



# SINTOMA'24

PARCERIA **soho**  
society of hematologic oncology

APOIO  
INSTITUCIONAL

**bp** Educação  
e Pesquisa

# How Do I apply iPET-CT for HL in my daily practice?

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Medical School Israelita Albert Einstein

Santa Casa Medical School



# Disclosures

Speaker: Abbvie; Jansen; Takeda; Roche; Lilly, AstraZeneca, MSD, Beigene; Kite

Advisory board: Abbvie; Jansen; Takeda; Roche; Lilly, AstraZeneca, MSD, Beigene

No company actions

# Disclosure

I do BEACOPP since 2008 (really BEACOP(D)D)  
Moreover: In a public center

What a  
crazy!



# Disclosure

No access to brentuximab nor immunotherapy

No fast access to AutoPBSCT

# Introduction

- Curable disease
- Initial stage: 80-90%
- Advanced stage: 70-90 %
- Better strategy: High efficacy with low toxicity

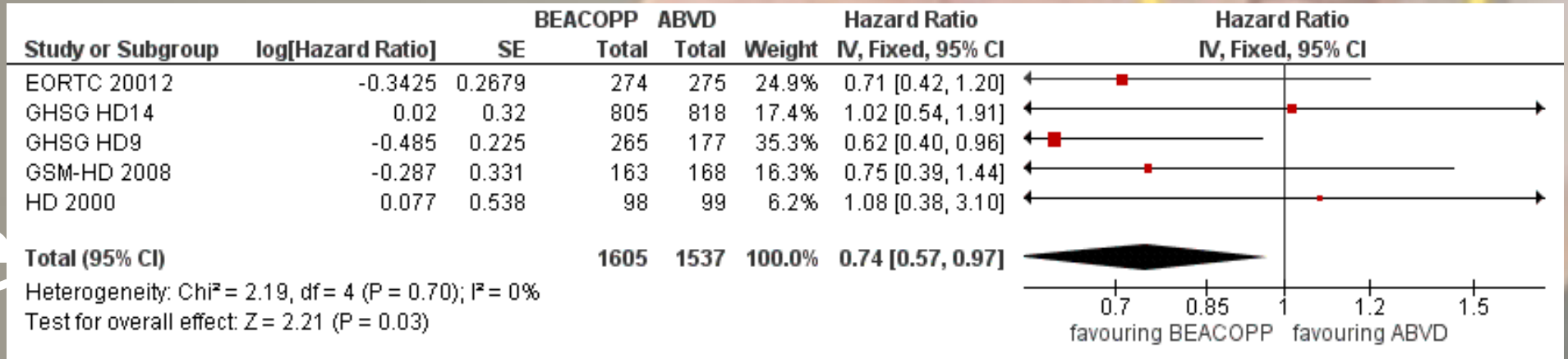
# First line treatment



**Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma (Review)**

Skoetz N, Will A, Monsefi I, Brillant C, Engert A, von Tresckow E

**Figure 3. Forest plot of comparison: 1 Analysis of Overall Survival, outcome: 1.1 OS - all - same recruitment period between the 2 arms (HD9).**



The



# PET interim is the best predictor of PFS



International Prognostic Score (IPS) 1 point per factor (advanced disease)<sup>†</sup>

- Albumin <4 g/dL
- Hemoglobin <10.5 g/dL
- Male
- Age ≥45 years
- Stage IV disease
- Leukocytosis (white blood cell count at least 15,000/mm<sup>3</sup>)
- Lymphocytopenia (lymphocyte count less than 8% of white blood cell count, and/or lymphocyte count less than 600/mm<sup>3</sup>)

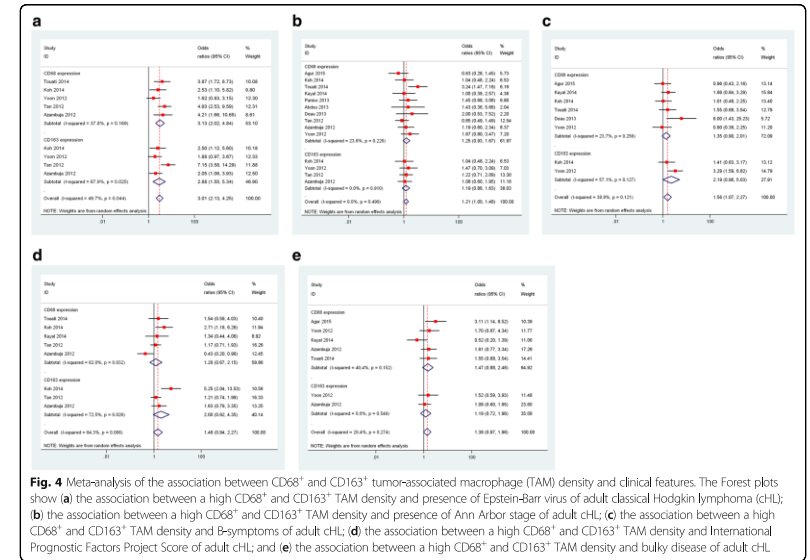
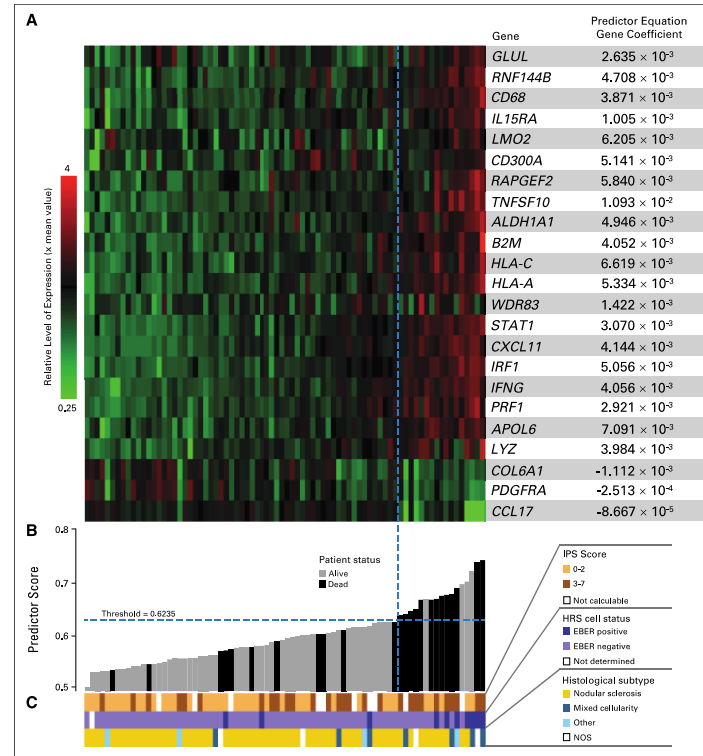


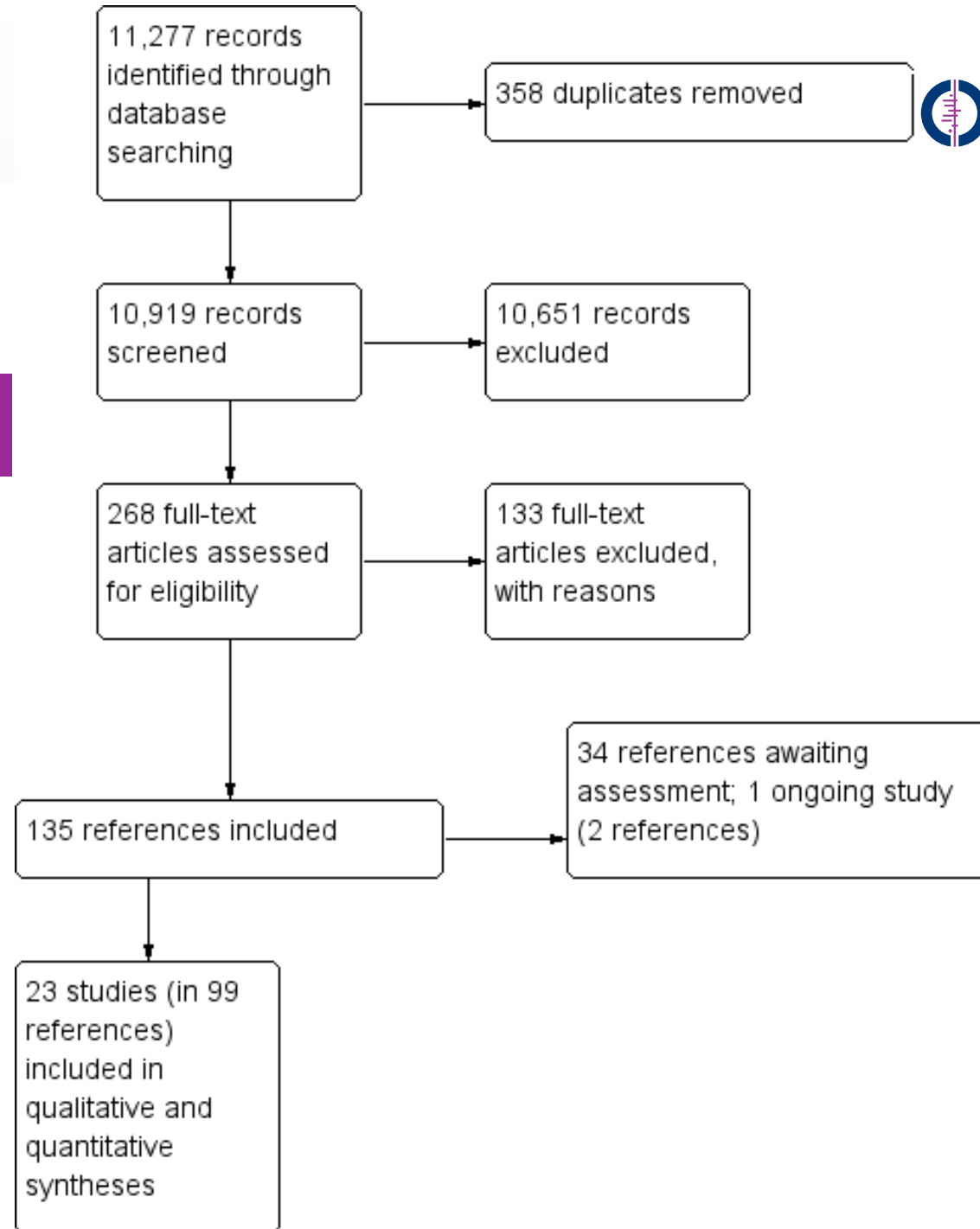
Fig. 4 Meta-analysis of the association between CD68<sup>+</sup> and CD163<sup>+</sup> tumor-associated macrophage (TAM) density and clinical features. The Forest plots show (a) the association between a high CD68<sup>+</sup> and CD163<sup>+</sup> TAM density and presence of Epstein-Barr virus of adult; classical Hodgkin lymphoma (cHL); (b) the association between a high CD68<sup>+</sup> and CD163<sup>+</sup> TAM density and presence of Ann Arbor stage of adult; cHL; (c) the association between a high CD68<sup>+</sup> and CD163<sup>+</sup> TAM density and B-symptoms of adult; cHL; (d) the association between a high CD68<sup>+</sup> and CD163<sup>+</sup> TAM density and International Prognostic Factors Project Score of adult; cHL; and (e) the association between a high CD68<sup>+</sup> and CD163<sup>+</sup> TAM density and bulky disease of adult; cHL.



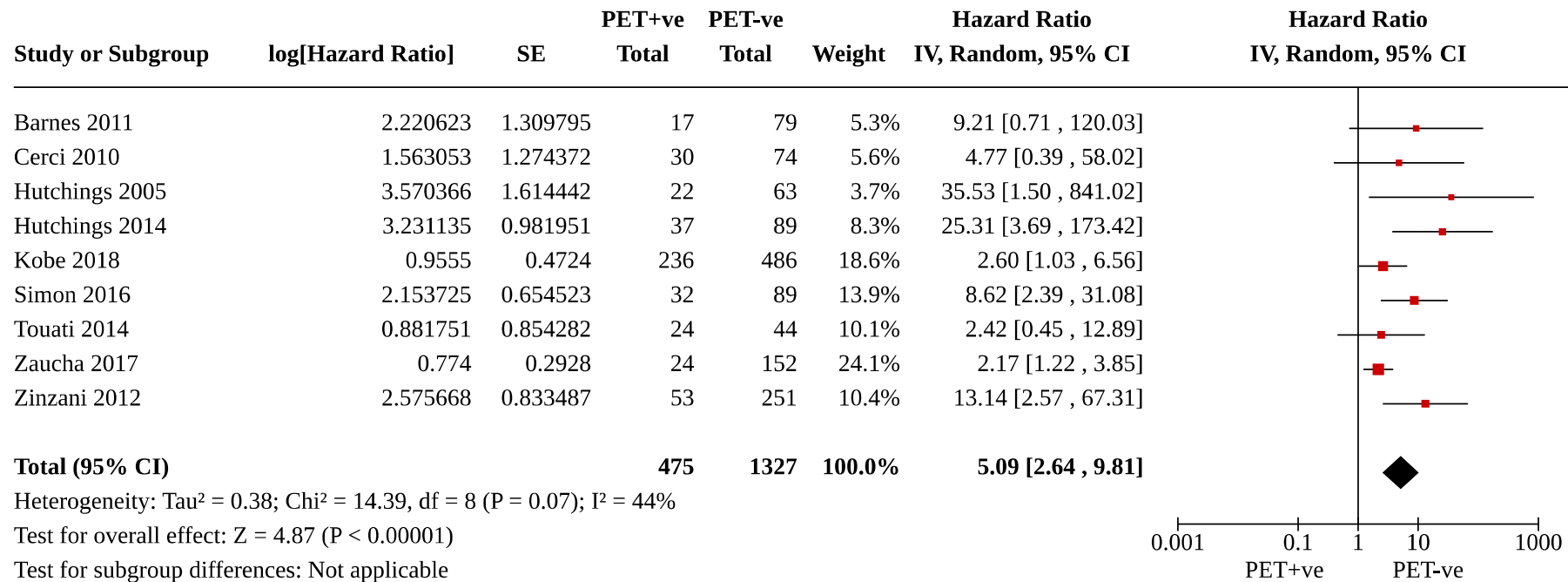
Can treatment modification by PET overcome the probably bad hepatic pathways related to risk factors of refractoriness?

Hasenclever D. *N Engl J Med.* 1998  
 Guo B. *BMC Medicine.* 2016  
 Scott DW. *J Clin Oncol.* 2013

**Interim PET-results for prognosis in adults with Hodgkin lymphoma: a systematic review and meta-analysis of prognostic factor studies (Review)**

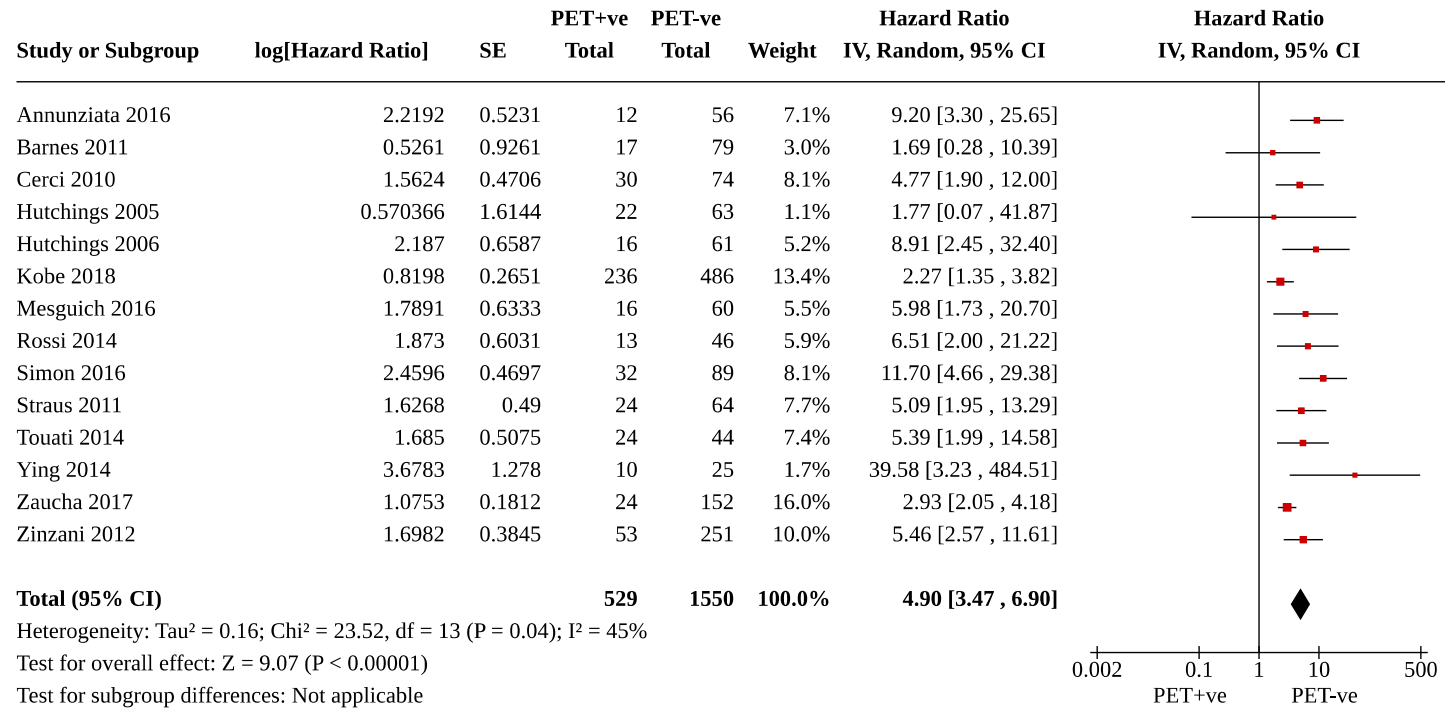


**Figure 3. Forest plot of comparison: 1 Univariable comparison of PET+ve vs. PET-ve, outcome: 1.1 Overall survival**



Moderate certainty of evidence

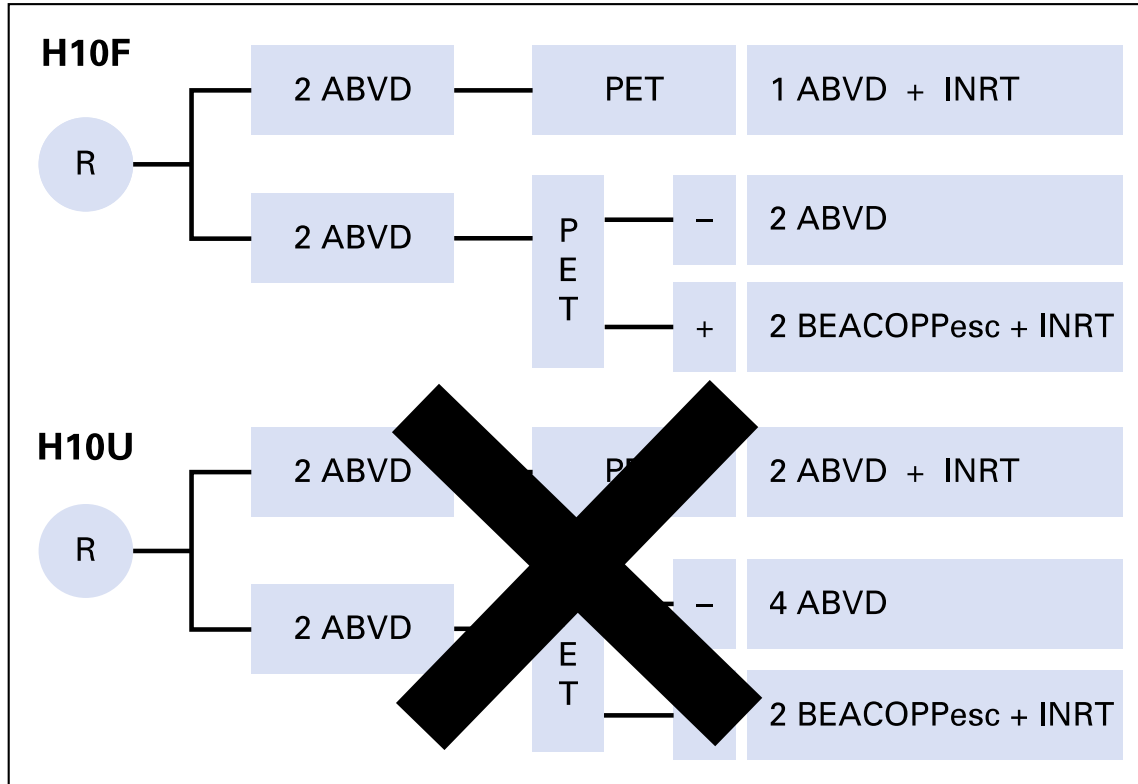
**Figure 4. Forest plot of comparison: 1 Univariable comparison of PET+ve vs. PET-ve, outcome: 1.2 Progression-free survival**



