Supplemental material: The relative effectiveness of eribulin versus different chemotherapy for advanced breast cancer treatment using treatment line matching: a study of the Southeast Netherlands Advanced Breast Cancer (SONABRE) Registry

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## Overlap in patient characteristics before matching

In the following two figures, one can observe how baseline characteristics of the eribulin and unmatched non-eribulin (patient level and treatment lines separately) overlap before matching has been performed. For matching to be successful, baseline characteristics have to overlap, otherwise matching will not resolve the disbalance in baseline characteristics. In Figures 1 and 2, one can see that baseline characteristics overlap between eribulin en both non-eribulin groups, hence, matching is a suitable method to adjust the comparison of eribulin versus non-eribulin.

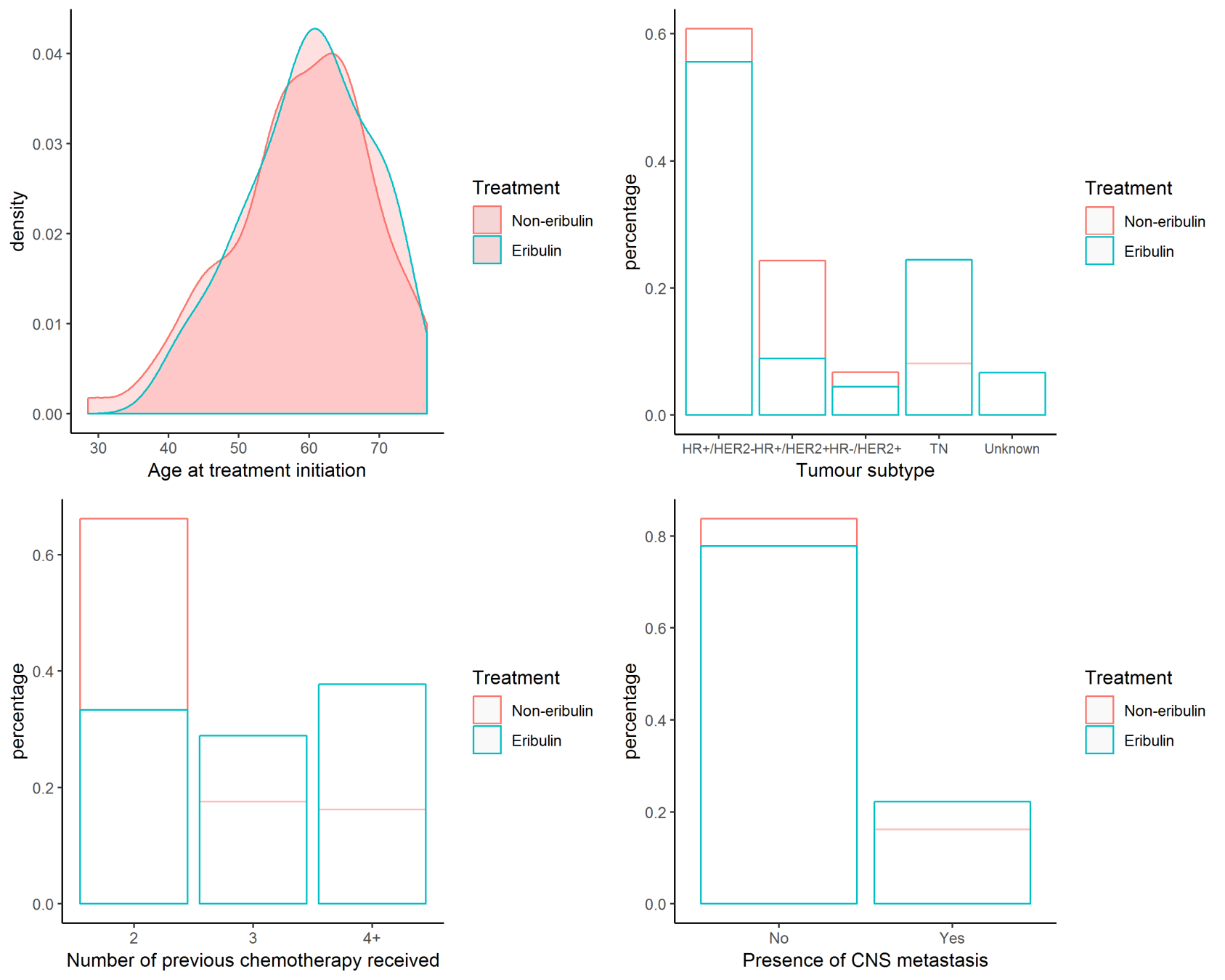


Figure 1: Overlap in baseline characteristics between the eribulin group and the unmatched non-eribulin group (patient level)

