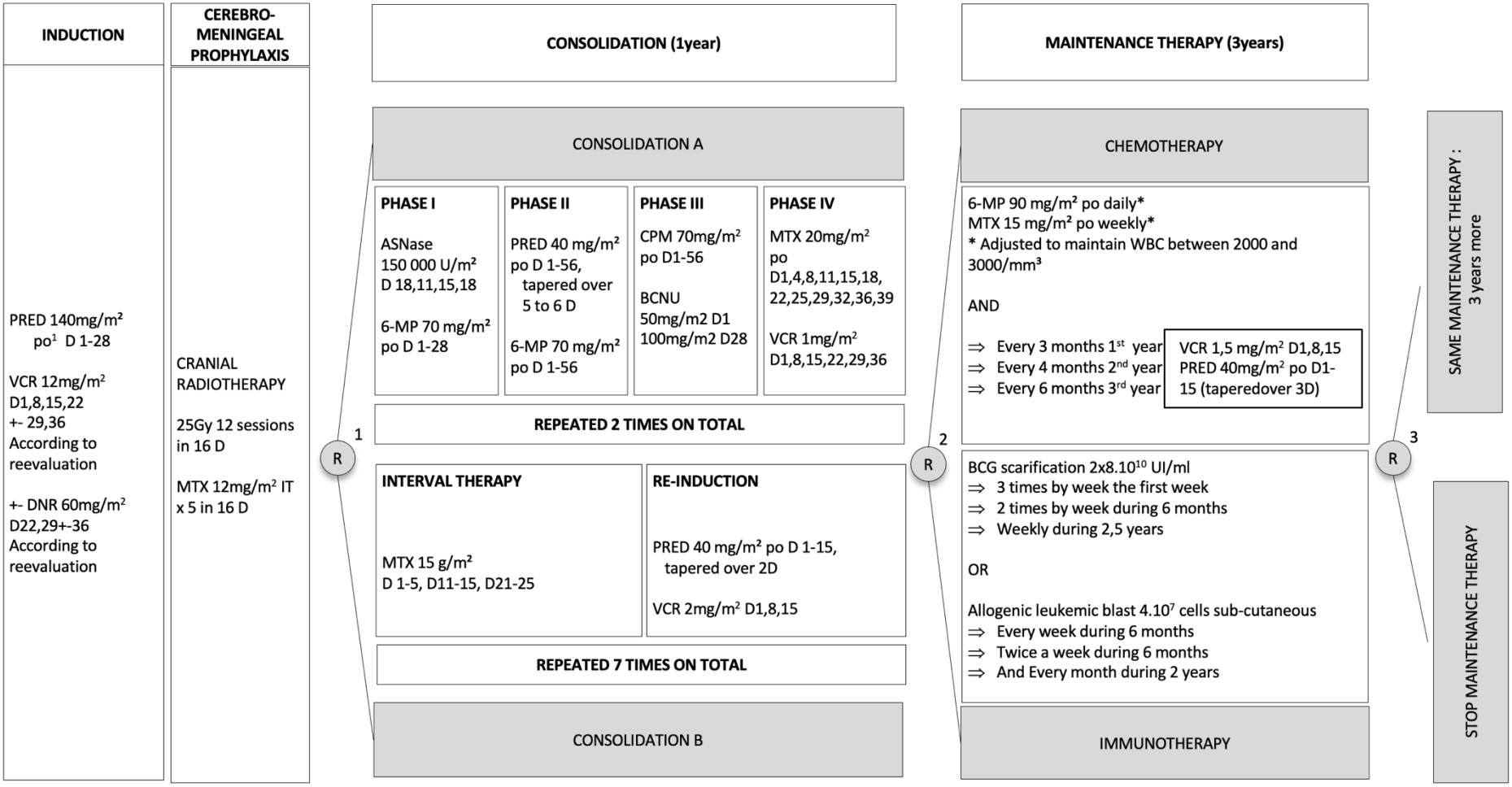
**Figure S1:** Treatment protocols in detail

