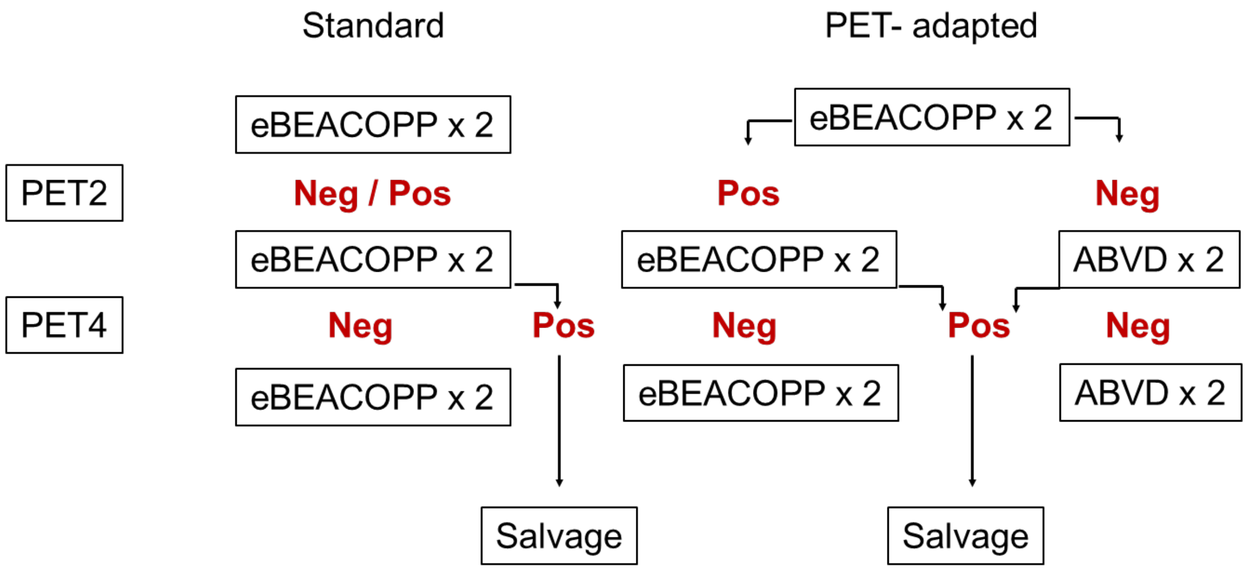


Toxicity

	Standard treatment group (n=412)				PET-driven treatment group (n=407)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Blood and lymphatic system disorders								
Anaemia	402 (98%)	249 (60%)	37 (9%)	0	394 (97%)	107 (26%)	7 (2%)	0
Leucopenia	189 (46%)	138 (33%)	243 (59%)	0	273 (67%)	102 (25%)	285 (70%)	0
Neutropenia	157 (38%)	65 (16%)	294 (71%)	0	221 (54%)	60 (15%)	306 (75%)	0
Febrile neutropenia	0	129 (31%)	16 (4%)	0	0	85 (21%)	8 (2%)	0
Thrombocytopenia	342 (83%)	148 (36%)	123 (30%)	0	306 (75%)	99 (24%)	64 (16%)	0
Gastrointestinal disorders								
Mucositis	101 (25%)	13 (3%)	3 (<1%)	0	91 (22%)	18 (4%)	1 (<1%)	0
Vomiting	161 (39%)	9 (2%)	1 (<1%)	0	141 (35%)	10 (2%)	0	0
Diarrhoea	93 (23%)	6 (1%)	1 (<1%)	0	88 (22%)	7 (2%)	0	0
Other	280 (68%)	16 (3%)	1 (<1%)	0	291 (72%)	11 (3%)	1 (<1%)	0
General disorders								
Fatigue	262 (64%)	16 (4%)	1 (<1%)	0	228 (56%)	11 (3%)	0	0
Fever	132 (32%)	5 (1%)	3 (1%)	0	125 (31%)	1 (<1%)	1 (<1%)	0
Other	87 (21%)	5 (1%)	3 (1%)	0	96 (24%)	5 (1%)	0	0
Infections and infestations								
Sepsis	3 (<1%)	0	27 (7%)	2 (<1%)	2 (<1%)	0	14 (3%)	0
Lung infection	17 (4%)	12 (3%)	0	0	16 (4%)	4 (1%)	0	0
Other	118 (29%)	45 (11%)	4 (1%)	0	120 (30%)	23 (6%)	5 (1%)	1 (<1%)
Investigation								
AST and/or ALT increased	136 (33%)	12 (3%)	3 (<1%)	0	132 (32%)	9 (2%)	2 (<1%)	0
Creatinine increased	14 (3%)	1 (<1%)	1 (<1%)	0	25 (6%)	0	0	0
Other	92 (22%)	16 (4%)	1 (<1%)	0	80 (20%)	13 (3%)	0	0
Nervous system disorders								
Peripheral neuropathy	85 (21%)	8 (2%)	0	0	87 (21%)	2 (<1%)	0	0
Other	66 (16%)	6 (2%)	0	0	66 (16%)	5 (1%)	0	0
Respiratory, thoracic, and mediastinal disorder								
Pneumonitis	4 (1%)	3 (<1%)	0	0	5 (1%)	3 (<1%)	1 (<1%)	0
Other	121 (29%)	11 (3%)	1 (<1%)	2 (<1%)	108 (26%)	11 (3%)	2 (<1%)	0
Vascular disorders								
Thromboembolic event	20 (5%)	7 (2%)	1 (<1%)	0	29 (7%)	7 (2%)	1 (<1%)	0
Hypotension	18 (4%)	4 (1%)	2 (<1%)	0	12 (3%)	0	2 (<1%)	0
Other	23 (6%)	3 (<1%)	2 (<1%)	0	24 (6%)	2 (<1%)	1 (<1%)	0
Skin and subcutaneous disorders	122 (30%)	4 (1%)	0	0	125 (31%)	8 (2%)	0	0
Metabolism and nutrition disorder	58 (14%)	5 (1%)	0	0	40 (10%)	5 (1%)	0	0
Cardiac disorders								
Dysrhythmia	17 (4%)	1 (<1%)	0	0	14 (3%)	0	0	0
Other	24 (6%)	1 (<1%)	1 (<1%)	1 (<1%)	12 (3%)	4 (1%)	0	0
Renal and urinary disorders								
Haematuria	6 (2%)	0	0	0	1 (<1%)	0	0	0
Other	20 (5%)	7 (2%)	0	0	15 (4%)	0	1 (<1%)	0
Immune system disorder	6 (2%)	1 (<1%)	0	0	9 (2%)	2 (<1%)	0	0
Hepatobiliary disorders	5 (1%)	2 (<1%)	1 (<1%)	0	4 (1%)	0	1 (<1%)	0
Secondary malignancy possibly related to Hodgkin lymphoma treatment	0	2 (<1%)	7 (2%)	1 (<1%)	0	0	4 (1%)	1 (<1%)

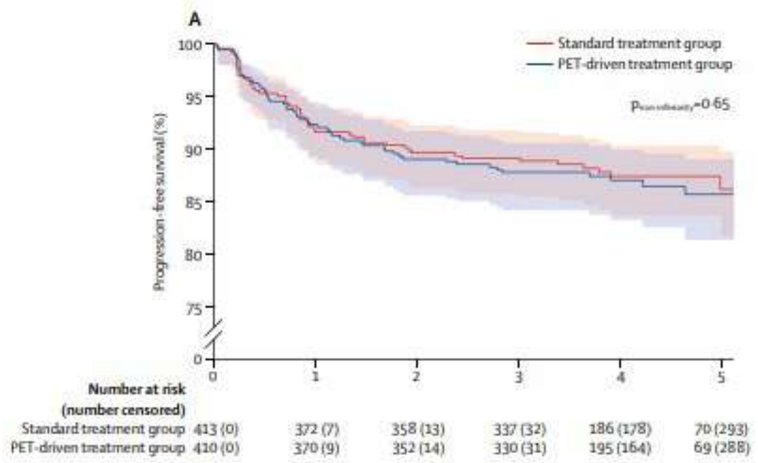
Data are n (%). Adverse events that occurred in at least 10% of patients in either group and all grade 3–5 adverse events are shown. AST=aspartate aminotransferase. ALT=alanine aminotransferase.

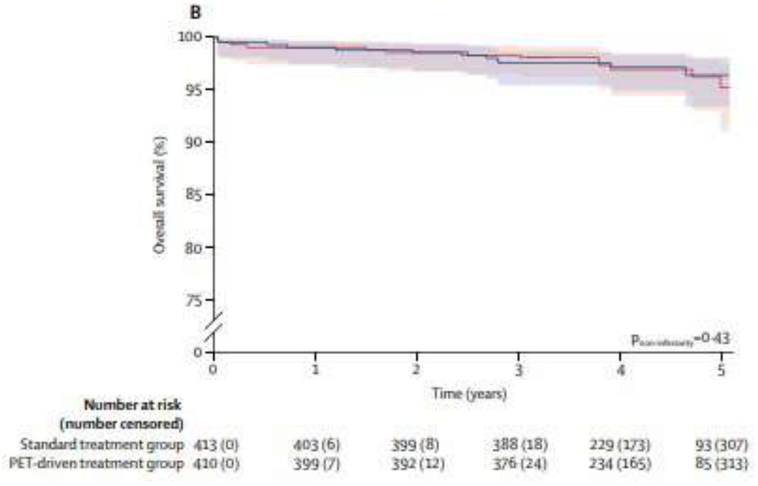
Table 4: Adverse events per treatment group in the safety population

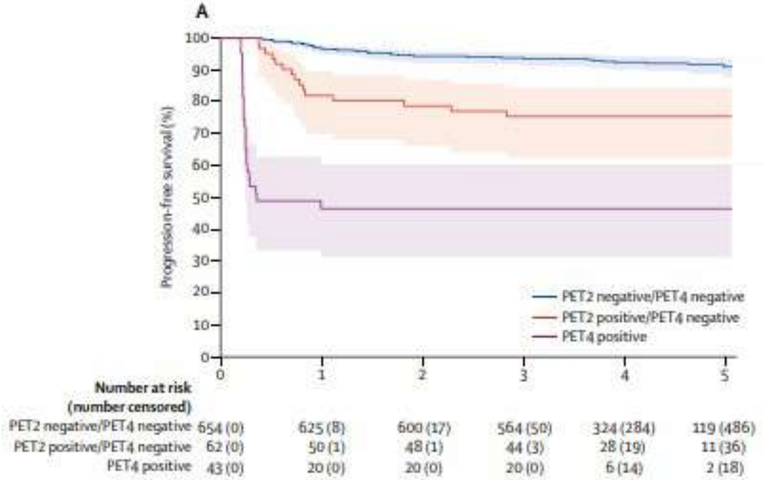
Casasnovas R.O. wt al. Lancet Oncol Jan 2019

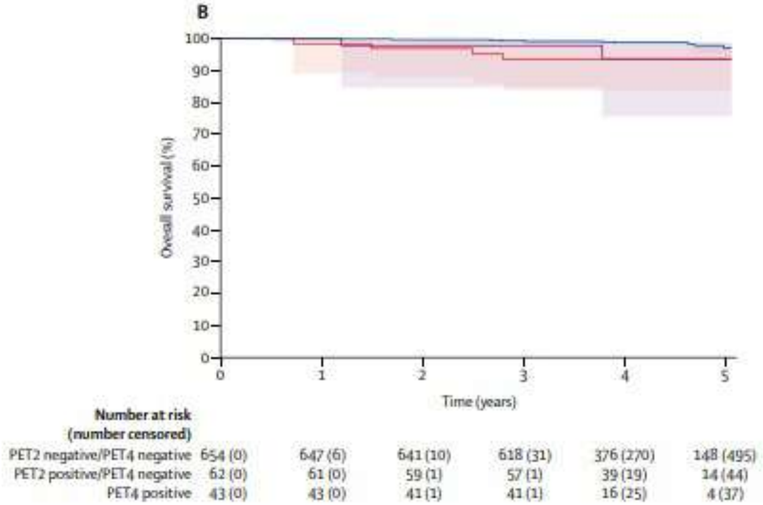
PET-Adapted Treatment- *De-Escalation*

AHL2011 Trial









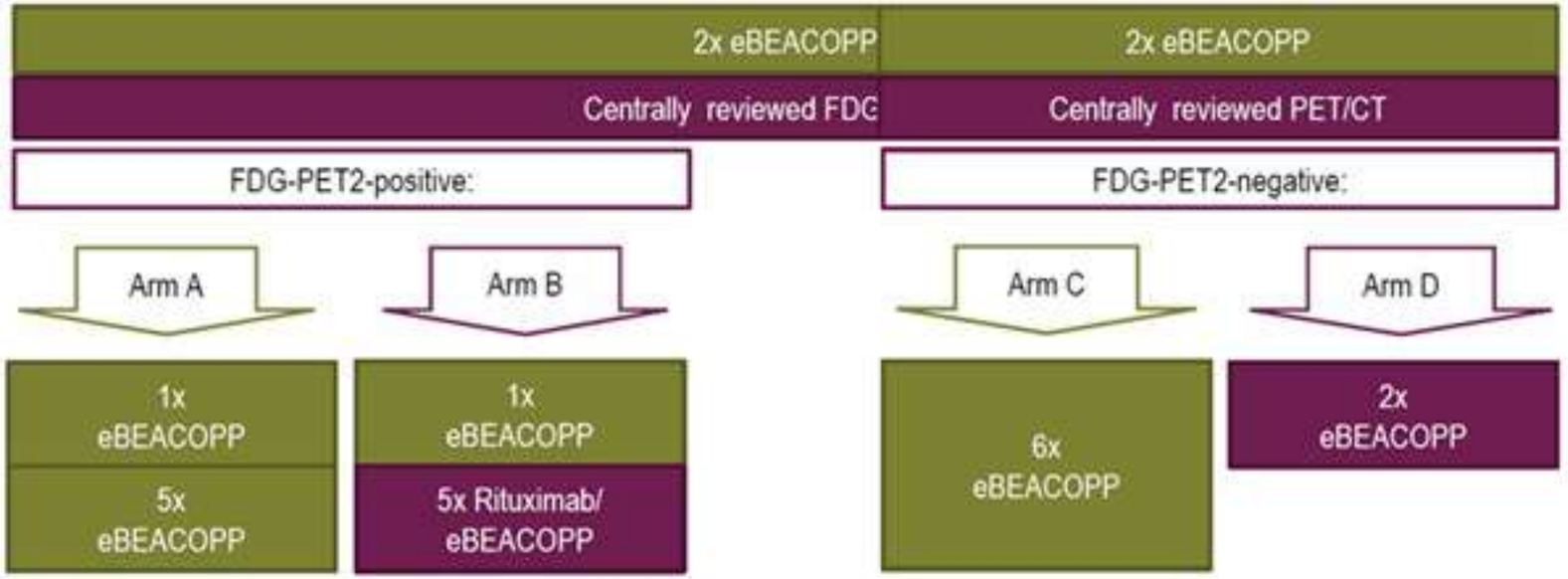
	5-Yr PFS	5-Yr OS
eBEACOPPx6 (NPA)	87.5%	97.7%
eBEACOPPx2 (PA)	86.7%	97.7%
PET2-/PET4-	92.3%	98.2%
PET2+/PET4-	75.4%	93.5%
PET4+	46.5%	91.9%

- PET-driven strategy of 4 cycles of ABVD in PET negative patients after 2 cycles of eBEACOPP is non inferior compared to standard 6 cycles of eBEACOPP
- PET4 provides additional prognostic information to PET2 and identifies patients with particularly poor prognosis

Casasnovas R.O. wt al. Lancet Oncol Jan 2019

PET-Adapted Treatment- *De-Escalation*

HD18 Trial



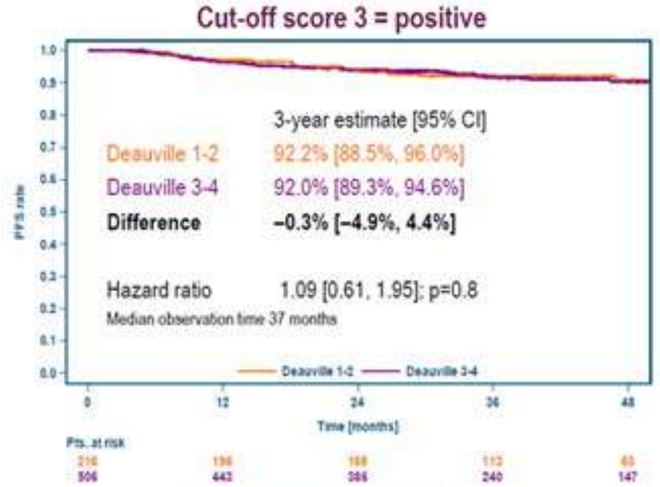
Toxicity

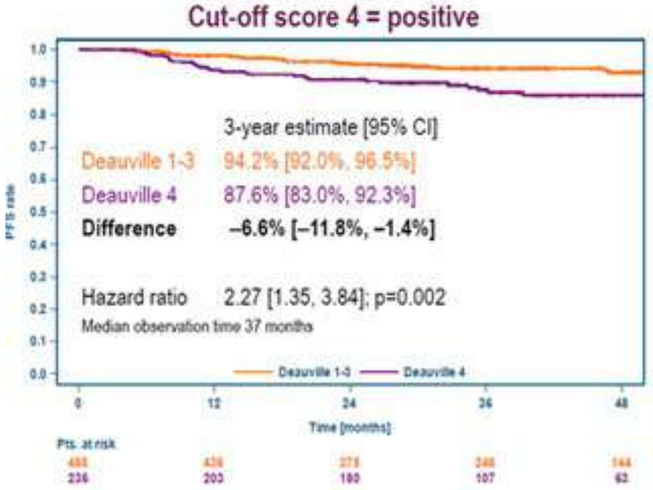
	8 x eBEACOPP (n=288)	6 x eBEACOPP (n=216)	4 x eBEACOPP (n=501)
Severe protocol deviations			
Discontinuation due to toxicity	11 (4%)	6	2 (<1%)
Patient withdrawn from chemotherapy	18 (6%)	4 (2%)	1 (<1%)
Administration of more than target number of chemotherapy cycles	0	0	6 (1%)
Other or unknown*	7 (2%)	4 (2%)	7 (1%)
Any severe protocol deviation	36 (13%)	8 (4%)	16 (3%)
Toxicity and supportive measures†			
Haematological toxicities of CTCAE grade III or IV			
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	17 (13%)	15 (7%)	17 (3%)
Any organ toxicity‡	62 (22%)	29 (13%)	38 (8%)
Toxicities of CTCAE grade III or IV			
Any toxicity‡	280 (98%)	205 (95%)	455 (91%)
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%)	105 (53%)	182 (38%)
Treatment-related morbidity	189 (66%)	132 (62%)	204 (41%)
Onset of treatment-related morbidity			
Cycles 1–4	135 (47%)	100 (47%)	204 (41%)
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%)

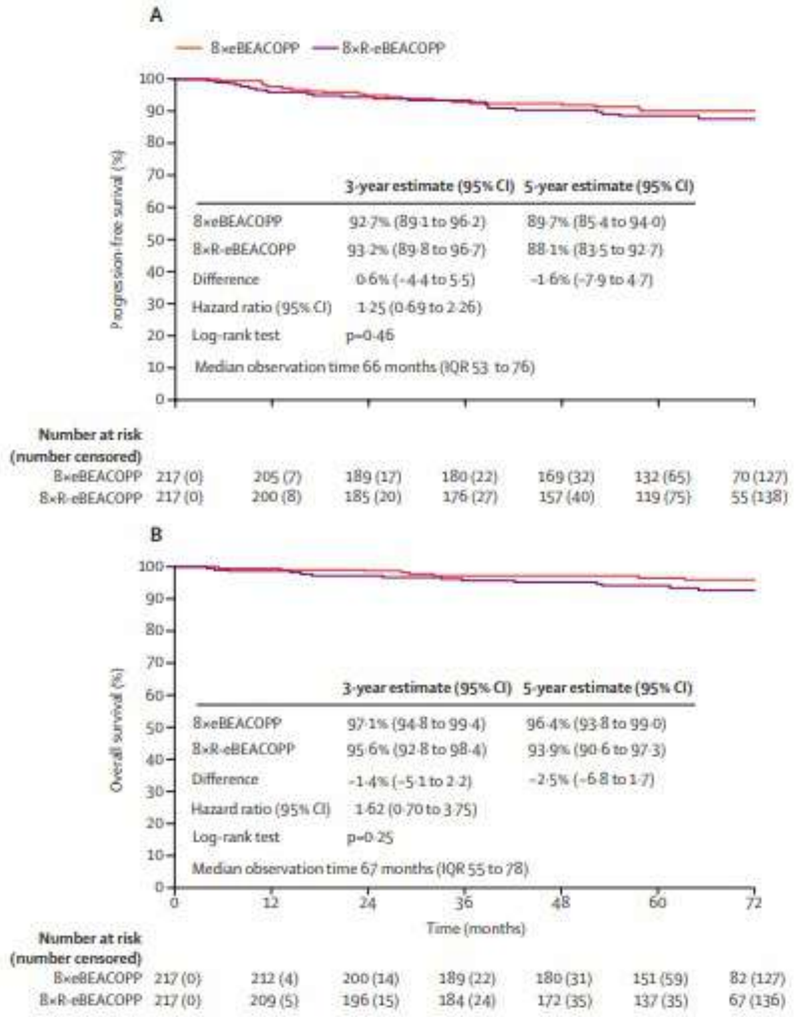
Borchmann. P et al. Lancet Vol 390, P2790-2802,

