Klassiskt Hodgkins lymfom –
avancerade stadier

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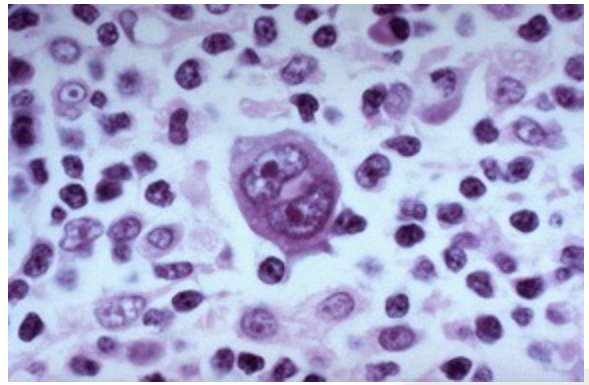
Akademiska sjukhuset.

Klassiskt Hodgkins lymfom



- Bimodal åldersfördelning
- God prognos för yngre, sämre för äldre
- CD30-positiva Hodgkin- och Reed-Sternberg-celler
- Uttrycker PD-L1 och PD-L2 (9p24.1 amplifiering)
- Primärbehandlingen *hittills* kombinationscytostatika för avancerade stadier
- PET viktigt för tidig behandlings-utvärdering för avancerade stadier. TARC komplement (liksom SR).
- Viktigt att skilja klassiska HL från nodulära lymfocytdominerade (NLPHL) som är CD20-positiva indolenta lymfom

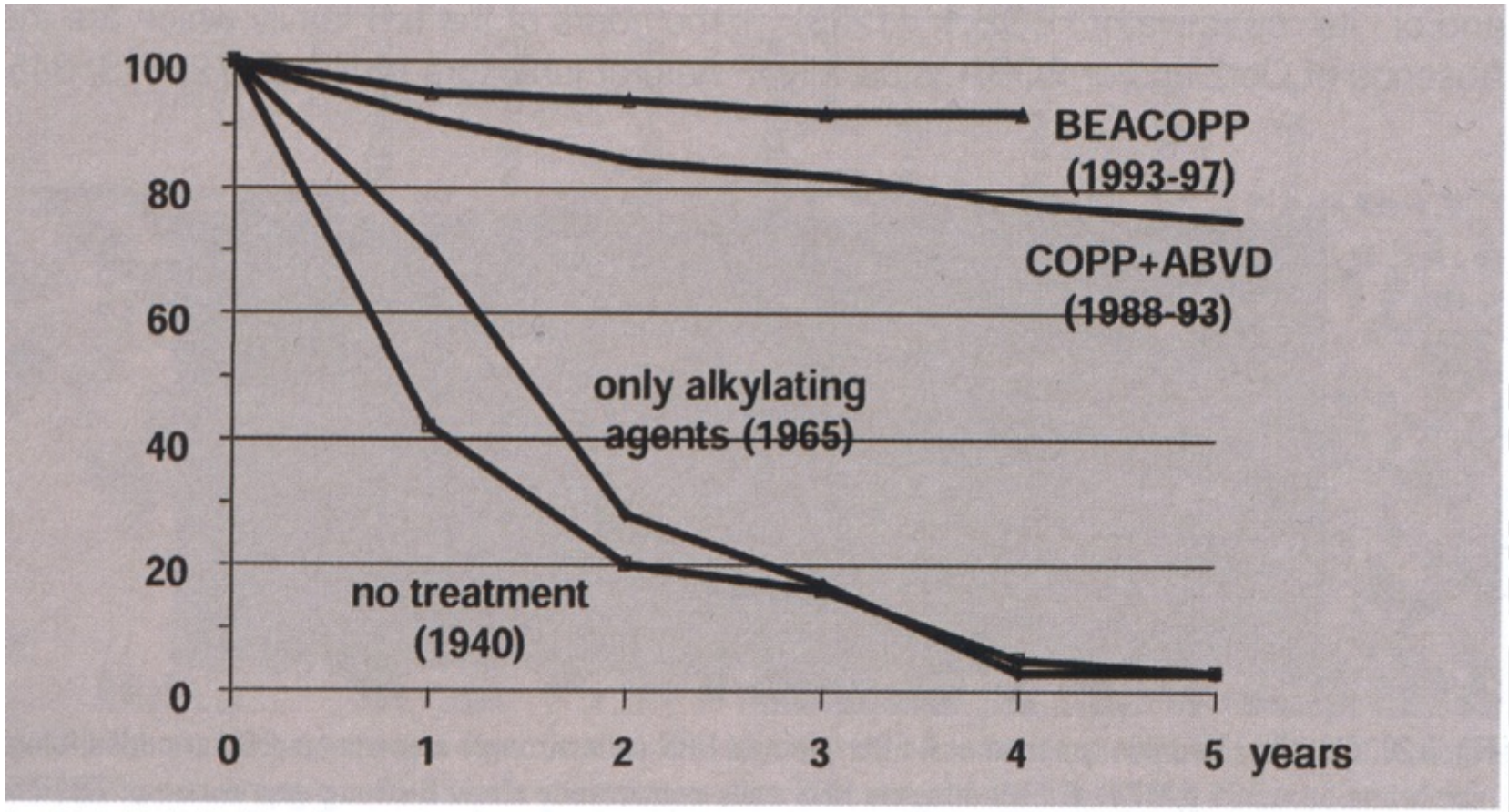
Bakgrund

- Tidiga stadier (I-IIA), unga: Extremt stor andel botade.
  - Minimera toxicitet, behålla antal botade.
  - Sena biverkningar mycket viktiga.
- Avancerade stadier (IIB-IV), unga: Stor andel botade.
  - Maximera antal botade, hålla nere toxicitet.
  - Sena biverkningar viktiga.
- Äldre: Låg andel botade.
  - Förbättra antal botade, hålla behandlingen tolerabel.
  - Sena biverkningar inte viktiga.

Bakgrund

- Tidiga stadier (I-IIA), unga: Extremt stor andel botade.
  Minimera toxicitet, behålla antal botade.
  Sena biverkningar mycket viktiga.
- **Avancerade stadier (IIB-IV), unga: Stor andel botade.**
  Maximera antal botade, hålla nere toxicitet.
  Sena biverkningar viktiga.
- **Äldre: Låg andel botade.**
  Förbättra antal botade, hålla behandlingen tolerabel.
  Sena biverkningar inte viktiga.

Historia: kombinationscytostatika



Singelbehandling botar inte Hodgkins lymfom

Avancerade stadier

- Stadium IIB-IV
- Riskfaktorer enligt IPS:

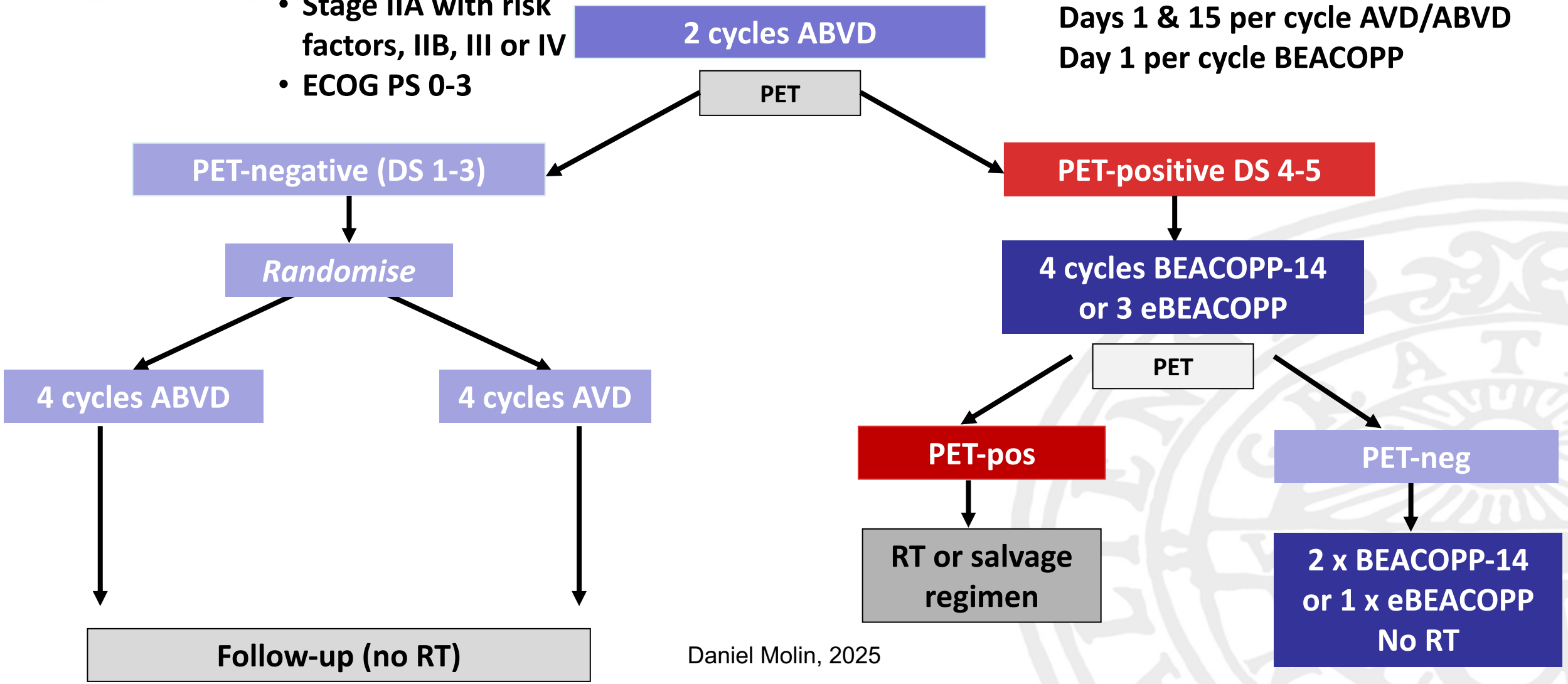
1. Man
2. > 45 år
3. Stadium IV
4. Hb < 105 g/L
5. S-Albumin < 40 g/L
6. LPK > 15 x 109/L
7. B-lymfocyter < 8 % eller < 0,6 x 109/L

IPS styr inte behandlingen idag.

Avancerade stadier: RATHL

- Classical HL
- Stage IIA with risk factors, IIB, III or IV
- ECOG PS 0-3

Bleomycin dose: 10,000 iU/m²
Days 1 & 15 per cycle AVD/ABVD
Day 1 per cycle BEACOPP



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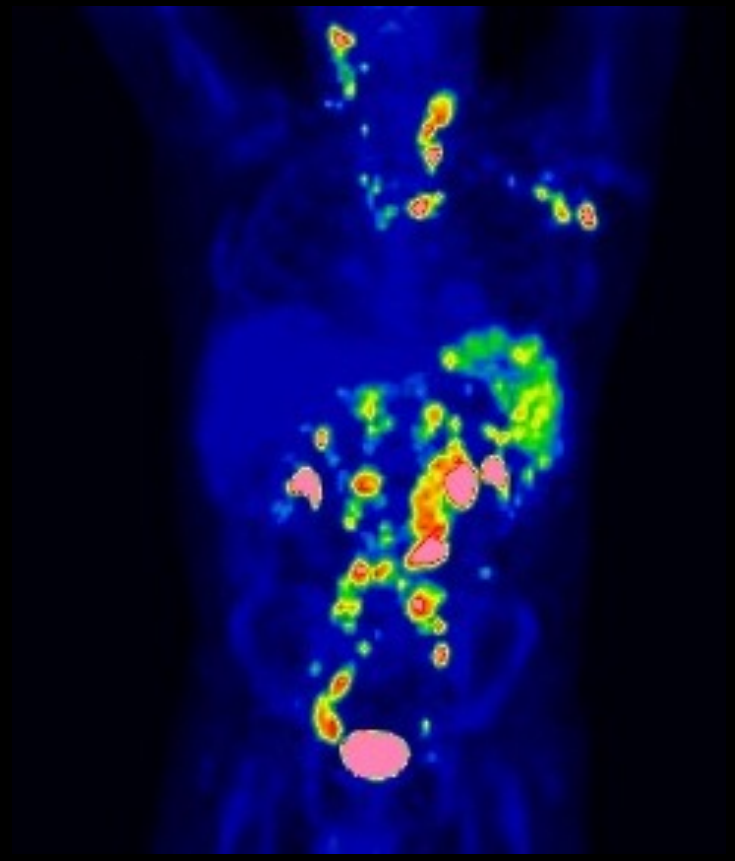
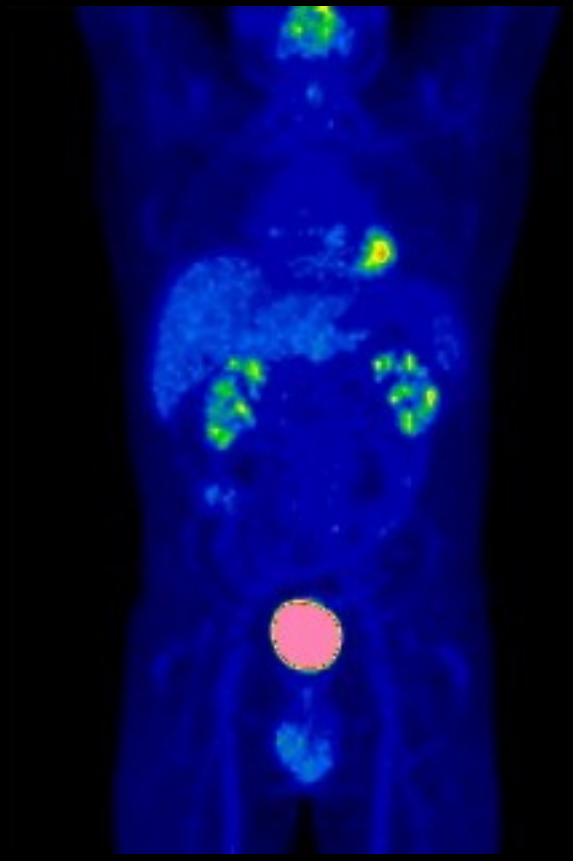
FDG-PET/CT för att styra behandlingen (öka eller minska intensitet)