**EORTC study 58741**

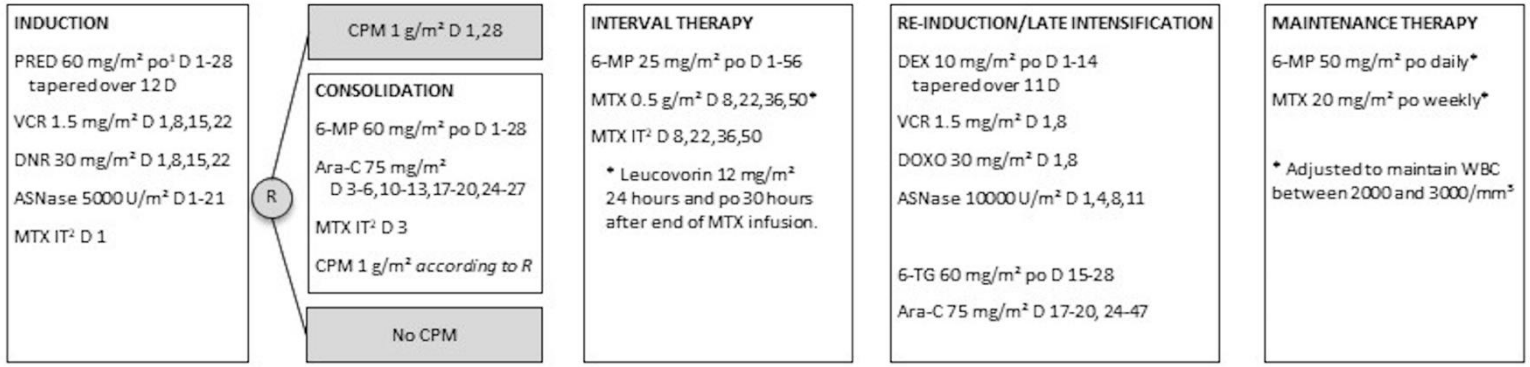



**Notes:**

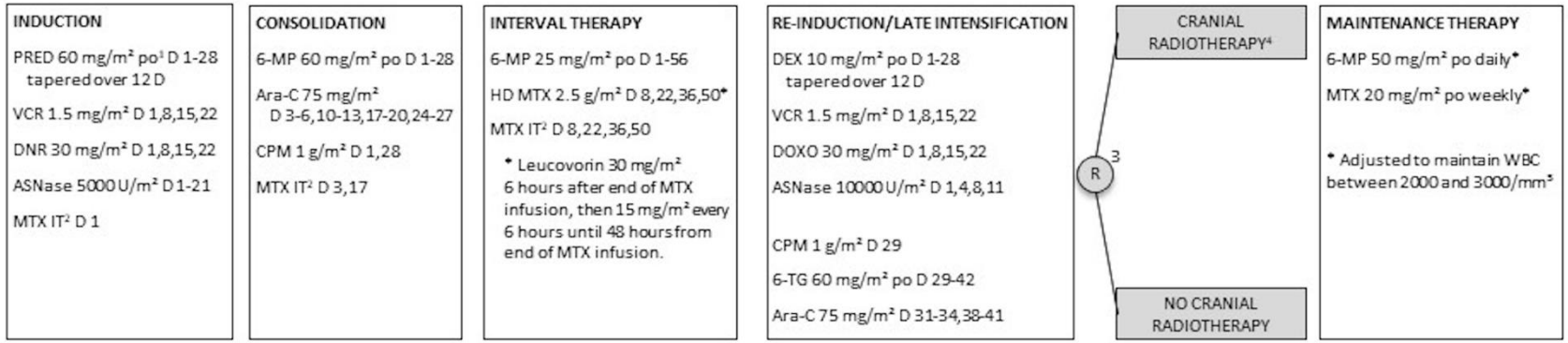
[1] per oral (when not specified, administration is intravenous)

**Abbreviations:** ASNase: asparaginase, BCNU : Carmustine, CPM: cyclophosphamide, DNR: daunorubicin, 6-MP: 6-mercaptopurine, MTX: methotrexate, PRED: prednisone, R: randomization, VCR: vincristine

**EORTC study 58831**: standard risk patients (RF<1.2) in CR at the end of induction




**EORTC study 58832**: medium risk patients (RF 1.2-1.69), high risk patients (RF≥1.7), and standard risk patients (RF<1.2) not in CR at the end of induction




**Notes:**

[1] Per oral (when not specified, administration is intravenous)

[2] Intrathecal at the dose of 6 mg < 1 year, 8 mg 1-< 2 year, 10 mg 2-<3 year, 12 mg ≥ 3 year

[3] Patients in complete remission at the end of consolidation and still in complete remission after the end of late intensification

[4] Dose according to age : 16 Gy (if age < 1 year), 20 Gy (if age 1-< 2 years) or 24 Gy (if age ≥ 2 years)

