# La desescalada del tratamiento individualizado en Linfoma de Hodgkin mejora los resultados generales

*"Desescalando en Cuenca"*

Dr Germán Stemmelin
Jefe de Hematología del Htal Británico de Bs As
Jefe de la Unidad de Linfoma del Htal Británico de Bs As

Linfomashb@gmail.com
stemmelingr@gmail.com

# Germán Stemmelin

## Declaración de Conflictos de Intereses

| Categoría | |
|---|---|
| Empleado | |
| Consultor | ***Roche, Janssen, Takeda, Teva Ivax, Abbvie, Bristol Myers Squibb, Novartis, Raffo, Elea, Sandoz, Astra Zeneca, Biotoscana, Biostatera.*** |
| Propiedad accionaria | |
| Fondos de Investigación | |
| Honorarios por conferencia | ***Roche, Bristol Myers Squibb, Takeda, MSD, Raffo, Knight, Elea*** |
| Formar parte del grupo de oradores | |
| Formar parte del comité asesor | |
| Otros | |

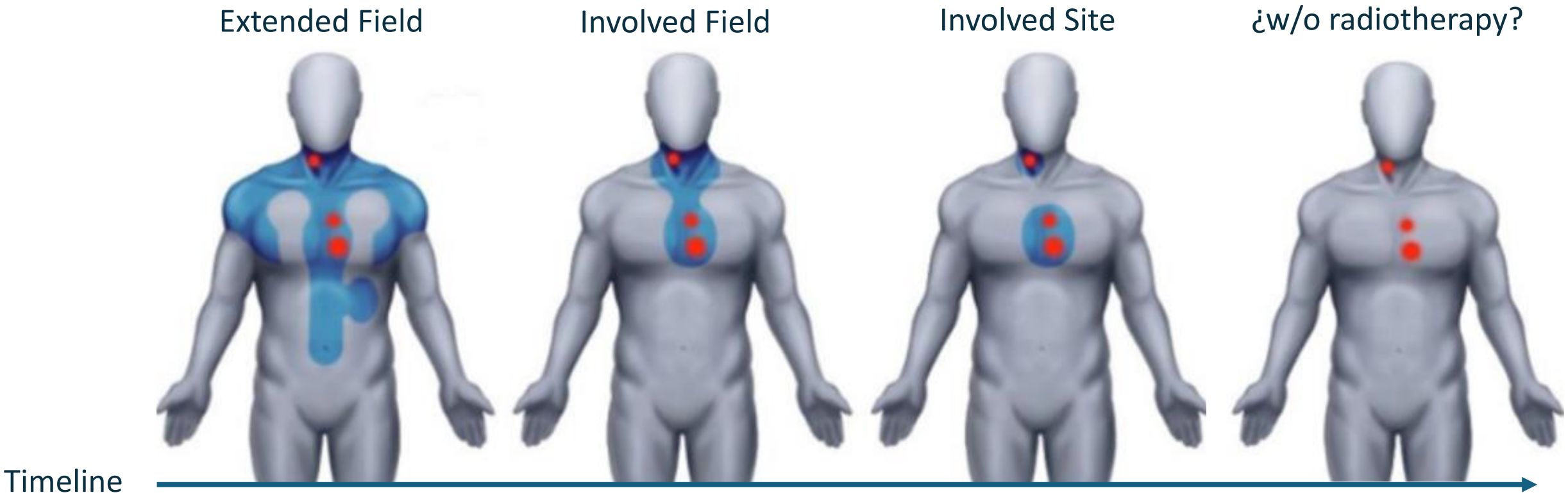
REAL ACADEMIA ESPAÑOLA

# Desescalar/Des-escalar

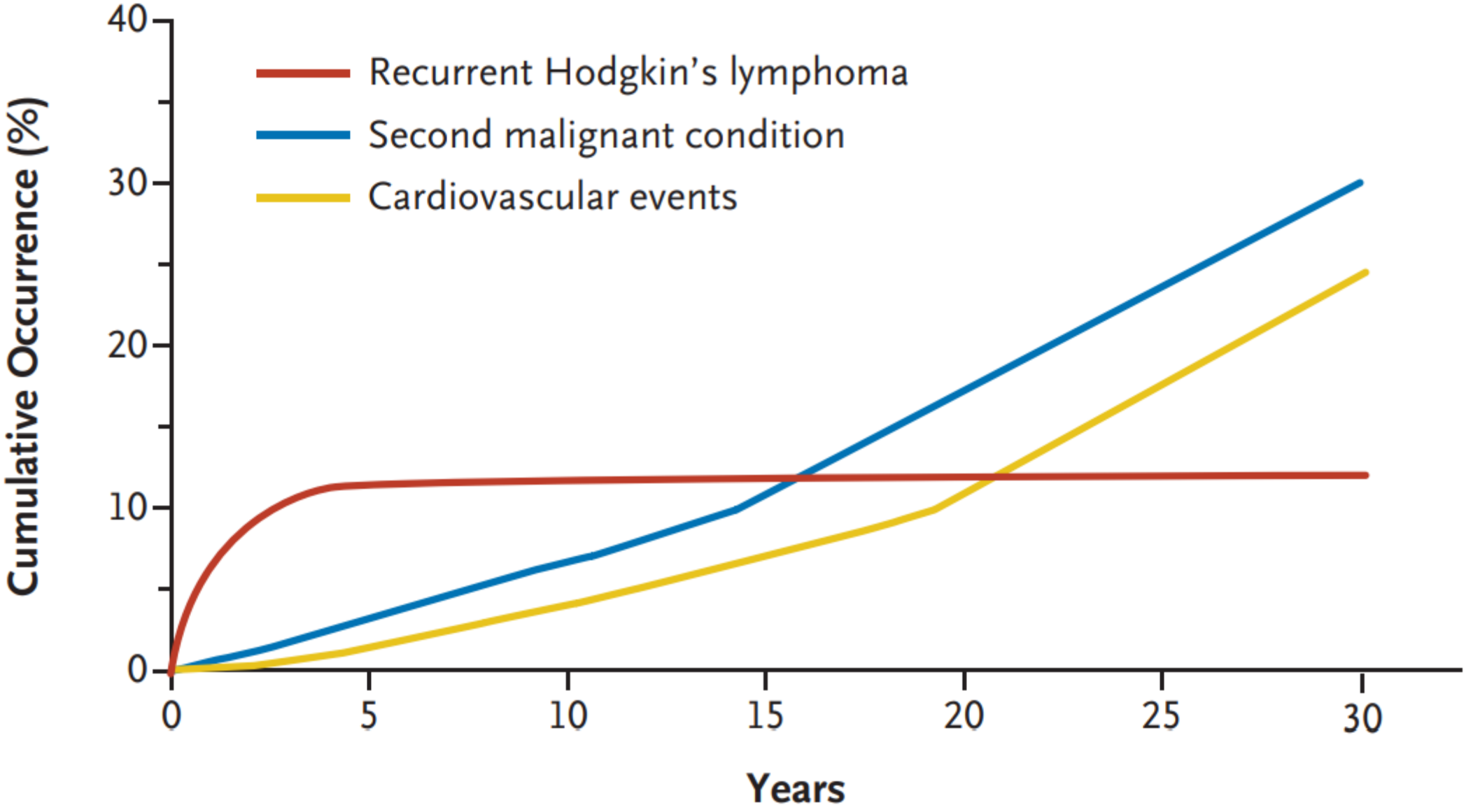
## Desescalar/des-escalar:

- Disminuir la intensidad del tratamiento con el propósito de reducir la toxicidad del mismo, sin afectar la efectividad.

# “Des-escalando” la Radioterapia y su toxicidad

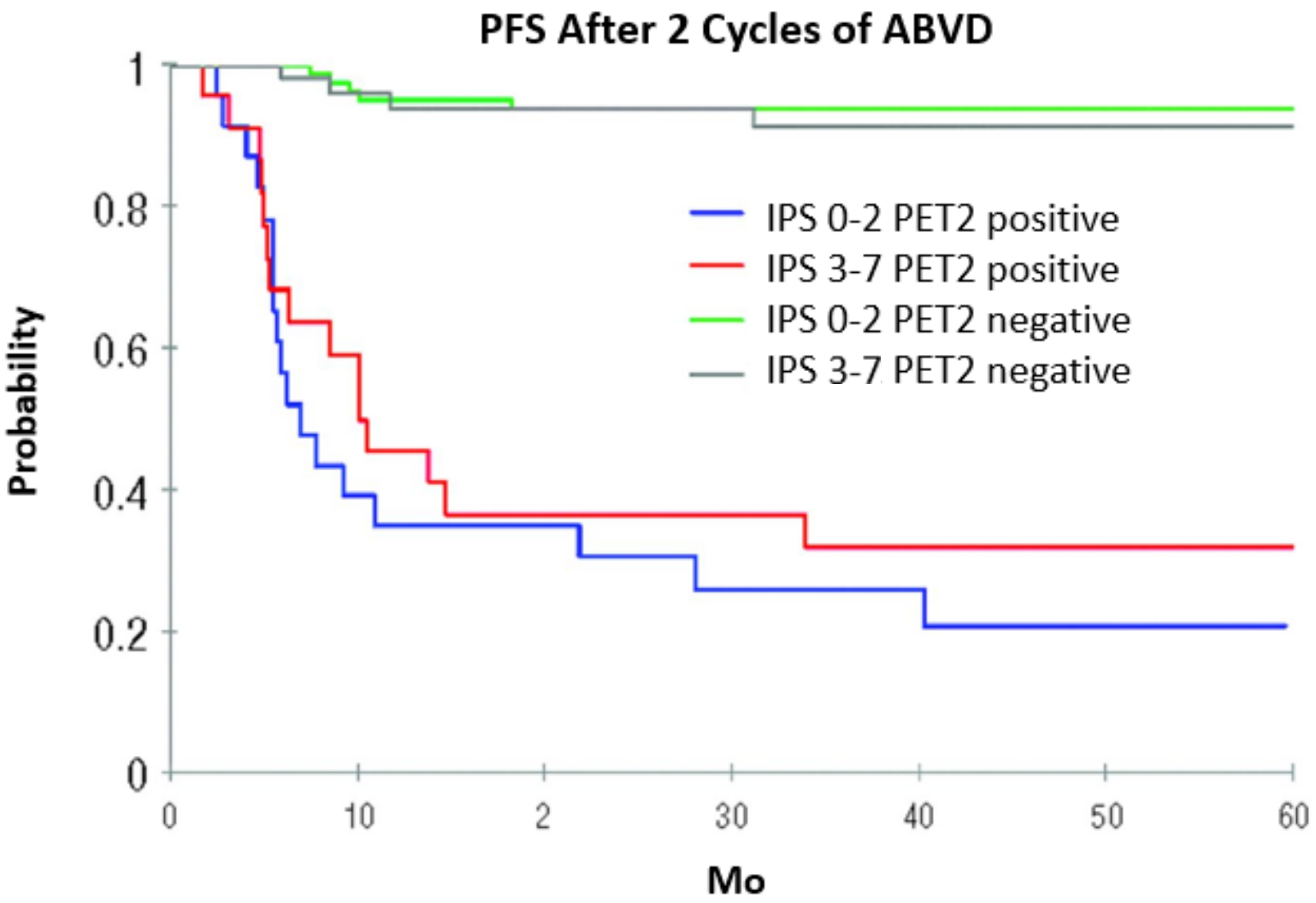



Eich HT et al, *Lymphatics* 2023




Armitage J. *NEJM* 2010

# Valor predictivo del PET interino




¿Desescalar?

¿Escalar?

Gallamini A. *Haematologica* 2014

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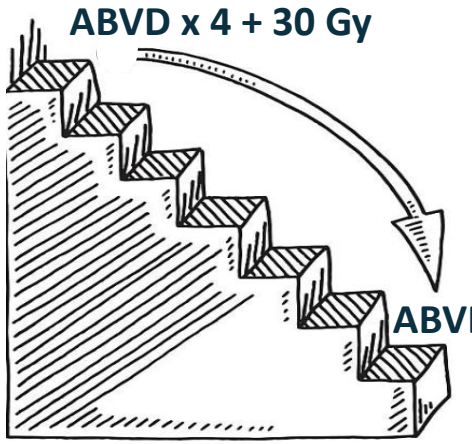
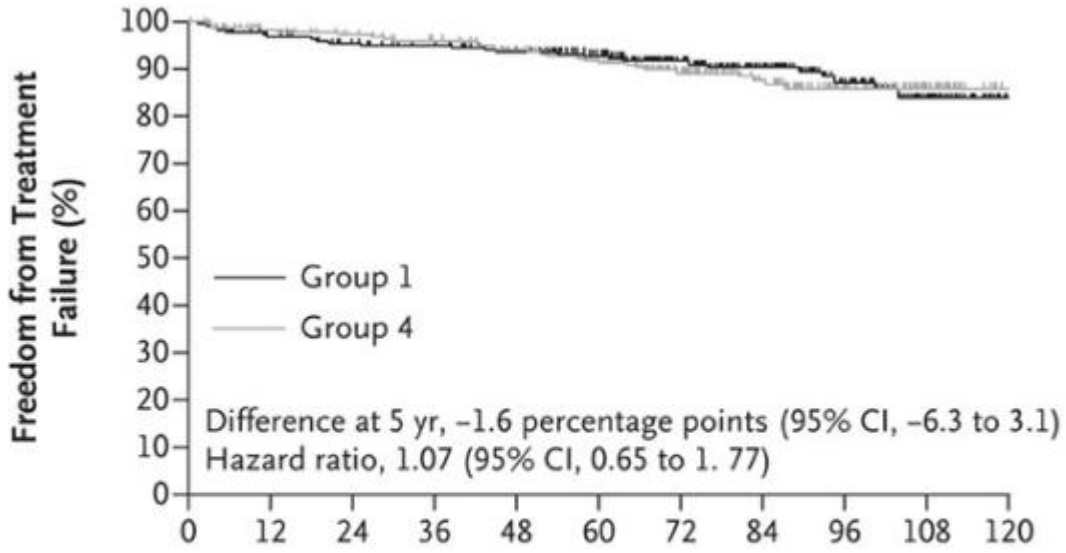
# Primera línea en LHc temprano favorable (I-IIA, no voluminoso)

Linfomashb@gmail.com
stemmelingr@gmail.com

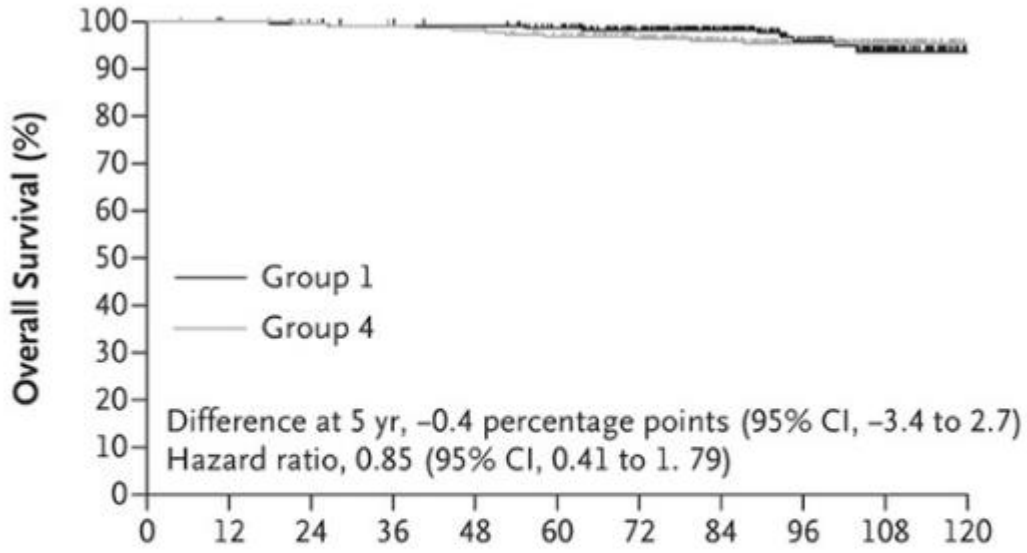
# HD10: ABVD x 2 + 20 Gy




**Comparison of Groups 1 and 4**



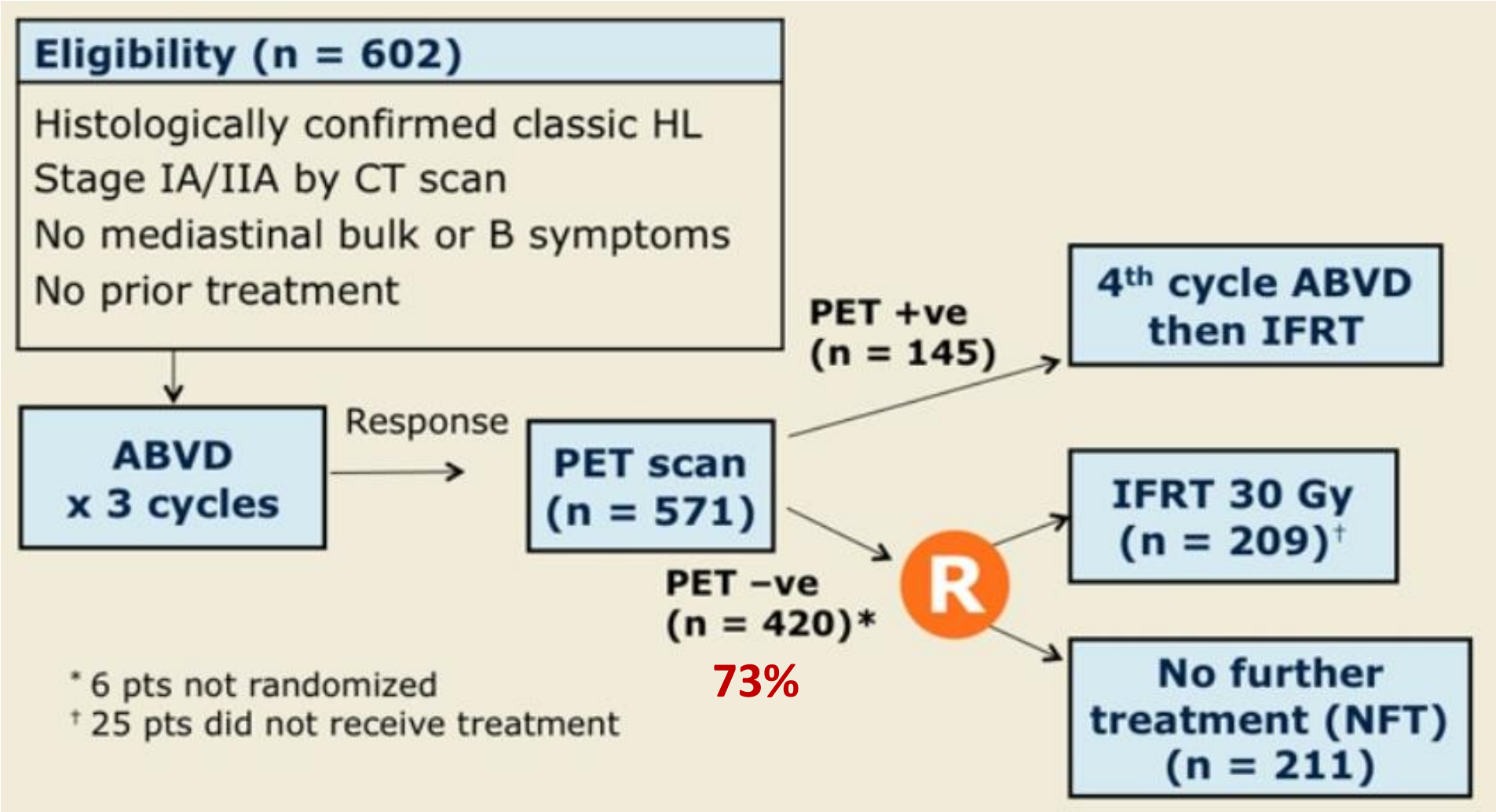

| No. of Patients at Risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Group 1 | 298 | 277 | 264 | 255 | 239 | 217 | 167 | 121 | 74 | 35 | 3 |
| Group 4 | 299 | 275 | 265 | 252 | 239 | 199 | 151 | 110 | 66 | 28 | 4 |




| No. of Patients at Risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Group 1 | 298 | 293 | 289 | 286 | 283 | 271 | 240 | 182 | 116 | 63 | 12 |
| Group 4 | 299 | 298 | 293 | 289 | 285 | 273 | 241 | 182 | 122 | 64 | 16 |

