

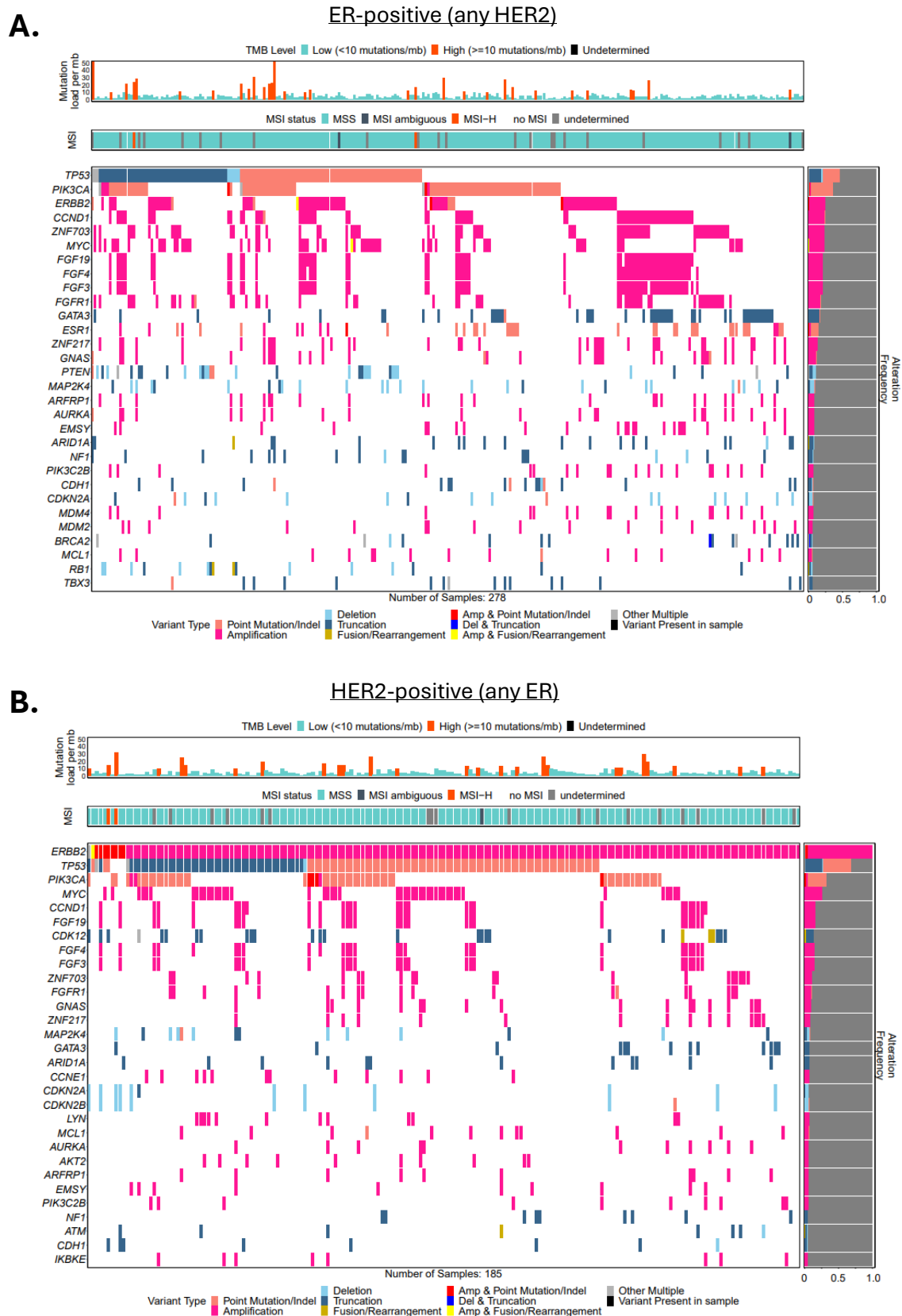
**Supplementary Table 1. Targeted therapy and/or immunotherapy in breast cancer brain metastases.** The % frequency of BCBM targetable biomarkers by receptor status as identified in this study with a selection of current clinical trials. \*Trials excluding untreated or uncontrolled CNS but including treated and/or asymptomatic CNS. \*\*TMB % prevalence.