**Abbreviations:** Ara-C: cytarabine, ASNase: asparaginase, CPM: cyclophosphamide, CR: complete remission, D: day, DEX: dexamethasone, DNR: daunorubicin, DOXO: doxorubicin, HD: high-dose, IT: intrathecal, 6-MP: 6-mercaptopurine, MTX: methotrexate, PRED: prednisone, R: randomization, 6-TG: 6-thioguanine, VCR: vincristine, WBC: white blood cells

**Table S1:** Summary of predictors of interest, QoL outcome subscales and covariates used for the adjusted models.

| Predictors of QoL of interest | QoL outcome | Covariates for adjusted model |
|---|---|---|
| Gender | • SF-12: Mental and Physical component summary<br>• IOC-CS: Life challenges, Personal growth, Socializing and Body and health | Protocol, Age at follow-up |
| Age at diagnosis | • SF-12: Mental component summary<br>• IOC-CS: Life challenges, Personal growth, Socializing and Body and health | Protocol, Age at follow-up, Gender |
| Relapse/SN | • SF-12: Mental and Physical component summary<br>• IOC-CS: Life challenges, Personal growth, Socializing and Body and health | Protocol, Age at follow-up, Gender |
| NCI risk group | • SF-12: Mental and Physical component summary | Protocol, Age at follow-up, Gender |
| CRT and its interaction with age at diagnosis | • SF-12: Physical component summary<br>• IOC-CS : Thinking/memory problems | Age at diagnosis, Age at follow-up, Gender |

Abbreviations: CRT: Cranial Radiotherapy, IOC-CS: Impact of Cancer-Childhood Survivors, NCI: National Cancer Institute, QoL: quality of life, SF-12: Short-Form Health Survey, SN: second neoplasm

**Table S2:** Descriptive summary of the SF-12 and IOC-CS scales used

| | **Total (N=186)** |
|---|---|
| ***SF-12*** | |
| Mental component summary | |
| Median | 49.5 |
| Range | 18.4 - 62.5 |
| Mean (SD) | 47.25 (9.97) |
| N | 171 |
| Physical component summary | |
| Median | 57.1 |
| Range | 24.7 - 67.0 |
| Mean (SD) | 54.52 (7.87) |
| N | 170 |
| ***IOC-CS*** | |
| Life challenges (-) | |
| Median | 1.9 |
| Range | 1.0 - 4.6 |
| Mean (SD) | 1.95 (0.70) |
| N | 141 |
| Personal growth (+) | |
| Median | 3.1 |
| Range | 1.0 - 5.0 |
| Mean (SD) | 3.02 (1.08) |
| N | 138 |
| Socializing (+) | |
| Median | 4.7 |
| Range | 1.0 - 5.0 |
| Mean (SD) | 4.23 (0.80) |
| N | 139 |
| Thinking and memory problems (-) | |
| Median | 2.0 |
| Range | 1.0 - 4.4 |
| Mean (SD) | 2.24 (0.83) |
| N | 141 |
| Body and health (+) | |
| Median | 3.6 |
| Range | 1.4 - 5.0 |
| Mean (SD) | 3.53 (0.75) |
| N | 140 |

Abbreviations: IOC-CS: Impact of Cancer-Childhood Survivors, SF-12: Short-Form Health Survey.
Note. (+) is indicated for positive impact scales of the IOC-CS, (-) is indicated for negative impact scales of the IOC-CS. For positive impact scales, a higher mean score indicates a larger positive impact, while for the negative impact scales, a higher mean score indicates a larger negative impact.