low certainty of evidence

# Early – Stage Hodgkin Lymphoma

Favorable disease

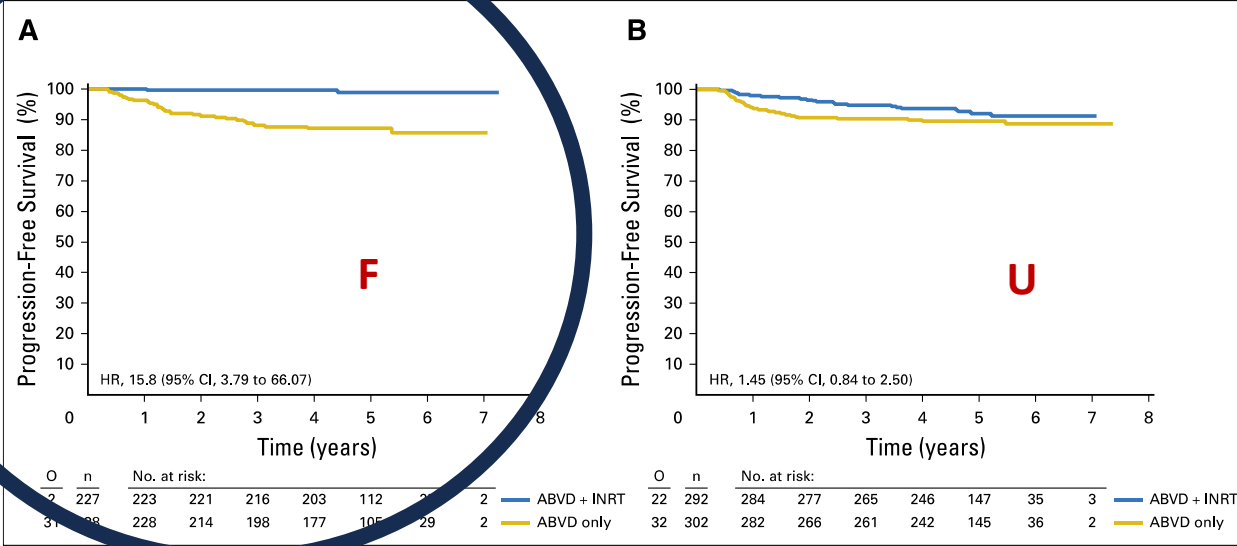


**Table 1. Patient Characteristics**

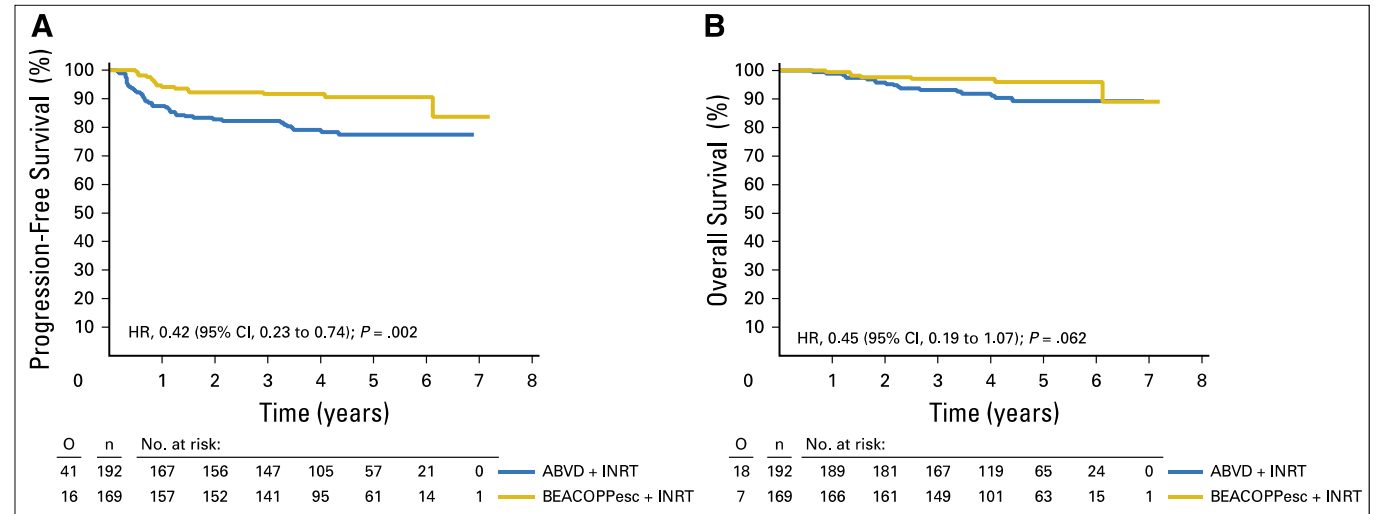
| Characteristic                  | Treatment Arm                                 |  |  |                     |  |                     |                      |                       |
|---------------------------------|---|--|--|---------------------|--|---------------------|----------------------|-----------------------|
|                                 | ePET Positive (n = 361)                       |  |  |                     | ePET Negative                          |                     |                      |                       |
|                                 | Favorable (n = 97) and Unfavorable* (n = 264) |  | Treated per Initial Protocol (n = 1,059) |                     | Treated per Safety Amendment (n = 505) |                     |                      |                       |
|                                 | 3 or 4 ABVD + INRT (n = 192)                  | 2 ABVD + 2 BEACOPPesc + INRT (n = 169) | 3 ABVD + INRT (n = 227)                  | 4 ABVD (n = 238)    | 4 ABVD + INRT (n = 292)                | 6 ABVD (n = 302)    | 3 ABVD + INRT†       | 4 ABVD + INRT†        |
| Age, years                      |   |  |  |                     |  |                     |                      |                       |
| Median                          | 30  | 30                                     | 31                                       | 30                  | 32                                     | 31                  | 28                   | 31                    |
| Range                           | 15-66   | 15-70                                  | 15-49                                    | 15-49               | 15-70                                  | 16-70               | 17-49                | 16-68                 |
| Female sex                      | 94 (49.0)                                     | 74 (43.8)                              | 96 (42.3)                                | 124 (52.1)          | 151 (51.7)                             | 165 (54.6)          | 101 (54.6)           | 181 (56.6)            |
| Ann Arbor stage I               | 47 (24.5)                                     | 31 (18.3)                              | 65 (28.6)                                | 76 (31.9)           | 56 (19.2)                              | 59 (19.5)           | 50 (27.0)            | 44 (13.8)             |
| B symptoms                      | 67 (34.9)                                     | 63 (37.3)                              | 18 (7.9)                                 | 20 (8.4)            | 108 (37.0)                             | 121 (40.1)          | 19 (10.3)            | 129 (40.3)            |
| Bulky mediastinum‡              | 71 (37.0)                                     | 69 (40.8)                              | 1 (0.4)                                  | 1 (0.4)             | 121 (41.4)                             | 119 (39.4)          | 0 (0.0)              | 135 (42.2)            |
| Unfavorable prognostic factors* | 135 (70.3)                                    | 122 (72.2)                             | 3 (1.3)                                  | 3 (1.3)             | 280 (96.0)                             | 290 (96.0)          | 0 (0.0)              | 320 (100)             |
| Nodular sclerosis histology     | 148 (77.1)                                    | 135 (79.9)                             | 175 (77.1)                               | 175 (73.5)          | 252 (86.3)                             | 249 (82.5)          | 149 (80.5)           | 285 (89.1)            |
| Baseline PET scan               | 178 (92.7)                                    | 160 (94.7)                             | 219 (96.5)                               | 227 (95.4)          | 278 (95.2)                             | 287 (95.0)          | 180 (97.3)           | 310 (96.9)            |
| Follow-up, years                |   |  |  |                     |  |                     |                      |                       |
| Median (range)                  | 4.6 (0.5-6.9)                                 | 4.4 (0.2-7.2)                          | 5.0 (0.5-7.3)                            | 5.0 (1.0-7.1)       | 5.1 (0.7-7.1)                          | 5.1 (0.2-7.4)       | 3.3 (0.5-4.2)        | 3.5 (0.8-4.3)         |
| 5-Year PFS, % (95% CI)          | 77.4 (70.4 to 82.9)                           | 90.6 (84.7 to 94.3)                    | 99.0 (95.9 to 99.7)                      | 87.1 (82.1 to 90.8) | 92.1 (88.0 to 94.8)                    | 89.6 (85.5 to 92.6) | 98.9§ (95.6 to 99.7) | 95.5§ (92.5 to 97.3)  |
| 5-Year OS, % (95% CI)           | 89.3 (83.4 to 93.2)                           | 96.0 (91.1 to 98.2)                    | 100.0 (na)                               | 99.6 (97.0 to 99.9) | 96.7 (93.7 to 98.3)                    | 98.3 (96.0 to 99.3) | 100§ (na)            | 99.7§ (97.7 to 100.0) |

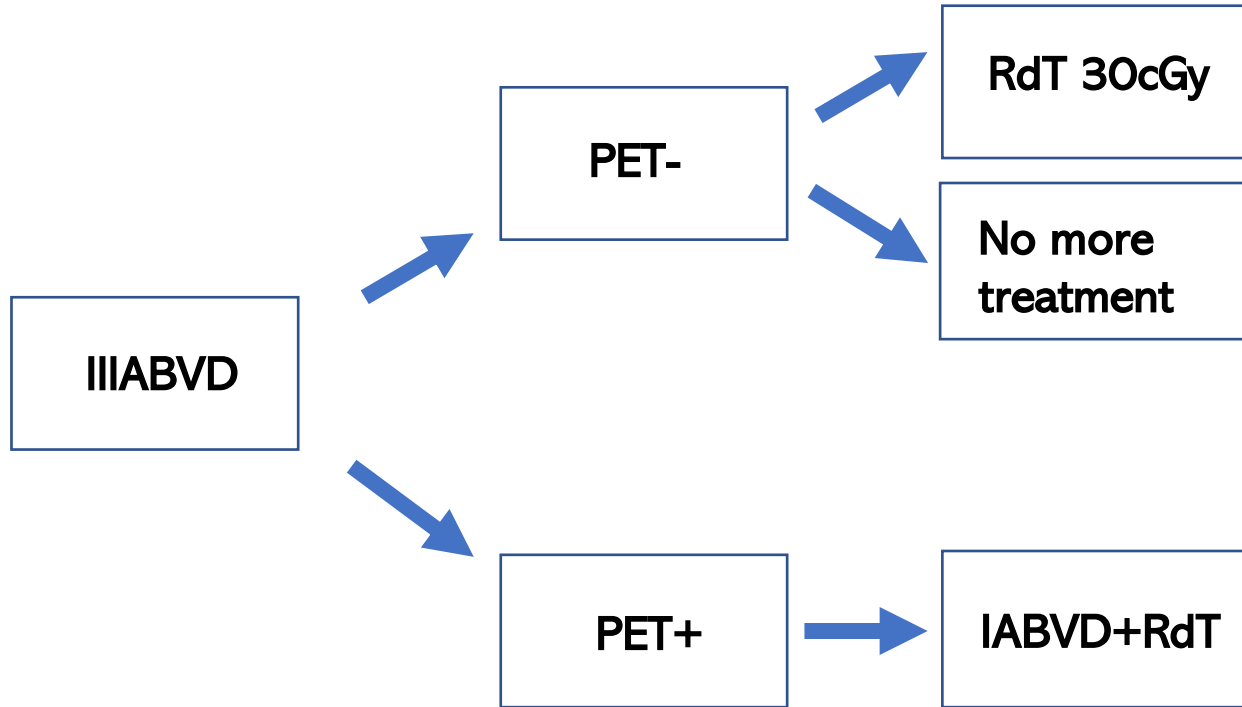
NOTE. Data given as No. (%) unless otherwise noted.  
 Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPPesc, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone; INRT, involved-node radiotherapy; na, not applicable; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival.  
 \*Unfavorable: at least one of the following criteria: age ≥ 50 years or > 3 nodal areas or mediastinal-thoracic ratio ≥ 0.35 or no B symptoms and erythrocyte sedimentation rate (ESR) ≥ 50 or B symptoms and ESR ≥ 30.  
 †Favorable: all others  
 ‡All early PET-negative patients who were included after the safety amendment received treatment with ABVD + INRT, as the independent data monitoring committee recommended to close the ABVD only arm.  
 §Bulky mediastinum is defined as a mediastinal-thoracic ratio ≥ 0.35.  
 §As the median follow-up is shorter in these groups that were included after the safety amendment, PFS and OS are given at 3 years.

# EORTC/LYSA?FIL H10 trial



**iPET+**

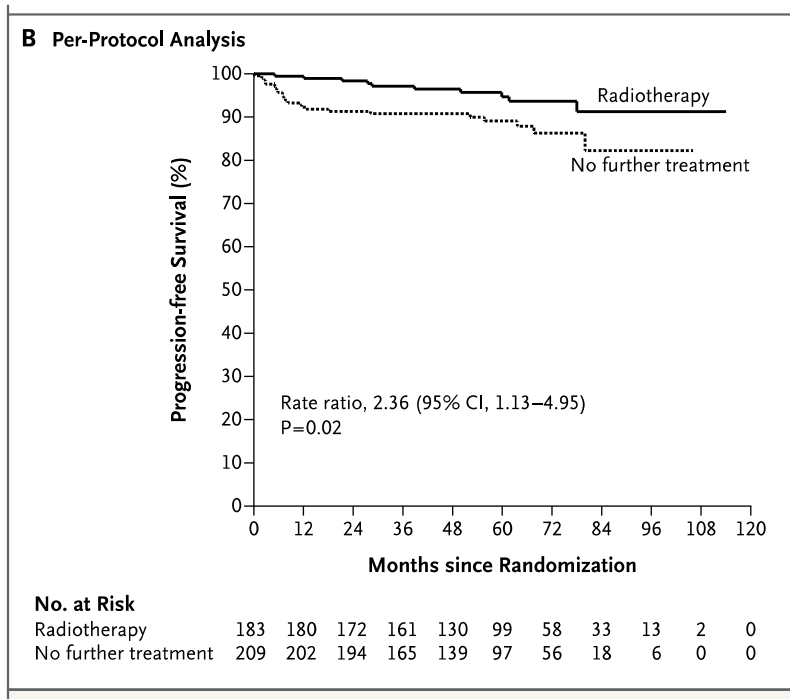




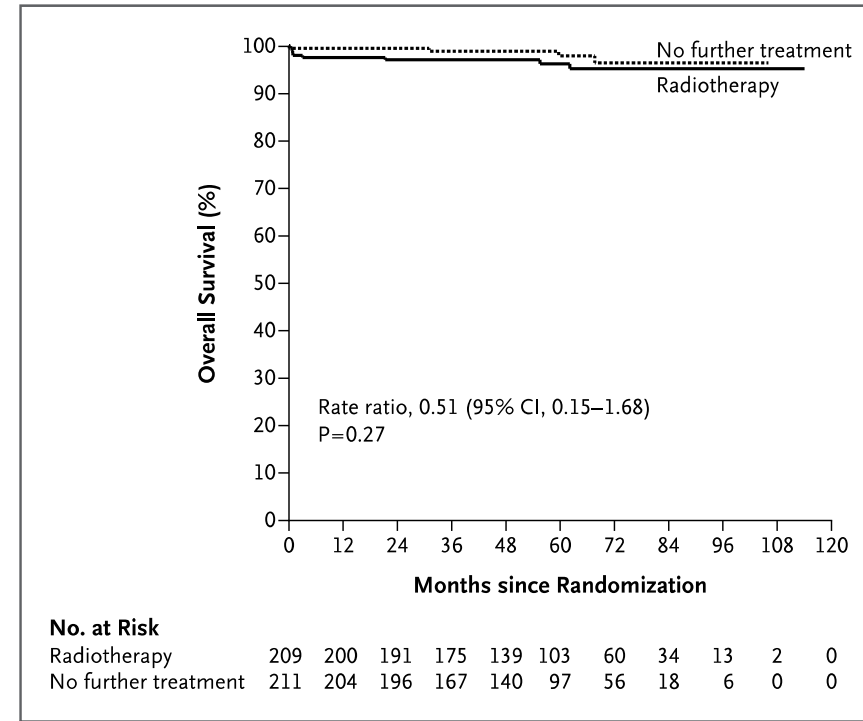
**Table 1.** Pretreatment Characteristics of the Patients.

| Characteristic                                       | Negative PET Findings     |                                      | Positive PET Findings<br>(N = 145) |
|--|---------------------------|--------------------------------------|------------------------------------|
|  | Radiotherapy<br>(N = 209) | No Further<br>Treatment<br>(N = 211) |                                    |
| Age — yr   |                           |                                      |                                    |
| Median   | 34                        | 34                                   | 36                                 |
| Range  | 16–74                     | 16–75                                | 18–75                              |
| Sex — no. (%)  |                           |                                      |                                    |
| Male   | 103 (49.3)                | 107 (50.7)                           | 96 (66.2)                          |
| Female   | 106 (50.7)                | 104 (49.3)                           | 49 (33.8)                          |
| Ann Arbor stage — no. (%)*                           |                           |                                      |                                    |
| IA   | 69 (33.0)                 | 70 (33.2)                            | 48 (33.1)                          |
| IIA  | 140 (67.0)                | 141 (66.8)                           | 97 (66.9)                          |
| Favorable pretreatment features — no./total no. (%)† |                           |                                      |                                    |
| EORTC criteria <sup>14</sup>                         | 118/184 (64.1)            | 122/185 (65.9)                       | 85/158 (53.8)                      |
| GHSG criteria <sup>15,24</sup>                       | 114/175 (65.1)            | 136/184 (73.9)                       | 97/153 (63.4)                      |
| No. of nodal sites — no./total no. (%)               |                           |                                      |                                    |
| 1  | 77/208 (37.0)             | 71/210 (33.8)                        | 51/145 (35.2)                      |
| 2  | 67/208 (32.2)             | 78/210 (37.1)                        | 44/145 (30.3)                      |
| ≥3   | 64/208 (30.8)             | 61/210 (29.0)                        | 50/145 (34.5)                      |
| Nonmediastinal bulk present — no. (%)                | 2 (1.0)                   | 1 (0.5)                              | 3 (2.1)                            |





35% unfavourable  
No Bulky  
3 cycles

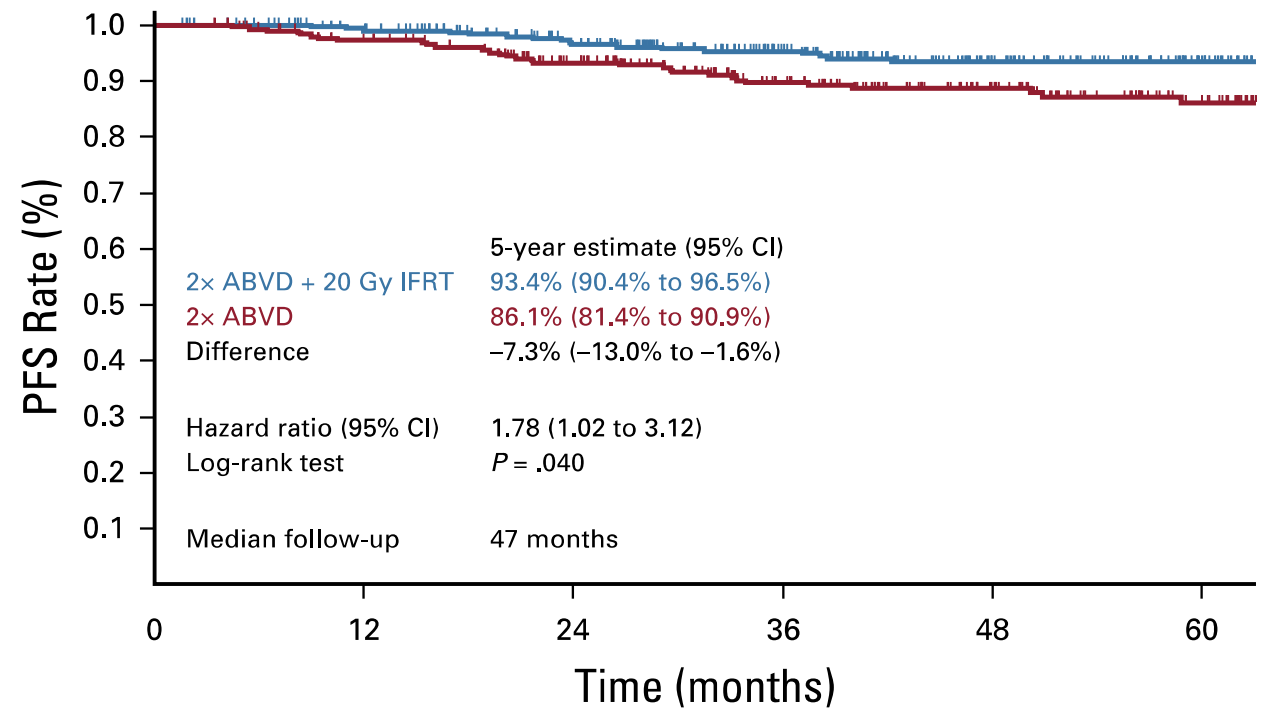


# HD16 trial

**TABLE 1.** Baseline Characteristics of the PET-2–Negative Per-Protocol Population

| Characteristic                    | 2× ABVD + 20 Gy IFRT (n = 328) | 2× ABVD (n = 300) | Total (N = 628) |
|-----------------------------------|--------------------------------|-------------------|-----------------|
| <b>Age, years</b>                 |                                |                   |                 |
| Median (range)                    | 39 (18-75)                     | 39 (18-75)        | 39 (18-75)      |
| 18-59                             | 294 (90)                       | 261 (87)          | 555 (88)        |
| 60-75                             | 34 (10)                        | 39 (13)           | 73 (12)         |
| <b>Sex</b>                        |                                |                   |                 |
| Female                            | 138 (42)                       | 132 (44)          | 270 (43)        |
| Male                              | 190 (58)                       | 168 (56)          | 358 (57)        |
| <b>Ann Arbor stage</b>            |                                |                   |                 |
| IA                                | 105 (32)                       | 94 (31)           | 199 (32)        |
| IB                                | 16 (5)                         | 16 (5)            | 32 (5)          |
| IIA                               | 191 (58)                       | 175 (58)          | 366 (58)        |
| IIB                               | 16 (5)                         | 15 (5)            | 31 (5)          |
| <b>ECOG performance status</b>    |                                |                   |                 |
| 0                                 | 307 (94)                       | 276 (92)          | 583 (93)        |
| 1                                 | 20 (6)                         | 24 (8)            | 44 (7)          |
| 2                                 | 1 (< 1)                        | 0                 | 1 (< 1)         |
| <b>Disease characteristics</b>    |                                |                   |                 |
| Albumin < 4 g/dL                  | 57 (17)                        | 58 (19)           | 115 (18)        |
| Infradiaphragmatic disease        | 39 (12)                        | 36 (12)           | 75 (12)         |
| Bulky disease                     | 59 (18)                        | 54 (18)           | 113 (18)        |
| <b>Histologic subtype</b>         |                                |                   |                 |
| Nodular sclerosis cHL             | 88/237 (37)                    | 64/206 (31)       | 152/443 (34)    |
| Mixed cellularity cHL             | 74/237 (31)                    | 75/206 (36)       | 149/443 (34)    |
| Lymphocyte-rich cHL               | 35/237 (15)                    | 31/206 (15)       | 66/443 (15)     |
| Lymphocyte-depleted cHL           | 2/237 (1)                      | 0/206             | 2/443 (< 1)     |
| cHL, not otherwise specified      | 19/237 (8)                     | 15/206 (7)        | 34/443 (8)      |
| Nodular lymphocyte-predominant HL | 19/237 (8)                     | 21/206 (10)       | 40/443 (9)      |

