PI3K Inhibitor Synergistically Boosts HER2-Targeted Antibody/ADC Therapy in Brain Metastatic Breast Cancer

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Abstract

Breast cancer brain metastases (BCBM) have limited therapeutic options, and PI3K pathway activation is a major driver of resistance to HER2-targeted therapies. We evaluated whether PI3Kα inhibition enhances the efficacy of trastuzumab/pertuzumab (HP) or trastuzumab-deruxtecan (T-DXd) in HER2-positive BCBM. Using three complementary HER2+ brain metastasis models—a syngeneic py8119-hHER2 intracardiac/intracranial brain metastasis model in immunocompetent mice, an intracranial BT474 HER2+ brain metastasis model in NOD/SCID mice, and a human HER2 + BCBM patient-derived xenograft (PDX) model—we compared Inavolisib monotherapy with combination regimens. Inavolisib alone produced minimal intracranial tumor control, whereas combining Inavolisib with HP or T-DXd resulted in marked brain tumor shrinkage and significantly prolonged survival across all models. The Inavolisib + high-dose T-DXd group achieved the greatest benefit, with near-complete suppression of brain tumor signal and the most pronounced improvement in neurological behavior. Disease control was durable and exceeded that of current standard regimens. Combination treatment was well-tolerated, with no significant weight loss or overt added toxicity. Overall, these data demonstrate robust, reproducible therapeutic synergy between PI3Kα inhibition and HER2-targeted antibody/ADC therapy in multiple HER2+ BCBM models and support clinical exploration of PI3K inhibitor–based combinations to improve intracranial disease control in HER2-positive BCBM.

Introduction

Breast cancer brain metastases occur in ~15–30% of metastatic breast cancer patients and confer poor prognosis, with a median survival of only ~6 months despite current treatments[1]. Novel systemic strategies are needed to improve intracranial disease control. The PI3K–AKT signaling pathway is frequently upregulated in BCBM, identified in the majority of metastatic lesions regardless of breast cancer subtype[1]. PI3K activation promotes tumor cell survival and therapeutic resistance; for instance, loss of PTEN or activating PIK3CA mutations (common in ~50% of breast cancers) drive PI3K hyperactivation and have been associated with poor response to trastuzumab and shorter survival[2]. These observations implicate PI3K as a key therapeutic target in HER2-positive BCBM. Indeed, combining PI3K pathway inhibitors with HER2-targeted therapy is a rational approach to overcome resistance, and a brain-penetrant PI3K inhibitor (paxalisib) is already under clinical trial with trastuzumab in HER2+ BCBM patients[3]. Inavolisib (GDC-0077) is a potent selective PI3K-alpha inhibitor recently approved for PIK3CA-mutant breast cancer, with unique capacity to degrade mutant p110α and improved tolerability[4]. Trastuzumab deruxtecan (T-DXd) is a HER2-targeted antibody-drug conjugate shown to penetrate brain lesions and induce intracranial responses in pretreated HER2+ patients[5]. We hypothesized that combining Inavolisib with HER2-targeted antibodies (trastuzumab/pertuzumab) or T-DXd would synergistically suppress HER2+ BCBM growth. Here, we evaluated the therapeutic efficacy of this combination in both murine and human xenograft HER2+ BCBM models and explored the underlying mechanisms, including effects on tumor biology and the brain metastatic microenvironment.

Methods and Materials

Study models

These HER2-positive breast cancer brain metastasis (BCBM) models were used:
(1) py8119-hHER2 intracardiac/intracranial brain metastasis model in immunocompetent mice;
(2) Intracranial BT474 HER2+ brain metastasis model in NOD/SCID mice;
(3) human HER2+ BCBM patient-derived xenograft (PDX) in NOD/SCID mice.
Mice (n = 5-8/group) were randomized once brain lesions were confirmed by bioluminescence imaging (BLI).

Treatment regimens

The PI3Kα inhibitor Inavolisib was given once daily. Combination arms received Inavolisib plus trastuzumab/pertuzumab (HP) or T-DXd. A tucatinib + trastuzumab + capecitabine (TTC) regimen served as standard-of-care comparator; vehicle/IgG served as controls. Treatment continued for 4–6 weeks or until humane endpoints.