**e S3:** Distribution of predictors of interest by covariates used for the adjusted models

| | Age at diagnosis, years | | Sex | | Relapse or Second cancer | | NCI risk group | | Cranial radiotherap | |
|---|---|---|---|---|---|---|---|---|---|---|
| | <6 (N=115) N (%) | >=6 (N=71) N (%) | Male (N=77) N (%) | Female (N=109) N (%) | No (N=151) N (%) | Yes (N=35) N (%) | Standard Risk (N=131) N (%) | High Risk (N=55) N (%) | No (N=157) N (%) | Yes (N=29) N (%) |
| **Male** | 45 (39.1) | 32 (45.1) | | | 64 (42.4) | 13 (37.1) | 55 (42.0) | 22 (40.0) | 66 (42.0) | 11 (37.9 |
| **Female** | 70 (60.9) | 39 (54.9) | | | 87 (57.6) | 22 (62.9) | 76 (58.0) | 33 (60.0) | 91 (58.0) | 18 (62.1 |
| **t diagnosis, years** | | | | | | | | | | |
| **<6** | | | 45 (58.4) | 70 (64.2) | 97 (64.2) | 18 (51.4) | 91 (69.5) | 24 (43.6) | 99 (63.1) | 16 (55.2 |
| **>=6** | | | 32 (41.6) | 39 (35.8) | 54 (35.8) | 17 (48.6) | 40 (30.5) | 31 (56.4) | 58 (36.9) | 13 (44.8 |
| **t follow-up, years** | | | | | | | | | | |
| **<18-24** | 72 (62.6) | 13 (18.3) | 37 (48.1) | 48 (44.0) | 75 (49.7) | 10 (28.6) | 67 (51.1) | 18 (32.7) | 82 (52.2) | 3 (10.3 |
| **>=25** | 43 (37.4) | 58 (81.7) | 40 (51.9) | 61 (56.0) | 76 (50.3) | 25 (71.4) | 64 (48.9) | 37 (67.3) | 75 (47.8) | 26 (89.7 |
| **col** | | | | | | | | | | |
| **58741** | 9 (7.8) | 8 (11.3) | 7 (9.1) | 10 (9.2) | 12 (7.9) | 5 (14.3) | 11 (8.4) | 6 (10.9) | 0 (0.0) | 17 (58.6 |
| **58831** | 26 (22.6) | 17 (23.9) | 15 (19.5) | 28 (25.7) | 30 (19.9) | 13 (37.1) | 30 (22.9) | 13 (23.6) | 35 (22.3) | 8 (27.6 |
| **58881** | 80 (69.6) | 46 (64.8) | 55 (71.4) | 71 (65.1) | 109 (72.2) | 17 (48.6) | 90 (68.7) | 36 (65.5) | 122 (77.7) | 4 (13.8 |

**Table S4:** Univariate associations between gender and SF-12 subscales and IOC-CS subscales based on a univariate analysis

| | ***SF-12*** | | | | ***IOC-CS*** | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | ***Mental component summary*** | | ***Physical component summary*** | | ***Positive impact subscale*** | | | | |
| | | | | | ***Body and health (+)*** | | ***Personal growth (+)*** | | |
| *Parameter* | Estimate (SE) | P-value | Estimate (SE) | P-value | *Estimate (SE)* | *P-value* | *Estimate (SE)* | *P-value* | *Esti (S* |
| Intercept | 48.34 (1.20) | <.001 | 55.73 (0.94) | <.0.001 | 3.70 (0.10) | <.0001 | 2.92 (0.15) | <.0001 | 4.22 |
| Gender (ref: Male) | -1.83 (1.55) | 0.24 | -2.04 (1.22) | 0.10 | -0.27 (0.13) | **0.04** | 0.16 (0.19) | 0.40 | 0.02 |

Note. (+) is indicated for positive impact scales of the IOC-CS, (-) is indicated for negative impact scales of the IOC-CS. For positive impact scales, a higher mean score indicates a larger positive impact, while for the negative impact scales, a higher mean score indicates a larger negative impact.

**Table S5:** Univariate associations between age at diagnosis and the SF-12 mental subscale and IOC-CS subscales based on a univariate analysis

| | ***SF-12*** | | ***IOC-CS*** | | | | | |
|---|---|---|---|---|---|---|---|---|
| | ***Mental component summary*** | | ***Positive impact subscale*** | | | | | |
| | | | ***Body and health (+)*** | | ***Personal growth (+)*** | | ***Socializing*** | |
| *Parameter* | Estimate (SE) | P-value | *Estimate (SE)* | *P-value* | *Estimate (SE)* | *P-value* | *Estimate (SE)* | *P* |
| Intercept | 48.14 (1.25) | <.0001 | 3.58 (0.10) | <.0001 | 3.25 (0.14) | <.0001 | 4.39 (0.11) | |
| Age at diagnosis (Ref: >=6) | -1.42 (1.58) | 0.37 | -0.08 (0.13) | 0.53 | -0.37 (0.19) | 0.05 | -0.27 (0.14) | |

Note. (+) is indicated for positive impact scales of the IOC-CS, (-) is indicated for negative impact scales of the IOC-CS. For positive impact scales, a higher mean score indicates a larger positive impact, while for the negative impact scales, a higher mean score indicates a larger negative impact.