**A**

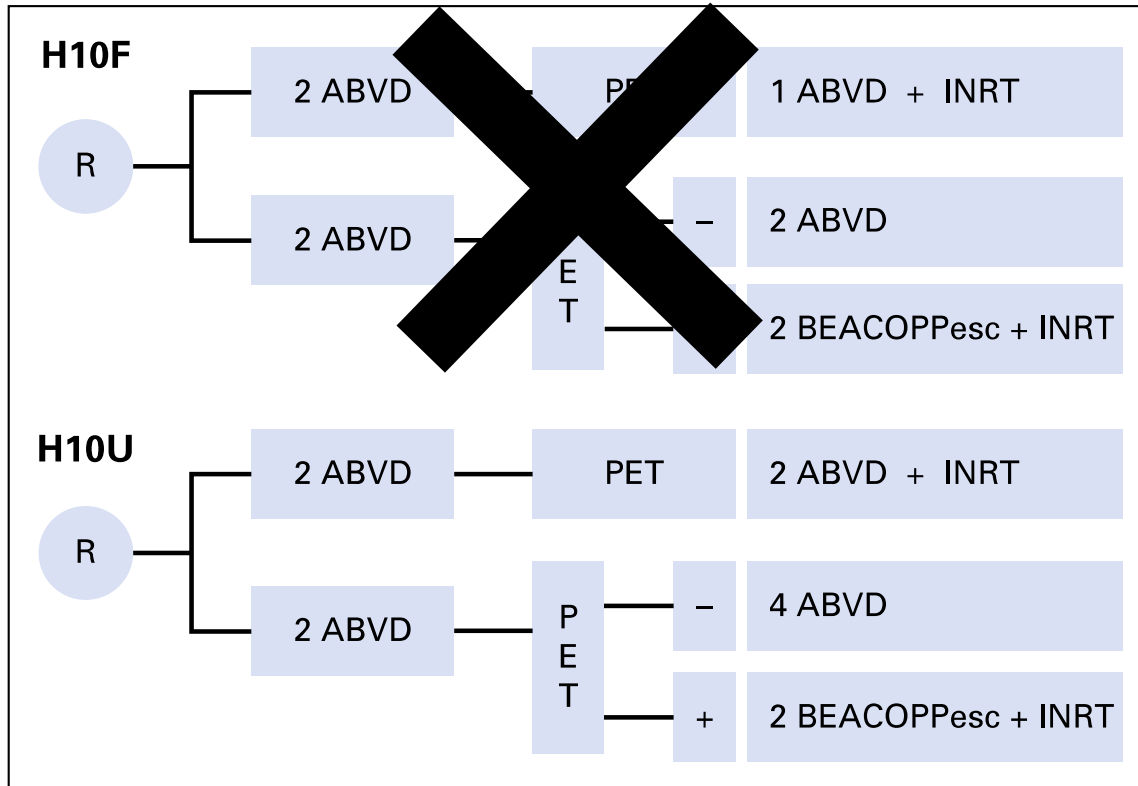


These 3 trials failed to show the non-inferiority of Rdt omission in PET negative patients  
However, the OS is the same; so concerns can be made in which patient you could eventually avoid Rdt

# Early – Stage Hodgkin Lymphoma

Unfavorable disease

# EORTC/LYSA HD10 trial



**Table 1. Patient Characteristics**

| Characteristic                  | Treatment Arm                                 |  |  |                     |                         |                     |  |                        |
|---------------------------------|---|--|--|---------------------|-------------------------|---------------------|--|------------------------|
|                                 | ePET Negative                                 |  |  |                     |                         |                     |  |                        |
|                                 | ePET Positive (n = 361)                       |  | Treated per Initial Protocol (n = 1,059) |                     |                         |                     | Treated per Safety Amendment (n = 505) |                        |
|                                 | Favorable (n = 97) and Unfavorable* (n = 264) |  | Favorable (n = 465)                      |                     | Unfavorable* (n = 594)  |                     | Favorable (n = 185)                    | Unfavorable* (n = 320) |
|                                 | 3 or 4 ABVD + INRT (n = 192)                  | 2 ABVD + 2 BEACOPPesc + INRT (n = 169) | 3 ABVD + INRT (n = 227)                  | 4 ABVD (n = 238)    | 4 ABVD + INRT (n = 292) | 6 ABVD (n = 302)    | 3 ABVD + INRT†                         | 4 ABVD + INRT†         |
| Age, years                      |   |  |  |                     |                         |                     |  |                        |
| Median                          | 30  | 30                                     | 31                                       | 30                  | 32                      | 31                  | 28                                     | 31                     |
| Range                           | 15-66   | 15-70                                  | 15-49                                    | 15-49               | 15-70                   | 16-70               | 17-49                                  | 16-68                  |
| Female sex                      | 94 (49.0)                                     | 74 (43.8)                              | 96 (42.3)                                | 124 (52.1)          | 151 (51.7)              | 165 (54.6)          | 101 (54.6)                             | 181 (56.6)             |
| Ann Arbor stage I               | 47 (24.5)                                     | 31 (18.3)                              | 65 (28.6)                                | 76 (31.9)           | 56 (19.2)               | 59 (19.5)           | 50 (27.0)                              | 44 (13.8)              |
| B symptoms                      | 67 (34.9)                                     | 63 (37.3)                              | 18 (7.9)                                 | 20 (8.4)            | 108 (37.0)              | 121 (40.1)          | 19 (10.3)                              | 129 (40.3)             |
| Bulky mediastinum‡              | 71 (37.0)                                     | 69 (40.8)                              | 1 (0.4)                                  | 1 (0.4)             | 121 (41.4)              | 119 (39.4)          | 0 (0.0)                                | 135 (42.2)             |
| Unfavorable prognostic factors* | 135 (70.3)                                    | 122 (72.2)                             | 3 (1.3)                                  | 3 (1.3)             | 280 (96.0)              | 290 (96.0)          | 0 (0.0)                                | 320 (100)              |
| Nodular sclerosis histology     | 148 (77.1)                                    | 135 (79.9)                             | 175 (77.1)                               | 175 (73.5)          | 252 (86.3)              | 249 (82.5)          | 149 (80.5)                             | 285 (89.1)             |
| Baseline PET scan               | 178 (92.7)                                    | 160 (94.7)                             | 219 (96.5)                               | 227 (95.4)          | 278 (95.2)              | 287 (95.0)          | 180 (97.3)                             | 310 (96.9)             |
| Follow-up, years                |   |  |  |                     |                         |                     |  |                        |
| Median (range)                  | 4.6 (0.5-6.9)                                 | 4.4 (0.2-7.2)                          | 5.0 (0.5-7.3)                            | 5.0 (1.0-7.1)       | 5.1 (0.7-7.1)           | 5.1 (0.2-7.4)       | 3.3 (0.5-4.2)                          | 3.5 (0.8-4.3)          |
| 5-Year PFS, % (95% CI)          | 77.4 (70.4 to 82.9)                           | 90.6 (84.7 to 94.3)                    | 99.0 (95.9 to 99.7)                      | 87.1 (82.1 to 90.8) | 92.1 (88.0 to 94.8)     | 89.6 (85.5 to 92.6) | 98.9§ (95.6 to 99.7)                   | 95.5§ (92.5 to 97.3)   |
| 5-Year OS, % (95% CI)           | 89.3 (83.4 to 93.2)                           | 96.0 (91.1 to 98.2)                    | 100.0 (na)                               | 99.6 (97.0 to 99.9) | 96.7 (93.7 to 98.3)     | 98.3 (96.0 to 99.3) | 100§ (na)                              | 99.7§ (97.7 to 100.0)  |

NOTE. Data given as No. (%) unless otherwise noted.

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPPesc, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone; INRT, involved-node radiotherapy; na, not applicable; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival.

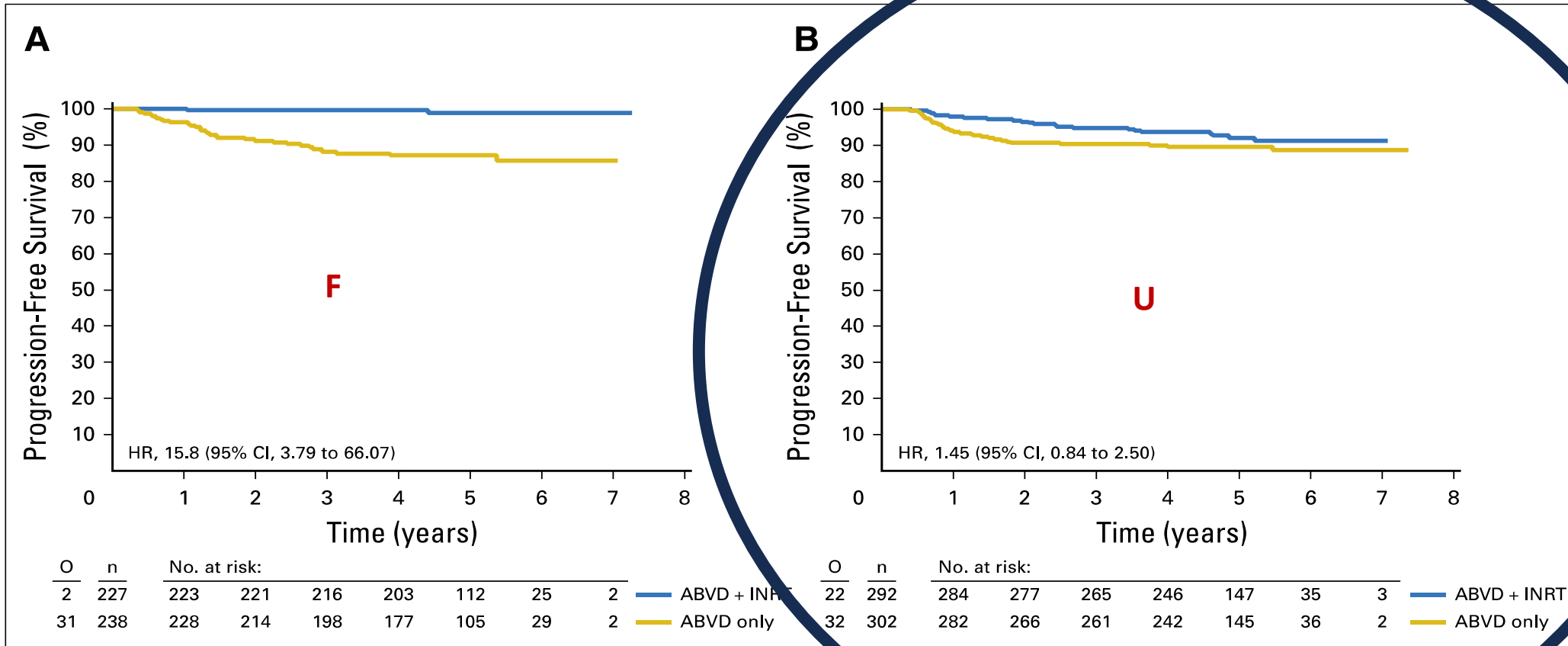
\*Unfavorable: at least one of the following criteria: age  $\geq$  50 years or  $>$  3 nodal areas or mediastinal-thoracic ratio  $\geq$  0.35 or no B symptoms and erythrocyte sedimentation rate (ESR)  $\geq$  50 or B symptoms and ESR  $\geq$  30. Favorable: all others

†All early PET-negative patients who were included after the safety amendment received treatment with ABVD + INRT, as the independent data monitoring committee recommended to close the ABVD only arm.

‡Bulky mediastinum is defined as a mediastinal-thoracic ratio  $\geq$  0.35.

§As the median follow-up is shorter in these groups that were included after the safety amendment, PFS and OS are given at 3 years.

# EORTC/LYSA HD10 trial



|   | Standard combined-modality treatment group (n=546) | PET4-guided treatment group (n=550) |
|---|--|-------------------------------------|
| <b>Age, years</b>                               |  |                                     |
| Mean  | 32.8 (11.0)  | 32.9 (11.0)                         |
| Median  | 30 (24–39)   | 31 (24–40)                          |
| >50   | 56 (10%)   | 62 (11%)                            |
| <b>Sex</b>                                      |  |                                     |
| Female  | 294 (54%)  | 294 (53%)                           |
| Male  | 252 (46%)  | 256 (47%)                           |
| <b>Ann Arbor stage</b>                          |  |                                     |
| IA  | 20 (47%)   | 18 (3%)                             |
| IB  | 18 (3%)  | 12 (2%)                             |
| IIA   | 347 (64%)  | 376 (68%)                           |
| IIB   | 134 (25%)  | 143 (26%)                           |
| IIIA  | 0  | 1 (<1%)                             |
| <b>ECOG performance status</b>                  |  |                                     |
| 1   | 448 (82%)  | 444 (81%)                           |
| 2   | 98 (18%)   | 102 (19%)                           |
| 3   | 0  | 4 (1%)                              |
| <b>GHSg risk factors</b>                        |  |                                     |
| Large mediastinal mass                          | 98 (18%)   | 101 (18%)                           |
| Extranodal disease                              | 46 (8%)  | 43 (8%)                             |
| Elevated erythrocyte sedimentation rate         | 243 (45%)  | 252 (46%)                           |
| ≥3 nodal areas involved                         | 393 (72%)  | 400 (73%)                           |
| <b>Other risk factors</b>                       |  |                                     |
| Infra-diaphragmatic disease                     | 35 (6%)  | 33 (6%)                             |
| Bulky disease                                   | 283 (52%)  | 305 (55%)                           |
| <b>Histological subtype</b>                     |  |                                     |
| Nodular sclerosis                               | 210/339 (62%)                                      | 211/323 (65%)                       |
| Mixed cellularity                               | 54/339 (16%)                                       | 46/323 (14%)                        |
| Lymphocyte-depleted                             | 1/339 (<1%)  | 0                                   |
| Lymphocyte-rich                                 | 8/339 (2%)   | 7/323 (2%)                          |
| Unspecified classical Hodgkin lymphoma          | 59/339 (17%)                                       | 52/323 (16%)                        |
| Nodular lymphocyte-predominant Hodgkin lymphoma | 7/339 (2%)   | 7/323 (2%)                          |

Data are mean (SD), median (IQR), n (%), or n/N (%). PET4=PET scan at the end of four cycles of chemotherapy. ECOG=Eastern Cooperative Oncology Group. GHSg=German Hodgkin Study Group.

**Table 1: Baseline characteristics**

|  | Standard combined-modality treatment group (n=546) | PET4-guided treatment group (n=550) |
|--|--|-------------------------------------|
| <b>Dose reductions during eBEACOPP cycles</b>                  |  |                                     |
| Reduction for any reason                                       | 92/532 (17%)                                       | 119/530 (23%)                       |
| Reduction because of a toxicity event                          | 79/532 (15%)                                       | 103/530 (19%)                       |
| <b>Dose reductions during ABVD cycles</b>                      |  |                                     |
| Reduction for any reason                                       | 100/496 (20%)                                      | 91/508 (18%)                        |
| Reduction because of a toxicity event                          | 89/496 (18%)                                       | 79/508 (14%)                        |
| <b>Observation time, months in the per-protocol population</b> |  |                                     |
| For disease status   | 45.8 (32.4–61.0)                                   | 46.4 (32.9–61.2)                    |
| For survival status  | 47.4 (35.6–63.0)                                   | 48.5 (35.0–62.5)                    |
| <b>Tumour events in the per-protocol population</b>            |  |                                     |
| Any tumour event   | 5/428 (1%)   | 15/477 (3%)                         |
| Any progression-free survival event                            | 8/428 (2%)   | 17/477 (4%)                         |
| <b>Tumour events</b>   |  |                                     |
| Progression  | 2 (<1%)  | 6 (1%)                              |
| Relapse  |  |                                     |
| ≤1 year after end of therapy                                   | 3 (<1%)  | 5 (<1%)                             |
| >1 year after end of therapy                                   | 6 (1%)   | 8 (1%)                              |
| Any tumour event   | 11 (2%)  | 19 (3%)                             |
| Any progression-free survival event                            | 15 (3%)  | 23 (4%)                             |
| <b>Cause of death</b>  |  |                                     |
| Hodgkin lymphoma   | 0  | 2 (<1%)                             |
| Toxicity of study therapy                                      | 0  | 1 (<1%)                             |
| Other disease*   | 2 (<1%)  | 3 (<1%)                             |
| Second primary malignant neoplasm                              | 2 (<1%)  | 0                                   |
| Any death  | 4 (<1%)  | 6 (1%)                              |
| <b>Second primary malignant neoplasms</b>                      |  |                                     |
| Acute myeloid leukaemia or myelodysplastic syndrome            | 0  | 1 (<1%)                             |
| Non-Hodgkin lymphoma   | 1 (<1%)  | 1 (<1%)                             |
| Solid tumour†  | 6 (1%)   | 6 (1%)                              |
| Any event  | 7 (1%)   | 8 (1%)                              |

Data are n/N (%), n (%), or median (IQR). PET4=PET scan at the end of four cycles of chemotherapy. eBEACOPP=escalated doses of etoposide, cyclophosphamide, and doxorubicin, and regular doses of bleomycin, vincristine, procarbazine, and prednisone. ABVD=doxorubicin, bleomycin, vinblastine, dacarbazine. \*Included cardiovascular disease (n=2), subarachnoid haemorrhage (n=1), HIV-related cachexia (n=1), and an unknown disease unrelated to Hodgkin lymphoma (n=1). †Included malignant melanoma (n=2), mammary carcinoma (n=2), colorectal cancer (n=1), prostate cancer (n=1), and other rare solid cancers (n=5).

**Table 2: Outcomes of the intention-to-treat population**

|   | Standard combined-modality treatment group (n=546) | PET4-guided treatment group (n=550) |
|---|--|-------------------------------------|
| <b>Age, years</b>                               |  |                                     |
| Mean  | 32.8 (11.0)  | 32.9 (11.0)                         |
| Median  | 30 (24-39)   | 31 (24-40)                          |
| >50   | 56 (10%)   | 62 (11%)                            |
| <b>Sex</b>                                      |  |                                     |
| Female  | 294 (54%)  | 294 (53%)                           |
| Male  | 252 (46%)  | 256 (47%)                           |
| <b>Ann Arbor stage</b>                          |  |                                     |
| IA  | 20 (47%)   | 18 (3%)                             |
| IB  | 18 (3%)  | 12 (2%)                             |
| IIA   | 347 (64%)  | 376 (68%)                           |
| IIB   | 134 (25%)  | 143 (26%)                           |
| IIIA  | 0  | 1 (<1%)                             |
| <b>ECOG performance status</b>                  |  |                                     |
| 1   | 448 (82%)  | 444 (81%)                           |
| 2   | 98 (18%)   | 102 (19%)                           |
| 3   | 0  | 4 (1%)                              |
| <b>GHSg risk factors</b>                        |  |                                     |
| Large mediastinal mass                          | 98 (18%)   | 101 (18%)                           |
| Extranodal disease                              | 46 (8%)  | 43 (8%)                             |
| Elevated erythrocyte sedimentation rate         | 243 (45%)  | 252 (46%)                           |
| ≥3 nodal areas involved                         | 393 (72%)  | 400 (73%)                           |
| <b>Other risk factors</b>                       |  |                                     |
| Infra-diaphragmatic disease                     | 35 (6%)  | 33 (6%)                             |
| Bulky disease                                   | 283 (52%)  | 305 (55%)                           |
| <b>Histological subtype</b>                     |  |                                     |
| Nodular sclerosis                               | 210/339 (62%)                                      | 211/323 (65%)                       |
| Mixed cellularity                               | 54/339 (16%)                                       | 46/323 (14%)                        |
| Lymphocyte-depleted                             | 1/339 (<1%)  | 0                                   |
| Lymphocyte-rich                                 | 8/339 (2%)   | 7/323 (2%)                          |
| Unspecified classical Hodgkin lymphoma          | 59/339 (17%)                                       | 52/323 (16%)                        |
| Nodular lymphocyte-predominant Hodgkin lymphoma | 7/339 (2%)   | 7/323 (2%)                          |

Data are mean (SD), median (IQR), n (%), or n/N (%). PET4=PET scan at the end of four cycles of chemotherapy. ECOG=Eastern Cooperative Oncology Group. GHSg=German Hodgkin Study Group.