Efficacy and mechanistic analyses

Overall survival (Kaplan–Meier), intracranial tumor burden (weekly IVIS BLI; endpoint MRI in PDX), body weight and clinical signs were recorded. Mechanistic studies included spatial transcriptomics on brain sections and IHC for Ki-67, cleaved caspase-3, and CD3/CD8. In the syngeneic model, flow cytometry quantified infiltrating immune cells. HER2+ cell lines were treated with Inavolisib ± T-DXd; viability/apoptosis were measured and synergy assessed by Bliss analysis.

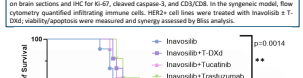


Figure 1. Inavolisib combinations improve survival in intracardiac py8119-HER2+ BCBM

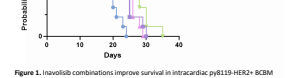


Figure 2. Survival benefit of Inavolisib + T-DXd/HP in HER2+ BCBM PDX

Results

1. PI3K inhibition plus HER2 therapy markedly prolongs survival

Across py8119-hHER2, BT474, and HER2+PDX BCBM models, Inavolisib monotherapy produced only modest delay of intracranial progression and little survival gain. In contrast, Inavolisib combined with T-DXd or HP significantly prolonged median survival and delayed neurologic decline versus single agents and TTC. The Inavolisib + high-dose T-DXd arm achieved the longest survival and most durable disease control.

2. Combination therapy robustly reduces brain tumor burden with a clear dose–response

Serial IVIS and MRI imaging showed that combination groups had markedly lower brain bioluminescence than vehicle or monotherapy by week 3, with many mice in the Inavolisib + high-dose T-DXd group having signals near or below the detection limit. Histology confirmed much smaller, necrotic metastases in combination-treated brains. Body weight and general condition remained stable across groups, indicating that the enhanced intracranial control was achieved without added systemic toxicity.

3. Mechanistic studies show decreased proliferation, increased apoptosis, enhanced immune infiltration

Spatial transcriptomics and IHC demonstrated reduced proliferation (↓Ki-67), increased apoptosis (↑cleaved caspase-3), and a shift toward a less aggressive, luminal-like gene expression profile in combination-treated tumors. In the syngeneic model, flow cytometry and IHC revealed a several-fold increase in CD8+ T-cell and myeloid cell infiltration in the brain metastases. In vitro, Inavolisib + T-DXd induced supra-additive growth inhibition and apoptosis in HER2+ cells, confirming strong pharmacologic synergy.

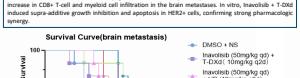


Figure 3. Dose-dependent survival with Inavolisib + T-DXd/HP in intracranial py8119-HER2+ model

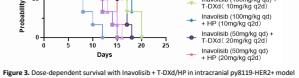


Figure 4. Dose-dependent IVIS tumor reduction with Inavolisib + T-DXd/HP

Discussion

This study demonstrates that PI3K pathway inhibition combined with HER2-directed therapy can overcome resistance and markedly improve intracranial disease control in HER2-positive breast cancer brain metastasis (BCBM). Across three complementary HER2+ brain metastasis models (py8119-hHER2, BT474, and PDX), we provide the first intracranial evidence that Inavolisib synergizes with both HER2 antibodies and a HER2-targeted ADC, achieving deeper tumor shrinkage and longer survival than standard regimens such as TTC. These findings extend prior observations that PI3K activation drives BCBM progression and anti-HER2 resistance[2][6][7], and are highly consistent with the emerging clinical activity of T-DXd in HER2+ brain lesions[5].