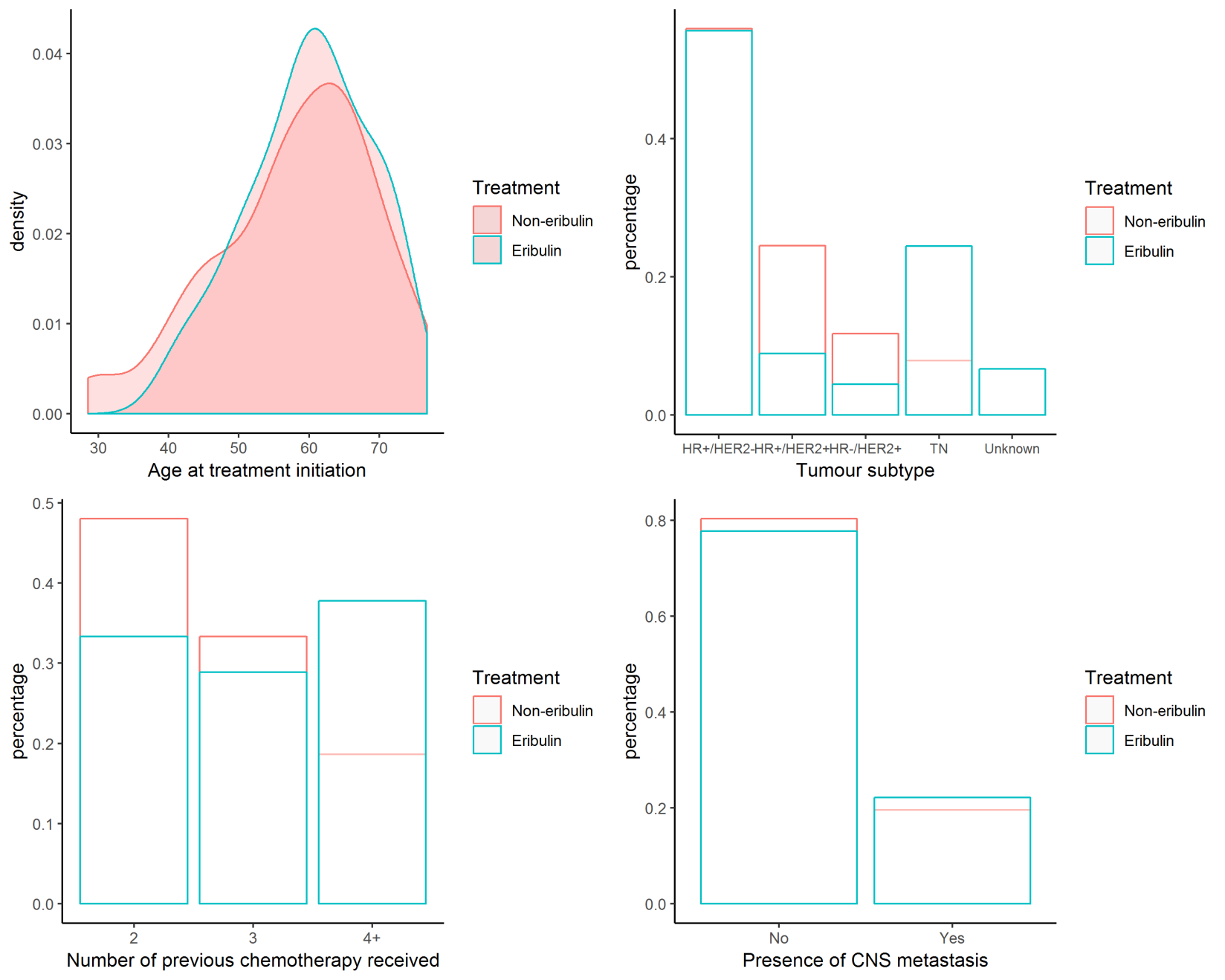


Figure 2: Overlap in baseline characteristics between the eribulin group and the unmatched non-eribulin treatment lines

## Covariate balance comparison between the different non-eribulin groups

Covariates balance was improved for tumour subtype, and the number of previous chemotherapy received, but not for the age at treatment initiation and the proportion of patients having CNS metastasis in the treatment line matched non-eribulin group compared to patient level matched non-eribulin group. The variance ratio of all covariates covariates (except for the presence of CNS metastasis) was the most similar between the eribulin group and the treatment line matched non-eribulin group compared to the other non-eribulin groups.  
Compared to the unmatched non-eribulin group, both the treatment line matched and the patient level matched non-eribulin groups had better covariate balance overall, expect for the age at treatment initiation.  
The variance ratio should be as close as possible to 1 while the bootstrapped Kolmorogov Smirnov p-value should be maximized.

Table 1: Balance statistics for each non eribulin group

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variable names** | **Variance ratio unmatched non-eribulin** | **Variance ratio after treatment line matching** | **Variance ratio after patient level matching** | **Bootstrapped Kolmorogov Smirnov p-value unmatched non-eribulin** | **Bootstrapped Kolmorogov Smirnov p-value after treatment line matching** | **Bootstrapped Kolmorogov Smirnov p value after patient level matching** |
| Tumor subtype (continuous) | 2.906 | 1.694 | 2.043 | 0.011 | 0.835 | 0.505 |
| Number of previous chemotherapy (continuous) | 1.238 | 0.939 | 1.171 | 0.044 | 0.92 | 0.172 |
| Age at treatment initiation | 0.597 | 0.837 | 0.543 | 0.617 | 0.22 | 0.297 |
| Presence of CNS metastasis | 1.11 | 1.316 | 1.316 | NA | NA | NA |
| Abbreviations: CNS, central nervous system; NA, not applicable | | | | | | |

