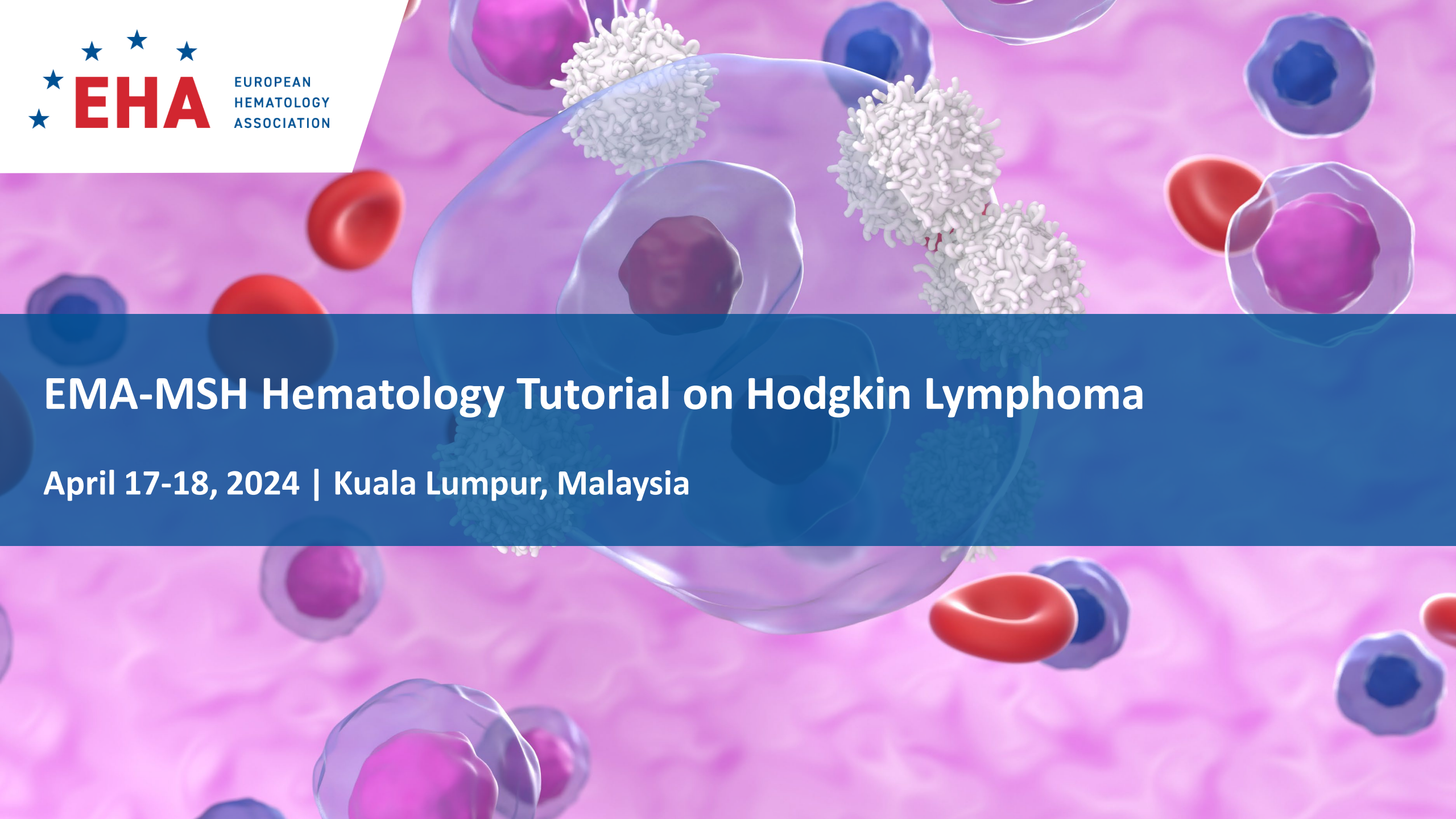


EUROPEAN HEMATOLOGY ASSOCIATION

EMA-MSH Hematology Tutorial on Hodgkin Lymphoma

April 17-18, 2024 | Kuala Lumpur, Malaysia

Evolving therapeutic landscape in newly diagnosed Hodgkin lymphoma: current and future approaches

Anna Czyz
Department of Hematology and Bone Marrow Transplantation
Wroclaw Medical University, Poland

UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Sf(PM)

Disclosures

Takeda

- Presenter has received lecture fees, honorarium as an advisory board member, travel grants

BMS

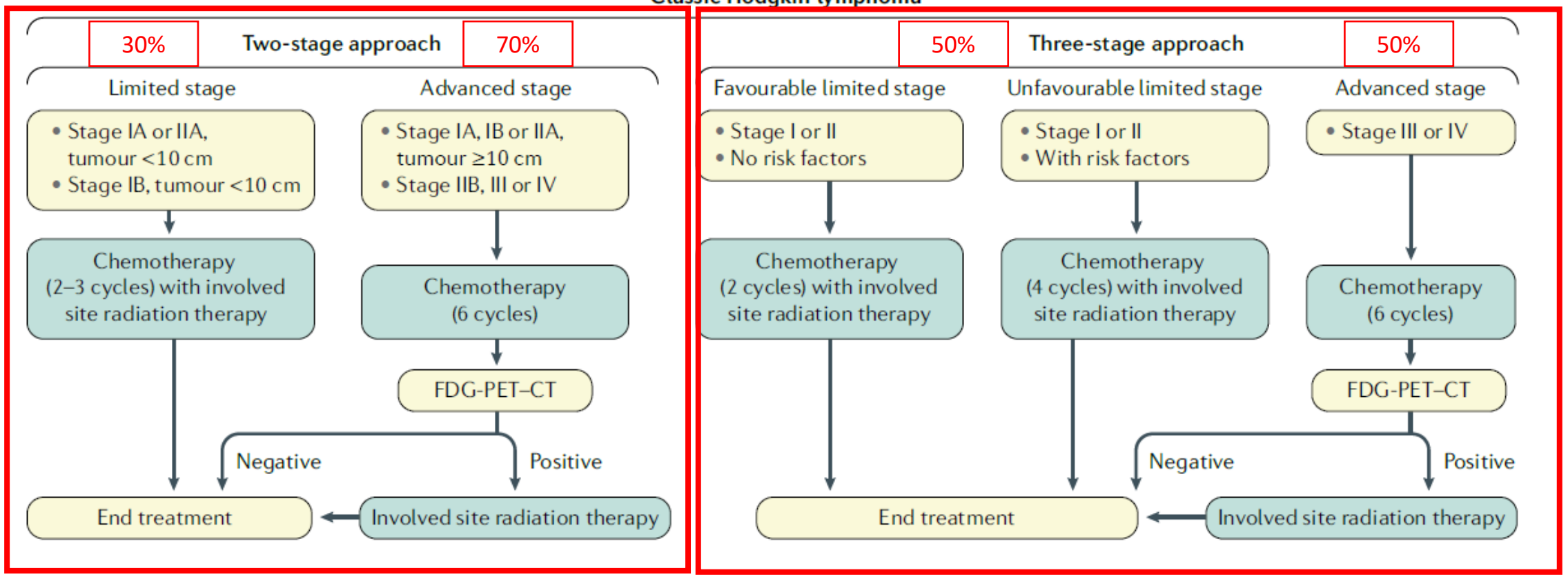
- Presenter has received lecture fees, travel grants

Epidemiology

- The overall incidence of ~2–3 per 100,000 individuals
- The global annual incidence of HL: app. 100,000 cases
- >1 million individuals worldwide cured of HL in the last 50 yrs
- The overall goal of treatment: to cure the disease while exposing the patient to the least acute or long-term toxicity
- Factors taken into consideration in treatment planning
  - the subtype of HL (cHL vs NLPHL)
  - the stage of the disease and risk factors
  - the patient's age and comorbidities

National Cancer Institute Surveillance Epidemiology and End Results Program. Cancer stat facts: HL SEER https://seer.cancer.gov/statfacts/ html/hodg.html (2019)
Connors JM Nature 2020

Management algorithm for HL



Connors JM Nature 2020

Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification

Table 2. Revised Staging System for Primary Nodal Lymphomas

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

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

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

Modification compared to Ann Arbor staging

- PET-CT should be recommended for routine staging of FDG-avid, nodal lymphomas
- Tumor bulk
  - the recommendation for HL is to record the longest measurement by CT scan, with the term X no longer necessary
- If PET-CT is performed, a bone marrow aspirate/biopsy is no longer required for the routine evaluation of patients with HL

Cheson BD et al. JCO 2014

Limited stage HL according to the EORTC/LYSA and the GHSG

	EORTC/LYSA	GHSG
Clinical stage	CS I-II without risk factors (supradiaphragmatic)	CS I and II without risk factors
Risk factors	A. Large mediastinal mass (MT ratio ≥ 0,35) B. age ≥50 years C. ESR ≥50mm/h w/o B symptoms D. ESR ≥30mm/h with B symptoms E. ≥4 nodal areas	A. Large mediastinal masss (MT ratio ≥ 0.35) B. Extranodal disease C. ESR ≥50mm/h w/o B symptoms ESR ≥30mm/h with B symptoms D. ≥3 nodal areas

Intermediate stage HL according to the EORTC/LYSA and the GHSG

	EORTC/LYSA	GHSG
Clinical stage	CS I-II with ≥ 1 risk factors (supradiaphragmatic)	CS I and IIA with ≥ 1 risk factors CS IIB with risk factors C and/or D, but not A/B
Risk factors	A. Large mediastinal mass (MT ratio ≥ 0,35) B. age ≥50 years C. ESR ≥50mm/h w/o B symptoms D. ESR ≥30mm/h with B symptoms E. ≥4 nodal areas	A. Large mediastinal masss (MT ratio ≥ 0.35) B. Extranodal disease C. ESR ≥50mm/h w/o B symptoms ESR ≥30mm/h with B symptoms D. ≥3 nodal areas

Advanced stages HL according to the EORTC/LYSA and the GHSG

	EORTC/LYSA	GHSG
Clinical stage	CS III-IV	CS IIB with RF A or B CS III-IV
Risk factors		A. Large mediastinal mass (MT ratio ≥ 0,35) B. Extranodal disease

www.esmo.org

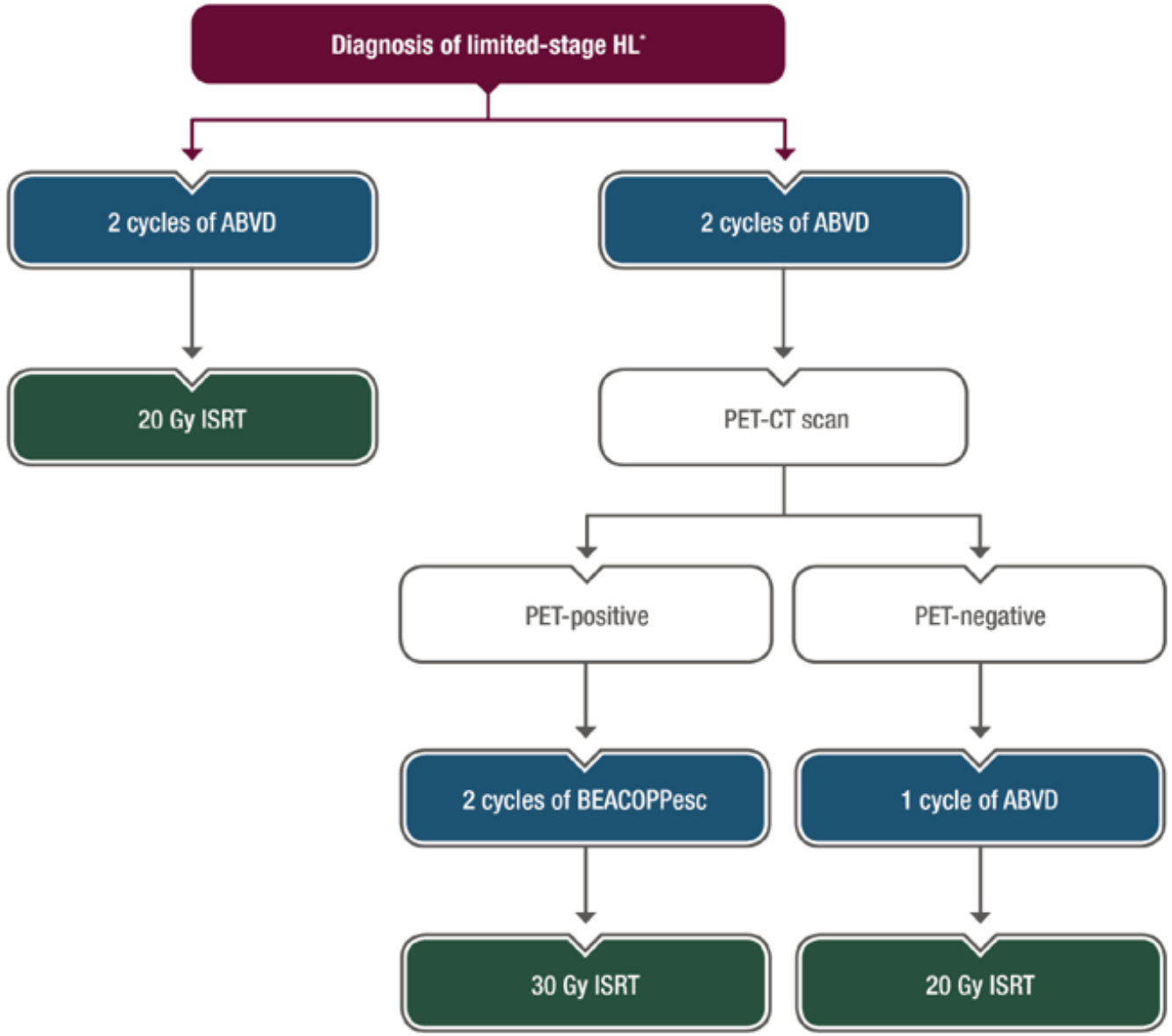
CLINICAL PRACTICE GUIDELINES

Diagnosis & treatment of limited-stage HL

Newly diagnosed patients ≤ 60 years

*Except for stage IA NLPHL without risk factors (treated with ISRT alone)

The figure includes one approach not guided by interim PET, based on the GHSG HD10 study (left) and one PET-guided approach based on the EORTC/LYSA/FIL H10 study (right)



ESMO

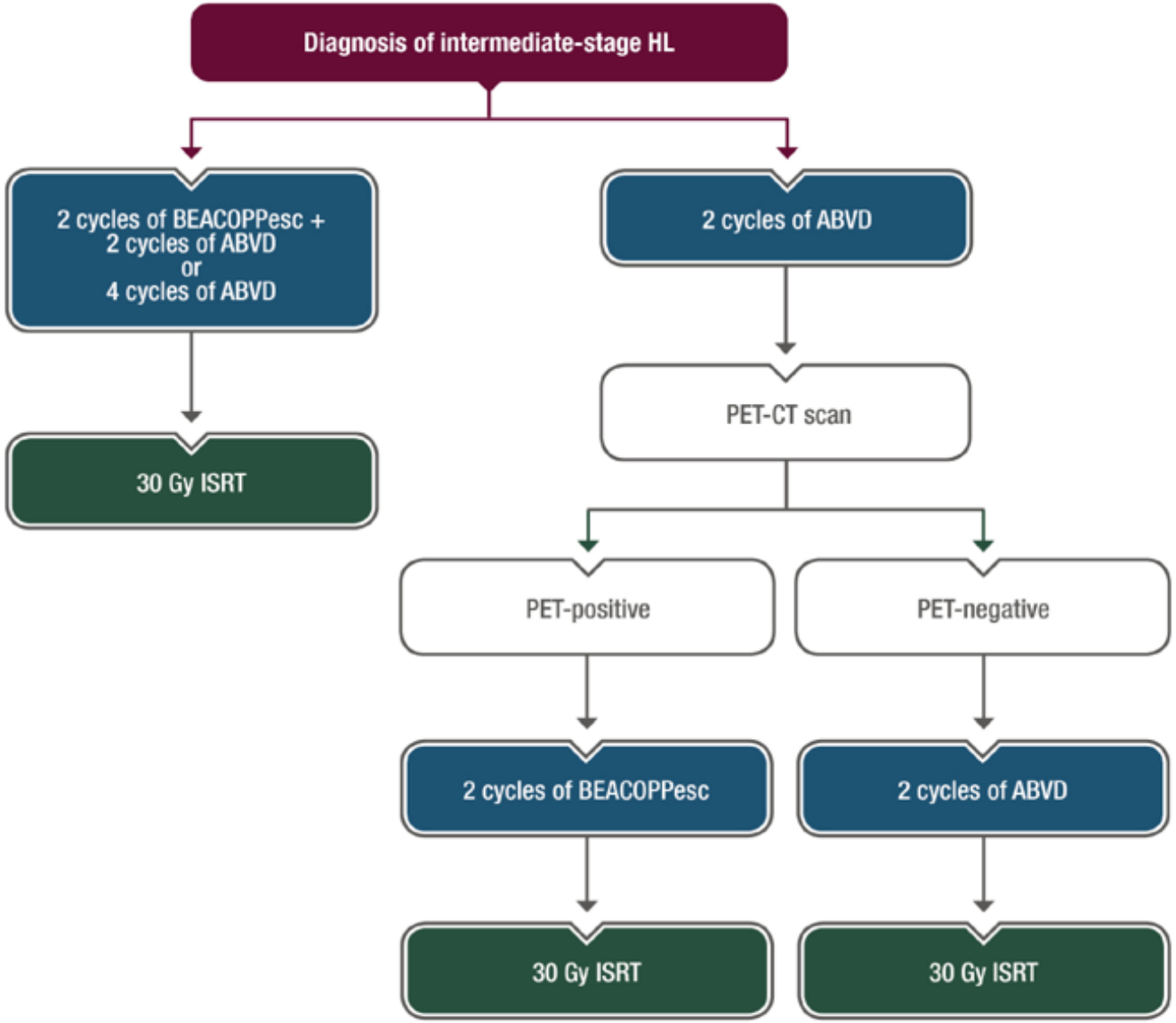
CLINICAL PRACTICE GUIDELINES

Diagnosis & treatment of intermediate-stage HL

Newly diagnosed patients ≤ 60 years

The figure includes one approach not guided by interim PET, based on the GHSG HD14 study (left) and one PET-guided approach based on the EORTC/LYSA/FIL H10 study (right)