Stadieindelning



Efter två kurer

Long Follow-up of the Response-Adjusted Therapy for Advanced Hodgkin Lymphoma (RATHL) Trial(CRUK/07/033) Confirms the Safety of Both De-Escalation and Intensification of Chemotherapy

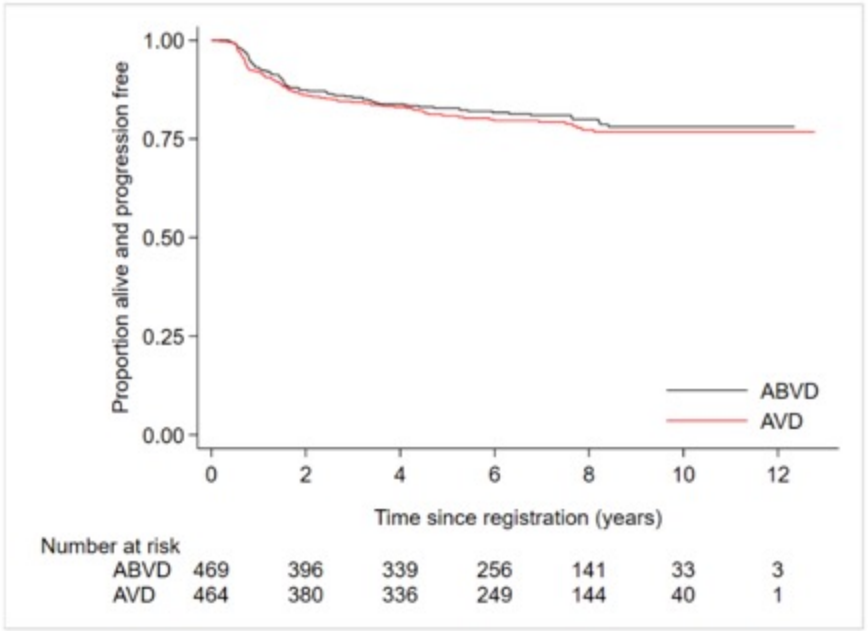
Stefano Luminari, Alexander Fosså, Judith Trotman, Daniel Molin, Francesco Annibale d'Amore, Gunilla Enblad, Leanne Berkahn, Sally F Barrington, John A. Radford, Massimo Federico, Amy Kirkwood and Peter Johnson

Published in JCO 2024

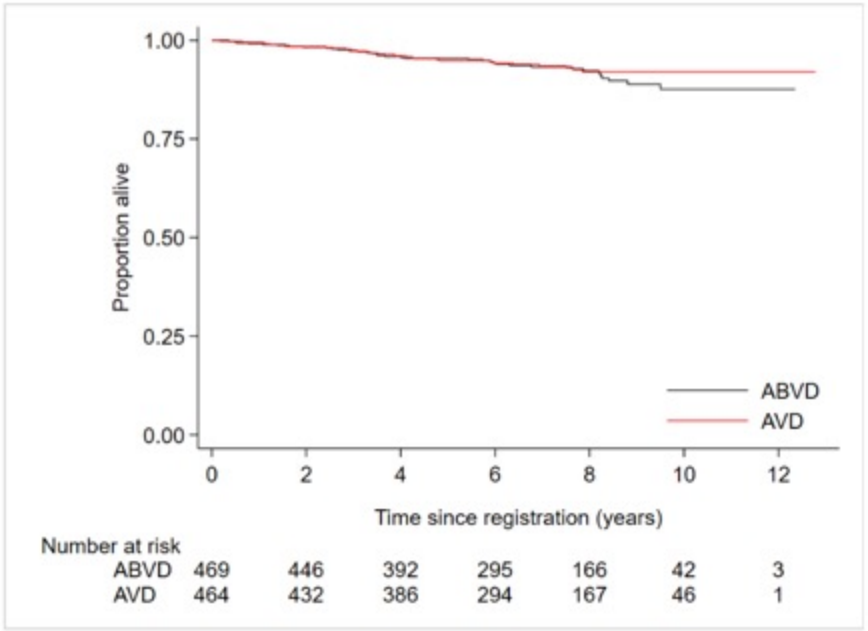
RATHL-uppdatering 2024

Det är säkert att utesluta bleomycin efter två cykler för PET-negativa.

PFS of PET-negative pts



OS of PET-negative pts



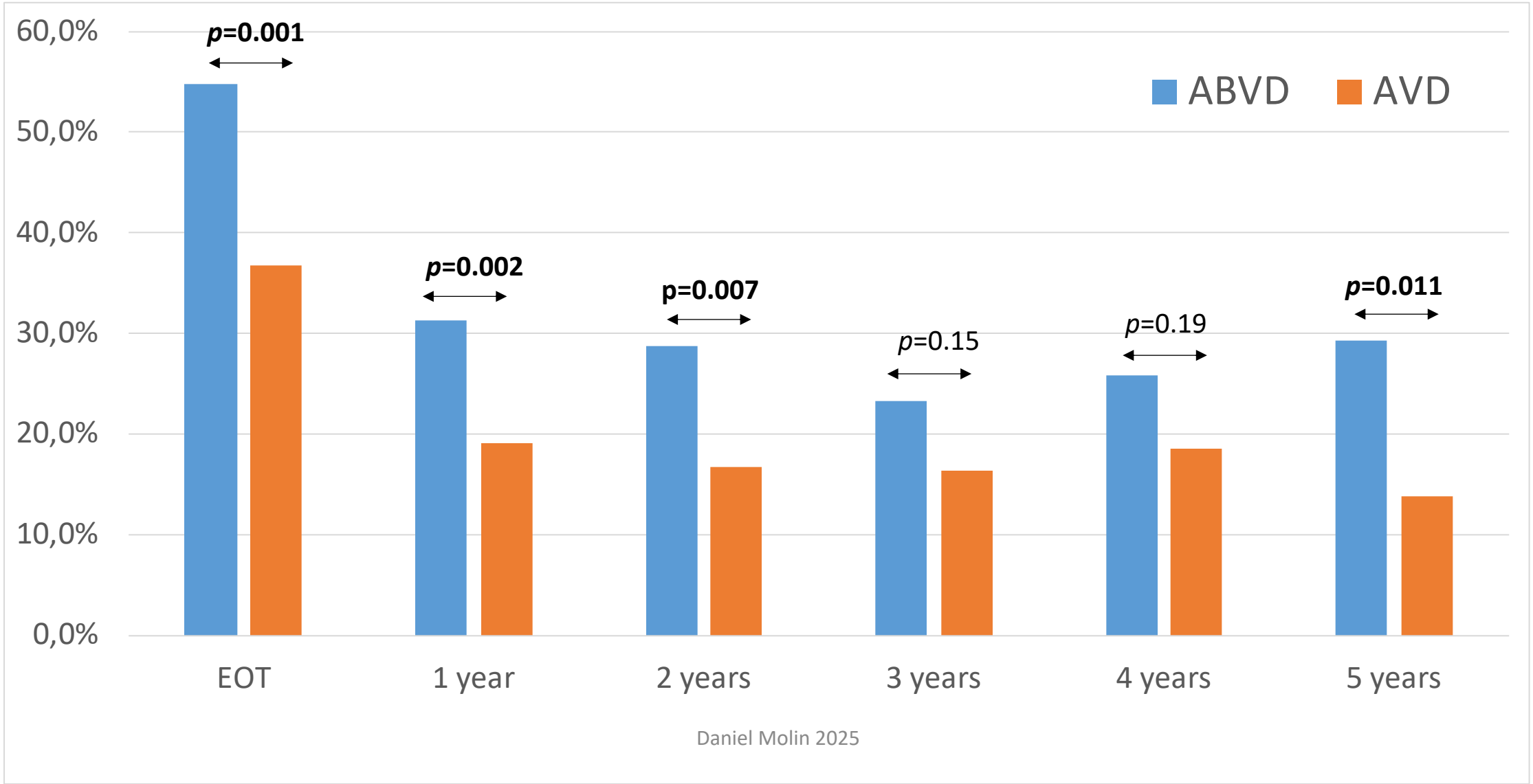
Daniel Molin 2025

ASH, December 2023

Bleomycin affects lung function for at least 5 years after treatment for Hodgkin lymphoma: data from the international, randomised phase 3 RATHL trial

Elizabeth Phillips, Amy Kirkwood, Christina Hague, Jorgen Vestbo, Massimo Federico, Francesco D'Amore, Alexander Fosså, Judith Trotman, Leanne Berkahn, Daniel Molin, Stefano Luminari, Sally Barrington, Peter Johnson, John Radford

Proportion of Patients with DLCO <75%



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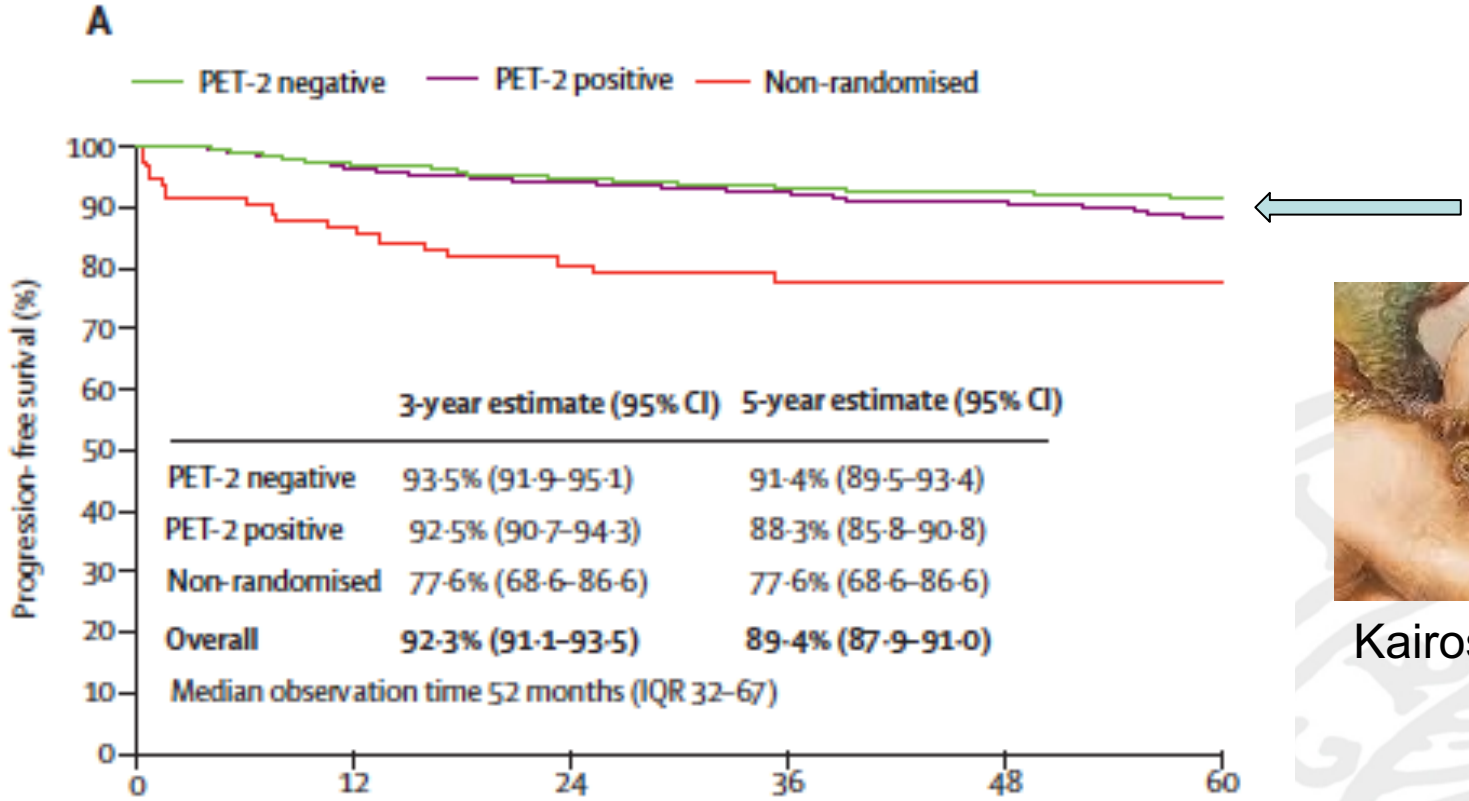
HD18 – PFS