### QQ plots patient characteristics before and after matching

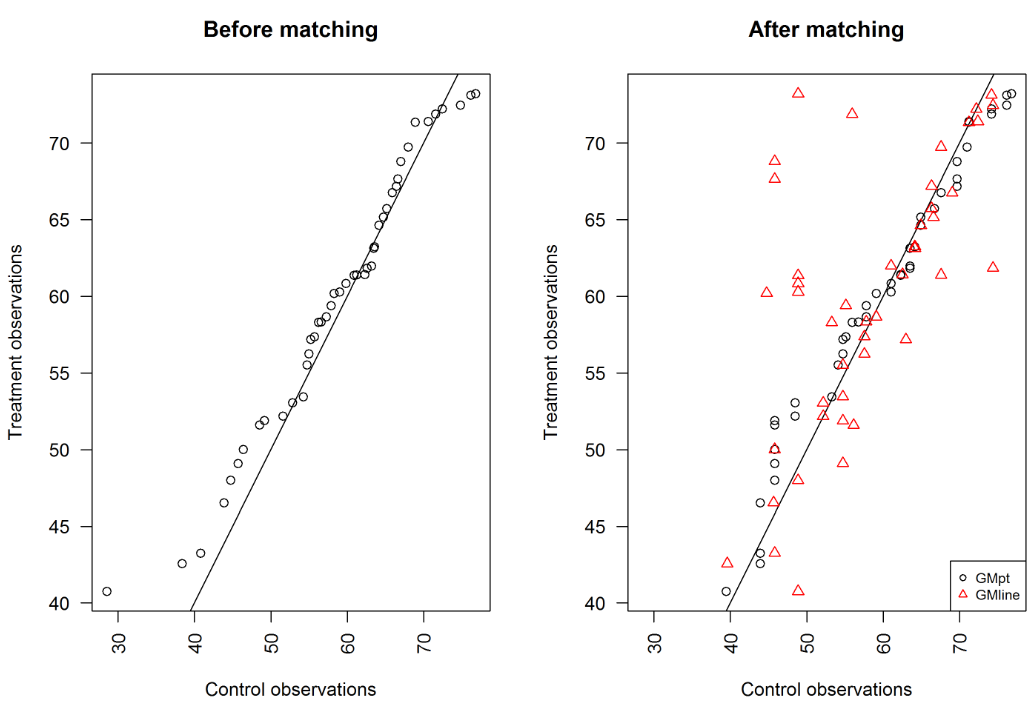


Figure 3: QQplot of the age at treatment initiation of eribulin (treatment observation) versus non-eribulin (control observations).  
Abbreviations: GMline, treatment line matched non-eribulin group; GMpt, patient level matched non-eribulin group; QQ, quantile-quantile

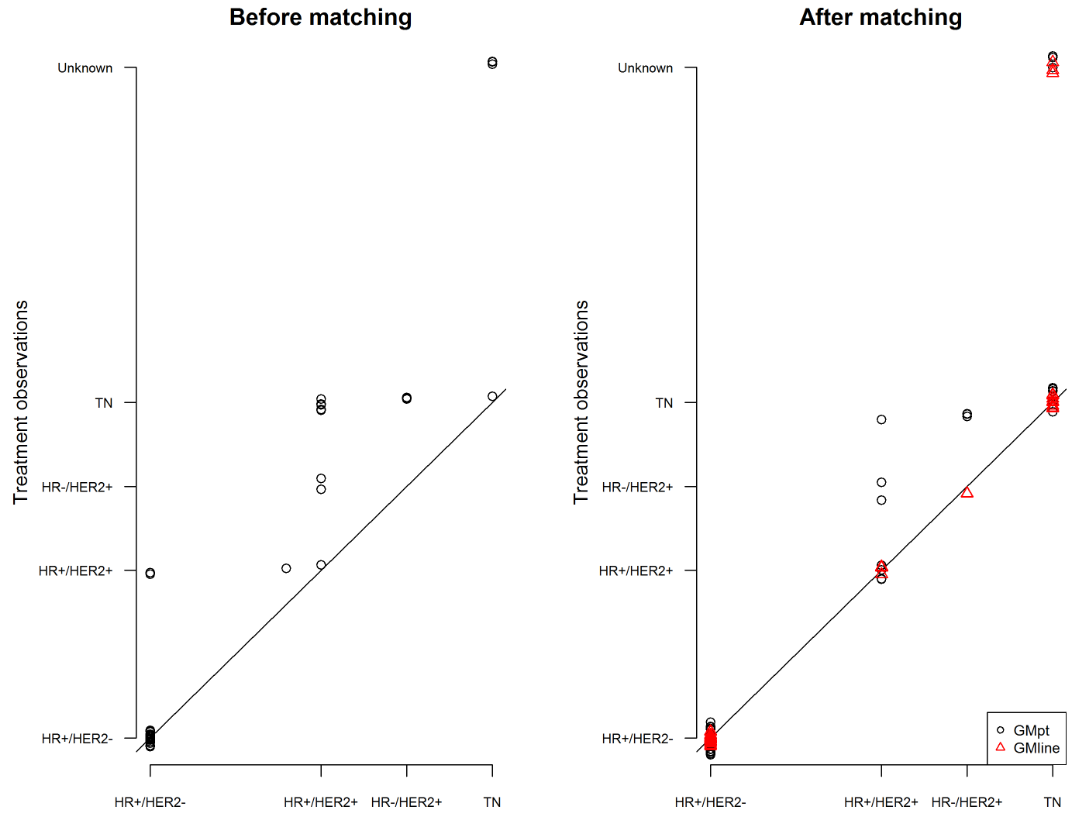


Figure 4: QQplot of the tumour subtype of eribulin (treatment observation) versus non-eribulin (control observations)  
Abbreviation: HR, hormonal status; HER2, human epidermal growth factor receptor 2; GMline, treatment line matched non-eribulin group; GMpt, patient level matched non-eribulin group; TN, triple negative; QQ, quantile-quantile