**Table S6:** Univariate associations between relapse/second cancer status and SF-12 subscales and IOC-CS subscales based on a univariate analysis

| | ***SF-12*** | | | | ***IOC-CS*** | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | ***Mental component summary*** | | ***Physical component summary*** | | ***Positive impact subscale*** | | | | |
| | | | | | ***Body and health (+)*** | | ***Personal growth (+)*** | | |
| *Parameter* | Estimate (SE) | P-value | Estimate (SE) | P-value | *Estimate (SE)* | *P-value* | *Estimate (SE)* | *P-value* | *Esti (S* |
| Intercept | 47.78(0.84) | <.0001 | 55.36(0.65) | <.0001 | 3.62(0.07) | <.0001 | 2.92 (0.10) | <.0001 | 4.32 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Relapse or second cancer (Ref=No) | -2.91 (1.97) | 0.14 | -4.75(1.55) | 0.003 | -0.58 (0.17) | **0.001** | 0.67 (0.25) | **0.01** | -0.57 | |

Note. (+) is indicated for positive impact scales of the IOC-CS, (-) is indicated for negative impact scales of the IOC-CS. For positive impact scales, a higher mean score indicates a larger positive impact, while for the negative impact scales, a higher mean score indicates a larger negative impact.

**Table S7:** Associations between NCI risk group versus mental component summary (MCS) and physical component summary (PCS) scores of the SF-12

| | ***Mental component summary*** | | | | ***Physical component summary*** | | | |
|---|---|---|---|---|---|---|---|---|
| | *Univariate* | | *Multivariable* | | *Univariate* | | *Multivariable* | |
| *Parameter* | *Estimate (SE)* | *P-value* | *Estimate (SE)* | *P-value* | *Estimate (SE)* | *P-value* | *Estimate (SE)* | *P-value* |
| Intercept | 46.73 (1.98) | <.0001 | 49.73 (2.51) | <.0001 | 58.75 (1.79) | <.0001 | 58.35 (1.40) | <.0001 |
| NCI risk group (Ref= Standard) | 1.76 (1.68) | 0.29 | 1.37 (1.73) | 0.43 | -3.28 (1.32) | 0.01 | -3.04(1.22) | **0.01** |
| Gender (ref: Male) | | | -1.90 (1.57) | 0.23 | | | -1.75(1.10) | 0.12 |
| Age at follow-up (Ref: >=25) | | | -2.22 (2.0) | 0.27 | | | -0.86(1.41) | 0.54 |
| Protocol (ref=58881) 58741 | | | 0.25 (2.97) | 0.93 | | | -11.91(2.09) | **<.0001** |
| 58831/2 | | | -1.19 (2.33) | 0.61 | | | -1.89(1.72) | 0.26 |

Note. (+) is indicated for positive impact scales of the IOC-CS, (-) is indicated for negative impact scales of the IOC-CS. For positive impact scales, a higher mean score indicates a larger positive impact, while for the negative impact scales, a higher mean score indicates a larger negative impact.

**Table S8:** Associations between CRT (interaction with age at diagnosis) versus PCS scores and TMP scores IOC-CS

| | ***SF-12-Physical component summary*** | | | | ***IOC-CS-Thinking and memory problems (-)*** | | | |
|---|---|---|---|---|---|---|---|---|
| | *Univariate* | | *Multivariable* | | *Univariate* | | *Multivariable* | |
| *Parameter* | *Estimate (SE)* | *P-value* | *Estimate (SE)* | *P-value* | *Estimate (SE)* | *P-value* | *Estimate (SE)* | *P-value* |
| Intercept | 55.80 (0.61) | <.0001 | 56.7 (1.22) | <.0001 | 2.18(0.07) | <.0001 | 2.11(0.15)) | <.0001 |
| CRT(Ref=No) | -8.13(1.53) | **<.0001** | -7.67(2.30) | **0.001** | 0.44 (0.20) | **0.03** | 0.32(0.29) | 0.28 |
| Age at diagnosis (Ref: >=6) | | | -0.87(2.83) | 0.67 | | | 0.51(0.37) | 0.17 |
| CRT* Age at diagnosis | | | 0.001(3.17) | 0.81 | | | 0.20(0.41) | 0.63 |
| Gender (ref: Male) | | | -1.55(1.16) | 0.13 | | | -0.06(0.15) | 0.69 |
| Age at follow-up (Ref: >=25) | | | 1.05(1.35) | 0.90 | | | -0.18(0.17) | 0.30 |

Note. (+) is indicated for positive impact scales of the IOC-CS, (-) is indicated for negative impact scales of the IOC-CS. For positive impact scales, a higher mean score indicates a larger positive impact, while for the negative impact scales, a higher mean score indicates a larger negative impact.