Supplementary appendix

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Appendix

Time, pattern, and outcome of medulloblastoma relapse and their association with tumour biology at diagnosis and therapy: a multicentre cohort study

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Supplementary Figure 1: Time to relapse and time from relapse to death according to era (before 2000 vs 2000 and after).

(A) Time to relapse according to treatment era in the age restricted (>3 years) irradiated group. (B) Time from relapse to death according to treatment era in the age restricted irradiated group. (C) Time to relapse according to treatment era in the age restricted (<5 years) non-irradiated group. (D) Time from relapse to death according to treatment era in the age restricted non-irradiated group.
## Patterns of relapse

|                      | Before 2000 (n=84) | 2000 and after (n=84) | p value |
|----------------------|---------------------|------------------------|---------|
| Nodular              | 19/41 (46%)         | 31/76 (41%)            | 0·70    |
| Distant relapse      | 35/42 (83%)         | 64/77 (83%)            | 1       |

## Treatment at disease relapse

|                      | Before 2000 (n=84) | 2000 and after (n=84) | p value |
|----------------------|---------------------|------------------------|---------|
| Resection            | 10/42 (24%)         | 19/76 (25%)            | 1       |
| Chemotherapy         | 28/40 (70%)         | 66/79 (84%)            | 0·10    |
| Craniospinal irradiation | NA | NA | NA |
| Focal radiotherapy   | 4/43 (9%)           | 12/76 (16%)            | 0·41    |

## Clinicopathological features and treatment at diagnosis

|                      | Before 2000 (n=84) | 2000 and after (n=84) | p value |
|----------------------|---------------------|------------------------|---------|
| Boys                 | 64/84 (76%)         | 61/84 (73%)            | 0·72    |
| Subtotal resection*  | 40/83 (48%)         | 16/83 (19%)            | 0·0010  |
| Chemotherapy*        | 49/84 (58%)         | 83/83 (100%)           | <0·0001 |
| Craniospinal irradiation | All | All | NA |
| Classic histology    | 63/80 (78%)         | 51/72 (71%)            |         |
| Large-cell anaplastic histology | 10/80 (13%) | 15/72 (21%) | 0·38 |
| Desmoplastic/nodular histology | 7/80 (9%) | 6/72 (8%) | |
| Distant disease      | 22/76 (29%)         | 32/84 (38%)            | 0·24    |

## Established molecular features at diagnosis

|                      | Before 2000 (n=84) | 2000 and after (n=84) | p value |
|----------------------|---------------------|------------------------|---------|
| MYC amplification*   | 5/71 (7%)           | 0/78 (0%)              | 0·023   |
| MYCN amplification   | 6/70 (9%)           | 13/77 (17%)            | 0·15    |
| TP53 mutation        | 3/63 (5%)           | 12/79 (15%)            | 0·056   |
| Isochromosome 17q    | 16/44 (36%)         | 21/65 (32%)            | 0·68    |
| TERT mutation        | 6/75 (8%)           | 4/79 (5%)              | 0·53    |
| MB\text{}\text{\textsubscript{WNT}} | 0/69 (0%) | 3/79 (4%) | |
| MB\text{}\text{\textsubscript{HH}} | 12/69 (17%) | 15/79 (19%) | |
| MB\text{}\text{\textsubscript{group3}} | 20/69 (29%) | 20/79 (25%) | 0·41 |
| MB\text{}\text{\textsubscript{group4}} | 37/69 (54%) | 41/79 (52%) | |

Data are n/N (%). MB=medulloblastoma. NA=not applicable. *=Chemotherapy at diagnosis was enriched in patients diagnosed in 2000 and after, subtotal resection was enriched in patients diagnosed before 2000. However, neither variable was associated with time to relapse or time to death after relapse in univariable or multivariable survival analyses. $^*=$MYC amplification was enriched in patients diagnosed before 2000. However, testing for MYC amplification was not era-specific and was uniformly performed on all suitable samples as part of this study.

