**Supplemental Table 1: Available Questionnaires**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Baseline** | **A:** | **190** | **B:** | **194** | **C:** | **240** | **D:** | **245** |
|  | **A6:** | **402** |  |  | **C6:** | **181** | **D4:** | **180** |
| **Chemotherapy** | **A:** | **177** | **B:** | **178** | **C:** | **228** | **D:** | **230** |
|  | **A6:** | **382** |  |  | **C6:** | **168** | **D4:** | **172** |
| **End of Therapy** | **A:** | **116** | **B:** | **106** | **C:** | **114** | **D:** | **96** |
|  | **A6:** | **228** |  |  | **C6:** | **85** | **D4:** | **70** |
| **Year 1** | **A:** | **127** | **B:** | **117** | **C:** | **175** | **D:** | **187** |
|  | **A6:** | **262** |  |  | **C6:** | **116** | **D4:** | **135** |
| **Year 2** | **A:** | **105** | **B:** | **109** | **C:** | **146** | **D:** | **155** |
|  | **A6:** | **229** |  |  | **C6:** | **105** | **D4:** | **109** |
| **Year 3** | **A:** | **77** | **B:** | **85** | **C:** | **111** | **D:** | **126** |
|  | **A6:** | **184** |  |  | **C6:** | **79** | **D4:** | **96** |
| **Year 4** | **A:** | **63** | **B:** | **72** | **C:** | **102** | **D:** | **99** |
|  | **A6:** | **148** |  |  | **C6:** | **63** | **D4:** | **86** |
| **Year 5** | **A:** | **55** | **B:** | **56** | **C:** | **91** | **D:** | **96** |
|  | **A6:** | **118** |  |  | **C6:** | **53** | **D4:** | **72** |

**Supplemental Table 2: HD18, HRQoL in the 2nd year after therapy in PET2-negative patients: effect of 4 vs. 8 cycles eBEACOPP**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | QLQ-C30 score | Baseline score#c | **Effect of cycle reduction**$ | **Male sex** | Agec |
| No. |  | b | β | P | b | ***β*** | P | b | β | P | b | β | P |
| 1 | Cognitive | 0.4 | 0.40 | <.0001 | 0.7 | ***0.01*** | ***0.26*** | 3.2 | 0.06 | 0.24 | -0.33 | -0.17 | 0.003 |
| 2 | Emotional | 0.3 | 0.35 | <.0001 | 1.0 | ***0.02*** | ***0.70*** | 7.2 | **0.14** | **0.0095** | -0.51 | -0.25 | <.0001 |
| 3 | Physical | 0.2 | 0.21 | 0.0001 | 2.0 | ***0.07*** | ***0.17*** | 0.6 | 0.02 | 0.69 | -0.44 | -0.41 | <.0001 |
| 4 | Role | 0.1 | 0.16 | .0031 | 3.5 | ***0.07*** | ***0.20*** | 4.1 | 0.08 | 0.15 | -0.76 | -0.37 | <.0001 |
| 5 | Social | 0.2 | 0.22 | <.0001 | 0.6 | ***0.01*** | ***0.84*** | 0.6 | 0.01 | 0.84 | -0.62 | -0.27 | <.0001 |
| 6 | Fatigue | 0.2 | 0.27 | <.0001 | -3.4 | ***-0.07*** | ***0.19*** | **-**3.5 | -0.07 | 0.19 | 0.61 | 0.32 | <.0001 |
| 7 | Dyspnoea | 0.2 | 0.23 | <.0001 | -0.3 | ***-0.01*** | ***0.92*** | -1.3 | -0.03 | 0.62 | 0.77 | 0.39 | <.0001 |
| 8 | Sleep | 0.2 | 0.21 | 0.0002 | -1.3 | ***-0.02*** | ***0.69*** | -11.1 | **-0.18** | **0.0014** | 0.71 | 0.29 | <.0001 |
| b= regression coefficient, β= standardized regression coefficient, P= significance,  #QLQ-C30 scores at baseline (before treatment); ccontinuous variable; $ effect of 4 cycles (=1) vs. 8 cycles eBEACOPP (=0), PET2 positivity with uptake > mediastinum: DS ≥ 3 |