PET-Adapted Treatment- *De-Escalation*

HD18 Trial



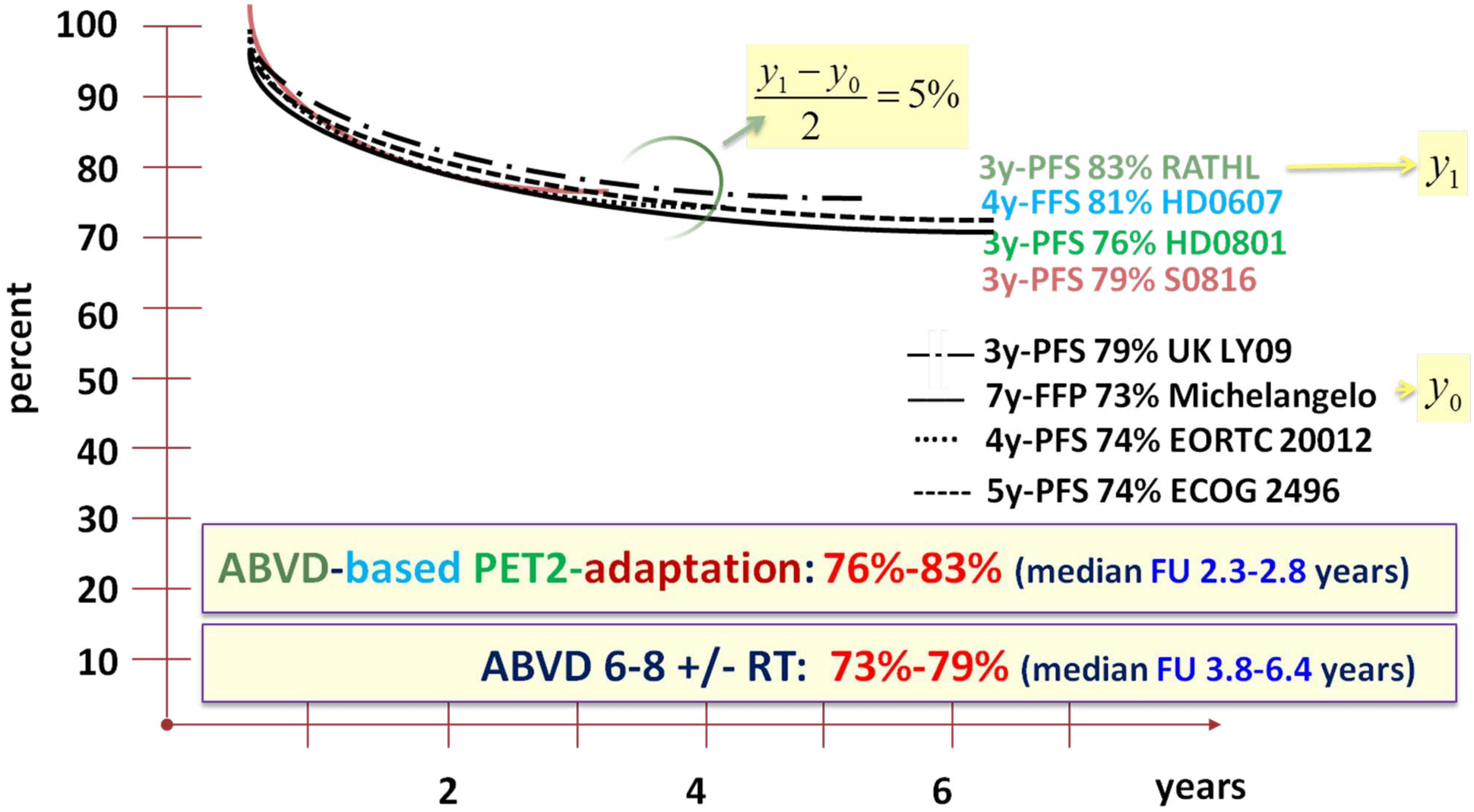




- **PET2 DS4 allows identification of those patients who need intensive therapy with 6 cycles of eBEACOPP**
- **Survival in this high-risk group is very good and not deserves further escalation**
- **PET2 DS 1-3 has a very good negative predictive value and allows to treat 75% of all patients with only 4 cycles**

Borchmann. P et al. Lancet Vol 390, P2790-2802,

PET adapted trials overall



Summary of PET-guided escalation strategies
PFS/OS for PET-2 Positive (DS 4-5) Pts. (advanced stages)

		Baseline Rx	PFS PET-2 POS (%)	OS PET-2 POS (%)	Escalation/De-escalation strategies
GITIL/FIL 0607	FIL	ABVD x 2	60 (@ 3-Yrs)	89 (@ 3-Yrs)	eBEACOPP/bas.BEACOPP
SWOG 0816	SWOG	ABVD x 2	65 (@ 5-Yrs)	65 (@ 5-Yrs)	eBEACOPP
HD0801	FIL	ABVD x 2	74 (@ 2-Yrs)	NA	IGEV + BEAM/ASCT
RATHL*	NCRI	ABVD x 2	63.9(@ 3-Yrs)	88 (@ 3-Yrs)	BEACOPP14/eBEACOPP
AHL2011	LYSA	eBEACOPP x 2	75.4 (@ 5-Yrs)	93.5 (@ 5-Yrs)	ABVD
HD18	GHSG	eBEACOPP x 2	92.5 (@ 3-Yrs)	98 (@ 3-Yrs)	EscBEACOPP

*42% stage II patients

ABVD vs BEACOPP escalated in advanced-stage Hodgkin's lymphoma: Results from a multicenter European study

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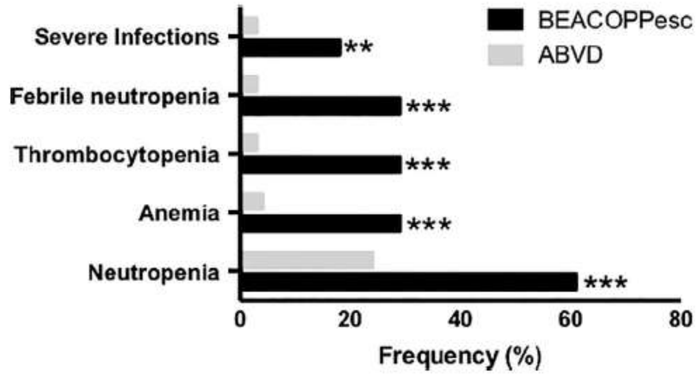
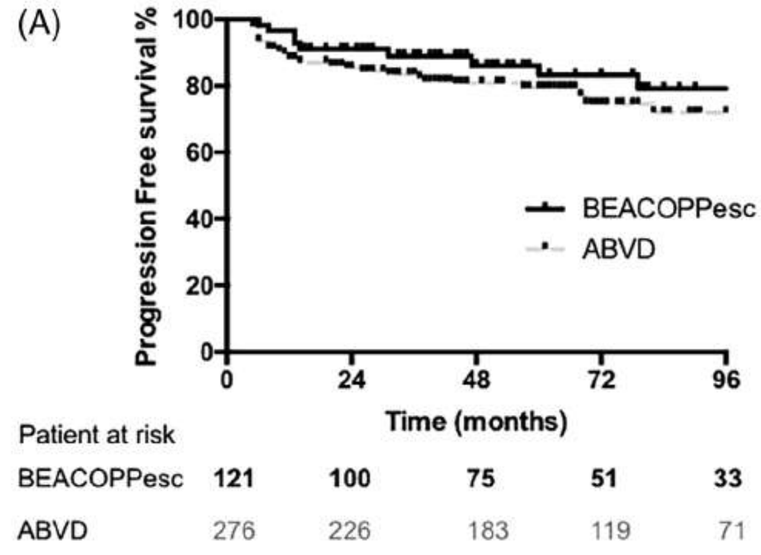
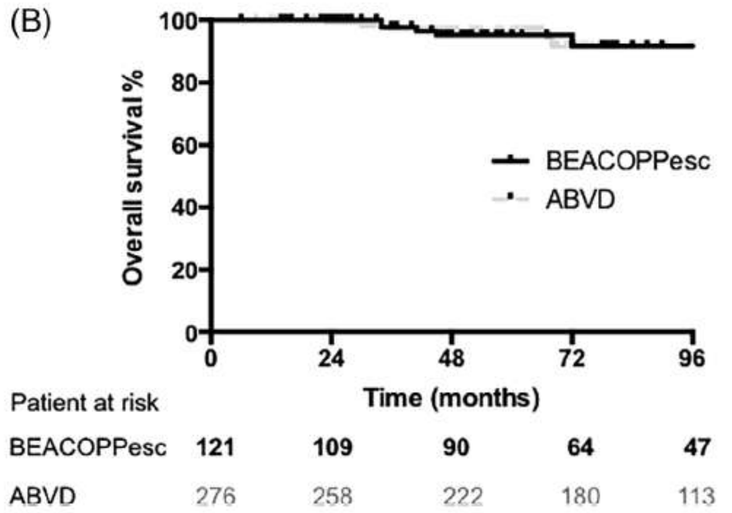
	BEACOPPesc (*n* = 121)		ABVD (*n* = 276)		*p*-value
	n	%	*n*	%	
Age					
Median, years	37	N.A.	36.5	N.A.	N.A
>50 years (EORTC)	24	19.8	60	21.7	.42
>60 years	4	3.3	11	4	.77



8-year PFS:

- **Irrespective of PET2: 80% vs 75%**
- **PET2-negative patients: 84% vs 80%**
- **PET2-positive patients: 69% vs 63.5%**

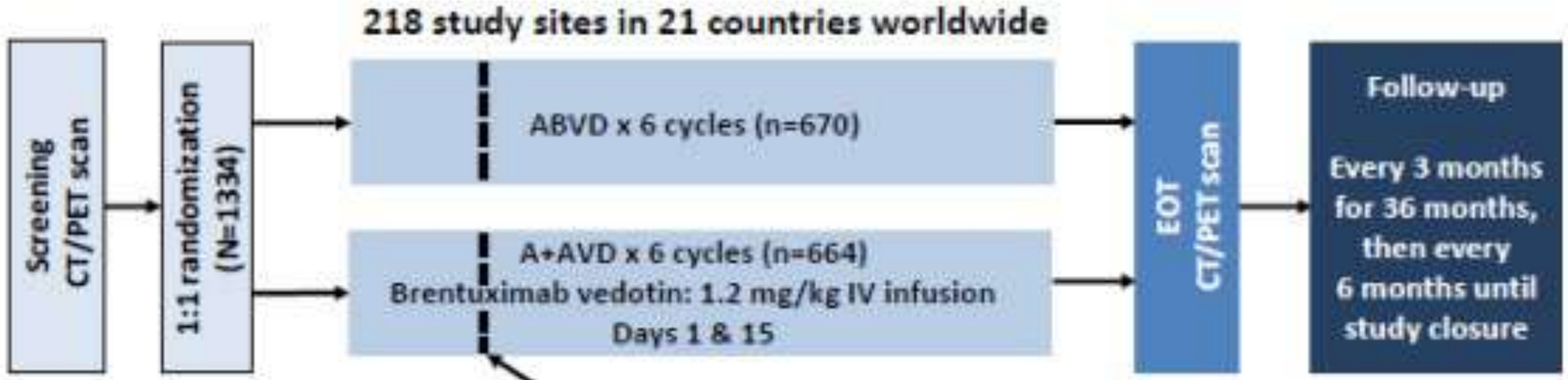




Am J Hematol. 2020;95:1030–1037.

Non PET-Adapted Treatment

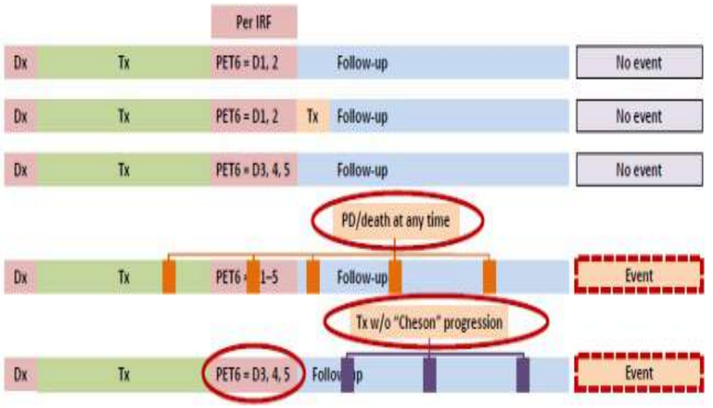
Phase 3 ECHELON-1 Study



- Inclusion criteria
  - cHL stage III or IV
  - ECOG PS 0, 1 or 2
  - Age ≥18 years
  - Measurable disease
  - Adequate liver and renal function

A modified PFS event:

- ✓ Progression
- ✓ Death from any cause
- ✓ PET-6= DS 3,4,5 after completion of frontline therapy followed by subsequent anticancer therapy



Connors et al. *NEJM* 2017

Non PET-Adapted Treatment

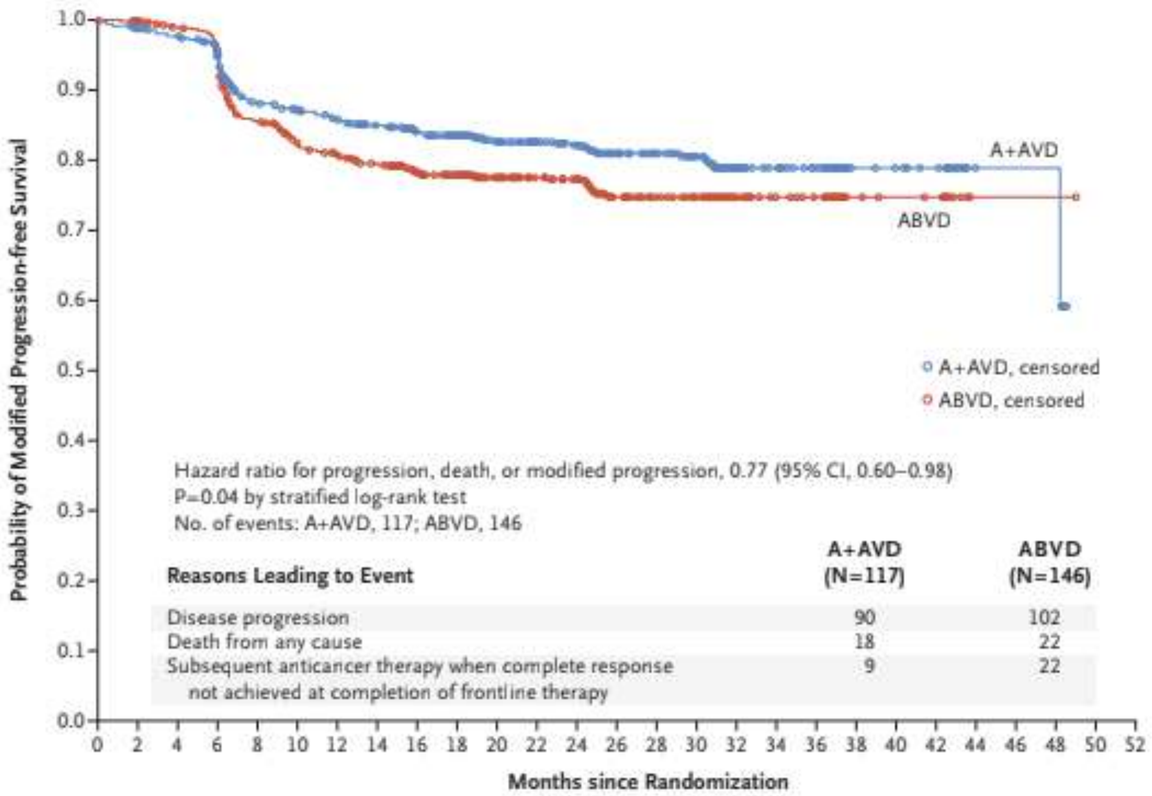
Patients characteristics

Baseline Pt Characteristics[1,2]	A + AVD N=664	ABVD N=670
Male, %	57	59
Not Hispanic or Latino, %[2]	86	86
White, %	84	83
Median age, years (range)	35 (18–82)	37 (18–83)
Age, years, %		
<45	68	63
45–59	19	22
60–64	4	6
≥65	9	9
Median time since initial diagnosis, months[2]	0.92	0.89
Region, %		
Americas	39	39
Europe	50	50
Asia	11	11
Ann Arbor stage, %		
III	36	37
IV	64	63
IPS risk factors, %*		
0–1	21	21
2–3	53	52
4–7	25	27
ECOG PS, %		
0	57	57
1	39	39
2	4	4
B symptoms, %	60	57
Bone marrow involvement, %	22	23
Sites of extranodal involvement, %†		
None	33	34
1	33	33
>1	29	29

- **7 deaths in the A + AVD arm were due to neutropenia or associated complications; 11 deaths in the ABVD group were associated with pulmonary-related toxicity**
- **The most common treatment-emergent AEs (any grade) occurring in > 20% of pts in the A + AVD arm included neutropenia, constipation, vomiting, fatigue, peripheral sensory neuropathy, diarrhea, pyrexia, abdominal pain, and stomatitis.**
- **Gr 3 or higher neutropenia occurred in 54% of pts in the A + AVD group and 39% of the ABVD group.**

Non PET-Adapted Treatment

2-years mPFS



Reasons Leading to Event	A+AVD (N=117)	ABVD (N=146)
Disease progression	90	102
Death from any cause	18	22
Subsequent anticancer therapy when complete response not achieved at completion of frontline therapy	9	22

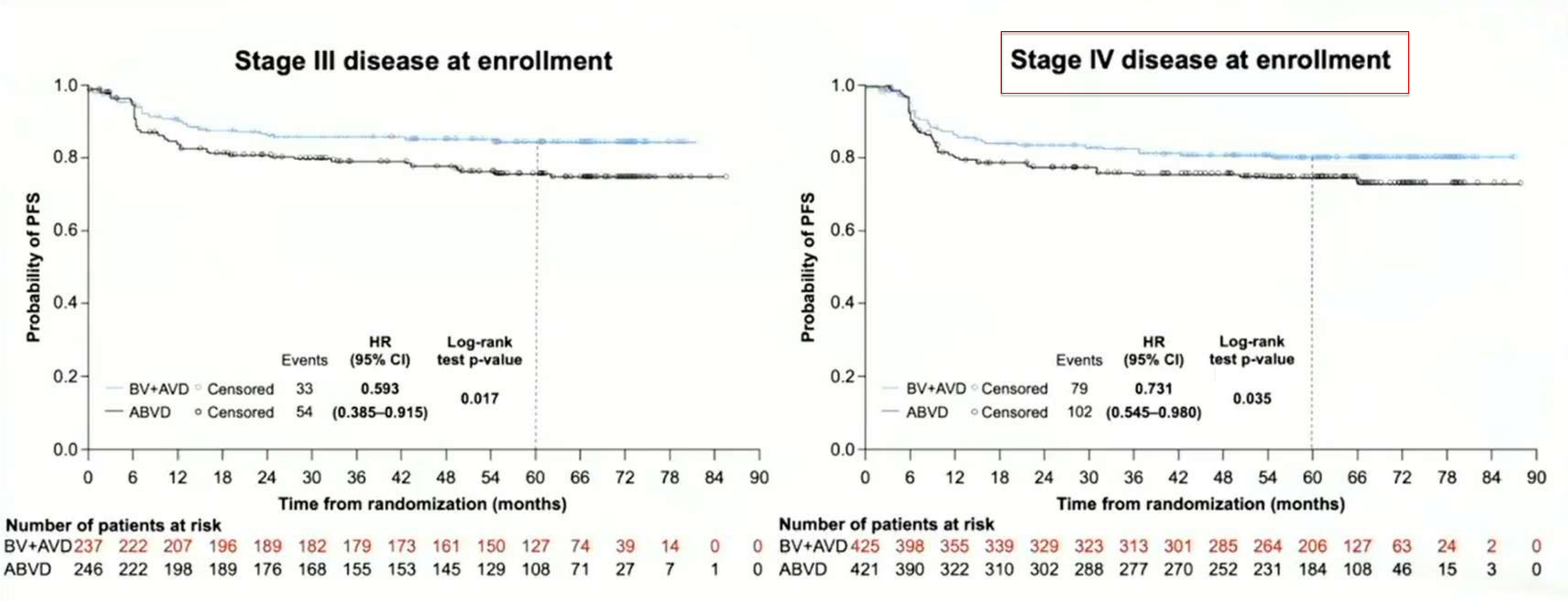
No. at Risk

A+AVD	664	637	623	600	541	528	513	493	463	439	347	328	309	196	185	169	96	85	77	26	24	21	4	4	4	0	0
ABVD	670	636	626	593	521	490	474	459	432	413	326	306	292	177	164	153	76	66	62	16	13	12	1	1	1	0	0