### Supplementary Table 1: Comparison by era (before 2000 vs 2000 and after) of the patterns of relapse, clinical and molecular features in the irradiated group
| Patterns of relapse | Before 2000 (n=21) | 2000 and after (n=29) | p value |
|---------------------|---------------------|-----------------------|---------|
| Nodular             | 8/18 (45%)          | 13/27 (48%)           | 1       |
| Distant relapse     | 13/19 (68%)         | 19/27 (70%)           | 1       |

| Treatment at disease relapse | | |
|------------------------------|---------------------|-----------------------|---------|
| Resection                    | 6/19 (32%)          | 5/24 (21%)            | 0.49    |
| Chemotherapy*                | 5/20 (25%)          | 16/24 (67%)           | 0.0077  |
| Craniospinal irradiation     | 9/20 (45%)          | 5/26 (19%)            | 0.10    |
| Focal radiotherapy           | 1/20 (5%)           | 3/26 (12%)            | 0.62    |

| Clinicopathological features and treatment at diagnosis | | |
|---------------------------------------------------------|---------------------|-----------------------|---------|
| Boys                                                     | 14/21 (67%)         | 18/29 (62%)           | 0.77    |
| Subtotal resection                                       | 7/21 (33%)          | 6/29 (21%)            | 0.35    |
| Chemotherapy                                             | 20/21 (95%)         | 27/27 (100%)          | 0.44    |
| Focal radiotherapy*                                      | 3/21 (14%)          | 14/29 (48%)           | 0.016   |
| Classic histology                                        | 11/20 (55%)         | 16/27 (59%)           |         |
| Large-cell anaplastic histology                         | 2/20 (10%)          | 6/27 (22%)            | 0.32    |
| Desmoplastic/nodular histology                          | 7/20 (35%)          | 5/27 (19%)            |         |
| Distant disease                                          | 5/21 (24%)          | 8/29 (28%)            | 1       |

| Established molecular features at diagnosis              | | |
|----------------------------------------------------------|---------------------|-----------------------|---------|
| MYC amplification                                        | 2/18 (11%)          | 4/28 (14%)            | 1       |
| MYCN amplification                                       | 0/17 (0%)           | 2/28 (7%)             | 0.52    |
| TP53 mutation                                            | 0/19 (0%)           | 0/28 (0%)             | 1       |
| Isochromosome 17q                                        | 1/14 (7%)           | 4/23 (17%)            | 0.63    |
| TERT mutation                                            | 1/18 (6%)           | 1/24 (4%)             | 1       |
| MB1rhl                                                   | 14/18 (78%)         | 11/25 (44%)           |         |
| MB1monp3                                                 | 4/18 (22%)          | 11/25 (44%)           | 0.060   |
| MB1monp4                                                 | 0/18 (0%)           | 3/25 (12%)            |         |

Data are n/N (%). MB=medulloblastoma. * =Chemotherapy at relapse and focal radiotherapy at diagnosis were enriched in patients diagnosed in 2000 and after, but neither variable was associated with time to relapse or time to death after relapse in univariable or multivariable survival analyses.

**Supplementary Table 2: Comparison by era (before 2000 vs 2000 and after) of the patterns of relapse, clinical and molecular features in the non-irradiated group**
Supplementary Figure 2: Contingency tables illustrating significant associations observed. (A) Age and upfront treatment in the entire cohort. (B) Location and pattern of disease relapse in the irradiated group. (C) Location and pattern of MB_{SHH} relapse in the irradiated group. (D) Diffuse MB_{SHH} tumours frequently display \textit{MYCN} amplification in the irradiated group. (E) Diffuse patterns in MB_{Group3} are associated with early relapses (within 18 months of initial diagnosis) in the irradiated group.
## Patterns of disease relapse

|                | Frequency | Univariable analyses | Multivariable analyses |
|----------------|-----------|----------------------|------------------------|
|                |           | Time to death after relapse | Overall survival | Time to death after relapse | Overall survival |
|                |           | HR (95% CI) | p value | HR (95% CI) | p value | HR (95% CI) | p value |
| Nodular        | 53/125 (42%) | 0·55 (0·37-0·82) | 0·064 | 0·59 (0·40-0·88) | 0·063 | ·· | ·· |
| Distant relapse| 108/129 (84%) | 1·57 (0·92-2·67) | 0·29 | 1·28 (0·75-2·18) | 0·55 | ·· | ·· |