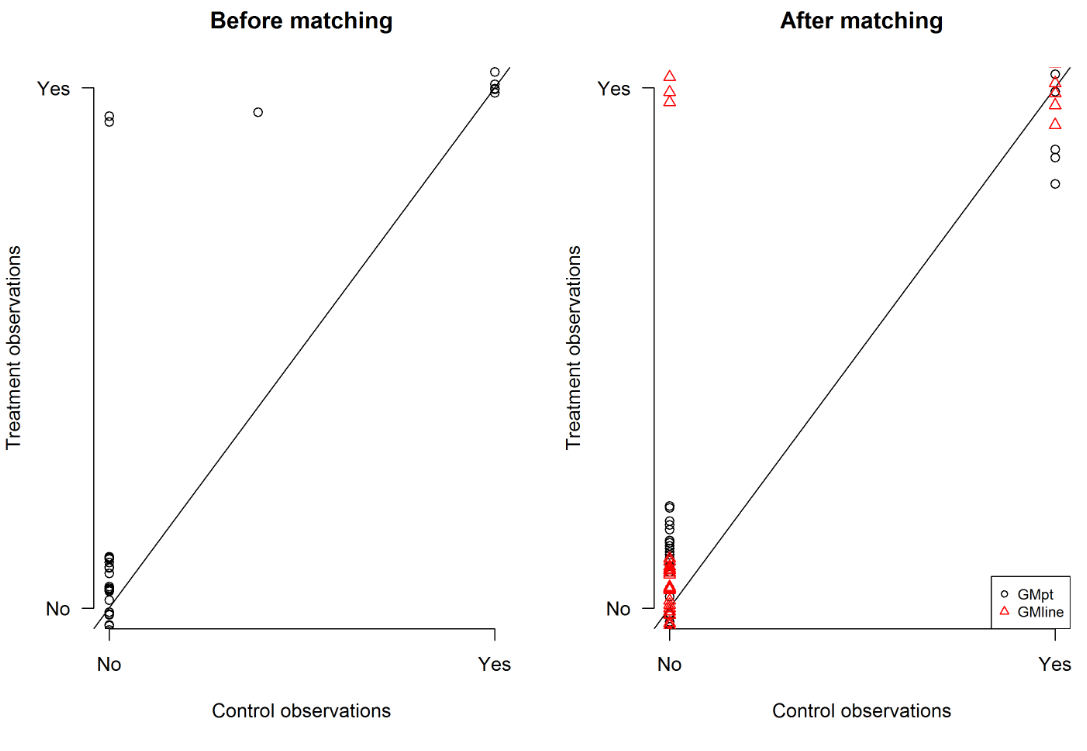


Figure 5: QQplot of the presence of CNS metastasis in the eribulin (treatment observation) versus non-eribulin (control observations) group.  
Abbreviation: CNS, central nervous metastasis; GMline, treatment line matched non-eribulin group; GMpt, patient level matched non-eribulin group; QQ, quantile-quantile

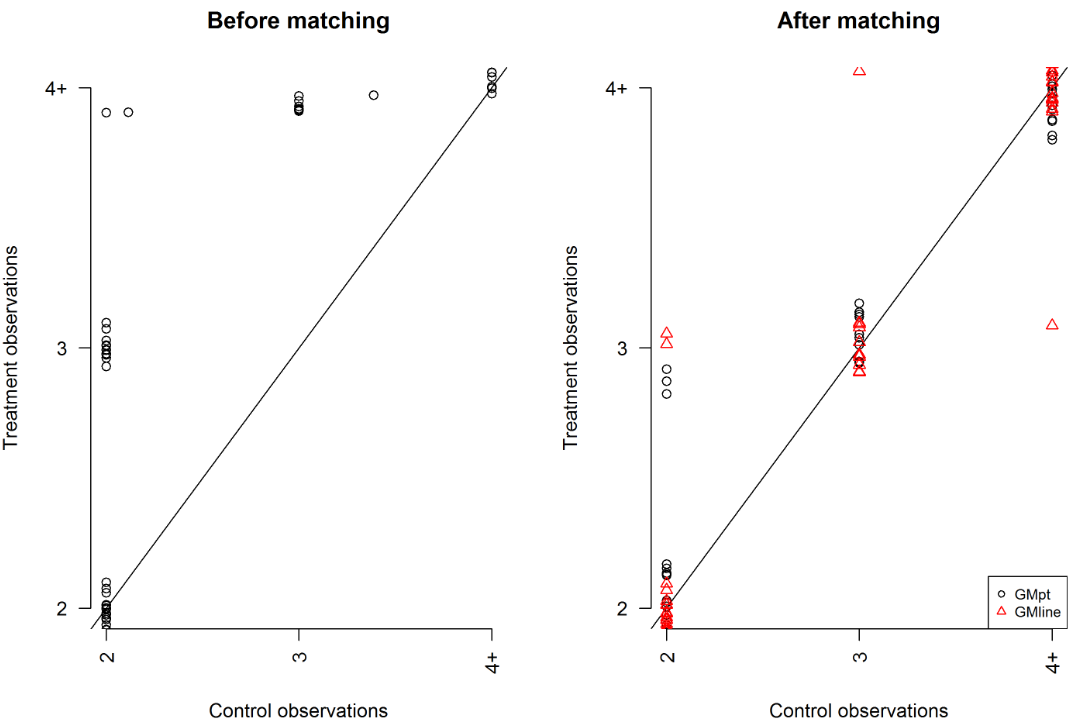


Figure 6: QQplot of the number of previous chemotherapy received in the eribulin (treatment observation) versus non-eribulin (control observations) group.  
Abbreviation: GMline, treatment line matched non-eribulin group; GMpt, patient level matched non-eribulin group; QQ, quantile-quantile