J.M. Connors et al. NEJM 378;4 January 25, 2018

Non PET-Adapted Treatment

Echelon-1: PFS per investigator @ 5 years according to clinical Stage



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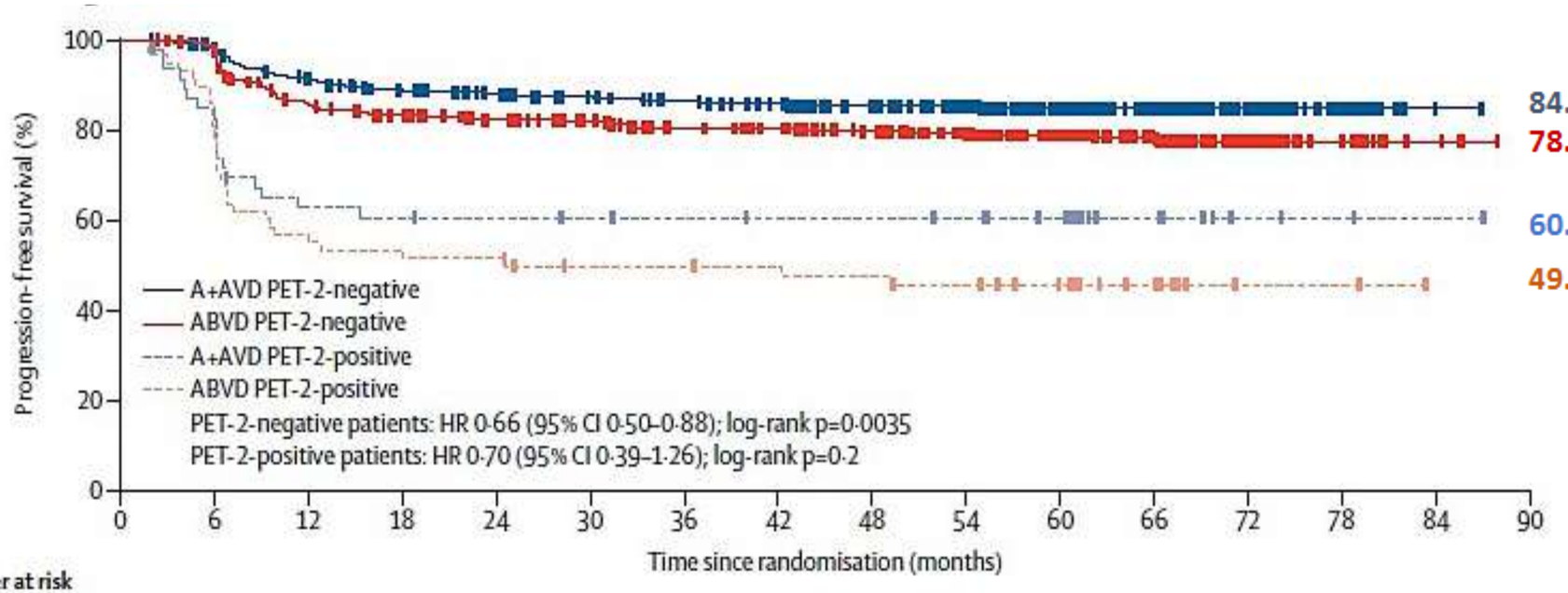
Non PET-Adapted Treatment

5-year analysis PFS



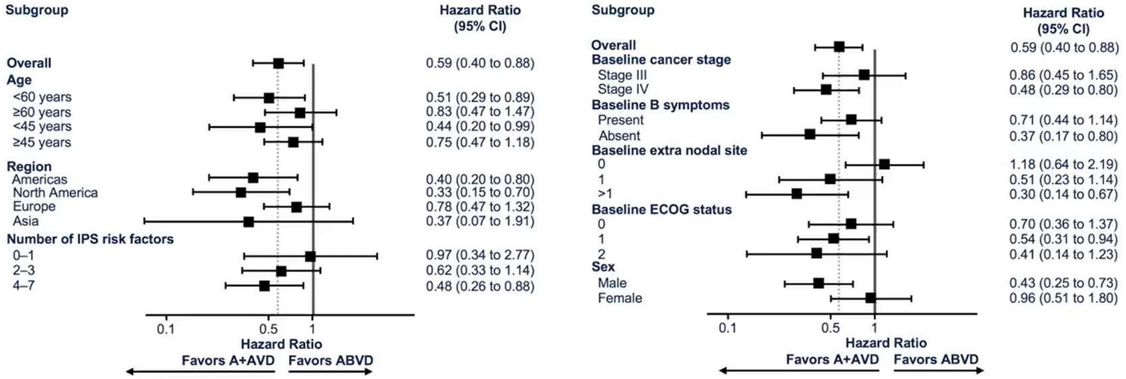
84.9% (95% CI: 81.7-87.6)
78.9% (95% CI: 75.2-82.1)
60.6% (95% CI: 81.7-87.6)
49.9% (95% CI: 32.7-58.2)

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)

- **A+AVD *vs.* ABVD**
  - Durable progression-free survival
  - Independent of:
    - stage
    - age
    - baseline risk
    - interim PET-2 status

Non PET-Adapted Treatment

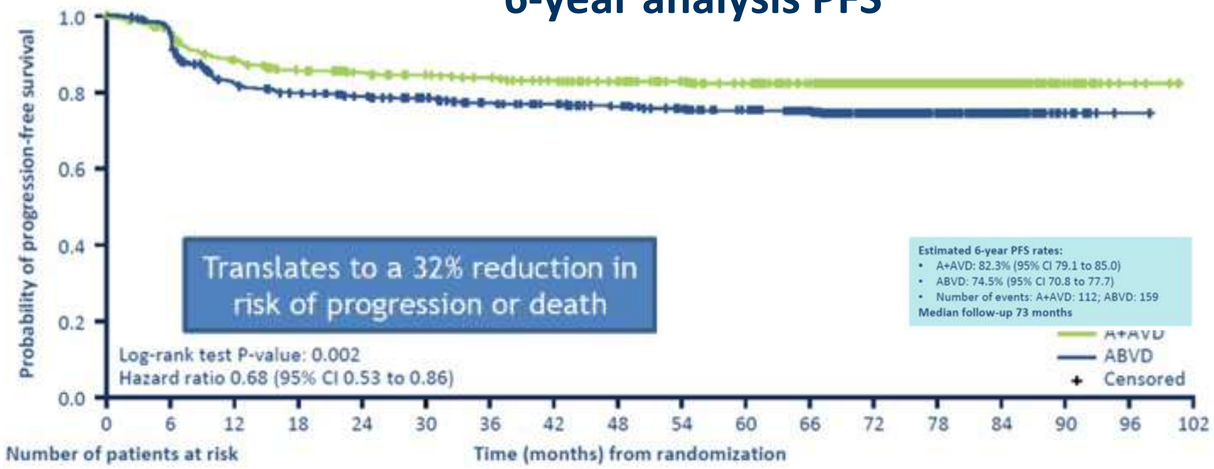
OS benefit was generally consistent across subgroups



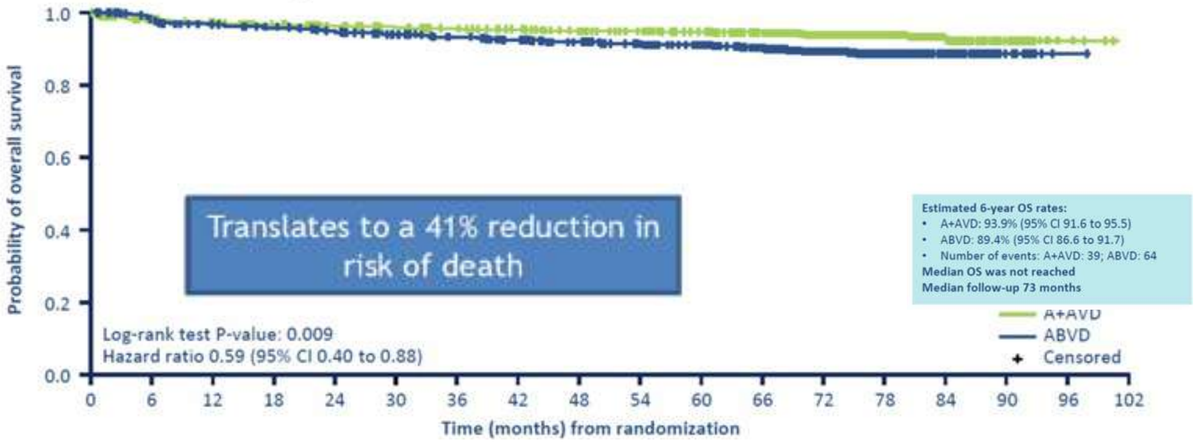
- The OS benefit with A+AVD was preserved in a multivariable analysis when simultaneously adjusting for baseline demographic and disease factors (HR 0.53; 95% CI, 0.34 to 0.83)
  - Age, non-white race, ECOG performance status score, and PET2 status were identified as the covariates with greatest evidence of association with overall survival

ECOG, Eastern Cooperative Oncology Group.

6-year analysis PFS



6-year analysis OS



Hutchings M et al. Hemasphere 2022, 6: S3 - Presented at EHA 2022, Wien 9-17 June 2022

6-year analysis: Cause of death & subsequent therapy

Cause of death per investigator	A+AVD (n=662)	ABVD (n=659)
Total Deaths	**39 (5.9%)**	**64 (9.7%)**
Hodgkin lymphoma or complications	32	45
Second malignancies	1	11
Other causes	**6**	**8**
Unknown cause	1	5*
Accident or suicide	3	0
COVID-19	0	1
Heart failure	1	1
Intracranial hemorrhage	1	0
Lower respiratory tract infection	0	1

*In 2 patients in the ABVD arm, death was reported to be of indeterminate cause, but the event occurred following investigator-documented disease progression.

	A+AVD n=662	ABVD n=659	Total N=1,321
Patients with ≥1 subsequent anticancer therapy, n (%)	135 (20)	157 (24)	292 (22)
Type of therapy, n (%)			
Brentuximab vedotin or chemotherapy regimens	78 (12)	108 (16)	186 (14)
Brentuximab vedotin monotherapy	8 (1)	49 (7)	57 (4)
Brentuximab vedotin + chemotherapy	2 (<1)	20 (3)	22 (2)
Radiation	54 (8)	54 (8)	108 (8)
Chemotherapy + radiation	1 (<1)	4 (<1)	5 (<1)
High-dose chemotherapy + transplant	44 (7)	59 (9)	103 (8)
Allogeneic transplant	4 (<1)	12 (2)	16 (1)
Immunotherapy*	18 (3)	24 (4)	42 (3)
Brentuximab vedotin + nivolumab	0 (0)	4 (<1)	4 (<1)
Nivolumab	15 (2)	18 (3)	33 (2)
Pembrolizumab	2 (<1)	6 (<1)	8 (<1)
Nivolumab combinations	1 (<1)	1 (<1)	2 (<1)
Other	0 (0)	1 (<1)	1 (<1)

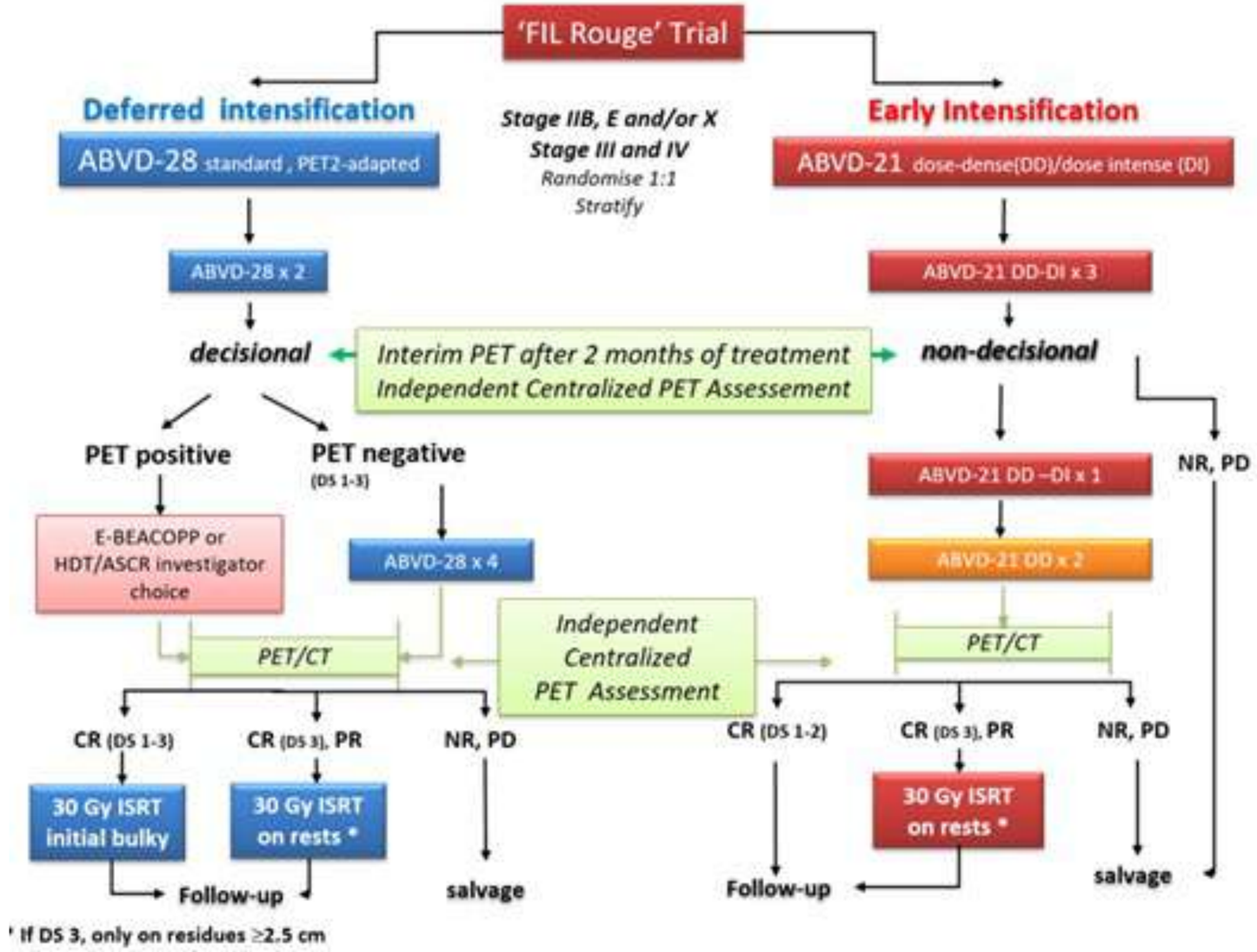
*Immunotherapy was based predominantly on anti-PD-1 agents.
PD-1, programmed death receptor 1.

6-year analysis: Pregnancies

Pregnancies

- Fertility was not formally assessed
- A total of 191 pregnancies were reported among patients and their partners (A+AVD: 113; ABVD: 78)
  - Among female patients with A+AVD and ABVD:
    - Pregnancies: 49 and 28
    - Live births: 56 and 23
- Among partners of male patients with A+AVD and ABVD:
  - Pregnancies: 33 and 33
  - Live births: 40 and 36
- No still births were reported in either arm

PET-Adapted vs. non PET-Adapted Treatment



ABVD DD-DI *Schedule*

	Course n°	1		2		3		4		5		6	
	Day	1	11	1	11	1	11	1	11	1	11	1	11
ABVD DD-DI		dose densification											
		dose intensification											
ADM	35 mg/m²	✓	✓	✓	✓	✓	✓	✓	✓				
		vs.											
ADM	25 mg/m²									✓	✓	✓	✓
BLM	10 mg /m²	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
VLB	6 mg/m²	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
DTIC	375 mg/m²	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Lenograstim dd 6 →8		☒		☒		☒		☒		☒		☒	
Lenograstim dd 17→19			☒		☒		☒		☒		☒		☒

Single course duration: 3 weeks ; total treatment lenght : 18 weeks (4.2 mo.s)

Patients Characteristics

Factor	Variable	Total	Comparator Arm	Experimental Arm
		N=503	N=252	N=251
Age, median		33.6 (26.2-43.0)	32.8 (24.8-42.7)	34.4 (27.5-43.0)
Sex	Male vs. Female	273 (54.3%) vs. 230 (45.7%)	139 (55.2%) vs. 113 (44.8%)	134 (53.4%) vs. 117 (46.6%)
Ann Arbor Stage	III-IV vs. II	400 (79.5%) vs.103 (20.5%)	200 (79.4%) vs. 52 (20.6%)	200 (79.7%) vs. 51 (20.3%)
B Symptoms	Si vs. No	294 (58.4%) vs. 203 (40.4%)	148 (58.7%) vs. 102 (40.5%)	146 (58.2%) vs. 101 (40.2%)
Bulky Disease	Absent	310 (61.6%)	156 (61.9%)	154 (61.4%)
	Nodal Bulky (> 10 cm)	68 (13.5%)	36 (14.3%)	32 (12.7%)
	Mediastinal Bulky	120 (23.9%)	58 (23.0%)	62 (24.7%)
IPS	0-1	139 (27.6%)	75 (29.8%)	64 (25.5%)
	2	151 (30.0%)	74 (29.4%)	77 (30.7%)
	3	127 (25.2%)	61 (24.2%)	66 (26.3%)
	>=4	86 (17.1%)	42 (16.7%)	44 (17.5%)
Extranodal Sites	0	221 (43.9%)	120 (47.6%)	101 (40.2%)
	1	153 (30.4%)	69 (27.4%)	84 (33.5%)
	>=2	121 (24.1%)	59 (23.4%)	62 (24.7%)

Study	IPS ≥3	Stage II
UK RATHL	37%	41%*
HD 0607	39%	34%
US S0816	51%	0
HD 0801	46%	19%

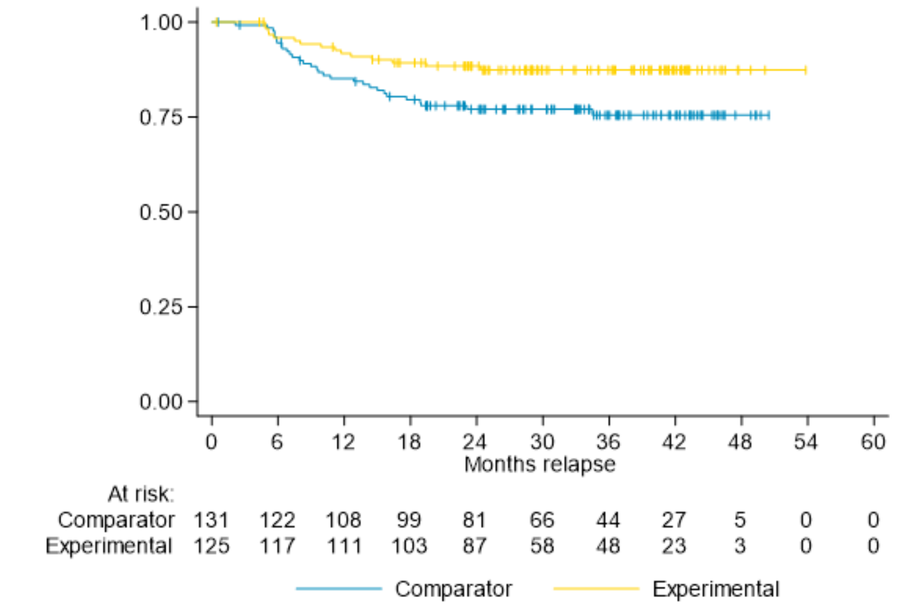
* Stage IIA (bulky or >2 sites) included

FIL ROUGE: Stage II: 20%

BEACOPP esc HD 18: Stage II: 22%

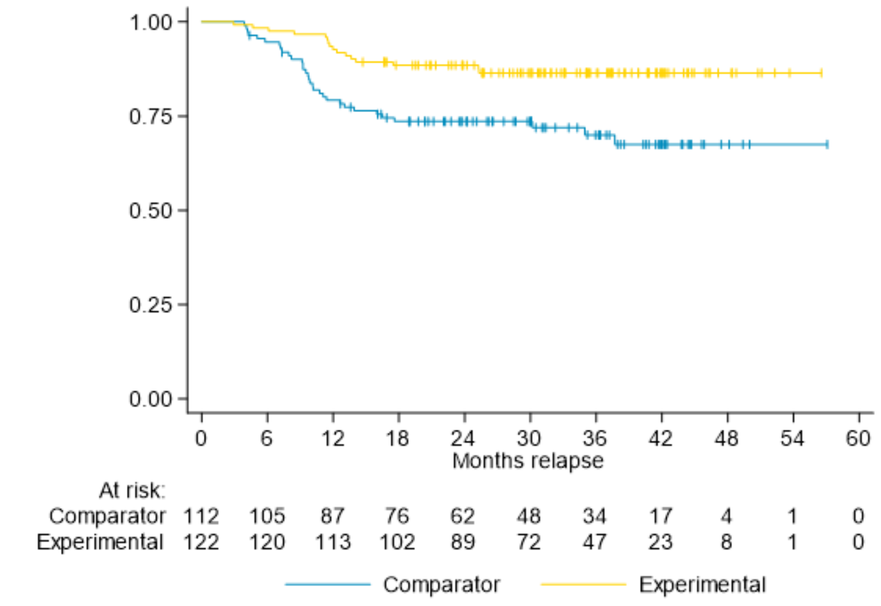
FIL ROUGE Trial: PFS by ARM according to Stage