In patients > 60 years, bleomycin should be discontinued after the second ChT cycle



ESMO

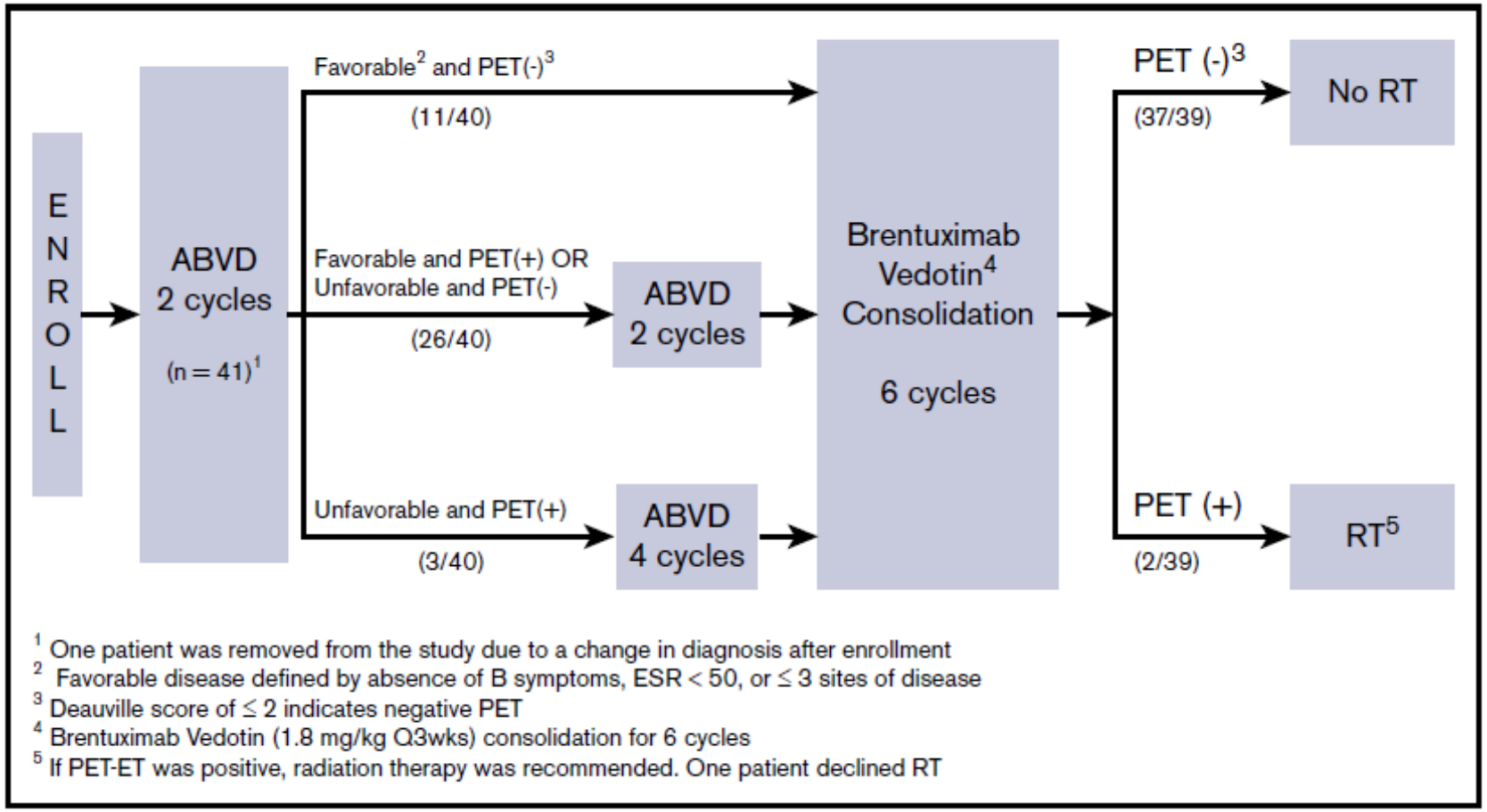
Novel treatment strategies for limited stage HL

- The new strategies aim to reduce the exposure to conventional cytotoxic chemotherapy and radiation therapy while retaining a high probability of cure
  - the stratification of patients based on initial response and subsequent iPET-guided therapy
  - incorporating novel agents into first line treatment
    - brentuximab vedotin (BV)
    - nivolumab (Niv)
  - the removal of consolidative radiotherapy

Incorporatin novel agents into first line treatment of limited-stage cHL

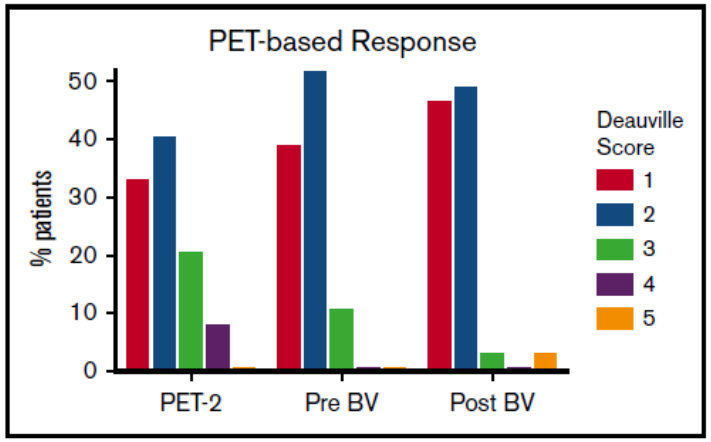
- Brentuximab vedotin
- Nivolumab

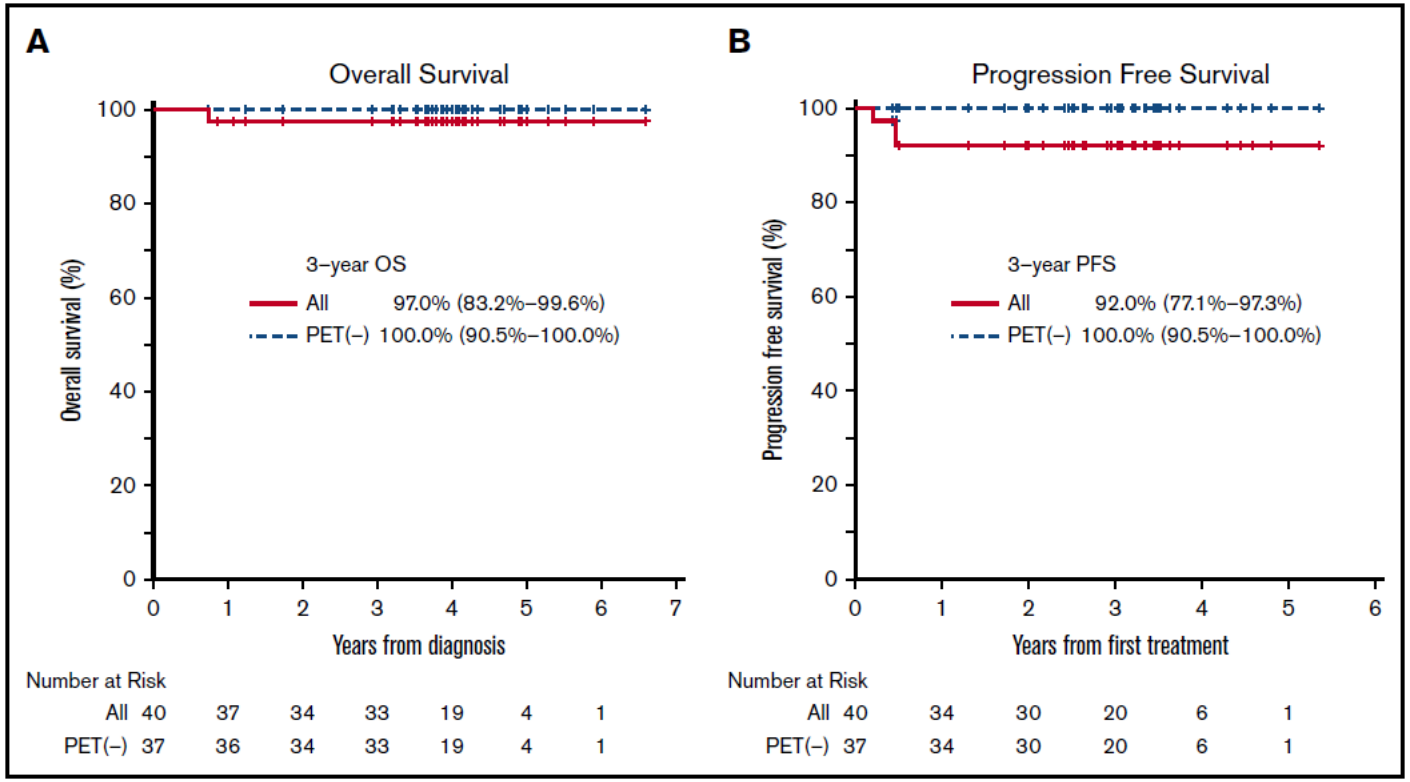
ABVD followed by BV consolidation in risk-stratified patients with limited-stage HL



Park SI Blood Adv 2020

ABVD followed by BV consolidation in risk-stratified patients with limited-stage HL





Park SI Blood Adv 2020

Nivolumab and AVD in early-stage unfavorable HL: The GHSG Phase II NIVAHL Trial

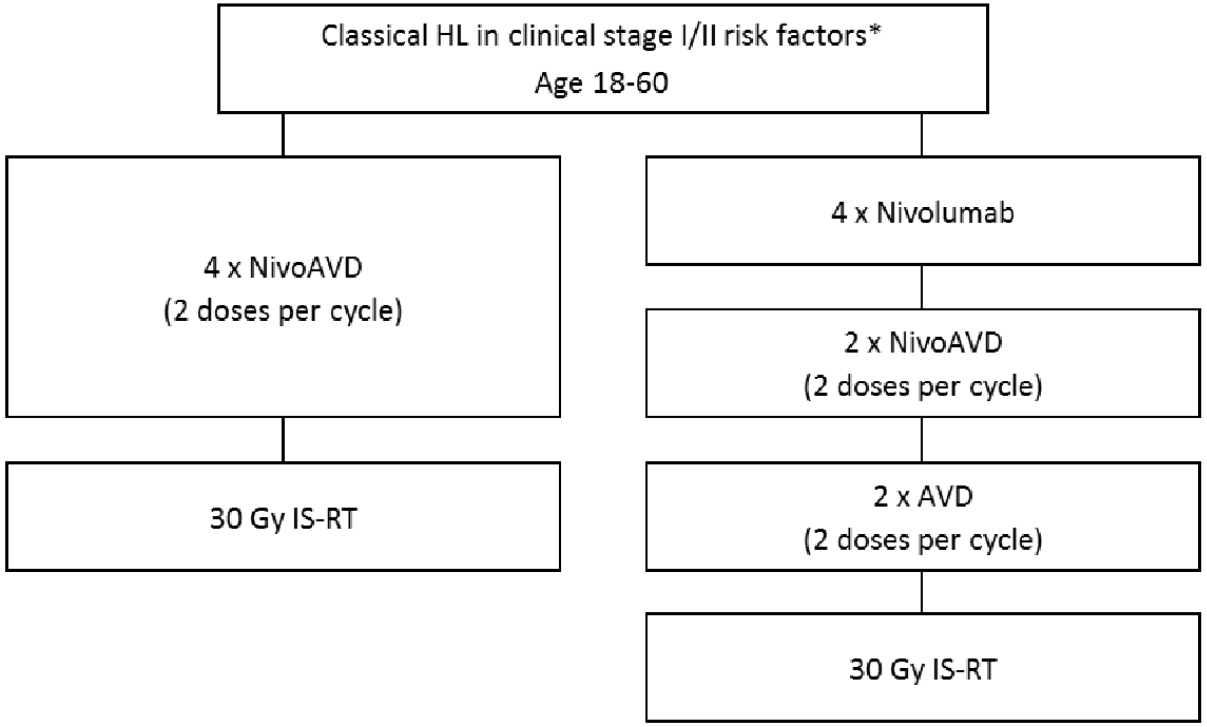
Primary objective

- To evaluate safety and efficacy of nivolumab- and AVD-based first-line treatment of early-stage unfavorable HL with extended follow-up.

Endpoints

- Progression-free survival (PFS) at 3 years
- Overall survival (OS) at 3 years
- Toxicities and morbidity during follow-up
- Cardiac and pulmonary function during follow-up
- Patient-reported outcomes (PROs): Quality-of-life (QoL) & Fatigue

NIVAHL: background



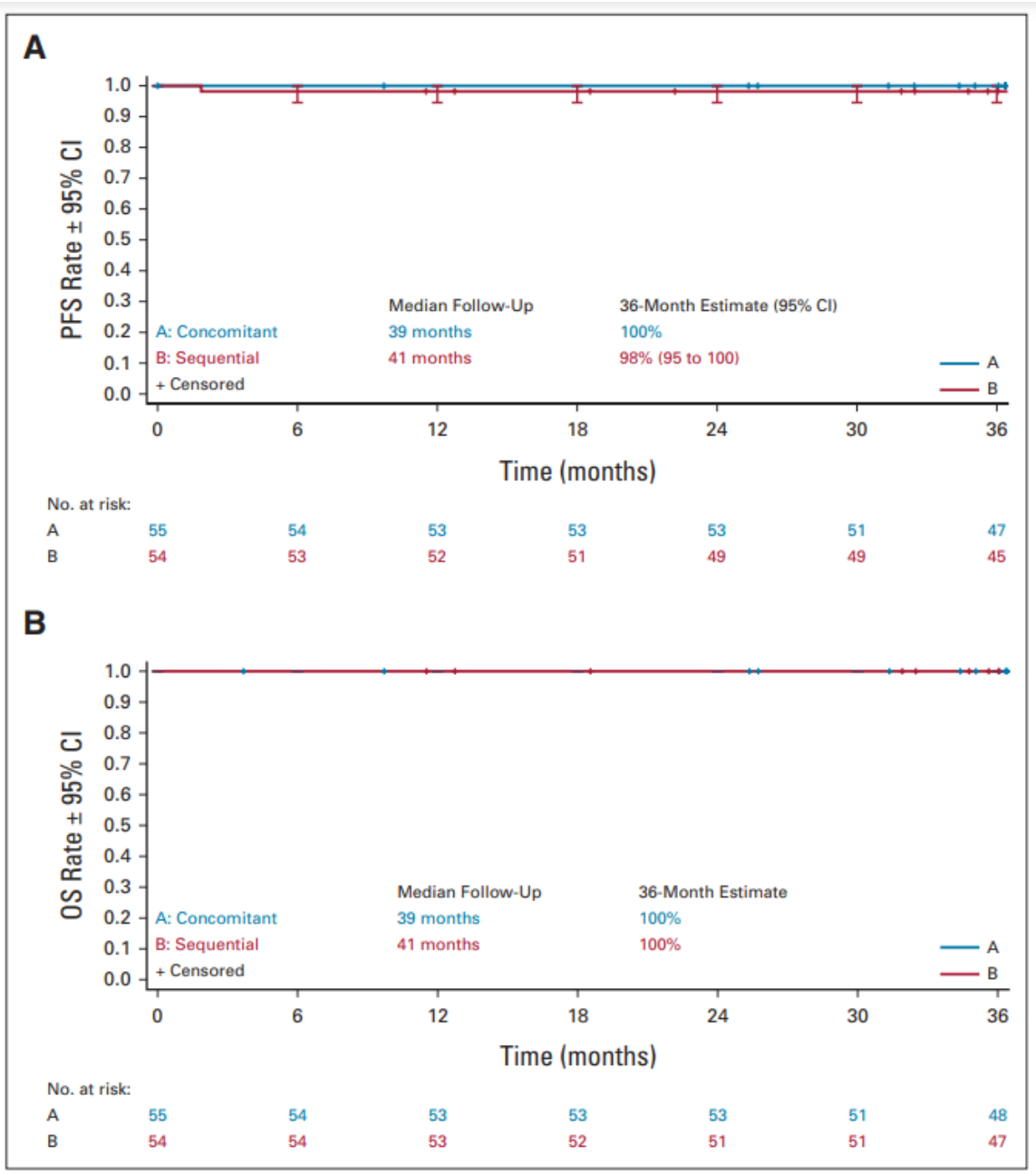
Risk factors:
In stage IA/IB/IIA

a) large mediastinal mass
b) extranodal lesions
c) elevated ESR
d) ≥ 3 nodal areas

I**n stage IIB** only c) and/or d)