## Treatment at disease relapse

|                | Frequency | Univariable analyses | Multivariable analyses |
|----------------|-----------|----------------------|------------------------|
|                |           | Time to death after relapse | Overall survival | Time to death after relapse | Overall survival |
|                |           | HR (95% CI) | p value | HR (95% CI) | p value | HR (95% CI) | p value |
| Resection      | 32/124 (26%) | 0·72 (0·46-1·13) | 0·33 | 0·63 (0·40-0·98) | 0·15 | ·· | ·· |
| Chemotherapy   | 102/127 (80%) | 0·54 (0·34-0·86) | 0·095 | 0·65 (0·41-1·03) | 0·19 | ·· | ·· |
| Focal radiotherapy | 18/127 (14%) | 0·73 (0·40-1·34) | 0·46 | 0·82 (0·45-1·50) | 0·65 | ·· | ·· |

## Clinicopathological features and treatment at diagnosis

|                | Frequency | Univariable analyses | Multivariable analyses |
|----------------|-----------|----------------------|------------------------|
|                |           | Time to death after relapse | Overall survival | Time to death after relapse | Overall survival |
|                |           | HR (95% CI) | p value | HR (95% CI) | p value | HR (95% CI) | p value |
| Boys           | 133/178 (75%) | 1·27 (0·88-1·83) | 0·36 | 1·21 (0·84-1·75) | 0·50 | ·· | ·· |
| Subtotal resection | 58/178 (33%) | 1·31 (0·94-1·84) | 0·27 | 1·15 (0·82-1·62) | 0·59 | ·· | ·· |
| Chemotherapy   | 142/177 (80%) | 1·15 (0·77-1·73) | 0·61 | 1·24 (0·82-1·87) | 0·53 | ·· | ·· |
| Classic histology | 123/162 (76%) | 0·77 (0·52-1·14) | 0·35 | 0·74 (0·50-1·09) | 0·27 | ·· | ·· |
| Large-cell anaplastic histology | 26/162 (16%) | 1·66 (1·04-2·65) | 0·23 | 1·70 (1·06-2·71) | 0·14 | 1·66 (1·04-2·65) | 0·033 | 1·82 (1·12-2·97) | 0·015 |
| Desmoplastic/nodular histology | 13/162 (8%) | 0·88 (0·49-1·60) | 0·72 | 0·93 (0·52-1·69) | 0·91 | ·· | ·· |
| Distant disease | 57/170 (34%) | 1·19 (0·85-1·68) | 0·44 | 1·38 (0·98-1·95) | 0·17 | ·· | ·· |

## Established molecular features at diagnosis

|                | Frequency | Univariable analyses | Multivariable analyses |
|----------------|-----------|----------------------|------------------------|
|                |           | Time to death after relapse | Overall survival | Time to death after relapse | Overall survival |
|                |           | HR (95% CI) | p value | HR (95% CI) | p value | HR (95% CI) | p value |
| MYC amplification | 5/157 (3%) | 2·44 (0·99-6·05) | 0·22 | 3·72 (1·51-9·20) | 0·046 | ·· | ·· |
| MYCN amplification | 20/155 (13%) | 1·58 (0·95-2·64) | 0·28 | 1·51 (0·91-2·52) | 0·26 | ·· | ·· |
| TP53 mutation   | 18/150 (12%) | 1·12 (0·67-1·86) | 0·75 | 1·34 (0·80-2·26) | 0·51 | ·· | ·· |
| Isochromosome 17q | 40/117 (34%) | 0·96 (0·64-1·44) | 0·86 | 0·94 (0·63-1·40) | 0·88 | ·· | ·· |
| TERT mutation   | 10/162 (6%) | 1·27 (0·66-2·42) | 0·62 | 1·023 (0·54-1·95) | 0·99 | ·· | ·· |
| MB2/NG1         | 5/156 (3%) | 0·44 (0·11-1·81) | 0·42 | 0·60 (0·15-2·42) | 0·62 | ·· | ·· |
| MB2/NG1         | 29/156 (19%) | 1·11 (0·71-1·74) | 0·76 | 1·013 (0·65-1·59) | 0·95 | ·· | ·· |
| MB2/NG1         | 40/156 (26%) | 1·50 (1·02-2·19) | 0·20 | 1·76 (1·20-2·58) | 0·080 | ·· | ·· |
| MB2/NG1         | 82/156 (52%) | 0·75 (0·54-1·06) | 0·27 | 0·69 (0·49-0·98) | 0·15 | ·· | ·· |