6 eller 8 eBEACOPP för PET+
4 vs **6**/8 eBEACOPP för PET-



Number at risk (number censored)						
PET-2 negative	1010 (0)	921 (63)	845 (118)	685 (265)	548 (396)	385 (553)
PET-2 positive	948 (0)	854 (62)	766 (131)	600 (284)	476 (398)	276 (588)
Non-randomised	115 (0)	72 (31)	61 (37)	47 (49)	35 (61)	24 (72)

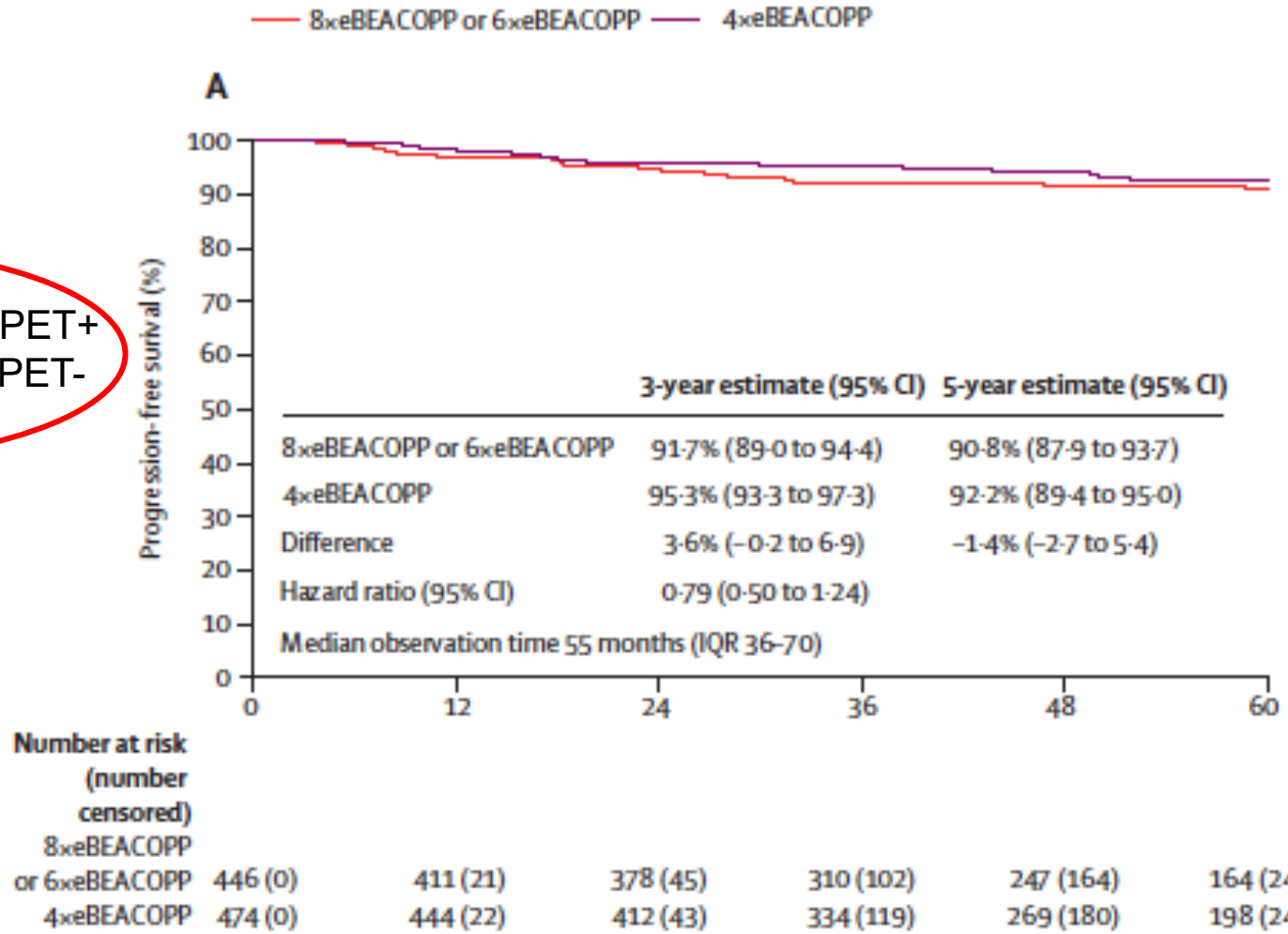
Kairos

Daniel Molin 2025

Borchmann et al (2017) Lancet

HD18 – 4x BEACOPPesk lika bra som 6/8 om PET2 negativ

6 eller 8 eBEACOPP för PET+
4 vs **6**/8 eBEACOPP för PET-



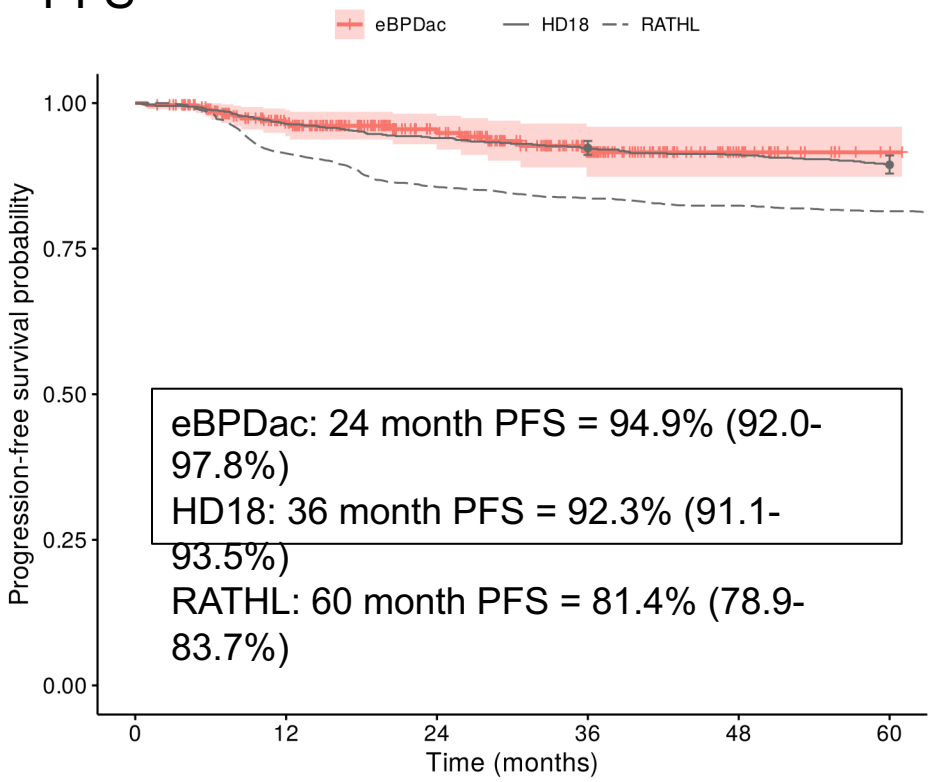
Kairos

Daniel Molin 2025

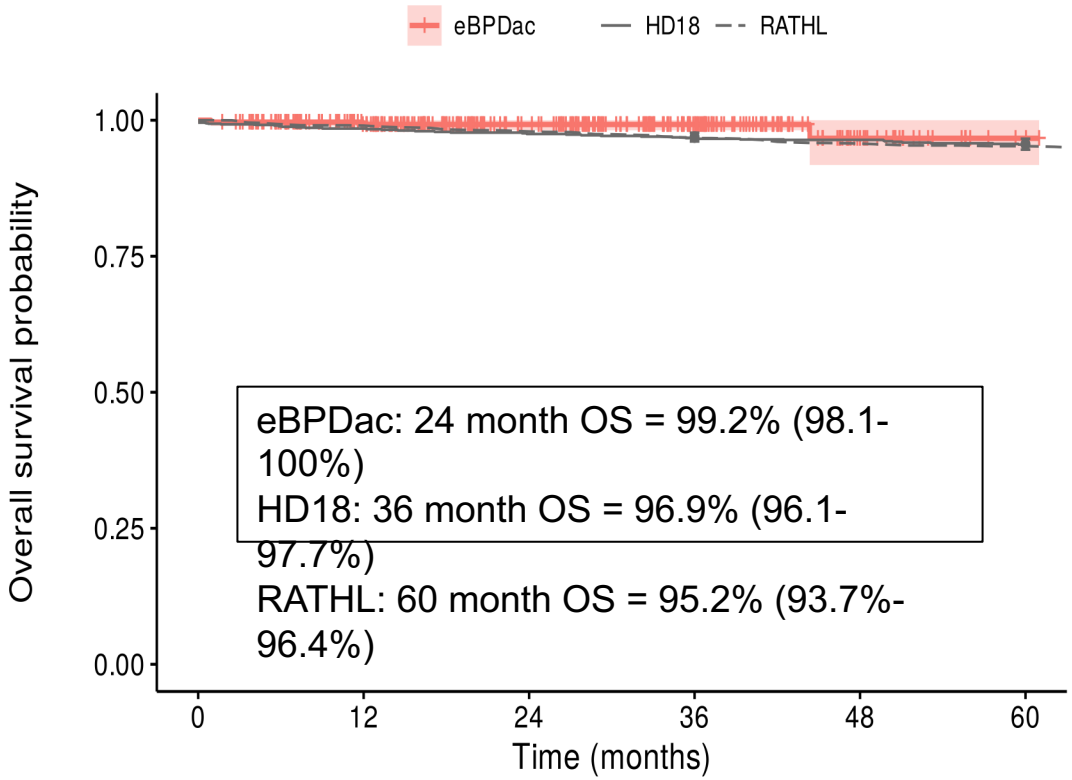
Borchmann et al (2017) Lancet

BEACOPDac (procarbazin⟹dacarbazin)

PFS



OS

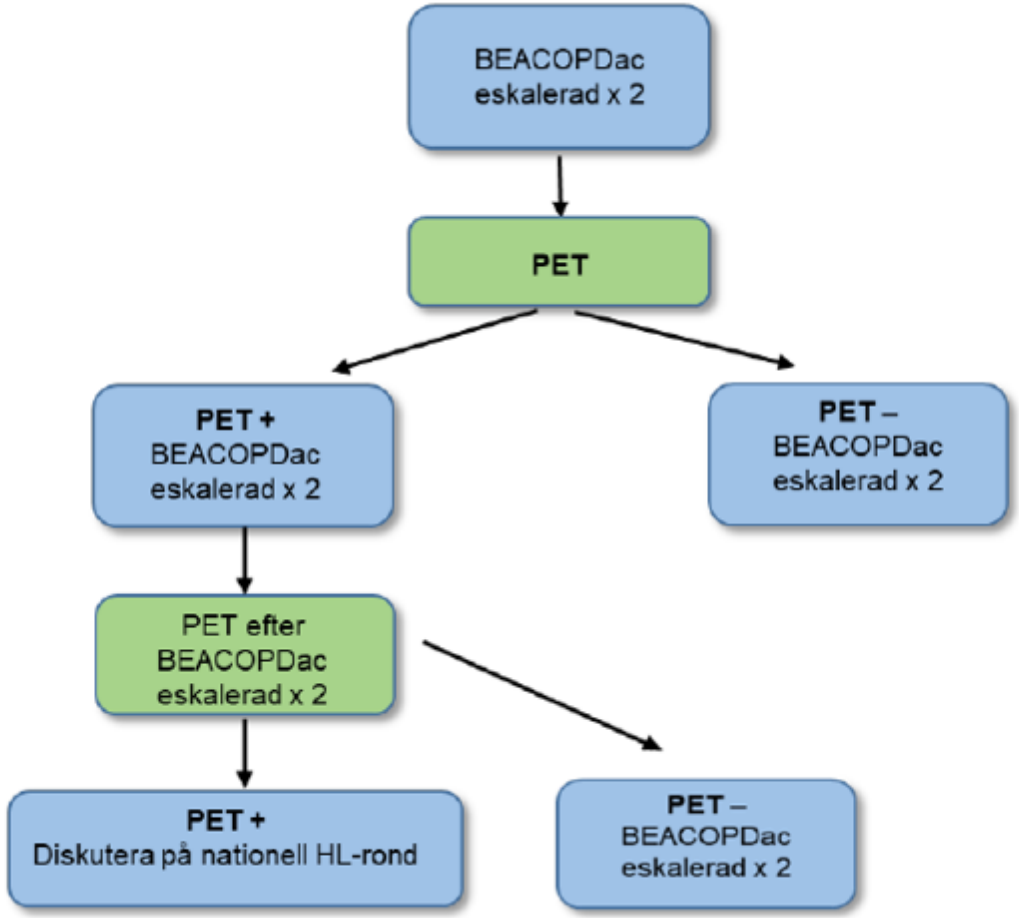


Färre transfusioner, färre vårddagar, tidigare återkomst av menstruation och högre spermieantal med BEACOPDac än BEACOPP.