## Results of the sensitivity analysis: eribulin versus patient-level matched non-eribulin

Table 2: Patient characteristics in each group

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Treatment group** | | **Eribulin (N)** | **%** | **Patient level matched non-eribulin** | **%** |
| Number of patient | | 45 |  | 45 |  |
| Median age | | 61 |  | 61 |  |
| Minimum age | | 41 |  | 39 |  |
| Maximum age | | 73 |  | 77 |  |
| Tumour status | HR+/HER2- | 25 | 56 % | 25 | 56 % |
| HR+/HER2+ | 4 | 9 % | 7 | 16 % |
| HR-/HER2+ | 2 | 4 % | 3 | 7 % |
| Triple Negative | 11 | 24 % | 10 | 22 % |
| Unknown | 3 | 7 % | 0 | 0 |
| Dominant metastatic site | CNS | 10 | 22 % | 10 | 22 % |
| Visceral | 31 | 69 % | 29 | 64 % |
| Non-visceral | 4 | 9 % | 6 | 13 % |
| Bone only\* | 2 | 4 % | 6 | 13 % |
| Unknown | 0 | 0 % | 0 | 0 % |
| Number of metastatic sites | 1 | 2 | 4 % | 3 | 7 % |
| 2 | 12 | 27 % | 10 | 22 % |
| 3 | 15 | 33 % | 9 | 20 % |
| 4 | 8 | 18 % | 12 | 27 % |
| 5+ | 8 | 17 % | 11 | 25 % |
| Number of previous endocrine therapy in the ABC setting | 0 | 16 | 36 % | 16 | 36 % |
| 1 | 7 | 16 % | 6 | 13 % |
| 2 | 7 | 16 % | 9 | 20 % |
| 3 | 5 | 11 % | 7 | 16 % |
| 4+ | 10 | 22 % | 7 | 15 % |
| Number of previous chemotherapy in the ABC setting | 2 | 15 | 33 % | 18 | 40 % |
| 3 | 13 | 29 % | 10 | 22 % |
| 4+ | 17 | 37 % | 17 | 38 % |
| \* Subgroup of non-visceral metastasis  Abbreviations: ABC, advanced breast cancer; GM, genetic matched; HER2, human epidermal growth factor 2 receptor; HR, hormonal status | | | | | |

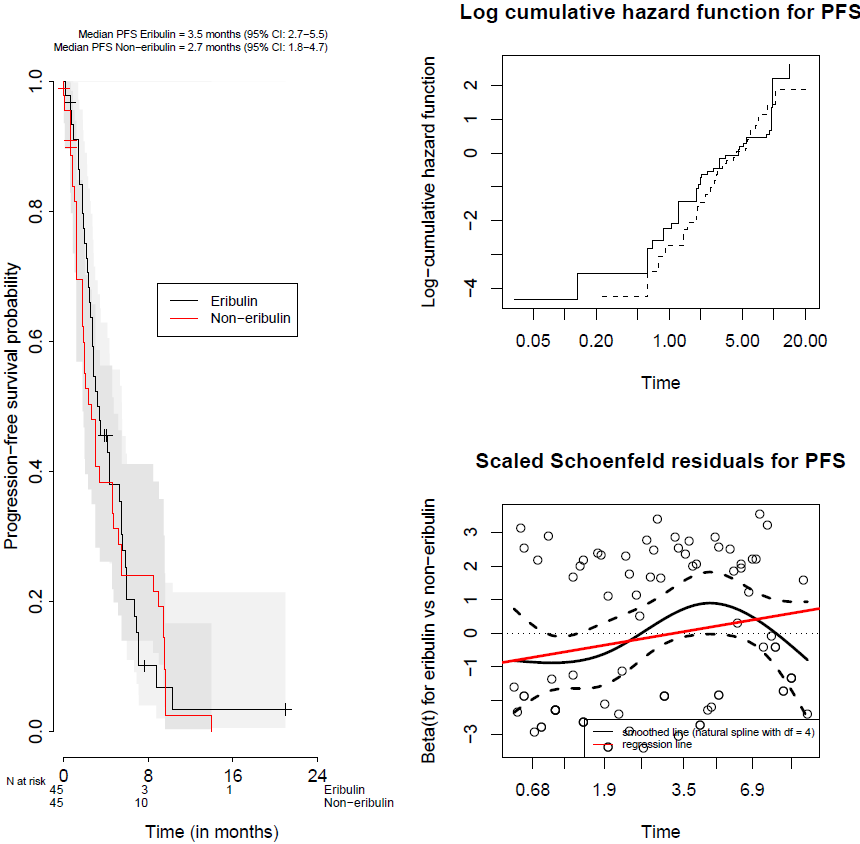


Figure 9: KM curves, log cumulative hazard plots and Scaled Schoenfeld residual plots of PFS for eribulin and the patient level matched non-eribulin group,