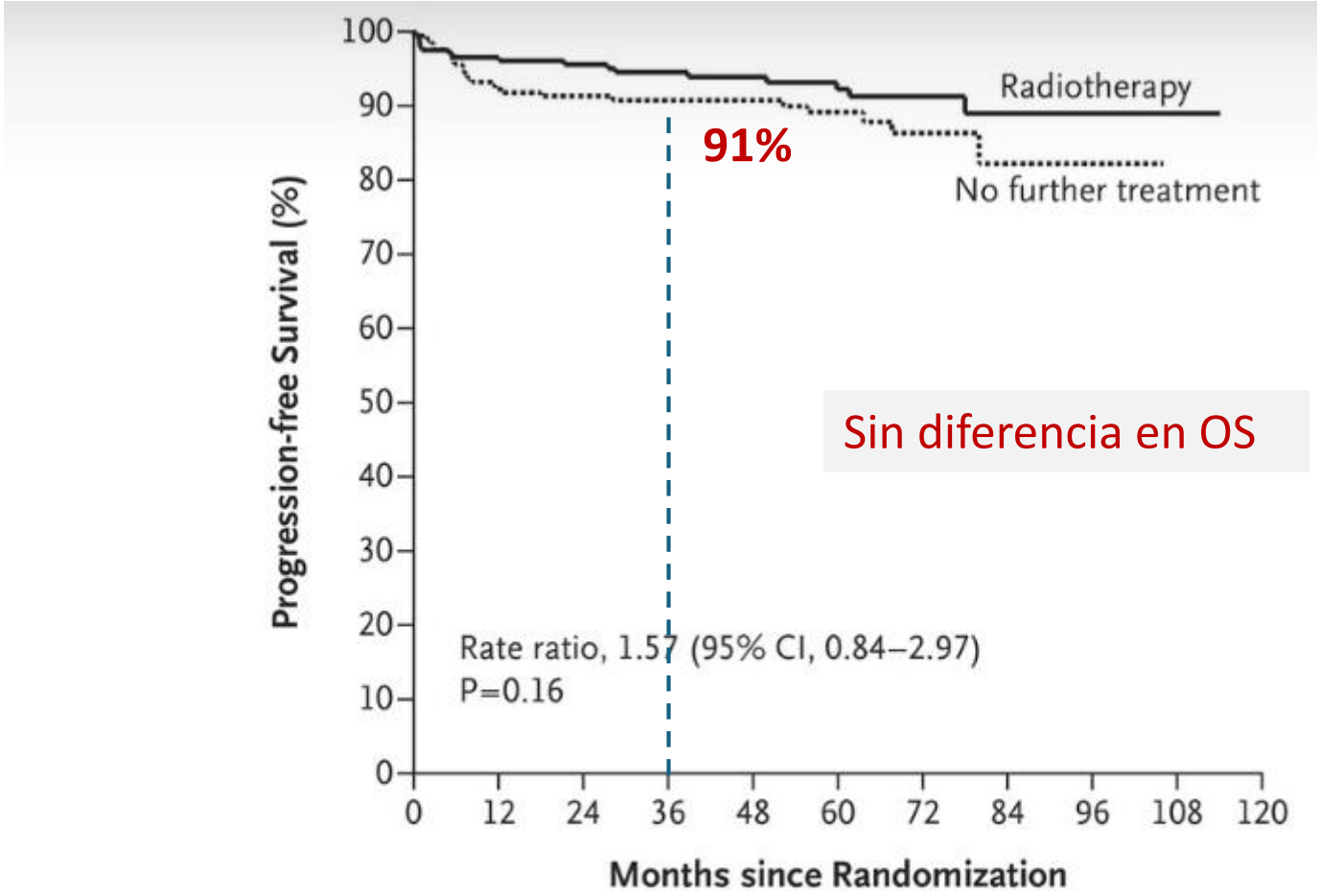
Engert A et al. *NEJM* 2010

# RAPID trial y otros (H10F y HD16)




Radford J et al. *NEJM* 2015

# RAPID trial



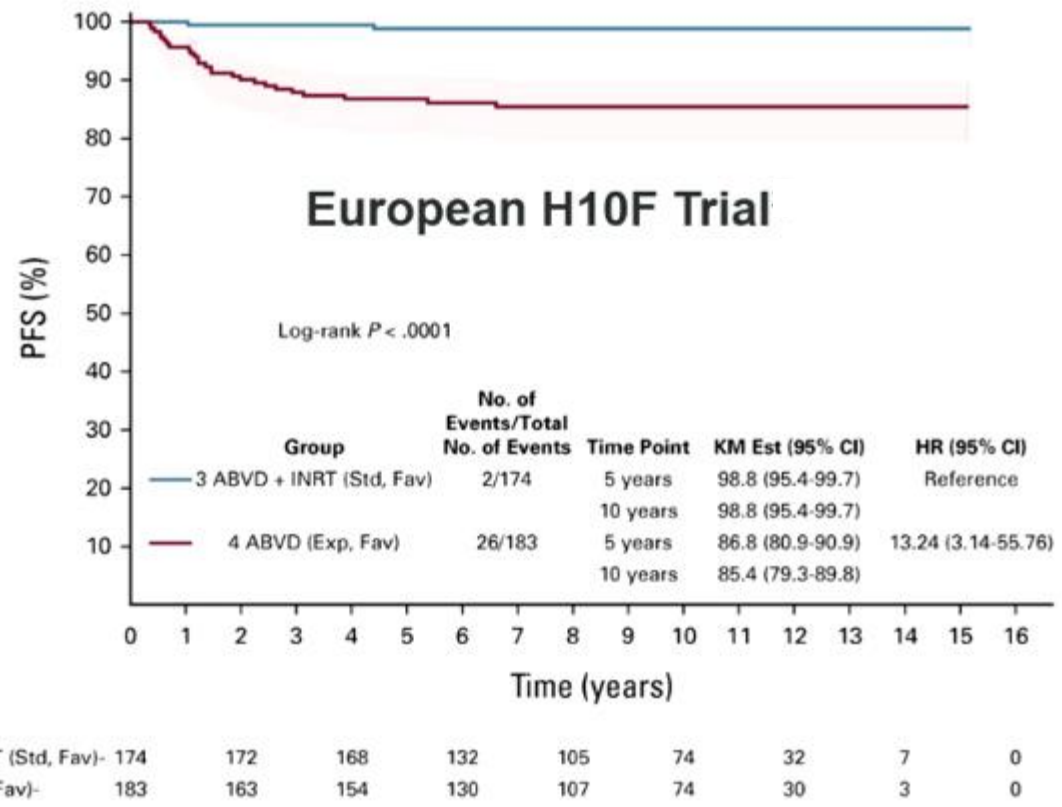

Sin diferencia en OS

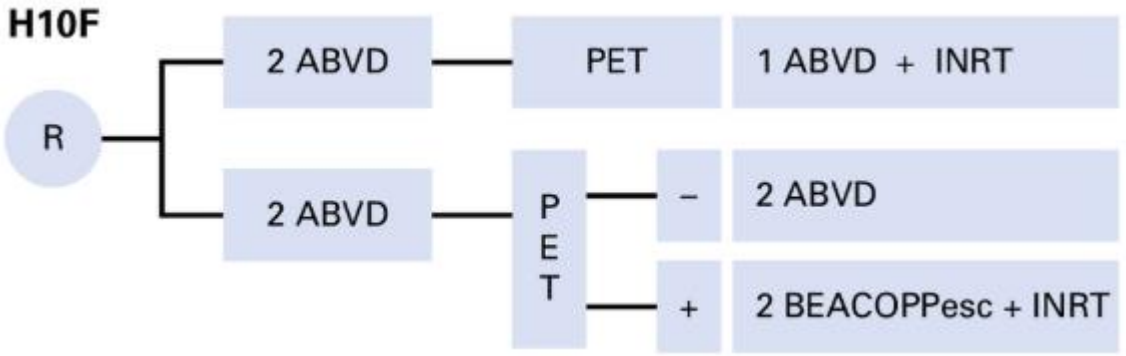
Se necesita irradiar a 30 ptes para sumar una curación más

Radford J et al. *NEJM* 2015

# H10F. Early-stage Favorable HL. 10 yrs follow up

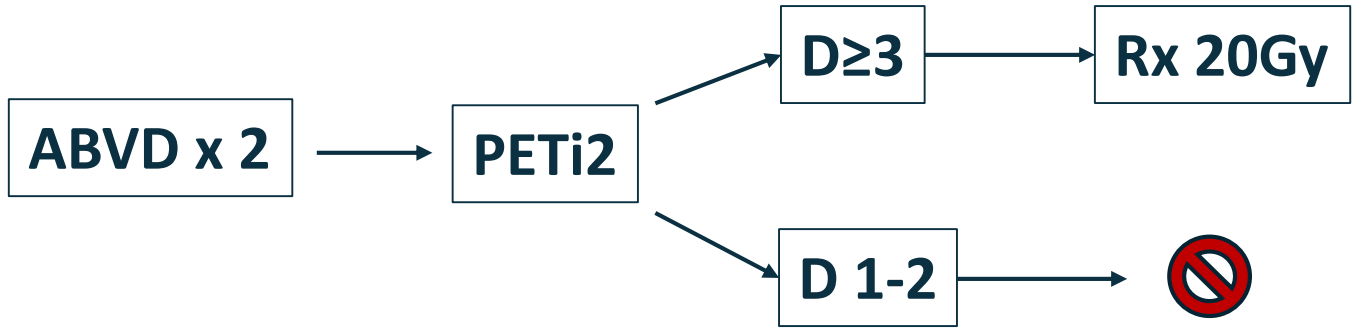
CALGB 50604




Federico M, et al. *JCO* 2024

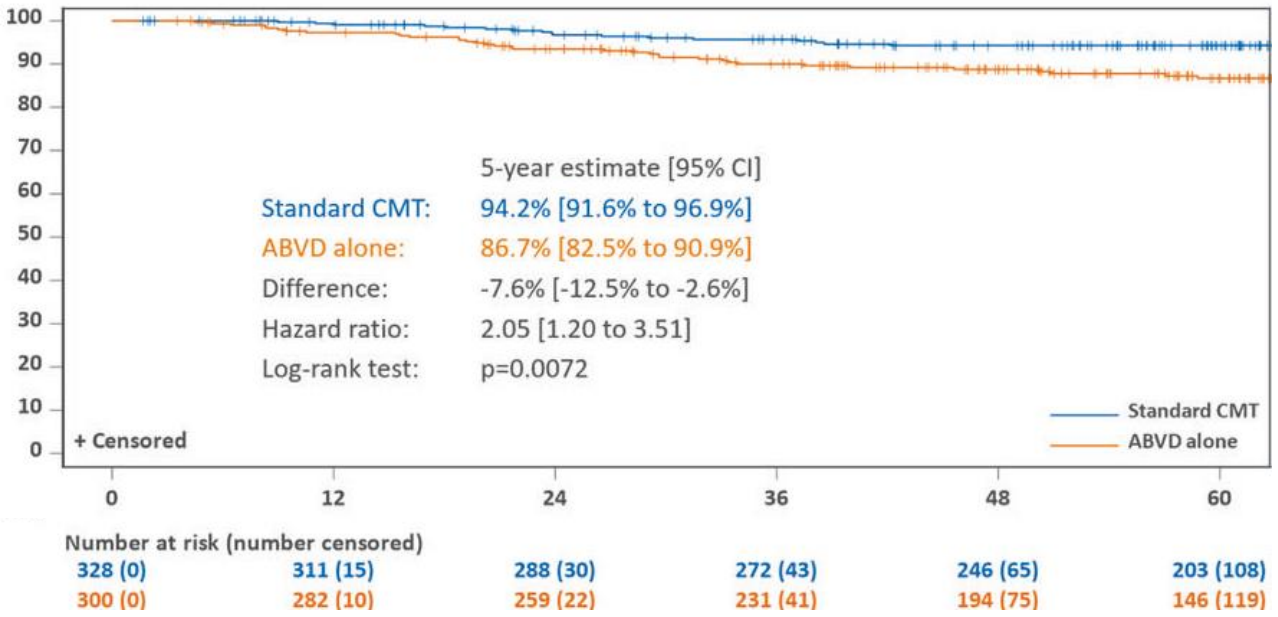
# HD16. Early-stage Favorable HL. 5 yrs follow up