Daniel Molin 2025

Santarsieri et al. Blood 2022

Avancerade stadier: behandling i Sverige, 18-60 år



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Klassiska Hodgkins lymfom uttrycker CD30

Brentuximab vedotin

Three components:

Antibody: specific for human CD30

Cytotoxic agent: antimicrotubule agent MMAE

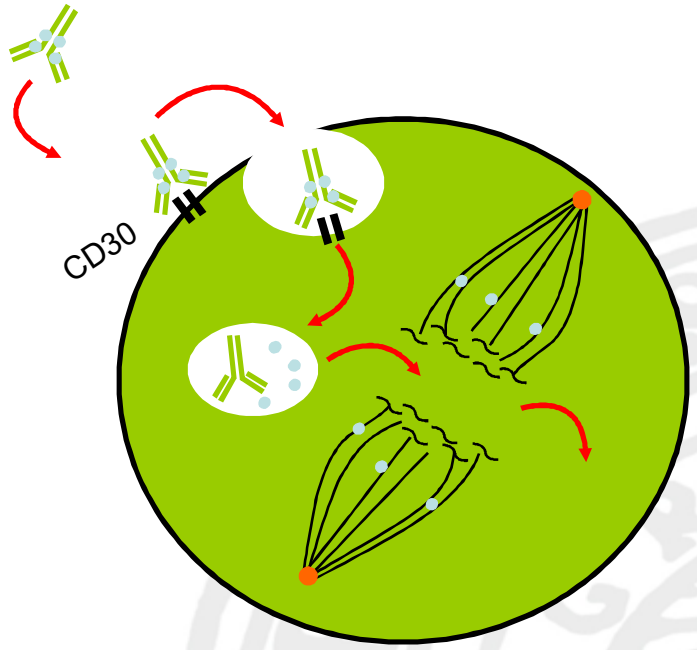
Linker: protease-cleavable linker that attaches MMAE to antibody

Antibody delivers drug to target cells by binding to CD30

When internalised, the conjugate is trafficked to the lysosomes

MMAE is released when the linker is degraded

MMAE inhibits tubulin polymerisation resulting in cell cycle arrest and apoptosis



Bartlett NL, et al. Poster presentation at ASCO 2010 Chicago, IL, USA (Abstract #8062).

Senter PD. Curr Opin Chem Biol 2009;13:235–44.

Younes A, et al. Poster presentation at ASH 2008, San Francisco, CA, USA (Abstract #1006).

ASH 2011.

Treatment related morbidity in patients with classical Hodgkin Lymphoma: results of the ongoing, randomized phase III HD21 Trial by The German Hodgkin Study Group

Peter Borchmann, Alden Moccia, Richard Greil, Mark Hertzberg, Valdete Schaub, Andreas Hüttmann, Felix Keil, Judith Dierlamm, Mathias Hänel, Urban Novak, Julia Meissner, Andreas Zimmermann, Stephan Mathas, Josée M Zijlstra, Alexander Fossa, Andreas Viardot, Bernd Hertenstein, Sonja Martin, Pratush Giri, Peter Kamper, Daniel Molin, Stefanie Kreissl, Michael Fuchs, Gundolf Schneider, Andreas Rosenwald, Wolfram Klapper, Hans Eich, Christian Baues, Michael Hallek, Markus Dietlein, Carsten Kobe, Volker Diehl, Andreas Engert

Lancet, 2024

BV in the treatment of advanced stage classical Hodgkin Lymphoma

Remodelling eBEACOPP

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

GHSG

BrECADD, brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; eBEACOPP, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone

1. Diehl V, et al. N Engl J Med 2003;348:2386–95.

GHSG HD21 clinical implications of observed differences

Toxicity	eBEACOPP (%)	BrECADD (%)
Anemia (at least 1 red cell transfusion)	22	8
Thrombocytopenia (at least 1 platelet transfusion)	13	6

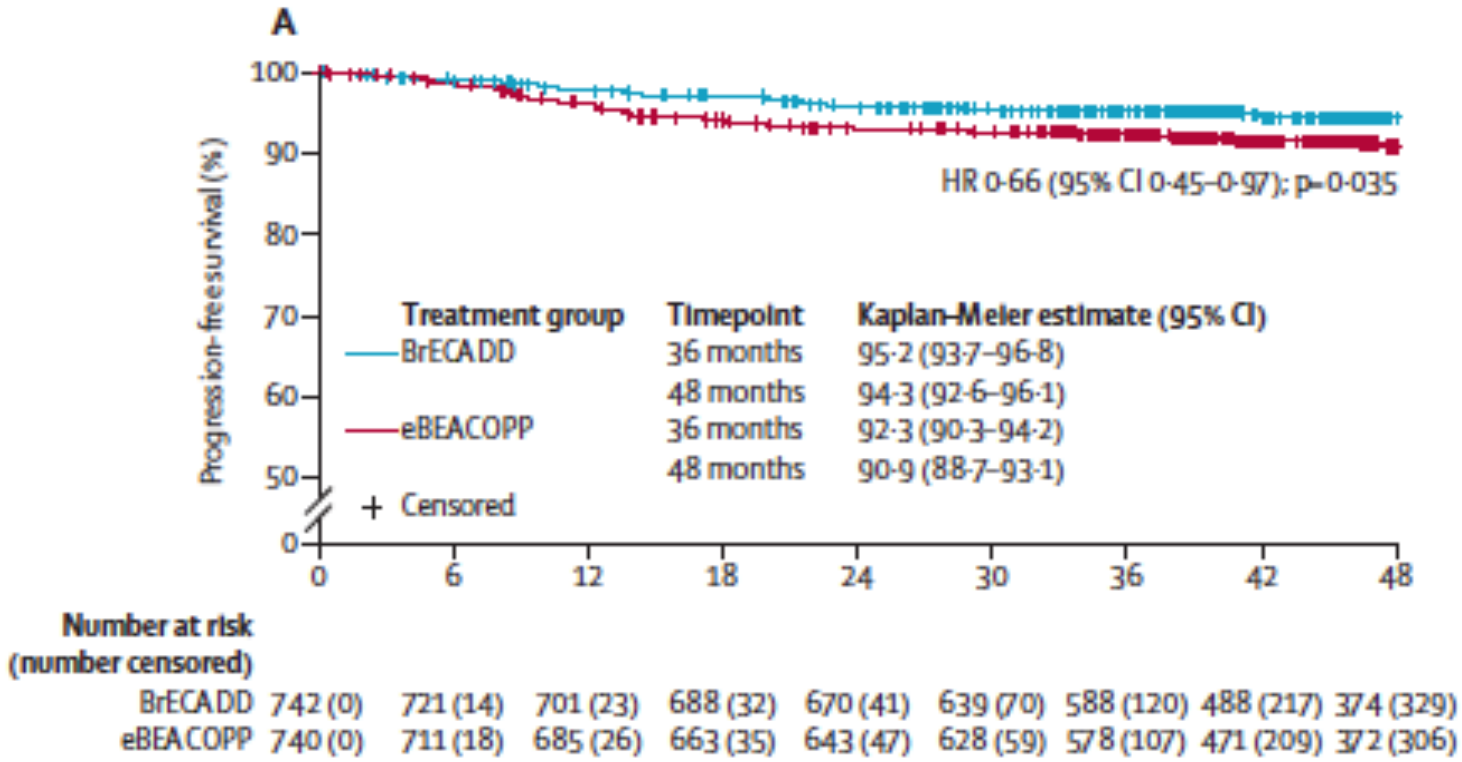
	eBEACOPP (%)	BrECADD (%)
Sensory PNP		
All grades	49	38
Grade 2	14	6
Grade 3	2	1

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

GHSG

Borchmann, Lancet, 2024

HD21 PFS



3 year OS 98.5%

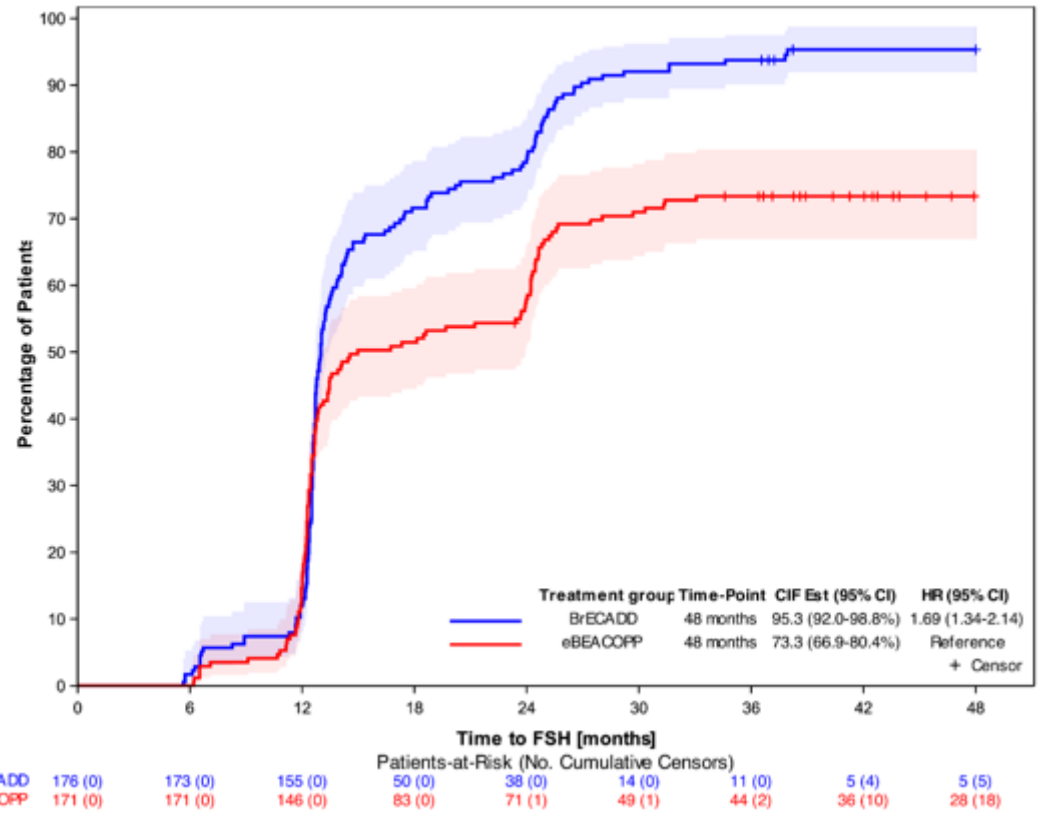
Borchmann, Lancet, 2024

Gonadal Function Recovery and Fertility in the Phase III German Hodgkin Study Group HD21 trial

J Ferdinandus, G Schneider, A Moccia, R Greil, M Hertzberg, V Schaub, A Hüttmann, F Keil, J Dierlamm, M Hänel, U Novak, J Meissner, A Zimmermann, S Mathas, JM Zijlstra, A Fosså, A Viardot, B Hertenstein, S Martin, P Giri, P Kamper, D Molin, AS Robertz, J Rosenbrock, M Fuchs, P Borchmann, Karolin Behringer

Accepted in *Lancet Oncology*

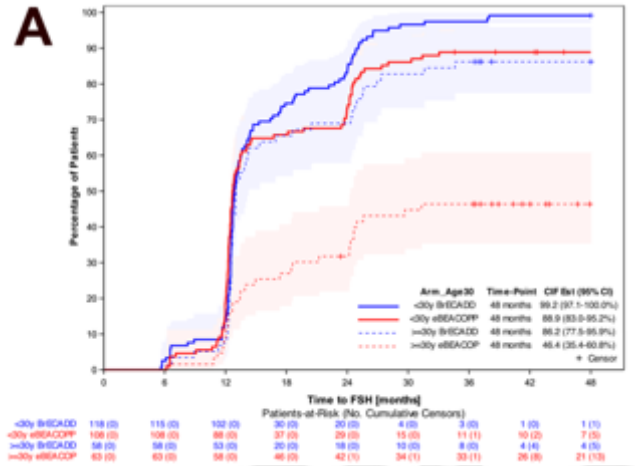
Gonadal function recovery – female patients