Table 1: Baseline characteristics

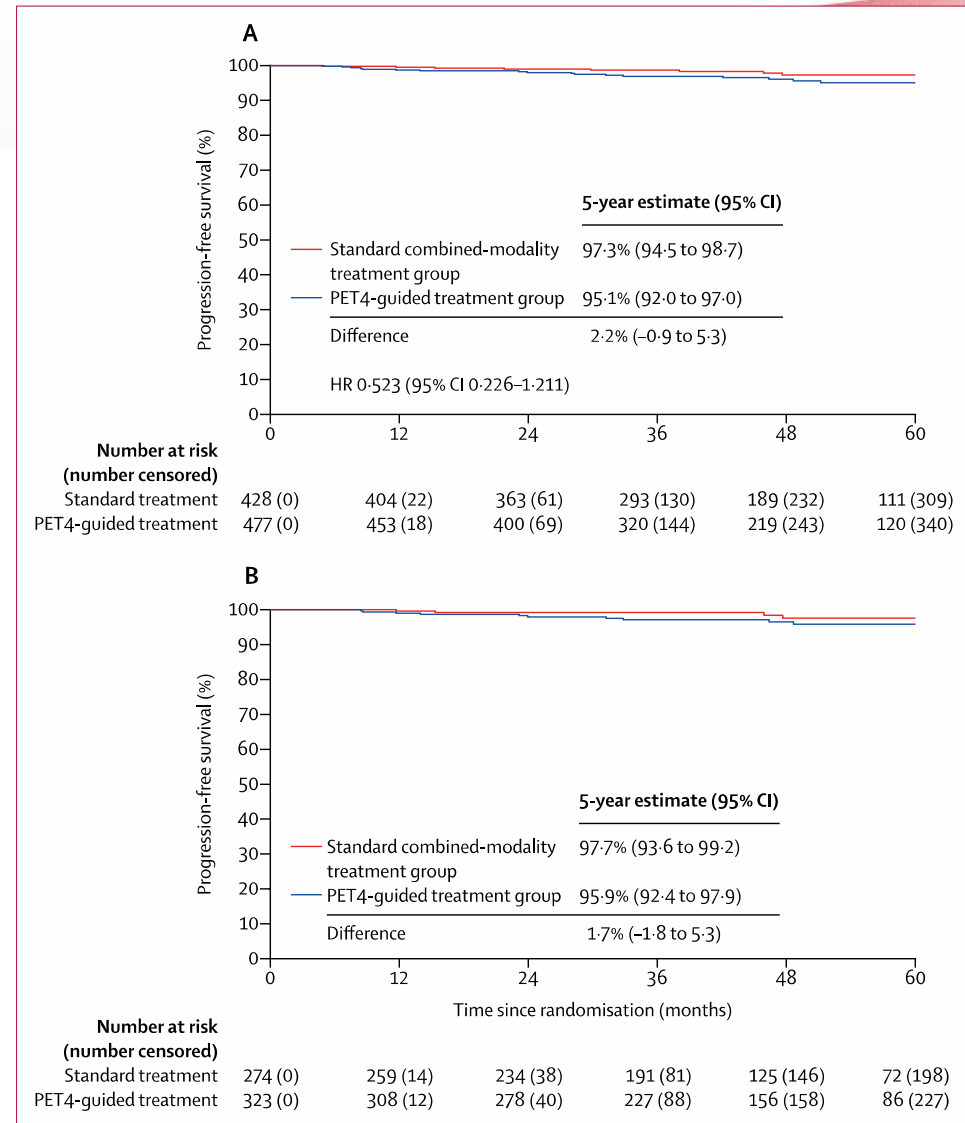
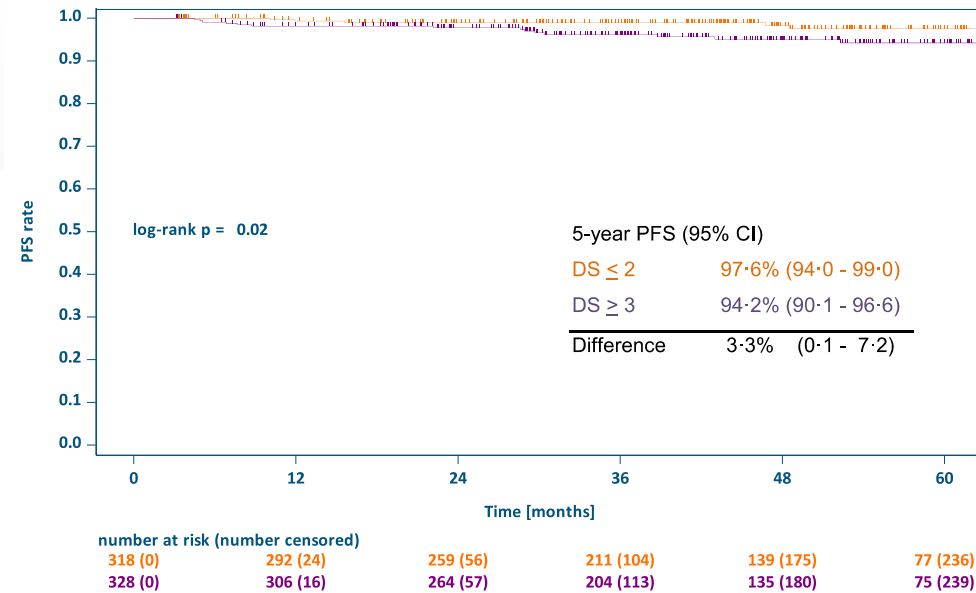


Figure 2: Kaplan-Meier estimates of 5-year progression-free survival in the per-protocol analysis population (A) and in a subset of PET4-negative patients in the per-protocol analysis population (B) PET4=PET scan at the end of four cycles of chemotherapy.

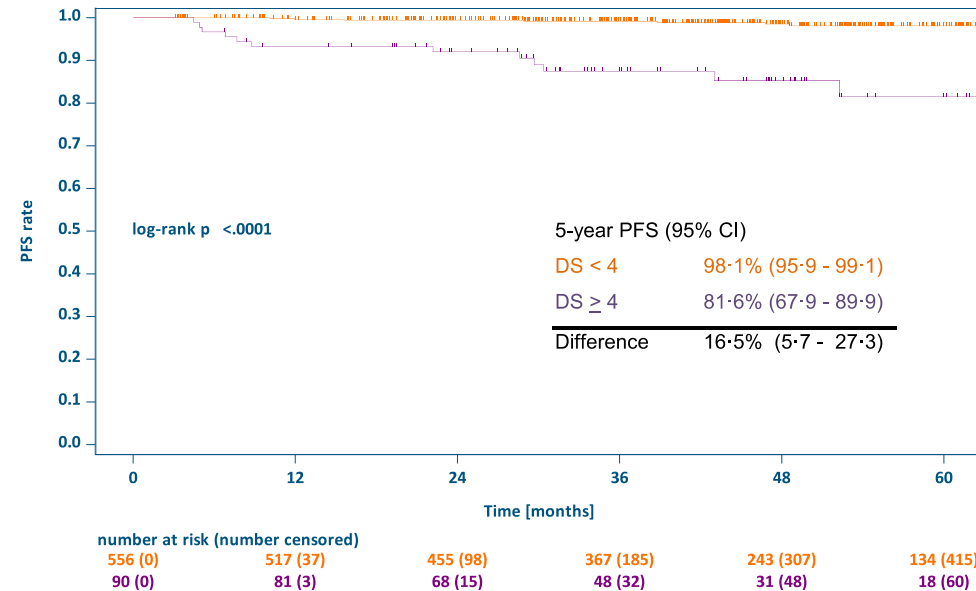


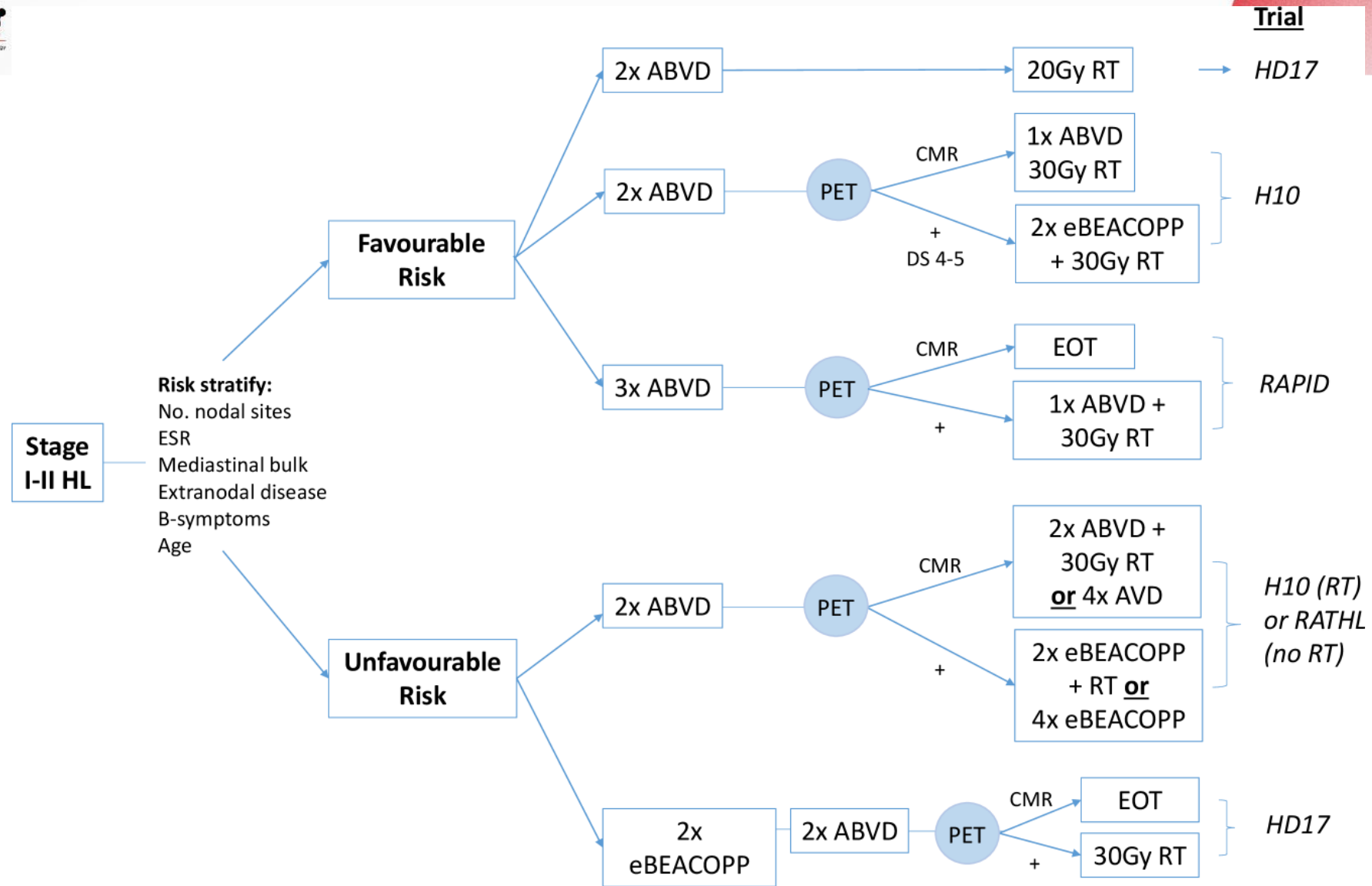
Intention-to-treat analysis of PET4-negative and PET4-positive patients assigned to receive radiotherapy:

(1) Progression-free survival, PET4-positivity defined as DS  $\geq 3$



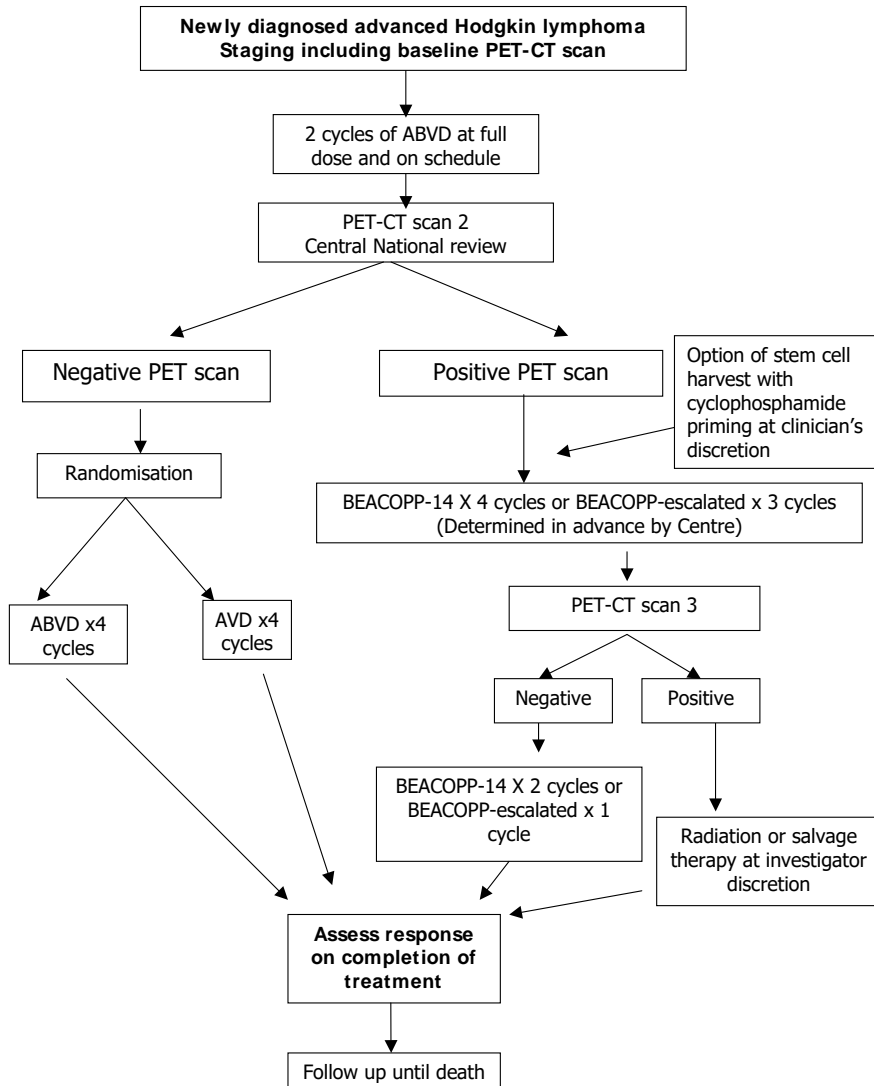
(2) Progression-free survival, PET4-positivity defined as DS  $\geq 4$





# Advantage Stage Hodgkin Lymphoma

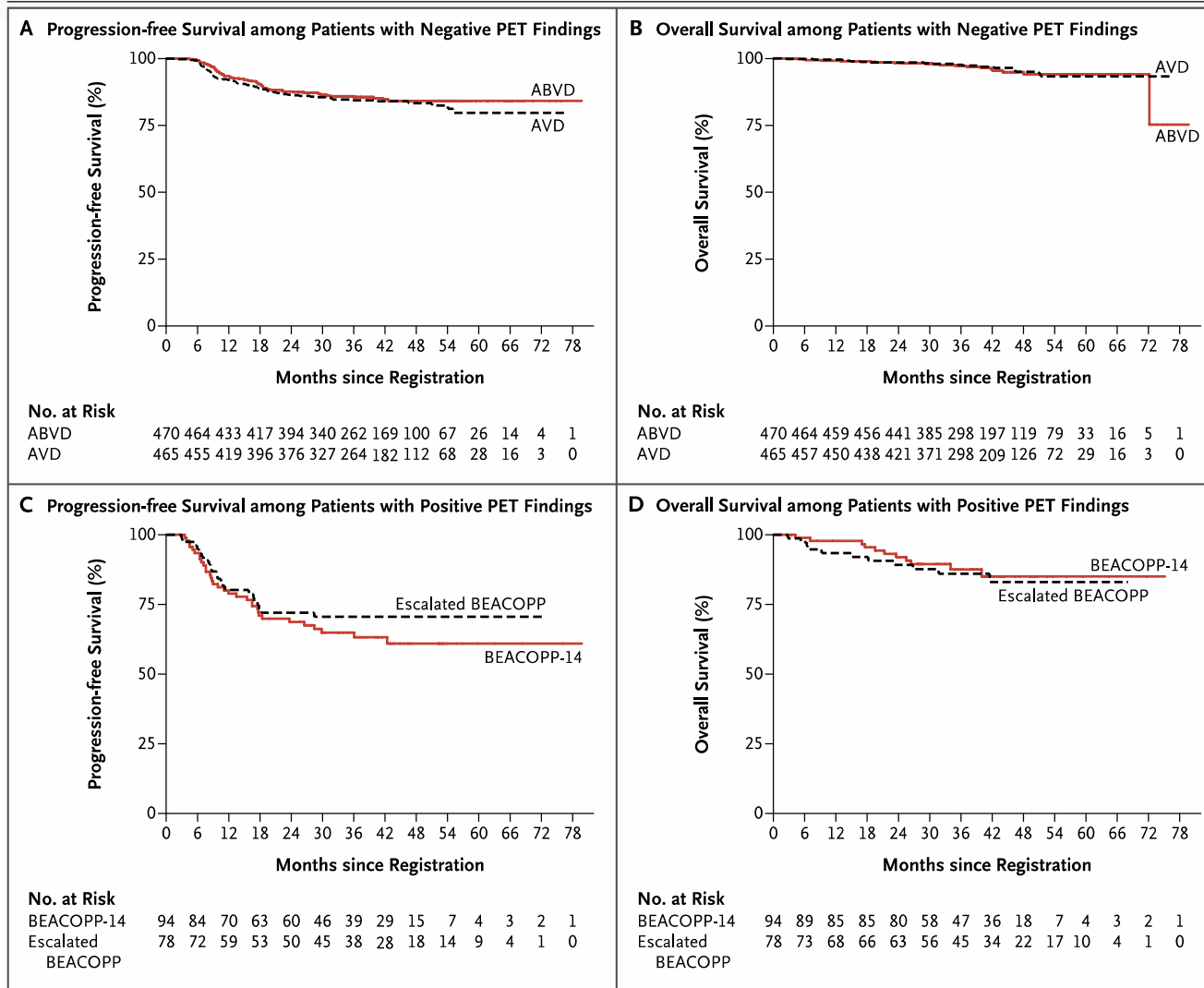
# Rathl trial



**Table 1.** Pretreatment Characteristics of Patients Included in the Analyses.\*

| Characteristic  | Patients with Negative PET Findings |               | Patients with Positive PET Findings Who Received BEACOPP (N = 172) | All Eligible Patients (N = 1203) |
|---|-------------------------------------|---------------|--|----------------------------------|
|   | ABVD (N = 470)                      | AVD (N = 465) |  |                                  |
| 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)                       |
| ECOG performance status — no. (%) <sup>†</sup>        |                                     |               |  |                                  |
| 0   | 340 (72.3)                          | 354 (76.1)    | 123 (71.5)   | 889 (73.9)                       |
| 1   | 113 (24.0)                          | 96 (20.6)     | 40 (23.3)  | 271 (22.5)                       |
| 2   | 11 (2.3)                            | 9 (1.9)       | 6 (3.5)  | 28 (2.3)                         |
| 3   | 6 (1.3)                             | 6 (1.3)       | 2 (1.2)  | 14 (1.2)                         |
| Missing   | 0                                   | 0             | 1 (0.6)  | 1 (0.1)                          |
| 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. (%) <sup>‡</sup>                     | 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)                       |
| International prognostic score — no. (%) <sup>§</sup> |                                     |               |  |                                  |
| 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)                       |
| Missing   | 6 (1.3)                             | 2 (0.4)       | 2 (1.2)  | 11 (0.9)                         |

# Rathl trial



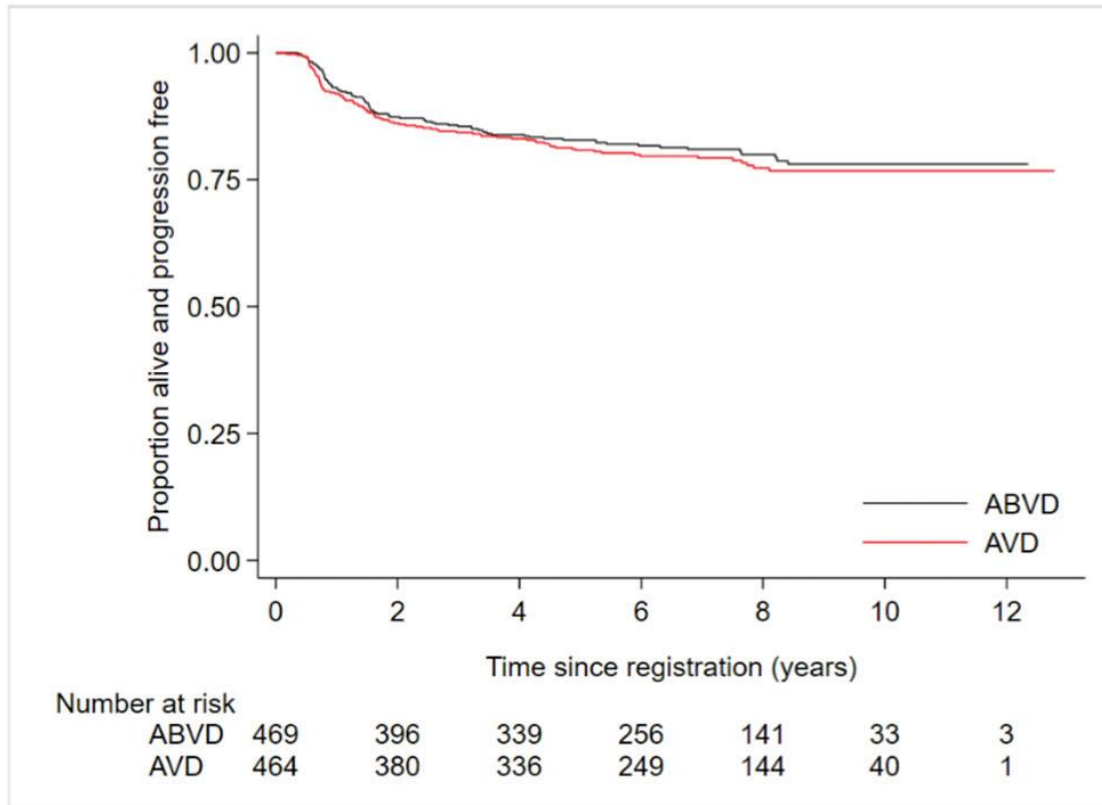
PET+ ➔ PFS 67,5%  
D5 worse

**Figure 2. Progression-free and Overall Survival.**

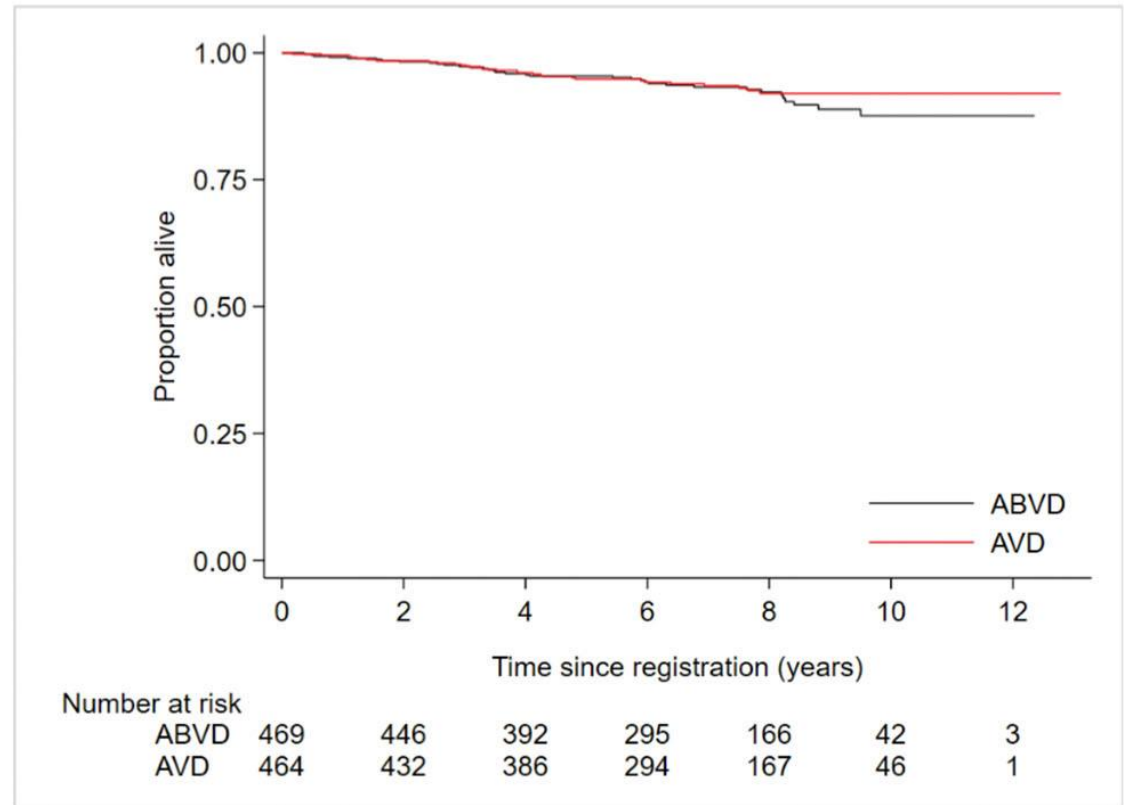
Panel A shows progression-free survival among patients with negative PET findings after two cycles of ABVD who underwent randomization, Panel B overall survival among patients with negative PET findings who underwent randomization, Panel C progression-free survival among patients with positive PET findings,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