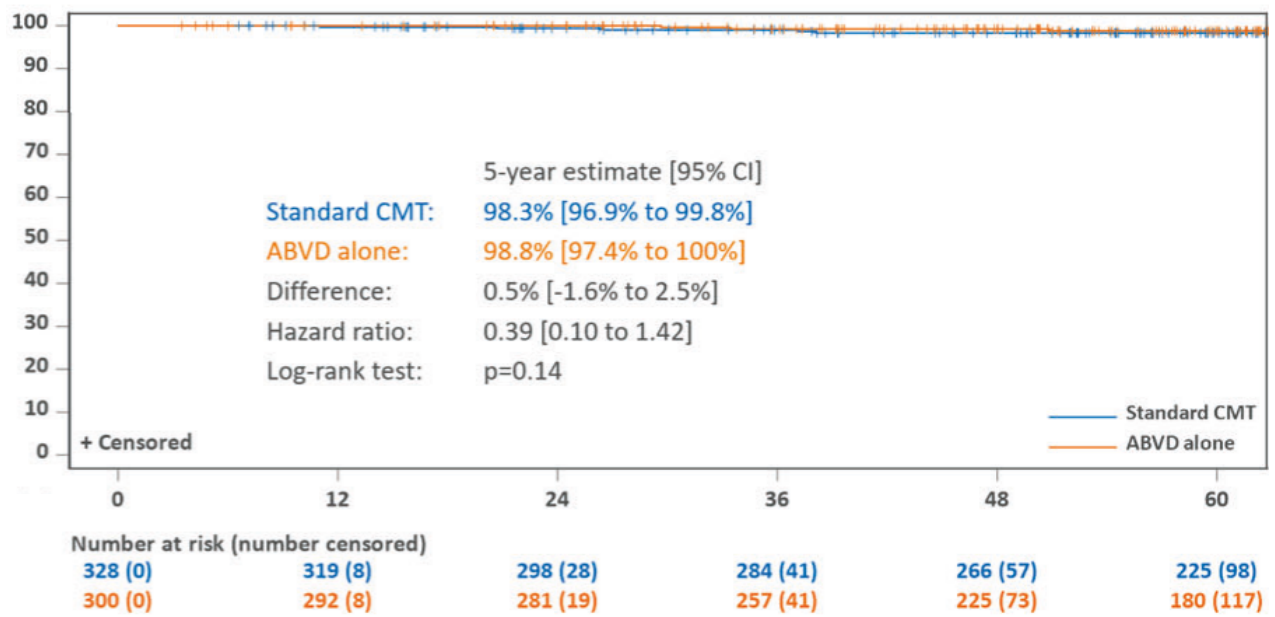

**Standard CMT**

**ABVD alone**

PFS




OS




Fuchs M, et al. *Leukemia* 2024

# SLP en LH temprano favorable
# ABVD x 3 (RAPID)

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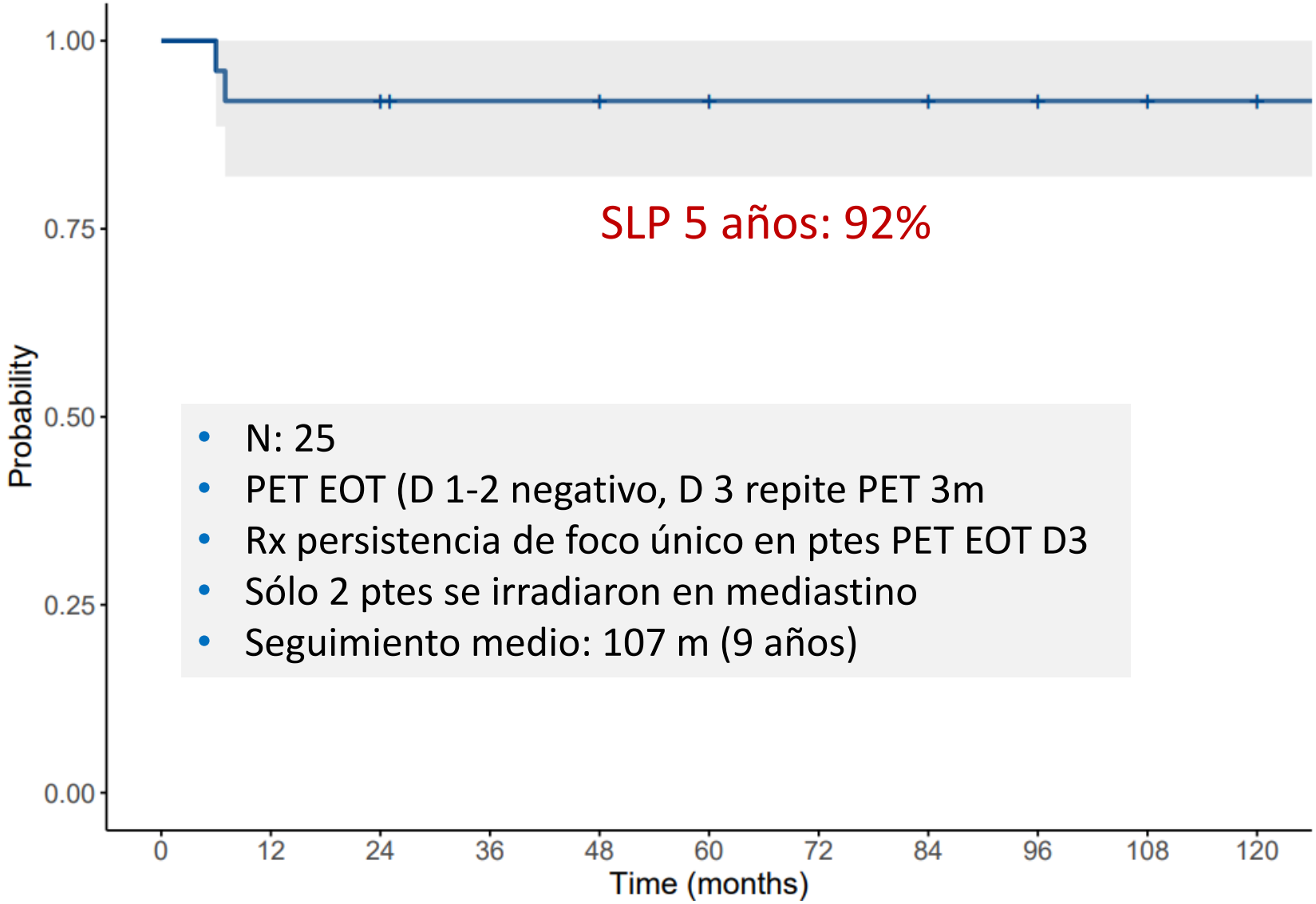
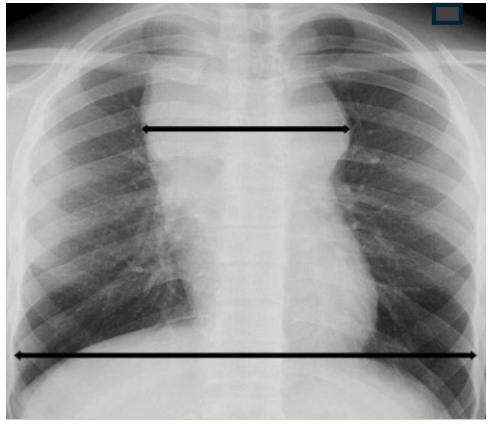



SLP 5 años: 92%

- N: 25
- PET EOT (D 1-2 negativo, D 3 repite PET 3m
- Rx persistencia de foco único en ptes PET EOT D3
- Sólo 2 ptes se irradiaron en mediastino
- Seguimiento medio: 107 m (9 años)

Rivarola S (unpublished)



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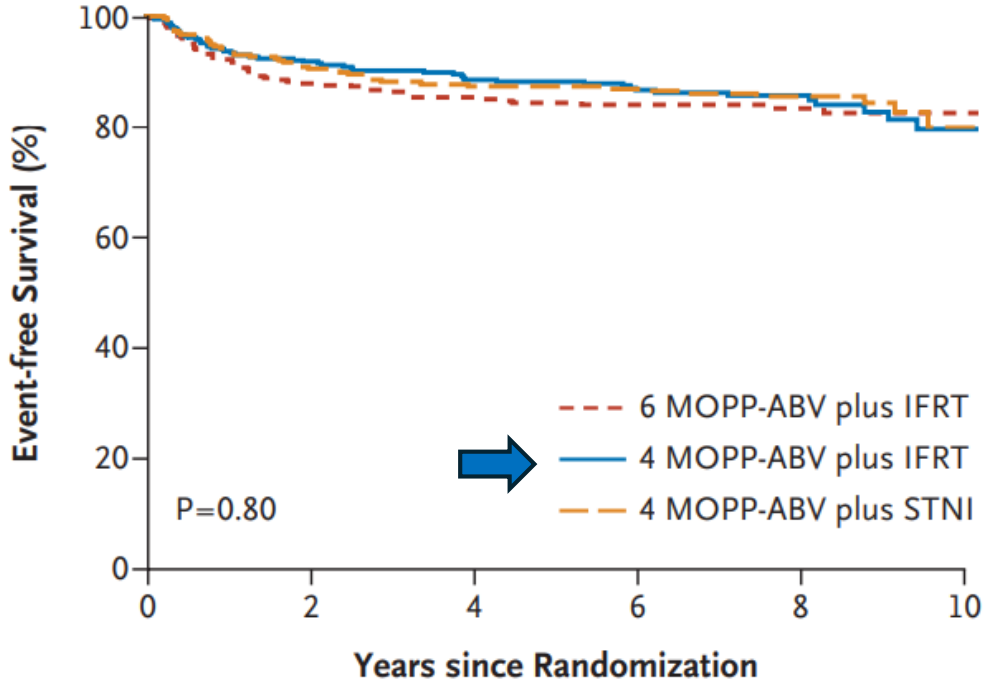
# Primera línea en LHc temprano desfavorable (I-IIB y/o voluminoso)

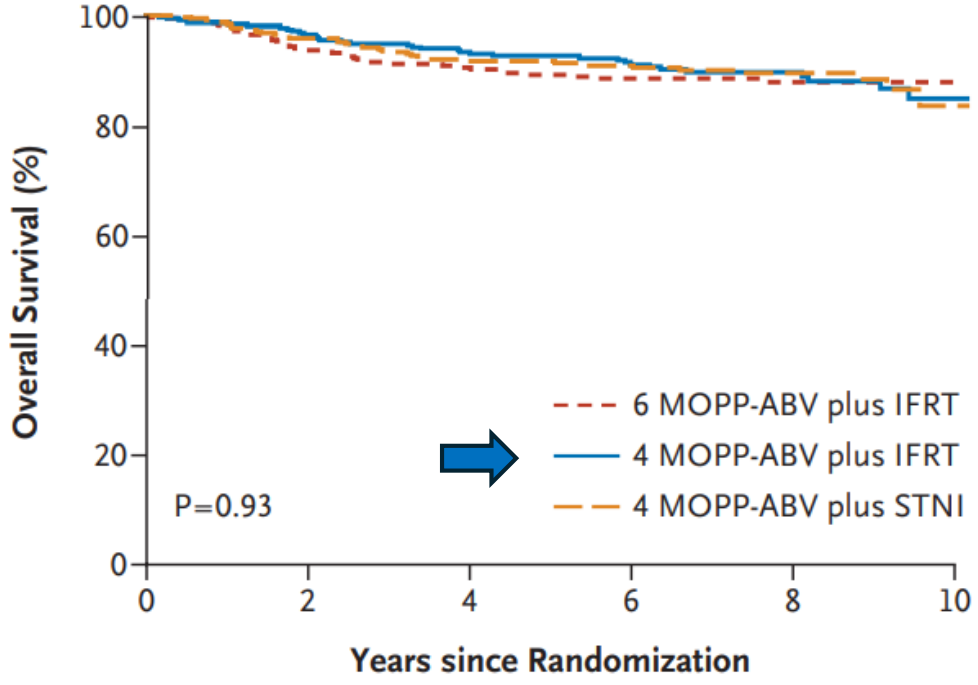
Linfomashb@gmail.com
stemmelingr@gmail.com

SNTI

# H8-U trial. LH temprano desfavorable




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| 6 MOPP-ABV plus IFRT | 336 | 283 | 258 | 206 | 114 | 21 |
| 4 MOPP-ABV plus IFRT | 333 | 297 | 270 | 216 | 112 | 30 |
| 4 MOPP-ABV plus STNI | 327 | 288 | 265 | 215 | 118 | 18 |




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| 6 MOPP-ABV plus IFRT | 336 | 303 | 276 | 219 | 119 | 21 |
| 4 MOPP-ABV plus IFRT | 333 | 312 | 283 | 228 | 120 | 33 |
| 4 MOPP-ABV plus STNI | 327 | 303 | 277 | 223 | 119 | 18 |

Fermé C, et al. *NEJM* 2007

# LHc Temprano desfavorable

**Stage I/II Unfavorable CHL (B symptoms or bulky mediastinal disease or >10 cm adenopathy)**

**ABVD x 2 cycles** → **Restage with FDG-PET/CT**

**Deauville 1–3**

**Combined modality therapy**
**ABVD x 2 cycles + ISRT 30 Gy** (adapted from H10U)

**Chemotherapy alone**
**AVD x 4 cycles** (adapted from RATHL)

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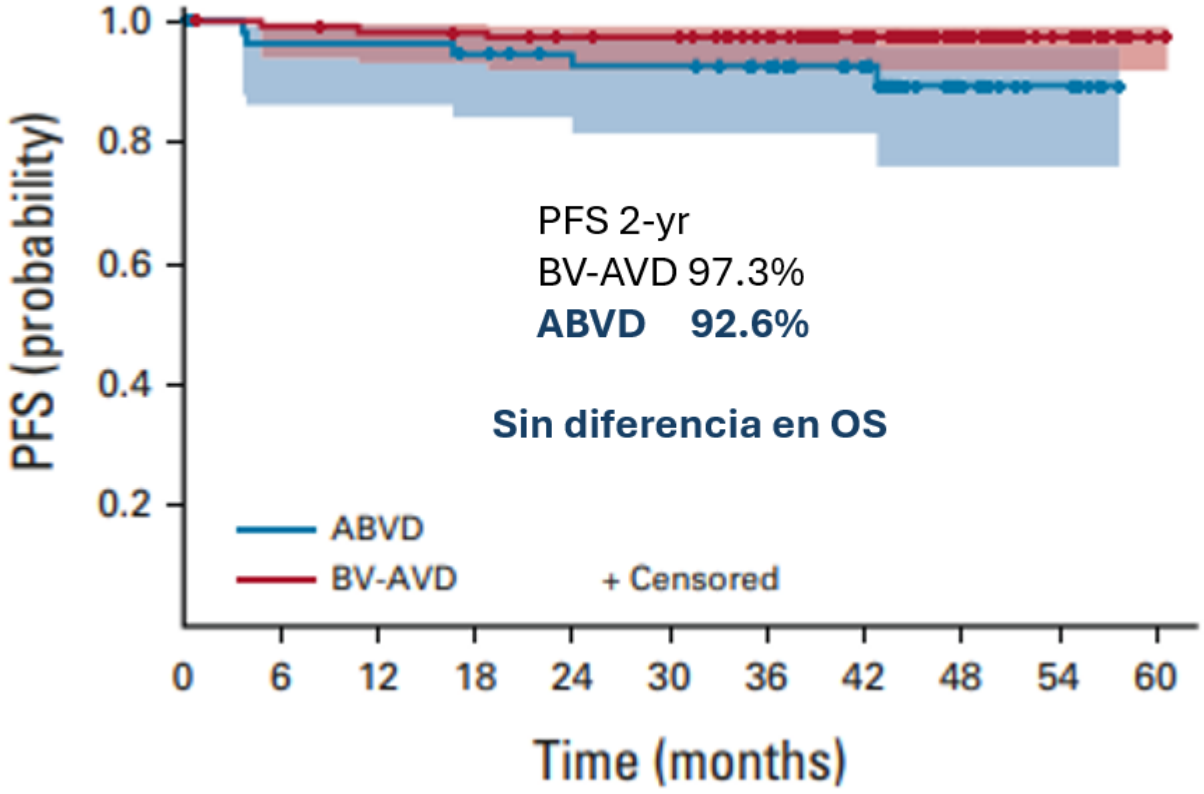
National Comprehensive Cancer Network®

**NCCN Guidelines Version 2.2025**
**Hodgkin Lymphoma (Age 18–60 years)**


Federico M, et al. *JCO* 2024

# LHc Temprano desfavorable




National Comprehensive Cancer Network®

**NCCN Guidelines Version 2.2025**
**Hodgkin Lymphoma (Age 18–60 years)**

**Stage I/II Unfavorable CHL[p] (B symptoms or bulky mediastinal disease or >10 cm adenopathy)** →

**Nivolumab-AVD x4 cycles[r] + ISRT 30 Gy[t] (B symptoms and/or bulky disease, adapted from NIVAHL)[6]**

**or**

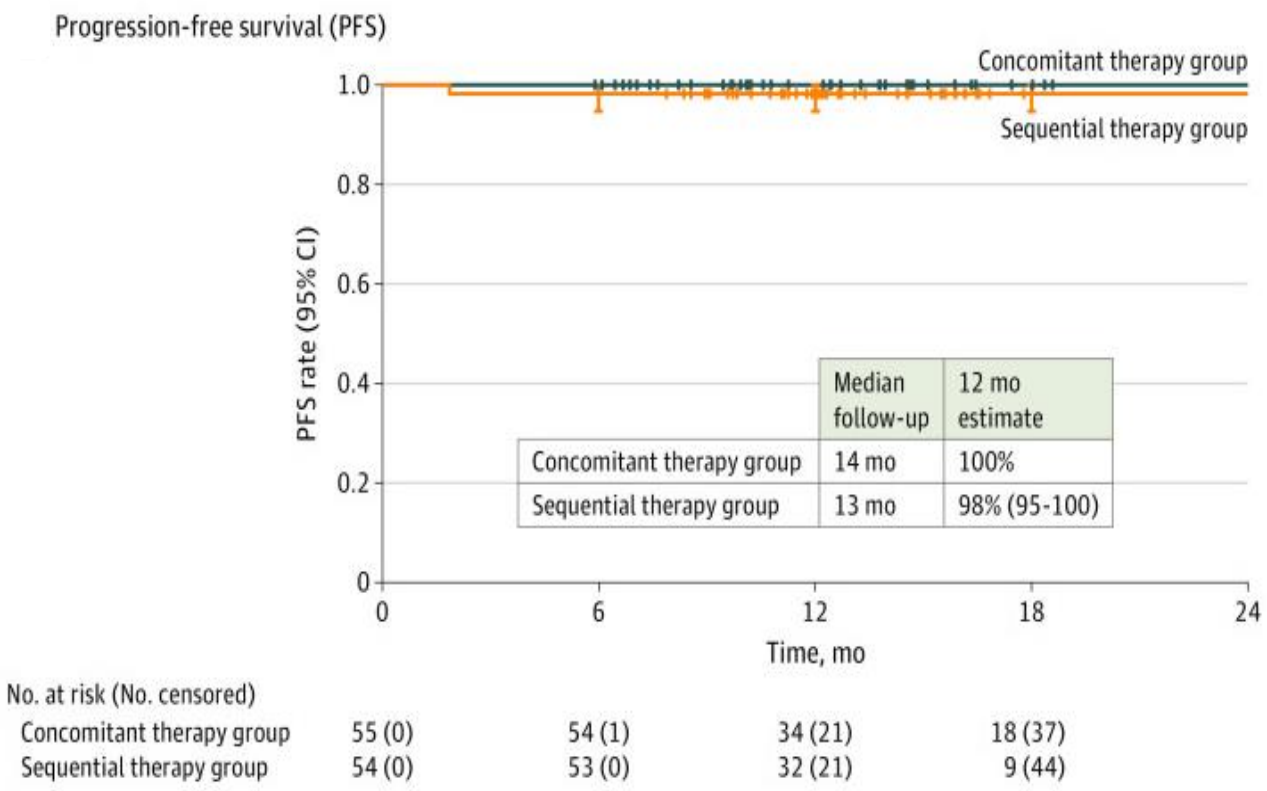
**Brentuximab vedotin (BV)-AVD + G-CSF x4 cycles[r] + ISRT 30 Gy[t] (adapted from BREACH)[7]**

**or**

**BrECADD + G-CSF x 2 cycles[r] (Bulky disease and either B symptoms or extranodal disease, ages 18-61, adapted from HD21)[8]**

Luc-Matthiey Fornecker et al. *JCO* 2023

# LHc Temprano desfavorable




National Comprehensive Cancer Network®

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**BrECADD + G-CSF x 2 cycles[r] (Bulky disease and either B symptoms or extranodal disease, ages 18-61, adapted from HD21)[8]**

Bröckelman P et al. *Jama Oncol* 2020


# NIVAHL trial
## ¿Se puede evitar la radioterapia?

**Paul Bröckelmann**
para mí

Dear Germán,

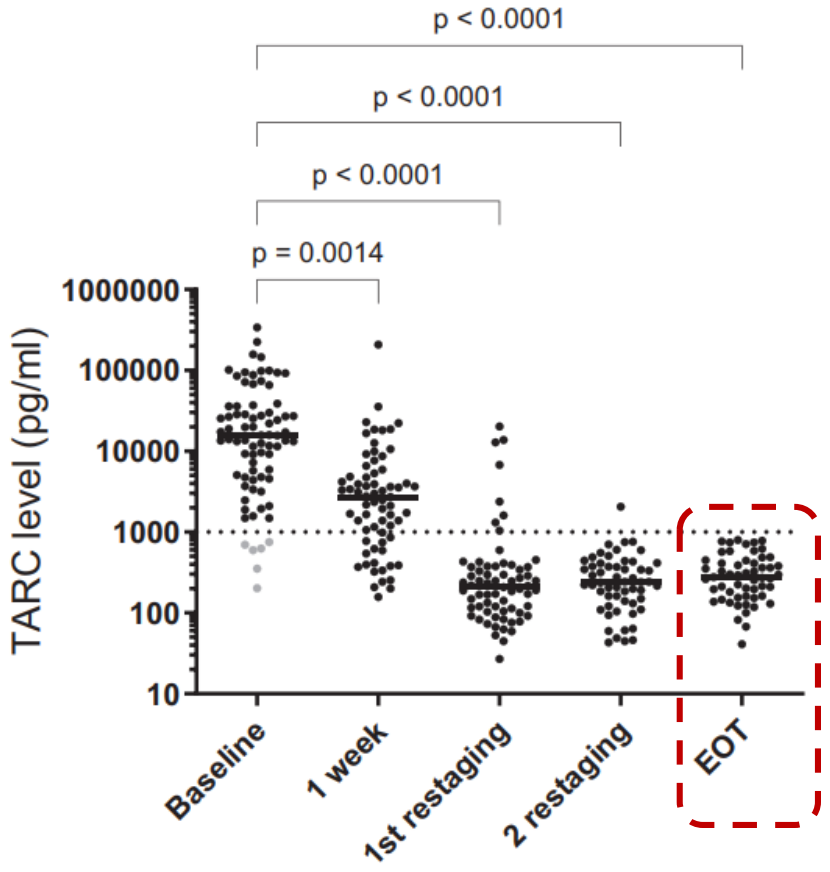
thank you for reaching out regarding the NIVAHL-based treatment of your patient. We dont have any data to support omission of radiotherapy in case of PET-negative CMR after 4x N-AVD, since all patients received 30Gy IS-RT in NIVAHL. If you want to deviate from this evidence in an individual case (which could be well justified in a young female patient with extensive RT field), you might find our recent study, showing TARC negativity in all patients after 4x N-AVD prior to RT encouraging: https://pubmed.ncbi.nlm.nih.gov/40862220/, since it suggests not only PET-negativity but also resolution of measurable cHL by this well established soluble biomarker.