**Supplemental Table 3: HD18, HRQoL in the 2nd year after therapy in PET2-negative patients: effect of 4 vs. 6 cycles eBEACOPP**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | QLQ-C30 score | Baseline score#c | **Effect of cycle reduction$** | **Male sex** | Agec |
| No. |  | b | β | P | b | **β** | **P** | b | β | P | b | β | P |
| 1 | Cognitive | 0.4 | 0.39 | <.0001 | 0.7 | ***0.01*** | ***0.21*** | 5.2 | 0.11 | 0.10 | -0.34 | -0.19 | 0.006 |
| 2 | Emotional | 0.2 | 0.25 | 0.0003 | 0.6 | ***0.01*** | ***0.86*** | *5.8* | *0.12* | *0.076* | -0.32 | -0.18 | 0.0124 |
| 3 | Physical | 0.2 | 0.28 | <.0001 | -0.1 | ***0.00*** | ***0.99*** | 0.1 | 0.00 | 0.95 | -0.39 | -0.38 | <.0001 |
| 4 | Role | 0.2 | 0.26 | 0.0002 | 1.1 | ***0.02*** | ***0.74*** | 0.9 | 0.02 | 0.80 | -0.77 | -0.39 | <.0001 |
| 5 | Social | 0.3 | 0.30 | <.0001 | -1.9 | ***-0.04*** | ***0.57*** | 3.9 | 0.08 | 0.26 | -0.41 | -0.21 | 0.0026 |
| 6 | Fatigue | 0.2 | 0.20 | 0.0044 | -0.6 | ***-0.01*** | ***0.85*** | **-**4.7 | -0.10 | 0.17 | 0.60 | 0.32 | <.0001 |
| 7 | Dyspnoea | 0.1 | 0.15 | 0.0231 | -1.3 | ***-0.03*** | ***0.68*** | 4.2 | 0.09 | 0.21 | 0.59 | 0.31 | <.0001 |
| 8 | Sleep | 0.1 | 0.16 | 0.0215 | -6.5 | ***-0.11*** | ***0.12*** | *-5.2* | *-0.08* | *0.24* | 0.73 | 0.30 | <.0001 |
| b= regression coefficient, β= standardized regression coefficient, P= significance, #QLQ-C30 scores at baseline (before treatment); ccontinuous variable; $ effect of 4 cycles BEACOPPesc (=1) vs. 6 cycles BEACOPPesc (=0), PET2 positivity with uptake > mediastinum: DS ≥ 3 |

**Supplemental Table 4: HD18, HRQoL in the 2nd year after therapy in PET2-positive patients: effect of 8 cycles R-BEACOPPesc**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | QLQ-C30 score | Baseline score#c | **Effect of R-eBEACOPP$** | **Male sex** | Agec |
| No. |  | b | β | P | b | **β** | **P** | b | β | P | b | β | P |
| 1 | Cognitive | 0.4 | 0.40 | <.0001 | -1.1 | ***-0.02*** | ***0.71*** | 2.8 | 0.06 | 0.37 | -0.49 | -0.22 | 0.0008 |
| 2 | Emotional | 0.4 | 0.38 | <.0001 | 0.7 | ***0.01*** | ***0.83*** | *6.0* | *0.12* | *0.0598* | -0.35 | -0.16 | 0.018 |
| 3 | Physical | 0.1 | 0.20 | 0.0035 | -2.3 | ***-0.09*** | ***0.18*** | 1.4 | 0.05 | 0.43 | -0.47 | -0.39 | <.0001 |
| 4 | Role | 0.2 | 0.22 | 0.0012 | -1.0 | ***-0.02*** | ***0.75*** | 3.3 | 0.07 | 0.30 | -0.86 | -0.38 | <.0001 |
| 5 | Social | 0.2 | 0.21 | 0.0030 | 1.5 | ***0.03*** | ***0.66*** | 0.3 | 0.01 | 0.92 | -0.53 | -0.23 | 0.0012 |
| 6 | Fatigue | 0.2 | 0.29 | <.0001 | 2.3 | ***0.05*** | ***0.44*** | **-**1.3 | -0.03 | 0.66 | 0.80 | 0.37 | <.0001 |
| 7 | Dyspnoea | 0.1 | 0.20 | 0.0043 | 2.3 | ***0.05*** | ***0.48*** | -0.9 | -0.02 | 0.78 | 0.73 | 0.33 | <.0001 |
| 8 | Sleep | 0.2 | 0.21 | 0.0021 | -1.6 | ***-0.03*** | ***0.64*** | **-8.3** | **-0.16** | **0.0170** | 0.84 | 0.34 | <.0001 |
| b= regression coefficient, β= standardized regression coefficient, P= significance, , #QLQ-C30 scores at baseline (before treatment); ccontinuous variable $ effect of 8 cycles R-eBEACOPP (=1) vs. 8 cycles eBEACOPP (=0), PET2 positivity with uptake > mediastinum: DS ≥ 3 |