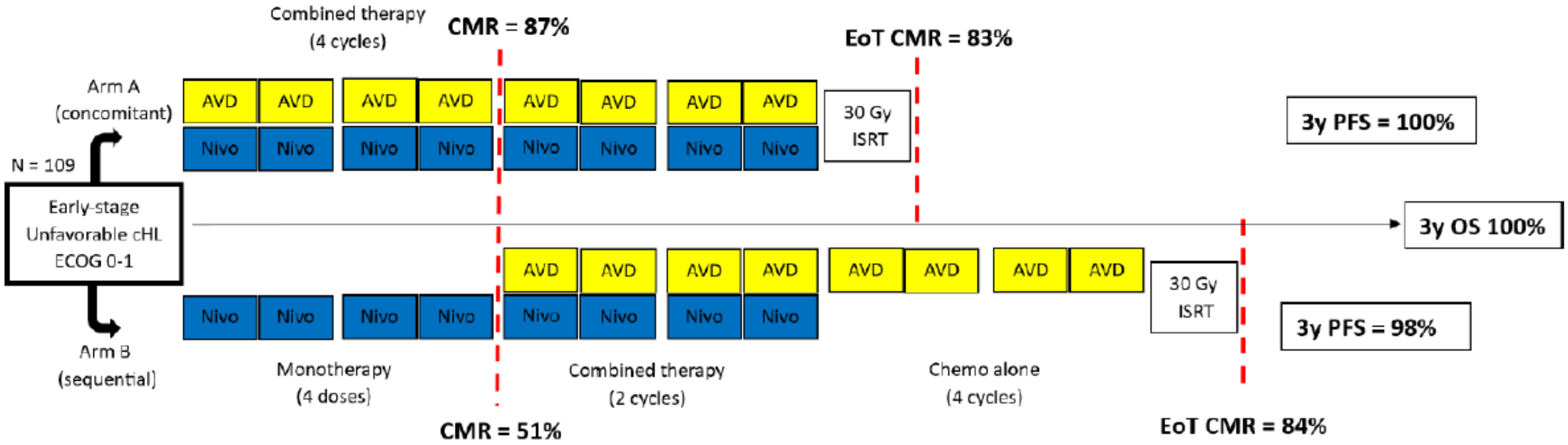
Brockelmann PJ
J Clin Oncol 2022

NIVAHL: PFS i OS



Brockelmann PJ
J Clin Oncol 2023

NIVAHL: response rates

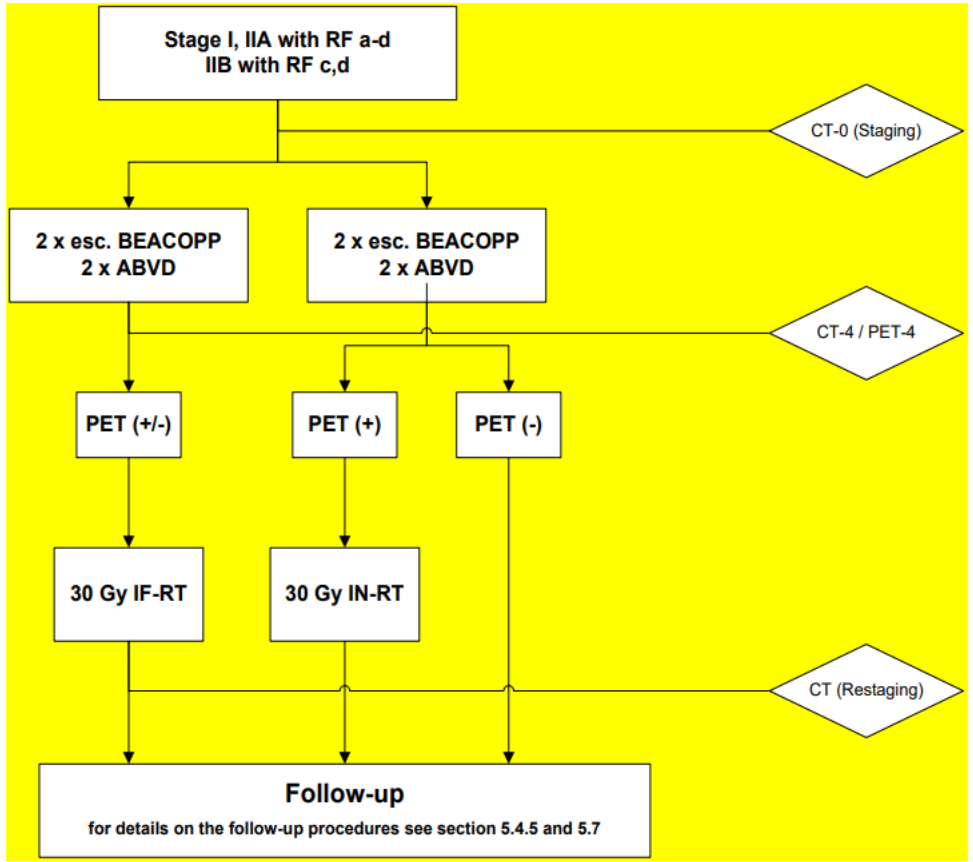


Brockelmann PJ JAMA 2020
Figure from: Vassilakopoulos TP IJMS 2023

Radiotherapy omission in first line treatment of limited stage cHL

PET-guided omission of radiotherapy in early-stage unfavourable Hodgkin lymphoma (GHSG HD17): a multicentre, open-label, randomised, phase 3 trial

Peter Borchmann, Annette Plütschow, Carsten Kobe, Richard Greil, Julia Meissner, Max S Topp, Helmut Ostermann, Judith Dierlamm,



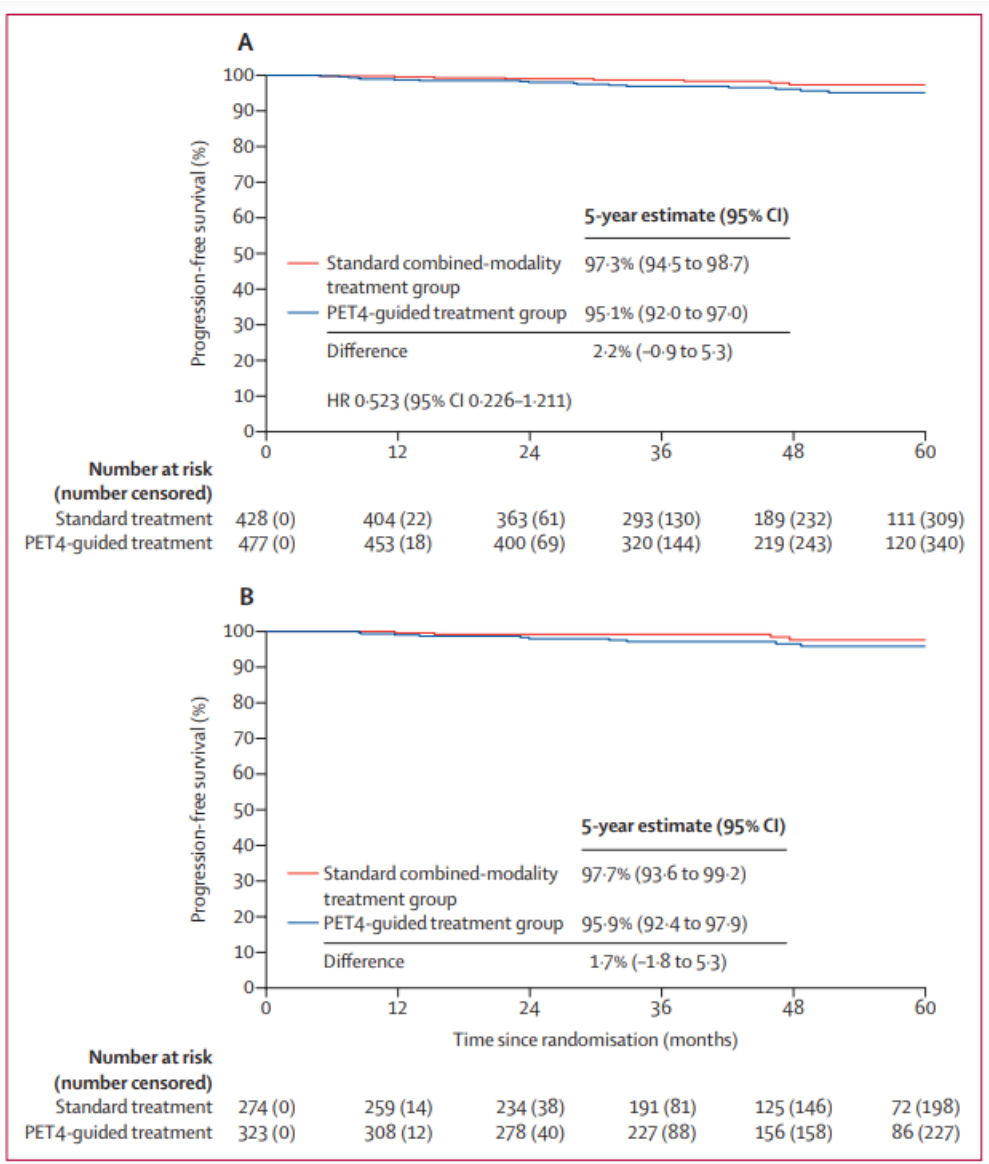


Figure 2: **Kaplan-Meier estimates of 5-year progression-free survival in the per-protocol analysis population (A) and in a subset of PET4-negative patients in the per-protocol analysis population (B)**

Brockmmann P Lancet Oncol 2021

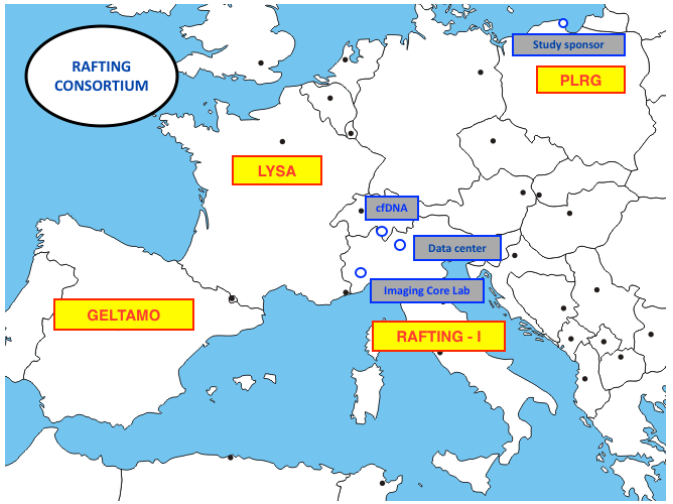
RAFTING trial

Radiation-Free Therapy for the Initial treatment of Good prognosis early non-bulky HL, defined by a low Metabolic Tumor Volume and a negative interim PET after 2 chemotherapy cycles

EudraCT no. 2020-002382-33

PI: Jan Maciej Zaucha

AGENCJA BADAŃ MEDYCZNYCH



Key points of the RAFTING trial

- Identification of **LOW** risk patients in whom RT could be avoided using modern tools (MTV iPET2)- First trial in the world based on MTV
- Identification of **HIGH** risk patients treated with RT combined with NIVOLUMAB
- Prospective assessment of response with tumor cell DNA for 2 years

Courtesy of dr Zaucha

Key hypotheses of the RAFTING trial

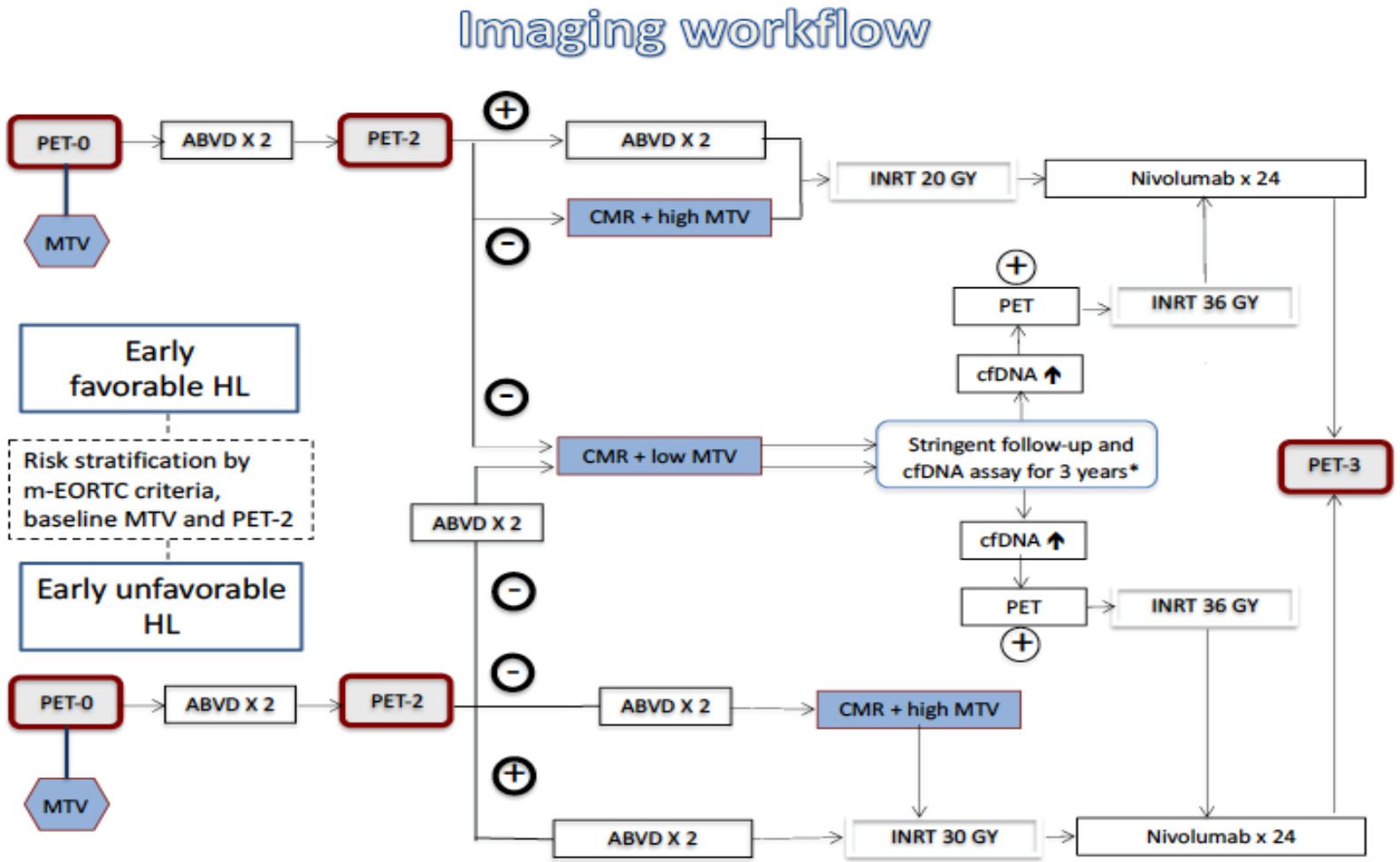
- **70%** of early-stage **HL are low-risk patients** in whom radiotherapy could be avoided using modern tools (MTV iPET2) without worsening progression-free survival
- The addition of Nivolumab in **HIGH-risk** patients will improve progression-free-survival
- Prospective assessment of response with tumor cell-free DNA in LOW risk patients will be a good predictive marker of early relapse

Courtesy of dr Zaucha

RAFTING trial – personalized approach to early stage HL

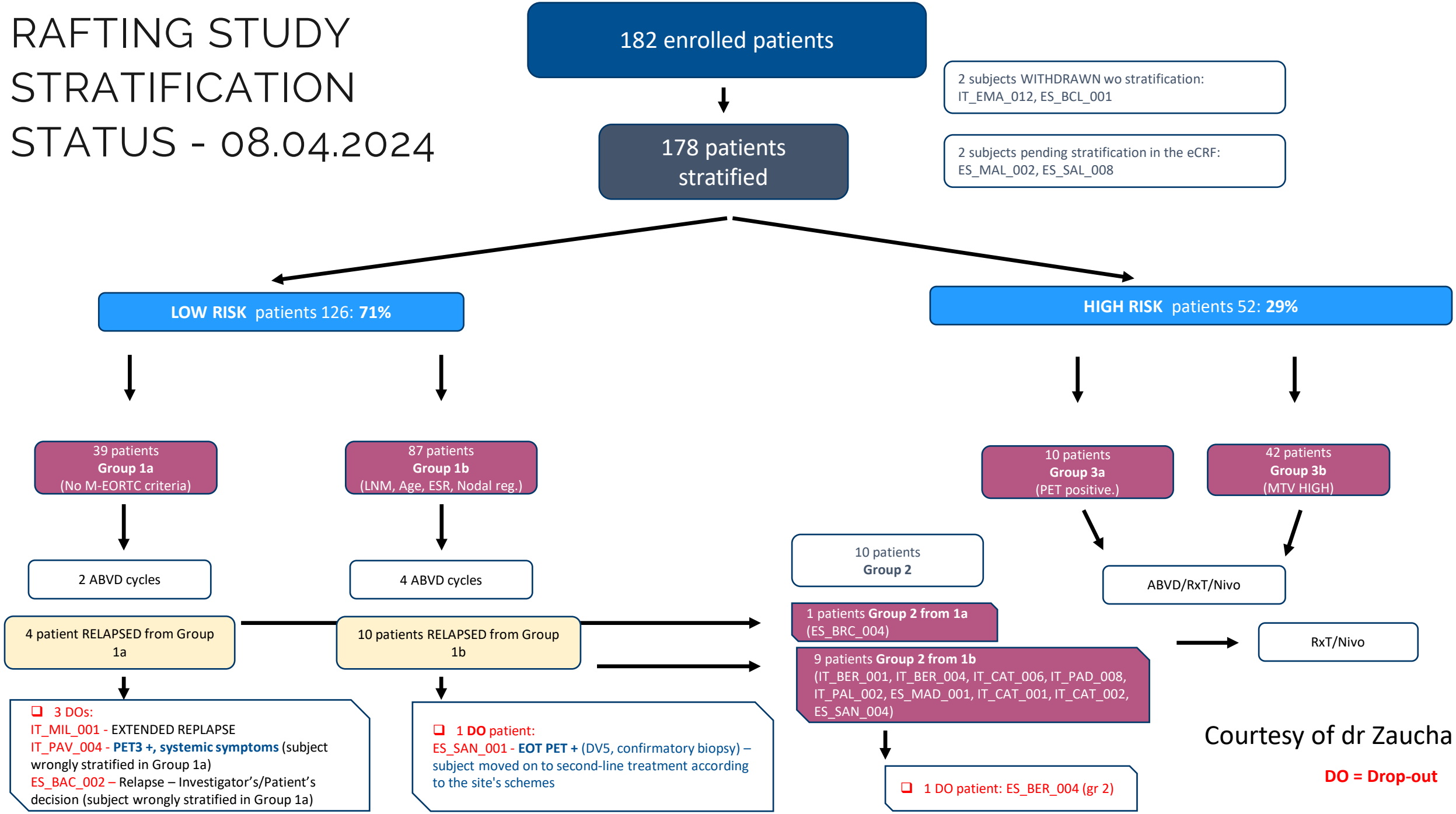
MEDICAL UNIVERSITY OF GDAŃSK

=MTV = PET



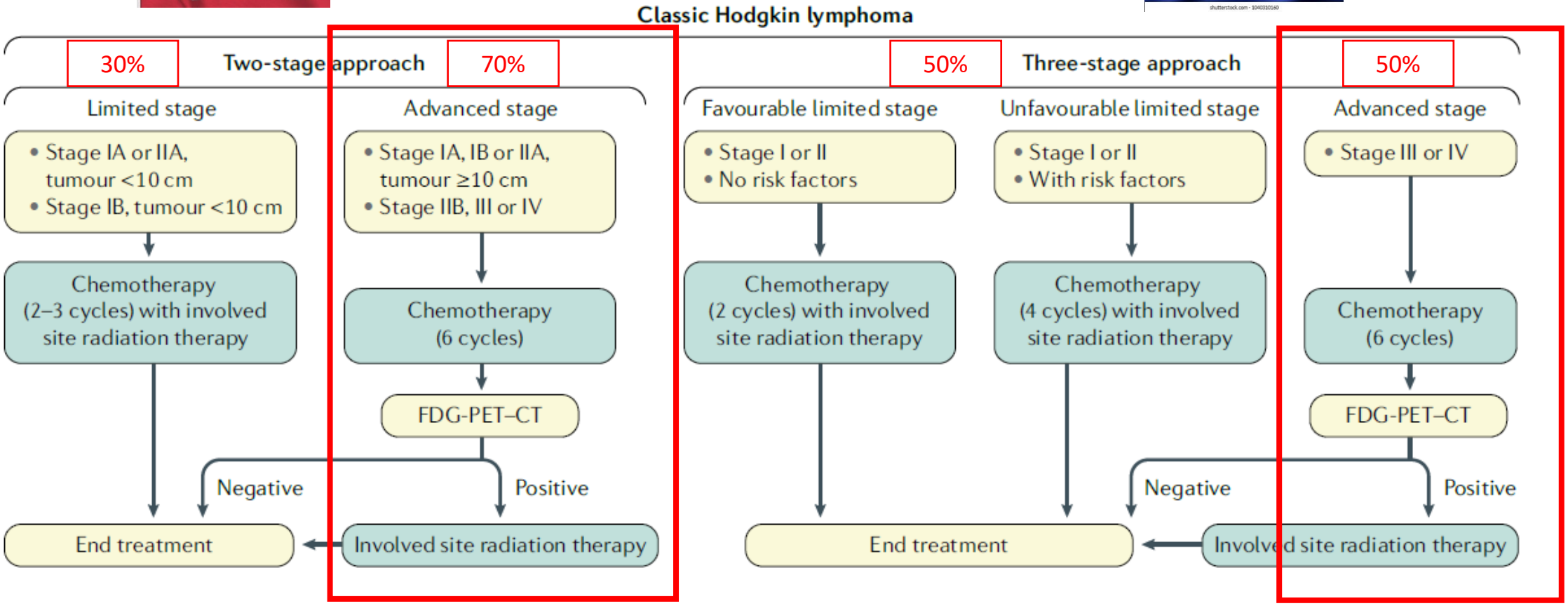
Courtesy of dr Zaucha

RAFTING STUDY STRATIFICATION STATUS - 08.04.2024



Treatment of newly diagnosed advanced-stage cHL

Management algorithm for HL



Connors JM Nature 2020

Standard regimens for first line tretment of advanced cHL: ABVD and escalated BEACOPP

