|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Cell line | BrMPanel#[[1]](#endnote-1) or reference/ | Preclinical therapies | | Injection/Disease Burden Methods | Result(s)[[2]](#endnote-2) | Clinical trials | Refs |
| **Type of therapy** | **Treatment** |
| MDA-MB-231Br | #14 | Radiation | WBRT, 3Gy x 10 or 15Gy x 1 | Intracardiac/Histology | Micromets ↓ 58-88%; Large mets ↓ 47-55% |  | [61] |
| Intracranial/Survival | OS ↑ to 46-81 D (vs 24 D) |
| WBRT, 4Gy x 3 | Intracardiac/MRI | New mets ↓ to 21% (vs 42%) |  | [62] |
| WBRT, 10Gy x 1 (pre-cells) | Intracardiac/MRI | RT ↑ mets and tumor vol (vs nonRT) |  | [63] |
| B16-F10 | [65] ATCC | Radiation | SRS, 18Gy x 1 | Intracranial/MRI | SRS ↓ tumor vol, OS not reached (vs no SRS, 11 D) |  | [65] |
| SUM149 | #36 | Chemo | Carboplatin ± ABT888 | Intracranial/Survival | Carboplatin ± ABT888 ↑ OS, 58-64 D (vs PBS, 36 D) | NCT02595905 | [67] |
| MDA-MB-436 | #37 | Carboplatin ± ABT888 ↑ OS, >65 D (vs PBS, 44 D) |
| MDA-MB-468 | #38 | Carboplatin ± ABT888 no effect on OS |
| MDA-MB-231Br | [67] | Carboplatin ± ABT888 no effect on OS |
| MDA-MB-231Br | #14 | Chemo | Vinorelbine, 12 mg/kg | Intracardiac/Histology | Variably ↑ TUNEL due to poor/inconsistent exposure | NCT00795678 | [68] |
| Docetaxel | Docetaxel pretreatment ↑ 2x brain mets number |  | [69] |
| Temozolomide | Intracardiac/ Histology, Survival | Early Temo (5-50 mg/kg) ↓ brain mets 100%; ↑ OS | NCT00831545  NCT00638963 | [90] |
| JIMT-1-BR3 | #16 | Chemo | Temozolomide | Early Temo no effect on brain mets |
| MDA-MB-231Br-HER2 | #15 | SMI (TKI) | Lapatinib, 30 or 100 mg/kg | Intracardiac/Histology | Micromets no effect; Large mets ↓ 50-53% |  | [70] |
| SUM149 | #36 | SMI (TKI) | Buparlisib ± Selumetinib | Intracranial/Survival | OS ↑ to 52-87 D (vs Control, 45 D) |  | [71] |
| Selumetinib ± Pazopanib | OS ↑ to 63-92.5 D (vs Control, 34 D) |  |
| MDA-MB-436 | #37 | Buparlisib ± Selumetinib | OS no effect |  |
| Selumetinib ± Pazopanib | ND |  |
| MDA-MB-468 | #38 | Buparlisib ± Selumetinib | OS no effect |  |
| Selumetinib ± Pazopanib | ND |  |
| MDA-MB-231Br | [67] | Buparlisib ± Selumetinib | OS ↑ to 37-55 D (vs Control, 30 D) |  |
| Selumetinib ± Pazopanib | OS ↑ to 38 D (vs Control, 28 D) |  |
| H1-DL2 | #55 | SMI (TKI) | Buparlisib ± Trametinib | Subcutaneous | ↓ tumor vol |  | [73] |
| BT474 | #30 | Targeted | Ado-trastuzumab emtansine | Intracranial/Survival | TDMI ↑ OS 4x (vs trast) | NCT03190967 NCT01494662 | [34] |
| Intracarotid/Survival | TDMI OS HR 10.98 (vs trast) |
| Lapatinib ± Trastuzumab ± Anti-VEGFR2 DC101 | Intracranial/Survival | OS: DC101 ↑ >2.4x; Dual HER2i ↑ 2x; HER2i + DC101 ↑ >2.5x; Triplet ↑ 5x | NCT00543504 | [74] |
| Buparlisib ± LJM716/ Pertuzumab | Intracranial/Survival | OS HR ≤ 0.20 (doublets vs buparlisib alone) | NCT01026142 | [75], [82] |
| Trastuzumab/Neratinib ± LJM716/ Pertuzumab | Intracranial/Survival | OS HR ≤ 0.25 (doublets vs buparlisib alone) |
| Intracarotid/Survival | OS HR 0.30 (trast + LJM716 vs trast alone) |
| TDM-1 ± Macitentan | Intracranial/Survival | Combo ↑ OS >1.25x (vs TDM-1 alone) |