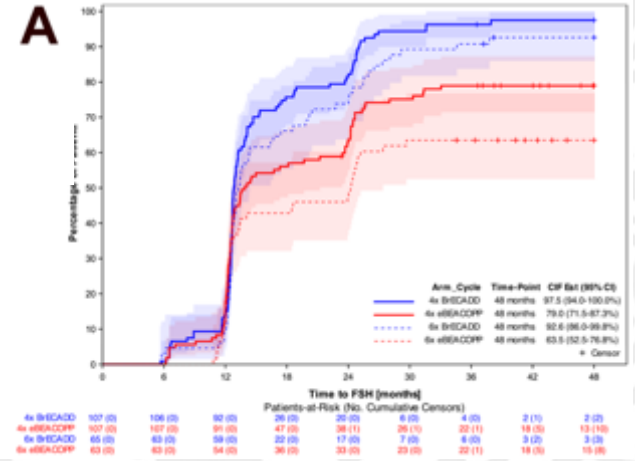
95·3% (95% CI 92·0-98·8)

73·3% (95% CI 66·9-80·4)

Age



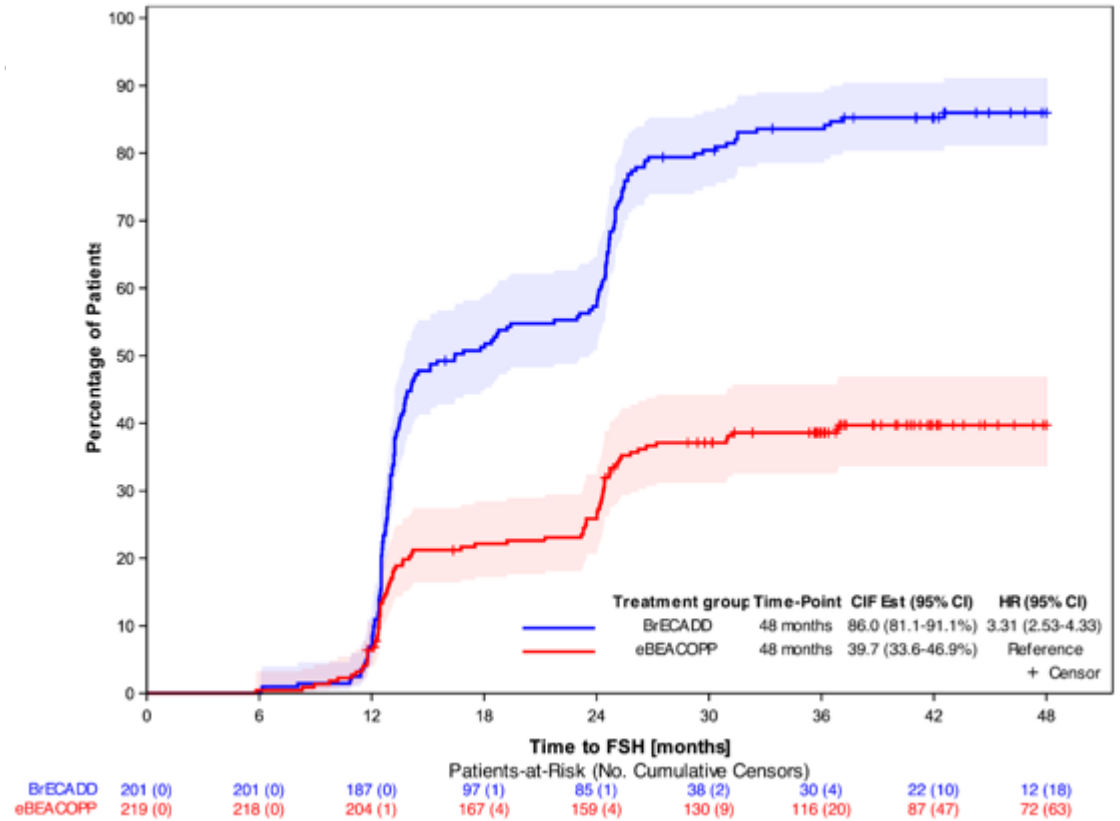
Number of cycles



Abbreviations: FSH, Follicle stimulating hormone; CI, confidence interval

Fernandius et al., accepted in Lancet Oncology

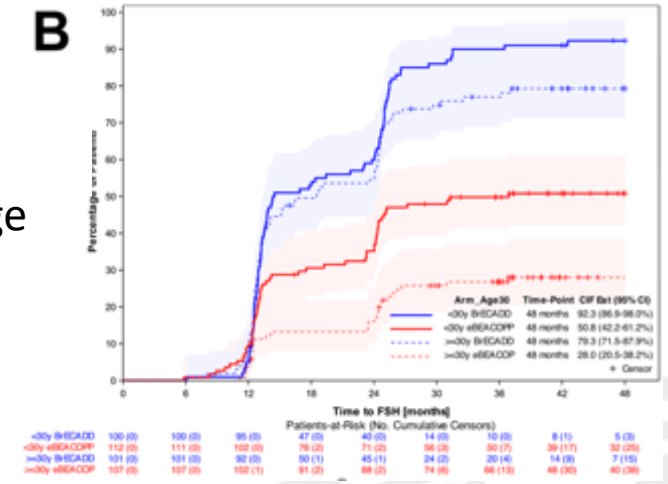
Gonadal function recovery – male patients



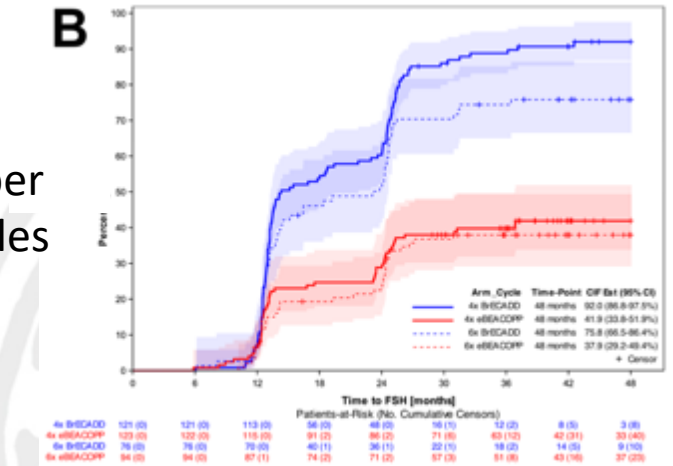
86·0% (95% CI 81·1-91·1)

39·7% (95% CI 33·6-46·9)

Age



Number of cycles

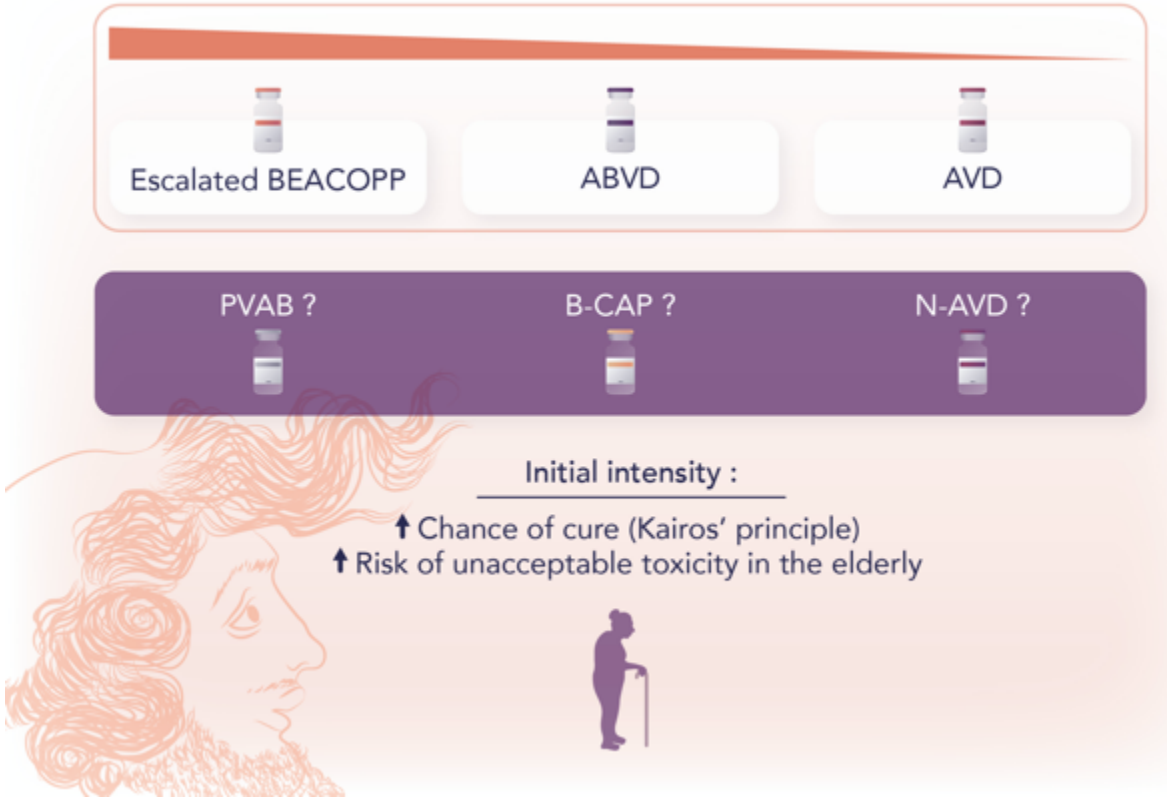


Abbreviations: FSH, Follicle stimulating hormone; CI, confidence interval

BrECADD ska utvärderas hälsoekonomiskt

Fernandius et al., accepted in Lancet Oncology

Aging Kairos: treating older Hodgkin patients



Daniel Molin, Aging Kairos: treating older Hodgkin patients, commentary,

Blood, 2024.

AVD – a possible golden standard in the first-line treatment of older classical Hodgkin lymphoma patients

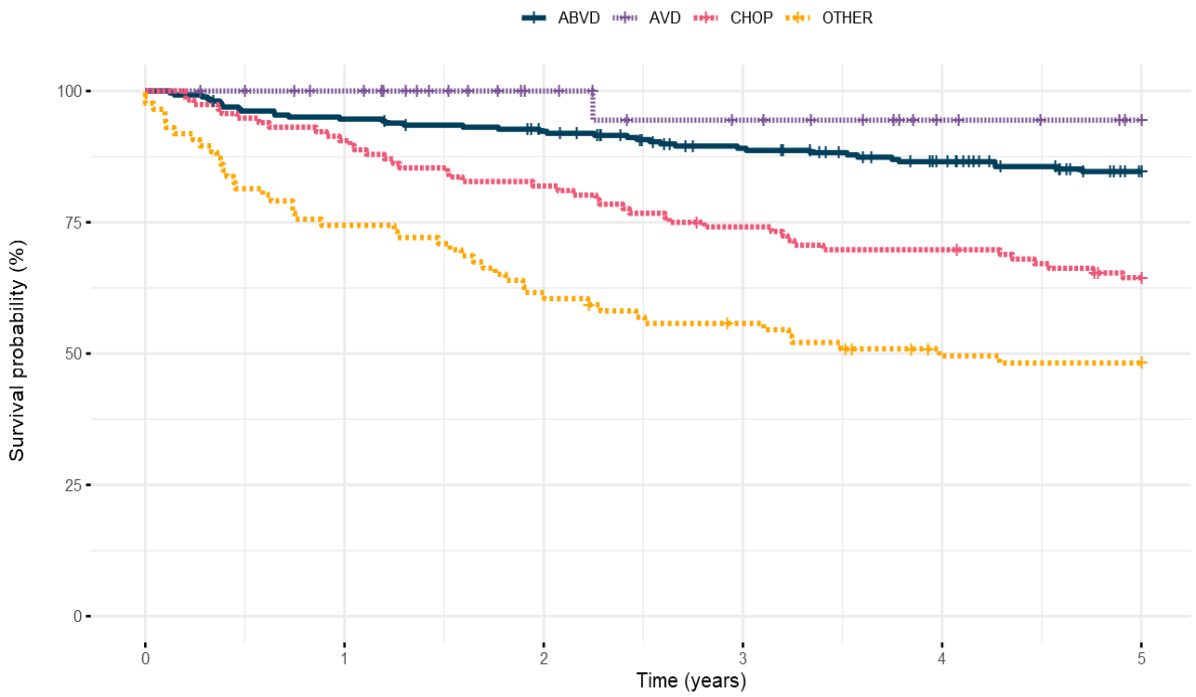
Ninja Övergaard, Kjersti Lia, Peter H Asdahl, Per Wikman, Ingrid Glimelius, Ingemar Lagerlöf, Ann-Sofie Johansson, Lotta Hansson, Gunilla Enblad, Johan Linderoth, Christina Goldkuhl, Alexander Fosså, Peter Kamper and Daniel Molin

Sweden, Denmark and Norway.