Thymus and Activation Regulating Chemokine (TARC, or CCL17)

Bröckelman P et al. *Jama Oncol* 2020

# NIVAHL trial
# Serum TARC dynamics

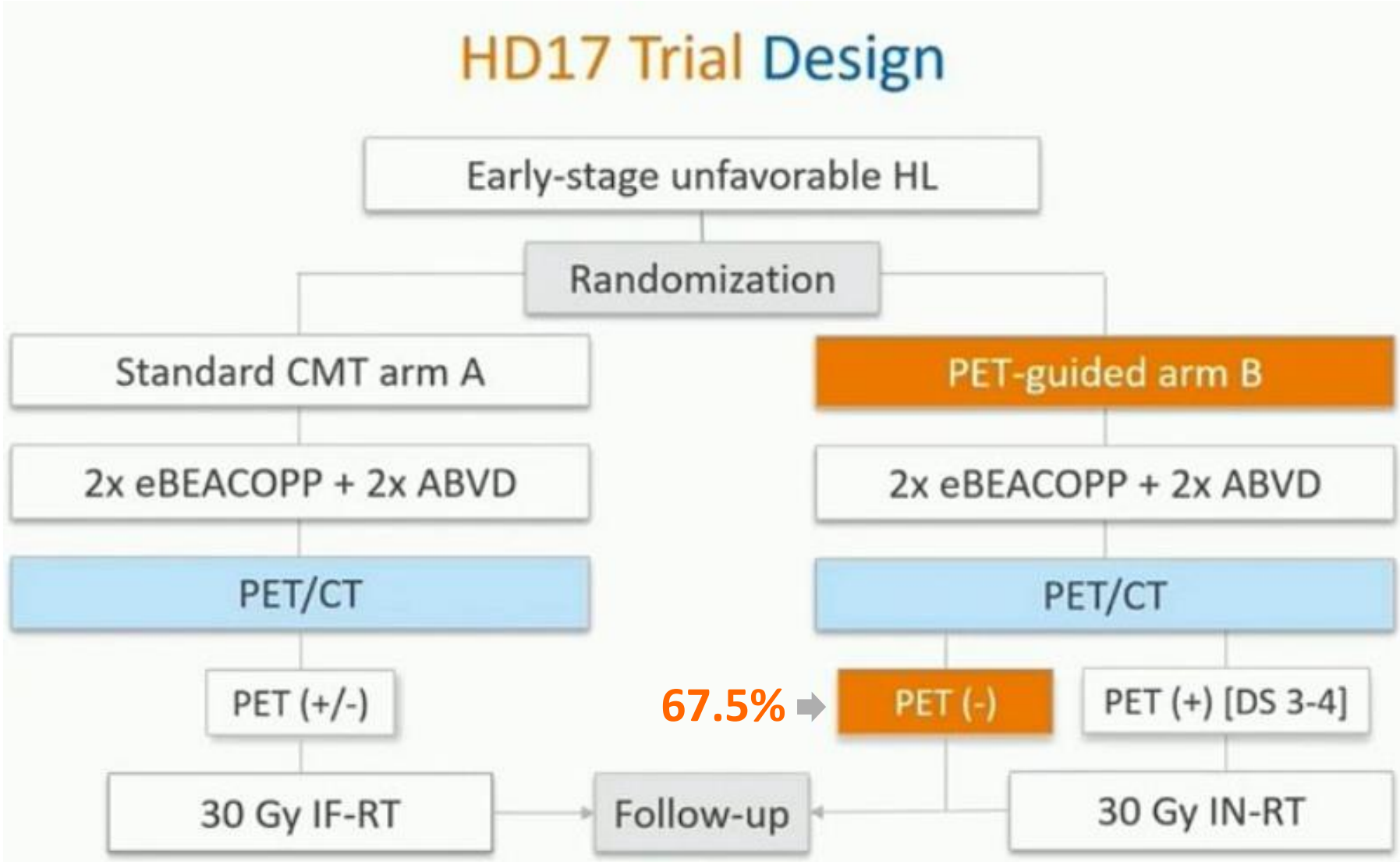
TARC:
by ELISA (R&D Systems, USA, Human CCL17/TARC Quantikine Elisa Kit




| | | | | | |
|---|---|---|---|---|---|
| Median | 14830 | 2160 | 212 | 243 | 286 |
| %TARC+ | 91% | 72% | 12% | 2% | 0% |

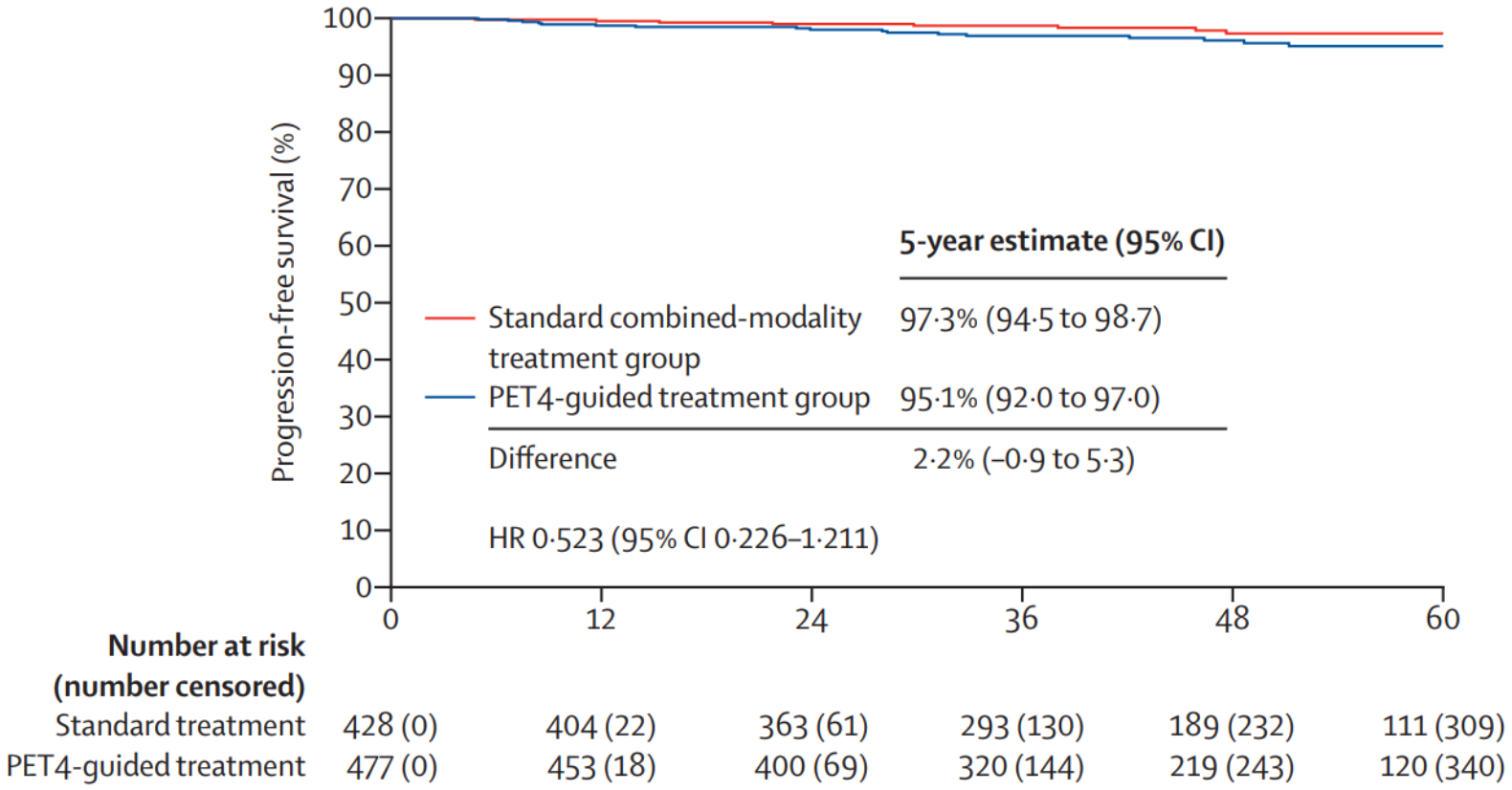
Plattel WJ et al. *HemaSphere* 2025

GHSG




Borchmann P, et al. *Lancet Oncol* 2021

# HD17 trial




Borchmann P, et al. *Lancet Oncol* 2021

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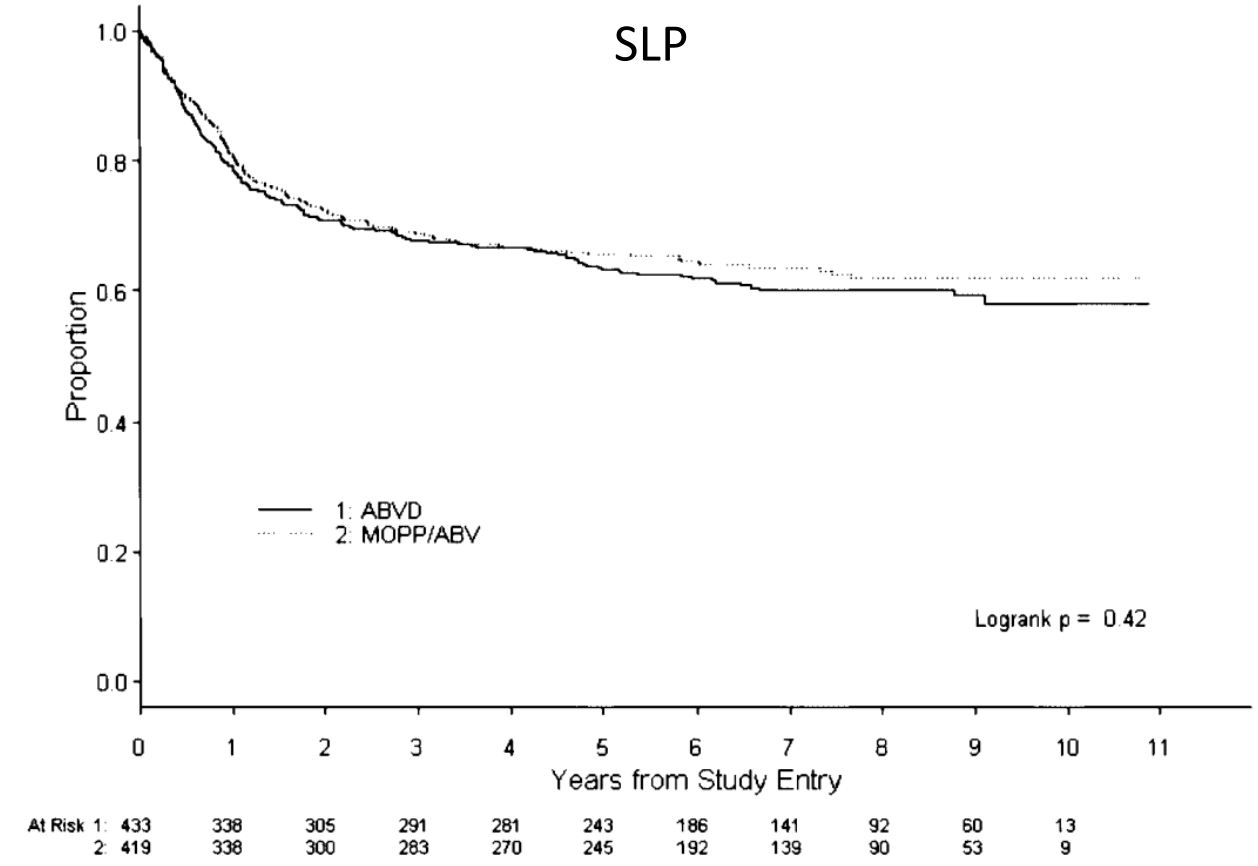
# Primera línea en LHc avanzado (III-IV)