- ABVD
  - Bonadonna G. et al. Cancer 1975
    - ABVD vs MOPP
- eBEACOPP
  - Diehl V et al. NEJM 2005
  - Engert A et al. JCO 2009

Study	Regimen	EFS (%)	P	OS (%)	P	Ref.
GISL HD2000	eBEACOPP	69 (10 years)	0.06	85 (10 years)	NS	175
	ABVD	75 (10 years)		84 (10 years)		
GSM-HD	eBEACOPP	78 (7 years)	0.15	89 (7 years)	0.39	178
	ABVD	71 (7 years)		84 (7 years)		
EORTC (HD7) IPS 0–2	e/bBEACOPP 4/4	77 (5 years)	0.07	99 (5 years)	0.06	177
	ABVD	62 (5 years)		92 (5 years)		
EORTC (HD8) IPS 3–7	e/bBEACOPP 4/4	69 (4 years)	0.31	90 (4 years)	0.21	176
	ABVD	64 (4 years)		87 (4 years)		

Merli F et al. JCO 2016

Viviani S et al. NEJM 2011

Mounier N et al. Ann Oncol 2014

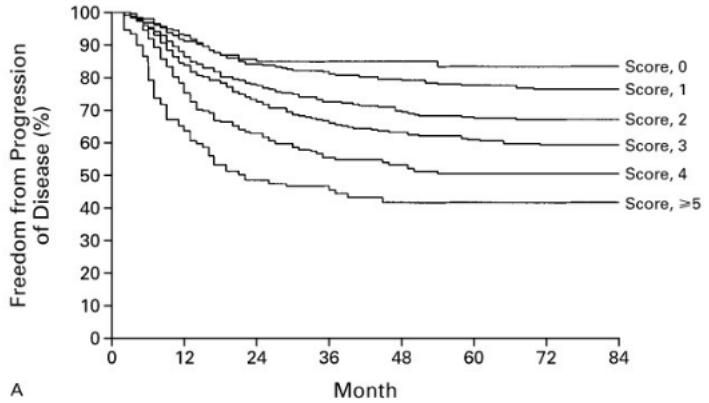
Carde P et al. JCO 2016

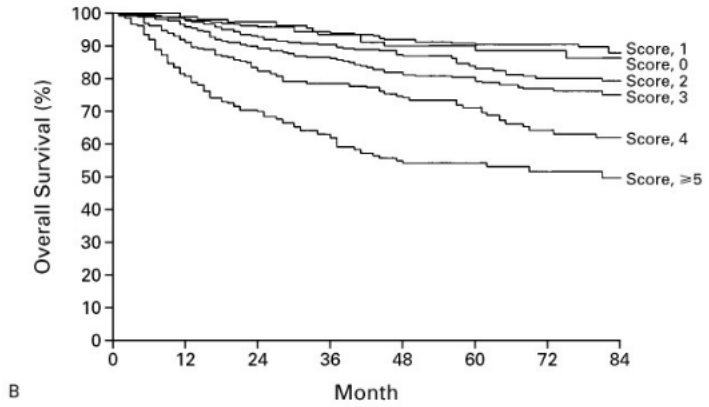
Connors JM Nat Rev Dis Primers 2020

International Prognostic Factors Project score (IPS)

- developed in 1980s, based on the number of independent predictors of progression
- provides validated estimates of probable PFS and OS for pts with advanced disease

Patient	**age**	**≥45 years**
	gender	**male**
Tumor	**CS**	**IV**
Laboratory markers	**anemia**	**Hgb <10.5 g/dL**
	albumin	**<4 g/dL**
	leukocytosis	**>15,000/mm³**
	limfopenia	**<600/mm³ or <8% of WBC**



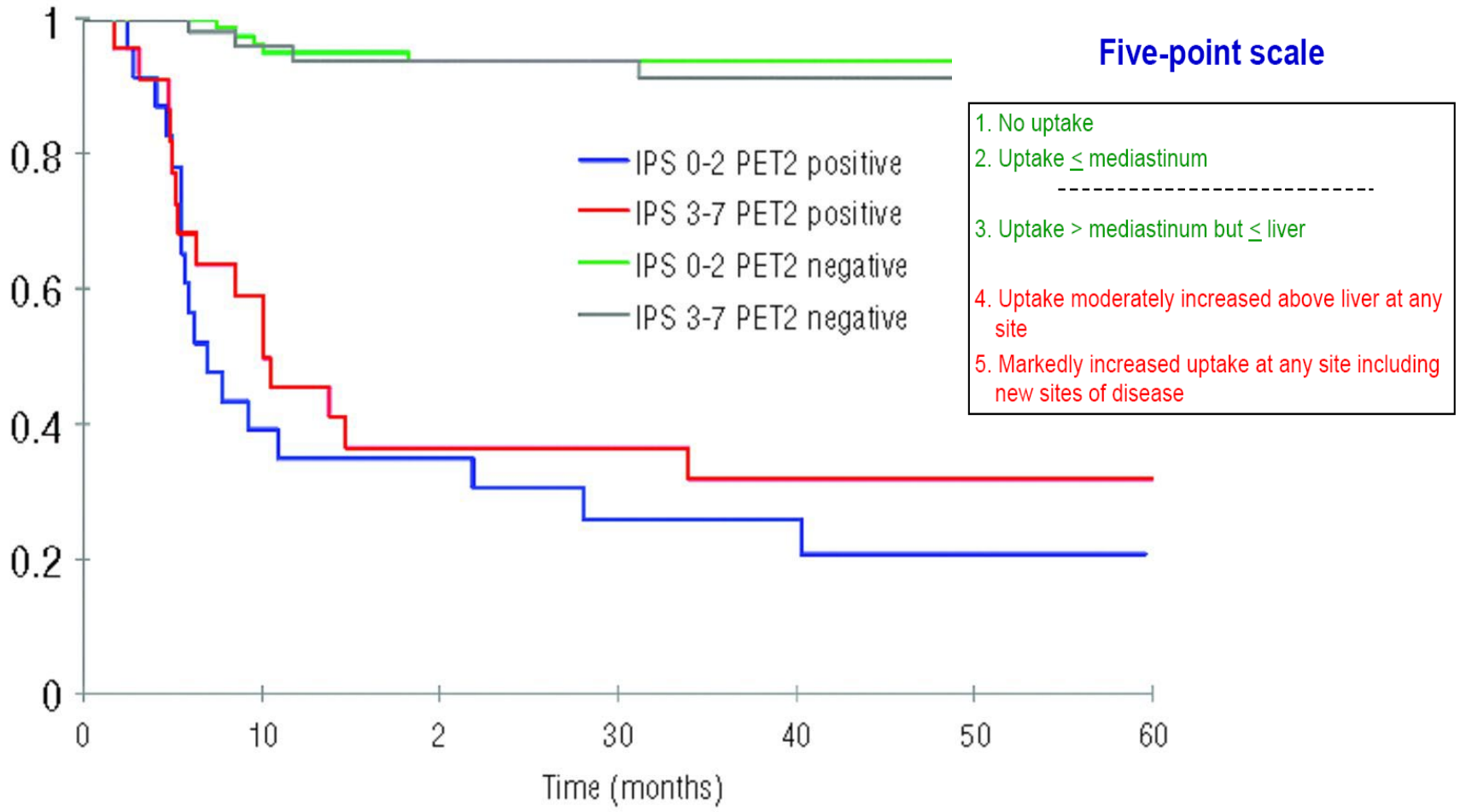


Hasenclever D, Diehl V NEJM 1998

EHA EUROPEAN HEMATOLOGY ASSOCIATION Sf(PM)

Prognostic significance of interim PET after 2 cycles of ABVD in adv HL

IPS: 7 factors (age> 45, male sex, hemoglobin<10.5, stage IV, leukocytosis > 15,000, lymphopenia < 600, albumin <4 g/dl)

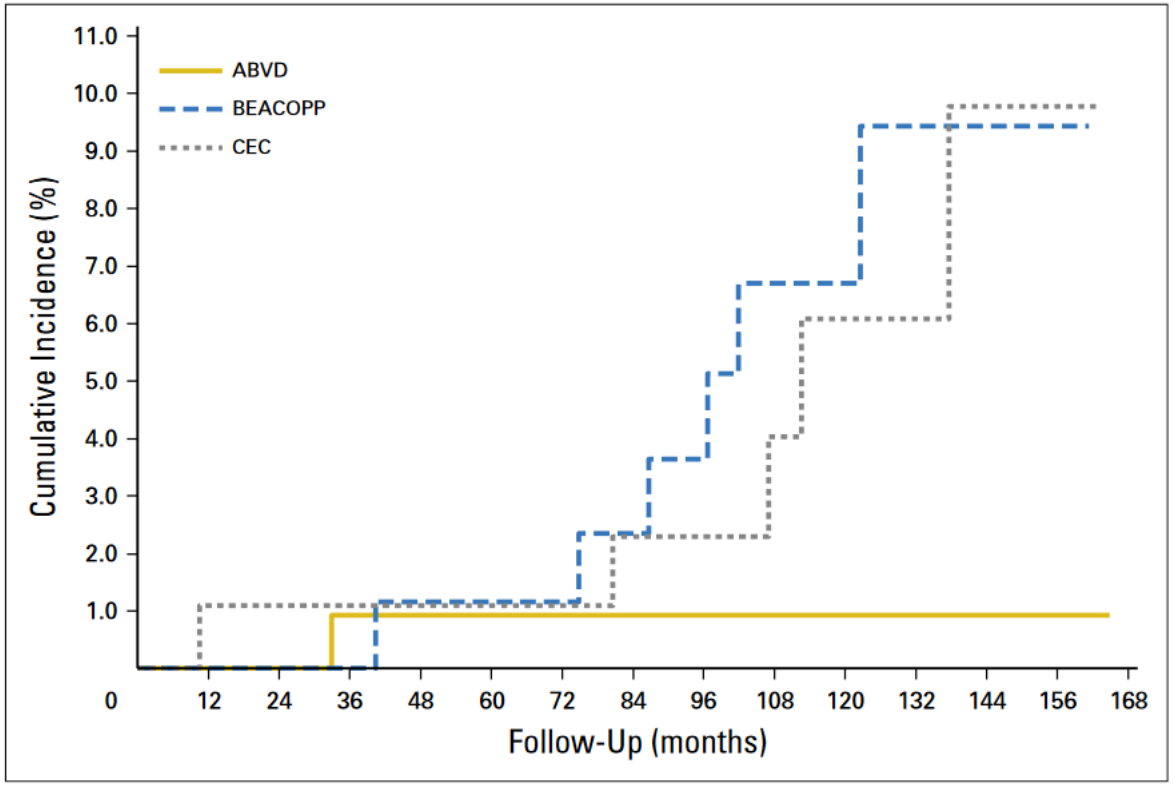


Andrea Gallamini et al. Haematologica 2014;99:1107-1113

haematologica
the hematology journal

Cumulative incidence risk of developing second malignancies: ABVD vs BEACOPP

HD2000 trial- the median follow-up 120 months



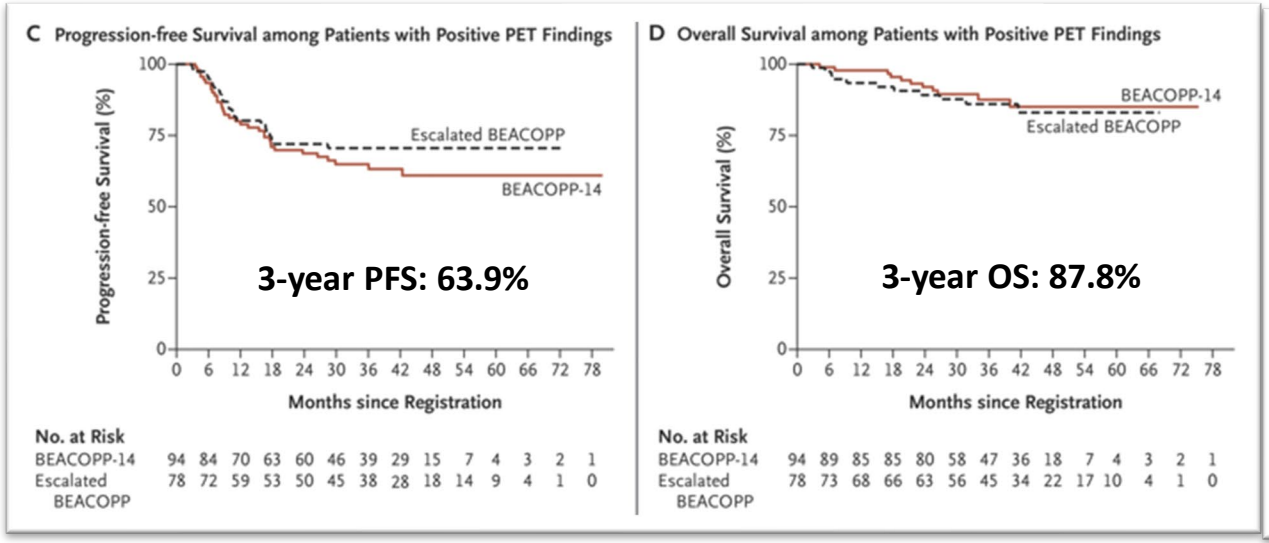
Merli F JCO 2016

PET-guided treatment for personalised therapy of advanced stage cHL

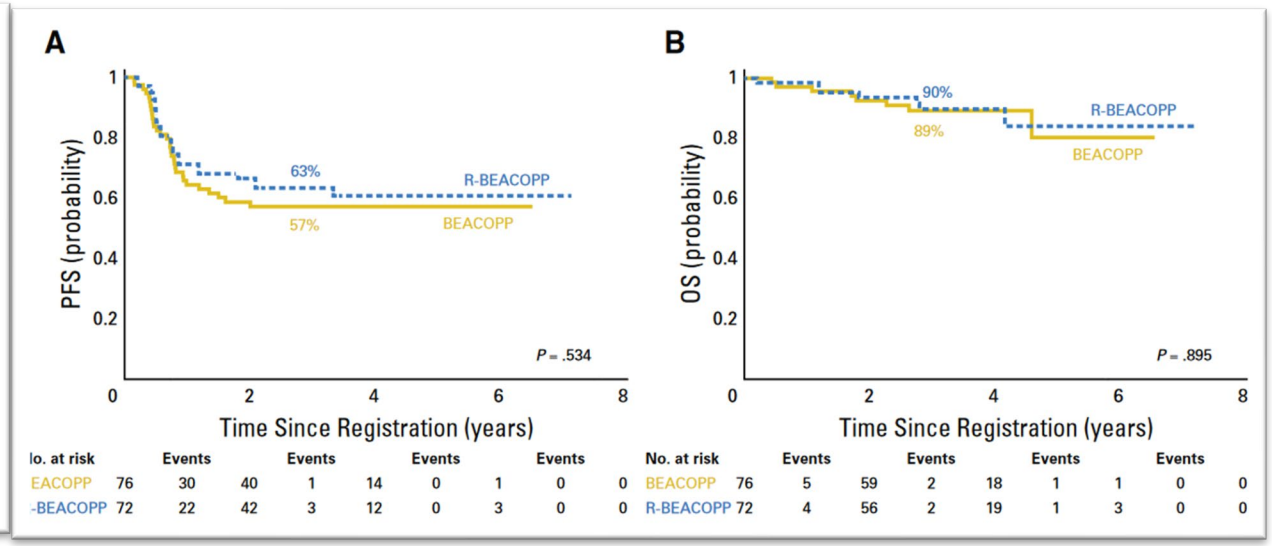
- **Escalation strategy strategy (positive PET-2)**
  - ABVD → escBEACOPP

- **De-escalation strategy (negative PET-2)**
  - ABVD → AVD
  - 6 eBEACOPP → 4 escBEACOPP
  - eBEACOPP → AB(V)D

Trials evaluating therapy escalation in interim PET-positive patients after 2 cycles of ABVD



RATHL study[1]