Bleomycin – lungtoxicitet, fr a hos äldre!

Results – Overall survival

Limited stage OS

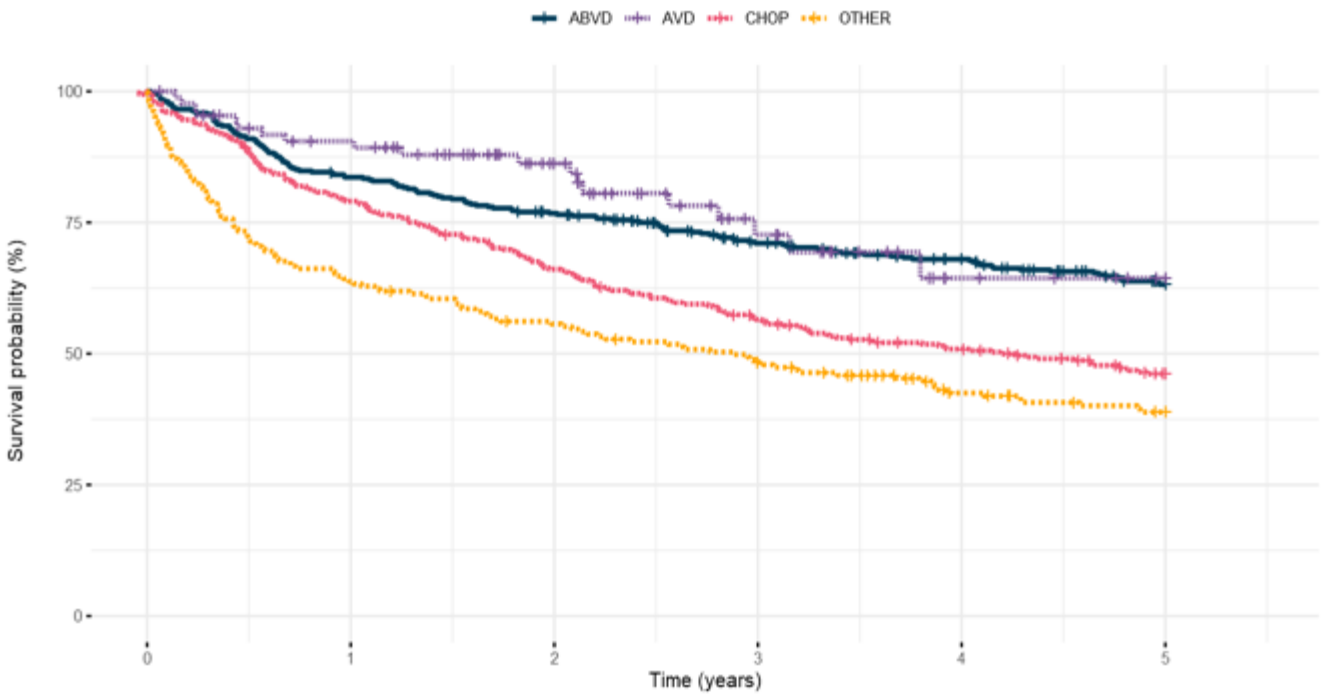


Number at risk

ABVD	262	247	236	214	196	171
AVD	35	31	20	15	8	4
CHOP	116	105	95	85	80	71
OTHER	85	64	53	46	37	36

Time (years)

Advanced stage OS



Number at risk

ABVD	409	341	309	264	237	200
AVD	87	72	48	24	8	3
CHOP	347	275	229	193	168	140
OTHER	210	134	115	98	73	62

Time (years)

Bleomycin på väg ut generellt

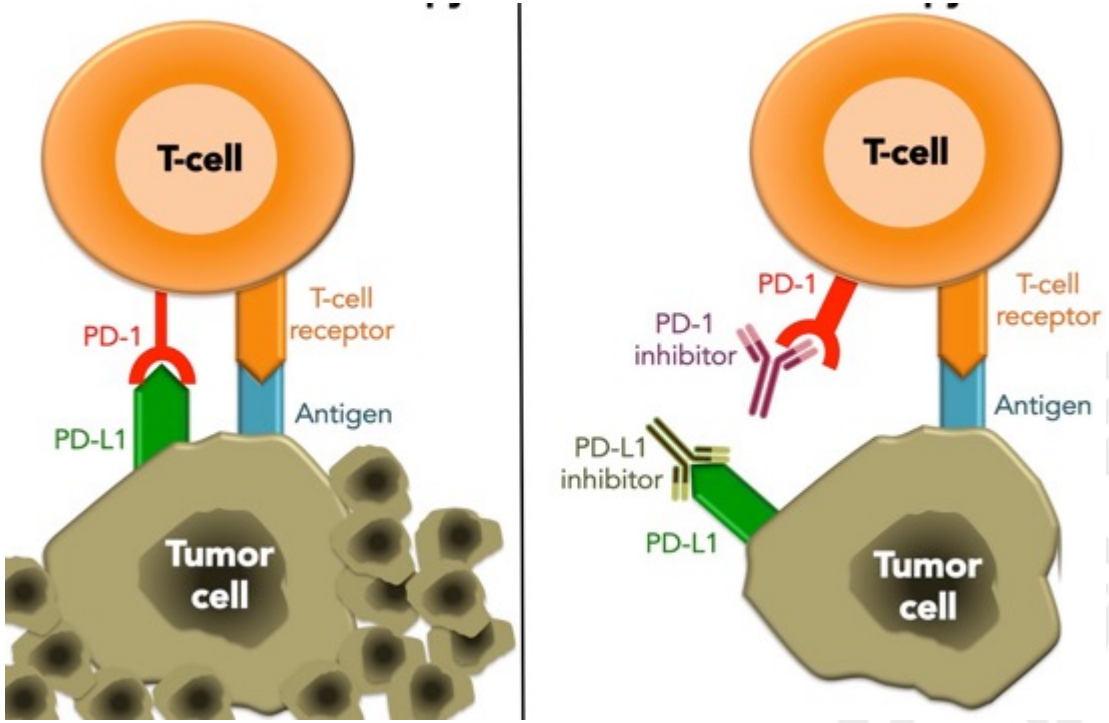
- RATHL visar att bleomycin ger långtidspåverkan på lungfunktionen och att det kan uteslutas efter två cykler
- AVD är minst lika effektivt som ABVD för äldre

- Ingår inte i nya regimerna BrECADD eller N-AVD för avancerade stadier

- Kommer nu att uteslutas från ABVD efter två cykler (senast) för alla åldrar och indikationer, vilket betyder att begränsade stadier med riskfaktorer kommer att behandlas med 2 ABVD+2 AVD+RT

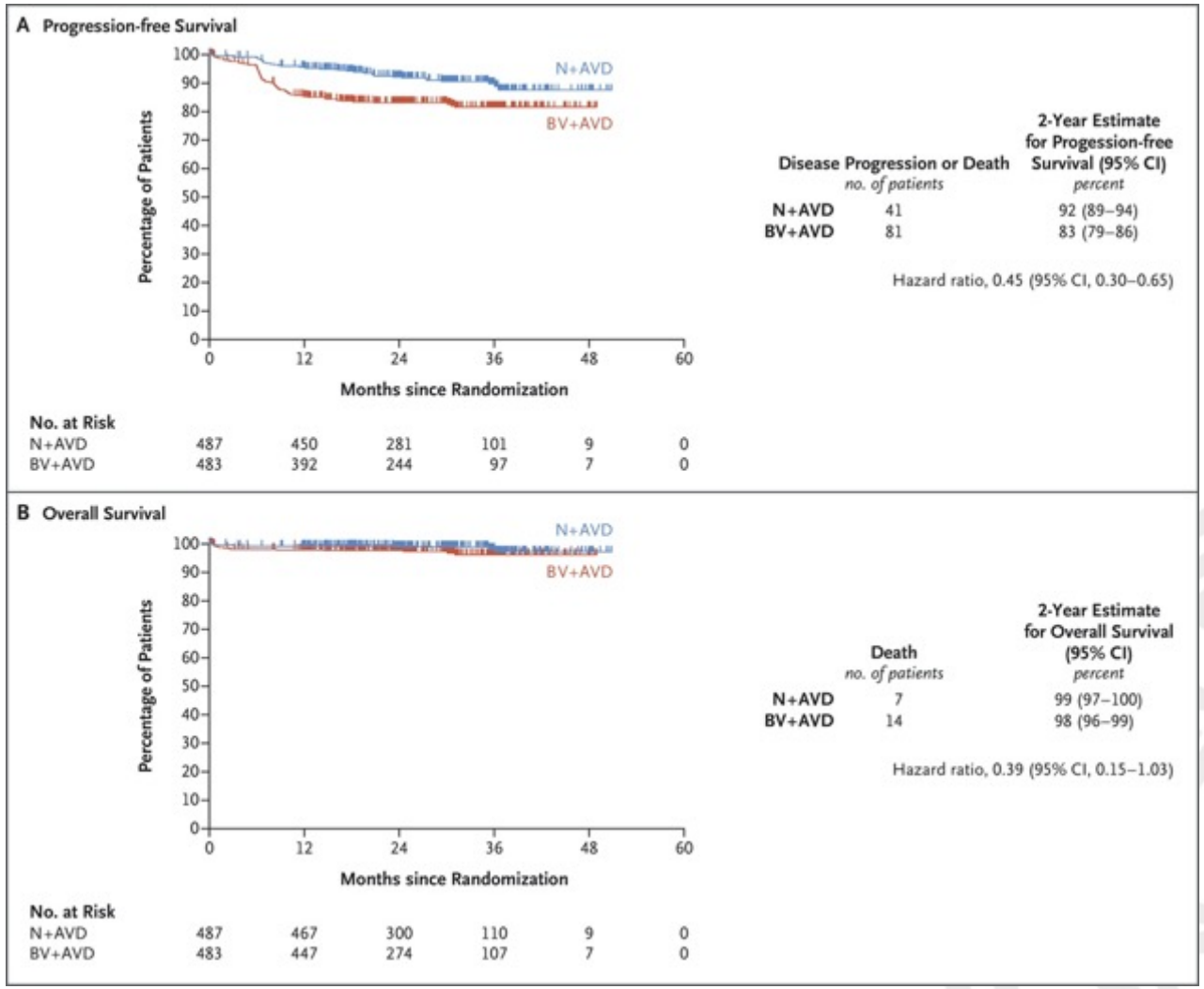
PD-1-hämmare

HRS-celler:
9p24.1 amplifiering,
PD-L1, PD-L2



Nivolumab-AVD: SWOG S1826

Progression-free Survival and Overall Survival (Modified Intention-to-Treat Population).

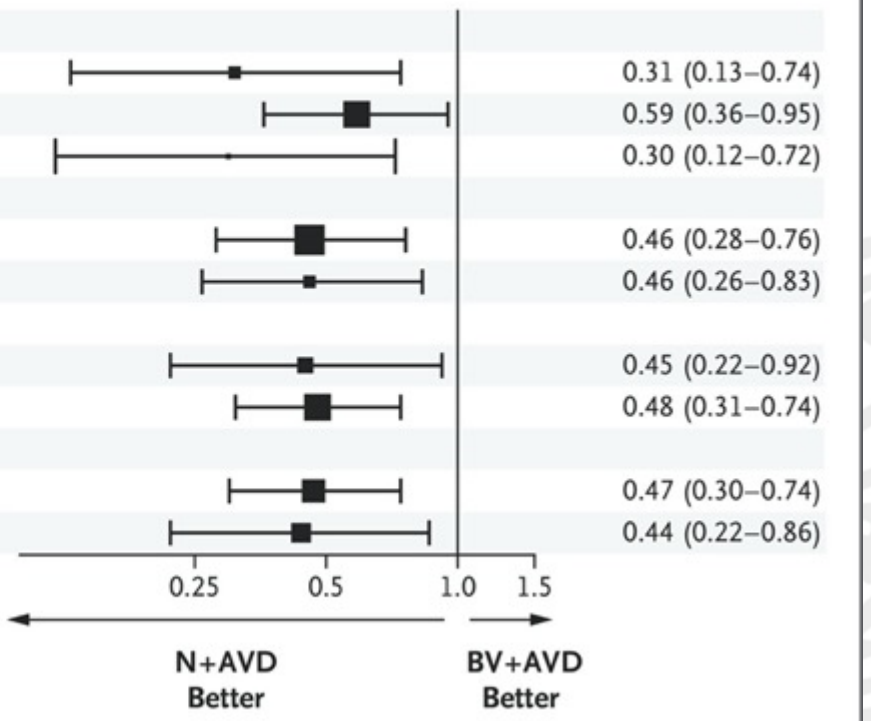


N=994 (958)

Herrera AF et al. N Engl J Med2024;391:1379-1389

Subgroup Analysis of Progression-free Survival (Modified Intention-to-Treat Population).