Linfomashb@gmail.com
stemmelingr@gmail.com

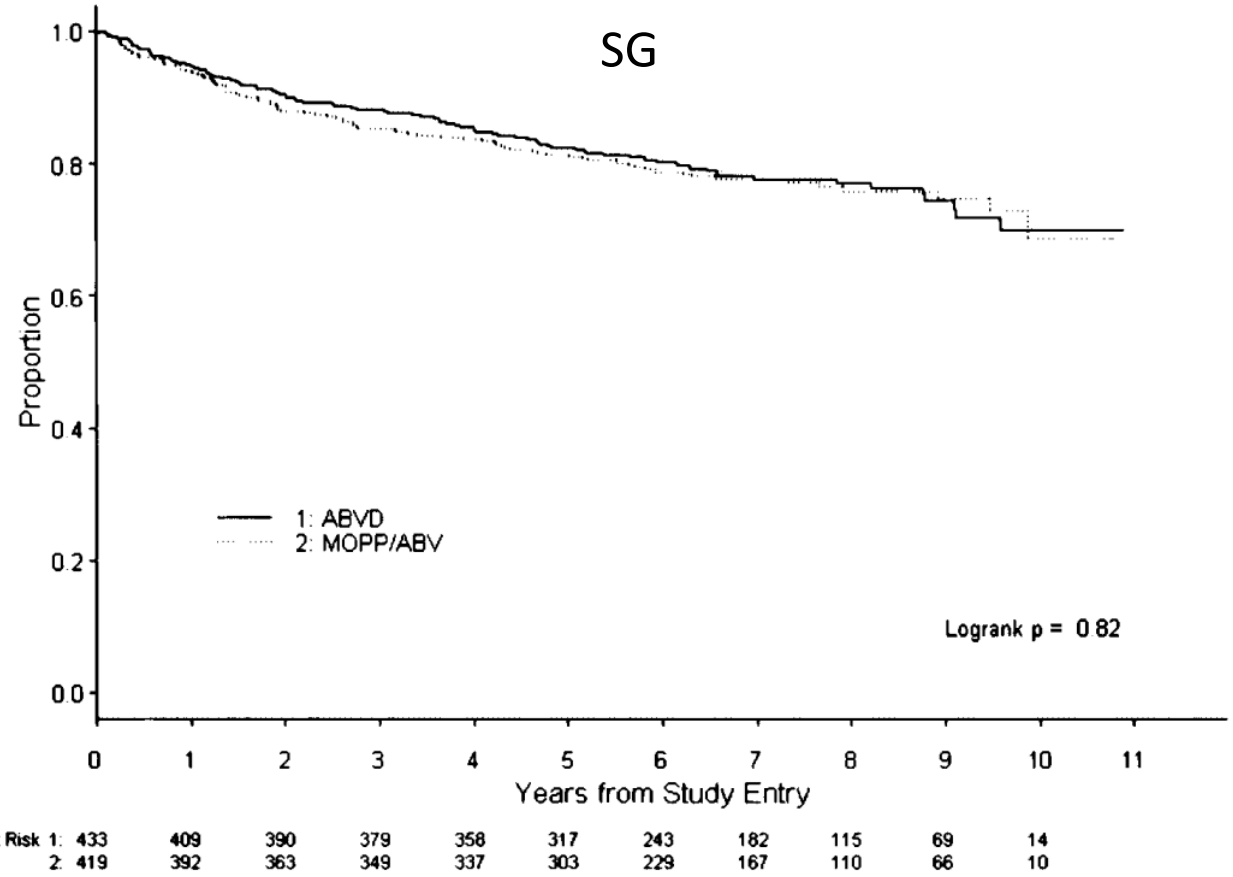
# CALGB 8952 Trial. LH avanzado 1L

## ABVD vs ~~MOPP/ABV~~ (8 ciclos)

SLP

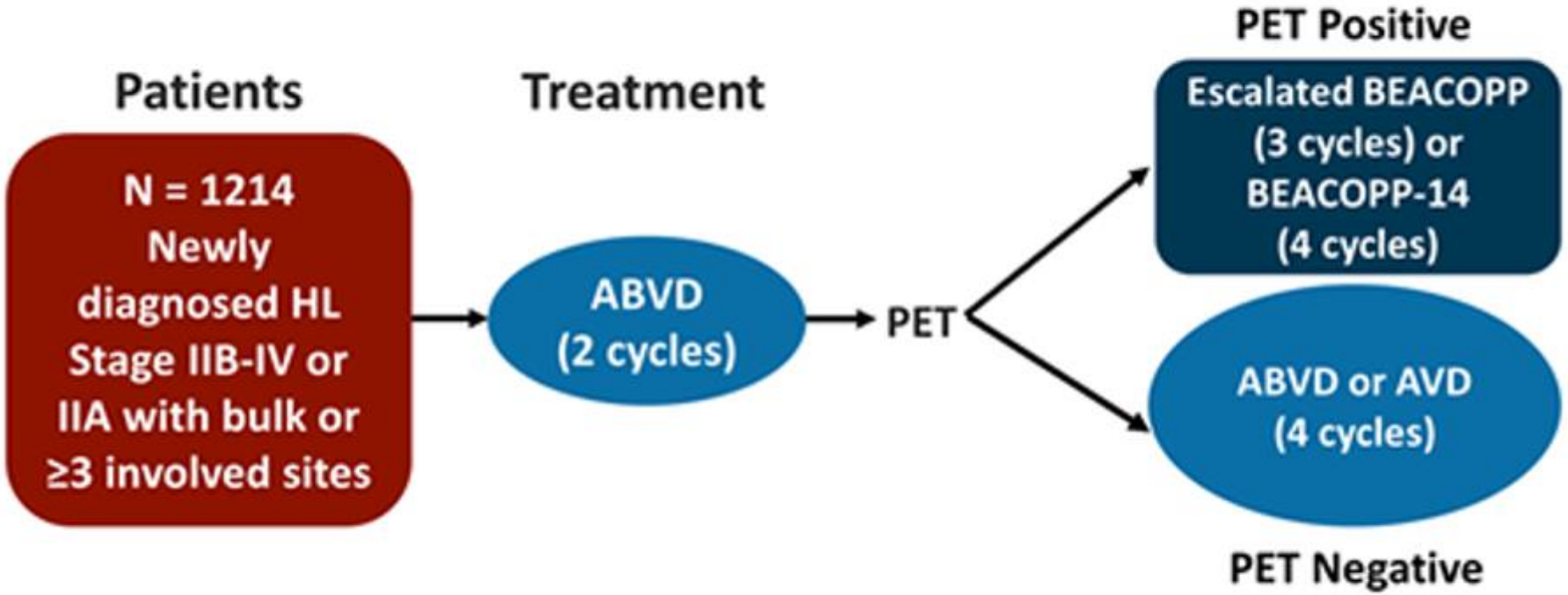



SG




Duggan DV et al. *J Clin Oncol* 2003

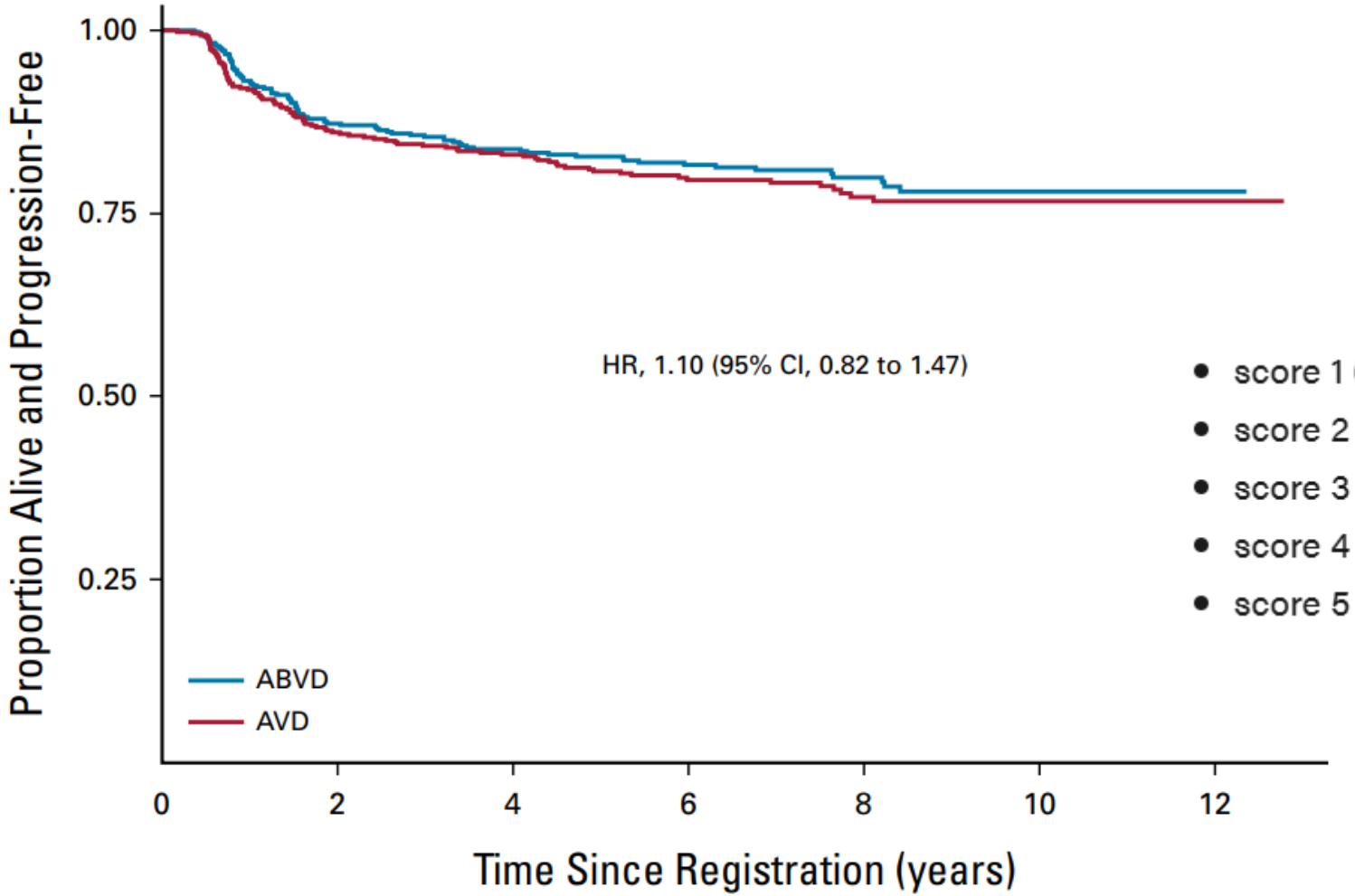
# RATHL: Response-adapted Treatment in Hodgkin Lymphoma FDG-PET




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

Johnson P y col. *NEJM* 2016; 374: 2419-29

# RATHL: PFS 7 años



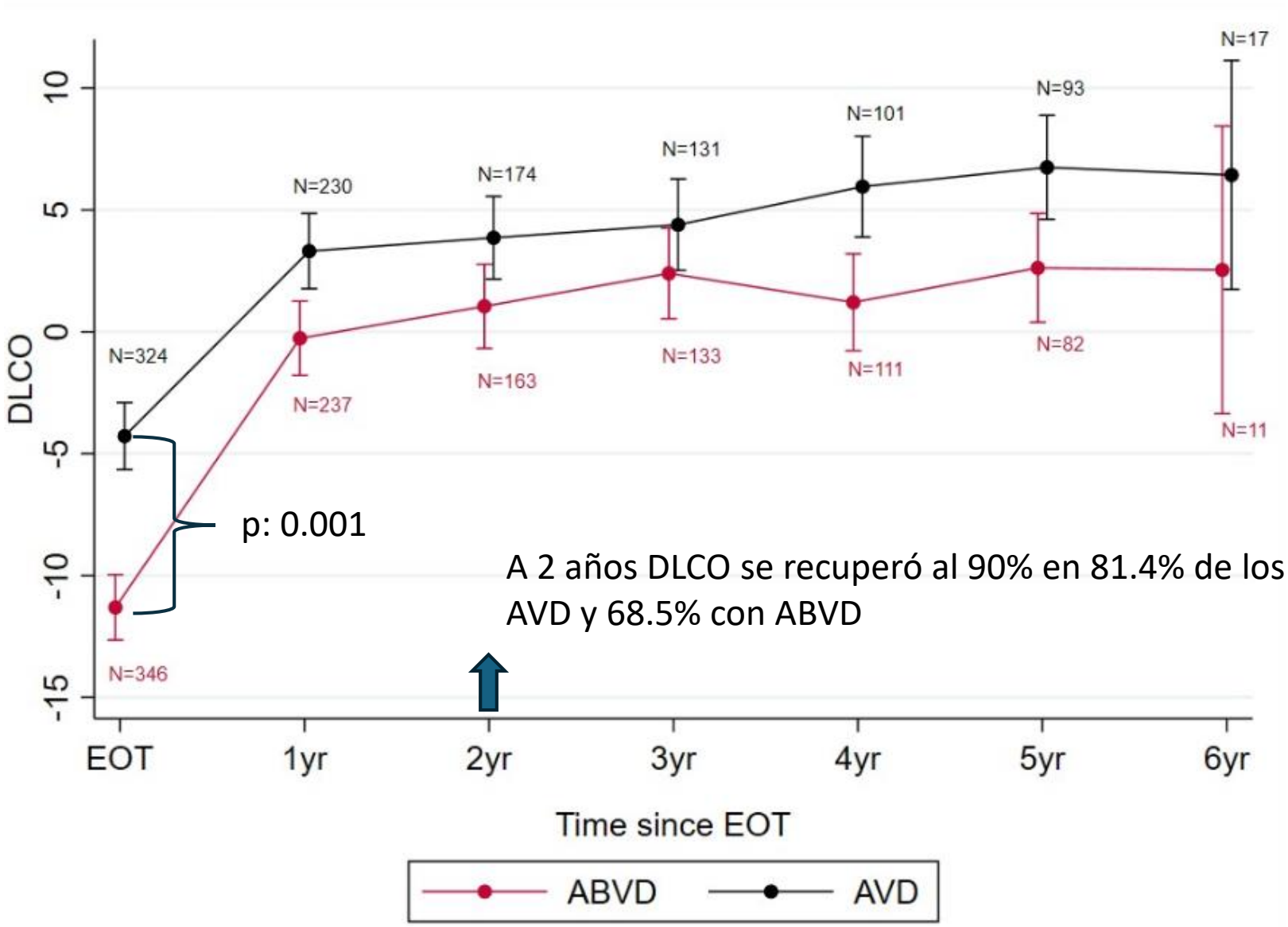

- score 1 (n=111; 9.9%)
- score 2 (n=483; 43.2%)
- score 3 (n=343; 30.7%)
- score 4 (n=144; 12.9%)
- score 5 (n=38; 3.4%)

84%

| No. at risk: | | | | | | | |
|---|---|---|---|---|---|---|---|
| ABVD | 469 | 396 | 339 | 256 | 141 | 33 | 3 |
| AVD | 464 | 380 | 336 | 249 | 144 | 40 | 1 |

Luminari S et al, *JCO* 2023

# RATHL. Toxicidad pulmonar

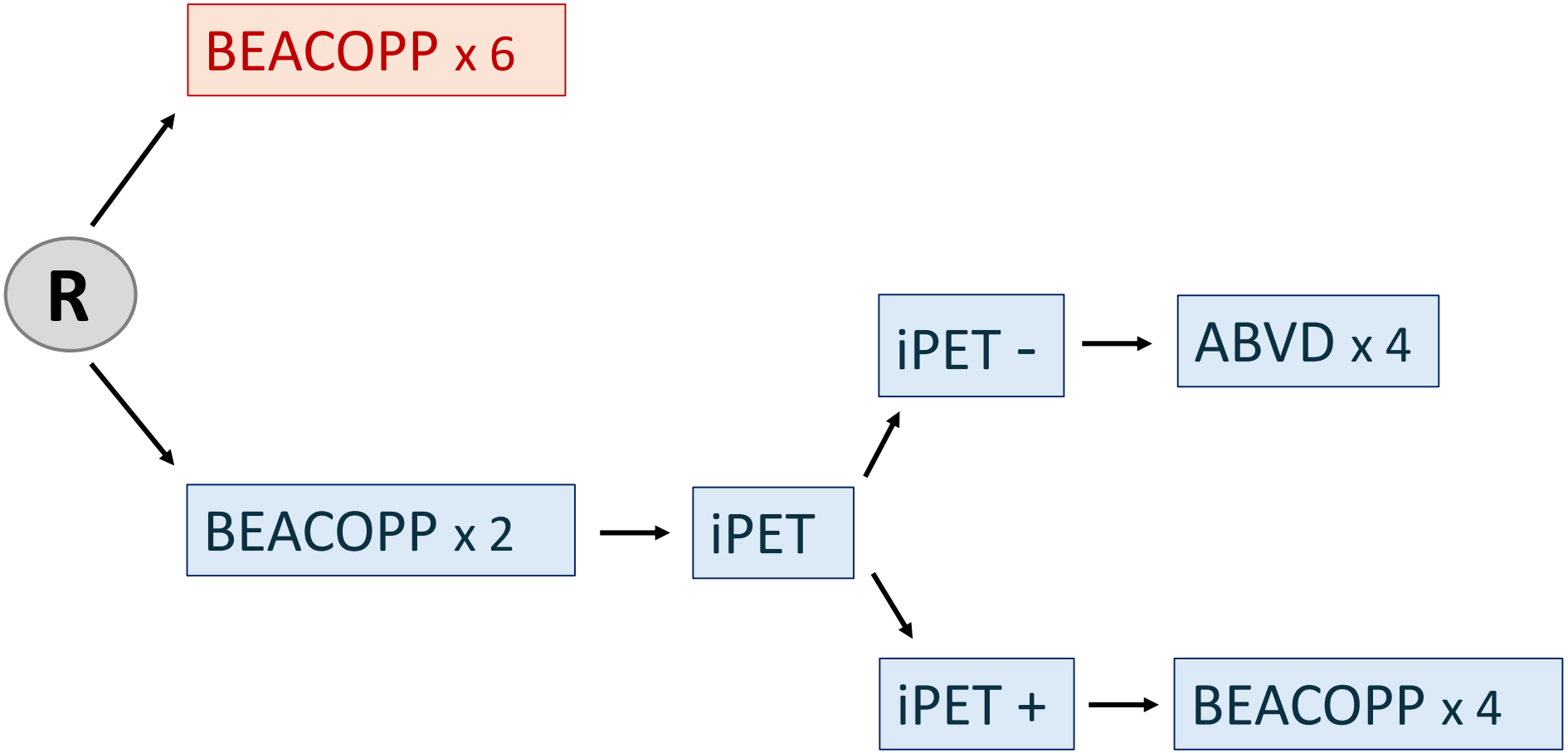



~~ABVD x 6~~

A 2 años DLCO se recuperó al 90% en 81.4% de los ptes con AVD y 68.5% con ABVD

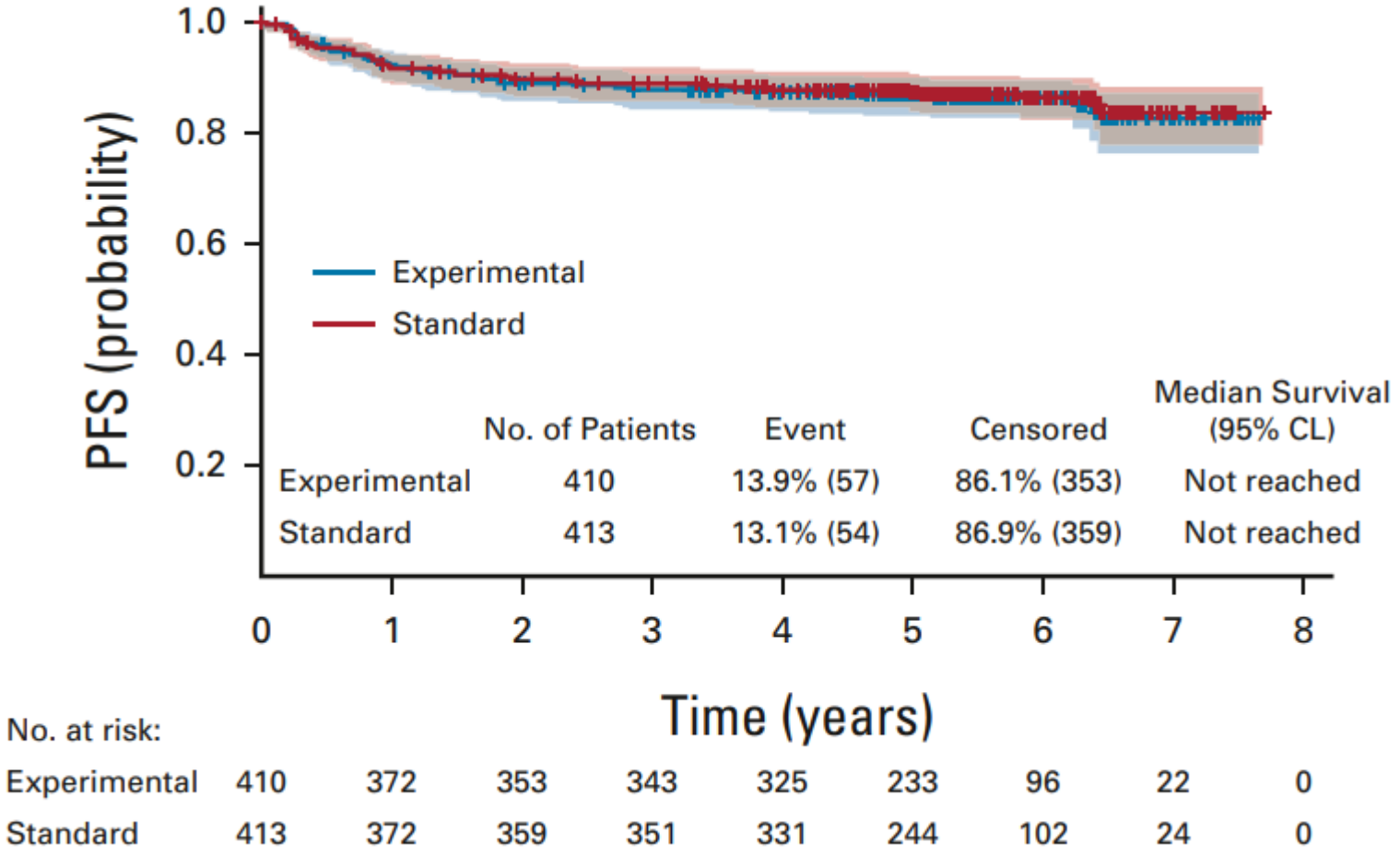
Elizabeth Phillips et al, ASH Meeting 2023 # 612