STAGE II-III



Time	Survivor Function	Std. Error	[95% Conf.	Int.]
Comparator				
12	0.8516	0.0314	0.7772	0.9027
24	0.7702	0.0375	0.6863	0.8344
36	0.7548	0.0398	0.6661	0.8231
Experimental				
12	0.9179	0.0249	0.8528	0.9550
24	0.8840	0.0292	0.8119	0.9296
36	0.8737	0.0306	0.7990	0.9220

STAGE IV



Time	Survivor Function	Std. Error	[95% Conf.	Int.]
Comparator				
12	0.7918	0.0386	0.7035	0.8565
24	0.7356	0.0422	0.6423	0.8082
36	0.6998	0.0472	0.5964	0.7815
Experimental				
12	0.9262	0.0237	0.8630	0.9609
24	0.8849	0.0290	0.8133	0.9301
36	0.8645	0.0317	0.7879	0.9149

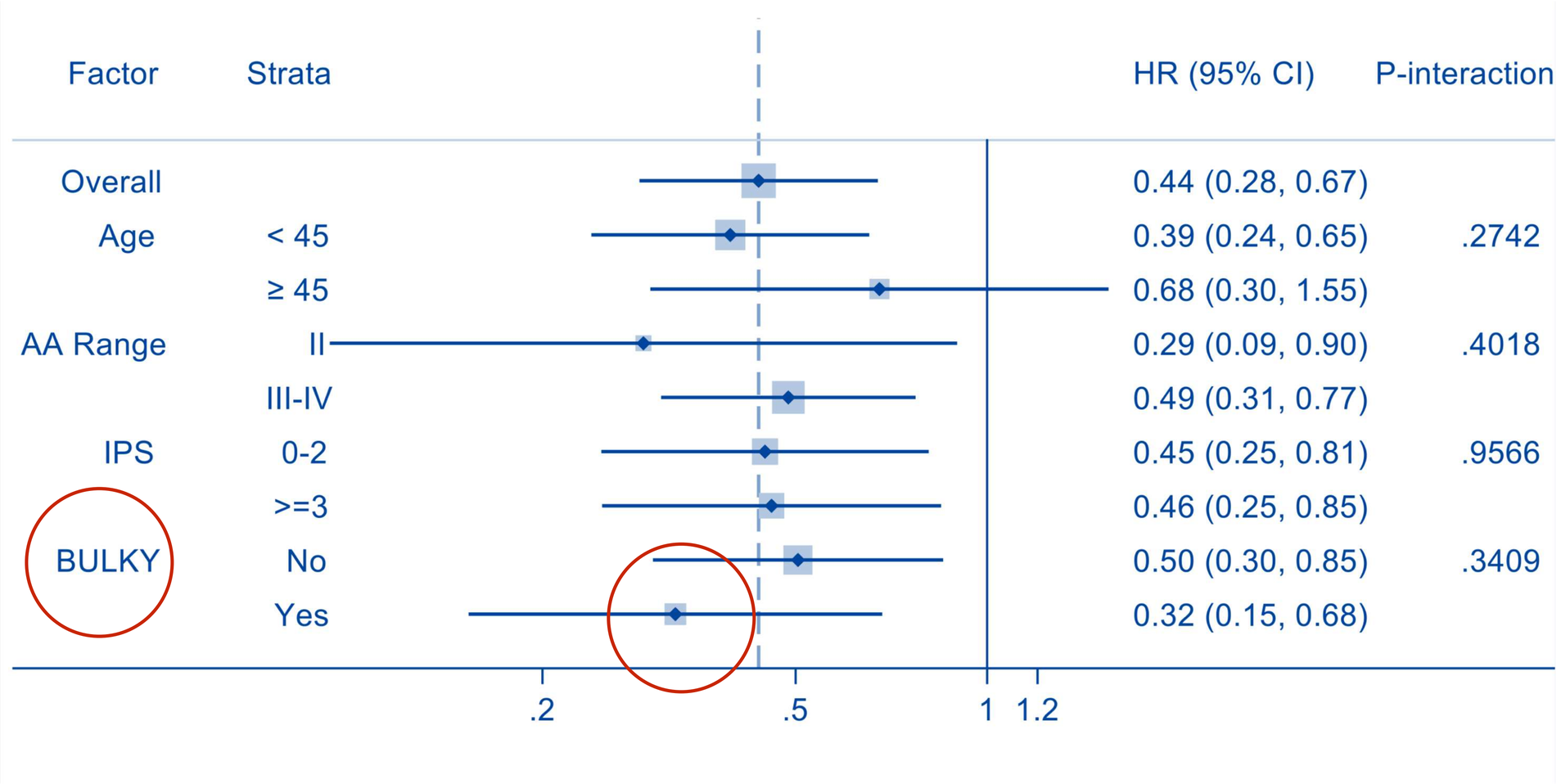
Bulky disease

Cotswolds modif. Ann Arbor
Lugano 2014

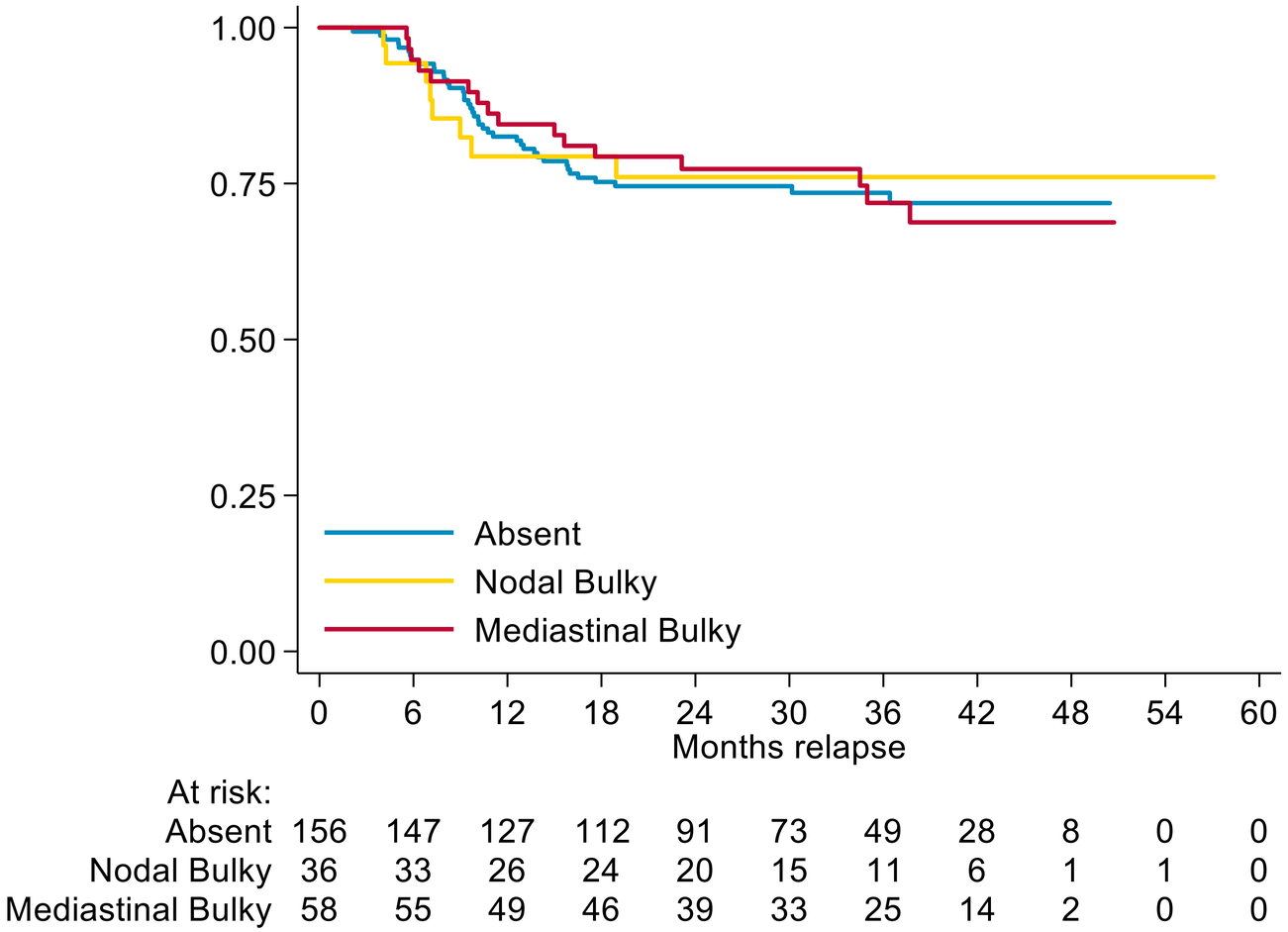
- Bulky nodale : Dmax ≥ 10 cm
  and/or
- Bulky mediastinico: M/T ≥ 1/3

Studio	Numero/TOT	nodal >10 cm	Med >1/3	%
FIL-Rouge	180 / 502	☒	☒	35
FIL-HD0801	181 / 512	☒	☒	35
RATHL	386/1203	☒	☒	32
GHSG – HD15	631/2316	☐	☒	30
GHSG – HD18	561/1945	☐	☒	29
GITIL- HD0607	155 /782	☒	☐	19.8
SWOG S0816	60/336	☒	☐	18

FIL Rouge trial: Subgroup Analysis for overall PFS

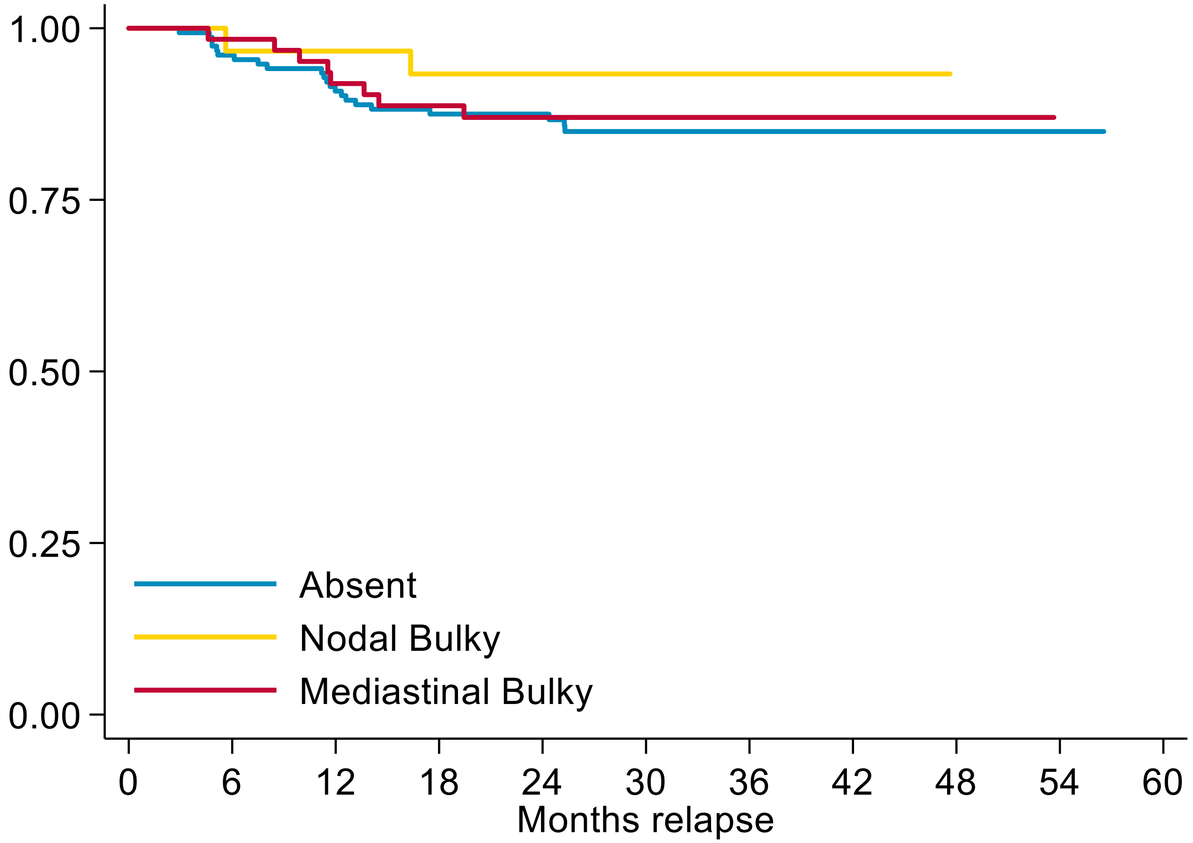


FIL ROUGE Trial: Bulky disease in COMPARATOR ARM



Time	Survivor Function
Absent	
12	0.8252
24	0.7458
36	0.7351
Nodal Bulky (> 10 cm	
12	0.7934
24	0.7604
36	0.7604
Mediastinal Bulky (M	
12	0.8448
24	0.7733
36	0.7190

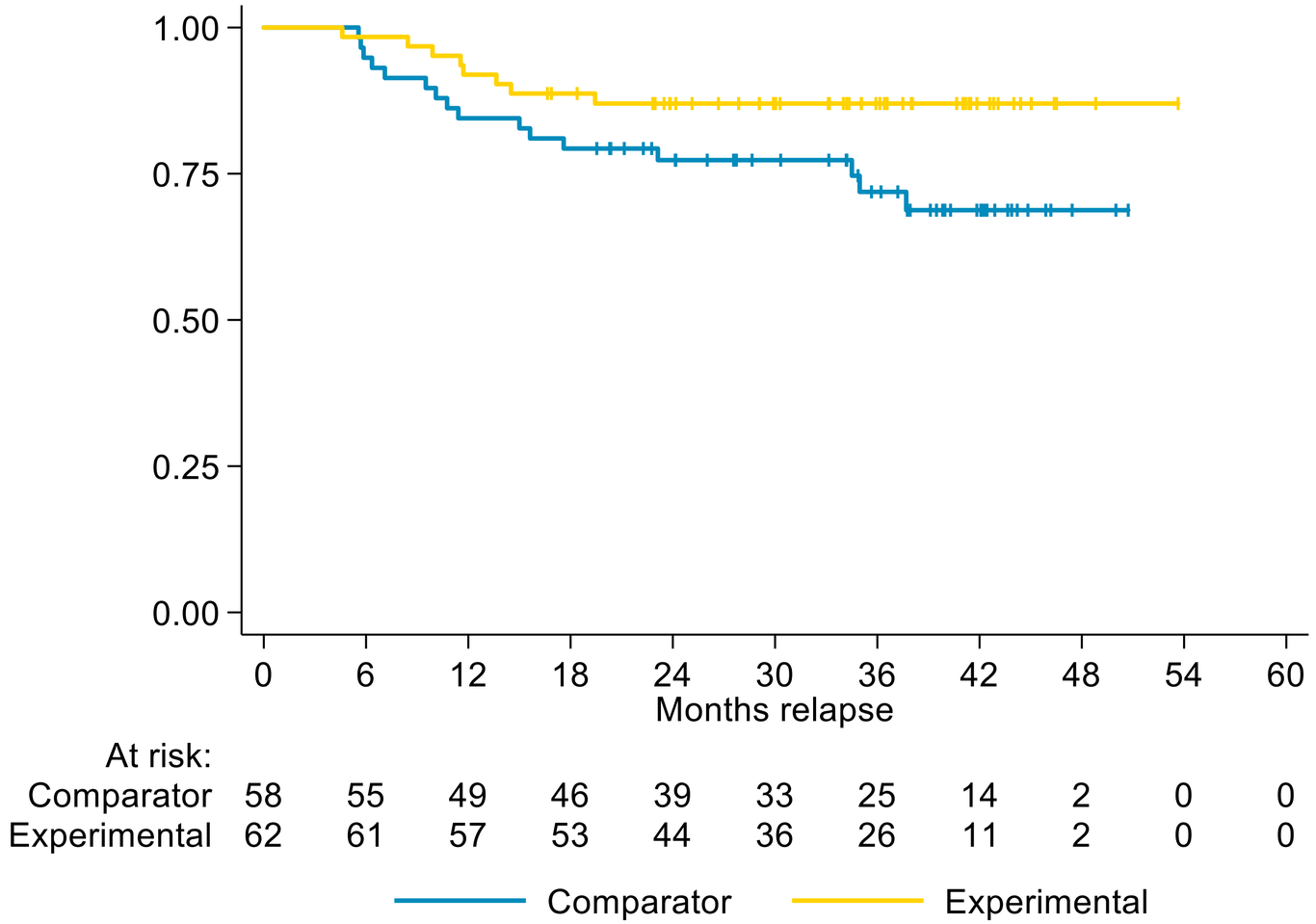
FIL ROUGE Trial: Bulky disease in EXPERIMENTAL ARM



At risk:											
Absent	154	147	138	124	106	81	60	29	9	1	0
Nodal Bulky	32	29	29	28	26	14	11	8	0	0	0
Mediastinal Bulky	62	61	57	53	44	36	26	11	2	0	0

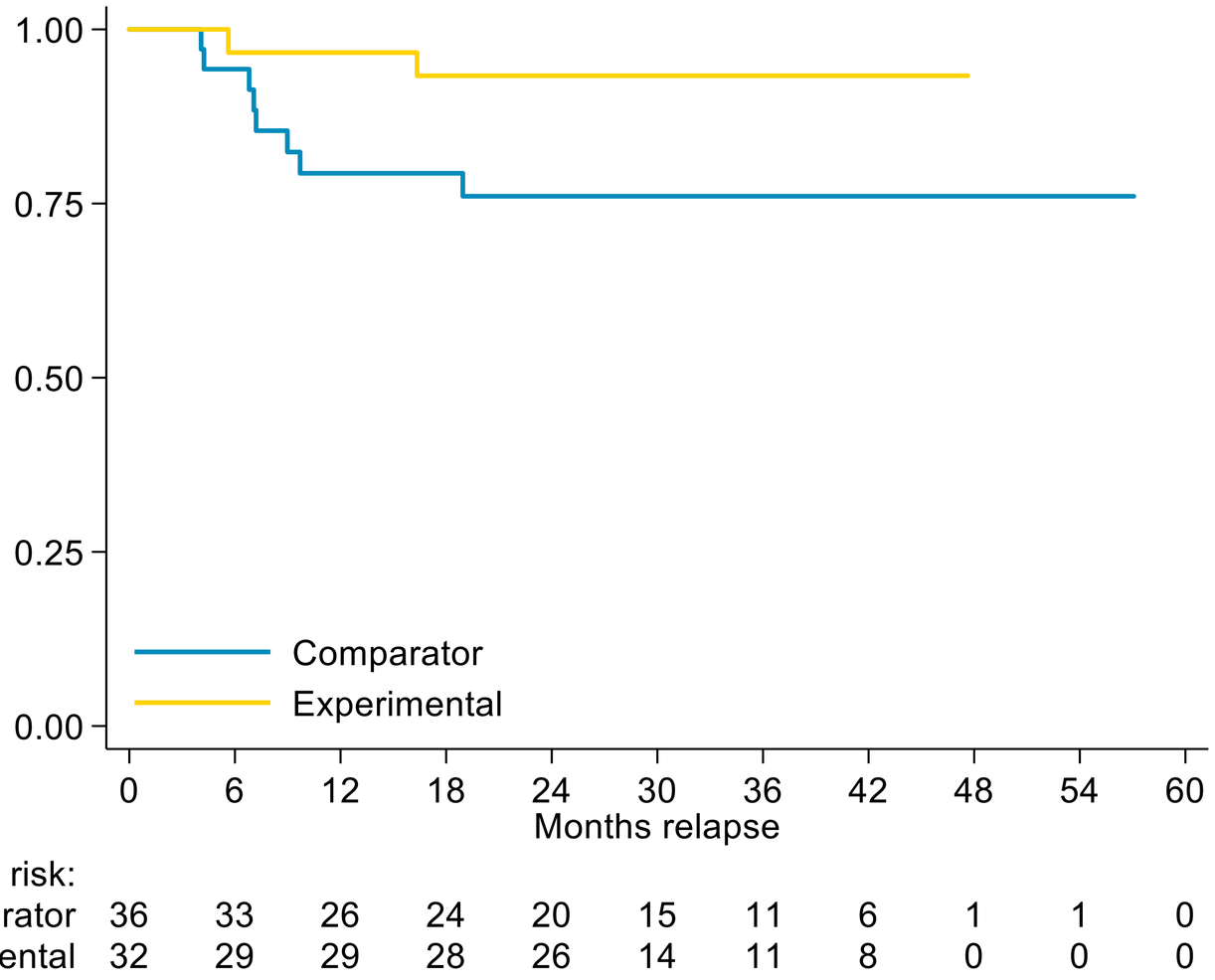
Time	Survivor Function
Absent	
12	0.9083
24	0.8749
36	0.8495
Nodal Bulky (> 10 cm	
12	0.9667
24	0.9333
36	0.9333
Mediastinal Bulky (M	
12	0.9194
24	0.8700
36	0.8700