# Rathl trial

PFS of PET-negative pts



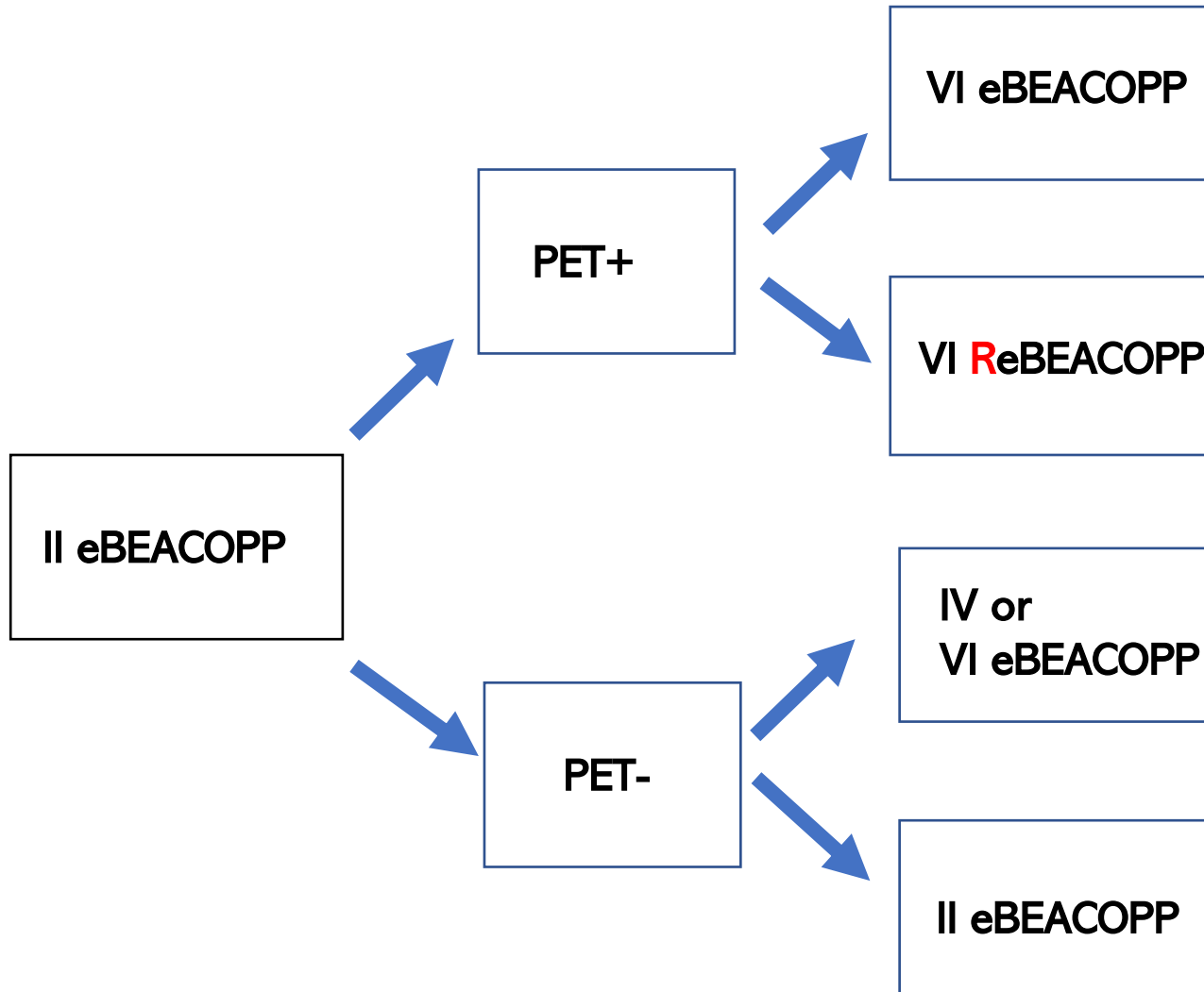
OS of PET-negative pts



**Table 2. Outcomes of Therapy.**

| Outcome   | ABVD<br>(N = 470) | AVD<br>(N = 465) | BEACOPP<br>(N = 172) | All Eligible Patients<br>(N = 1203)* |
|---|-------------------|------------------|----------------------|--------------------------------------|
| Alive without disease progression — no. of patients     | 402               | 391              | 117                  | 999                                  |
| Alive after disease progression — no. of patients       | 49                | 57               | 33                   | 142                                  |
| Died — no. of patients                                  | 19                | 17               | 22                   | 62                                   |
| From Hodgkin's lymphoma                                 | 4                 | 8                | 10                   | 24†                                  |
| Owing to initial therapy                                | 4                 | 0                | 4                    | 8                                    |
| Owing to salvage therapy                                | 4                 | 1                | 5                    | 10                                   |
| From second cancer                                      | 4‡                | 6§               | 0                    | 11†                                  |
| From cardiac event                                      | 1                 | 1                | 1                    | 4†                                   |
| From cause unrelated to Hodgkin's lymphoma or treatment | 2                 | 1                | 2                    | 5                                    |
| 3-Yr progression-free survival (95% CI) — %¶            | 85.7 (82.1–88.6)  | 84.4 (80.7–87.5) | 67.5 (59.7–74.2)     | 82.6 (80.2–84.7)                     |
| 3-Yr overall survival (95% CI) — %**                    | 97.2 (95.1–98.4)  | 97.6 (95.6–98.7) | 87.8 (81.5–92.1)     | 95.8 (94.4–96.8)                     |
| Second cancer — no. of patients                         | 13                | 11               | 3                    | 29                                   |
| Ann Arbor stage III or IV and age ≤60 yr                |                   |                  |                      |                                      |
| 3-Yr progression-free survival (95% CI) — %             | 82.1 (76.5–86.5)  | 82.1 (76.3–86.4) | 63.9 (52.9–72.9)     | 79.8 (76.3–82.9)                     |
| 3-Yr overall survival (95% CI) — %                      | 95.9 (92.2–97.9)  | 97.8 (94.8–99.1) | 87.8 (78.9–93.0)     | 94.6 (92.5–96.2)                     |

# HD18 trial

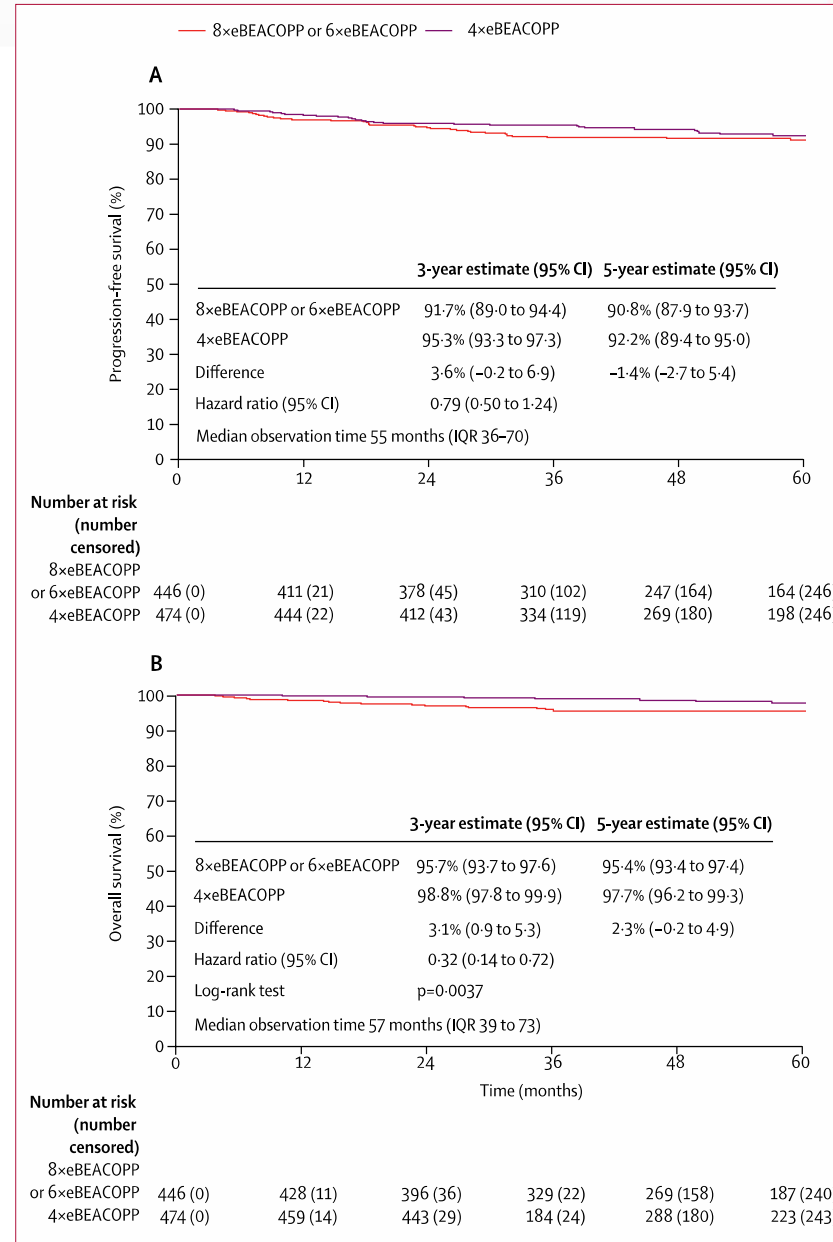
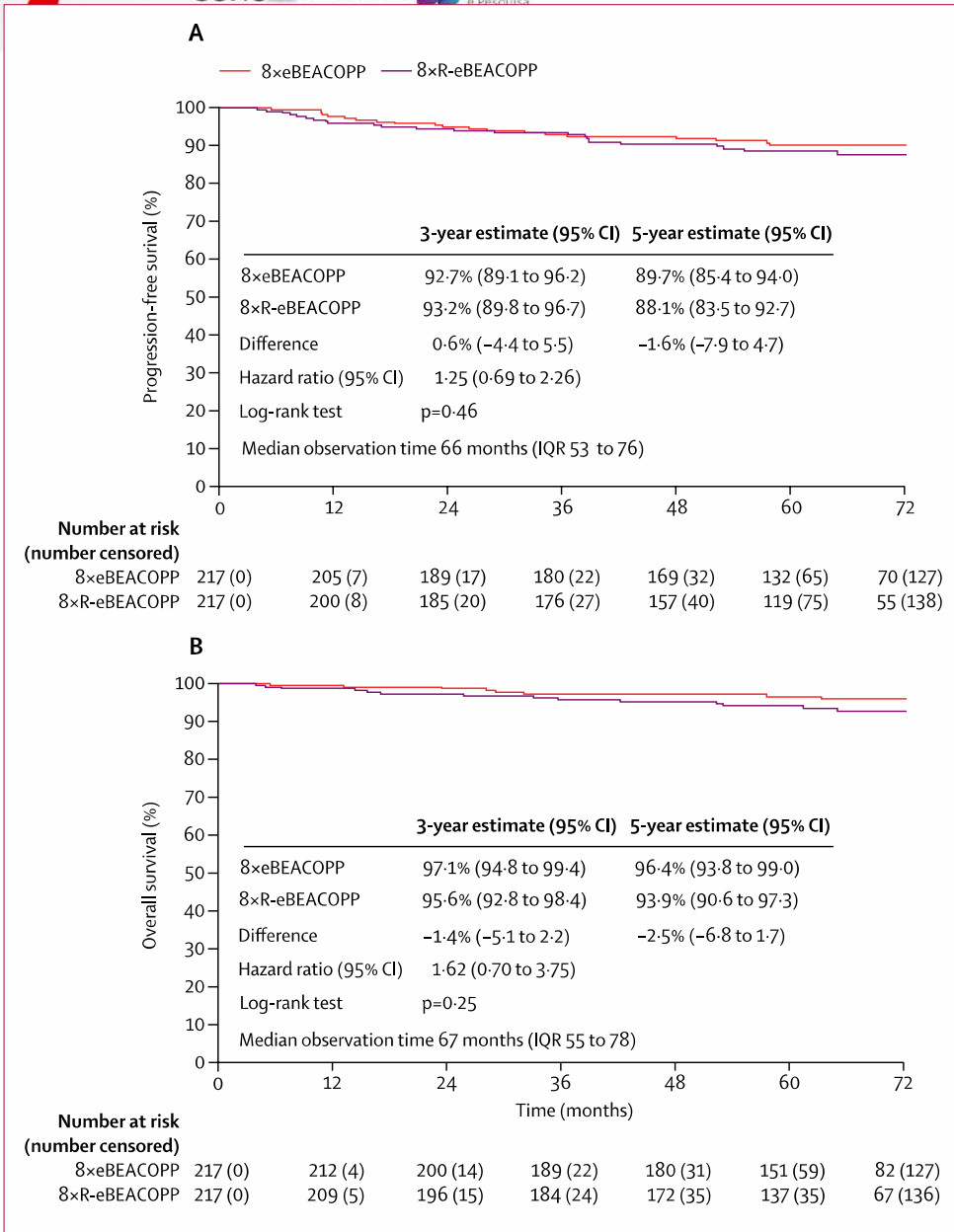


|                             | PET-2-positive cohort      |                             |                            | PET-2-negative cohort                   |                             |
|-----------------------------|----------------------------|-----------------------------|----------------------------|---|-----------------------------|
|                             | 8 × eBEACOPP<br>(n=217)    | 6 × eBEACOPP<br>(n=506)     | 8 × R-eBEACOPP<br>(n=217)  | 6 × eBEACOPP or<br>8 × eBEACOPP (n=504) | 4 × eBEACOPP<br>(n=501)     |
| Time of recruitment (range) | May, 2008, to<br>May, 2011 | May, 2011, to<br>July, 2014 | Dec, 2008, to<br>May, 2011 | May, 2008, to<br>July, 2014             | May, 2008, to<br>July, 2014 |
| Age (years)*                |                            |                             |                            |   |                             |
| Median (IQR)                | 30 (23–40)                 | 31 (24–42)                  | 29 (23–41)                 | 32 (24–44)                              | 33 (25–44)                  |
| 18–19                       | 18 (8%)                    | 30 (6%)                     | 21 (10%)                   | 34 (7%)                                 | 44 (9%)                     |
| 20–29                       | 84 (39%)                   | 195 (39%)                   | 91 (42%)                   | 186 (37%)                               | 166 (33%)                   |
| 30–39                       | 59 (27%)                   | 142 (28%)                   | 45 (21%)                   | 104 (21%)                               | 122 (24%)                   |
| 40–49                       | 41 (19%)                   | 84 (17%)                    | 42 (19%)                   | 91 (18%)                                | 89 (18%)                    |
| 50–60                       | 15 (7%)                    | 55 (11%)                    | 18 (8%)                    | 89 (18%)                                | 80 (16%)                    |
| Sex                         |                            |                             |                            |   |                             |
| Female                      | 88 (41%)                   | 211 (42%)                   | 86 (40%)                   | 188 (37%)                               | 188 (38%)                   |
| Male                        | 129 (59%)                  | 295 (58%)                   | 131 (60%)                  | 316 (63%)                               | 313 (62%)                   |

(Table 1 continues on next page)



# HD18 trial





# SINTOMA'24 HD18 trial

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|  | 8 × eBEACOPP<br>(n=288) | 6 × eBEACOPP<br>(n=216) | 4 × eBEACOPP<br>(n=501) |
|--|-------------------------|-------------------------|-------------------------|
| <b>Severe protocol deviations</b>                                |                         |                         |                         |
| Discontinuation due to toxicity                                  | 11 (4%)                 | 0                       | 2 (<1%)                 |
| Patient withdraws 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%)                 |
| <b>Toxicity and supportive measures†</b>                         |                         |                         |                         |
| <b>Haematological toxicities of CTCAE grade III or IV</b>        |                         |                         |                         |
| 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%)                 |
| <b>Organ toxicities of CTCAE grade III or IV</b>                 |                         |                         |                         |
| 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   | 37 (13%)                | 15 (7%)                 | 17 (3%)                 |
| Any organ toxicity‡  | 62 (22%)                | 29 (13%)                | 38 (8%)                 |
| <b>Toxicities of CTCAE grade III or IV</b>                       |                         |                         |                         |
| Any toxicity‡  | 280 (98%)               | 205 (95%)               | 455 (91%)               |
| <b>Treatment-related morbidity</b>                               |                         |                         |                         |
| 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%)               | 115 (53%)               | 187 (38%)               |
| Treatment-related morbidity                                      | 189 (66%)               | 132 (61%)               | 204 (41%)               |
| <b>Onset of treatment-related morbidity</b>                      |                         |                         |                         |
| Cycles 1–4   | 135 (47%)               | 100 (47%)               | 204 (41%)               |
| Cycles 5–6   | 30 (10%)                | 32 (15%)                | NA                      |
| Cycles 7–8   | 24 (8%)                 | NA                      | NA                      |
| <b>Febrile neutropenia</b>                                       |                         |                         |                         |
| Occurrence of febrile neutropenia                                | 96 (33%)                | 49 (23%)                | 109 (22%)               |
| Hospitalisation due to febrile neutropenia                       | 71 (25%)                | 39 (18%)                | 90 (18%)                |
| <b>Onset of febrile neutropenia</b>                              |                         |                         |                         |
| Cycles 1–4   | 69 (24%)                | 39 (18%)                | 109 (22%)               |
| Cycles 5–6   | 16 (6%)                 | 10 (5%)                 | NA                      |
| Cycles 7–8   | 11 (4%)                 | NA                      | NA                      |
| <b>Supportive measures</b>                                       |                         |                         |                         |
| 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%)               |

Data are n (%). PET-2=positron emission tomography after two cycles of chemotherapy. eBEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated dose. CTCAE=Common Terminology Criteria for Adverse Events. G-CSF=granulocyte-colony stimulating factor. NA=not applicable. \*Including patient refusal to continue with radiotherapy (n=1), no radiotherapy in spite of panel recommendation (n=1), radiotherapy without panel recommendation (n=4), violation of inclusion or exclusion criteria (n=3), lack of compliance (n=3), withdrawal of consent (n=2), treatment in non-participating centre (n=1), restaging not timely performed (n=1), unknown (n=2). †Documentation of chemotherapy missing in five (<1%) of 1005 patients; toxicity and supportive measures assessed in 287 patients in the 8 × eBEACOPP group, 215 patients in the 6 × eBEACOPP group, and 498 patients in the 4 × eBEACOPP group. ‡Also including urogenital tract, cardiac and skin disorders, drug fever, and allergy.