| MDA-MB-361 | #31 | Targeted | Buparlisib ± LJM716/ Pertuzumab | Intracranial/Survival | OS HR ≤ 0.20 (doublets vs buparlisib alone) |
| Ado-trastuzumab emtansine | Intracranial/Survival | TDMI ↑ OS 2.7x (vs trast) | NCT03190967 NCT01494662 | [34] |
| MDA-MB-231Br | #14 | Nanoparticle | Liposomal irinotecan (nal-IRI) | Intracardiac/Survival | Nal-IRI ↑ OS >32% (vs vehicle) | NCT03328884 NCT01770353 | [76] |
| HA-paclitaxel conjugate | HA-paclitaxel ↑ OS >30% (vs vehicle) |  | [79] |
| A549 | [77] Caliper | Nanoparticle | PRINT-(C2)-docetaxel | Intracranial/Survival | PRINT-C2-PRINT↑ OS >40% (vs PBS) |  | [77] |
| MDA-MB-231Br | [79] | Nanoparticle | Doxil® (liposomal docetaxel) ± Veliparib | Intracranial/Survival | Doxil ± Veliparib ↑ OS >20% (vs PBS) | NCT00465673  NCT00795678 | [78] |
| D4M | [81] | IT | Anti-PD1 ± radiation | Intracranial/Survival | Anti-PD1+radiation ↑ OS >2x (vs control or alone) | NCT02978404 | [81] |
| B16 | [26] ATCC | IT | Anti-PD1 ± Anti-CTLA4 | Intracranial/Survival | Anti-PD1+Anti-CTLA4 ↑ OS (vs control or alone) | NCT02374242 | [26] |
| B16F10 | [87] ATCC | IT + Radiation | Anti-CD25 + WBRT, 15Gy | Intracranial/Survival | Anti-CD25 + 15Gy ↑ OS (vs 15Gy alone and control) |  | [87] |
| PC14-PE6 | #46 | Anti-angiogenic | Anti-VEGF-A | Carotid/Imaging | Anti-VEGF-A ↓ angiogenesis, macrometastases |  | [55] |
| MDA-MB-435 | [55] | Anti-VEGF-A no effect on angiogenesis or growth |  |
| TS1\_BrM2 | #11 | Cell Based | TRAIL HSCs | Intracranial/Survival | IV TRAIL HSCs ↑ OS >1.25x (vs control) |  | [83] |
| MDA-MB-231Br | #1 | Novel | VBY-999 (Cathepsin S inh) | Intracardiac/BLI | VBY-999 ↓ brain mets 65-77% if treat early |  | [84] |
| Tonabersat/Meclofenamate ± Carboplatin | Intracardiac/BLI | Tona and Meclo alone and with Carbo ↓ brain mets, ↓ growth of established brain mets | NCT02429570 | [85] |
| H2030-BrM3 | #39 | Novel |
| H1\_DL2 | #55 | Novel | K16ApoE ± Dabrafenib | Intracardiac/MRI, OS | K16+dabra ↓brain mets 30%, ↑OS >1.2x (vs. dabra) |  | [88] |
| MDA-MB-231Br | #14 | Novel | GSK461364A | Intracardiac/Histology, OS | GSK ↓ large brain mets 43-62%, ↑ OS >17% |  | [91] |
| BT478 | [51] | Novel | Apomorphine | Intracardiac/FACS | Apo ↓ brain mets from intracardiac 100% |  | [51] |
| B16/F10-BrM | #47 | Novel | Silibinin (STAT3 inhibitor) | Intracardiac, intracranial/BLI, Histology | Silibinin ↓ large brain mets 56-62% in mice and 75% of ORR in patients with ↑ OS from 4 to 15 months |  | [53] |

**Supplementary Table 2.** Preclinical therapies applied to experimental brain metastatic cells *in vivo* and translation to clinical trials.

1. [↑](#endnote-ref-1)
2. (i)See Table 1. (ii) Abbreviations: BLI = bioluminescence intensity; Chemo = chemotherapy; D = days; HR = hazard ratio; HSCs = hematopoietic stem cells; inh = inhibitor; IT = immunotherapy; IV = intravenous; mets = metastases; mTKI = multi-tyrosine kinase inhibitor; ND = not determined; OS = overall survival; ORR = overall response rate; RT = radiation therapy; SMI = small molecule inhibitor; SRS = stereotactic radiosurgery; TKI = tyrosine kinase inhibitor; vol = volume; WBRT = whole brain radiation therapy. [↑](#endnote-ref-2)