FIL ROUGE Trial: Mediastinal Bulky



Time	Survivor Function
Comparator	
12	0.8448
24	0.7733
36	0.7190
Experimental	
12	0.9194
24	0.8700
36	0.8700

FIL Rouge trial: Nodal Bulky



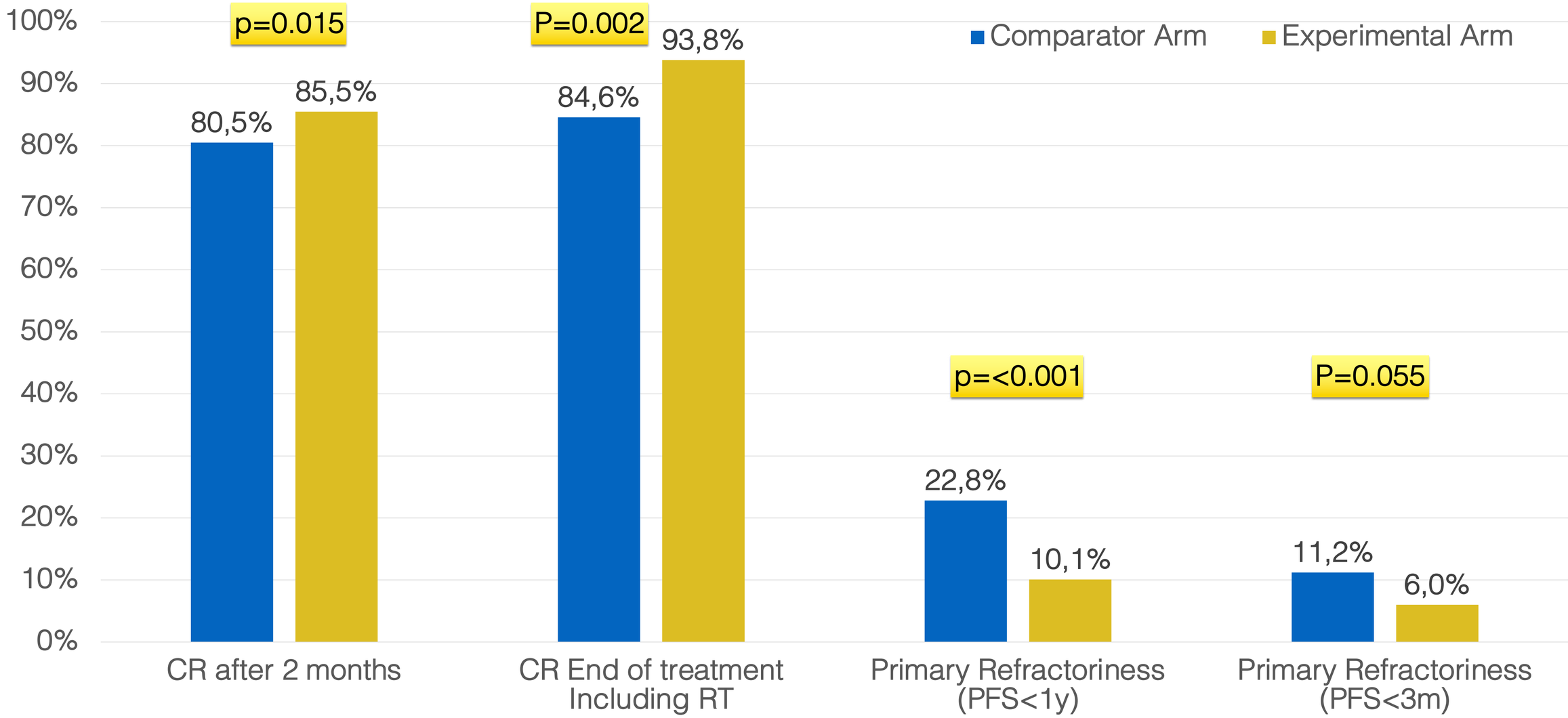
Time	Survivor Function
Comparator	
12	0.7934
24	0.7604
36	0.7604
Experimental	
12	0.9667
24	0.9333
36	0.9333

Toxicity

CTCAE Type	COMPARATOR G1	%	G2	%	G3	%	G4	%	G5	%	EXPERIMENTAL G1	%	G2	%	G3	%	G4	%	G5	%
Anemia	10	4.0	9	3.6	5	2.0	1	0.4	0	0.0	16	6.3	23	9.1	11	4.4	0	0	0	0
Febrile Neutropenia	1	0.4	1	0.4	3	1.2	1	0.4	0	0.0	1	0.4	2	0.8	9	3.6	2	0.8	0	0
Leucopenia	7	2.8	4	1.6	3	1.2	3	1.2	0	0.0	6	2.4	2	0.8	2	0.8	0	0	0	0
Neutropenia	7	2.8	9	3.6	43	17.2	33	13.2	0	0.0	7	2.8	6	2.4	51	20.2	52	20.6	0	0
Thrombocytopenia	3	1.2	0	0.0	2	0.8	1	0.4	0	0.0	2	0.8	2	0.8	0	0	0	0	0	0
Cardiac disorders	9	3.6	1	0.4	1	0.4	0	0.0	0	0.0	4	1.6	5	2	2	0.8	0	0	0	0
Ear and labyrinth disorders	2	0.8	2	0.8	1	0.4	0	0.0	0	0.0	1	0.4	0	0	0	0	0	0	0	0
Eye disorders	0	0.0	1	0.4	0	0.0	0	0.0	0	0.0	4	1.6	3	1.2	0	0	0	0	0	0
Gastrointestinal disorders	38	15.2	30	12.0	4	1.6	2	0.8	0	0.0	48	19	39	15.5	8	3.2	1	0.4	0	0
General disorders and administration site conditions	30	12.0	16	6.4	1	0.4	0	0.0	0	0.0	37	14.7	22	8.7	3	1.2	0	0	0	0
Hepatobiliary disorders	5	2.0	2	0.8	1	0.4	0	0.0	0	0.0	2	0.8	1	0.4	1	0.4	0	0	0	0
Immune system disorders	3	1.2	1	0.4	0	0.0	0	0.0	0	0.0	5	2	1	0.4	1	0.4	0	0	0	0
Infections and infestations	6	2.4	6	2.4	8	3.2	1	0.4	0	0.0	16	6.3	24	9.5	7	2.8	1	0.4	0	0
Injury/poisoning/procedural complications	1	0.4	0	0.0	1	0.4	0	0.0	0	0.0	1	0.4	1	0.4	0	0	0	0	0	0
Investigations	4	1.6	6	2.4	0	0.0	0	0.0	0	0.0	19	7.5	1	0.4	3	1.2	0	0	0	0
Metabolism and nutrition disorders	2	0.8	0	0.0	0	0.0	0	0.0	0	0.0	4	1.6	1	0.4	1	0.4	0	0	0	0
Musculoskeletal and connective tissue disorders	8	3.2	8	3.2	1	0.4	0	0.0	0	0.0	14	5.6	10	4	0	0	0	0	0	0
Nervous system disorders	11	4.4	8	3.2	0	0.0	0	0.0	0	0.0	23	9.1	18	7.1	5	2	0	0	0	0
Other (specify)	17	6.8	12	4.8	1	0.4	2	0.8	1*	0.4*	20	7.9	17	6.7	6	2.4	1	0.4	0	0
Psychiatric disorders	1	0.4	2	0.8	0	0.0	0	0.0	0	0.0	3	1.2	1	0.4	0	0	0	0	0	0
Renal and urinary disorders	1	0.4	1	0.4	0	0.0	0	0.0	0	0.0	1	0.4	1	0.4	0	0	0	0	0	0
Reproductive system and breast disorders	5	2.0	3	1.2	1	0.4	0	0.0	0	0.0	3	1.2	1	0.4	0	0	0	0	0	0
Respiratory/thoracic and mediastinal disorders	10	4.0	11	4.4	3	1.2	1	0.4	0	0.0	19	7.5	15	6	5	2	2	0.8	0	0
Skin and subcutaneous tissue disorders	7	2.8	4	1.6	1	0.4	1	0.4	0	0.0	26	10.3	14	5.6	1	0.4	0	0	0	0
Vascular disorders	4	1.6	9	3.6	0	0.0	0	0.0	0	0.0	5	2	11	4.4	1	0.4	0	0	0	0

- Neutropenia ≥G3 was 40.8% in Experimental Arm and 30.4% in the Comparator arm
- No cardiac toxicity excess (Experimental: G2: 0.8%, G3: 0.8%; Comparator: G2 0.4%, G3 0.4%)
- No high rates of respiratory toxicities (Experimental G2: 6%, G3: 2.4%, G4 0.4%; Comparator: G2: 4.4%, G3: 1.2%, G4 0.4%)

Response Endpoints required by AIFA



FIL ROUGE Trial: PROGRESSION FREE SURVIVAL ITT by ARM

Time	Survivor Function	Std. Error	[95% Conf.	Int.]
Comparator				
12	0.8261	0.0241	0.7728	0.8680
24	0.7548	0.0276	0.6957	0.8040
36	0.7323	0.0297	0.6689	0.7855
Experimental				
12	0.9193	0.0173	0.8777	0.9472
24	0.8823	0.0205	0.8350	0.9167
36	0.8669	0.0220	0.8168	0.9041

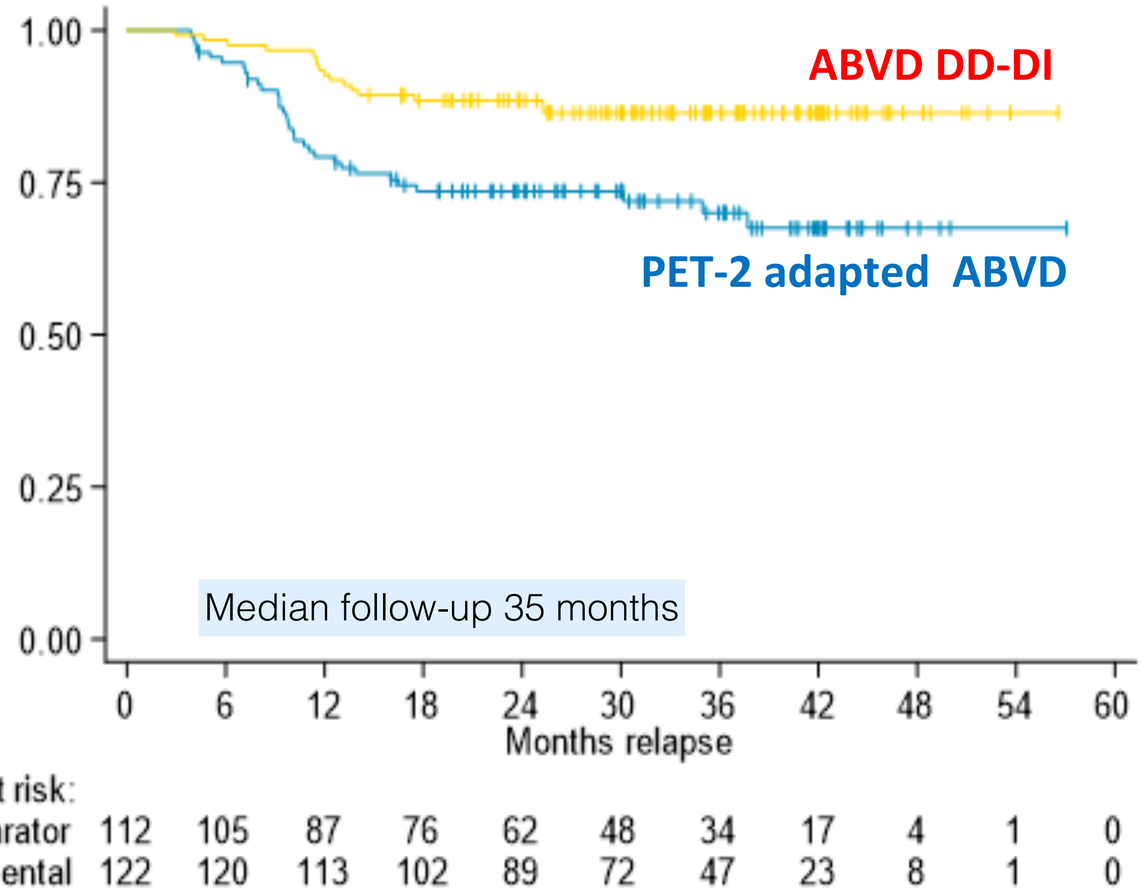
arm	Events observed	Events expected(*)
Comparator Arm	65	46.33
Experimental Arm	32	50.67
Total	97	97.00

chi2(1) = 14.91
Pr>chi2 = 0.0001

3y-PFS **Δ P1-P0= 13,46**

	HR*	95%CI	p
Experimental vs comparator	0.44	0.28,0.67	0.0002

*HR stratified by age, AA stage, Bulky, IPS, Planned intensification



FIL ROUGE Trial: PROGRESSION FREE SURVIVAL per Protocol by ARM

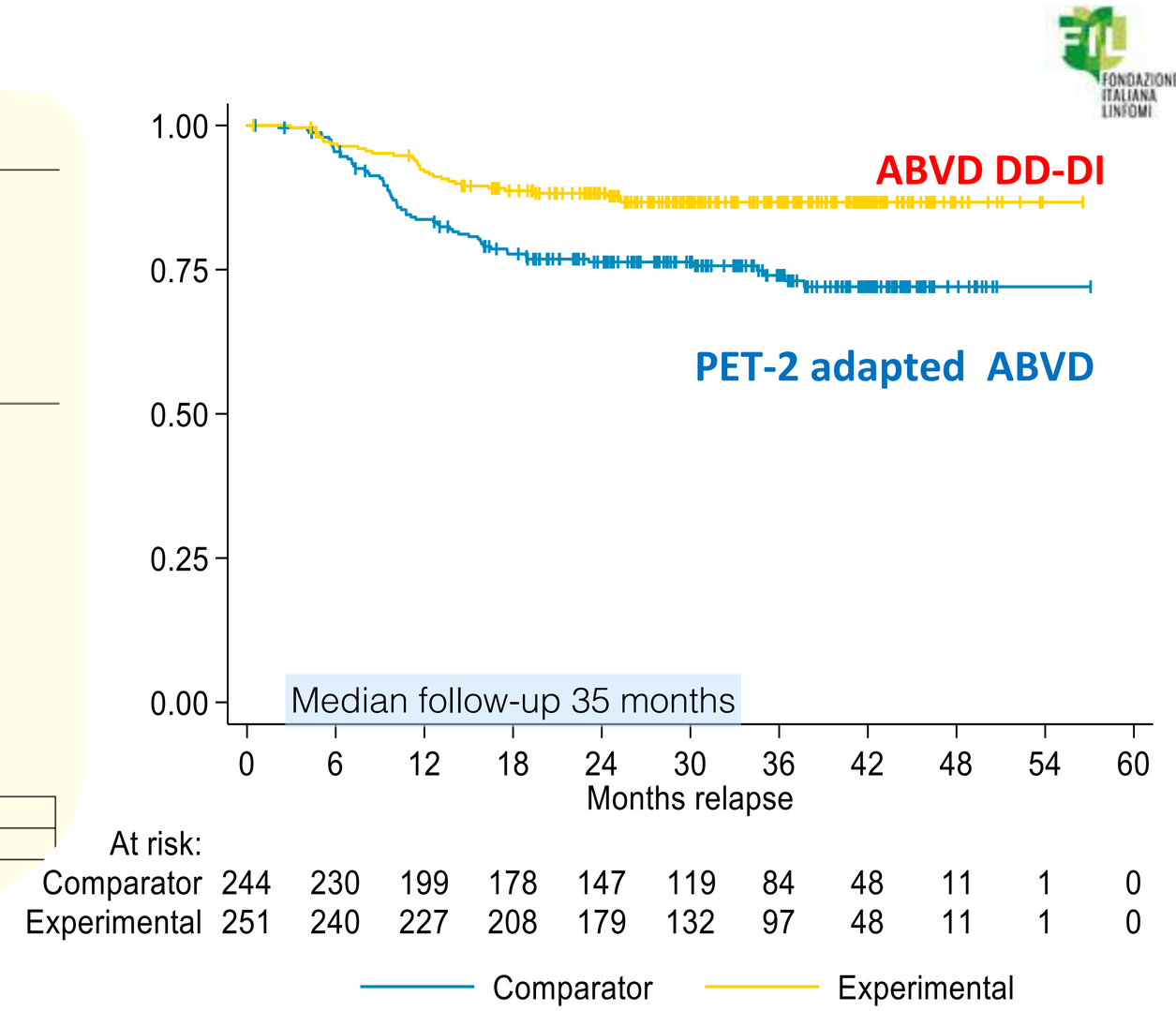
Time	Survivor Function	Std. Error	[95% Conf.	Int.]
Comparator				
12	0.8369	0.0239	0.7837	0.8781
24	0.7632	0.0277	0.7035	0.8125
36	0.7400	0.0300	0.6757	0.7934
Experimental				
12	0.9193	0.0173	0.8777	0.9472
24	0.8823	0.0205	0.8350	0.9167
36	0.8669	0.0220	0.8168	0.9041

arm	Events observed	Events expected(*)
Comparator Arm	61	43.49
Experimental Arm	32	49.51
Total	93	93.00