**Table 3:** Therapy adherence, acute toxicities and supportive measures during chemotherapy of patients with negative PET-2, randomised intention-to-treat set

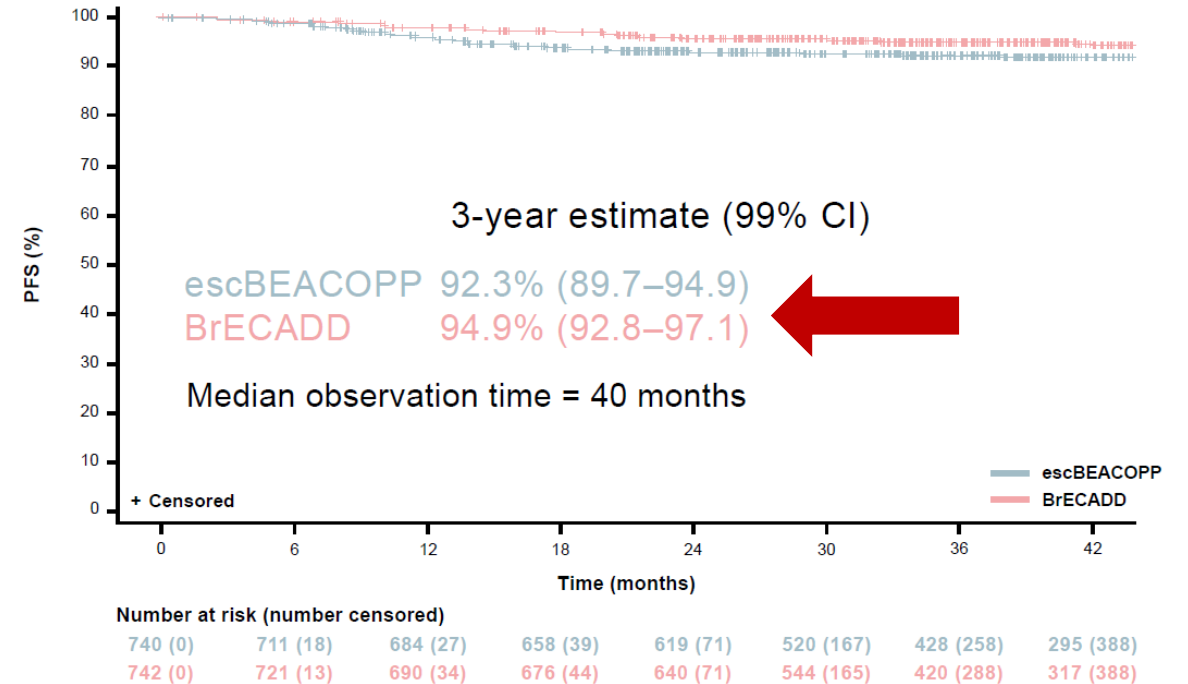
# PFS in the ITT population

# HD21 trial

## PFS events at a median follow-up of 40 months

|   | escBEACOPP (N=740) |            | BrECADD (N=742) |            |
|---|--------------------|------------|-----------------|------------|
|   | n                  | %          | n               | %          |
| Progression/relapse                           | 55                 | 7.4        | 32              | 4.3        |
| Progression                                   | 14                 | 1.9        | 5               | 0.7        |
| Early relapse, follow-up ≤1 year              | 23                 | 3.1        | 11              | 1.5        |
| Late relapse, follow-up >1 year               | 18                 | 2.4        | 16              | 2.2        |
| Death without previous progression or relapse | 6                  | 0.9        | 7               | 0.9        |
| <b>Total PFS events</b>                       | <b>61</b>          | <b>8.4</b> | <b>39</b>       | <b>5.3</b> |

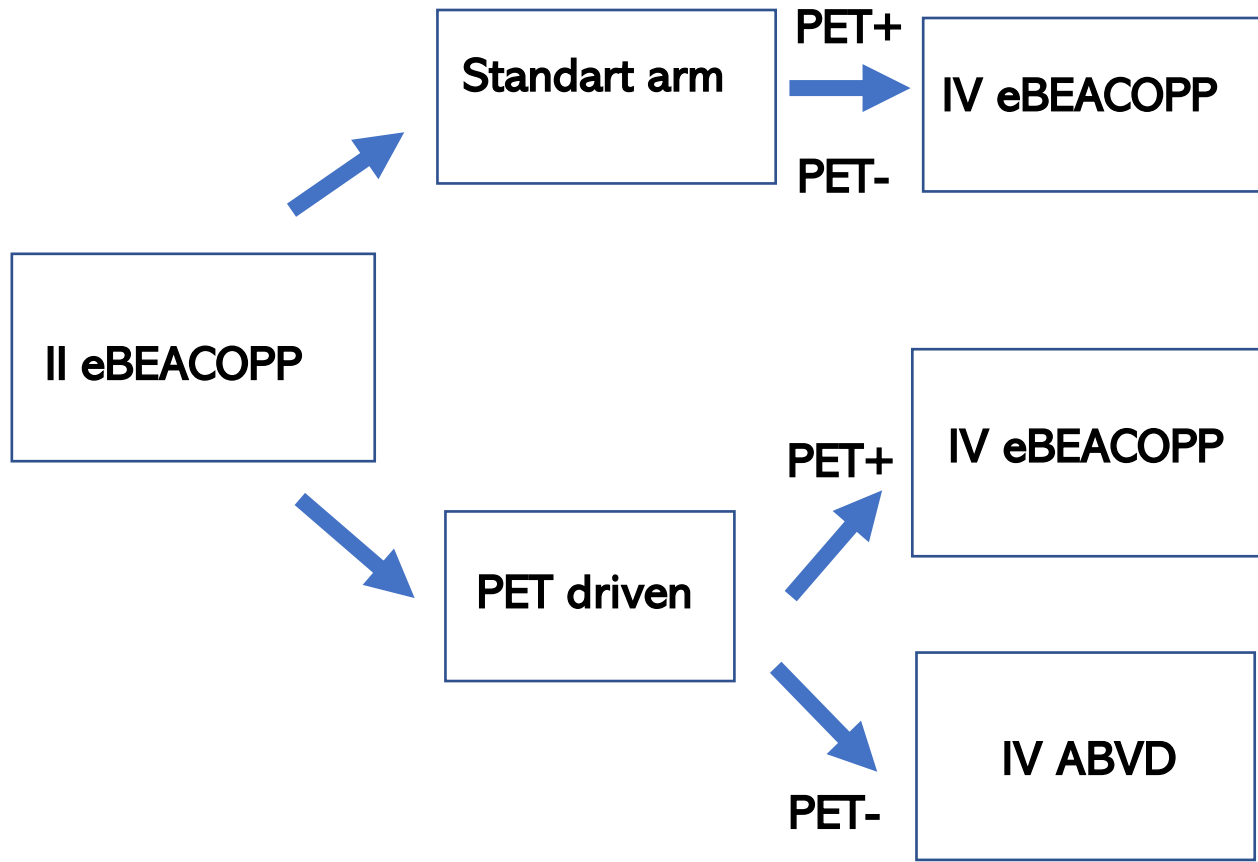
## 3-year PFS in the ITT population



With an HR of 0.63 for PFS (in favor of BrECADD), the HR bound of 1.02 is excluded and non-inferiority of BrECADD established vs escBEACOPP. The 99% CI for the HR (1.07–0.37) indicates a trend towards superiority (to be determined at final analysis with 95% CI)



# AHL2011 trial



|  | Standard treatment group (n=413) | PET-driven treatment group (n=410) |
|--|----------------------------------|------------------------------------|
| Median (IQR) age (years)                           | 31 (23–41)                       | 29 (24–40)                         |
| Men  | 263 (64%)                        | 253 (62%)                          |
| Women  | 150 (36%)                        | 157 (38%)                          |
| ECOG score   |                                  |                                    |
| 0  | 203 (49%)                        | 193 (47%)                          |
| 1  | 181 (44%)                        | 184 (45%)                          |
| 2  | 27 (7%)                          | 31 (8%)                            |
| Missing  | 2 (<1%)                          | 2 (<1%)                            |
| B symptoms   | 282 (68%)                        | 278 (68%)                          |
| Ann Arbor stage                                    |                                  |                                    |
| I  | 0                                | 2 (<1%)                            |
| II   | 44 (11%)                         | 52 (13%)                           |
| III  | 114 (28%)                        | 115 (28%)                          |
| IV   | 255 (62%)                        | 241 (59%)                          |
| Stage IIA  | 2 (<1%)                          | 7 (2%)                             |
| Stage IIB  | 42 (10%)                         | 45 (11%)                           |
| Mediastium to thorax ratio $\geq 0.33$             | 41 (98%)                         | 45 (100%)                          |
| Extra nodal localisation                           | 6 (14%)                          | 4 (9%)                             |
| Bulky mass   |                                  |                                    |
| $\geq 10$ cm                                       | 143 (35%)                        | 134 (33%)                          |
| <10 cm   | 233 (56%)                        | 229 (56%)                          |
| Missing  | 37 (9%)                          | 47 (11%)                           |
| Bone marrow involved                               | 33 (8%)                          | 32 (8%)                            |
| International prognosis score                      |                                  |                                    |
| 0–2  | 160 (39%)                        | 183 (45%)                          |
| $\geq 3$   | 250 (61%)                        | 225 (55%)                          |
| Missing  | 3 (<1%)                          | 2 (<1%)                            |
| Pathology review                                   |                                  |                                    |
| Hodgkin lymphoma                                   |                                  |                                    |
| Nodular sclerosis                                  | 273 (74%)                        | 264 (74%)                          |
| Mixed cellularity                                  | 20 (5%)                          | 22 (6%)                            |
| Lymphocyte-depleted                                | 2 (<1%)                          | 3 (<1%)                            |
| Lymphocytes rich                                   | 2 (<1%)                          | 1 (<1%)                            |
| Interfollicular                                    | 1 (<1%)                          | 0                                  |
| Unclassified                                       | 51 (14%)                         | 61 (17%)                           |
| Grey zone lymphoma                                 | 20 (5%)                          | 3 (<1%)                            |
| Anaplastic large cell lymphoma ALK negative        | 0                                | 2 (<1%)                            |
| EBV-associated B-cell lymphoproliferative disorder | 1 (<1%)                          | 0                                  |
| Insufficient material                              | 1 (<1%)                          | 1 (<1%)                            |
| Missing  | 42 (10%)                         | 53 (13%)                           |

Data are number (%) unless stated otherwise. ECOG=Eastern Cooperative Oncology Group. ALK=anaplastic lymphoma kinase. EBV=Epstein-Barr virus.

Table 1: Baseline characteristics

|   | Number of patients (%) | 5-year progression-free survival (95%CI) | Univariate analysis |         | Multivariate analysis |         |
|---|------------------------|--|---------------------|---------|-----------------------|---------|
|   |                        |  | HR (95% CI)         | p value | HR (95% CI)           | p value |
| <b>PET assessments</b>                          |                        |  |                     |         |                       |         |
| PET2 and PET4 negative                          | 654 (79%)              | 92.5 (90.1-94.3)                         | ..                  | ..      | ..                    | ..      |
| PET2 positive, PET4 negative                    | 62 (8%)                | 75.4 (62.5-84.4)                         | 3.59 (2.01-6.40)    | <0.0001 | 2.57 (1.33-4.92)      | 0.0046  |
| PET4 positive                                   | 43 (5%)                | 46.5 (31.2-60.4)                         | 13.14 (7.98-21.62)  | <0.0001 | 10.37 (6.03-17.79)    | <0.0001 |
| <b>Sex</b>                                      |                        |  |                     |         |                       |         |
| Female  | 516 (63%)              | 88.2 (81.9-92.5)                         | ..                  | ..      | ..                    | ..      |
| Male  | 307 (37%)              | 84.6 (81.1-87.5)                         | 1.73 (1.11-2.68)    | 0.013   | 1.41 (0.84-2.35)      | 0.19    |
| <b>Eastern Cooperative Oncology Group score</b> |                        |  |                     |         |                       |         |
| 0   | 396 (48%)              | 87.8 (84-90.8)                           | ..                  | ..      | ..                    | ..      |
| 1   | 365 (44%)              | 84.3 (78.7-88.5)                         | 1.14 (0.75-1.72)    | 0.53    | 0.85 (0.52-1.38)      | 0.44    |
| 2   | 58 (7%)                | 86.1 (74.1-92.8)                         | 1.29 (0.61-2.74)    | 0.50    | 1.27 (0.57-2.84)      | 0.34    |
| <b>B symptoms</b>                               |                        |  |                     |         |                       |         |
| No  | 263 (32%)              | 88.6 (83.5-92.2)                         | ..                  | ..      | ..                    | ..      |
| Yes   | 560 (68%)              | 84.7 (80.8-87.9)                         | 1.41 (0.90-2.18)    | 0.12    | 1.06 (0.60-1.83)      | 0.037   |
| <b>Ann Arbor stage</b>                          |                        |  |                     |         |                       |         |
| IIB   | 87 (11%)               | 86.3 (76.3-92.3)                         | ..                  | ..      | ..                    | ..      |
| III-IV  | 725 (89%)              | 85.8 (82.5-88.5)                         | 1.00 (0.53-1.86)    | 0.43    | 1.25 (0.57-2.74)      | 0.32    |
| <b>Bulk</b>                                     |                        |  |                     |         |                       |         |
| <10 cm  | 462 (63%)              | 87.8 (83.4-91.1)                         | ..                  | ..      | ..                    | ..      |
| ≥10 cm  | 277 (37%)              | 83.6 (78.4-87.7)                         | 1.60 (1.05-2.42)    | 0.027   | 1.246 (0.76-2.01)     | 0.79    |
| <b>International prognosis score</b>            |                        |  |                     |         |                       |         |
| 0-2   | 343 (42%)              | 91.9 (88.4-94.4)                         | ..                  | ..      | ..                    | ..      |
| ≥3  | 475 (58%)              | 83.7 (79.9-86.9)                         | 1.92 (1.24-2.94)    | 0.0025  | 1.60 (0.72-2.03)      | 0.044   |

HR=hazard ratio. PET2=PET after two cycles of chemotherapy. PET4=PET after four cycles of chemotherapy.

Table 3: Analysis of progression-free survival

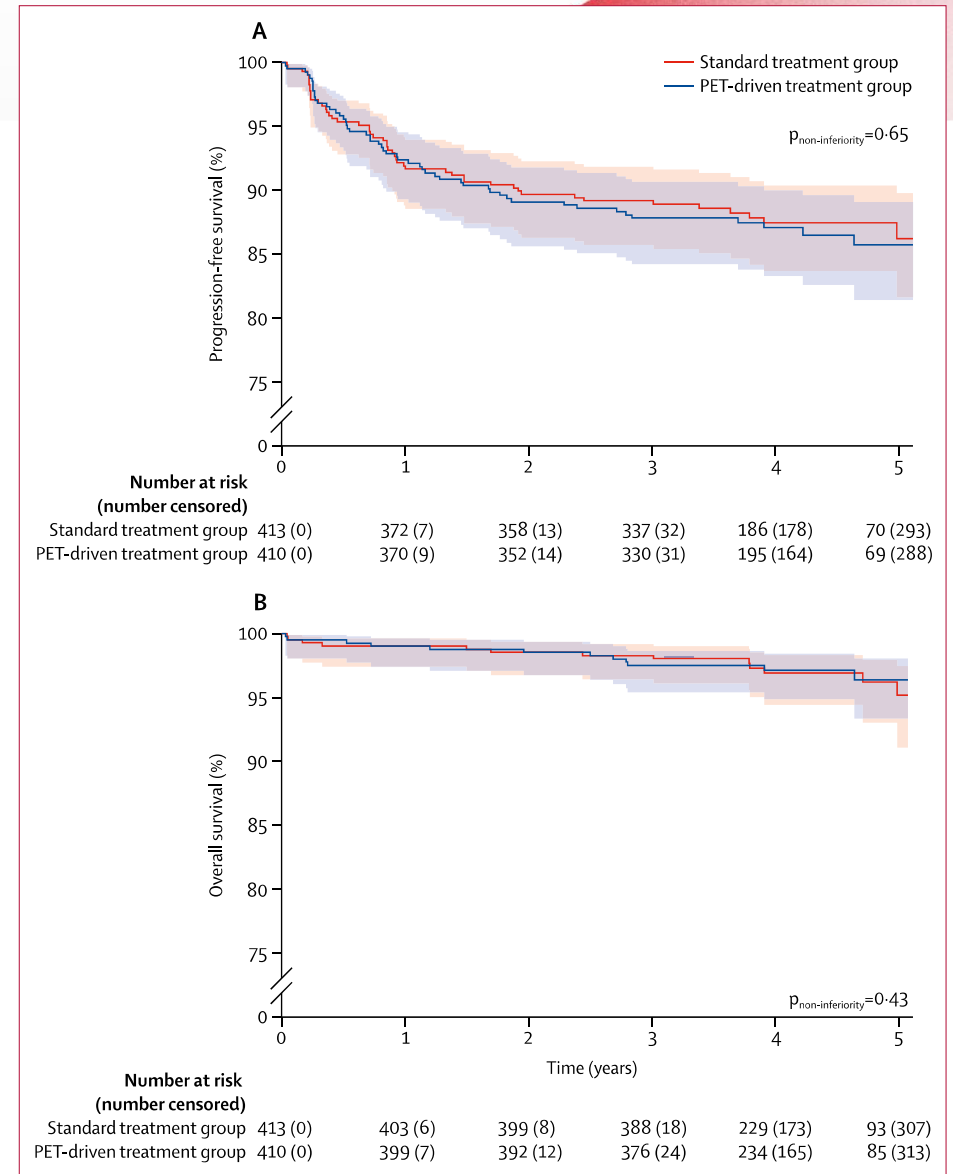
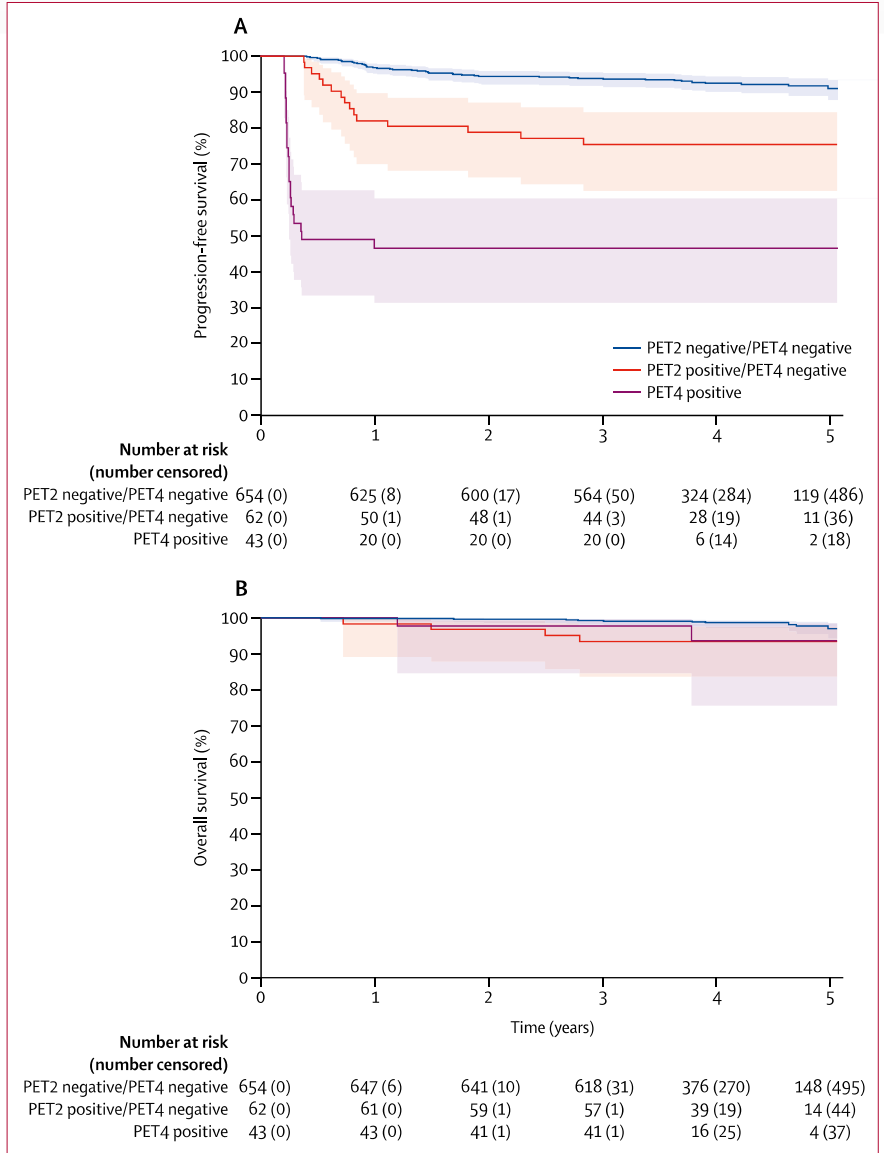
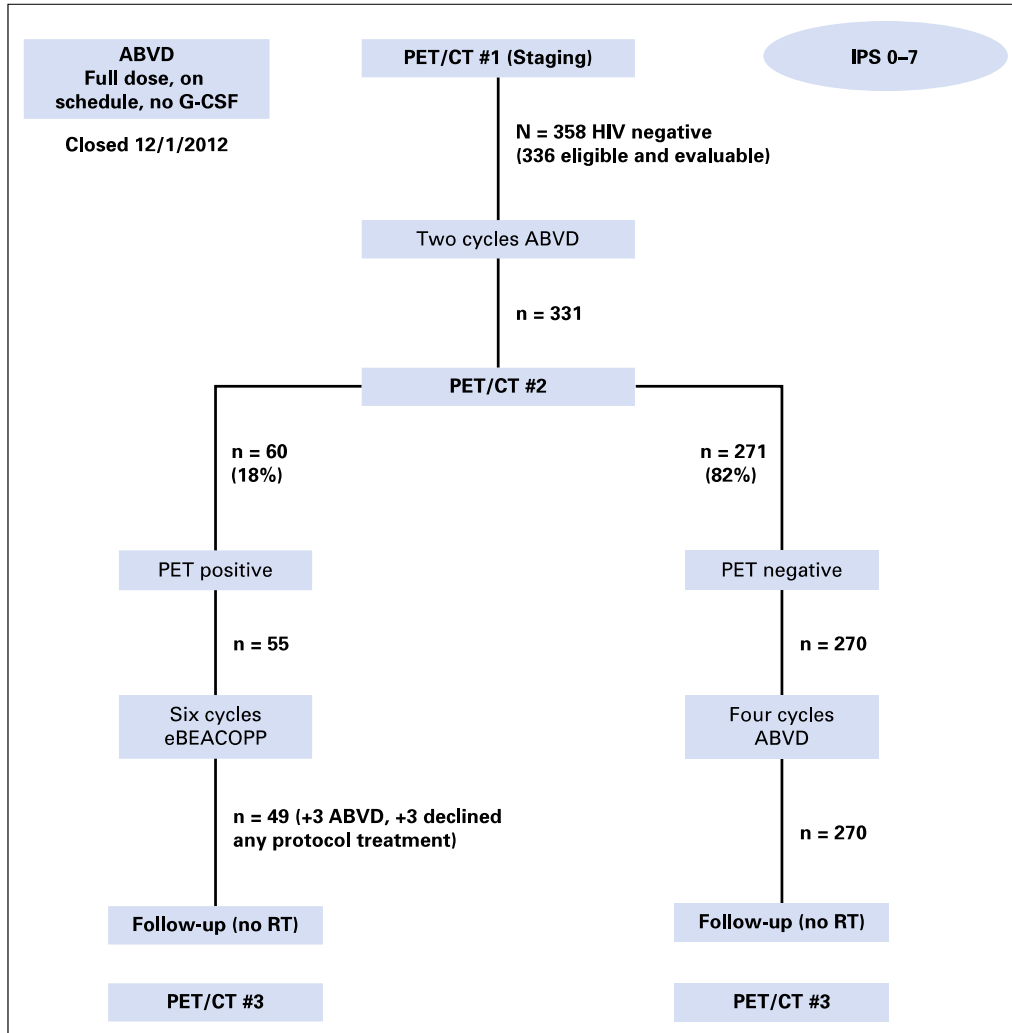


Figure 2: Kaplan-Meier curves of survival outcomes by treatment group in the intention-to-treat population (A) Progression-free survival. (B) Overall survival. Data are survival estimates with 95% CIs.

# AHL2011 trial



**Figure 3: Kaplan-Meier curves of survival outcomes by PET response**  
 (A) Progression-free survival. (B) Overall survival. Data are survival estimates with 95% CIs. PET2=PET after two induction cycles. PET4=PET after four induction cycles.