| Altered Gene / Pathway        | Targeted Therapy                       | Phase | Clinical Trials Identifier | ER+/HER2-BCBM | ER+/HER2+BCBM | ER-/HER2+BCBM | ER-/HER2-BCBM |
|-------------------------------|----------------------------------------|-------|----------------------------|---------------|---------------|---------------|---------------|
| <b>ERBB2/HER2 alterations</b> | Tucatinib, T-DM1                       | 3     | NCT03975647                | 2.83%         | 100%          | 100%          | 2.01%         |
|                               | Pertuzumab, Trastuzumab                | 2     | NCT02536339                |               |               |               |               |
|                               | Afatinib, T-DM1                        | 2     | NCT04158947                |               |               |               |               |
|                               | Cabozantinib, Trastuzumab              | 2     | NCT02260531                |               |               |               |               |
|                               | Paxalisib, Trastuzumab                 | 2     | NCT03765983                |               |               |               |               |
|                               | Everolimus, Vinorelbine, Trastuzumab   | 2     | NCT01305941                |               |               |               |               |
|                               | Pyrotinib, Vinorelbine                 | 2     | NCT03933982                |               |               |               |               |
|                               | GRN1005, Trastuzumab, 18F-FLT          | 2     | NCT01480583                |               |               |               |               |
|                               | Neratinib, Capecitabine, T-DM1         | 2     | NCT01494662                |               |               |               |               |
|                               | Afatinib, Vinorelbine                  | 2     | NCT01441596                |               |               |               |               |
|                               | Tucatinib, Capecitabine, Trastuzumab   | 2     | NCT02614794                |               |               |               |               |
|                               | Trastuzumab deruxtecan                 | 2     | NCT04420598                |               |               |               |               |
|                               | 68GaNOTA-Anti-HER2 VHH1                | 2     | NCT03331601                |               |               |               |               |
|                               | Cabazitaxel, Lapatinib                 | 2     | NCT01934894                |               |               |               |               |
|                               | Afatinib, Targeted radiotherapy        | 1/2   | NCT02768337                |               |               |               |               |
|                               | Trastuzumab deruxtecan                 | 2     | NCT04420598                |               |               |               |               |
|                               | Pyrotinib, Capecitabine, Radiotherapy  | 2     | NCT04582968                |               |               |               |               |
|                               | Trastuzumab, Pertuzumab, TKIs          | 2     | NCT04760431                |               |               |               |               |
|                               | Tucatinib, Pertuzumab, Trastuzumab     | 2     | NCT05041842                |               |               |               |               |
|                               | Lapatinib Ditosylate, Radiotherapy     | 2     | NCT01622868                |               |               |               |               |
|                               | Trastuzumab deruxtecan                 | 2     | NCT04752059                |               |               |               |               |
|                               | Trastuzumab deruxtecan                 | 3     | NCT04739761                |               |               |               |               |
|                               | ARX788                                 | 2     | NCT05018702                |               |               |               |               |
| <b>ESR1 alterations</b>       | Palbociclib                            | 2     | NCT02896335                | 16.98%        | 7.58%         | ND            | ND            |
|                               | Palbociclib, Als, Fulvestrant          | 2     | NCT04256941                |               |               |               |               |
|                               | Abemaciclib, Stereotactic radiotherapy | 1/2   | NCT04923542                |               |               |               |               |
|                               | Abemaciclib, Elacestrant               | 1/2   | NCT04791384                |               |               |               |               |
| <b>PIK3CA mutations</b>       | Paxalisib                              | 1     | NCT04192981                | 38.21%        | 24.24%        | 36.47%        | 23.49%        |
|                               | Paxalisib, Abemaciclib, Entrectinib    | 2     | NCT03994796                |               |               |               |               |
|                               | Buparlisib, Capecitabine, Trastuzumab  | 2     | NCT02000882                |               |               |               |               |
| <b>BRCA1/2 mutations</b>      | Veliparib, Cisplatin                   | 2     | NCT02595905                | 5.19%/7.55%   | ND            | 2.35%/2.35%   | 14.43%/6.04%  |
|                               | Olaparib                               | 3     | NCT02032823                |               |               |               |               |
|                               | Olaparib, Durvulumab                   | 1/2   | NCT04711824                |               |               |               |               |
|                               | Olaparib, chemotherapy                 | 3     | NCT02000622*               |               |               |               |               |
|                               | Olaparib                               | 3     | NCT03286842                |               |               |               |               |