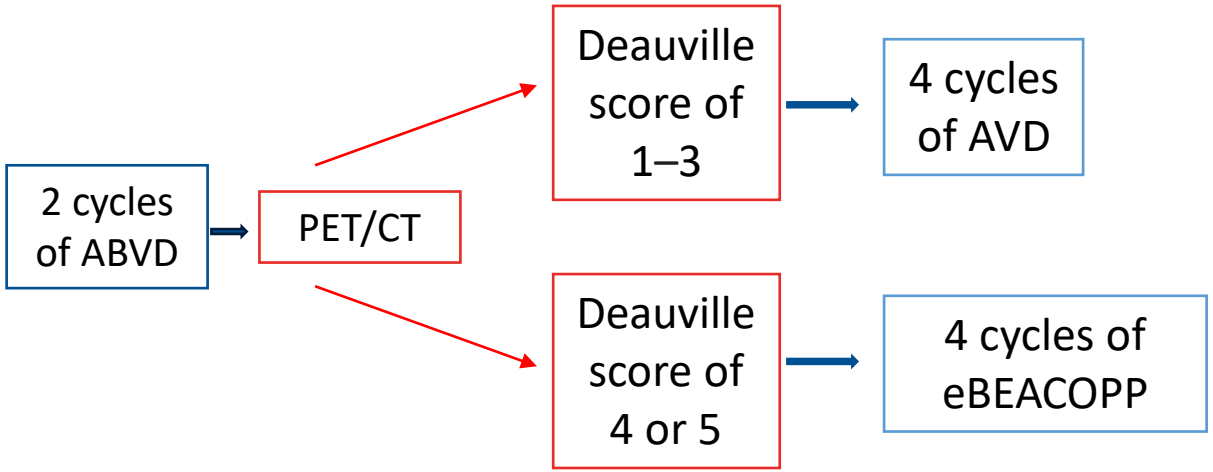


GITIL/FIL HD 0607 Trial[2]

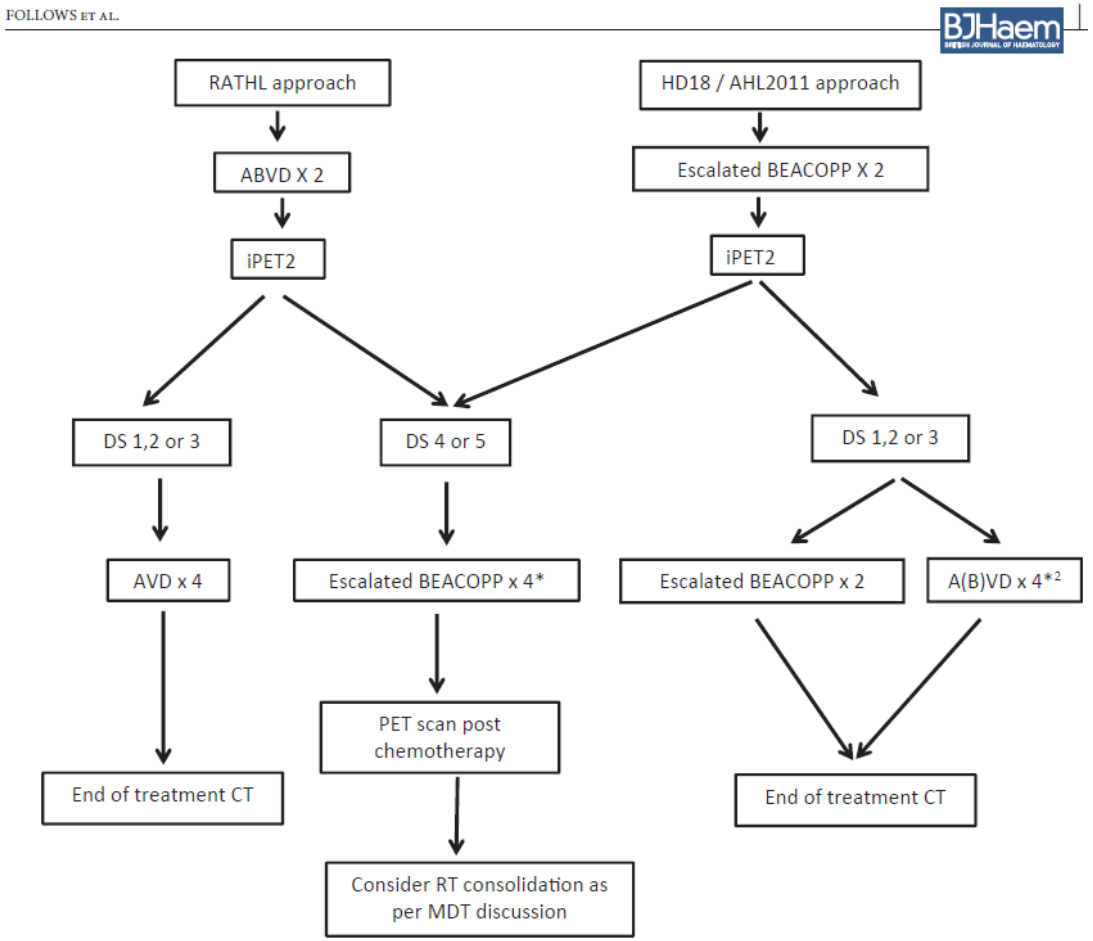
[1]Johnson P. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. N Engl J Med. 2016:23;374:2419-2429. [2]Gallamini A, et al. Early chemotherapy intensification with escalated BEACOPP in patients with advanced-stage Hodgkin lymphoma with a positive interim positron emission tomography/computed tomography scan after two ABVD cycles: Long-term results of the GITIL/FIL HD 0607 trial. J Clin Oncol. 2018; 36: 454-462.

Recommendation for patients with PET-2-positive advanced classical Hodgkin lymphoma treated with 2 cycles ABVD

NCCN Guidelines Version 3.2024
Hodgkin lymphoma (age 18–60 years)[1]



British Society for Haematology guidelines[2]



[1]NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Hodgkin Lymphoma Version 3.2024. https://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf.
[2]Follows GA, et al. Guideline for the first-line management of classical Hodgkin lymphoma - a British Society for Haematology guideline. Br J Haematol. 2022; 197: 558-572.

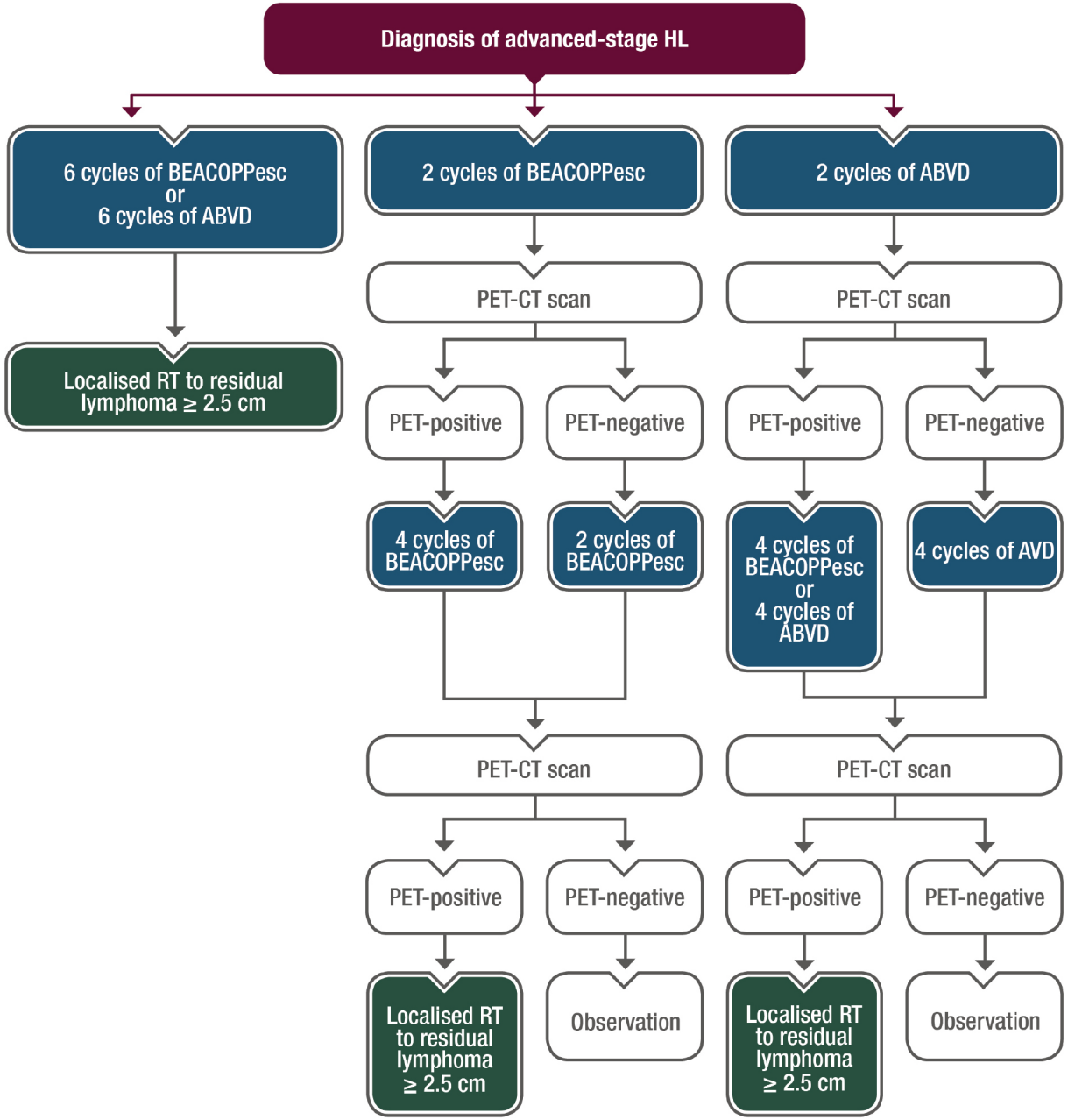
CLINICAL PRACTICE GUIDELINES

Diagnosis & treatment of advanced-stage HL

Newly diagnosed patients ≤ 60 years

The figure includes one approach not guided by interim PET (left) and two PET-guided approaches based on the GHSG HD18 study (middle) and the RATHL study (right)

ABVD is the standard of care for older patients fit enough for multiagent ChT, with discontinuation of bleomycin after the second cycle of ChT



PET-guided treatment for personalised therapy of advanced stage cHL

- **Escalation strategy strategy (positive PET-2)**
  - ABVD → escBEACOPP

- **De-escalation strategy (negative PET-2)**
  - ABVD → AVD
  - 6 eBEACOPP → 4 escBEACOPP
  - eBEACOPP → AB(V)D

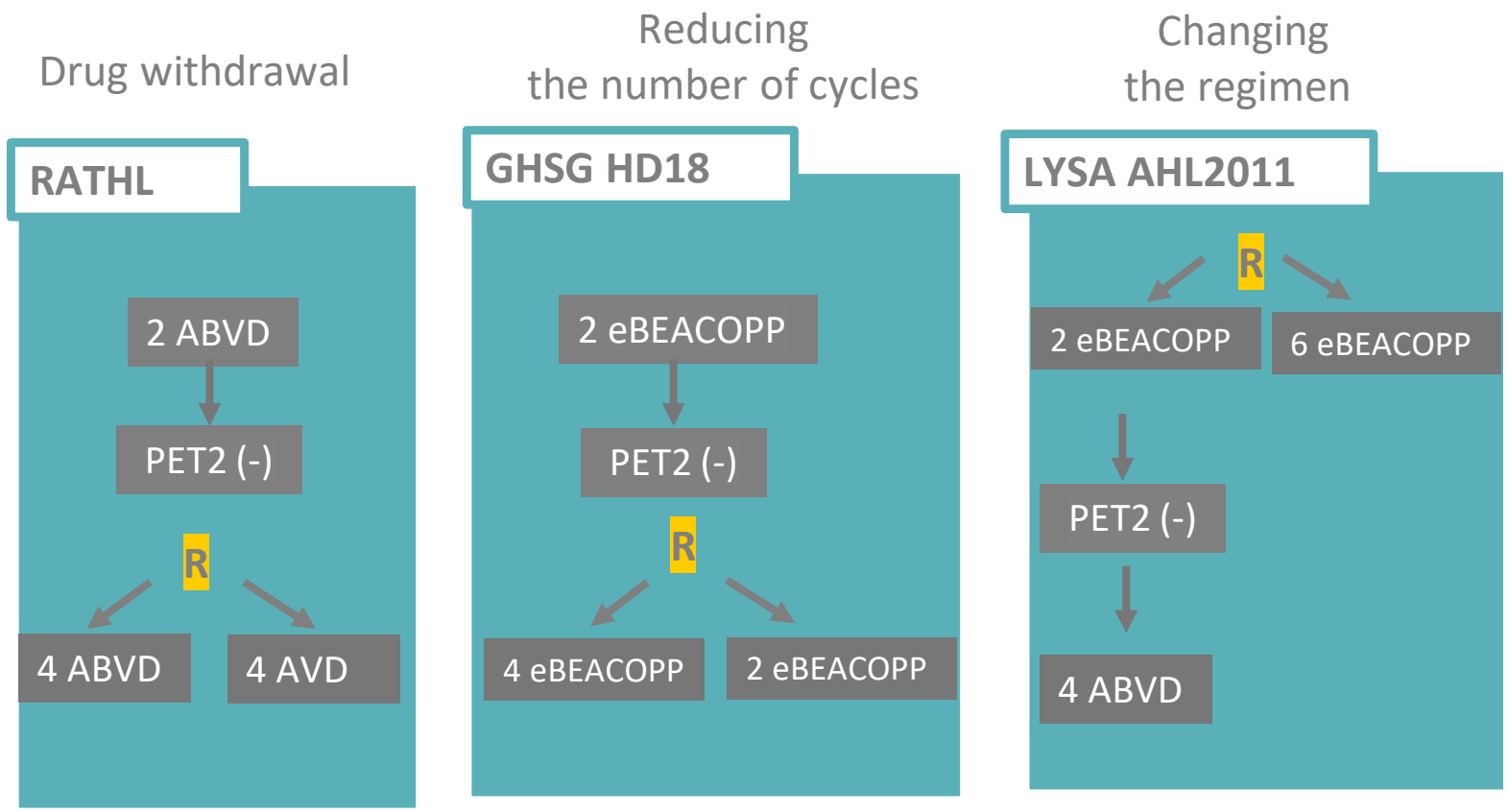
PET-guided treatment of advanced cHL

De-escalation in PET2 (-)

ABVD → AVD

6 eBEACOPP → 4 escBEACOPP

eBEACOPP → AB(V)D



Johnson P
NEJM 2016

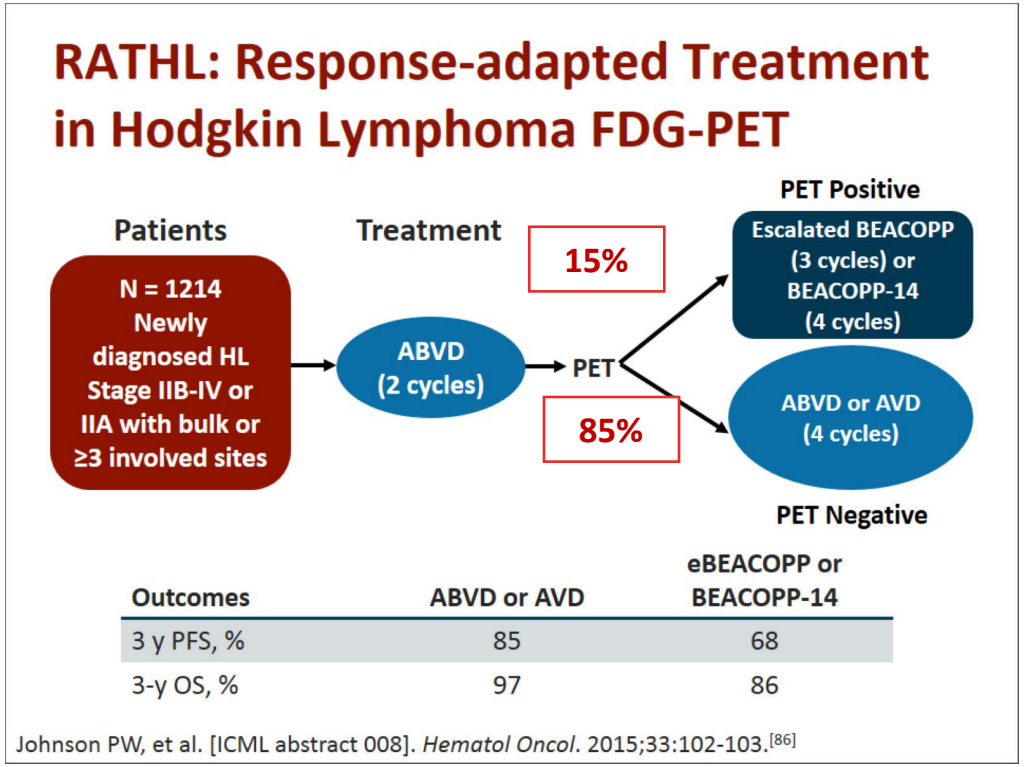
Borchmann P
Lancet 2017

Casasnovas RO
Lancet Oncol 2019

PET-guided treatment of advanced cHL– RATHL study

- Escalation
  - **2xABVD → PET-2(+) 3x escBEACOPP**

- De-escalation 85% of pts
  - **ABVD → PET-2(-) 4x AVD**



Outcomes	ABVD or AVD	eBEACOPP or BEACOPP-14
3 y PFS, %	85	68
3-y OS, %	97	86

Johnson PW, et al. [ICML abstract 008]. *Hematol Oncol*. 2015;33:102-103.[86]