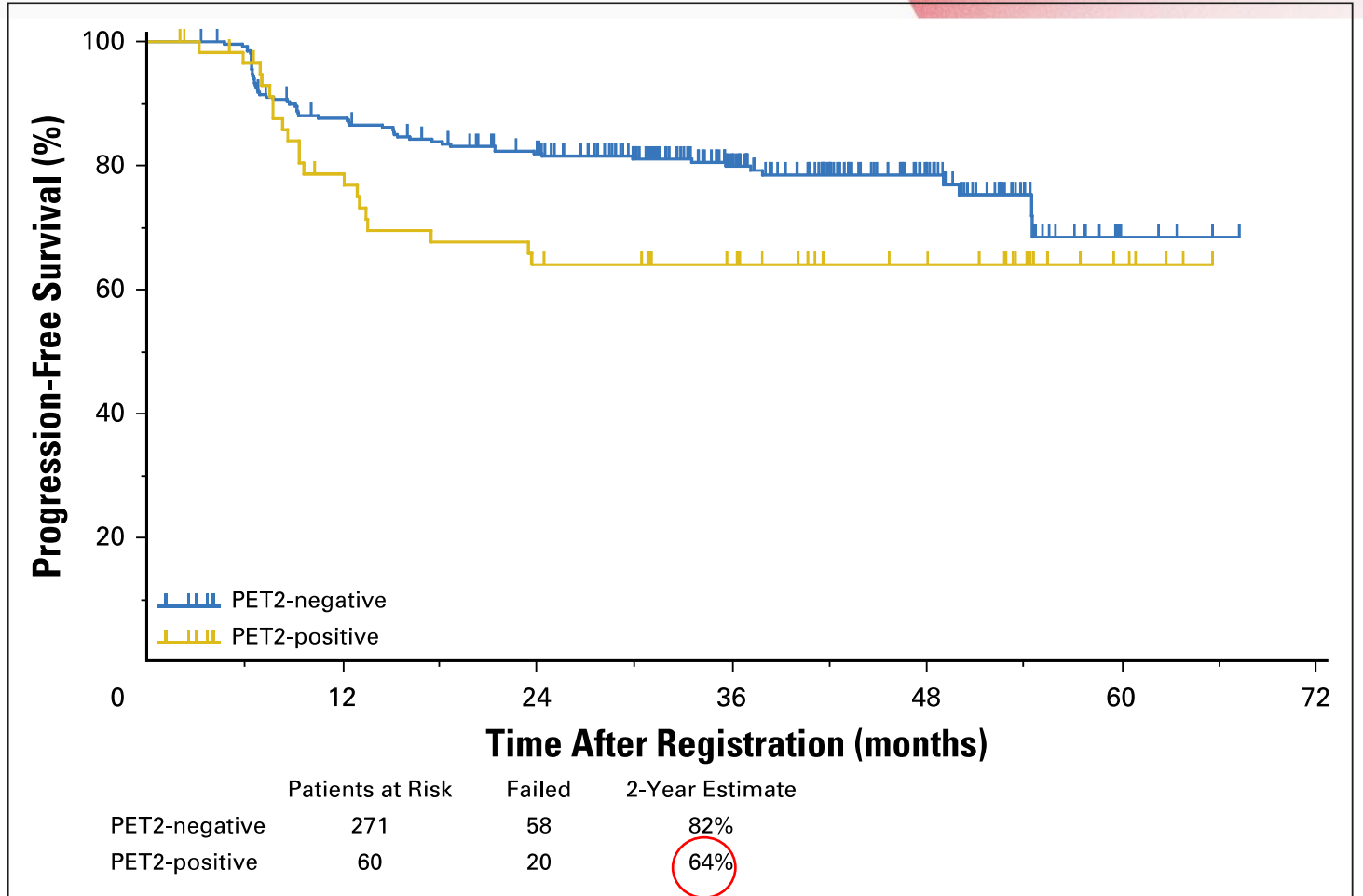
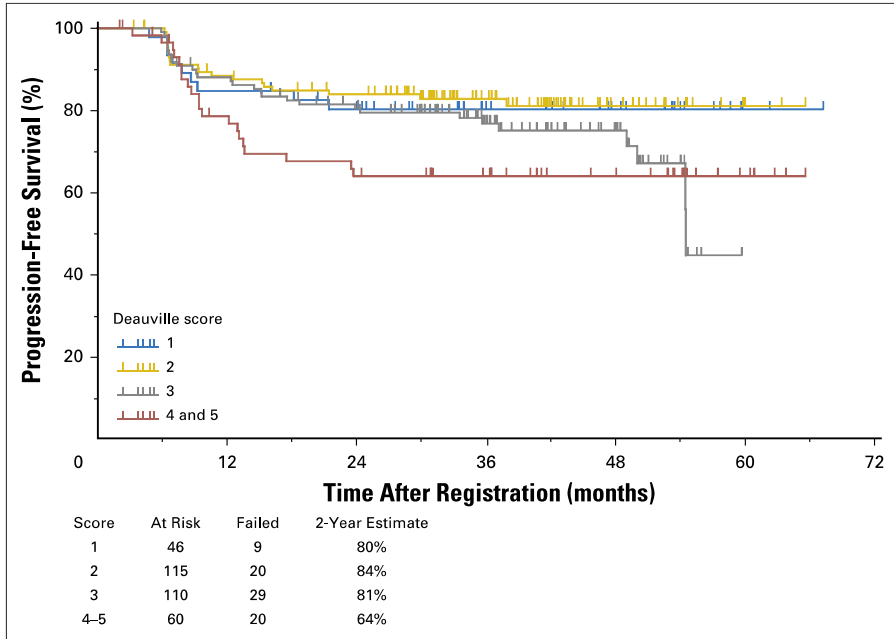


**Table 1.** Demographic Characteristics of Eligible and Evaluable Patients on SWOG S0816 (n = 336)

| Characteristic | No.   | %  |
|----------------|-------|----|
| Age, years     |       |    |
| Median         | 32    |    |
| Range          | 18-60 |    |
| Sex            |       |    |
| Male           |       | 56 |
| Female         |       | 44 |
| Race           |       |    |
| White          |       | 82 |
| Other          |       | 18 |
| Stage          |       |    |
| III            |       | 52 |
| IV             |       | 48 |
| "B" symptoms   |       | 62 |
| Bulk > 10 cm   |       | 18 |
| IPS            |       |    |
| 0-2            |       | 49 |
| 3-7            |       | 51 |

Abbreviations: IPS, International Prognostic Score; SWOG, Southwest Oncology Group.

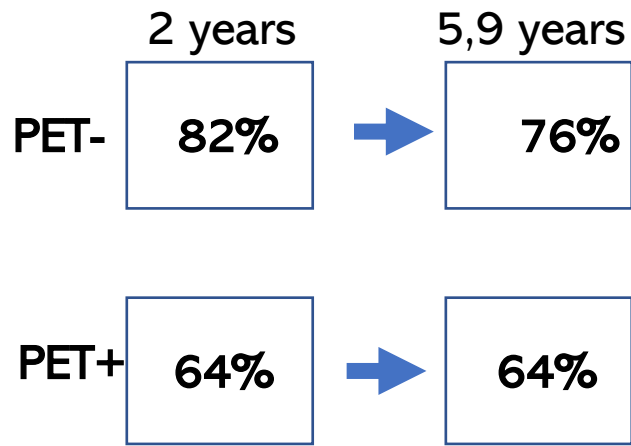
# SWOG S0816





### Key Points

- Nearly 25% of patients with a negative PET2 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.



**Table 4. Second Primary Cancers Reported By Patients Treated on S0816**

| S0816 Therapy Received | Type of Second Cancer    | Salvage Therapy for HL Prior to Second Cancer | SCT Prior to Second Cancer | Time from S0816 Treatment to Second Cancer (years) |
|------------------------|--------------------------|---|----------------------------|--|
| eBEACOPP               | Myelodysplastic Syndrome | Y   | N                          | 5.1  |
| eBEACOPP               | Kidney                   | N   | N                          | 2.9  |
| eBEACOPP               | Melanoma                 | N   | N                          | 5.0  |
| eBEACOPP               | Non-Hodgkin lymphoma     | N   | N                          | 1.1  |
| eBEACOPP               | Cervical                 | N   | N                          | 0.8  |
| eBEACOPP               | Medullary thyroid        | N   | N                          | 5.2  |
| eBEACOPP               | Basal cell carcinoma     | N   | N                          | 2.9  |
| ABVD                   | Kidney                   | N   | N                          | 0.6  |
| ABVD                   | Melanoma                 | N   | N                          | 3.9  |
| ABVD                   | Non-Hodgkin lymphoma     | N   | N                          | 0.6  |
| ABVD                   | Bladder                  | N   | N                          | 4.8  |
| ABVD                   | Prostate                 | N   | N                          | 4.4  |
| ABVD                   | Squamous cell carcinoma  | N   | N                          | 5.2  |

ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; eBEACOPP = escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; HL = Hodgkin lymphoma; SCT = stem cell transplantation

14% X 2% second neoplasia

# GATLA LH-05 TRIAL

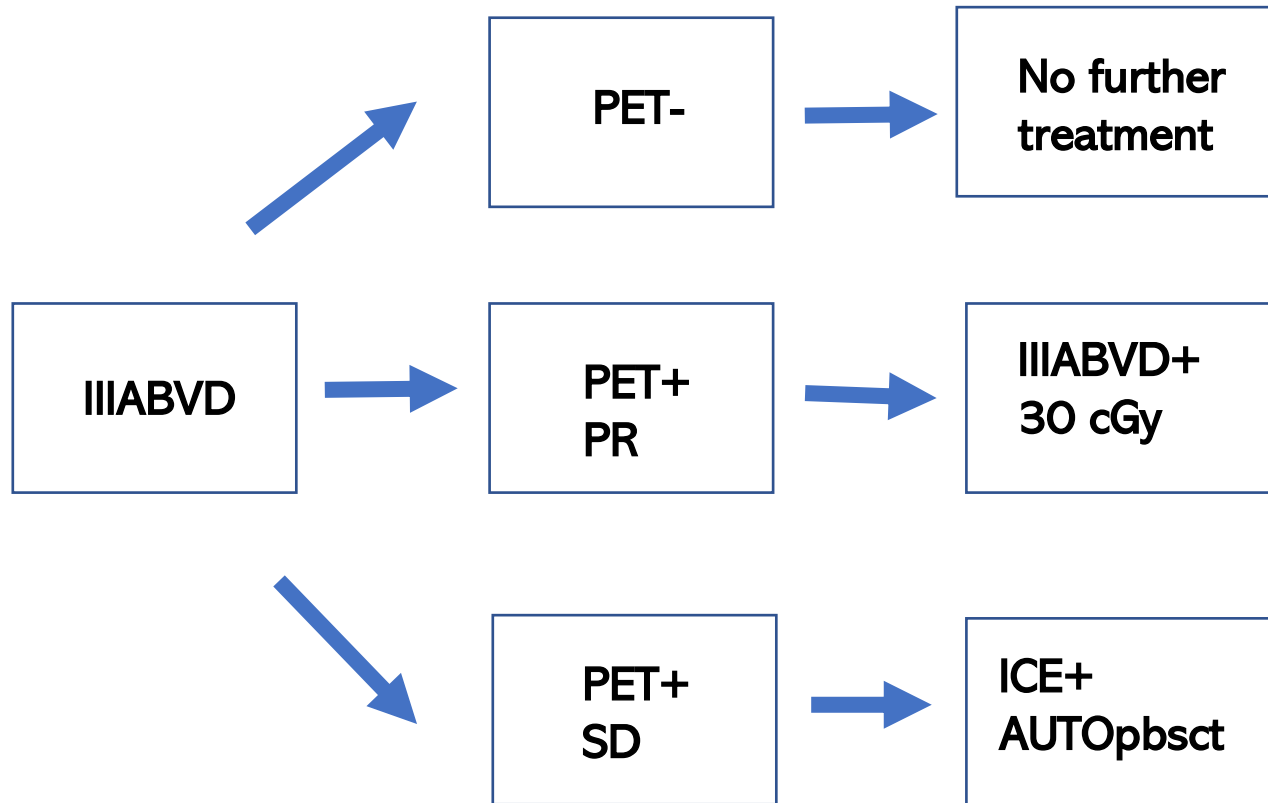
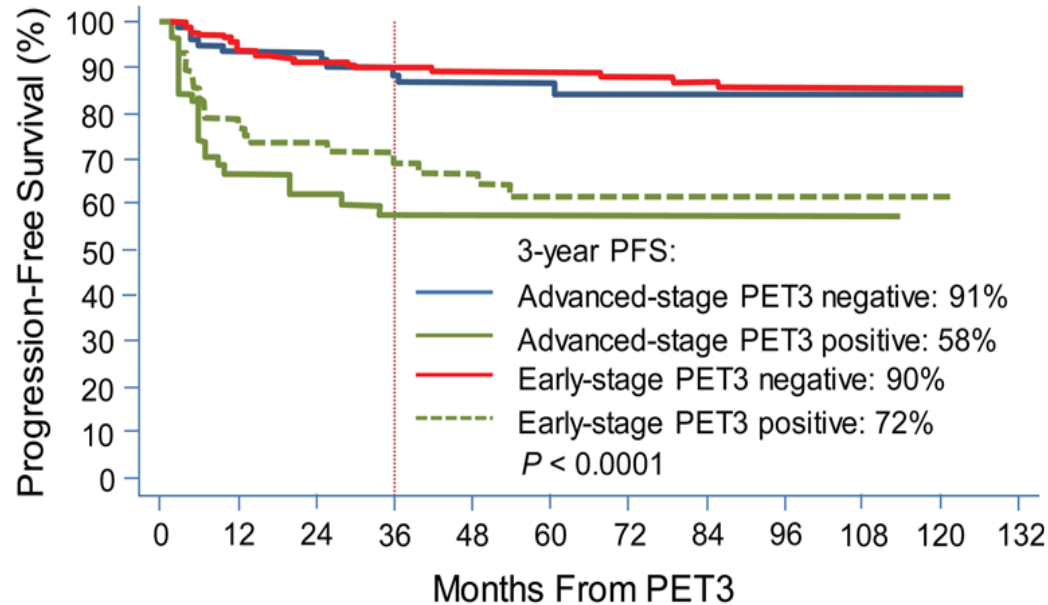


Table I. Clinical characteristics of evaluable patients.

| Characteristic              | All evaluable patients<br>(n = 377) |
|-----------------------------|-------------------------------------|
| Median age (range), years   | 31 (18–89)                          |
| Male sex, n (%)             | 173 (46)                            |
| Performance status, n (%)   |                                     |
| 0–1                         | 362 (95)                            |
| 2                           | 6 (2)                               |
| ≥3                          | 3 (1)                               |
| Not available               | 6 (2)                               |
| Ann Arbor stage, n (%)      |                                     |
| Early (I to II non-bulky)   | 239 (63)                            |
| Advanced (II, bulky-III-IV) | 138 (37)                            |
| Bulky disease, n (%)        | 66 (17)                             |



Follow-up: 69 months

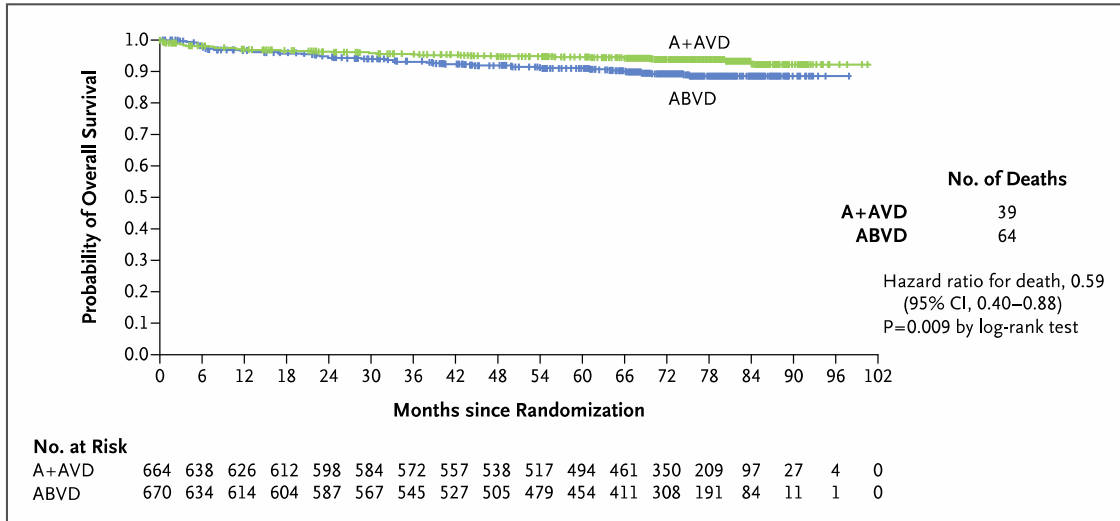
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| 2                           | 6 (2)                                   |
| $\geq 3$                    | 3 (1)                                   |
| Not available               | 6 (2)                                   |
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| Early (I to II non-bulky)   | 239 (63)                                |
| Advanced (II, bulky-III-IV) | 138 (37)                                |
| Bulky disease, $n$ (%)      | 66 (17)                                 |

Table III. Cox multivariate analysis for progression-free survival,

| Characteristic at diagnosis $N = 377$ | $P$ value | HR (95% CI)   |
|---------------------------------------|-----------|---------------|
| Age <60 vs. >60 years                 | 0.626     | 1.0 (0.9–1.0) |
| Bulky disease (yes versus no)         | 0.721     | 1.1 (0.4–1.4) |
| Early versus advanced stage           | 0.490     | 0.8 (0.4–1.4) |
| PET3 (positive versus negative)       | <0.0001   | 3.8 (2.4–6.3) |

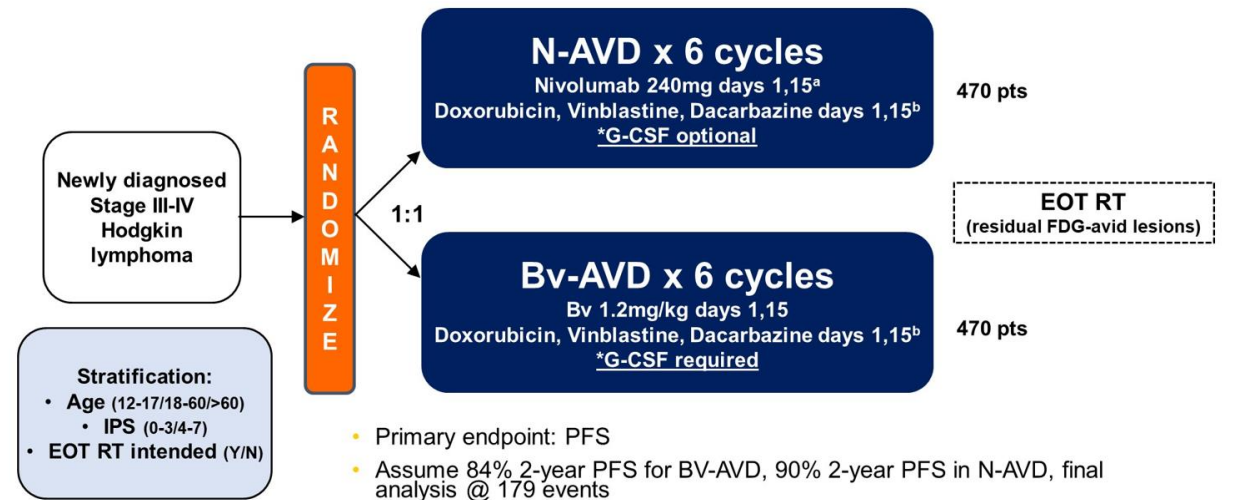
# Not PET driven (Echelon-1 and SWOG1826)



**Figure 1. Overall Survival (Intention-to-Treat Population).**

The intention-to-treat population included all the patients who underwent randomization. Tick marks indicate censored data. A+AVD denotes brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; and ABVD doxorubicin, bleomycin, vinblastine, and dacarbazine.

## S1826 Study Design



## 1) Detection-based discrepancies.

### 1) 1) Lesion not evaluable

One reader interpreted uptake as residual lymphoma, whilst the other reader considered that this region was not evaluable, e.g. due to the presence of activated brown fat tissue or motion artifacts.

### 1) 2) Lesion overlooked

One of the two readers interpreted a lesion as residual lymphoma and the other reader overlooked the lesion.

## 2) Interpretation-based discrepancies.

### 2) 1) Malignant vs. non-pathological

One reader interpreted uptake as residual lymphoma, whilst the other reader interpreted the uptake as physiological or artifactual uptake.

### 2) 2) Malignant vs. inflammatory

One reader interpreted a lesion as residual lymphoma, the other reader as inflammation or infection.

## 3) Evaluation-based discrepancies.

### 3) 1) Different hottest lesions

Both readers chose different 'hottest' lesions.

### 3) 2) Different vDS

The two readers agreed on the location of the 'hottest' residual lesion, yet disagreed in their interpretation of the vDS.