HR=hazard ratio. MB=medulloblastoma

Supplementary Table 3: Univariable and multivariable analyses of correlates of time-based measures in the irradiated group
|                         | Frequency | Patterns of disease relapse | Treatment at disease relapse | Clinicopathological features and treatment at diagnosis | Established molecular features at diagnosis |
|-------------------------|-----------|----------------------------|----------------------------|------------------------------------------------------|---------------------------------------------|
|                         | HR (95% CI) | p value | HR (95% CI) | p value | HR (95% CI) | p value | HR (95% CI) | p value | HR (95% CI) | p value | HR (95% CI) | p value |
| **Frequency**           |           |         |           |         |           |         |           |         |           |         |           |         |
| Nodular                 | 23/47 (49%) | ··       | 0·99 (0·49-2·01) | 1       | 0·78 (0·38-1·59) | 0·66 | ··       | ··       | ··       | ··       | ··       | ··       |
| Distant relapse         | 32/48 (67%) | ··       | 0·80 (0·38-1·68) | 0·73 | 1·01 (0·48-2·14) | 0·98 | ··       | ··       | ··       | ··       | ··       | ··       |
|                         |           |         |           |         |           |         |           |         |           |         |           |         |
| **Treatment at disease relapse** |           |         |           |         |           |         |           |         |           |         |           |         |
| Resection               | 12/45 (27%) | ··       | 0·29 (0·10-0·83) | 0·10 | 0·25 (0·09-0·73) | 0·054 | ··       | ··       | ··       | ··       | ··       | ··       |
| Chemotherapy            | 22/46 (48%) | ··       | 0·59 (0·29-1·22) | 0·39 | 0·72 (0·35-1·46) | 0·55 | ··       | ··       | ··       | ··       | ··       | ··       |
| Craniospinal irradiation | 15/48 (31%) | ··       | 0·21 (0·086-0·52) | 0·015 | 0·26 (0·11-0·65) | 0·026 | ··       | ··       | 0·27 (0·11-0·68) | 0·0054 | ··       | ··       |
| Focal radiotherapy      | 4/48 (8%) | ··       | 0·30 (0·04-2·22) | 0·40 | 0·31 (0·04-2·32) | 0·47 | ··       | ··       | ··       | ··       | ··       | ··       |
|                         |           |         |           |         |           |         |           |         |           |         |           |         |
| Clinicopathological features and treatment at diagnosis |           |         |           |         |           |         |           |         |           |         |           |         |
| Boys                    | 32/52 (62%) | 1·05 (0·60-1·87) | 1 | 0·88 (0·45-1·71) | 0·82 | 0·72 (0·37-1·41) | 0·56 | ··       | ··       | ··       | ··       | ··       |