# AHL2011 trial




Casasnovas RO et al, *JCO* 2022

# AHL2011 trial

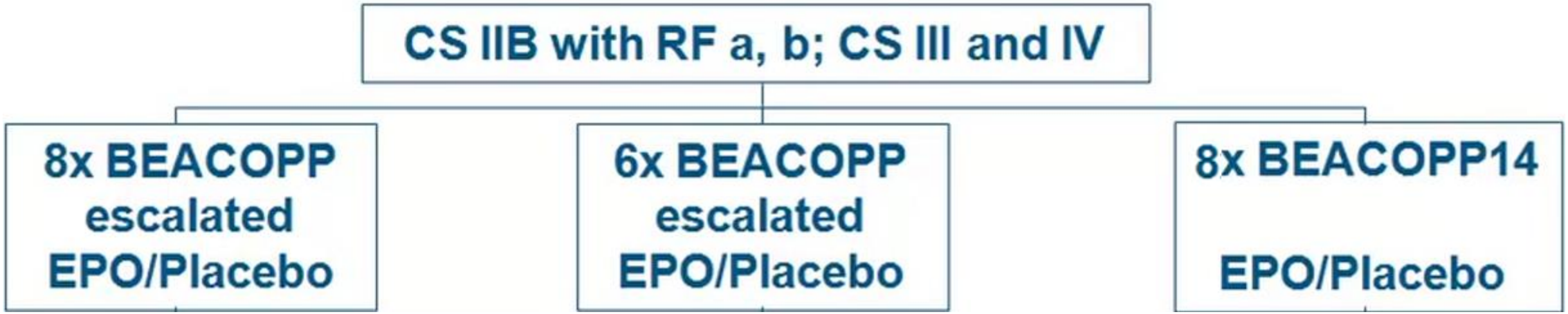



SLP 5 años:
PET 2+/PET 4 – **75.4%**
PET 4 + **46%**

Casasnovas RO et al, *JCO* 2022

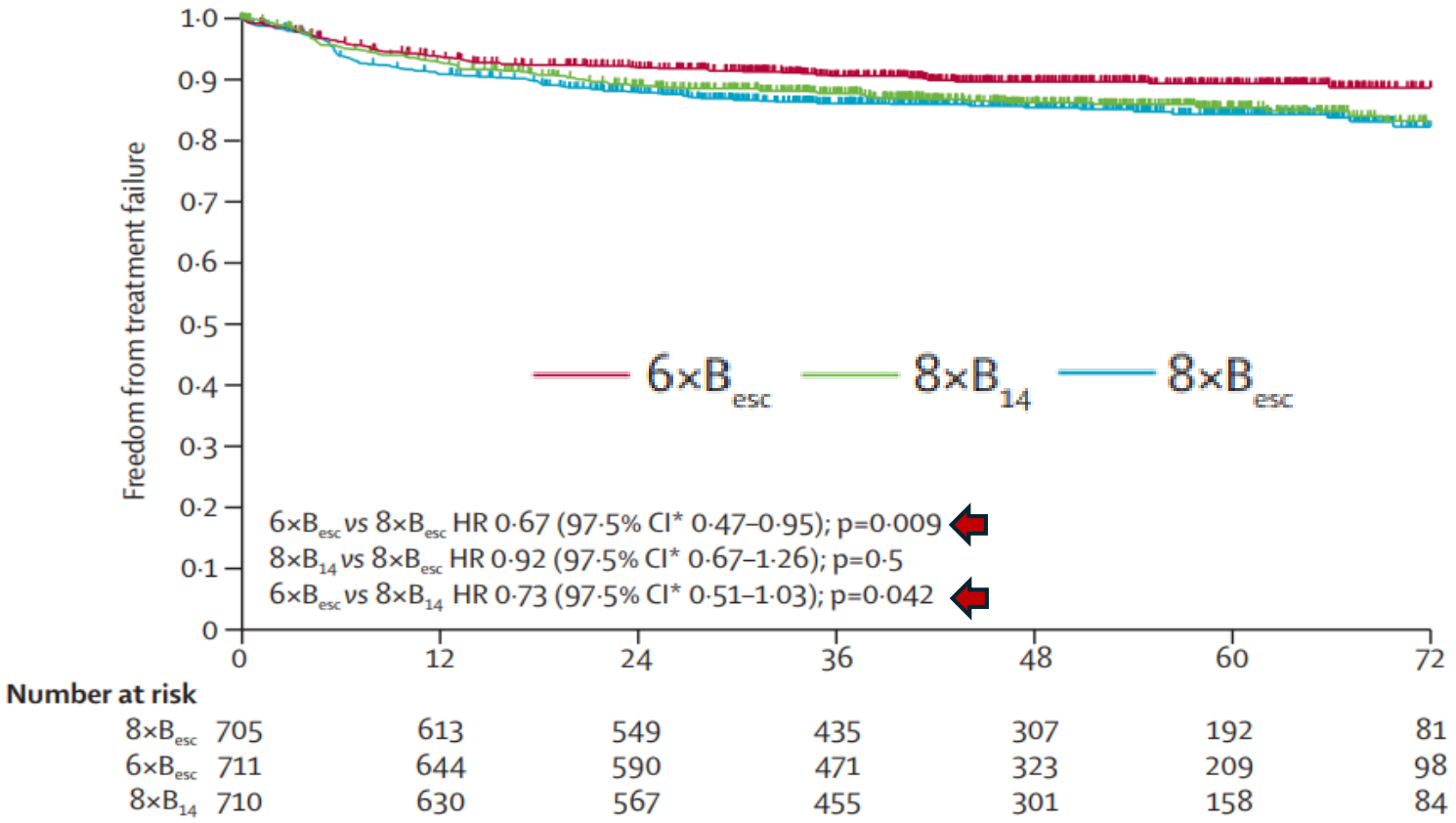
GHSG

# HD15 trial



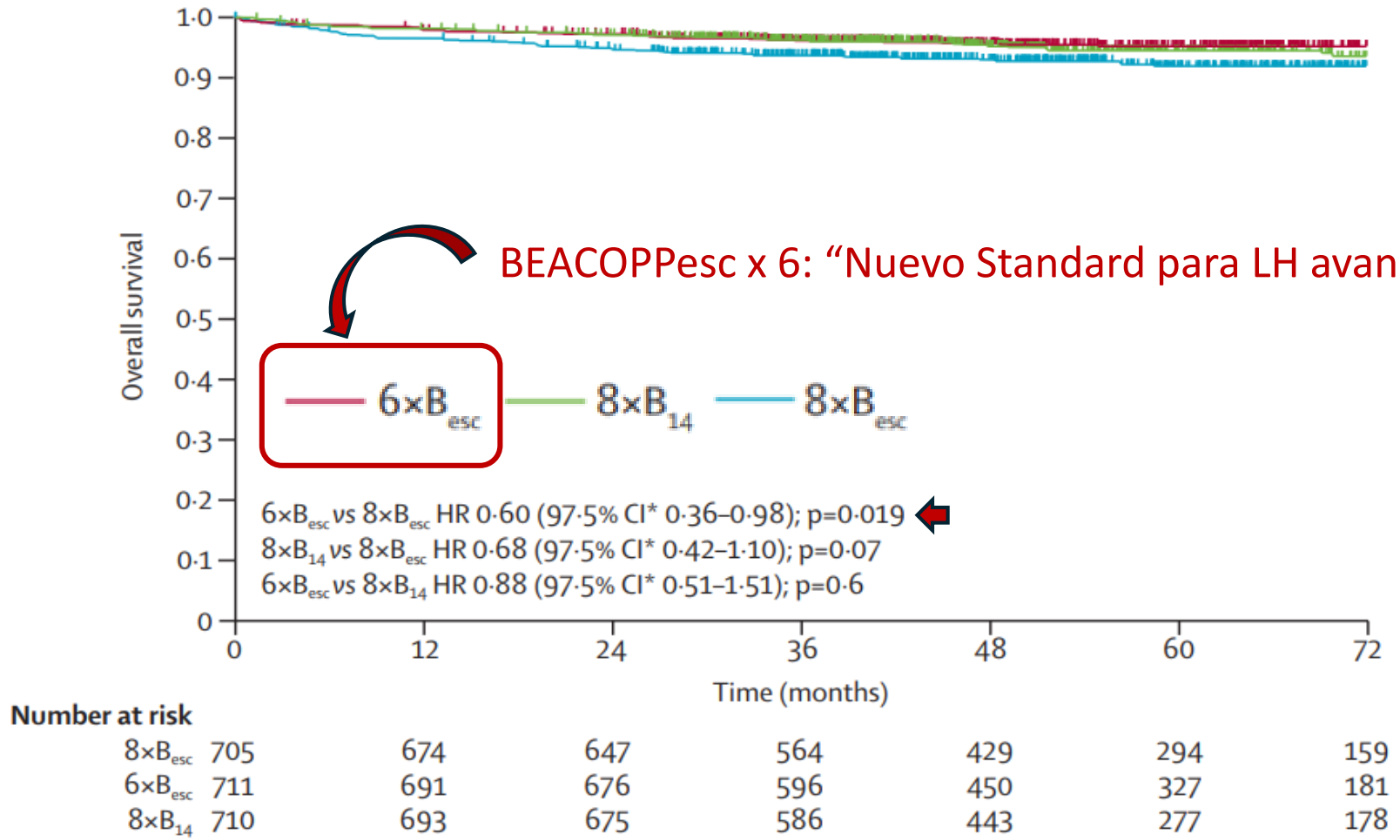

Engert A, et al. *Lancet* 2012

# HD15 trial. PFS/FFTF



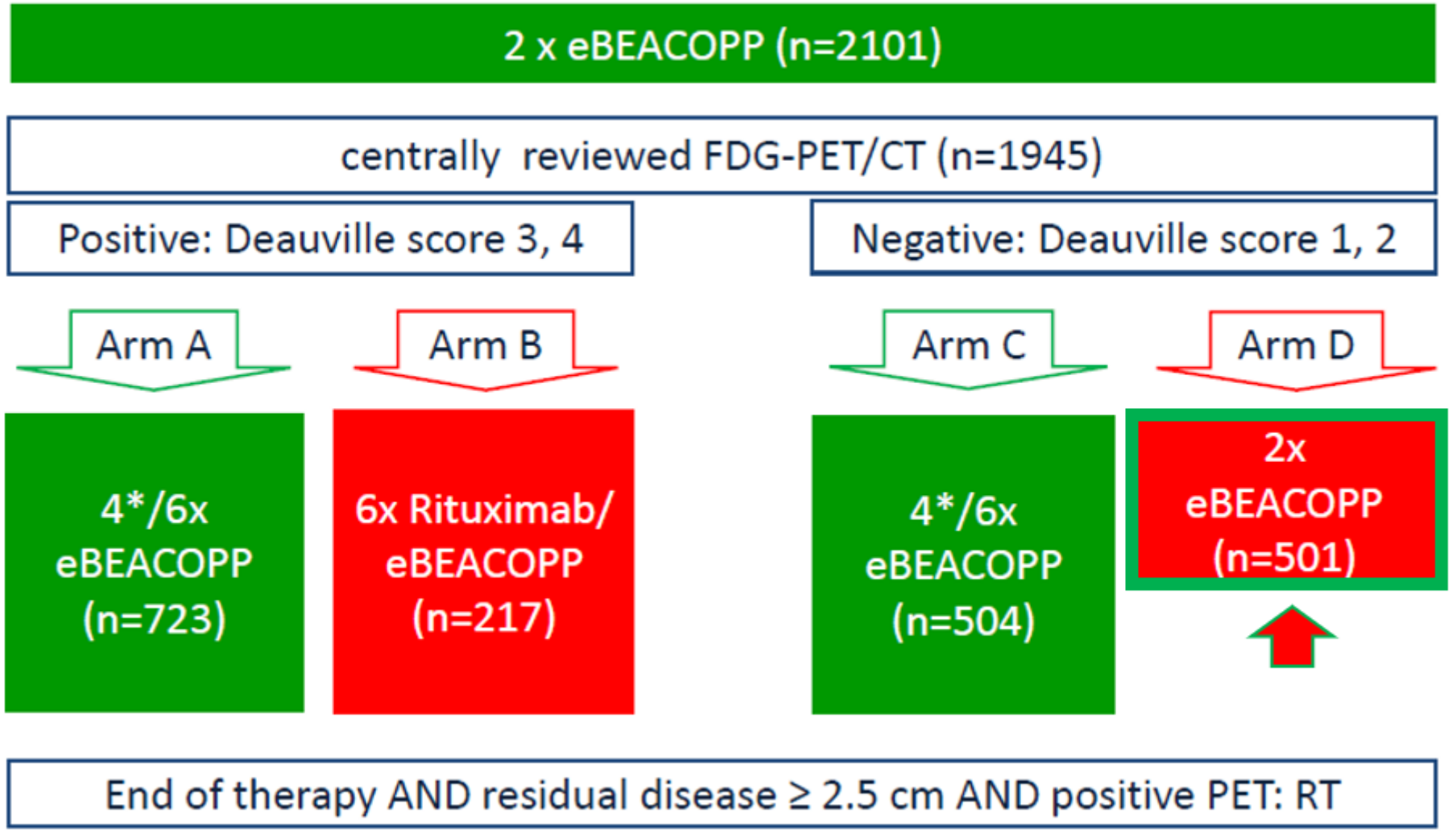

Engert A, et al. *Lancet* 2012

# HD15 trial. OS



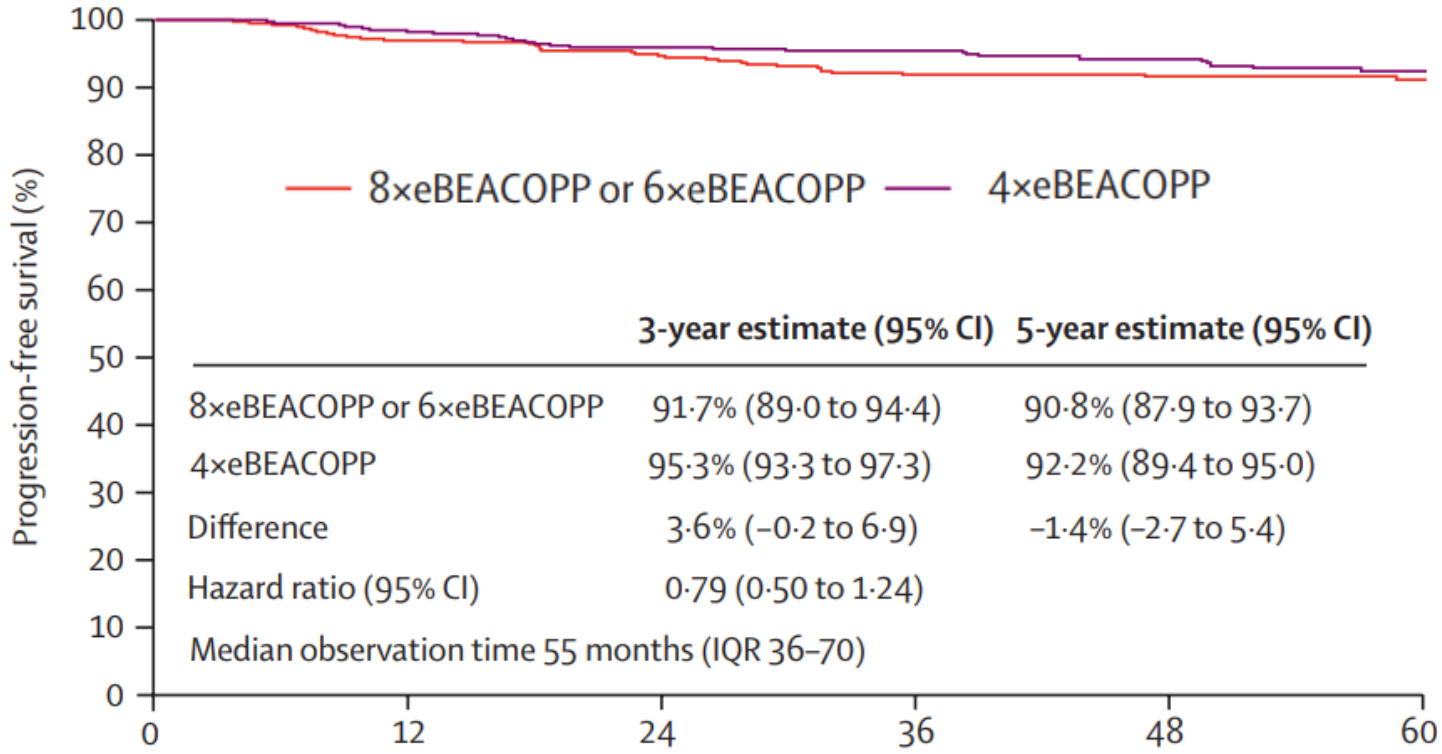

Engert A, et al. *Lancet* 2012

# HD18. LHc avanzado 1L




Borchmann P, et al. *Lancet* 2017

# HD18. SLP 6-8 ciclos vs 4 ciclos

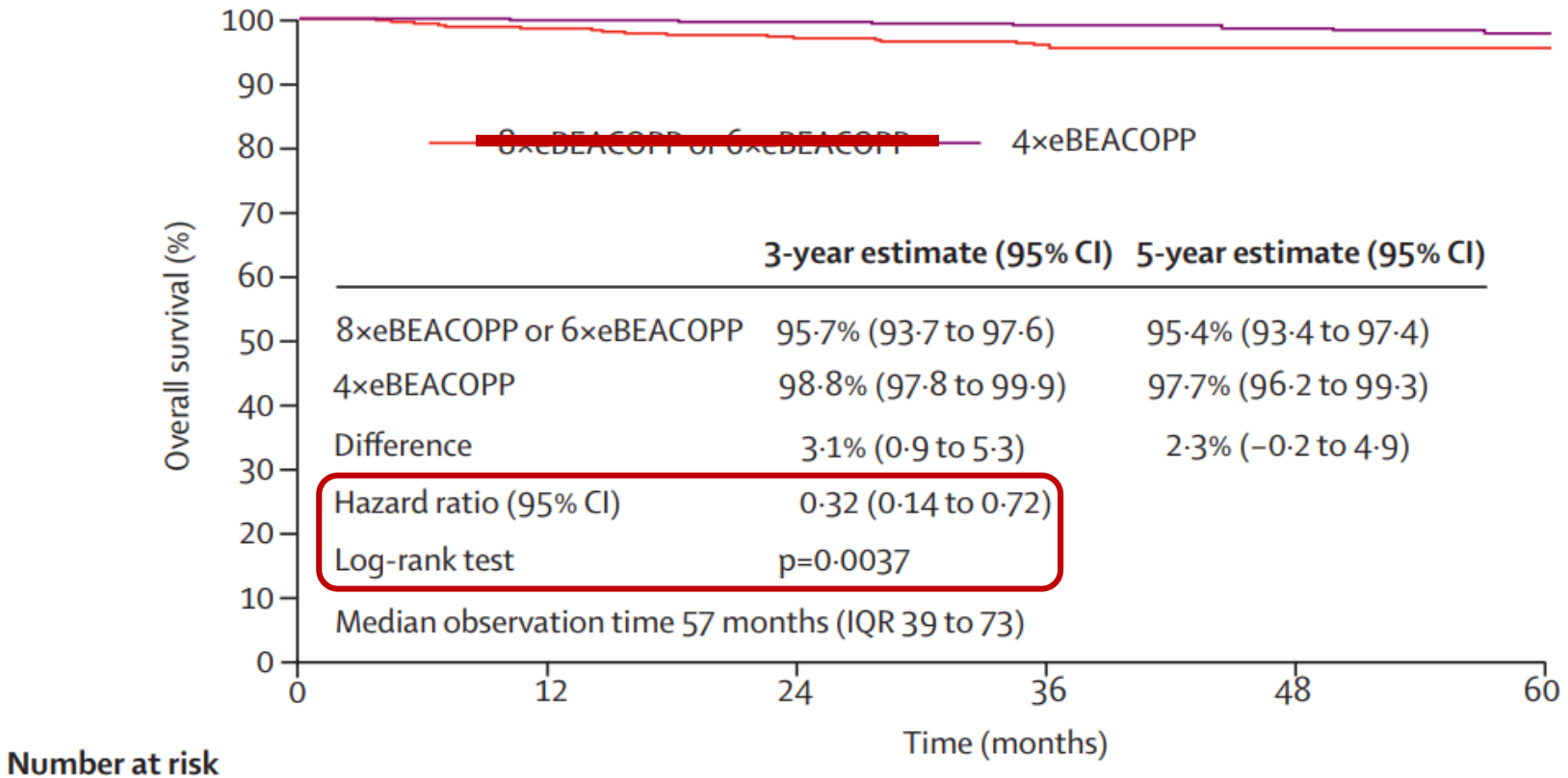



| | 3-year estimate (95% CI) | 5-year estimate (95% CI) |
|---|---|---|
| 8×eBEACOPP or 6×eBEACOPP | 91·7% (89·0 to 94·4) | 90·8% (87·9 to 93·7) |
| 4×eBEACOPP | 95·3% (93·3 to 97·3) | 92·2% (89·4 to 95·0) |
| Difference | 3·6% (−0·2 to 6·9) | −1·4% (−2·7 to 5·4) |
| Hazard ratio (95% CI) | 0·79 (0·50 to 1·24) | |
| Median observation time 55 months (IQR 36–70) | | |

| Number at risk (number censored) | | | | | | |
|---|---|---|---|---|---|---|
| 8×eBEACOPP or 6×eBEACOPP | 446 (0) | 411 (21) | 378 (45) | 310 (102) | 247 (164) | 164 (246) |
| 4×eBEACOPP | 474 (0) | 444 (22) | 412 (43) | 334 (119) | 269 (180) | 198 (246) |