**Table 2. Comparison of the visual Deauville scores (vDS) of reader 1 (R1) and reader 2 (R2).**

|          | R1 vDS 1 | R1 vDS 2 | R1 vDS 3 | R1 vDS 4 | R1 vDS 5 | Sum |
|----------|----------|----------|----------|----------|----------|-----|
| R2 vDS 1 | 109      | 32       | 12       | 12       | 0        | 165 |
| R2 vDS 2 | 44       | 81       | 10       | 3        | 0        | 138 |
| R2 vDS 3 | 11       | 33       | 39       | 7        | 2        | 92  |
| R2 vDS 4 | 3        | 3        | 8        | 7        | 8        | 29  |
| R2 vDS 5 | 0        | 1        | 1        | 2        | 13       | 17  |
| Sum      | 167      | 150      | 70       | 31       | 23       | 441 |

<https://doi.org/10.1371/journal.pone.0283694.t002>

**Table 3. Comparison of the quantitative Deauville score (qDS) in minor visual discrepancies.**

| Minor visual discrepancies |    |                |       |
|----------------------------|----|----------------|-------|
| Discrepancy between        | N  | Concordant qDS | Ratio |
| vDS 1/2                    | 76 | -              | -     |
| vDS 2/3                    | 43 | 22             | 51%   |
| vDS 3/4                    | 15 | 6              | 40%   |
| vDS 4/5                    | 10 | 7              | 70%   |
| Overall (without DS 1/2)   | 68 | 35             | 51%   |

<https://doi.org/10.1371/journal.pone.0283694.t003>

# TMTV at baseline- HD10

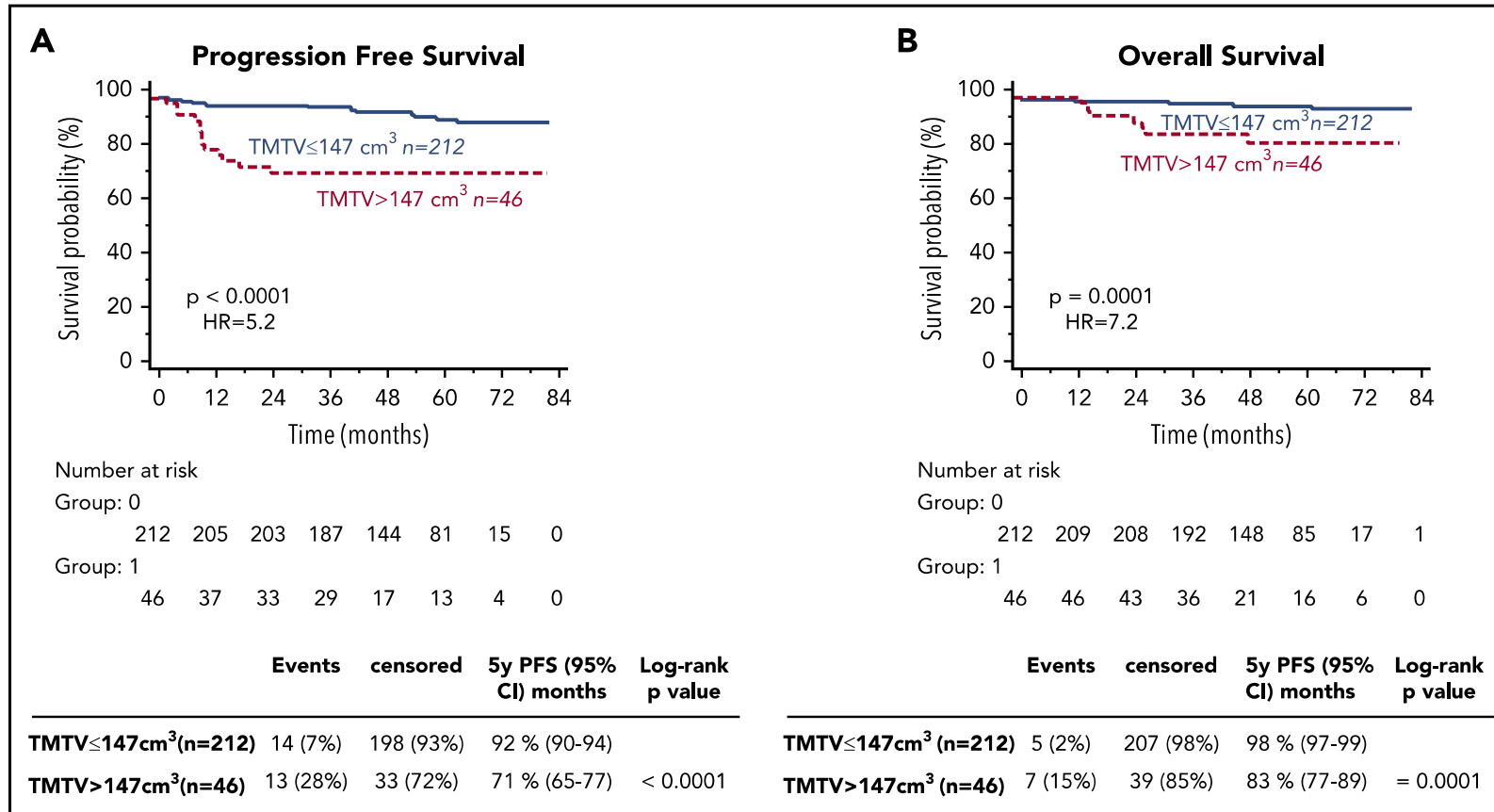
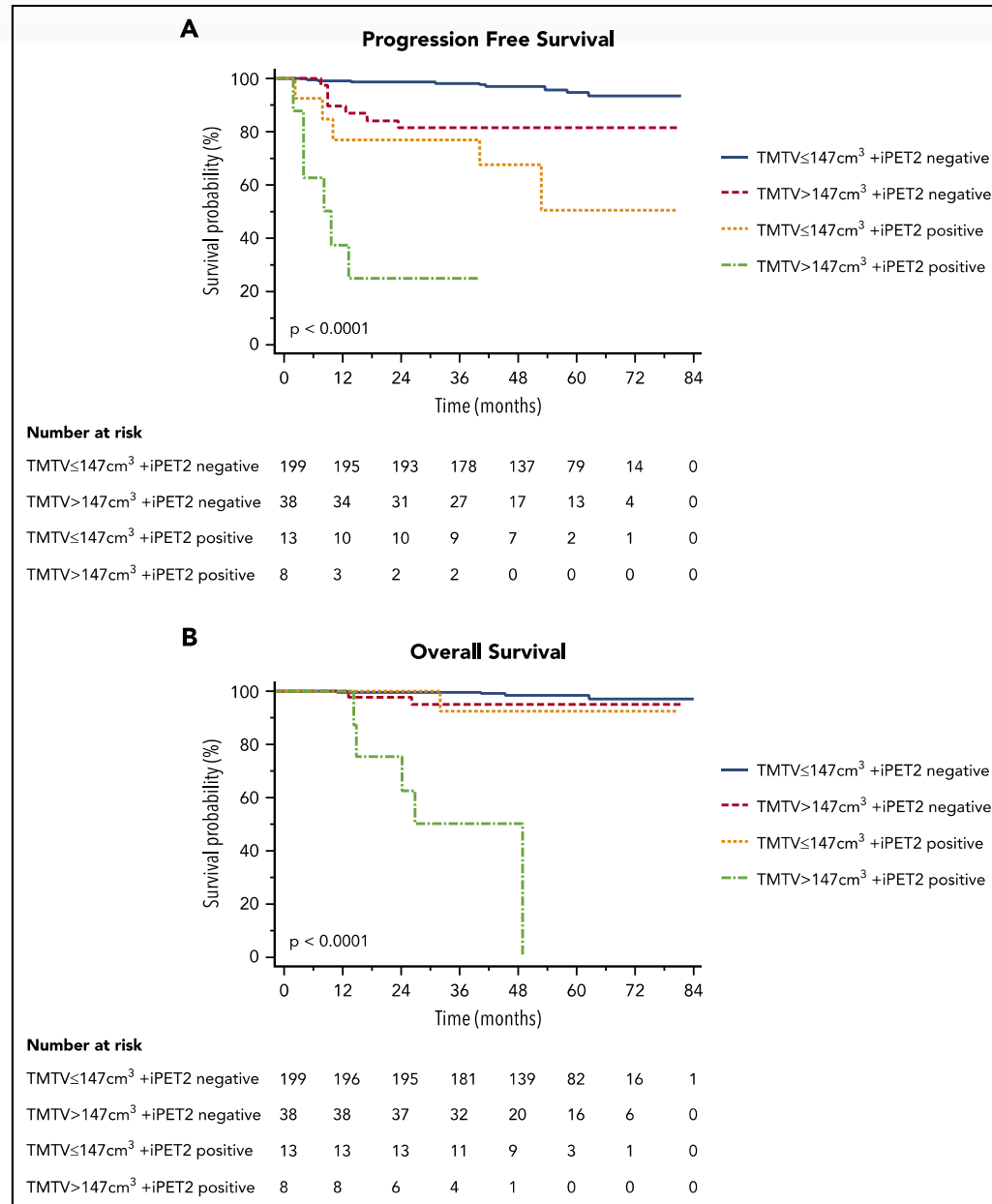


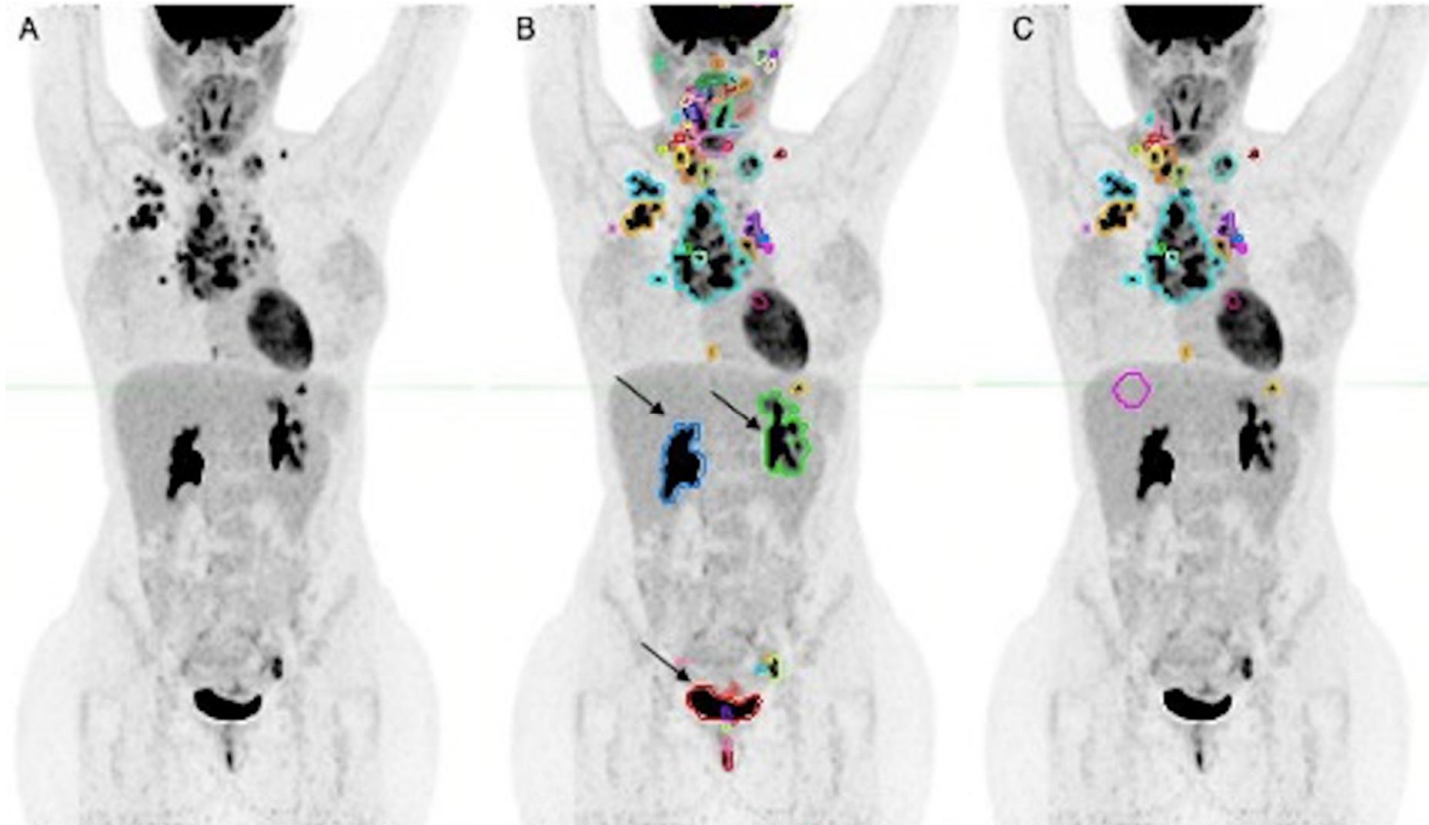
Figure 1. PFS and OS according to high total metabolic tumor volume (TMTV >147 cm<sup>3</sup>) or low TMTV (TMTV ≤147 cm<sup>3</sup>).



# TMTV at baseline- HD10



# TMTV at baseline



# TMTV at baseline

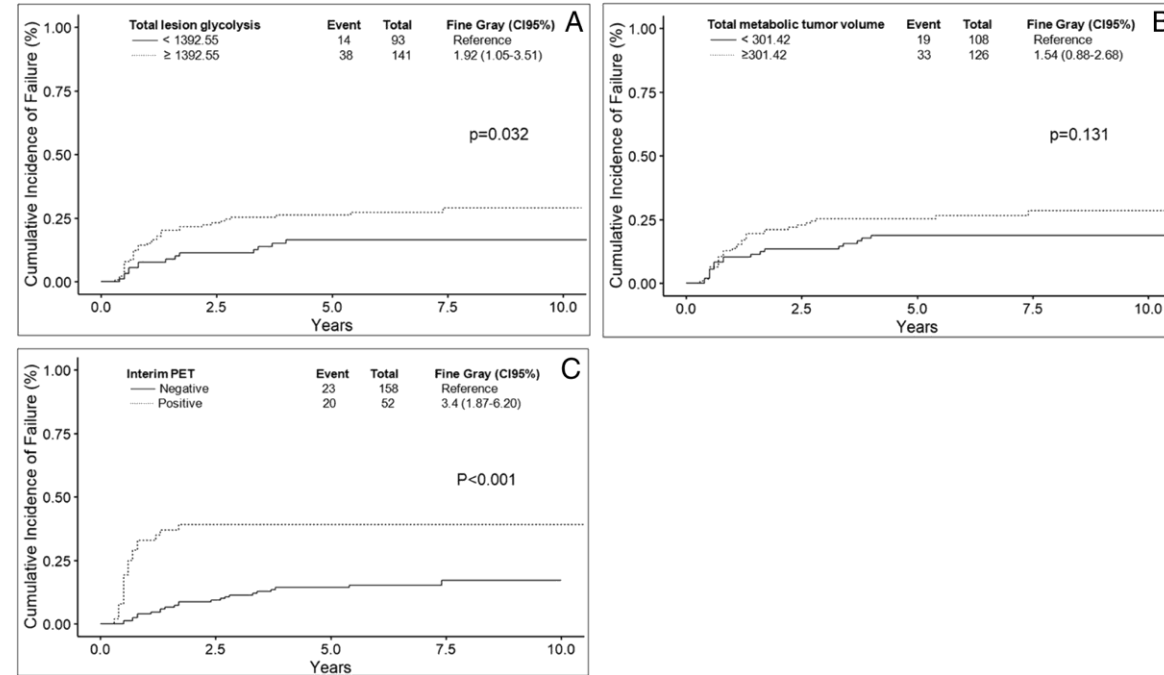
**Table 3.** Univariate and multivariate analysis.

| Variable   | Univariate <i>p</i> -Value | Multivariate <i>p</i> -Value |
|--|----------------------------|------------------------------|
| TMTV > 177.02 mL   | 0.002 *                    | 0.013 *                      |
| SUV <sub>max</sub> > 14.67   | 0.002 *                    | 0.002 *                      |
| Stage (advanced)   | 0.022 *                    | 0.067                        |
| Age ≥ 45 years   | 0.045 *                    | 0.05 *                       |
| Sex  | 0.478                      | Excluded                     |
| WBC ≥ 15,000/mm <sup>3</sup>   | 0.222                      | Excluded                     |
| Symptoms (present)   | 0.942                      | Excluded                     |
| Albuminemia ≥ 4 g/dL   | 0.287                      | Excluded                     |
| Fibrinogen ≥ 400 mg/dL   | 0.718                      | Excluded                     |
| Erythrocyte sedimentation rate (>30 mm/h with B symptoms vs. >50 mm/h without) | 0.714                      | Excluded                     |
| Hemoglobinemia < 10.5 g/dL   | 0.899                      | Excluded                     |
| Lymphocyte count < 600/mm <sup>3</sup> or <8% of WBC                           | 0.896                      | Excluded                     |
| LDH > normal range   | 0.846                      | Excluded                     |

TMTV: total metabolic tumor volume; SUV<sub>max</sub>: maximum standardized uptake value; Stage (advanced): Ann Arbor stages from IIB with bulk to IV; WBC: white blood cell count; LDH: lactate dehydrogenase; \*:  $p \leq 0.05$ .

**Table 1** Baseline characteristics of patients

| CHARACTERISTICS         | N = 234 (%) |
|-------------------------|-------------|
| Female                  | 131 (56)    |
| Age (years)             |             |
| Median                  | 30          |
| Range                   | 14–79       |
| Age ≥ 45                | 56 (24)     |
| Age ≥ 60                | 27 (11.5)   |
| Histological subtype    |             |
| Non-other specification | 95 (40.5)   |
| With subclassification  | 139 (59.5)  |
| Nodular sclerosis       | 114 (82)    |
| Mixed cellularity       | 18 (13)     |
| Lymphocyte-rich         | 7 (5)       |
| Clinical stage          |             |
| I – II                  | 95 (40.6)   |
| III – IV                | 139 (59.4)  |
| B Symptoms              | 165 (70.5)  |
| Bulky <sup>a</sup>      | 133 (57)    |
| Mediastinal bulky       | 81/133 (61) |
| Risk stratification     |             |
| GHSGB <sup>b</sup> ≥ 1  | 81/95 (88)  |
| IPS <sup>c</sup> > 2    | 79/139 (58) |
| ECOG > 2                | 18 (7.7)    |



**Fig. 1** Seven-year cumulative incidence of treatment failure with death as a competitor for: **A:** low and high TLG: 15.3% vs 26.6%, respectively; **B:** low and high TMTV: 18.0% vs 25.7%, respectively; **C:** interim PET negative: 15.1% vs positive: 39%

**Table 4** Impact of  $\Delta$ SUVmax,  $\Delta$ TMTV and  $\Delta$ TLG on progression-free survival

| Parameter       | cutoff        | Univariate analysis |                 | Multivariate analysis |                 |
|-----------------|---------------|---------------------|-----------------|-----------------------|-----------------|
|                 |               | HR (95% CI)         | <i>p</i> -Value | HR (95% CI)           | <i>p</i> -Value |
| $\Delta$ SUVmax | $\geq 68.8\%$ | 0.25<br>(0.09–0.66) | <b>0.005</b>    | 0.31<br>(0.11- 0.86)  | <b>0.024</b>    |
| $\Delta$ TMTV   | $\geq 92.7\%$ | 0.42<br>(0.19–0.95) | <b>0.037</b>    | 0.76<br>(0.32–1.76)   | 0.519           |
| $\Delta$ TLG    | $\geq 99.6\%$ | 0.16<br>(0.02–1.15) | 0.068           | 0.23<br>(0.03–1.79)   | 0.160           |

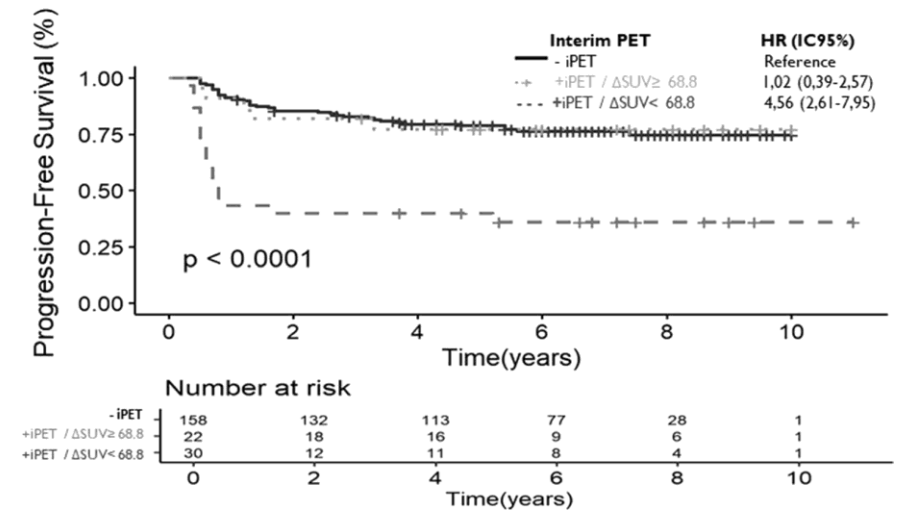
Cox proportional risk model

| Variable <sup>a</sup>                            | Univariate (N=234) |                  | Multivariate (N=161)       |                  |
|--|--------------------|------------------|----------------------------|------------------|
|  | HR (IC95%)         | p value          | HR (IC 95%)                | p value          |
| TMTV ≥ 301.4                                     | 1.54 (0.88–2.68)   | 0.133            | -                          | -                |
| TLG ≥ 1392.55                                    | 1.92 (1.05–3.51)   | 0.035            | -                          | -                |
| Positive iPET                                    | 3.40 (1.87–6.20)   | <0.001           | <b>3.40 (1.87–6.20)</b>    | <b>&lt;0.001</b> |
| Male sex   | 1.56 (0.91–2.67)   | 0.105            | -                          | -                |
| ERS ≥ 50   | 2.01 (1.08–3.75)   | 0.027            | -                          | -                |
| Leucocytes ≥ 15,000                              | 1.78 (0.95–3.33)   | 0.072            | -                          | -                |
| CRP ≥ 55.4                                       | 1.95 (1.02–3.74)   | 0.043            | <b>2.15 (1.02 – 4.54)</b>  | <b>0.043</b>     |
| Subset of early stage                            |                    |                  |                            |                  |
| Univariate (N=95)                                |                    |                  | <b>Multivariate (N=78)</b> |                  |
| TMTV ≥ 419.52                                    | 2.38(1.04–5.48)    | <b>0.041</b>     | -                          | -                |
| TLG ≥ 1392.55                                    | 3.81(1.51–9.62)    | <b>0.004</b>     | -                          | -                |
| Positive iPET                                    | 4.80 (2.03–11.3)   | <b>&lt;0.001</b> | <b>3.82(1.53–9.58)</b>     | <b>0.004</b>     |
| Nodal area ≥ 3                                   | 2.39 (0.42–0.92)   | <b>0.074</b>     | -                          | -                |
| ERS ≥ 30 and B symptoms or ERS ≥ 50 <sup>b</sup> | 3.51 (1.16–10.7)   | <b>0.027</b>     | 3.00(0.94–9.57)            | 0.063            |

<sup>a</sup>All variables with  $p < 0.20$  in the univariate and included in the multivariate

<sup>b</sup>Missing data: 14

**Fig. 2** Progression-free survival according to visual and quantitative iPET analysis: -iPET: negative iPET (Deauville score 1, 2 or 3), +iPET/ $\Delta$ SUVmax  $\geq$  68.8: positive iPET (Deauville score 4 or 5) and SUVmax reduction  $\geq$  68.8%, +iPET/ $\Delta$ SUVmax < 68.8: positive iPET (Deauville score 4 or 5) and SUVmax reduction < 68.8%



# Conclusions

- De-escalation based on iPET negative is effective and less toxic. Concerns about the predictive value of negative interim PET (mainly with ABVD protocols)
- Escalation with iPET positive is a more effective therapy but carries more toxicity
- It remains controversial which is the best approach in first line treatment for patients with advanced disease (nivo-avd x brecadd)
- iPET in immunotherapy era at first line? ctDNA will replace?



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APOIO INSTITUCIONAL **bp** Educação e Pesquisa

# Obrigada!

Talita Silveira