Johnson P NEJM 2016

RATHL study PFS and OS according to study arm

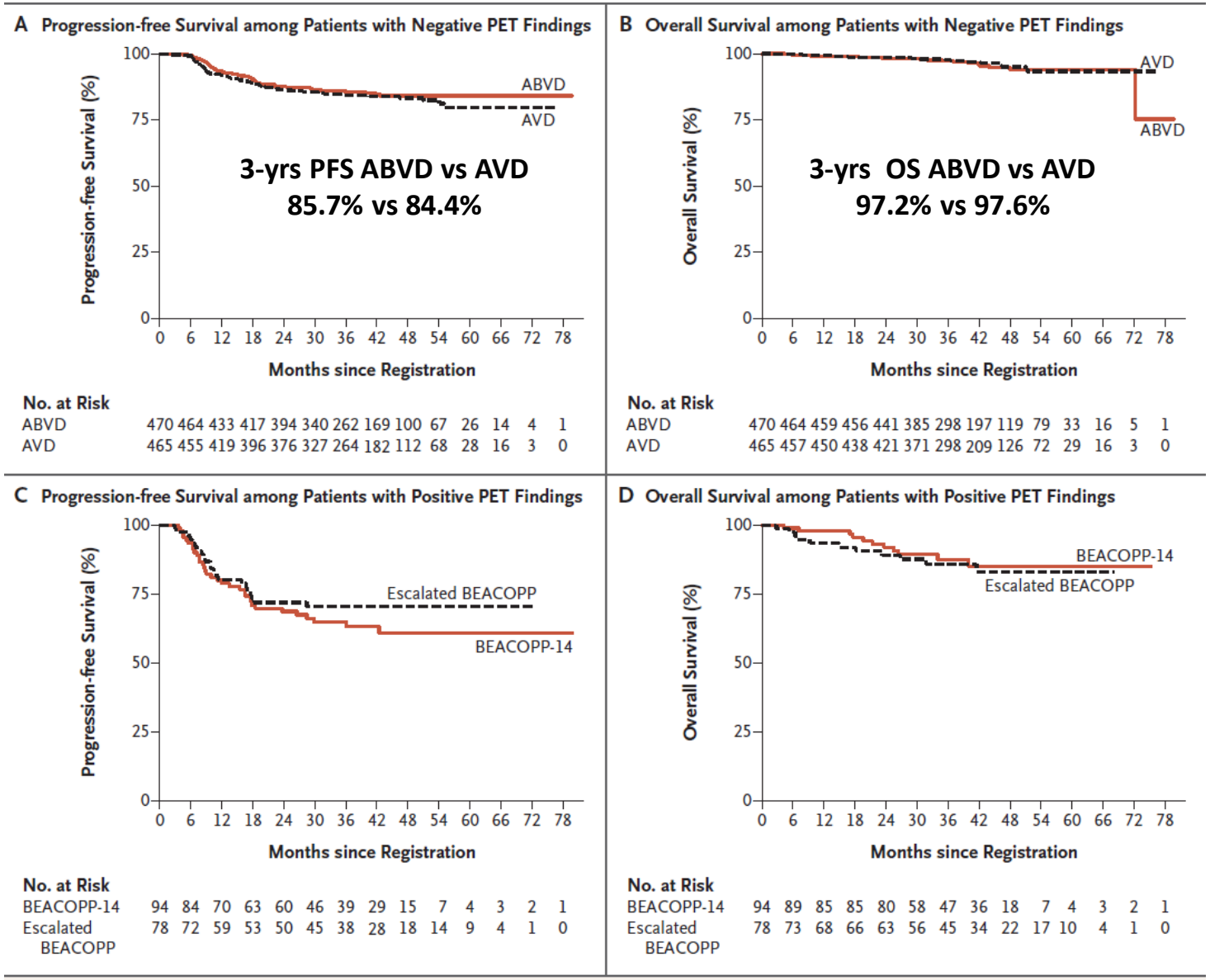


Figure 2. Progression-free and Overall Survival.

Panel A shows progression-free survival among patients with negative PET findings after two cycles of ABVD who underwent randomization, Panel B overall survival among patients with negative PET findings who underwent randomization, Panel C progression-free survival among patients with positive PET findings, and Panel D overall survival among patients with positive PET findings.

RATHL study PFS and OS in PET-2 (+) group

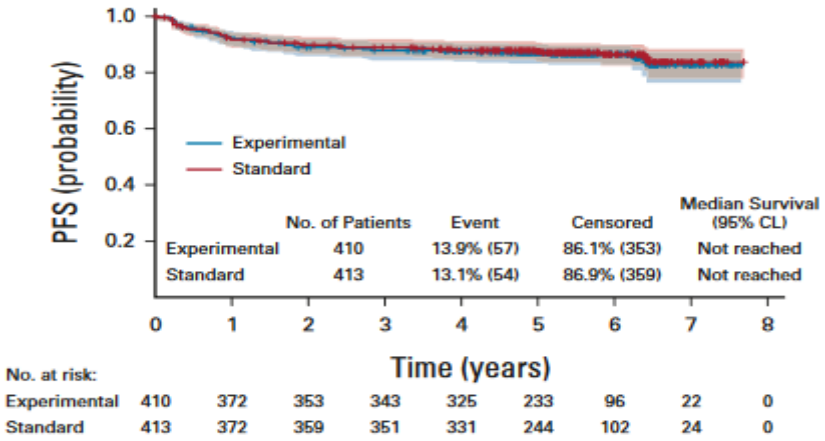
Johnson P NEJM 2016

PET- driven strategy in adv HL: prolonged Follow-Up of the AHL2011 Phase III LYSA Study

De-escalation

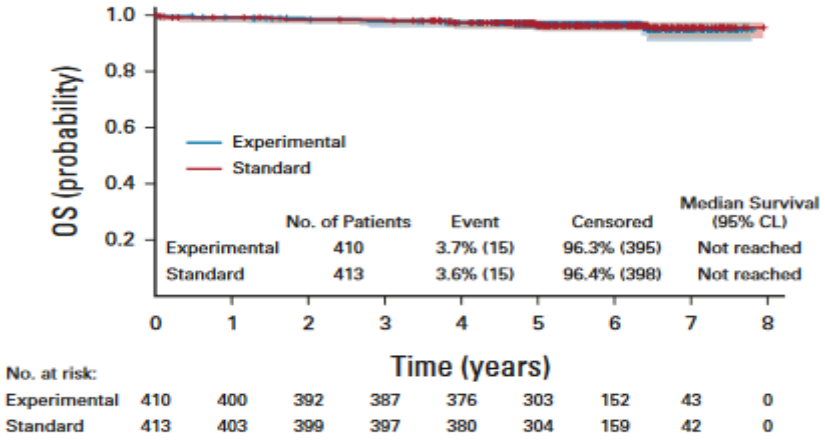
2x eBEACOPP → PET2(-) → 4xABVD
vs
6x eBEACOPP

A



5-year PFS
86.7% v 87.5%
P .67

C



5-year OS
97.7% in both arms
P .53

Casasnovas RO
JCO 2022

PFS and OS for patients PET-2 (-) in HD18 trial

De-escalation in PET-2 (-) group
PET(-) defined as Deauville ≤ 2

eBEACOPPx6 → eBEACOPP x4

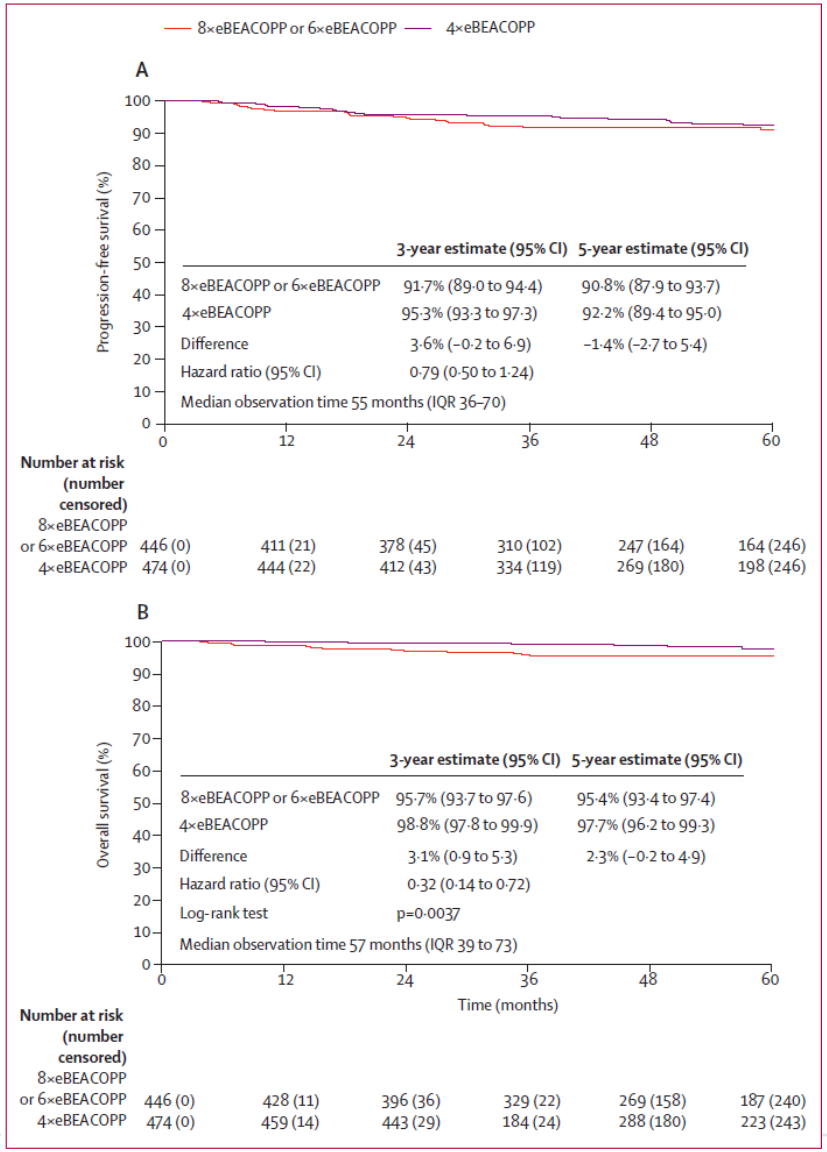


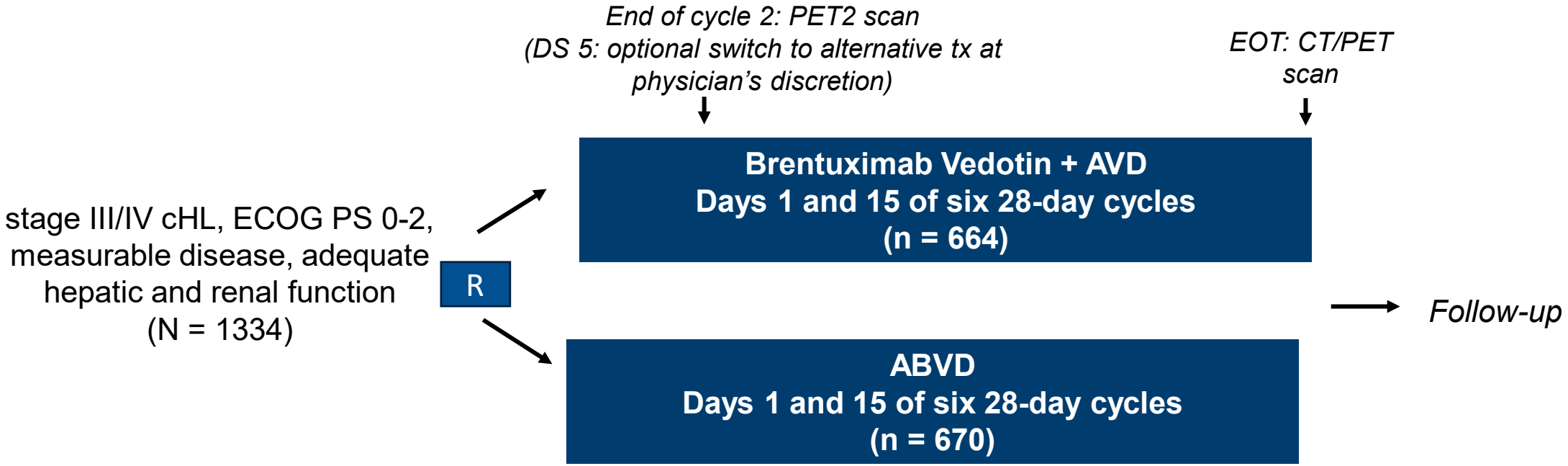
Figure 4: **Progression-free survival and overall survival for patients with negative PET-2**
Kaplan-Meier estimates of (A) progression-free survival and (B) overall survival for patients with negative PET-2, in the per-protocol set. PET-2=PET after two cycles of chemotherapy. eBEACOPP=bleomycin, etoposide,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

5-year PFS
according to study arm
90.8% vs 92.2%

5-year OS
according to study arm
95.4% vs 97.7%

Borchmann P Lancet 2017

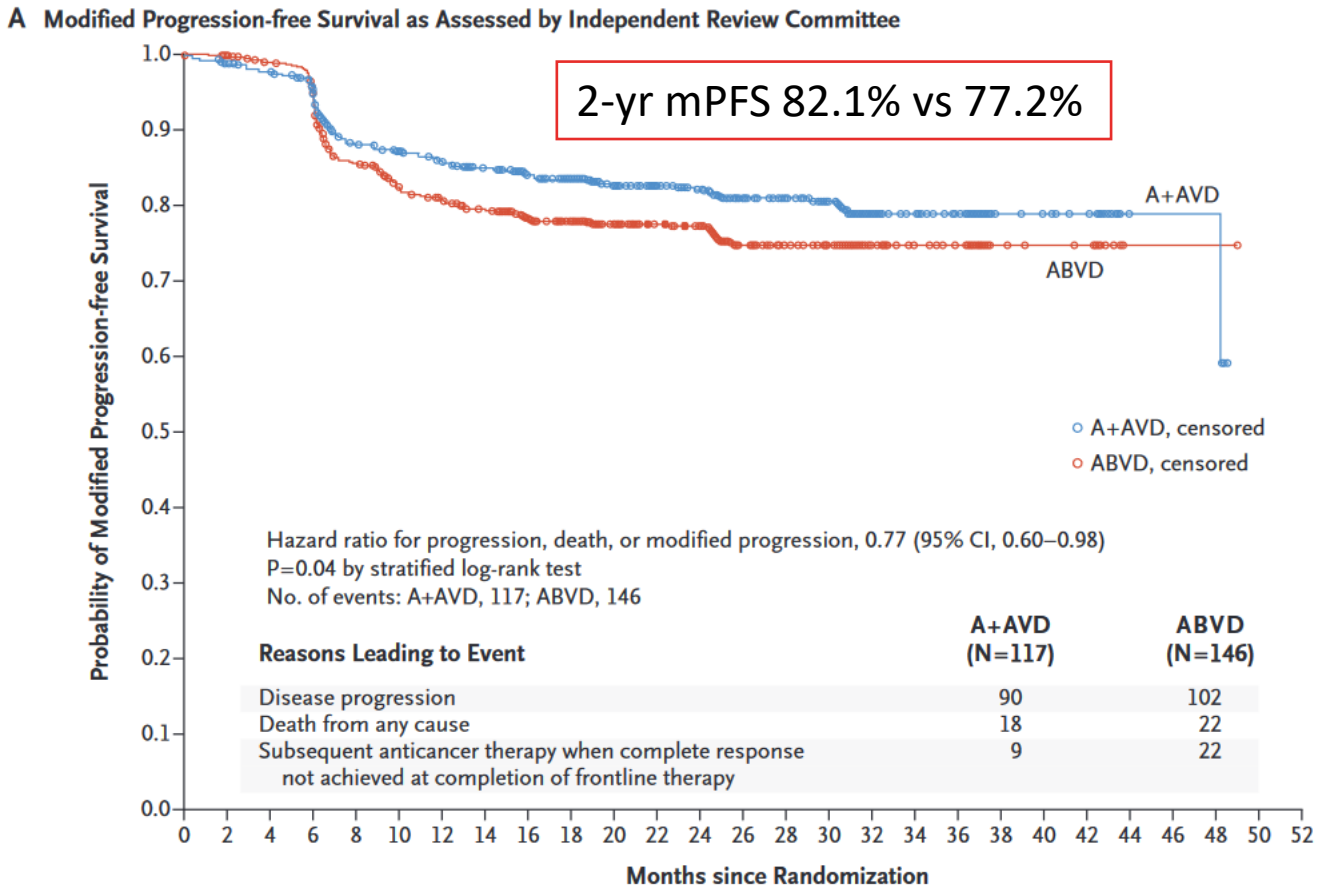
ECHELON-1: Study Design



- Primary endpoint: modified PFS per IRC
  - documented progression at any time after initiation of primary chtx, death from any cause, and detection of a response that was less than complete at the end of primary chemotherapy (DS 3-5), followed by the delivery of subsequent tx
- Secondary endpoints: response, OS, PET negativity per IRC, safety

Connors JM, et al. N Engl J Med. 2017

ECHELON-1 study



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

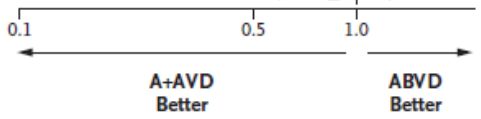
2-yr mPFS 82.1% vs 77.2%

HR for progression, death, or modified progression
0.77 [95% CI, 0.60 to 0.98]; P = 0.04