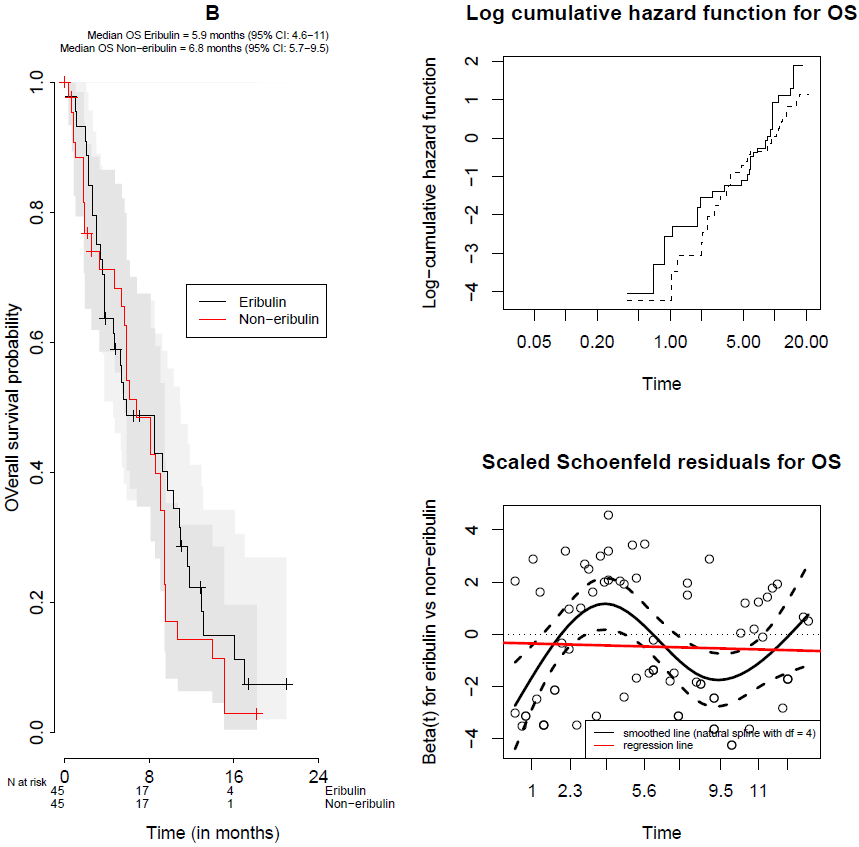


Figure 10: KM curves, log cumulative hazard plots, and Scaled Schoenfeld residual plots of OS for eribulin and the patient level matched non-eribulin group,

## Results of the sensitivity analysis: eribulin versus unmatched non-eribulin

Table 3: Patient characteristics in each group

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Treatment group** | | **Eribulin (N)** | **%** | **Unmatched non-eribulin** | **%** |
| Number of patient | | 45 |  | 74 |  |
| Median age | | 61 |  | 60 |  |
| Minimum age | | 41 |  | 29 |  |
| Maximum age | | 73 |  | 77 |  |
| Tumour status | HR+/HER2- | 25 | 56 % | 45 | 61 % |
| HR+/HER2+ | 4 | 9 % | 18 | 24 % |
| HR-/HER2+ | 2 | 4 % | 5 | 7 % |
| Triple Negative | 11 | 24 % | 6 | 8 % |
| Unknown | 3 | 7 % | 0 | 0 |
| Dominant metastatic site | CNS | 10 | 22 % | 12 | 16 % |
| Visceral | 31 | 69 % | 52 | 70 % |
| Non-visceral | 4 | 9 % | 10 | 14 % |
| Bone only\* | 2 | 4 % | 9 | 12 % |
| Unknown | 0 | 0 % | 0 | 0 % |
| Number of metastatic sites | 1 | 2 | 4 % | 12 | 16 % |
| 2 | 12 | 27 % | 17 | 23 % |
| 3 | 15 | 33 % | 18 | 24 % |
| 4 | 8 | 18 % | 14 | 19 % |
| 5+ | 8 | 17 % | 13 | 17 % |
| Number of previous endocrine therapy in the ABC setting | 0 | 16 | 36 % | 20 | 27 % |
| 1 | 7 | 16 % | 13 | 18 % |
| 2 | 7 | 16 % | 13 | 18 % |
| 3 | 5 | 11 % | 16 | 22 % |
| 4+ | 10 | 22 % | 12 | 16 % |
| Number of previous chemotherapy in the ABC setting | 2 | 15 | 33 % | 49 | 66 % |
| 3 | 13 | 29 % | 13 | 18 % |
| 4+ | 17 | 37 % | 12 | 16 % |
| \* Subgroup of non-visceral metastasis  Abbreviations: ABC, advanced breast cancer; GM, genetic matched; HER2, human epidermal growth factor 2 receptor; HR, hormonal status | | | | | |