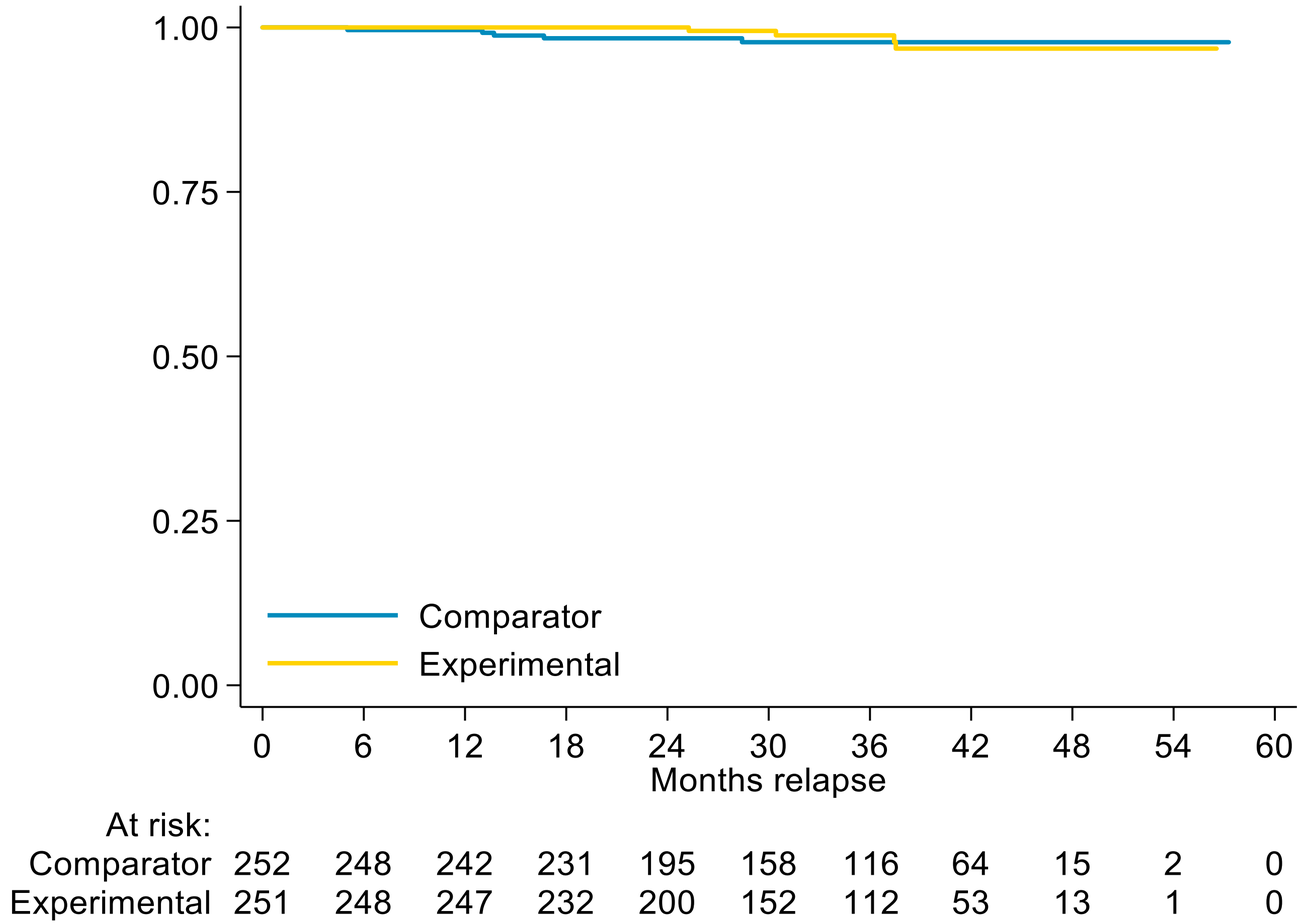
chi2(1) = 13.56
Pr>chi2 = 0.0002

	HR*	95%CI	p
Experimental vs comparator	0.45	0.29,0.70	0.0003

*HR stratified by age, AA stage, Bulky, IPS, Planned intensification



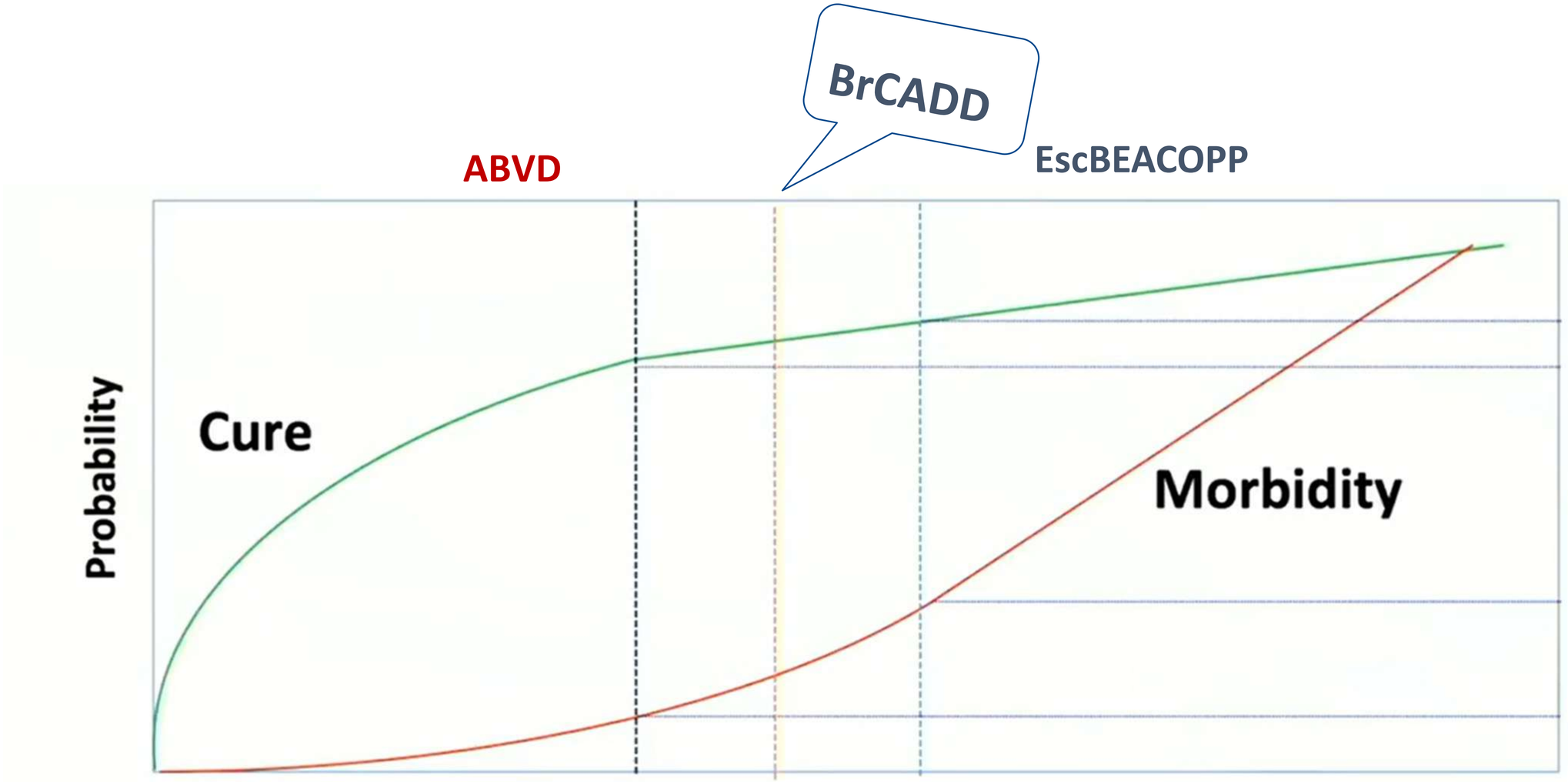
FIL Rouge trial: Overall Survival per Arm



Time	Survivor Function	Std. Error	[95% Conf.	Int.]
Comparator				
12	0.9960	0.0040	0.9718	0.9994
24	0.9834	0.0082	0.9564	0.9937
36	0.9775	0.0101	0.9462	0.9907
Experimental				
12	1.0000	.	.	.
24	1.0000	.	.	.
36	0.9879	0.0085	0.9521	0.9970

arm	Events observed	Events expected(*)
Comparator Arm	5	3.89
Experimental Arm	4	5.11
Total	9	9.00

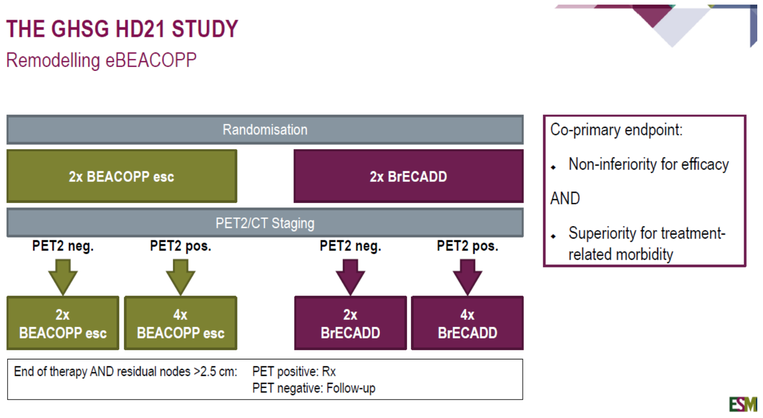
record_id	ARM	Death cause
41-16	Experimental Arm	Lymphoma
70-1	Experimental Arm	GVHD CNS post allogeneic transplant
73-3	Experimental Arm	COVID-19 infection at month +24
83-3	Experimental Arm	**Lymphoma**
89-9	Comparator Arm	Lymphoma
92-1	Comparator Arm	Lymphoma
159-3	Comparator Arm	Infection H1N1 positive
243-2	Comparator Arm	Lymphoma
71-8	Comparator Arm	Lymphoma



Johnson PWM (2017)
Moskowitz CH (2022)
[modified]

Brentuximab vedotin-containing escalated BEACOPP variants for newly diagnosed advanced-stage classical Hodgkin lymphoma: follow-up analysis of a randomized phase II study from the German Hodgkin Study Group

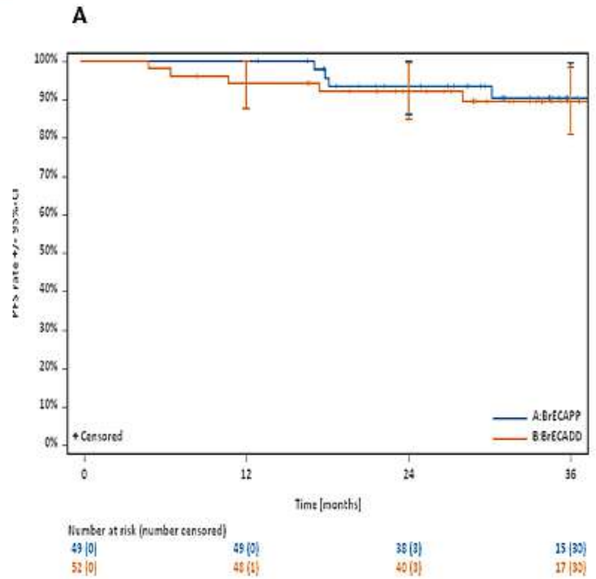
Carla Damaschin[1,2], Helen Goergen[1,2], Stefanie Kreissl[1,2], Annette Plütschow[1,2], Frank Breywisch[3], Stephan Mathas[4], Julia Meissner[5], Martin Sökler[6], Max S. Topp[7], Vladan Vucinic[8], Andreas Zimmermann[9], Bastian von Tresckow[2,10], Michael Fuchs[1,2], Andreas Engert[1,2], Peter Borchmann[1,2] and Dennis A. Eichenauer[1,2]✉

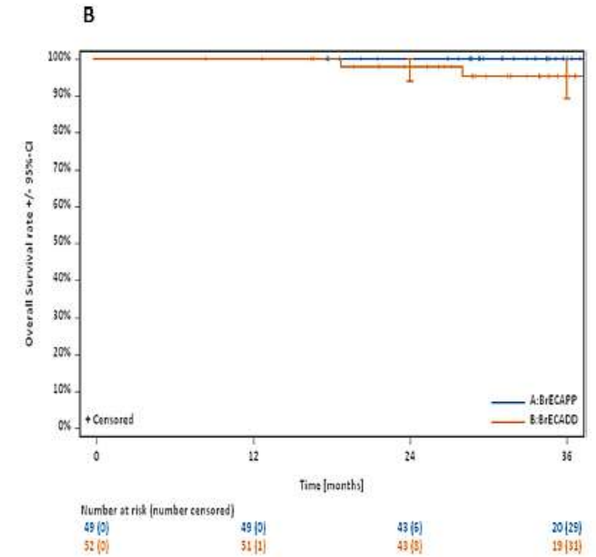


BrECADD regimen had been chosen to challenge eBEACOPP in the randomized GHSG HD21 study (NCT02661503) that recently finished recruitment for the cohort of patients aged 60 years or younger. Results of this trial are pending. Results were in part presented at the EHA 2021 Virtual Congress, June 9 to 17, 2021.

Table 1. Outcomes and events after BrECAPP and BrECADD treatment.

	6 × BrECAPP (*N* = 49)		6 × BrECADD (*N* = 52)	
Observation time				
Observation time for disease status, median	31 months		34 months	
Observation time for survival status, median	35 months		34 months	
3-year survival estimates				
Progression-free survival	90.2% (80.9–99.5%)		89.7% (81.0–98.3%)	
Overall survival	100%		95.4% (89.2–100%)	
Hodgkin lymphoma events[a]				
Any Hodgkin lymphoma event	4	(8%)	4	(8%)
Progression[b]	0		3	(6%)
Relapse[c]	4	(8%)	1	(2%)
Number of Hodgkin lymphoma events				
1	4	(8%)	2	(4%)
2	0		2	(4%)
Second-line treatment				
High-dose chemotherapy and autologous stem cell transplantation	4	(8%)	4	(8%)
Causes of death				
Any event	0		2	(4%)
Hodgkin lymphoma	0		1	(2%)
Accident	0		1	(2%)
Second primary malignancies				
Any event	0		0	

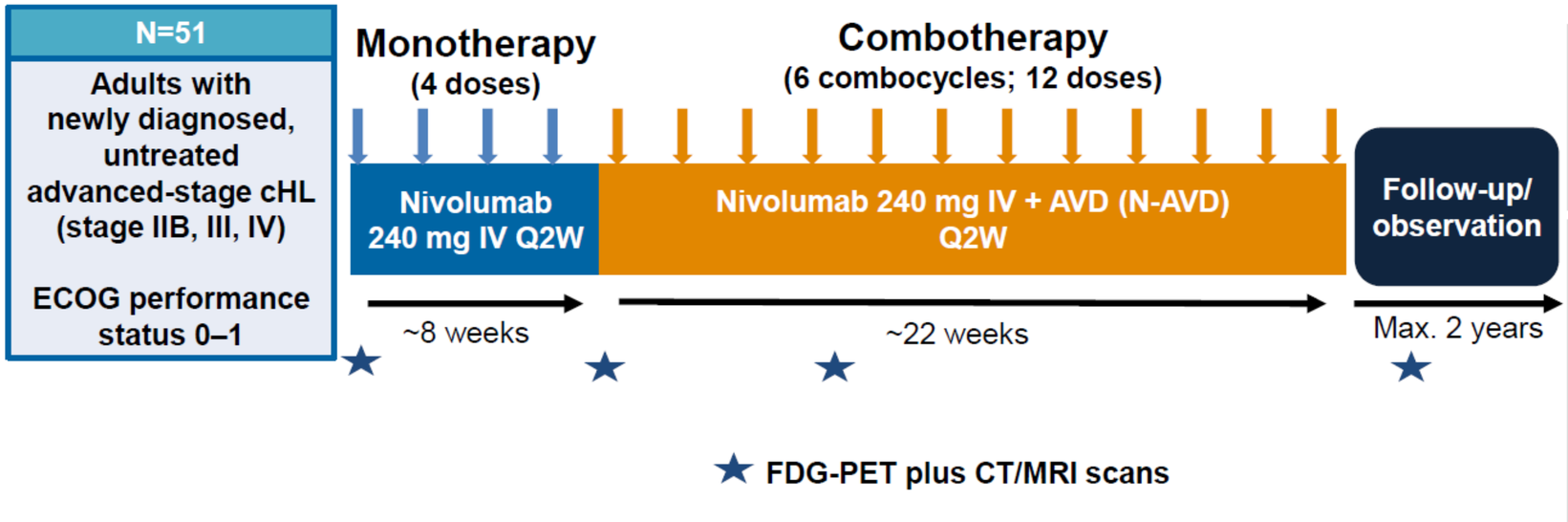




Leukemia; https://doi.org/10.1038/s41375-021-01386-z

Novel agents

Phase 2 CheckMate 205 Newly Diagnosed cHL Study Design



Primary endpoint

Safety and tolerability (G3–5 treatment-related AEs)

Additional endpoints

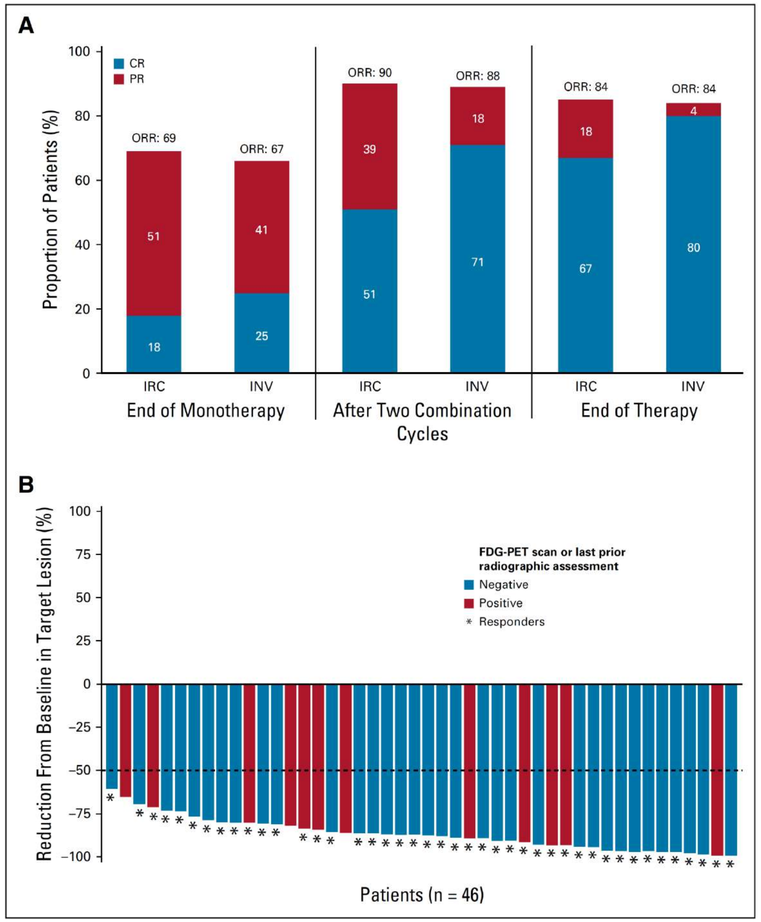
- Discontinuation rate
- CR and ORR by IRC
- CR and ORR by investigator
- mPFS
- OS

- **Responses were assessed using the IWG 2007 criteria**
- **Median duration of follow-up was 11.1 months (clinical cut-off 31 August 2017)**
- **Bleomycin was excluded due to potential overlapping pulmonary toxicity**

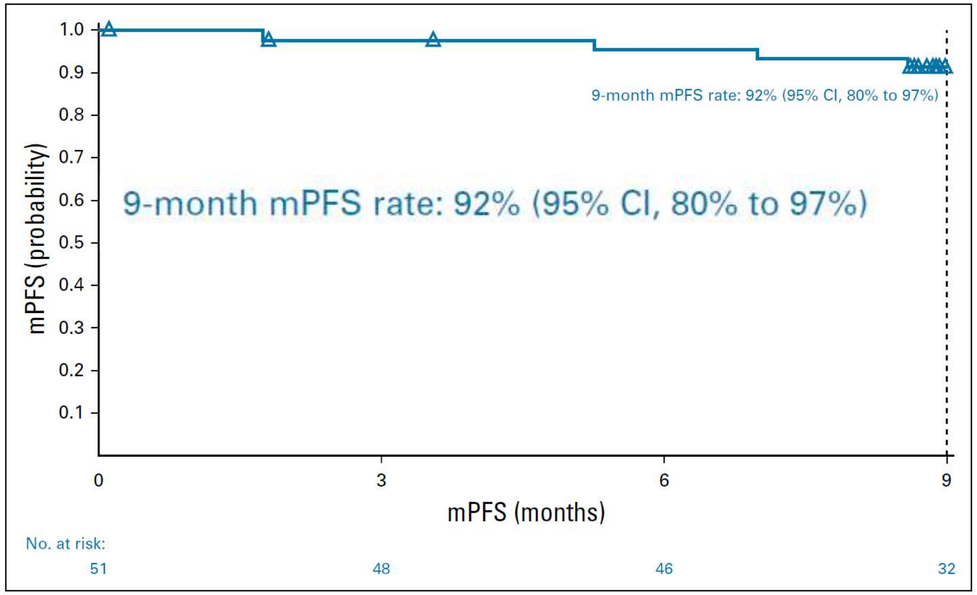
Novel agents

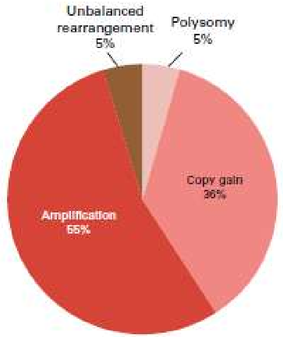
Nivolumab for Newly Diagnosed Advanced-Stage Classic Hodgkin Lymphoma: Safety and Efficacy in the Phase II CheckMate 205 Study

Radhakrishnan Ramchandren, MD[1,2]; Eva Domingo-Domènech, MD[3]; Antonio Rueda, MD, PhD[4]; Marek Trněný, MD[5]; Tatyana A. Feldman, MD[6]; Hun Ju Lee, MD[7]; Mariano Provencio, MD, PhD[8]; Christian Sillaber, MD[9]; Jonathon B. Cohen, MD, MS[10]; Kerry J. Savage, MD[11]; Wolfgang Willenbacher, MD[12,13]; Azra H. Ligon, PhD[14]; Jing Ouyang, PhD[15]; Robert Redd, MD[15]; Scott J. Rodig, MD[14,15]; Margaret A. Shipp, MD[15]; Mariana Sacchi, MD[16]; Anne Sumbul, MS[16]; Philippe Armand, MD, PhD[15]; and Stephen M. Ansell, MD, PhD[17]



- 51 advanced stage patients
- At the end of therapy, the ORR was 84%, with 67%, achieving complete remission.
- With a minimum follow-up of 9.4 months, 9-month modified progression-free survival was 92%.
- Patients with higher-level Hodgkin Reed-Sternberg programmed death-ligand 1 expression had more favorable responses to N-AVD