Connors JM, et al. N Engl J Med. 2017

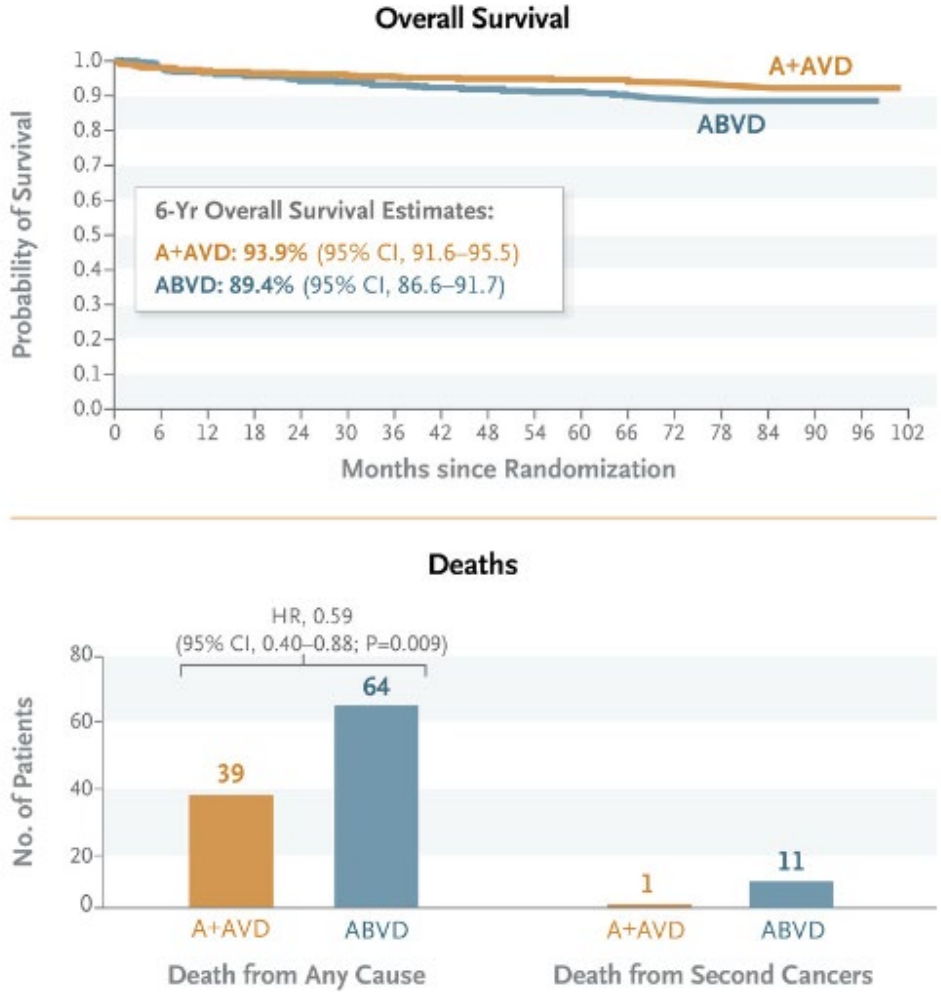
ECHELON-1 study

Subgroup	A+AVD	ABVD	Hazard Ratio (95% CI)
	no. of events/total no. (%)		
Overall	117/664 (17.6)	146/670 (21.8)	0.77 (0.60–0.98)
Age			
<60 yr	93/580 (16.0)	117/568 (20.6)	0.73 (0.56–0.96)
≥60 yr	24/84 (28.6)	29/102 (28.4)	1.00 (0.58–1.72)
<65 yr	99/604 (16.4)	128/608 (21.1)	0.74 (0.57–0.96)
≥65 yr	18/60 (30.0)	18/62 (29.0)	1.01 (0.53–1.94)
<45 yr	70/451 (15.5)	83/423 (19.6)	0.73 (0.53–1.01)
≥45 yr	47/213 (22.1)	63/247 (25.5)	0.86 (0.59–1.25)
Geographic region			
Americas	41/261 (15.7)	58/262 (22.1)	0.65 (0.44–0.97)
North America	38/250 (15.2)	57/247 (23.1)	0.60 (0.40–0.90)
Europe	62/333 (18.6)	74/336 (22.0)	0.83 (0.59–1.17)
Asia	14/70 (20.0)	14/72 (19.4)	0.91 (0.43–1.94)
IPS			
0–1	22/141 (15.6)	25/141 (17.7)	0.84 (0.47–1.49)
2–3	57/354 (16.1)	68/351 (19.4)	0.79 (0.55–1.12)
4–7	38/169 (22.5)	53/178 (29.8)	0.70 (0.46–1.07)
Baseline Ann Arbor stage			
Stage III	40/237 (16.9)	43/246 (17.5)	0.92 (0.60–1.42)
Stage IV	77/425 (18.1)	102/421 (24.2)	0.71 (0.53–0.96)
Baseline B symptoms			
Yes	77/400 (19.3)	94/381 (24.7)	0.74 (0.55–1.01)
No	40/264 (15.2)	52/289 (18.0)	0.79 (0.52–1.20)
Baseline extranodal sites			
0	40/217 (18.4)	39/228 (17.1)	1.04 (0.67–1.62)
1	36/217 (16.6)	45/223 (20.2)	0.75 (0.48–1.16)
>1	39/194 (20.1)	57/193 (29.5)	0.67 (0.44–1.00)
Baseline ECOG status			
0	61/376 (16.2)	79/378 (20.9)	0.74 (0.53–1.03)
1	48/260 (18.5)	57/263 (21.7)	0.83 (0.56–1.21)
2	8/28 (28.6)	10/27 (37.0)	0.54 (0.21–1.38)
Sex			
Male	64/378 (16.9)	90/398 (22.6)	0.70 (0.51–0.97)
Female	53/286 (18.5)	56/272 (20.6)	0.86 (0.59–1.26)



Connors JM, et al. N Engl J Med. 2017

ECHELON-1
A-AVD vs ABVD
Overall Survival (Intention-to-Treat Population).



Subgroup	A+AVD	ABVD	Hazard Ratio for Death (95% CI)
	no. of deaths/total no. of patients (%)		
Overall	39/664 (5.9)	64/670 (9.6)	0.59 (0.40–0.88)
Age			
<60 yr	19/580 (3.3)	35/568 (6.2)	0.51 (0.29–0.89)
≥60 yr	20/84 (24)	29/102 (28.4)	0.83 (0.47–1.47)
<45 yr	9/451 (2.0)	18/423 (4.3)	0.44 (0.20–0.99)
≥45 yr	30/213 (14.1)	46/247 (18.6)	0.75 (0.47–1.18)
Geographic region			
Americas	11/261 (4.2)	27/262 (10.3)	0.40 (0.20–0.80)
North America	9/250 (3.6)	26/247 (10.5)	0.33 (0.15–0.70)
Europe	26/333 (7.8)	32/336 (9.5)	0.78 (0.47–1.32)
Asia	2/70 (3)	5/72 (7)	0.37 (0.07–1.91)
No. of IPS risk factors			
0 or 1	7/142 (4.9)	7/141 (5.0)	0.97 (0.34–2.77)
2 or 3	17/355 (4.8)	26/357 (7.3)	0.62 (0.33–1.14)
4–7	15/167 (9.0)	31/172 (18.0)	0.48 (0.26–0.88)
Cancer stage at baseline			
III	17/237 (7.2)	20/246 (8.1)	0.86 (0.45–1.65)
IV	22/425 (5.2)	43/421 (10.2)	0.48 (0.29–0.80)
B symptoms at baseline			
Present	30/400 (7.5)	39/381 (10.2)	0.71 (0.44–1.14)
Absent	9/264 (3.4)	25/289 (8.7)	0.37 (0.17–0.80)
Extranodal site at baseline			
0	22/217 (10.1)	19/228 (8.3)	1.18 (0.64–2.19)
1	9/217 (4.1)	17/223 (7.6)	0.51 (0.23–1.14)
>1	8/194 (4.1)	25/193 (13.0)	0.30 (0.14–0.67)
ECOG performance-status score at baseline			
0	15/376 (4.0)	21/378 (5.6)	0.70 (0.36–1.37)
1	19/260 (7.3)	34/263 (12.9)	0.54 (0.31–0.94)
2	5/28 (18)	9/27 (33)	0.41 (0.14–1.23)
Sex			
Male	19/378 (5.0)	45/398 (11.3)	0.43 (0.25–0.73)
Female	20/286 (7.0)	19/272 (7.0)	0.96 (0.51–1.80)

SM Ansell et al. N Engl J Med 2022;387:310-320.

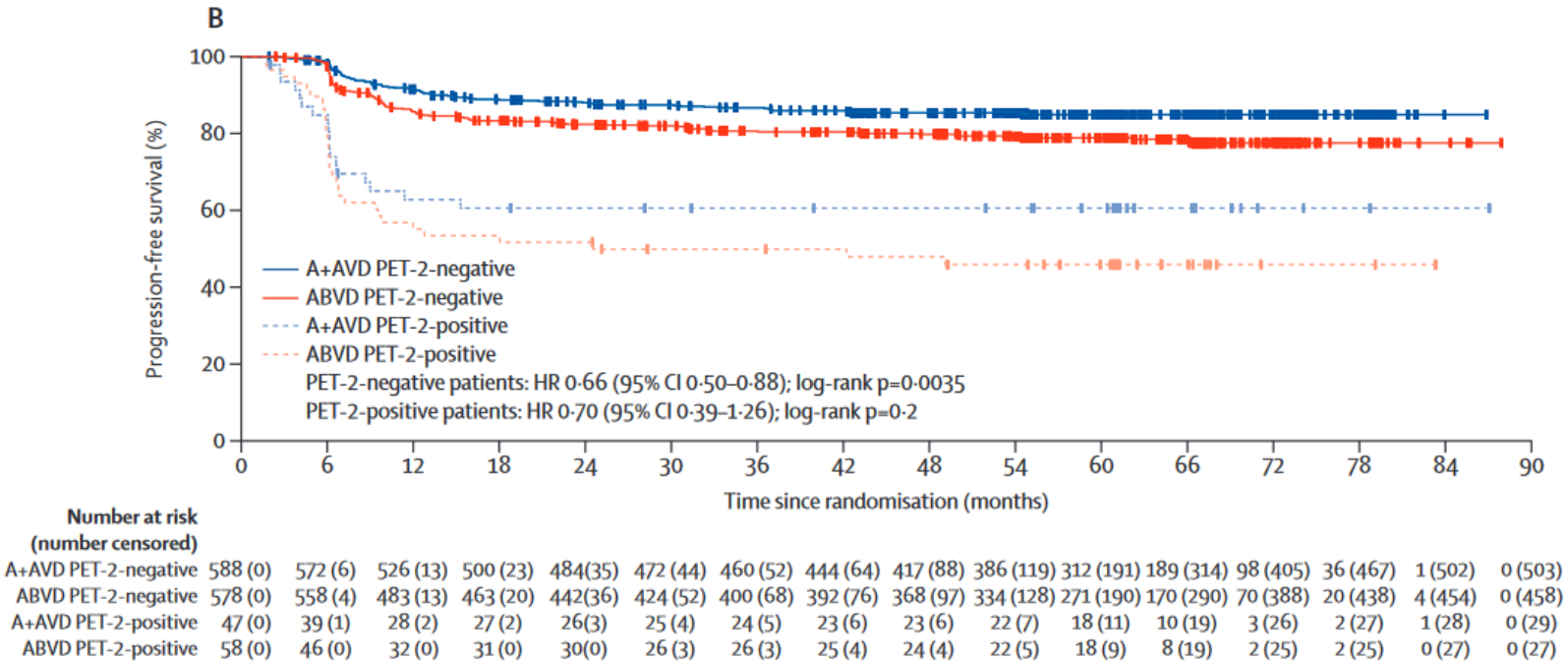
ECHELON-1 study

- Fewer patients in the A+AVD group than in the ABVD group received subsequent therapy, including HSCT, and fewer second cancers were reported with A+AVD (in 23 vs. 32 patients)
- Primary prophylaxis with G-CSF was recommended after an increased incidence of febrile neutropenia was observed with A+AVD
- More patients had peripheral neuropathy with A+AVD than with ABVD, but most patients in the two groups had resolution/ amelioration of the event by the last follow-up

Ansell SM et al. N Engl J Med. 2017

Brentuximab vedotin with chemotherapy for stage III or IV classical Hodgkin lymphoma (ECHELON-1): 5-year update of an international, open-label, randomised, phase 3 trial

David J Straus, Monika Długosz-Danecka, Joseph M Connors, Sergey Alekseev, Árpád Illés, Marco Picardi, Ewa Lech-Maranda, Tatyana Feldman, Piotr Smolewski, Kerry J Savage, Nancy L Bartlett, Jan Walewski, Radhakrishnan Ramchandren, Pier Luigi Zinzani, Martin Hutchings, Javier Munoz, Hun Ju Lee, Won Seog Kim, Ranjana Advani, Stephen M Ansell, Anas Younes, Andrea Gallamini, Rachael Liu, Meredith Little, Keenan Fenton, Michelle Fanale, John Radford



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)

PET-2 (-) pts:
5-yr PFS A+AVD vs ABVD
84·9% vs 78·9%; HR 0·66 (p=0·0035)

PET-2 (+) pts:
5-yr PFS A+AVD vs ABVD
60·6% vs 45·9%; HR 0·70 (p=0·23)

Straus DJ Lancet Hem 2021

Novel Combinations with Brentuximab Vedotin for advanced cHL: BrECADD regimen

- the GHSG proposed the new BrECADD regimen to reduce eBEACOPP toxicity:
  - vincristine and bleomycin replaced with BV to avoid synergistic neurotoxicity
  - procarbazine replaced with dacarbazine to reduce genotoxicity and leukemogenicity
  - the 14-day prednisone course was replaced by a 4-day dexamethasone course to avoid prolonged steroid administration

clinicaltrials.gov/study/NCT02661503
Borchmann P, et al. Hematol Oncol. 2023; 41: 881–882. ICML 2023

BrECADD IS NON-INFERIOR TO EBEACOPP IN PATIENTS WITH ADVANCED STAGE CLASSICAL HODGKIN LYMPHOMA: EFFICACY RESULTS OF THE GHSG PHASE III HD21 TRIAL

- Multicenter randomized phase III trial
  - adult patients aged ≤60 with advanced stage-cHL
  - patients were randomized in a 1:1 ratio to PET2-guided 4–6 cycles of either eBEACOPP or BrECADD
  - Primary objective: non-inferiority of BrECADD as compared to eBEACOPP in terms of PFS

clinicaltrials.gov/study/NCT02661503
Borchmann P, et al. Hematol Oncol. 2023; 41: 881–882. ICML 2023

BrECADD IS NON-INFERIOR TO EBEACOPP IN PATIENTS WITH ADVANCED STAGE CLASSICAL HODGKIN LYMPHOMA: EFFICACY RESULTS OF THE GHSG PHASE III HD21 TRIAL

- **International open-label phase III trial**
- **Methods:**
  - adult patients aged ≤60 with advanced stage-cHL
  - patients were randomized in a 1:1 ratio to PET2-guided 4–6 cycles of either eBEACOPP or BrECADD
  - Primary objective: non-inferiority of BrECADD as compared to eBEACOPP in terms of PFS

clinicaltrials.gov/study/NCT02661503
Borchmann P, et al. Hematol Oncol. 2023; 41: 881–882. ICML 2023

BrECADD IS NON-INFERIOR TO EBEACOPP IN PATIENTS WITH ADVANCED STAGE CLASSICAL HODGKIN LYMPHOMA: EFFICACY RESULTS OF THE GHSG PHASE III HD21 TRIAL

Summary of the results:

- N= 1,500 patients from 9 countries
- Median follow-up was 40 months
  - 3-year PFS eBEACOPP vs BrECADD: 92.3% vs 94.9%; HR 0.63 (99% CI 0.37–1.07)
  - 3-year OS 98.5% in both groups

Conclusion:

- This interim analysis of the GHSG HD21 trial establishes non-inferiority of BrECADD compared to eBEACOPP
- A relavant reduction in early PFS events was observed
- The PFS rate suggests that individualized treatment with PET2-directed BrECADD is currently the most effective therapy for adult patients with AS-cHL

Borchmann P, et al. Hematol Oncol. 2023; 41: 881–882. ICML 2023

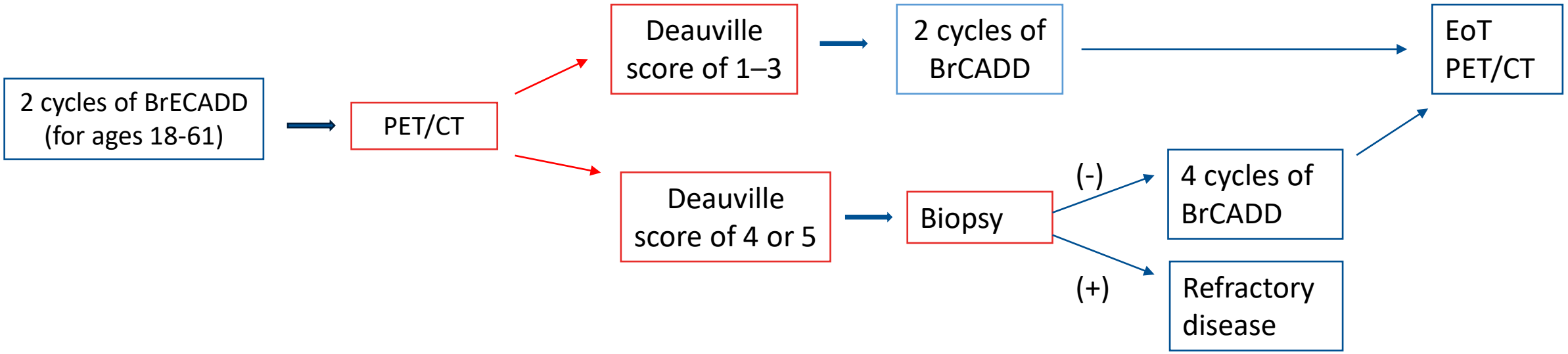
Treatment Related Morbidity (TRMB) in Patients with cHL: Results of the Ongoing, Randomized Phase III HD21 Trial By the GHSG

- **The final analysis of the TRMB endpoint from the HD21 study**
  - TRMB defined as any CTCAE grade 3 or 4 organ toxicity or grade 4 hematological toxicity
- **Summary of the results: eBEACOPP vs BrEACADD**
  - TRMB 59% vs 42 % (RR for BrECADD 0.72; 95% CI 0.65 - 0.79, p<0.001)
  - Hematological TRMB events 52% vs 31% (p<0.001) with the reduction in red cell and platelet transfusions
  - TRMB organ toxicity 17% vs 19% (p = 0.455)
  - Peripheral sensory neuropathy
    - all grades 49% vs 38%
    - grade 2 14% vs 6%,
    - grade 3 2% vs 1%
- **Conclusion:**
  - This analysis shows a significant and clinically relevant reduction in TRMB with BrECADD as compared to eBEACOPP

*Borchmann P Blood **2022**, 140, 771–773 (ASH 2022)*

Results of HD21 trial in NCCN v 3.2024 guidelines for patients with advanced cHL

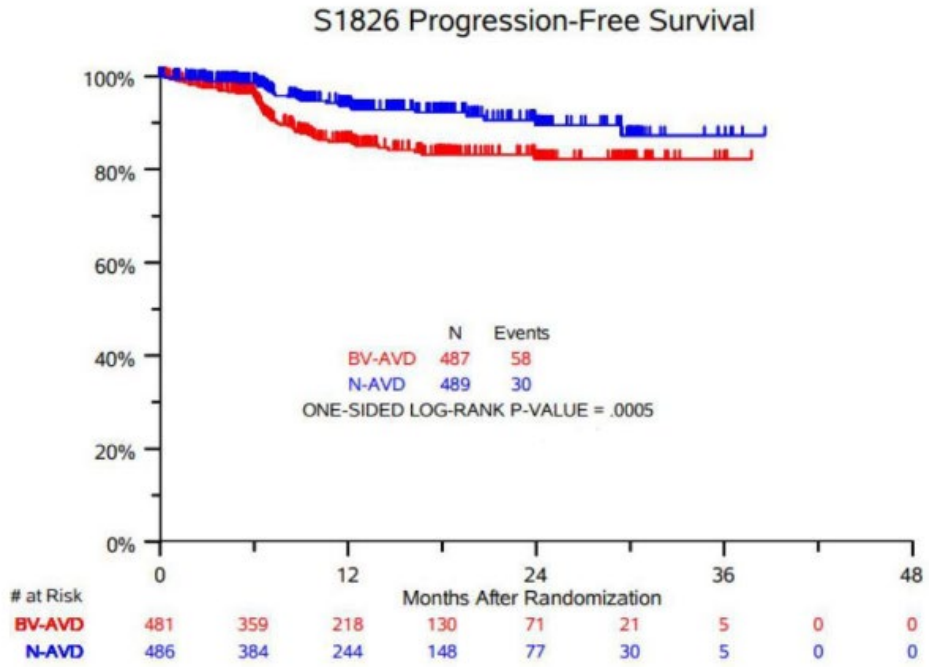
BreCADD: useful in certrain circumstances



Upfront 2 cycles of eBEACOPP: replaced by BrEACADD in NCCN v 3.2024 guidelines!