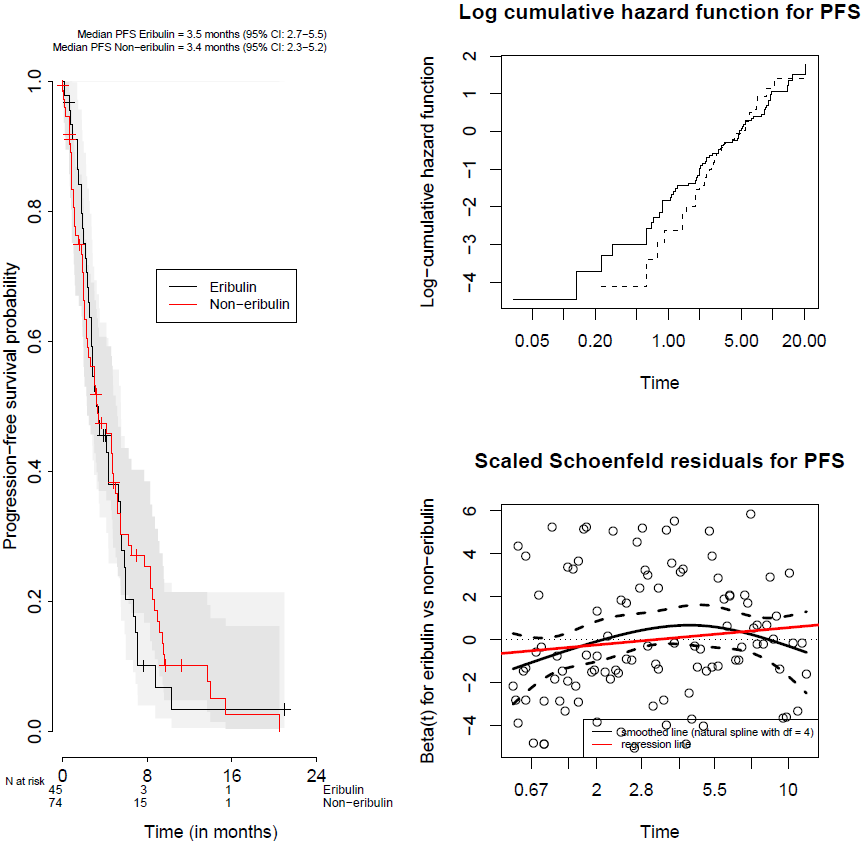


Figure 11: KM curves, log cumulative hazard plots and Scaled Schoenfeld residual plots of PFS for eribulin and the unmatched non-eribulin group,

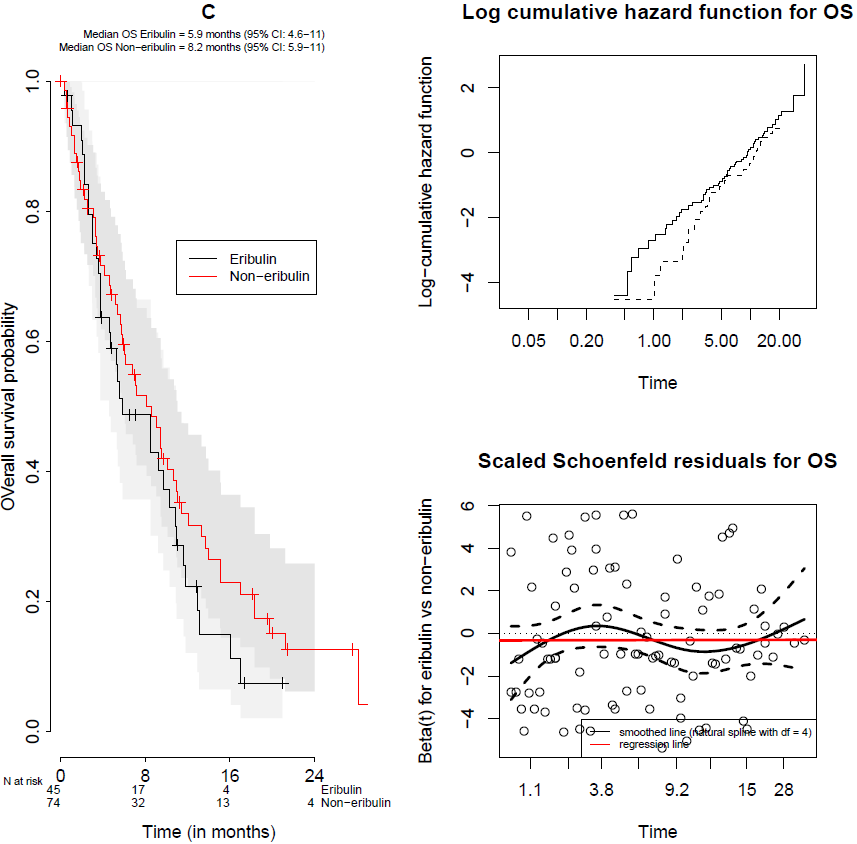


Figure 12: KM curves, log cumulative hazard plots and Scaled Schoenfeld residual plots of PFS for eribulin and the unmatched non-eribulin group,

## Multivariate Cox proportional hazard models (sensitivity analyses)

Table 4: Results of the Cox proportional hazard models performed during the sensitivity analyses