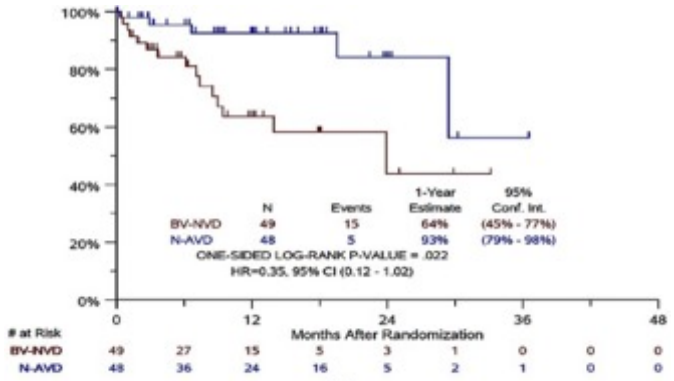
Subgroup	N+AVD	BV+AVD
	no. of events/total no. (%)	
Age		
12–17 yr	7/118 (5.9)	21/118 (17.8)
18–60 yr	27/321 (8.4)	43/318 (13.5)
>60 yr	7/48 (14.6)	17/47 (36.2)
IPS risk group		
0–3	24/332 (7.2)	48/328 (14.6)
4–7	17/155 (11.0)	33/155 (21.3)
Stage		
III	12/185 (6.5)	22/168 (13.1)
IV	29/302 (9.6)	59/315 (18.7)
Symptoms		
B	29/288 (10.1)	54/273 (19.8)
A	12/199 (6.0)	27/210 (12.9)



Herrera AF et al. N Engl J Med2024;391:1379-1389

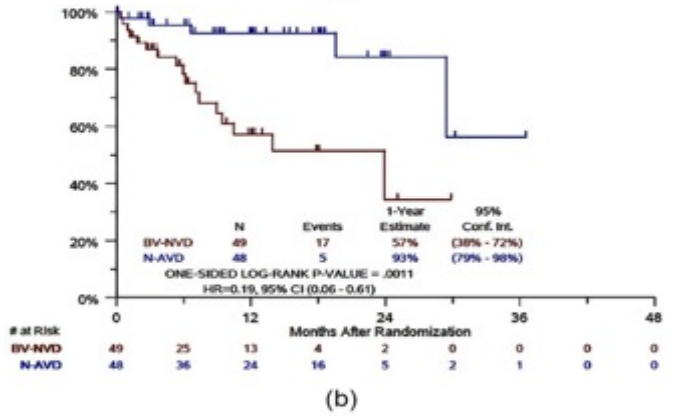
The NEW ENGLAND JOURNAL of MEDICINE

N-AVD vs BV-AVD äldre pat



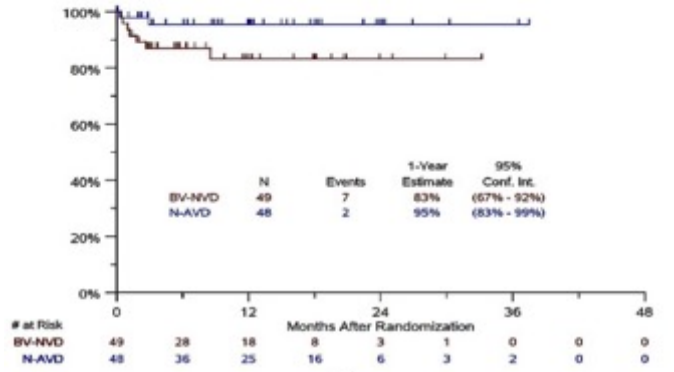
(a)

PFS



(b)

EFS



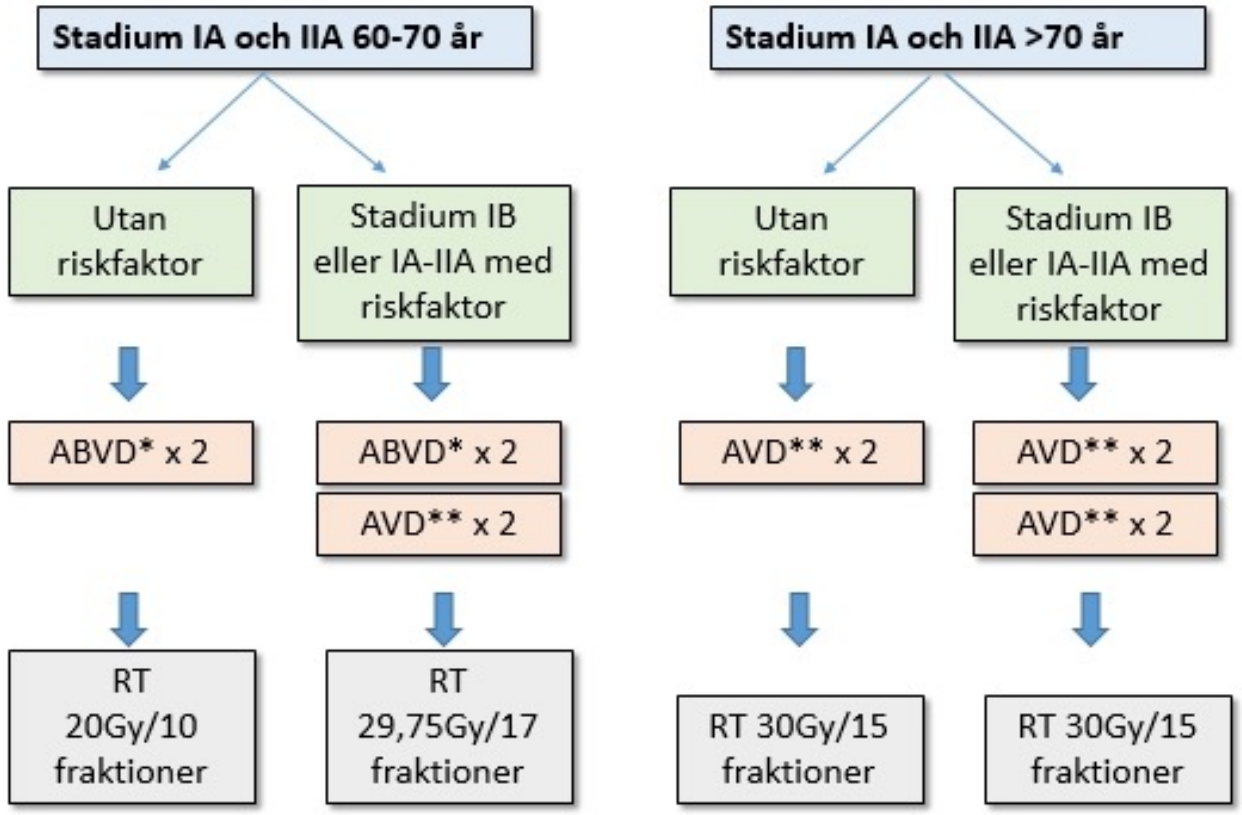
(c)

OS

S1826 (samma studie)
McKenna,
Seminars in Hematology, Volume 61, Issue 4, Aug 2024, P 236-244

Nytt vårdprogram: äldre patienter

Tidiga stadier:



Avancerade stadier, tidigare:

61–70 år

ABVD x 2 + AVD x 4 (++++) [32, 35].

> 70 år

AVD x 6 (++++) [32, 35].

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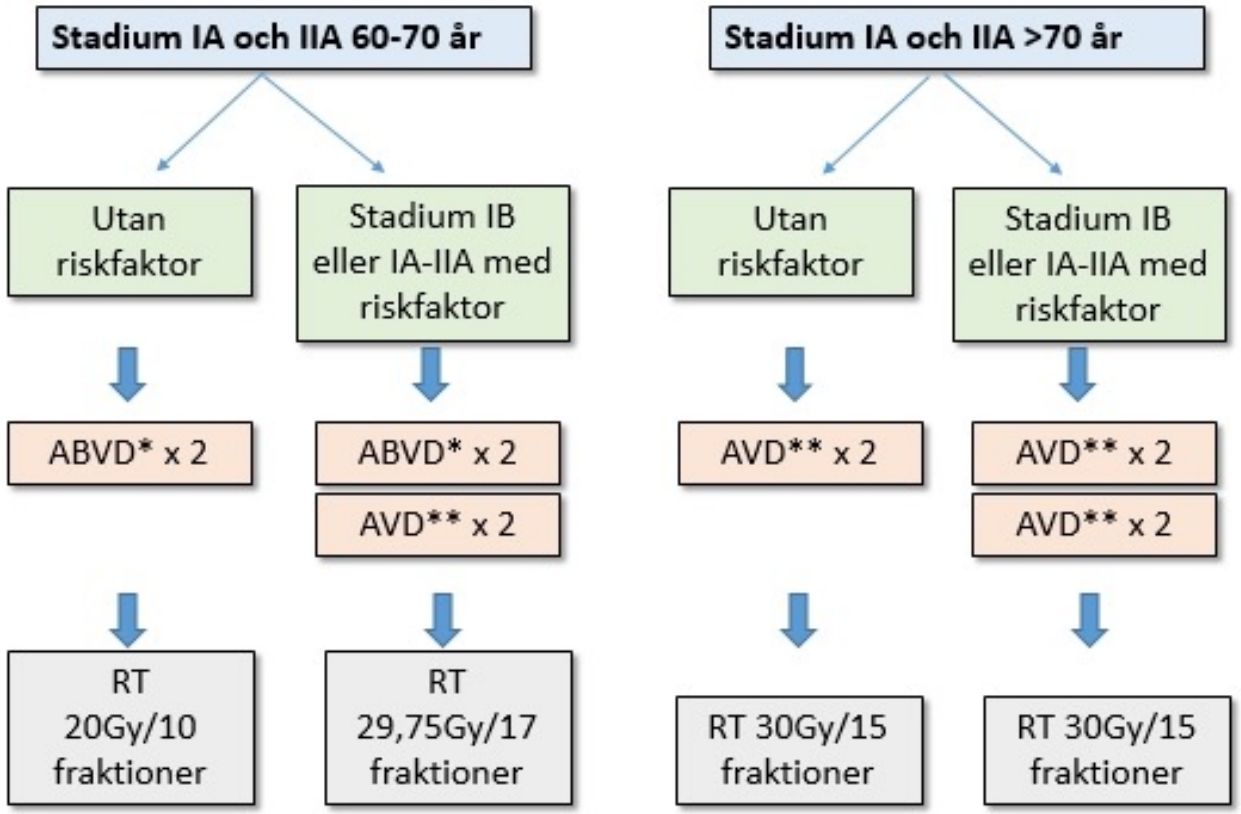
Nytt vårdprogram: äldre patienter

Tidiga stadier:



Avancerade stadier, nu:

Stadium IIB – IV, > 60 år

- Nivolumab-AVD x 6 (++++)[37, 38]

Daniel Molin 2025

PD-1 hämmare mot recidiverande Hodgkins lymfom

Phase II Study of the Efficacy and Safety of Pembrolizumab for Relapsed/Refractory Classic Hodgkin Lymphoma.
R Chen, PL Zinzani, MA Fanale, P Armand, N Johnson, P Brice, J Radford, V Ribrag, D Molin, TP Vassilakopoulos, A Tomita, B von Tresckow, MA Shipp, Y Zhang, AD Ricart, A Balakumaran, CH Moskowitz.
Journal of Clinical Oncology, 2017

Pembrolizumab in relapsed refractory Hodgkin lymphoma: Two year follow-up of KEYNOTE-087
R Chen, PL Zinzani, HJ Lee, P Armand, Nathalie Johnson, P Brice, J Radford, V Ribrag, D Molin, TP Vassilakopoulos, A Tomita, B Von Tresckow, MA Shipp, E Kim, A Nahar, A Balakumaran, CH Moskowitz
Blood 2019

Pembrolizumab monotherapy in patients with primary refractory classical Hodgkin lymphoma: KEYNOTE-087 subgroup analysis
PL Zinzani, R Chen, P Armand, NA Johnson, P Brice, J Radford, V Ribrag, D Molin, TP Vassilakopoulos, A Tomita, B von Tresckow, MA Shipp, J Lin, A Nahar, A Balakumaran, CH Moskowitz
Leukemia and Lymphoma 2020

Five-Year Follow-Up of KEYNOTE-087: Pembrolizumab Monotherapy in Relapsed/Refractory Classical Hodgkin Lymphoma
P Armand, PL Zinzani, HJ Lee, N Johnson, P Brice, J Radford, V Ribrag, D Molin, TP Vassilakopoulos, A Tomita, B von Tresckow, MA Shipp, AF Herrera, J Lin, E Kim, S Chakraborty, P Marinello, CH Moskowitz
Blood 2023