Borchmann P, et al. *Lancet* 2017

# HD18. SG 6-8 ciclos vs 4 ciclos

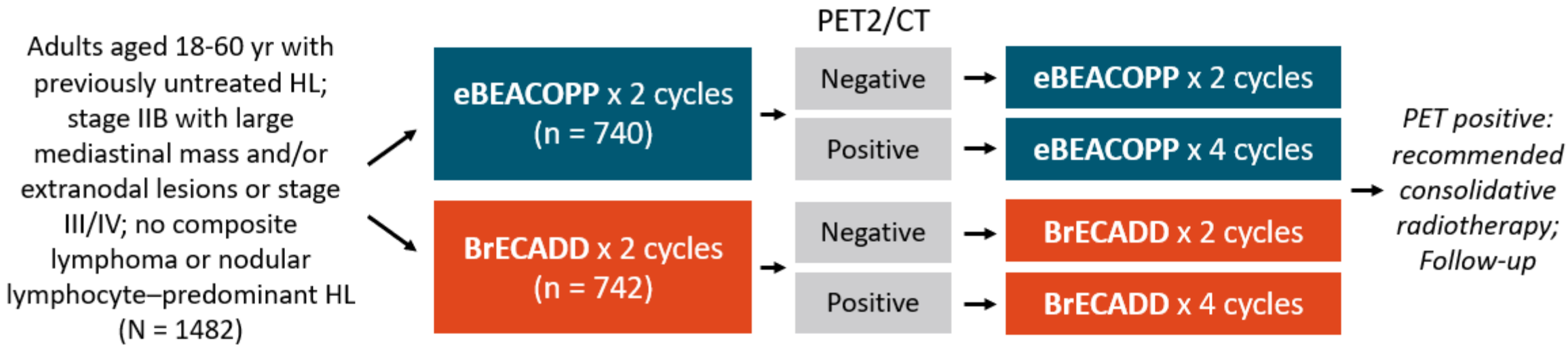



| Number at risk (number censored) | | | | | | |
|---|---|---|---|---|---|---|
| 8×eBEACOPP or 6×eBEACOPP | 446 (0) | 428 (11) | 396 (36) | 329 (22) | 269 (158) | 187 (240) |
| 4×eBEACOPP | 474 (0) | 459 (14) | 443 (29) | 184 (24) | 288 (180) | 223 (243) |

Borchmann P, et al. *Lancet* 2017

# HD21: BrECADD vs eBEACOPP

- Randomized, noninferiority phase III study




- **Primary endpoint:** PFS, treatment-related morbidity
- **Secondary endpoints:** CR, OS, EFS, gonadal toxicity, safety

Borchmann P et al. *Lancet* 2024

# HD21: BrECADD vs eBEACOPP

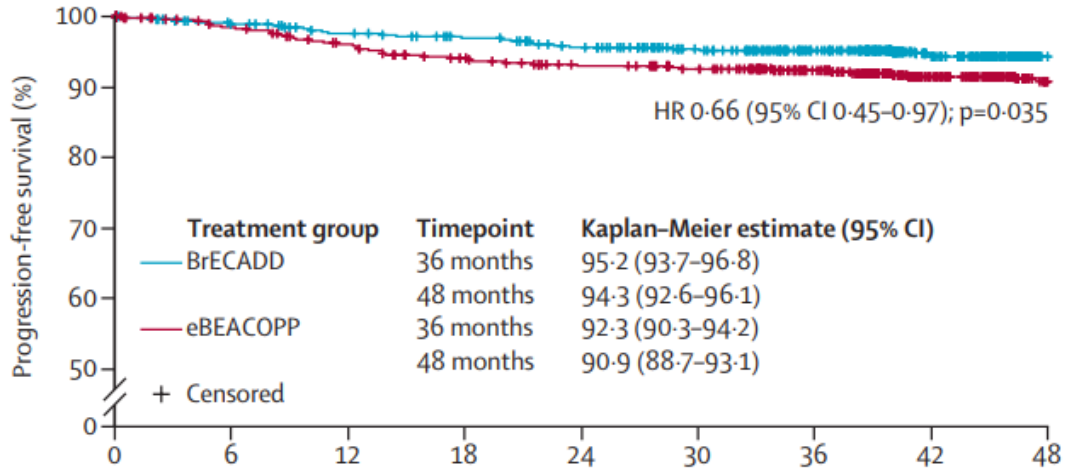
BrECADD x 4-6 ciclos c/21 días

1) BV 1.8 mg/kg (Max 180 mg) D0
2) Etopósido 150 mg/m2 D1-3
3) Ciclofosfamida 1250 mg/m2 D1
4) Doxorrubicina 40 mg/m2 D1
5) Dacarbacina 250 mg/m2 D2-3
6) Dexametasona 40 mg D1-4

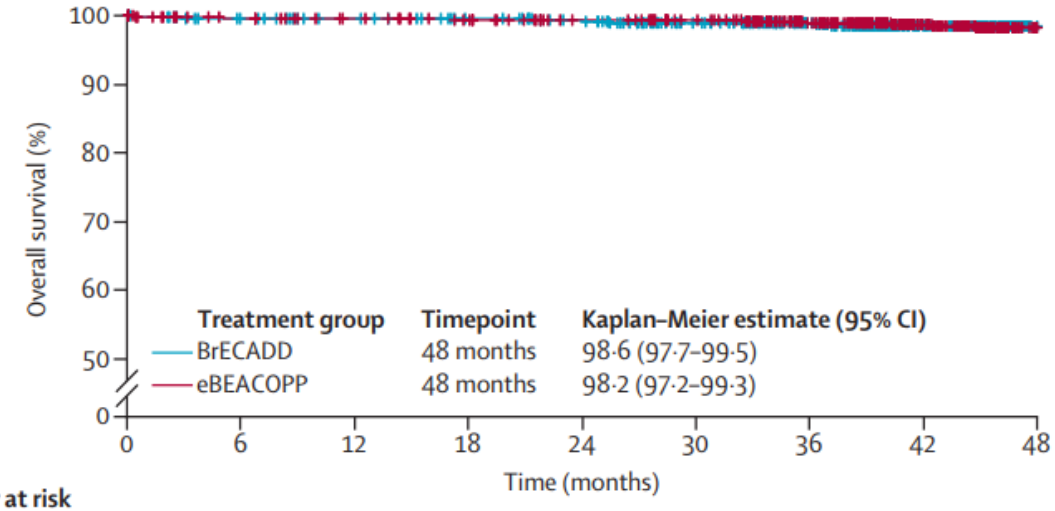
| | eBEACOPP | BrECADD |
|---|---|---|
| Anemia ≥G3 | 59% | 30% |
| Trombocitopenia ≥G3 | 72% | 55% |
| Neutropenia febril ≥G3 | 21% | 28% |
| Transf GR/Plt | 53/34% | 24/17% |
| NP sensitiva | 49% | 39% |

Borchmann P et al. *Lancet* 2024

# HD21: BrECADD vs ~~eBEACOPP~~




| Number at risk (number censored) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| BrECADD | 742 (0) | 721 (14) | 701 (23) | 688 (32) | 670 (41) | 639 (70) | 588 (120) | 488 (217) | 374 (329) |
| eBEACOPP | 740 (0) | 711 (18) | 685 (26) | 663 (35) | 643 (47) | 628 (59) | 578 (107) | 471 (209) | 372 (306) |

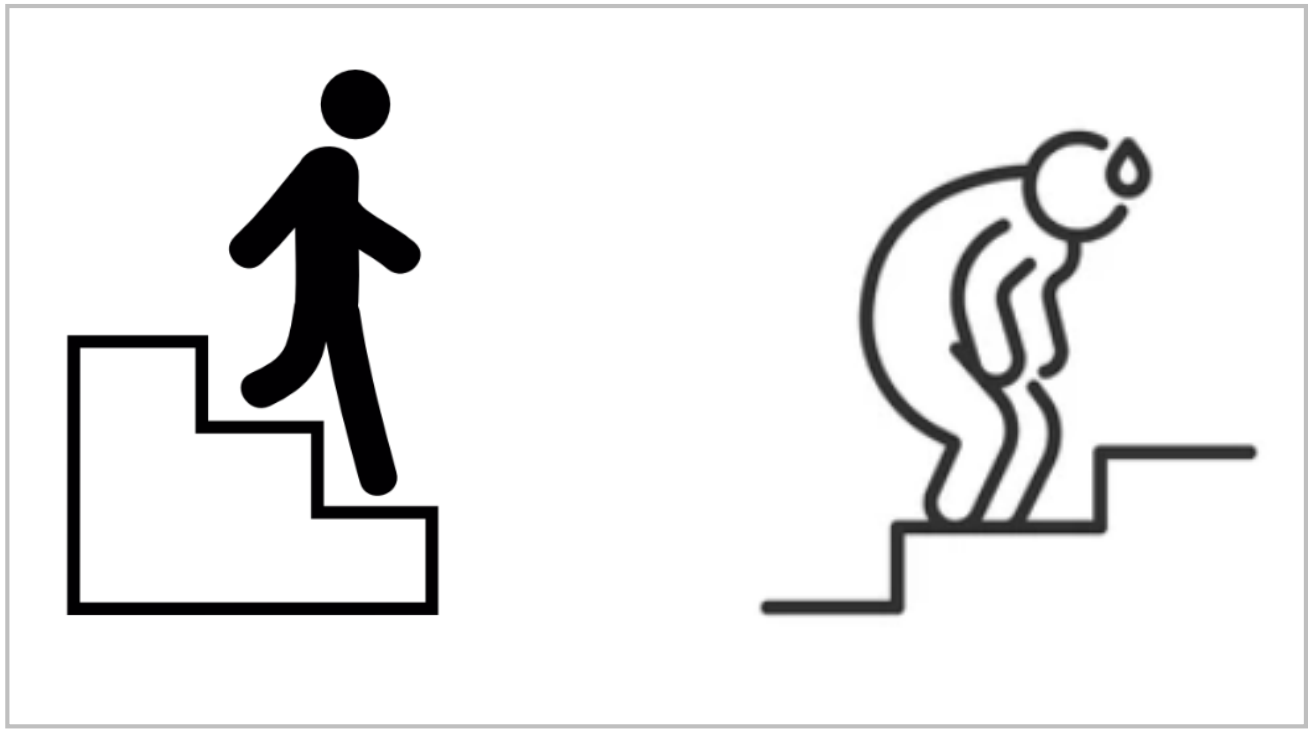



| Number at risk (number censored) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| BrECADD | 742 (0) | 725 (14) | 715 (23) | 705 (33) | 695 (42) | 661 (73) | 608 (126) | 504 (228) | 388 (344) |
| eBEACOPP | 740 (0) | 717 (20) | 708 (29) | 698 (38) | 683 (53) | 668 (67) | 614 (119) | 501 (230) | 395 (334) |

Borchmann P et al. *Lancet* 2024

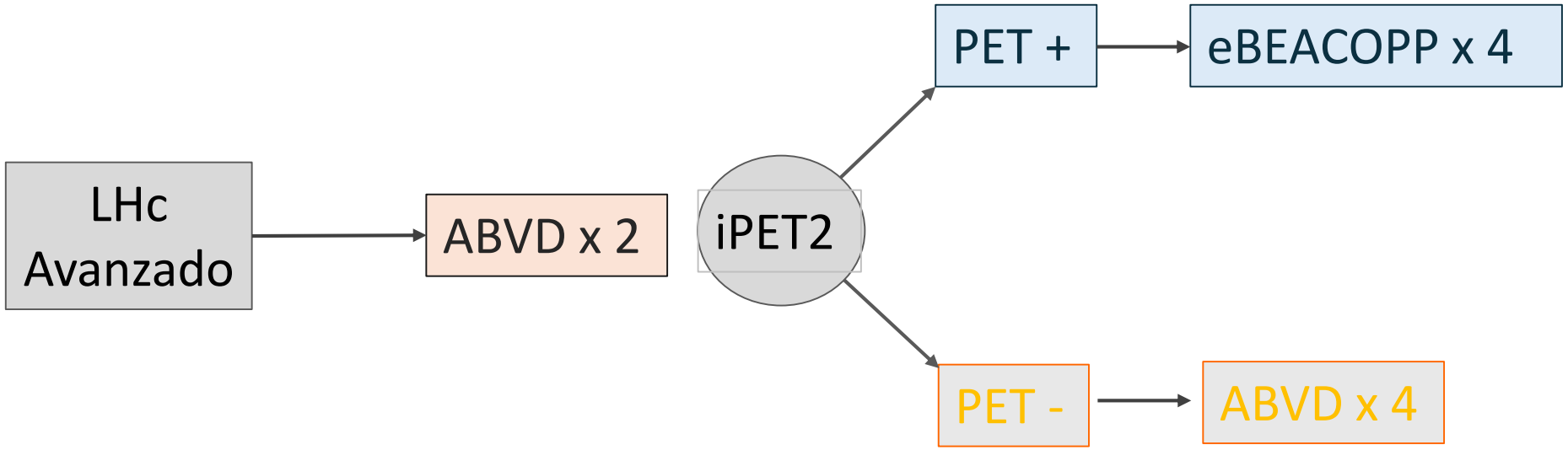
# Linfoma de Hodgkin

¿Es más “fácil” des-escalar que escalar?