| Subtotal resection      | 14/52 (27%) | 1·71 (0·91-3·20) | 0·21 | 1·56 (0·78-3·11) | 0·38 | 1·87 (0·93-3·74) | 0·17 | ··       | ··       | ··       | ··       | ··       |
| Chemotherapy            | 49/50 (98%) | ··       | ··       | ··       | 1·97 (0·71-5·17) | 1·89 (0·79-4·53) | 0·0038 | 4·26 (1·67-10·83) | 0·0024 | ··       | ··       |
| Focal radiotherapy      | 17/52 (33%) | 0·47 (0·25-0·88) | 0·066 | 1·27 (0·64-2·55) | 0·71 | 1·07 (0·53-2·16) | 0·94 | ··       | ··       | ··       | ··       | ··       |
| Classic histology       | 28/48 (58%) | 0·58 (0·32-1·07) | 0·22 | 1·59 (0·79-3·18) | 0·38 | 1·17 (0·58-2·34) | 0·83 | ··       | ··       | ··       | ··       | ··       |
| Large-cell anaplastic histology | 8/48 (17%) | 4·92 (2·05-11·78) | 0·0024 | 2·30 (1·00-5·32) | 1·7 | 5·00 (2·06-12·13) | 0·038 | ··       | ··       | ··       | ··       | ··       |
| Desmoplastic/nodular histology | 12/48 (25%) | 0·97 (0·50-1·90) | 1 | 0·28 (0·11-0·73) | 0·066 | 0·31 (0·12-0·81) | 0·049 | ··       | 0·23 (0·07-0·77) | 0·018 | ··       | ··       |
| Distant disease         | 13/52 (25%) | 1·09 (0·58-2·06) | 1 | 0·63 (0·28-1·38) | 0·38 | 0·71 (0·32-1·57) | 0·58 | ··       | ··       | ··       | ··       | ··       |
|                         |           |         |           |         |           |         |           |         |           |         |           |         |
| Established molecular features at diagnosis |           |         |           |         |           |         |           |         |           |         |           |         |
| MYC amplification       | 6/48 (13%) | 7·06 (2·68-18·57) | 0·0010 | 5·18 (1·89-14·25) | 0·014 | 13·14 (4·10-42·06) | 0·00028 | 5·61 (1·96-16·04) | 0·0013 | ··       | ··       |
| MYCN amplification      | 2/47 (4%) | 3·08 (0·69-13·69) | 0·28 | 1·36 (0·32-5·81) | 0·85 | 2·89 (0·65-12·95) | 0·33 | ··       | ··       | ··       | ··       | ··       |
| Isochromosome 17q       | 6/38 (16%) | 3·37 (1·35-8·39) | 0·043 | 1·99 (0·72-5·55) | 0·41 | 3·63 (1·29-10·24) | 0·049 | ··       | ··       | ··       | ··       | ··       |
| TERT mutation           | 2/44 (5%) | 1·58 (0·37-6·68) | 0·75 | 1·02 (0·24-4·28) | 0·98 | 1·32 (0·31-5·58) | 0·83 | ··       | ··       | ··       | ··       | ··       |
| MBSH2                  | 25/44 (57%) | 0·98 (0·53-1·81) | 0·95 | 0·51 (0·25-1·06) | 0·20 | 0·42 (0·20-0·87) | 0·049 | ··       | ··       | ··       | ··       | ··       |
| MBGroup1                | 15/44 (34%) | 1·38 (0·73-2·60) | 0·51 | 2·30 (1·10-4·82) | 0·11 | 2·51 (1·20-5·25) | 0·057 | ··       | ··       | ··       | ··       | ··       |
| MBGroup4                | 4/44 (9%) | 0·48 (0·14-1·57) | 0·39 | 0·77 (0·18-3·26) | 0·80 | 1·10 (0·26-4·66) | 0·95 | ··       | ··       | ··       | ··       | ··       |