Keynote-087 → Indikation för pembrolizumab

Pembrolizumab versus brentuximab vedotin in relapsed or refractory classical Hodgkin lymphoma (KEYNOTE-204): an interim analysis of a multicentre, randomised, open-label, phase 3 study
Kuruvilla J, et al.
Lancet Oncol. 2021

Keynote-204 → Utökad indikation för pembrolizumab (tidigare linje)

Behandling vid återfall

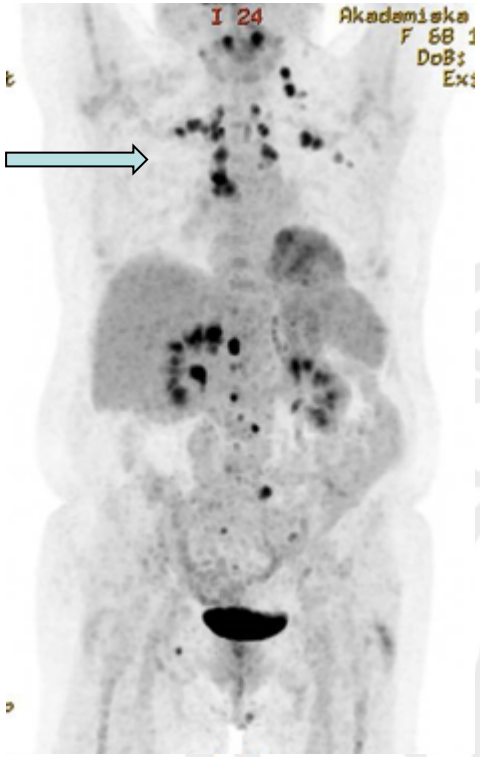
- PD-1-hämmare +/- platinumbaserad cytostatika (GDP, IKE, DHAP, DHAO)
- Autolog stamcellstransplantation (ASCT) för patienter som tål det (riktmärke <70 år), i vissa lokaliserade fall strålning
- Patienter som behandlats med 2 ABVD+RT primärt kan behandlas med t.ex. BEACOPDac utan ASCT*
- Brentuximab vedotin (BV) efter PD-1-hämmare (Keynote-204)
- Allogen stamcellstransplantation *enbart för selekterade* patienter
- PD-1-hämmare och BV har minskat antalet aktuella för allogen

*Bröckelmann *et al*, JCO, 2021

Progress på PD-1-hämmare

Before PD-1-blockade.
Severe B-symptoms.

Radiological progression after initial remission. No symptoms.



Almost CR at initial tumour bulk. Progression on *new sites*.
No clinical deterioration.

LYRIC-kriterier

Indeterminate response (IR)	Definition
IR (1)	Increase in overall tumor burden* ≥50%, in the first 12 weeks of therapy, without clinical worsening
IR (2)	Development of new lesions or Increase ≥50% of one or more existing lesion(s) at any time during treatment, without ≥50% increase of overall tumor burden*
IR (3)	Increase in FDG uptake of one or more lesions, without any increase in size of those lesions, or new lesions

*Tumor burden: sum of the product of the perpendicular diameters of up to six measurable lesions.

Framtiden för klassiska Hodgkins lymfom

Strålbehandling fortsatt en roll (Protoner? Studie PRO-Hodgkin)

Brentuximab vedotin i primärbehandling (ex BrECADD)

PD-1-hämmare i primärbehandling (ex N-AVD)

Anti-LAG3 + anti-PD1?? (Vi deltog i studie Keyform-08)

CD30 CAR-T-celler?? (Vi skulle ha deltagit i studie)

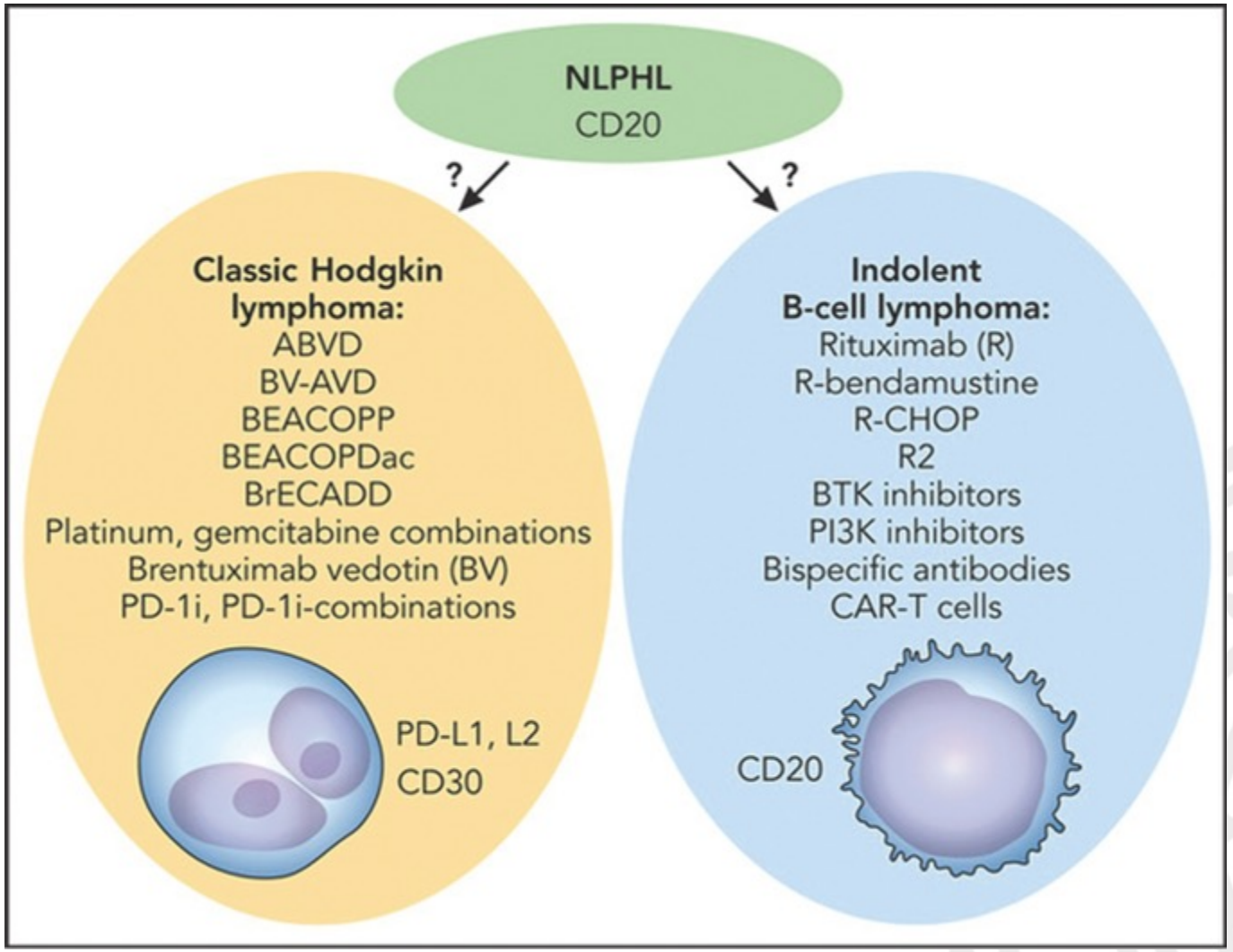
JAK-inhibitor (ruxolitinib) + anti-PD-1 (Science 2024)

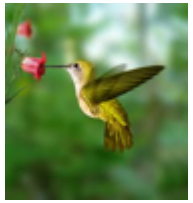
CD86-CTLA4 lovande target (Blood, 3 april 2025)

TARC och ctDNA lovande som ersättning/komplement till PET

Problem: Svårt att driva fas 1, 2 studier på recidiv – brist på nya terapier till primärbehandling

NLPHL: a hummingbird in an owl's nest

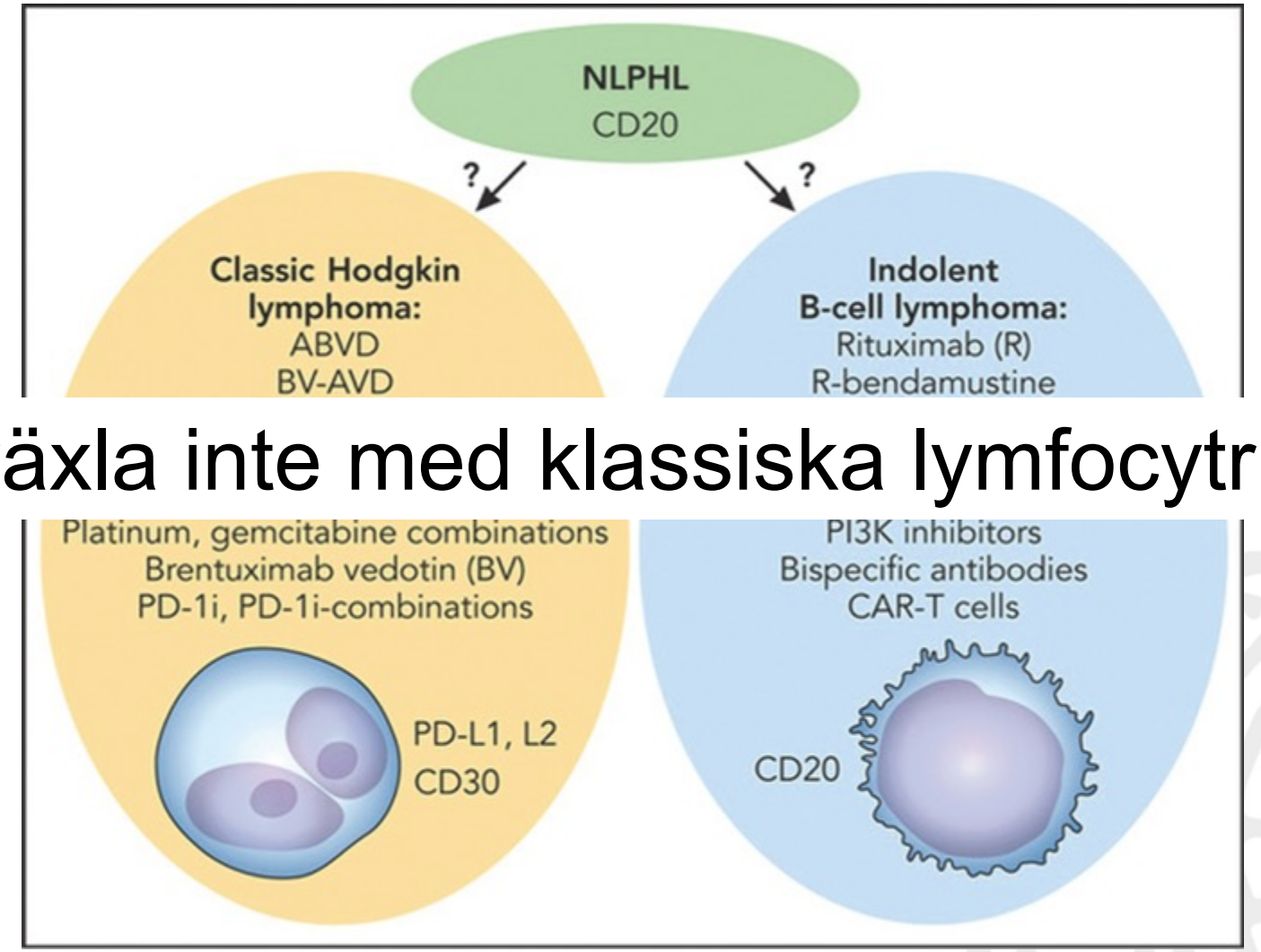


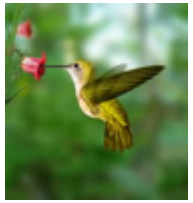


Daniel Molin 2025

Daniel Molin, NLPHL: a hummingbird in an owl's nest, commentary Blood, 2023.

NLPHL: a hummingbird in an owl's nest





Förväxla inte med klassiska lymfocytrika HL

Daniel Molin, NLPHL: a hummingbird in an owl's nest, commentary Blood, 2023.

Sammanfattning, avancerade stadier

- Yngre med stadium IIB-IV behandlas med 4-6 BEACOPDac/BrECADD
- Äldre med stadium IIB-IV behandlas med nivolumab-AVD
- BrECADD har bättre PFS och mindre toxicitet än BEACOPP men avvaktar hälsoekonomi innan NVP ändras
- Första recidiv behandlas med PD-1-hämmare +/- cytostatika följt av ASCT för pat som tål det (ev strålning)
- Följande recidiv behandlas med PD-1-hämmare, Adcetris och cytostatika

Tack!

Svenska Hodgkingruppen.

T Hodgkins originalpreparat, Guy's Hospital.

Volker Diehl.