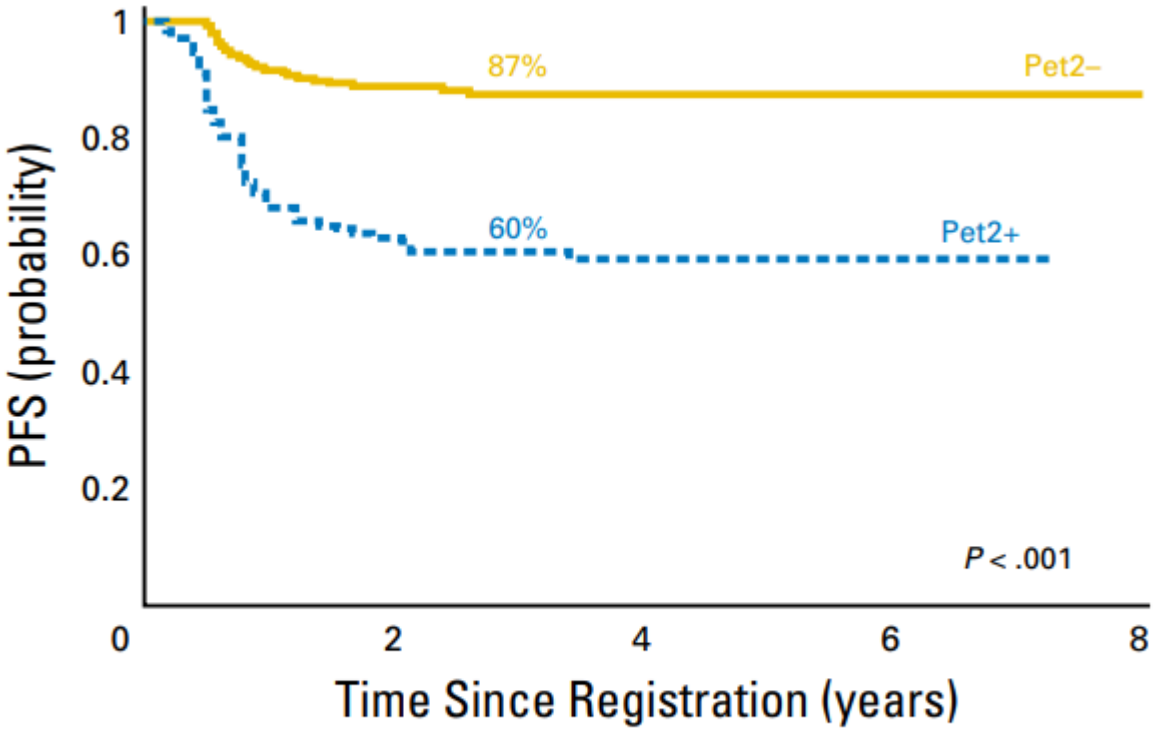
Linfomashb@gmail.com
stemmelingr@gmail.com

# HD 0607 trial

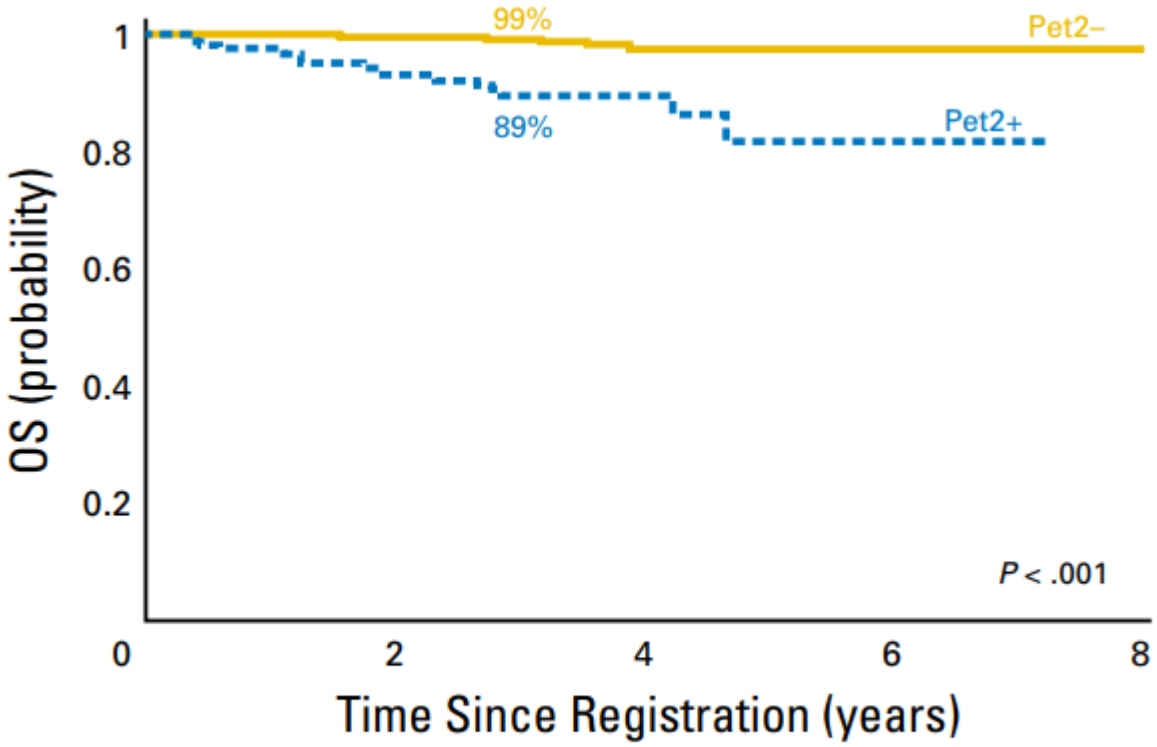



Gallamini A, et al. *J Clin Oncol* 2018

# HD 0607 trial




| No. at risk | | Events | | Events | | Events | | Events | |
|---|---|---|---|---|---|---|---|---|---|
| Pet2– | 630 | 73 | 528 | 8 | 147 | 0 | 40 | 0 | 0 |
| Pet2+ | 150 | 53 | 83 | 4 | 26 | 0 | 4 | 0 | 0 |

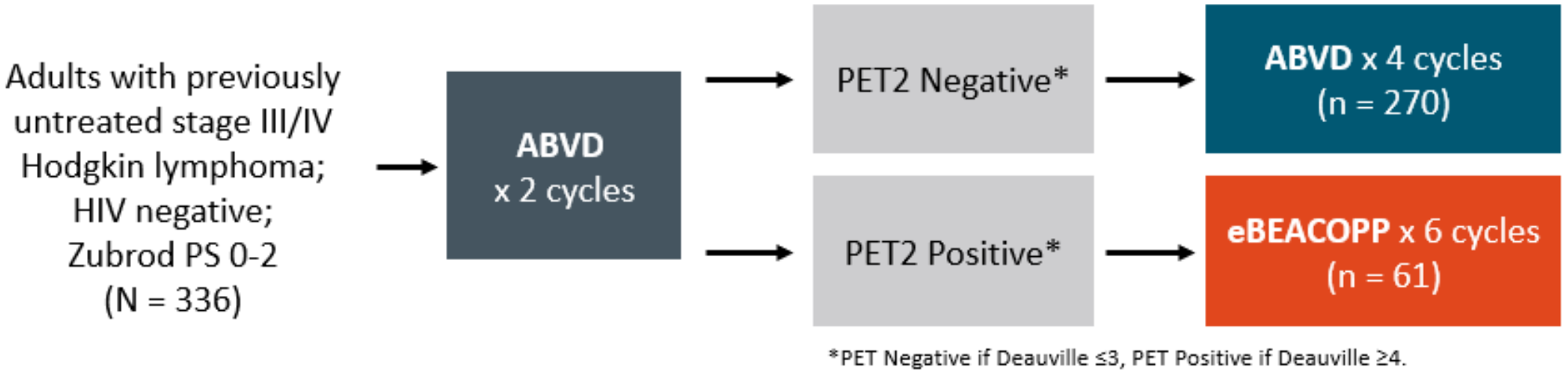



| No. at risk | | Events | | Events | | Events | | Events | |
|---|---|---|---|---|---|---|---|---|---|
| Pet2– | 630 | 3 | 583 | 9 | 169 | 0 | 42 | 0 | 0 |
| Pet2+ | 150 | 10 | 116 | 4 | 37 | 2 | 4 | 0 | 0 |

Gallamini A, et al. *J Clin Oncol* 2018

# S0816 trial

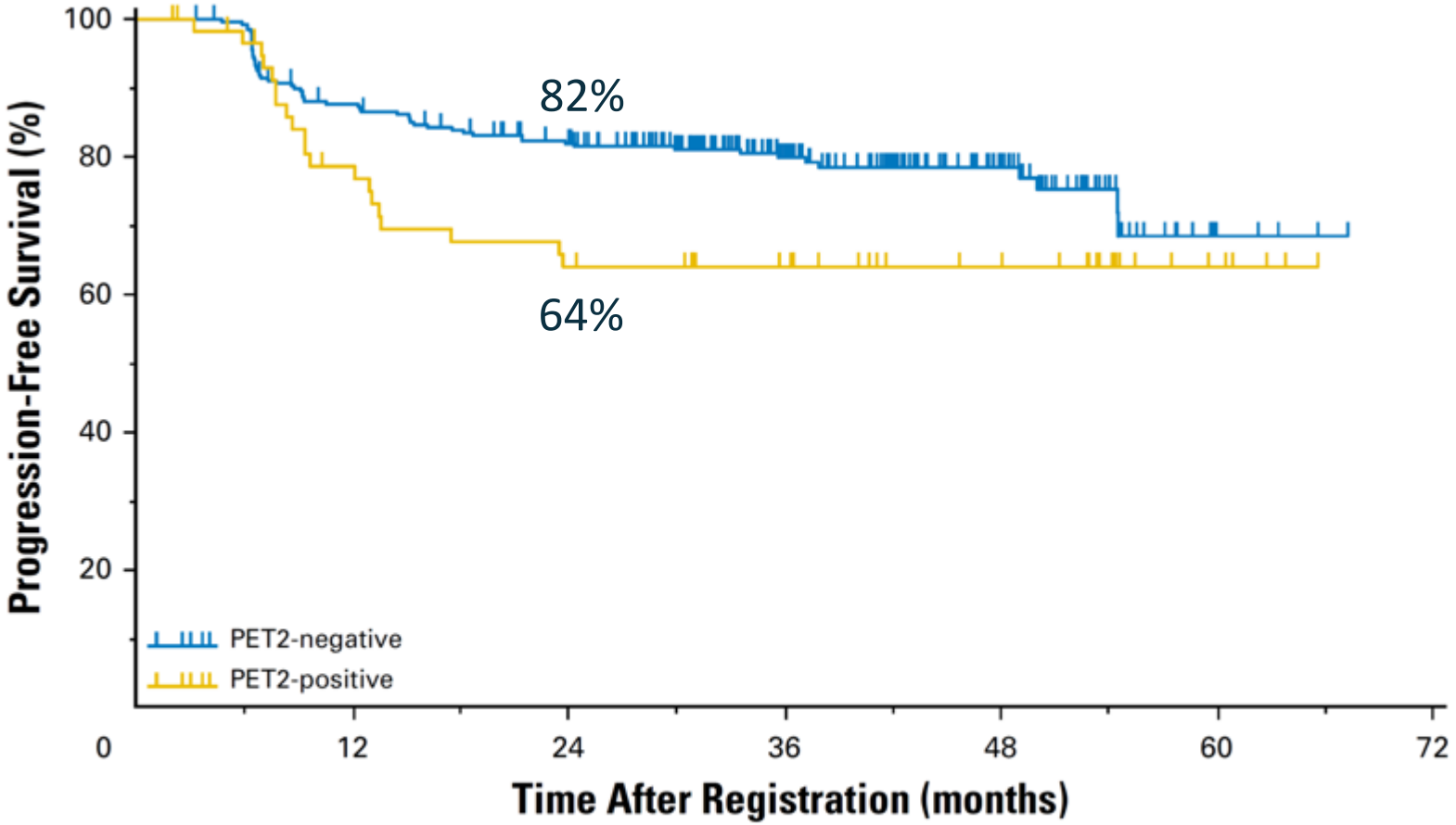
- PET-Guided, multicenter phase II study




- **Primary endpoint:** 2-Yr PFS
- **Secondary endpoints:** OS, CR, and PR rates

Stephens, et al. *Blood* 2019

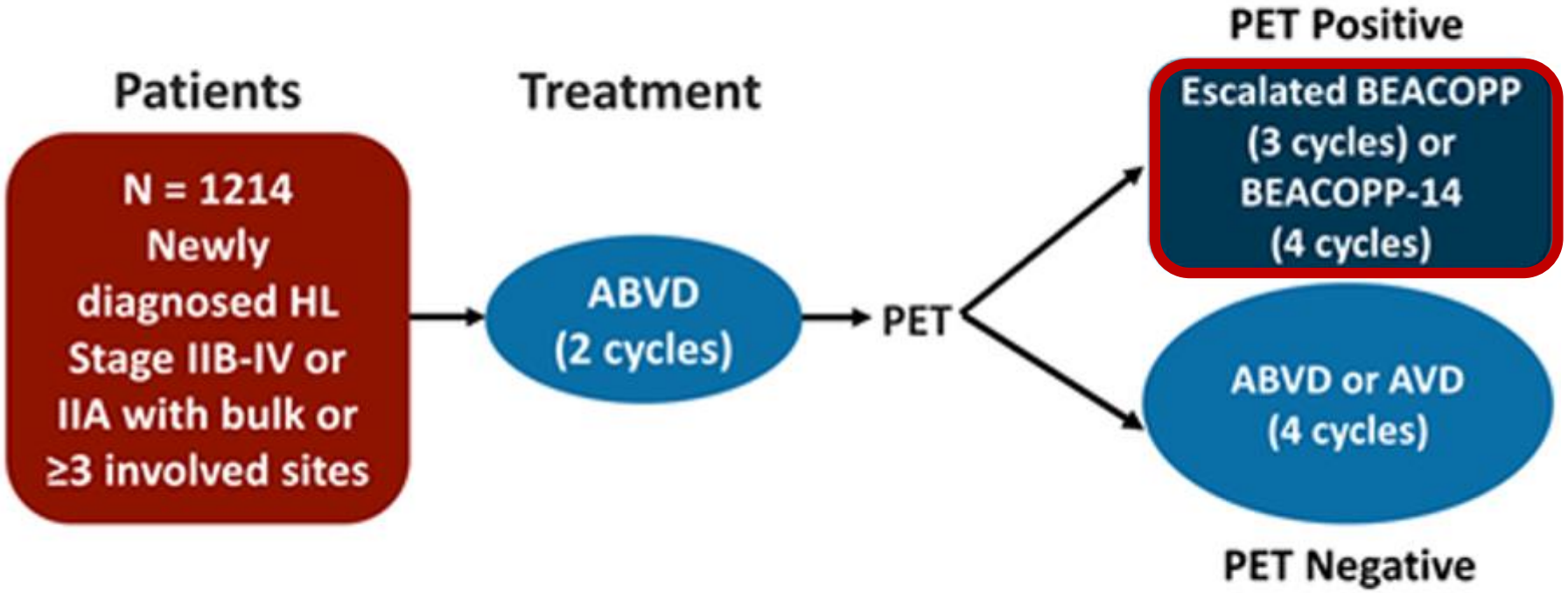
# S0816 trial




| | Patients at Risk | Failed | 2-Year Estimate |
|---|---|---|---|
| PET2-negative | 271 | 58 | 82% |
| PET2-positive | 60 | 20 | 64% |

Stephens, et al. *Blood* 2019

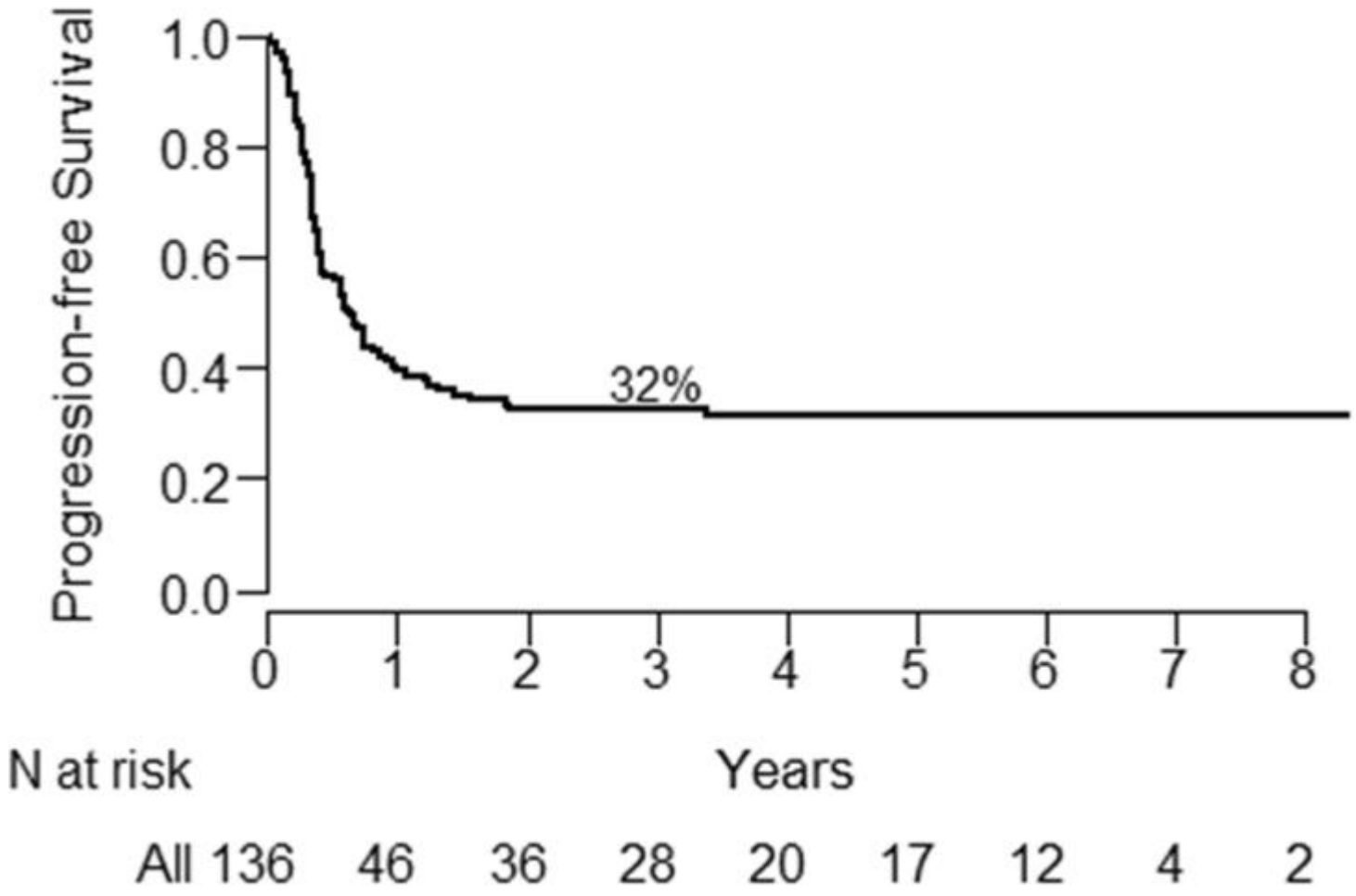
# RATHL: Response-adapted Treatment in Hodgkin Lymphoma FDG-PET




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

Johnson P y col. *NEJM* 2016; 374: 2419-29

# Deauville score **5** post 2 ABVD (Datos de RATHL, HD0607 y S0816)




Simonetta V, et al. *Blood Cancer Journal* 2025

# Conclusiones

- En los últimos 30 años hemos podido “des-escalar” en todas las etapas de la enfermedad conservando la efectividad. Hoy los tratamientos tienen mucho menos toxicidad temprana y alejada.

- En tempranos favorables la utilización de radioterapia post PETi negativo es debatible y debería ser consensuado con el pte

- En temprano desfavorable quizás se pueda evitar la radioterapia con esquemas acortados (N-AVD x 4, BV-AVD x 4, BrECADD x 2) luego de un PET EOT negativo, pero no hay evidencia sólida. El uso de esquemas de estadios avanzados (Ej RATHL) no requeriría radioterapia.

ULHB

Linfomashb@gmail.com
stemmelingr@gmail.com

# Conclusiones (cont)

- En estadios avanzados hay evidencia para des-escalar con esquemas a base de ABVD (RATHL) y BrECADD (HD18 y HD21) con iPET 2 negativo.
- El Score Deauville para des-escalar no ha sido definido (D 2 vs D 3)
- La efectividad de escalar con iPET2 positivo es sólo parcial.
- Los ptes con score Deauville 5 en iPET2 deberían ser considerado refractarios primarios y actuar en consecuencia.

ULHB
Linfomashb@gmail.com
stemmelingr@gmail.com

# ¡¡ Muchas Gracias Gell Cuenca25 !!

ULHB

Linfomashb@gmail.com
stemmelingr@gmail.com