|  |  |  | **PFS** | | | **OS** | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Comparison** | **Covariates** | | **Coefficient (SE)** | **Hazard ratio** | **Significance** | **Coefficient (SE)** | **Hazard ratio** | **Significance** |
| **(95% CI)** | **(95% CI)** |
| **Patient level matched non-eribulin** | Treatment | Non-eribulin | Reference | 1 | - | - | 1 | - |
| Eribulin | -0.096 (0.24) | 0.909 (0.568-1.454) | 0.69 | -0.478 (0.265) | 0.62 (0.369-1.042) | 0.071 |
| Tumour status | HR+/HER2- | Reference | 1 | - | - | 1 | - |
| HR+/HER2+ | -0.983 (0.47) | 0.374 (0.149-0.94) | 0.037 | -1.017 (0.415) | 0.362 (0.16-0.816) | 0.014 |
| HR-/HER2+ | -0.925 (0.595) | 0.397 (0.123-1.274) | 0.12 | -0.887 (0.618) | 0.412 (0.123-1.384) | 0.151 |
| Triple Negative tumour | 0.071 (0.325) | 1.073 (0.568-2.028) | 0.827 | 0.157 (0.346) | 1.169 (0.593-2.306) | 0.651 |
| Tumour subtype unknown | -1.321 (0.748) | 0.267 (0.062-1.157) | 0.078 | -0.331 (0.742) | 0.718 (0.168-3.075) | 0.655 |
| Age at treatment start | | 0 (0.014) | 1 (0.972-1.028) | 0.973 | 0.016 (0.015) | 1.016 (0.986-1.047) | 0.3 |
| Number of previous chemotherapy | 2 previous chemotherapy received | Reference | 1 | - | - | 1 | - |
| 3 previous chemotherapy received | -0.126 (0.302) | 0.882 (0.488-1.594) | 0.678 | 0.528 (0.328) | 1.696 (0.892-3.223) | 0.107 |
| 4+ previous chemotherapy received | -0.726 (0.336) | 0.484 (0.25-0.935) | 0.031 | 0.13 (0.345) | 1.139 (0.579-2.241) | 0.707 |
| Presence of CNS metastasis | No CNS metastasis | Reference | 1 | - | - | 1 | - |
| CNS metastasis | 1.823 (0.36) | 6.191 (3.058-12.534) | <0.01 | 1.532 (0.396) | 4.626 (2.13-10.051) | <0.01 |
| **Unmatched non-eribulin** | Treatment | Non-eribulin | Reference | 1 | - | - | 1 | - |
| Eribulin | -0.012 (0.253) | 0.989 (0.602-1.622) | 0.964 | -0.312 (0.268) | 0.732 (0.433-1.236) | 0.243 |
| Tumour status | HR+/HER2- | Reference | 1 | - | - | 1 | - |
| HR+/HER2+ | -0.378 (0.271) | 0.685 (0.403-1.165) | 0.163 | -0.542 (0.286) | 0.582 (0.332-1.019) | 0.058 |
| HR-/HER2+ | -1.34 (0.492) | 0.262 (0.1-0.687) | 0.006 | -1.789 (0.558) | 0.167 (0.056-0.499) | 0.001 |
| Triple Negative tumour | 0.176 (0.314) | 1.192 (0.644-2.206) | 0.576 | 0.611 (0.33) | 1.842 (0.966-3.514) | 0.064 |
| Tumour subtype unknown | -0.786 (0.696) | 0.456 (0.116-1.785) | 0.259 | 0.083 (0.693) | 1.087 (0.28-4.227) | 0.904 |
| Age at treatment start | | -0.01 (0.012) | 0.99 (0.968-1.013) | 0.387 | -0.007 (0.012) | 0.993 (0.969-1.017) | 0.559 |
| Number of previous chemotherapy | 2 previous chemotherapy received | Reference | 1 | - | - | 1 | - |
| 3 previous chemotherapy received | 0.456 (0.274) | 1.579 (0.922-2.703) | 0.096 | 1.004 (0.296) | 2.73 (1.527-4.882) | 0.001 |
| 4+ previous chemotherapy received | -0.107 (0.28) | 0.898 (0.518-1.556) | 0.702 | 0.661 (0.303) | 1.936 (1.068-3.509) | 0.029 |
| Presence of CNS metastasis | No CNS metastasis | Reference | 1 | - | - | 1 | - |
| CNS metastasis | 1.181 (0.31) | 3.256 (1.772-5.985) | <0.01 | 1.084 (0.293) | 2.955 (1.664-5.25) | <0.01 |
| Abbreviations: CI, confidence interval; CNS, central nervous system; HER2, human epidermal growth factor 2 receptor; HR, hormonal status; SE, standard error | | | | | | | | |

## Univariate Cox proportional hazard models

Table 5: Cox proportional hazard model results PFS - eribulin versus treatment line matched non-eribulin

|  |  |  |  |
| --- | --- | --- | --- |
| **Covariate** | **Coefficient (SE)** | **Hazard ratio (95% CI)** | **Significance** |
| Eribulin | 0.07 (0.232) | 1.073 (0.681-1.692) | 0.762 |
| Abbreviations: CI, confidence interval; SE, standard error | | | |

Table 6: Cox proportional hazard model results OS - eribulin versus treatment line matched non-eribulin

|  |  |  |  |
| --- | --- | --- | --- |
| **Covariate** | **Coefficient (SE)** | **Hazard ratio (95% CI)** | **Significance** |
| Eribulin | -0.28 (0.254) | 0.755 (0.459-1.243) | 0.27 |
| Abbreviations: CI, confidence interval; SE, standard error | | | |

Table 7: Cox proportional hazard model results PFS - eribulin versus patient level matched non-eribulin

|  |  |  |  |
| --- | --- | --- | --- |
| **Covariate** | **Coefficient (SE)** | **Hazard ratio (95% CI)** | **Significance** |
| Eribulin | -0.096 (0.225) | 0.908 (0.584-1.413) | 0.67 |
| Abbreviations: CI, confidence interval; SE, standard error | | | |

Table 8: Cox proportional hazard model results OS - eribulin versus patient level matched non-eribulin

|  |  |  |  |
| --- | --- | --- | --- |
| **Covariate** | **Coefficient (SE)** | **Hazard ratio (95% CI)** | **Significance** |
| Eribulin | -0.251 (0.24) | 0.778 (0.486-1.245) | 0.295 |
| Abbreviations: CI, confidence interval; SE, standard error | | | |

Table 9: Cox proportional hazard model results PFS - eribulin versus unmatched non-eribulin

|  |  |  |  |
| --- | --- | --- | --- |
| **Covariate** | **Coefficient (SE)** | **Hazard ratio (95% CI)** | **Significance** |
| Eribulin | 0.092 (0.204) | 1.097 (0.735-1.636) | 0.651 |
| Abbreviations: CI, confidence interval; SE, standard error | | | |

Table 10: Cox proportional hazard model results OS - eribulin versus unmatched non-eribulin

|  |  |  |  |
| --- | --- | --- | --- |
| **Covariate** | **Coefficient (SE)** | **Hazard ratio (95% CI)** | **Significance** |
| Eribulin | 0.259 (0.22) | 1.295 (0.842-1.993) | 0.239 |
| Abbreviations: CI, confidence interval; SE, standard error | | | |