|                                  |                                                   |     |              |        |        |        |        |
|----------------------------------|---------------------------------------------------|-----|--------------|--------|--------|--------|--------|
| <b>PDL1</b>                      | Pembrolizumab, Anti-HER2/3 Dendritic Cell Vaccine | 0   | NCT04348747  | ND     | 1.52%  | ND     | 7.72%  |
|                                  | Nivolumab, Stereotactic radiotherapy              | 1   | NCT03807765  |        |        |        |        |
|                                  | Atezolizumab, Stereotactic radiotherapy           | 2   | NCT03483012  |        |        |        |        |
|                                  | Pembrolizumab                                     | 1/2 | NCT03449238  |        |        |        |        |
|                                  | Atezolizumab, T-DM1                               | 3   | NCT04740918  |        |        |        |        |
| <b>PDL1/TMB**</b>                | Atezolizumab, Trastuzumab, Vinorelbine            | 2   | NCT04759248  | 11.40% | 9.68%  | 21.33% | 17.41% |
| <b>HRD</b>                       | Niraparib, Dostarlimab                            | 2   | NCT04983745  | 43.17% | 26.67% | 33.33% | 70.45% |
|                                  | Olaparib                                          | 2   | NCT03344965  |        |        |        |        |
|                                  | Talazoparib                                       | 2   | NCT02401347* |        |        |        |        |
| <b>FGFR</b>                      | E7090                                             | 3   | NCT04962867  | 21.7%  | 7.58%  | 10.59% | ND     |
| <b>TP53+other gene mutations</b> | Flucytosine, Vocimagene Amiretroreprevec          | 1   | NCT02576665  | 43.87% | 54.55% | 78.82% | 90.60% |
| <b>VEGFA</b>                     | Bevacizumab, Etoposide, Cisplatin, WBRT           | 2   | NCT02185352  | ND     | 1.52%  | 3.53%  | 8.05%  |
| <b>Multiple targets</b>          | The MATCH Screening Trial                         | 2   | NCT02465060  |        |        |        |        |

**Supplementary Table 2. Patient demographics and baseline disease characteristics.**

| <b>Category</b>                         | <b>BC</b>        | <b>BCBM</b>      | <b>N-CNS</b>     |
|-----------------------------------------|------------------|------------------|------------------|
| Number of samples                       | 11988            | 822              | 15516            |
| Age median[IQR], y                      | 55.0 [46.0-65.0] | 54.0 [45.0-62.0] | 59.0 [50.0-67.0] |
| <b>Sex %[n]</b>                         |                  |                  |                  |
| Male                                    | 1.018 [n=122]    | 0.608 [n=5]      | 1.044 [n=162]    |
| Female                                  | 98.982 [n=11862] | 99.392 [n=817]   | 98.956 [n=15352] |
| <b>Tumor type %[n]</b>                  |                  |                  |                  |
| breast carcinoma (nos)                  | 16.008[n=1919]   | 87.713 [n=721]   | 80.833 [n=12542] |
| breast invasive ductal carcinoma (idc)  | 72.598 [n=8703]  | 11.071[n=91]     | 14.089 [n=2186]  |
| breast invasive lobular carcinoma (ilc) | 8.008[n=960]     | 0.608 [n=5]      | 4.189 [n=650]    |
| breast metaplastic carcinoma            | 2.236 [n=268]    | 0.608 [n=5]      | 0.464 [n=72]     |
| breast phyllodes tumour                 | 0.375 [n=45]     | 0.0 [n=0]        | 0.199 [n=31]     |
| breast ductal carcinoma in situ (dcis)  | 0.309 [n=37]     | 0.0 [n=0]        | 0.0 [n=0]        |
| breast mucinous carcinoma               | 0.150 [n=18]     | 0.0 [n=0]        | 0.064 [n=10]     |
| breast inflammatory carcinoma           | 0.117 [n=14]     | 0.0 [n=0]        | 0.064 [n=10]     |
| breast lobular carcinoma in situ        | 0.067 [n=8]      | 0.0 [n=0]        | 0.045 [n=7]      |
| breast carcinosarcoma                   | 0.058 [n=7]      | 0.0 [n=0]        | 0.026 [n=4]      |
| breast myoepithelial carcinoma          | 0.042 [n=5]      | 0.0 [n=0]        | 0.013 [n=2]      |
| breast papillary carcinoma              | 0.033 [n=4]      | 0.0 [n=0]        | 0.013 [n=2]      |
| <b>Tumour subtype %[n]</b>              |                  |                  |                  |
| ER+/HER2-                               | 5.3% [n=641]     | 25.8% [n=212]    | 4.1% [n=634]     |
| ER+/HER2+                               | 0.7% [n=84]      | 8.0% [n=66]      | 0.3% [n=49]      |
| ER-/HER2+                               | 0.5% [n=57]      | 10.3% [n=85]     | 0.3% [n=51]      |
| ER-/HER2-                               | 4.9% [n=585]     | 36.3% [n=298]    | 1.9% [n=291]     |
| Unknown                                 | 88.6% [n=10621]  | 19.6% [n=161]    | 93.4% [n=14491]  |



**Supplementary Figure 1. Genomic Alterations in BCBM by receptor status.** Tile-plots of genomic alterations in BCBMs classified as **A.** ER-positive (Any HER2 status) and **B.** HER2-positive (Any ER status). The different types of genomic variation are indicated by different colours. MSI and TMB for each subtype are also included in the plots.