HR=hazard ratio. MB=medulloblastoma

Supplementary Table 4: Univariable and multivariable analyses of correlates of time-based measures in the non-irradiated group
Supplementary Figure 3: Clinical and molecular disease characteristics of all survivors following relapse. (A) Clinical and molecular disease characteristics of survivors in the irradiated group. (B) Clinical and molecular disease characteristics of survivors in the non-irradiated group. Each column represents one patient. Blue box=MBwNT. Red box=MBSHH. Yellow box=MBGroup3. Green box=MBGroup4. Black box=feature present. Grey box=missing data.
Supplementary Figure 4: Patterns of relapse are molecular subgroup dependent in the non-irradiated group. (A) Schematic representing the patients with distant disease at diagnosis, emergent distant disease at relapse, and distant disease at relapse according to molecular subgroup. (B) Different patterns of relapsed disease according to molecular subgroup and relapse pattern. MB\textsubscript{SHH}=23 patients, MB\textsubscript{Group3}=15 patients. MB=medulloblastoma.
Supplementary Figure 5: Second-generation MB_{Group3} and MB_{Group4} subtypes account for heterogeneous relapse characteristics. (A) Time from relapse to death according to second-generation MB_{Group3} and MB_{Group4} molecular subtype. (B) Overall survival according to second-generation MB_{Group3} and MB_{Group4} molecular subtype. I-VIII=MB_{Group3} and MB_{Group4} second-generation subtypes. Only MB_{Group3} and MB_{Group4} subtypes present in >10% of cohort included in analyses (I, IV and VI excluded from analyses).
| Frequency                  | Patterns of disease relapse | Treatment at disease relapse | Clinicopathological features and treatment at diagnosis | Established molecular features at diagnosis | Emerging molecular features at diagnosis |
|---------------------------|----------------------------|-------------------------------|---------------------------------------------------------|---------------------------------------------|------------------------------------------|
|                           | Nodular                    | Resection                    | Boys                                                    | MYC amplification                          | MB<sub>group3-LR</sub>                   |
|                           | Distant relapse            | Chemotherapy                 | Subtotal resection                                      | MYCN amplification                         | MB<sub>group3-HR</sub>                   |
|                           |                            | Cranio spinal irradiation*   | Chemotherapy                                            | TP53 mutation                              | MB<sub>group4-LR</sub>                   |
|                           |                            | Focal radiotherapy           | Subtotal resection                                      | Isochromosome 17q                          | MB<sub>group4-HR</sub>                   |
|                           |                            |                               | Classic histology                                       | TERT mutation                              | I                                        |
|                           |                            |                               | Large-cell anaplastic histology                        |                                             | II                                       |
|                           |                            |                               | Demoplasic/nodular histology                           |                                             | III                                      |
|                           |                            |                               | Distant disease                                         |                                             | IV                                       |
|                           |                            |                               |                                                           |                                             | V                                        |
|                           |                            |                               |                                                           |                                             | VI                                       |
|                           |                            |                               |                                                           |                                             | VII                                      |
|                           |                            |                               |                                                           |                                             | VIII                                     |