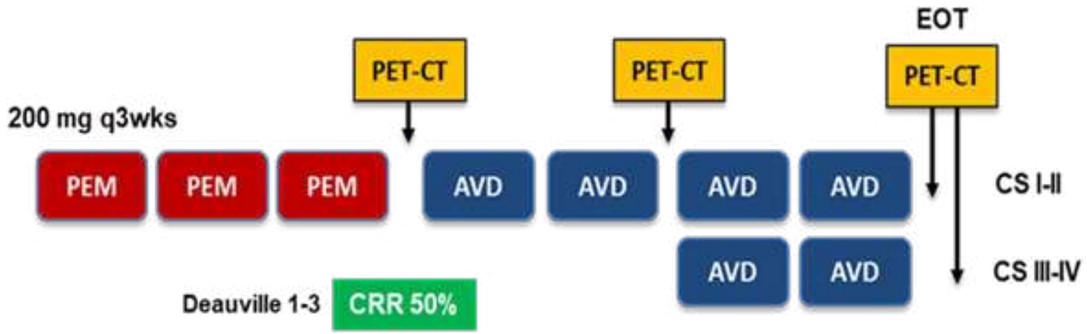
J Clin Oncol 37:1997-2007. © 2019

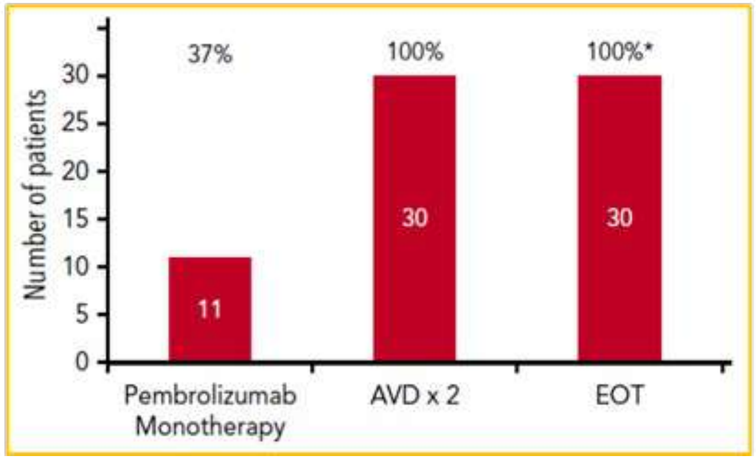
Novel agents

blood Regular Article

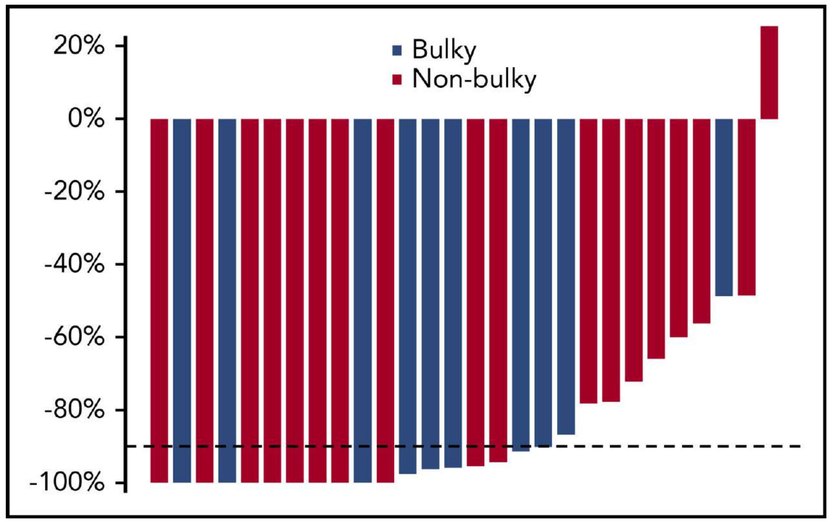
Pembrolizumab followed by AVD in untreated early unfavorable and advanced-stage classical Hodgkin lymphoma

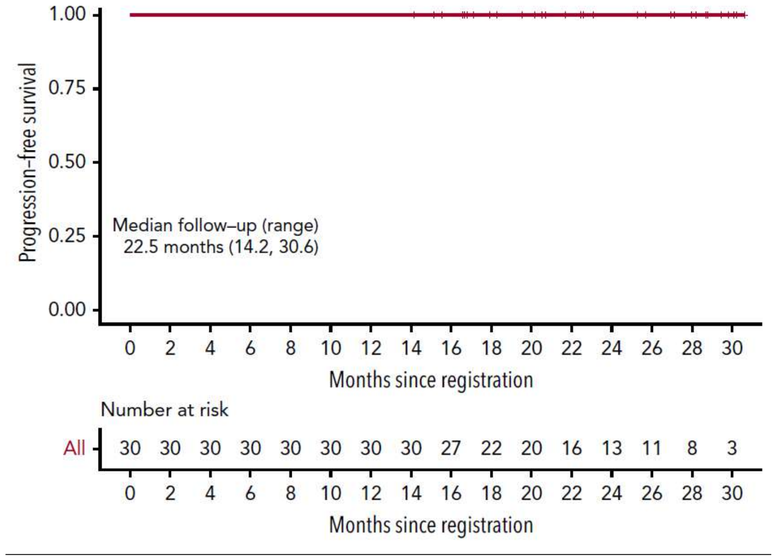
Pamela B. Allen,[1] Hatice Savas,[2,3] Andrew M. Evens,[4] Ranjana H. Advani,[5] Brett Palmer,[3] Barbara Pro,[3] Reem Karmali,[3] Eric Mou,[5] Jeffrey Bearden,[3] Gary Dillehay,[2,3] Robert A. Bayer,[3] Robert M. Eisner,[3] Joan S. Chmiel,[3,6] Kaitlyn O'Shea,[3,6] Leo I. Gordon,[3] and Jane N. Winter[3]





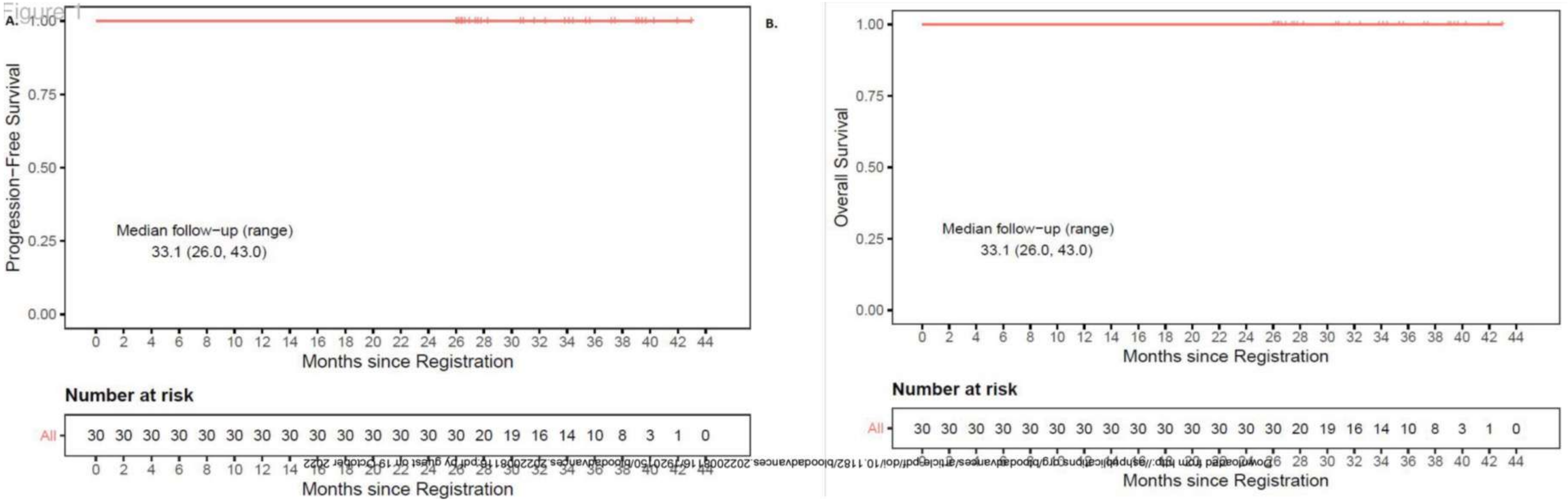
Characteristic	Patients (N = 30) n	%
Median age, y (range)	29 (21-77)	
Age 45-60	4	13.3
Age >60	4 (67-77)	13.3
Sex		
Male	11	36.7
Female	19	63.3
Disease stage		
IIA	6	20.0
IIB	6	20.0
IIB with >10 cm mass	5	16.7
IIIA	4	13.3
IIIB	1	3.3
IVA	6	20.0
IVB	7	23.3
IPS Score*		
0-1	4	13.3
2	6	20.0
3	6	20.0
≥4	2	6.7
ESR >50†	6	50
B symptoms	14	46.7
Extranodal disease	16	53.3
Bone‡	14	46.7
Lung‡	3	10.0
Bulky		
>7 cm†	11	91.7
>10 cm	10	33.3
MMR >1/3	9	30.0
>10 cm or MMR >1/3	12	40.0





Allen PB, et al,Blood 2021; 137(10):1318-1326

Long term Follow up



100% of patients remain alive without relapse following sequential pembrolizumab and AVD after nearly 3 years of follow up

Novel agents

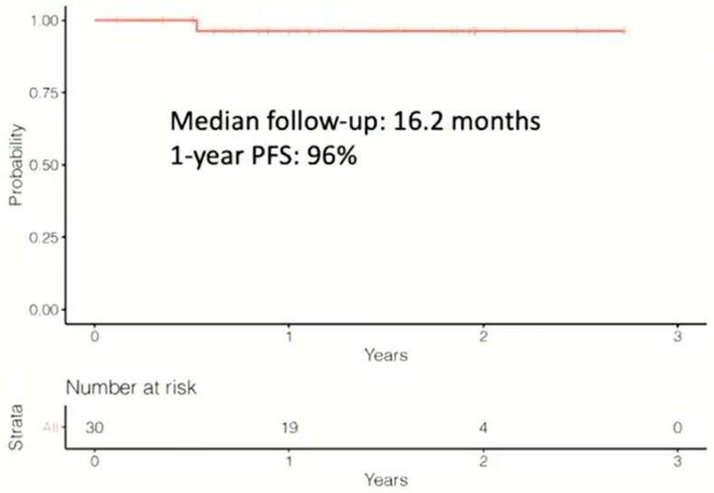
Blood 138 (2021) 233–235

Concurrent Pembrolizumab with AVD for Untreated Classical Hodgkin Lymphoma

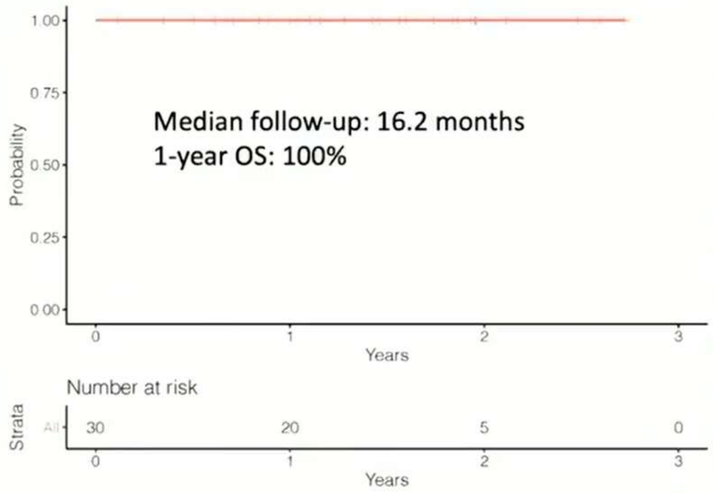
Ryan C. Lynch[1], Chaitra S. Ujjani[1], Christina Poh[2], Edus H. Warren[3], Stephen D. Smith[2], Mazyar Shadman[4], Andrei R Shustov[5], Brian G. Till[3], Yolanda D. Tseng[6], Hilary Coye[7], Megan Shelby[7], Susan Ottemiller[7], Hongyan Du[5], Jacquelin Vandermeer[8], Heather A. Rasmussen[1], Stefan Alig[9], Ash A. Alizadeh[9], Avanti Gulhane[10], Delphine Chen[10], Eric Wayne Dean[7], Jason Lukas[7], Paul S. Martin[7], Edmond A Marzbani[5], Jenna Voutsinas[11], Ajay K Gopal[12]

Long-term follow-up

Progression-free survival



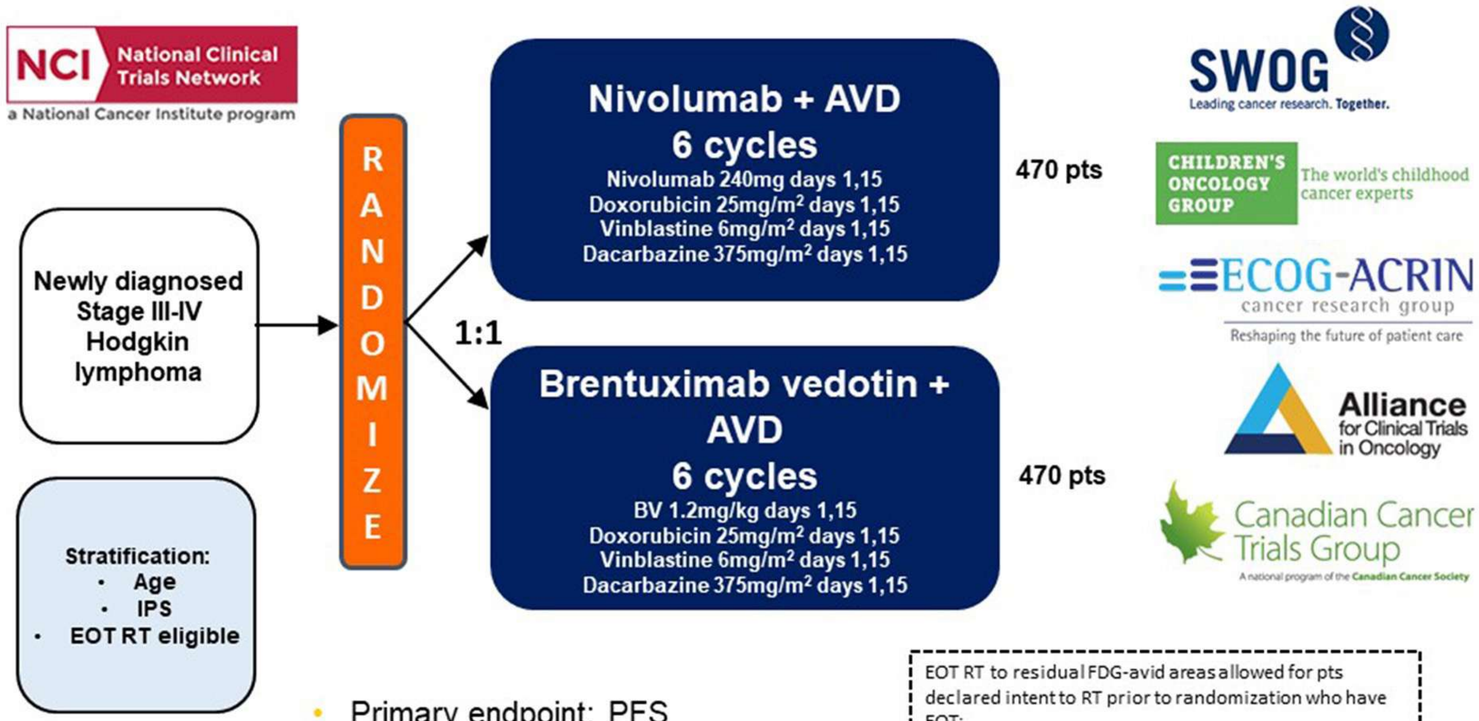
Overall survival



To date, no patients who interrupted or discontinued therapy due to an adverse event has progressed

Novel agents

S1826: A Phase III Randomized Trial of Nivolumab (Opdivo) or Brentuximab Vedotin (Adcetris) Plus AVD in Patients (Age ≥ 12 Years) With Newly Diagnosed Advanced Stage Classical Hodgkin Lymphoma



- Primary endpoint: PFS
- Secondary endpoints: EFS, OS, CR

EOT RT to residual FDG-avid areas allowed for pts declared intent to RT prior to randomization who have EOT:

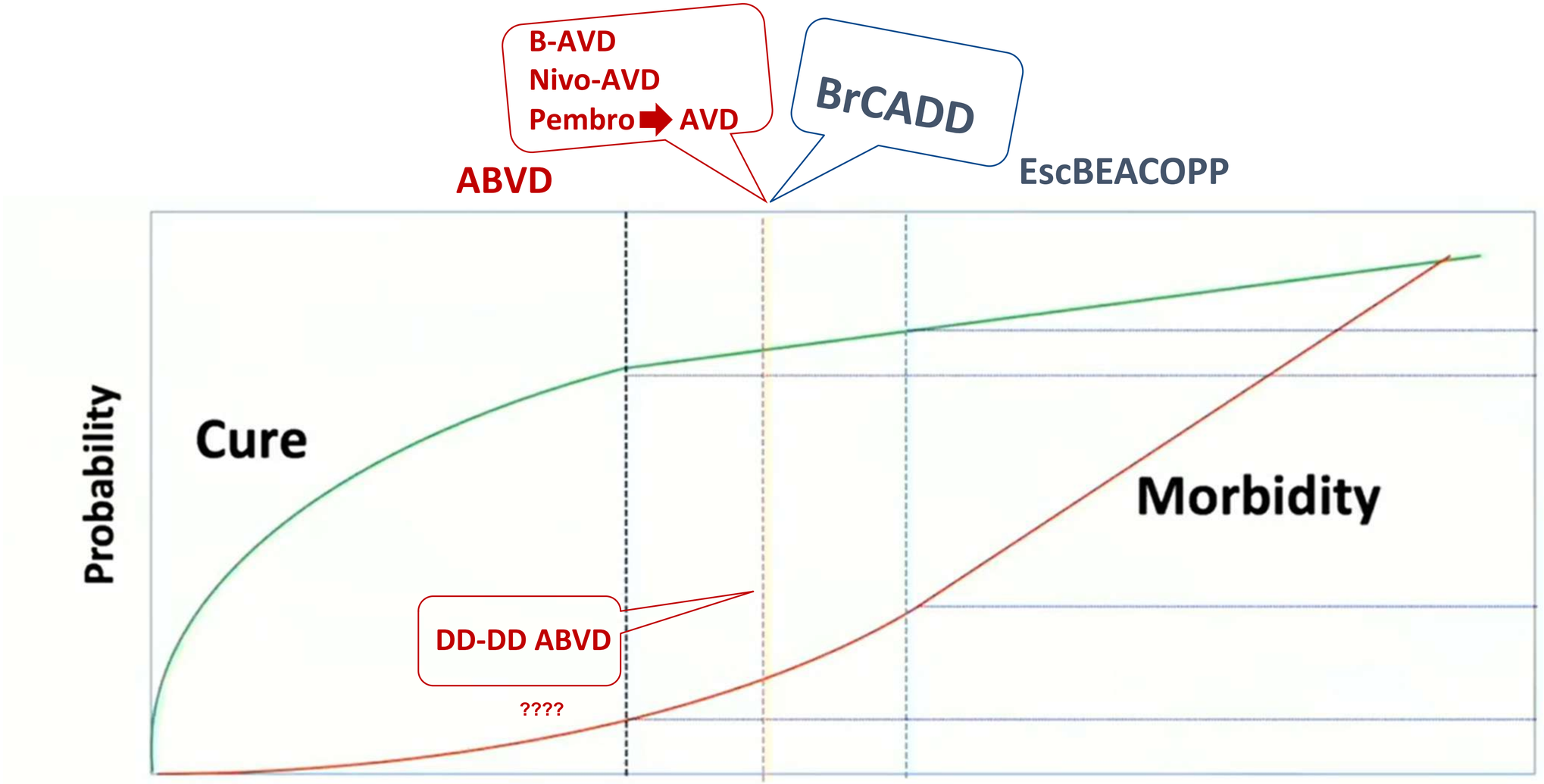
- DS 4-5
- ≥ 30% reduction in max transverse diameter

AND

- Residual LN ≥ 2.5cm

OR

- Residual extranodal lesion > 1cm



Johnson PWM (2017)
Moskowitz CH (2022)
[modified]