Novel Combinations for advanced cHL: BV+AVD vs N+AVD

- The S1826 SWOG trial:
  - patients with advanced-stage cHL (CS III/IV) randomized to receive BV-AVD or the combination N-AVD (nivolumab-AVD)



1y PFS: N-AVD vs BV-AVD
94% vs 86%

Further follow-up is needed to accurately estimate the efficacy and long-term toxicity of N-AVD

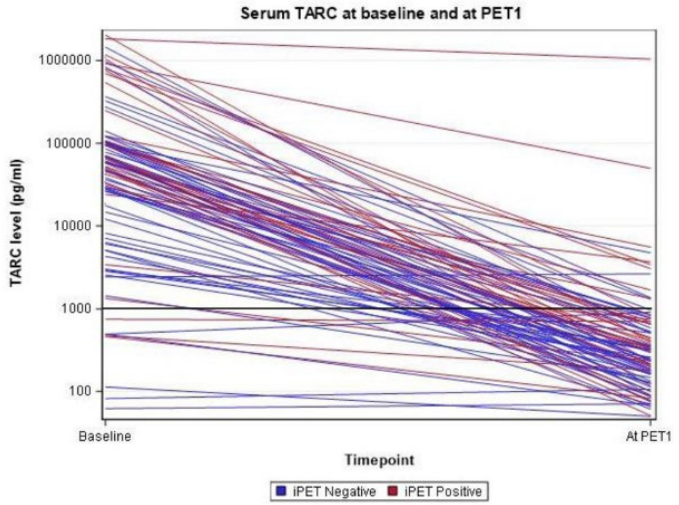
Herrera AF Hematol. Oncol. 2023, 41, 33–35
ICML 2023

T001: FDG-PET AND SERUM TARC LEVELS AFTER ONE CYCLE OF BV-AVD IN ADVANCED STAGE HODGKIN LYMPHOMA PATIENTS: RESULTS FROM THE VERY EARLY PET-RESPONSE ADAPTED EORTC-COBRA TRIAL

Arjan Diepstra[1], Lydia Visser[1], Catherine Fortpied[2], Walter Noordzij[3], Annika Loft[4], Anne Arens[5], Anna Sureda-Balari[6], Susana Carvalho[7], Andrej Vranovský[8], Ward Sents[2], Emanuel Buhrer[2], Wouter J. Plattel[9], Martin Hutchings[10]

Diepstra A. et al.
12th International Symposium on HL
HemaSphere 6():p 1, October 2022

- Single-arm multicenter phase II study
- Aim of the study: the value of very early PET-response adapted BV-based therapy for advanced stage cHL
- Methods:
  - Patients with a negative iPET after 1 cycle of BV-AVD: 5 additional BV-AVD cycles
  - iPET+ patients: escalation to six cycles of BV-ECADD
  - ELISA used to measure serum thymus and activation regulated chemokine (TARC) levels, which have been reported to reflect cHL disease activity and correspond with treatment response (Driessen J, Leuk 2022; Diepstra A Blood 2023)
  - TARC levels were measured both at baseline (bTARC) and after one cycle of BV-AVD (iTARC)



N=150
iPET was positive in 40% of pts
84 pts with available iTARC and positive bTARC
- iPET (+) in 33 cases (39%)
- iTARC positive in 12 cases (14%)
- 8/12 iTARC positive cases were also iPET positive

Conclusion: The majority of advanced stage Hodgkin patients showed a treatment response already after 1 cycle of BV-AVD, as measured by FDG-PET and serum TARC sults suggests

Management of cHL in patients > 60 yrs

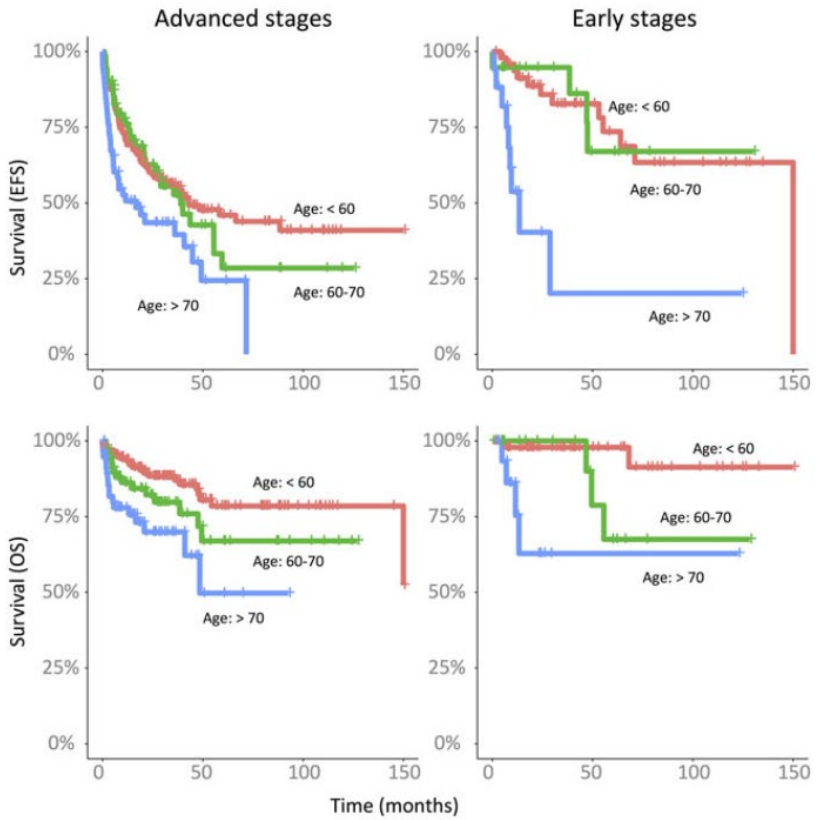
- **CHL in patients who are older is associated with poorer disease outcomes**

ORIGINAL ARTICLE: CLINICAL

Check for updates

Hodgkin lymphoma of the elderly patients: a retrospective multicenter analysis from the Polish Lymphoma Research Group*

Patients characteristics	Age 50–60 (Y)	Age >60 (O)	*p*
No (%)	201 (57%)	149 (43%)	
Age median	54	70	
Treatment: early (%)			
RT alone	3 (6%)	5 (15%)	
ABVD ± RT	47 (89%)	25 (76%)	
CHOP ± RT	0	1 (3%)	
BEACOPP	3 (6%)	0	
Palliative	0	2 (6%)	
Treatment: advanced (%)			
ABVD-/ABVD-like ± RT	125 (85%)	100 (86%)	
MOPP			
CHOP/PVAG	0	8 (7%)	
BEACOPP	18 (12%)	3 (3%)	
Palliative	5 (3%)	5 (4%)	



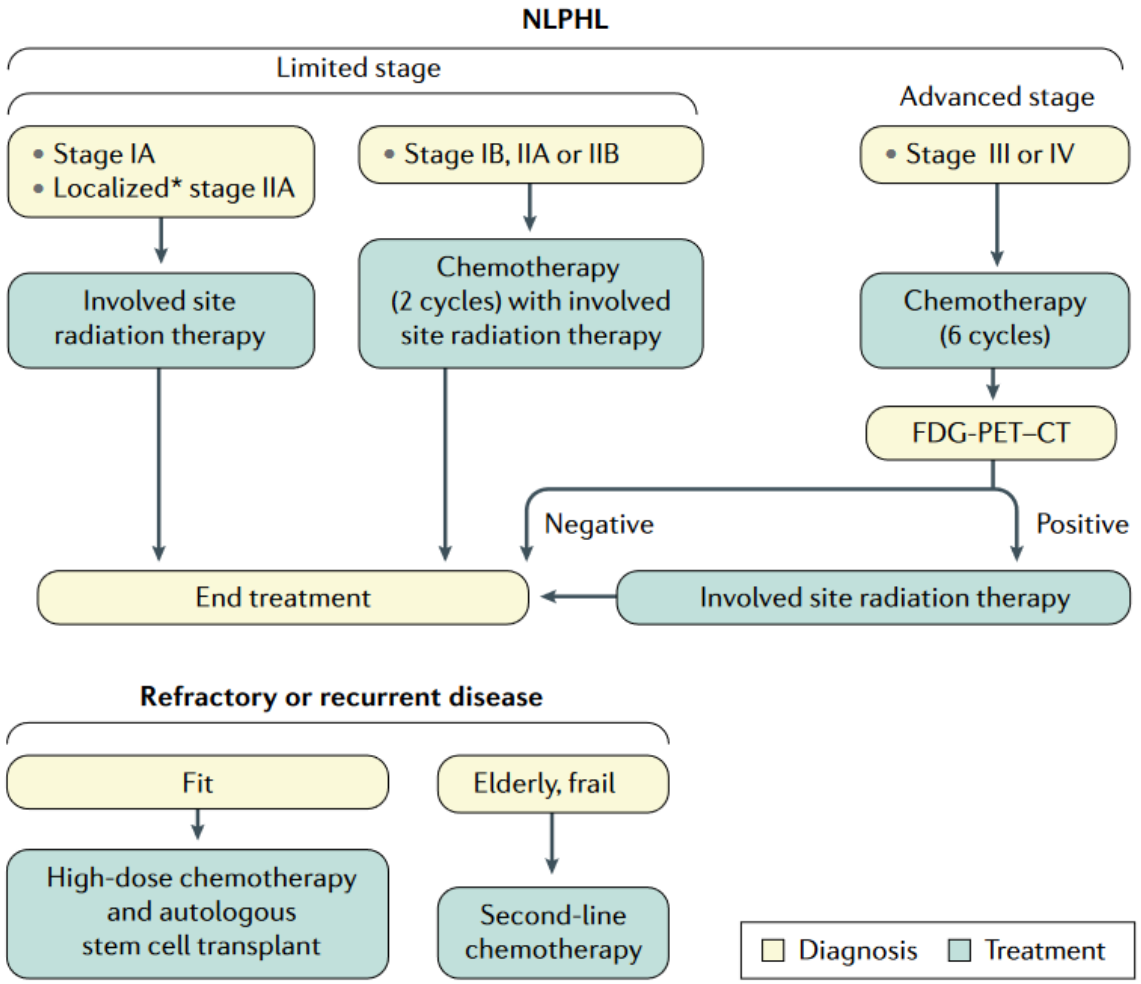
Wrobel T Leuk Lymph 2018

Management of cHL in patients > 60 yrs

Patients' Characteristics, Outcome, and Toxicity	BV Monotherapy (BREVITY) [95]	BV Monotherapy [96]	BV-Dacarbazine [97]	BV-Bendamustine [97]	BV-Bendamustine (HALO) [98]	BV-Nivolumab [99]
Patients (total, N)	35	27	22	20	60	20
Patients (evaluable, N)	31	26	19	17	59	19
Eligibility criteria	Stage IIBX/III/IV unfit for standard CT *	≥60 years old	≥60 years old	≥60 years old	Stage IIB/III/IV ≥60 years old	≥60 years old
Age [median (IQR or range)]	77 (72–82)	78 (64–92)	69 (62–88)	75 (63–86)	70.32 (62–79)	72 (NR–NR)
Ann Arbor Stage III, IV	80%	63%	68%	75%	80%	80%
ECOG PS ≥ 2	48%	22%	32%	20%	10%	5%
B-symptoms	71%	22%	29%	41%	68%	NA
CIRS [median (IQR or range)]	5 (4, 7)	NA	NA	NA	NA	NA
TRM	0.35%	0%	0%	0%	NA	0%
ORR	84% **	92% ***	100% ***	100% ***	63%	95%
CMR	26% **	73% ***	62% ***	88% ***	80.36%	NA
PFS Median 1-year 2-year	 7.3 months 14% 7%	 10.5 months ~35% ~30% +	 46.8 months NA NA	 40.3 months NA NA	 NR 84% 54%	 NR NA NA
OS Median 1-year 2-year	 19.5 months 73% 42%	 77.5 months NA NA	 64 months NA NA	 46.9 months NA NA	 83% 97% 83%	 NR NA NA

Vassilakopoulos P.…Galamini A. et al. IJMS 2023

Management algorithm for nodular lymphocyte-predominant HL



* two closely contiguous nodal sites

Connors JM Nature 2020

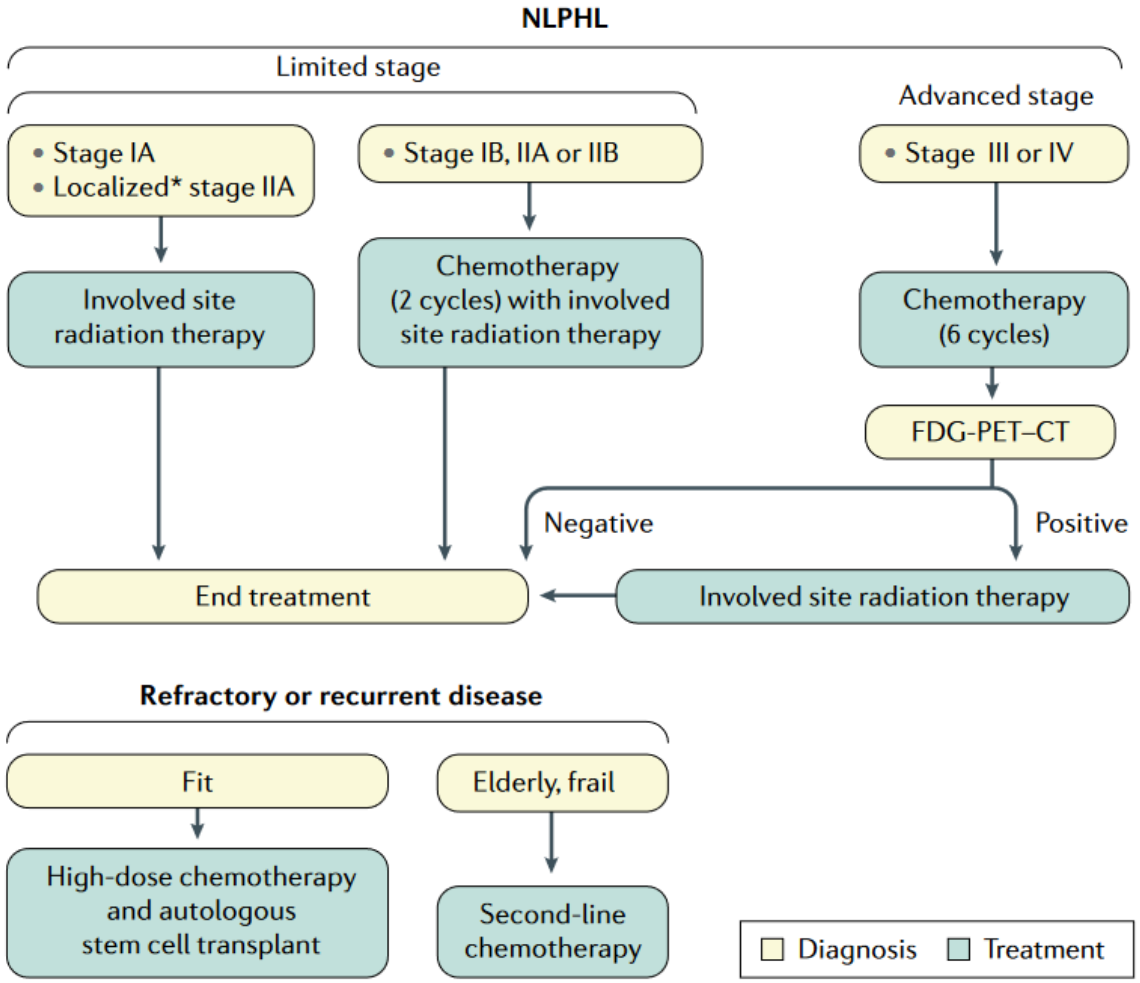
Immunophenotype of neoplastic cells of NLPHL

Table I. Immunophenotype of the neoplastic cells of NLPHL, cHL and THRLBCL.

	Entities Phenotype		
Antibody	*NLPHL*	*cHL*	*THRLBCL*
CD45	+	–	+
CD30	–	+	– (rarely +)
CD15	–	+	–
CD20	+	–	+
CD79a	+	– (rare + cases)	+
CD19	–/+	–	–/+
J-chain	+	–	n.a.
PAX-5	+	+ (weak) to –	+
OCT-2	+	– to + (weak)	+
BOB-1	+	– (few cases weak +)	+
BCL6	+	–	–/+
PU-1	+	–	–/+
IRF-4/MUM1	Variable	+	+
CD10	–	–	–/+
BTK	+	–	+
EMA	+	–	–/+

McKay P BJH 2016

Management algorithm for nodular lymphocyte-predominant HL



Recommended systemic therapy regimens by NCCN v3.2024:
Rituximab +

- ABVD
- CHOP
- CVbP

* two closely contiguous nodal sites

Connors JM Nature 2020

Thank you for your attention!