**Supplemental Table 5: Fatigue (EORTC-QLQ-C30) with 4x ABVD (HD14) in early unfavorable stages of HL and 6x eBEACOPP (HD15) in advanced stages of HL from baseline to second year after treatment**

|  |  |  |
| --- | --- | --- |
|  | 4x ABVDEarly-unfavorable stages of HLHD14 trial | 6x eBEACOPPAdvanced stages of HLHD15 trial |
|  | N | Mean | SD | N | Mean | SD |
| Baseline | 539 | 39.00 | 29.97 | 451 | 49.66 | 30.49 |
| Cycle 2-4 of chemotherapy | 520 | 60.31 | 26.70 | 444 | 59.58 | 25.50 |
| End of treatment | 239 | 55.74 | 26.25 | 256 | 59.77 | 26.33 |
| Year 1 | 486 | 31.91 | 24.65 | 420 | 32.00 | 24.93 |
| Year 2 | 439 | 28.08 | 24.49 | 377 | 29.59 | 24.99 |

N= number of patients, SD= standard deviation; Patients with an early-unfavorable stage of HL treated with 4 cycles of ABVD reported very similar fatigue as patients with advanced stages of HL treated with 6 cycles of escalated BEACOPP. Only at baseline, before start of chemotherapy, the patients of the HD14 trial reported significantly less fatigue than the patients of the HD15 trial.

**Supplemental Table 6: Summary of of time to recovery of fatigue (TTR-F) and return to work (TTR-W) results**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Median TTR-F** | **Recovery of fatigue after 24 months** | **Median TTR-W** | **Return to work after 24 months** |
|  | months (CI95) | % (CI95) | months (CI95) | % (CI95) |
| **PET2-positive patients** |  |  |  |  |
| Arm A: 8x eBEACOPP | 9.9 (8.7-12.9) | 74.7 (66.4-83.0) | 10.6 (9.5-13.9) | 74.5 (65.6-83.5) |
| Arm B: 8x R-eBEACOPP | 12.1 (10.0-15.5) | 69.6 (61.5-77.7) | 12.3 (10.3-15.5) | 72.3(63.2-81.4) |
| **PET2-negative patients** |  |  |  |  |
| Arm D4: 4x eBEACOPP post-amend. | 9.9 (7.9-13.3) | 62.9 (55.9-69.9) | 15.0 (9.2.19.6) | 61.4 (51.8-71.1) |
| Arm D: 4x eBEACOPP pre-amend. | 11.8 (7.8-15.4) | 71.3 (63.5-79.0) | 13.7 (11.5-17.8) | 57.1 (48.4-65.7) |
| Arm C6: 6x eBEACOPP | 12.9 (9.7-19.7) | 64.2 (55.3-73.1) | 15.2 (12.5-21.8) | 57.3 (46.4-68.3) |
| Arm C: 8x eBEACOPP | 19.1 (13.3-28.3) | 53.9 (46.3-61.4) | 18.1 (13.2-24.6) | 47.6 (38.8-56.4) |