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• GIVE THANKS

A. Pinto
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Lymphoma Unit
G. Pascale

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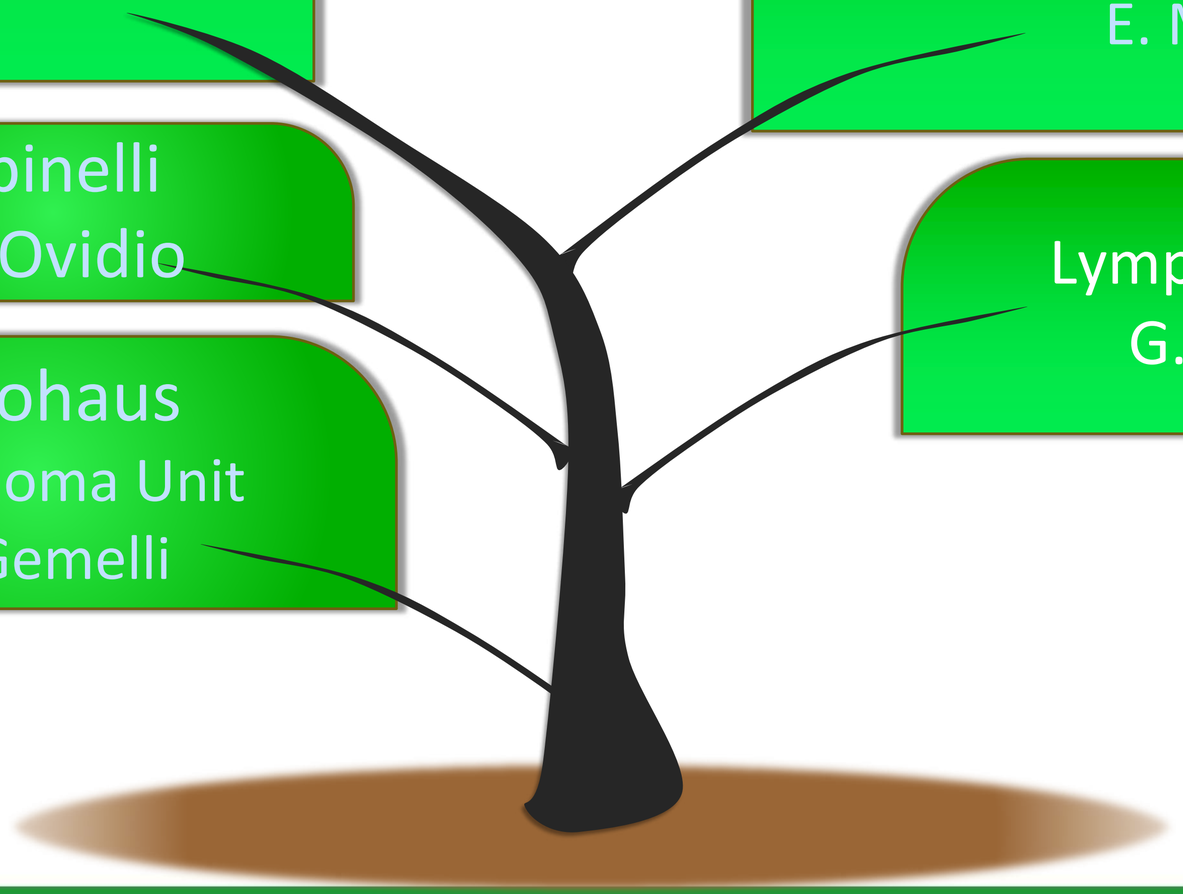
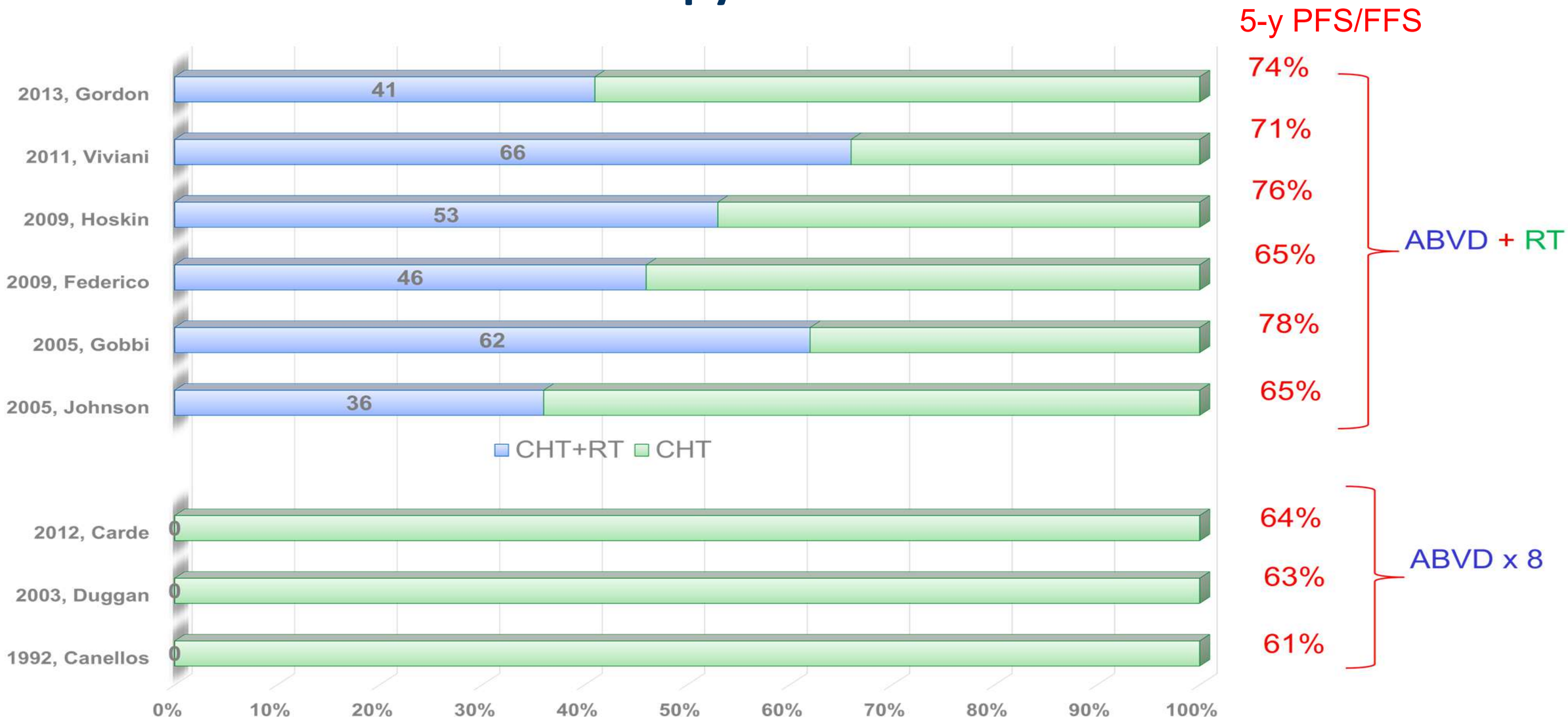
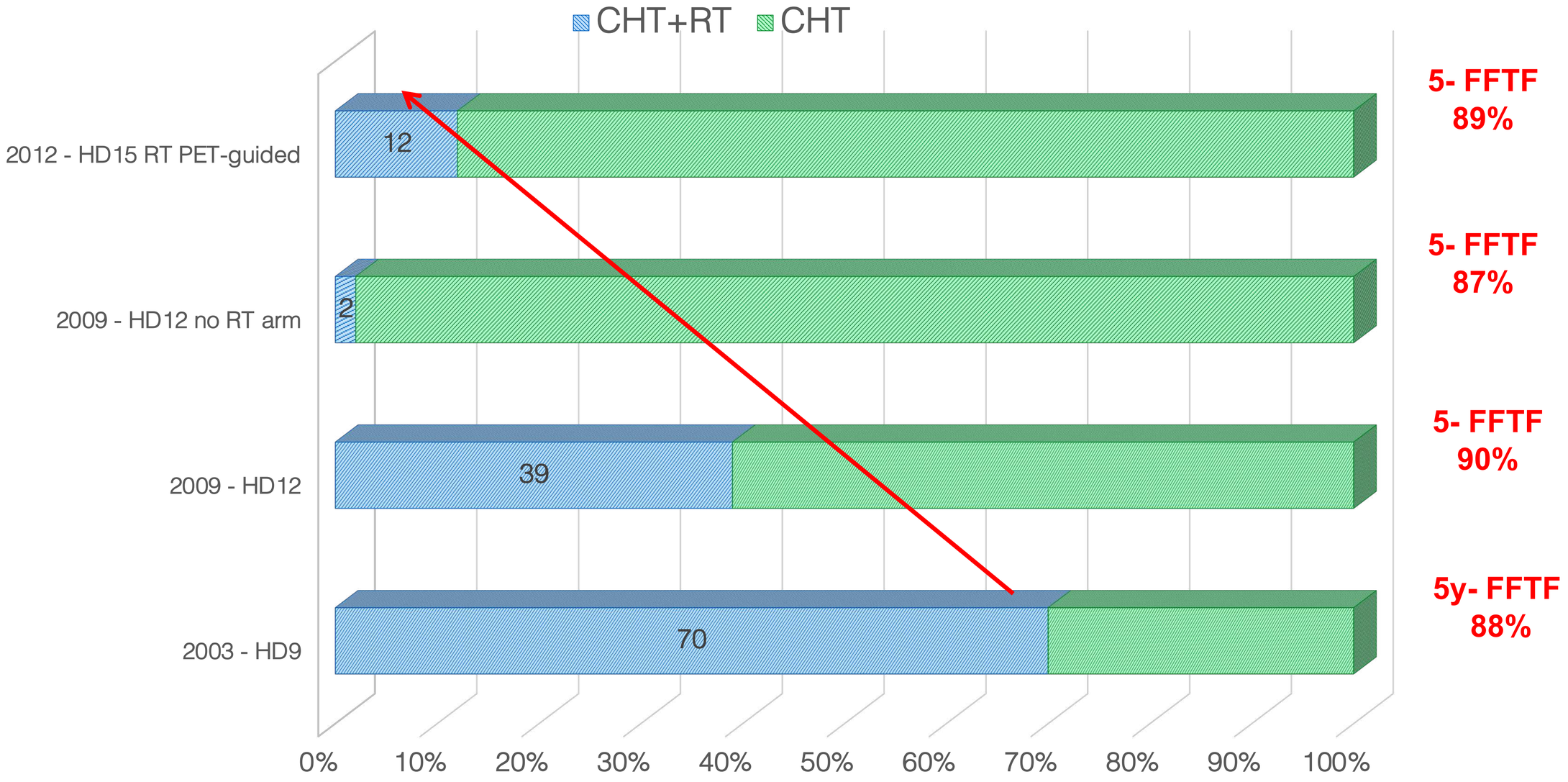
Lymphoma Unit
A. Gemelli



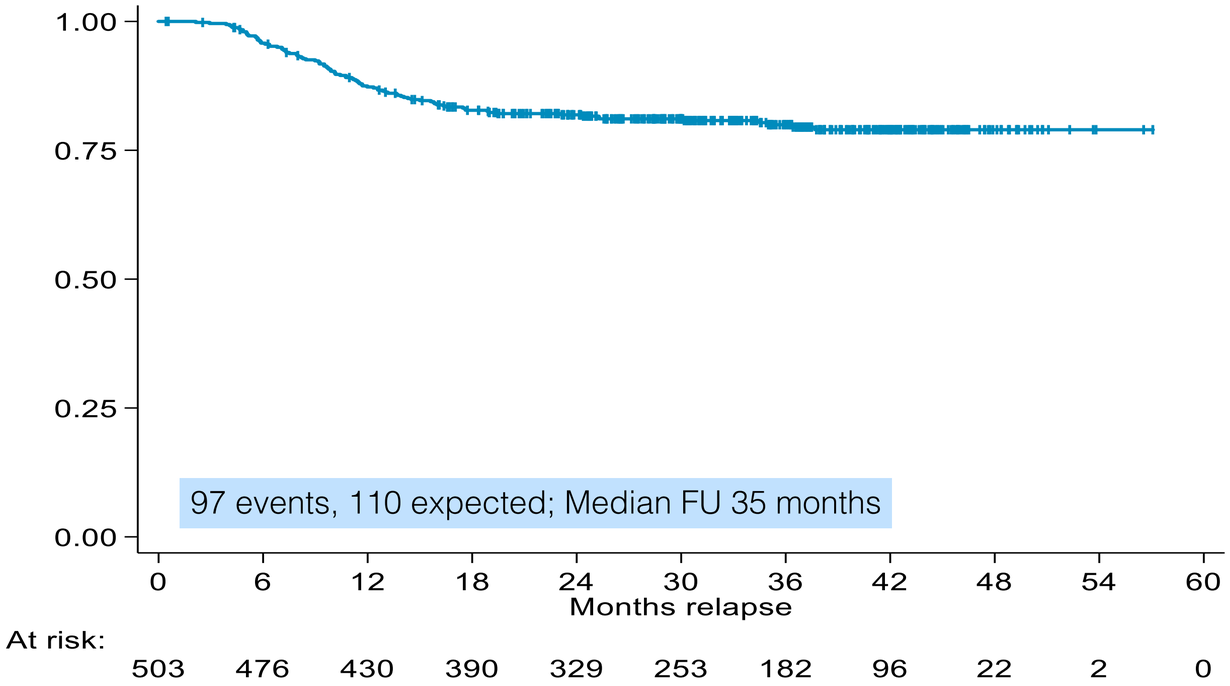
Evolution of Radiotherapy within the ABVD trials



Evolution of Radiotherapy within the BEACOPP GHSG trials

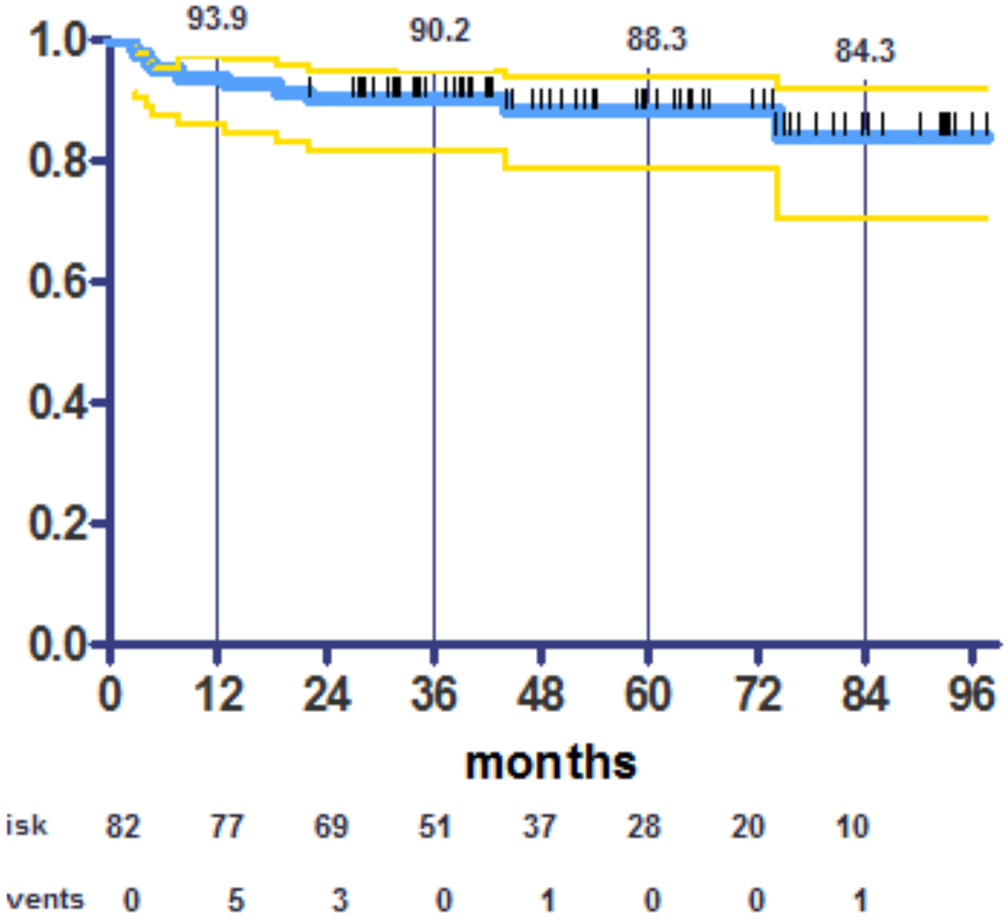


FIL Rouge trial: Overall PFS

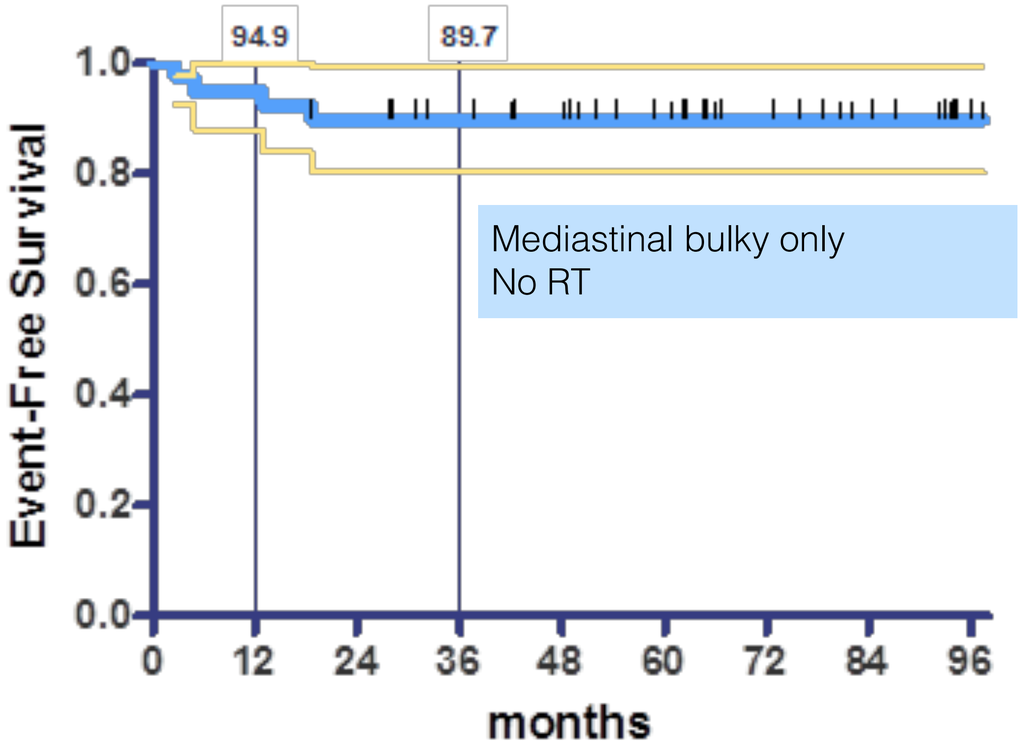


Time	Survivor Function	Std. Error	[95% Conf.	Int.]
12	0.8728	0.0150	0.8402	0.8992
24	0.8188	0.0174	0.7817	0.8501
36	0.7996	0.0187	0.7599	0.8335

ABVD DD-DI Phase 2 confirmed !



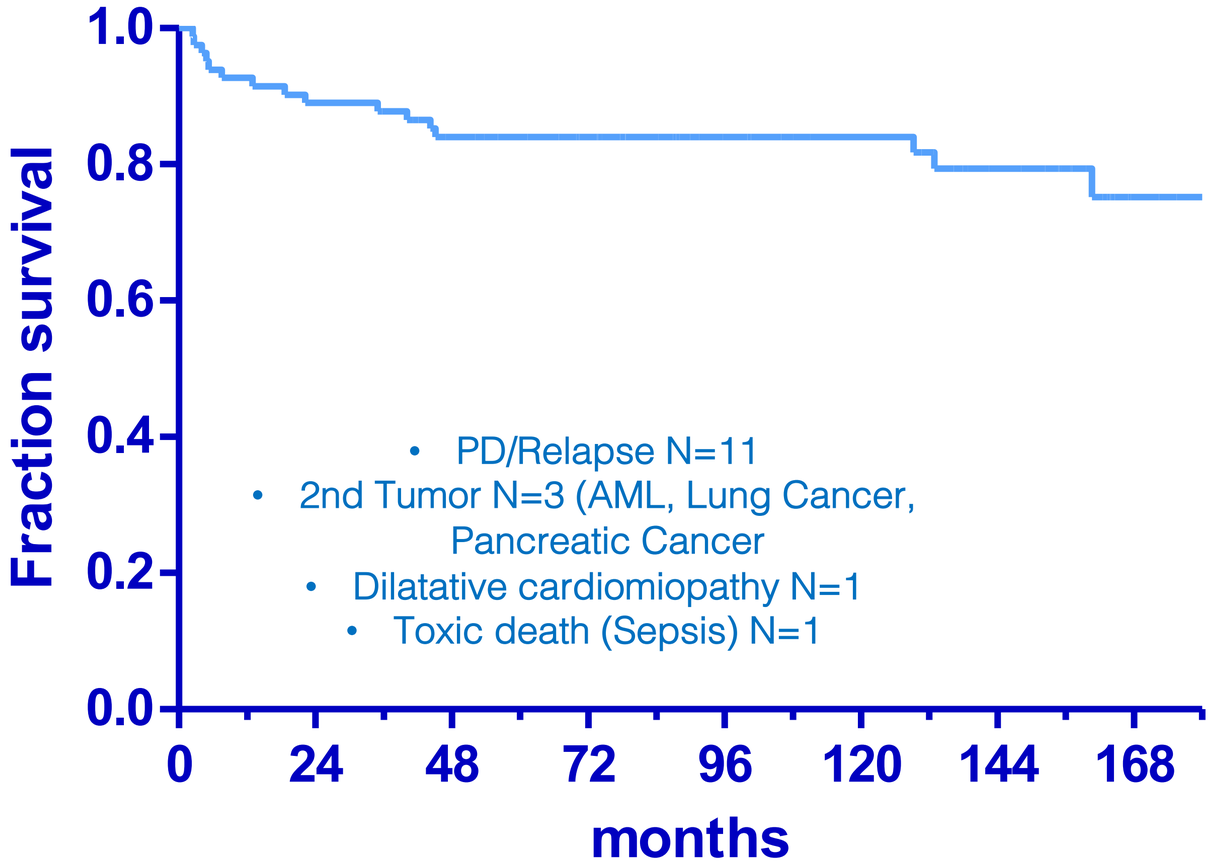
Br J Haem 2014, 166, 118-129



Journal of Clinical Oncology, 30, 2012 (suppl; Abstr 8066)

ABVD DD-DI Phase 2 update

Long-term Event Free Survival
(median Follow-up: 139 months)



ABVD DD-DI Phase 2 update !