|               | Time to relapse | Time to death after relapse | Overall survival | Time to relapse | Time to death after relapse | Overall survival |
|---------------|----------------|-----------------------------|------------------|----------------|-----------------------------|------------------|
|               | HR (95% CI)    | p value                     |                  | HR (95% CI)    | p value                     |                  |
|               |               |                            |                  |               |                            |                  |
| Nodular       | 32/84 (38%)   | 0.50 (0.30-0.81)            | 0.046            | 0.51 (0.31-0.83) | 0.045                       | 0.42 (0.21-0.81) | 0.010            |
| Distant relapse| 79/87 (91%)   | 2.23 (0.96-5.18)            | 0.18             | 1.80 (0.78-4.18) | 0.32                        |                  |
| Resection     | 18/86 (21%)   | 0.63 (0.36-1.12)            | 0.21             | 0.58 (0.32-1.02) | 0.19                        |                  |
| Chemotherapy  | 68/87 (78%)   | 0.49 (0.29-0.84)            | 0.055            | 0.61 (0.36-1.04) | 0.20                        |                  |
| Cranio spinal irradiation* | 1/88 (1%) |                            |                  |                |                            |                  |
| Focal radiotherapy | 14/88 (16%) | 0.75 (0.38-1.46)            | 0.58             | 0.91 (0.47-1.79) | 0.94                        |                  |
| Boys          | 94/122 (77%)  | 1.05 (0.69-1.61)            | 0.97             | 1.15 (0.74-1.78) | 0.65                        | 1.19 (0.77-1.85) | 0.68            |
| Subtotal resection | 41/121 (34%) | 0.71 (0.49-1.04)            | 0.23             | 1.12 (0.76-1.68) | 0.62                        | 0.88 (0.59-1.31) | 0.73            |
| Chemotherapy  | 102/121 (84%) | 0.95 (0.58-1.55)            | 0.93             | 1.05 (0.63-1.74) | 0.90                        | 1.05 (0.63-1.74) | 0.93            |
| Classic histology | 96/114 (84%) | 0.89 (0.53-1.51)            | 1                | 0.57 (0.33-0.96) | 0.15                        | 0.67 (0.40-1.12) | 0.26            |
| Large-cell anaplastic histology | 12/114 (11%) | 1.28 (0.70-2.33)            | 0.85             | 1.91 (1.03-3.53) | 0.12                        | 1.66 (0.90-3.07) | 0.26            |
| Demoplasic/nodular histology | 6/114 (5%) | 0.84 (0.33-2.13)            | 1                | 1.33 (0.58-3.06) | 0.69                        | 1.17 (0.51-2.68) | 0.90            |
| Distant disease | 42/119 (35%) | 1.52 (1.04-2.24)            | 0.11             | 1.15 (0.77-1.70) | 0.63                        | 1.38 (0.93-2.06) | 0.25            |
| MYC amplification | 3/114 (3%) | 19.65 (5.02-76.90)          | 0.00019          | 2.90 (0.91-9.28) | 0.16                        | 8.45 (2.55-28.04) | 0.0061          |
| MYCN amplification | 6/114 (5%) | 1.16 (0.51-2.65)            | 0.97             | 1.51 (0.61-3.73) | 0.62                        | 1.57 (0.63-3.88) | 0.55            |
| TP53 mutation  | 2/111 (2%)    | 0.89 (0.22-3.62)            | 0.92             | 0.70 (0.17-2.87) | 0.68                        | 0.87 (0.21-3.54) | 0.96            |
| Isochromosome 17q | 39/89 (44%) | 0.84 (0.55-1.29)            | 0.78             | 1.03 (0.67-1.60) | 0.89                        | 0.97 (0.62-1.50) | 0.88            |
| TERT mutation  | 3/119 (3%)    | 0.95 (0.30-3.00)            | 0.92             | 3.46 (1.06-11.24) | 0.14                        | 1.57 (0.50-4.99) | 0.65            |
| MB<sub>group3-LR</sub>* | 2/78 (3%) |                            |                  |                |                            |                  |
| MB<sub>group3-HR</sub>* | 25/78 (32%) | 2.68 (1.62-4.43)            | 0.00061          | 2.65 (1.55-4.54) | 0.0047                       | 3.21 (1.86-5.52) | 0.00065         |
| MB<sub>group4-LR</sub>* | 14/78 (18%) | 1.63 (0.89-2.98)            | 0.25             | 0.81 (0.44-1.49) | 0.65                        | 1.05 (0.57-1.93) | 0.90            |
| MB<sub>group4-HR</sub>* | 37/78 (47%) | 0.33 (0.20-0.54)            | 0.00023          | 0.58 (0.36-0.93) | 0.13                        | 0.41 (0.25-0.68) | 0.0043          |
| I *           | 7/90 (8%)     |                            |                  |                |                            |                  |
| II            | 11/90 (12%)   | 1.72 (0.90-3.29)            | 0.26             | 4.08 (1.92-8.67) | 0.0063                       | 2.43 (1.22-4.84) | 0.058           |
| III           | 13/90 (14%)   | 4.07 (2.10-7.86)            | 0.00020          | 1.32 (0.70-2.48) | 0.60                        | 1.89 (1.00-3.60) | 0.18            |
| IV *          | 2/90 (2%)     |                            |                  |                |                            |                  |
| V             | 11/90 (12%)   | 0.91 (0.46-1.79)            | 0.99             | 1.74 (0.90-3.38) | 0.19                        | 1.24 (0.64-2.37) | 0.69            |
| VI *          | 7/90 (8%)     |                            |                  |                |                            |                  |
| VII           | 12/90 (13%)   | 0.81 (0.44-1.52)            | 0.86             | 0.56 (0.29-1.09) | 0.18                        | 0.71 (0.37-1.36) | 0.53            |
| VIII          | 27/90 (30%)   | 0.57 (0.35-0.92)            | 0.081            | 0.62 (0.37-1.04) | 0.18                        | 0.57 (0.34-0.96) | 0.15            |

HR=hazard ratio. MB=medulloblastoma. *=variable not included in analyses due to infrequent events.

Supplementary Table 5: Univariable and multivariable survival analyses of correlates of time-based measures in the MB<sub>group3</sub> and MB<sub>group4</sub> irradiated group.
Local nodular | Distant nodular | Distant diffuse

**Distant disease at diagnosis**
- **MB\textsubscript{Group3-llt}**
  - 10/25 (40%)
  - 17/18 (94%)
  - 0.00030
- **MB\textsubscript{Group4-lt}**
  - 7/14 (50%)
  - 8/9 (89%)
  - 0.086
- **MB\textsubscript{Group4-hr}**
  - 12/36 (33%)
  - 31/33 (94%)
  - <0.0001

**Distant disease at relapse**
- **MB\textsubscript{Group3-llt}**
  - 12/13 (92%)
- **MB\textsubscript{Group4-lt}**
  - 4/5 (80%)
- **MB\textsubscript{Group4-hr}**
  - 21/22 (95%)

**p value comparing the proportion of distant disease at diagnosis versus distant disease at relapse within MB\textsubscript{Group3} and MB\textsubscript{Group4} second-generation subtypes.**

*No significant difference by molecular subtype p=0.55. No significant difference by molecular subtype p=0.84. *No significant difference by molecular subtype p=0.50.
Supplementary Figure 6: Assessment of relapse characteristics by second generation MB\textsuperscript{Group3} and MB\textsuperscript{Group4} subtypes. (A) Sankey plot of the relationship between consensus MB\textsuperscript{Group3} and MB\textsuperscript{Group4} and second-generation subtypes. (B) Time to relapse according to second-generation MB\textsuperscript{Group3} and MB\textsuperscript{Group4} molecular subtype. (C) Time from relapse to death according to second-generation MB\textsuperscript{Group3} and MB\textsuperscript{Group4} molecular subtype. (D) Overall survival according to second-generation MB\textsuperscript{Group3} and MB\textsuperscript{Group4} molecular subtype. (E) The prevalence of distant disease at diagnosis and distant disease acquired at relapse according to second-generation MB\textsuperscript{Group3} and MB\textsuperscript{Group4} molecular subtype. (F) The different patterns of relapsed disease according to second-generation MB\textsuperscript{Group3} and MB\textsuperscript{Group4} molecular subtype. MB\textsuperscript{Group3}-HR=18 patients, MB\textsuperscript{Group4}-LR=9 patients, MB\textsuperscript{Group4}-HR=30 patients. MB=medulloblastoma. #=MB\textsuperscript{Group3} low-risk. Only MB\textsuperscript{Group3} and MB\textsuperscript{Group4} subtypes present in >10% of cohort included in analyses.
Supplementary Figure 7: Pattern and timing of medulloblastoma relapse in our cohort according to upfront treatment and molecular subgroup: clinical relevance and recommendations. MB=medulloblastoma. SHH=sonic hedgehog. CSI=cranio-spinal irradiation. CLA=classic histology. DN=desmoplastic or nodular histology. LCA=large-cell anaplastic histology. M+=distant disease. MRI=Magnetic Resonance Imaging.

| Features at diagnosis | MB<sub>unt</sub> non-irradiated | MB<sub>unt</sub> irradiated | MB<sub>group1</sub> non-irradiated | MB<sub>group1</sub> irradiated | MB<sub>group2</sub> irradiated |
|-----------------------|---------------------------------|-----------------------------|---------------------------------|-------------------------------|-------------------------------|
| Gender                | Male                            | Female                      | Male                            | Female                        | Male                          |
| Age                   |                                 |                             |                                 |                               |                               |
| History               | CLA and DN                      | CLA, LCA and DN             | CLA and LCA                     | CLA                           | CLA                           |
| Distant disease       | M+ 16%                          | M+ 21%                      | M+ 40%                          | M+ 38%                        | M+ 34%                        |
| Patterns of relapse   | 33% M+ only                     | 40% M+ only                 | 33% M+ only                     | 76% M+ only                   | 58% M+ only                   |
| Post relapse survival | 33%                             | ~5%                         | ~5%                             | ~5%                           | ~5%                           |

Clinical relevance:

Observation:
- DN histology associated with post-relapse survival
- MYC amplification associated with distant diffuse relapse
- High-risk features (LCA & MYC amplification) associated with rapid disease course
- Nodular relapse associated with prolonged survival

Recommendation:
- Consider CSI and resection at relapse
- Consider focal radiotherapy/resection

No salvage options at relapse; urgent novel treatment strategies required:

- i) Prolonged time to relapse
- ii) Nodular relapse associated with prolonged survival
- i) Disease surveillance for 10 years
- ii) Consider focal radiotherapy/resection

Surveillance MRI of whole neuroaxis