Mechanistically, our data suggest that PI3Kα blockade not only sensitizes tumor cells to HER2 antibody/ADC–mediated killing, but also reprograms the brain metastatic niche. We observed reduced proliferation, increased apoptosis, enhanced CD8+ T-cell and myeloid cell infiltration, and a shift toward a less aggressive, luminal-like transcriptional phenotype[6]. This dual impact—on tumor-intrinsic survival signaling and the immune microenvironment—provides a biological rationale for the robust and reproducible synergy seen across models. Importantly, Inavolisib-based combinations were well tolerated, which is critical in light of historical toxicity concerns with earlier PI3K inhibitors and the vulnerability of patients with BCBM. From a translational standpoint, our results support clinical testing of PI3Kα inhibitor–based combinations in HER2+ BCBM, particularly in patients with PI3K pathway alterations or suboptimal responses to current HER2-targeted regimens. Ongoing trials of PI3K inhibitors plus trastuzumab in HER2+ BCBM (e.g. NCT03765983) underscore the feasibility of this strategy. Future work should refine optimal partners (HP vs T-DXd and dosing), identify predictive biomarkers of benefit, and explore whether early introduction of PI3K inhibition can delay or prevent brain metastasis relapse. Overall, integrating PI3K pathway inhibition with HER2-targeted treatment offers a rational avenue to extend survival and preserve neurologic function in patients with HER2-positive brain metastases.

Conclusions

In multiple HER2-positive breast cancer brain metastasis models, PI3Kα inhibition with Inavolisib combined with HER2-targeted antibody therapy (trastuzumab/pertuzumab) or the ADC T-DXd produced robust synergistic antitumor activity, significantly prolonging survival and reducing intracranial tumor burden compared with monotherapy or standard TTC treatment. The efficacy of these combinations was consistently validated across immunocompetent murine, BT474, and human PDX brain metastasis models, with Inavolisib plus high-dose T-DXd achieving the deepest and most durable brain tumor control. Mechanistic analyses showed that dual PI3K/HER2 targeting not only suppresses tumor cell proliferation and enhances apoptosis, but also reshapes the brain metastatic microenvironment by increasing immune cell infiltration and shifting tumors toward a less aggressive, luminal-like phenotype. Importantly, these regimens were well tolerated, supporting the translational potential of PI3K inhibitor–based combinations as a rational strategy to overcome PI3K-mediated resistance, improve intracranial disease control, and ultimately enhance survival and neurological outcomes in patients with HER2-positive breast cancer brain metastases.

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References

[1] Xu, Y., Wang, Y., Wu, J., et al. Characterization and clinical pathway of brain metastasis in breast cancer. Front Immunol. 2025;16:1581553. https://doi.org/10.3389/fimmu.2025.1581553
[2] Ni, J., Ramkissoon, S. H., Xie, S., et al. Combination inhibition of PI3K-mTORC1-TORC2 pathway and mitotic checkpoint kinase TTK impedes migration and invasion of breast cancer cells. Cancer Res. 2016;76(1):148–161. https://doi.org/10.1158/0008-5472.CAN-15-0139
[3] Ma, C. X., Gao, F., Luo, J., et al. Neoadjuvant trastuzumab and chemotherapy with or without PI3K inhibitor GDC-0032 in HER2-overexpressing breast cancer: Primary results from the window of opportunity randomized phase II trial. Clin Cancer Res. 2017;23(13):3314–3325. https://doi.org/10.1158/1078-0432.CCR-16-2071
[4] Andre, F., Ciruelos, E. M., Juric, D., et al. Alpelisib plus fulvestrant for PIK3CA-mutated, hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: final overall survival results from SOLAR-1. Ann Oncol. 2021;32(2):208–217. https://doi.org/10.1016/j.annonc.2020.11.011
[5] Bartsch, R., Berghoff, A. S., Furtner, J., et al. Trastuzumab deruxtecan in HER2-positive breast cancer with brain metastases: a single-arm, phase 2 trial. Nat Med. 2022;28(9):1844–1851. https://doi.org/10.1038/s41591-022-01935-8
[6] Ni, J., Ramkissoon, S. H., Xie, S., et al. Combination inhibition of PI3K-mTORC1-TORC2 pathway and mitotic checkpoint kinase TTK impedes migration and invasion of breast cancer cells. Cancer Res. 2016;76(1):148–161. https://doi.org/10.1158/0008-5472.CAN-15-0139
[7] Ma, C. X., Gao, F., Luo, J., et al. Neoadjuvant trastuzumab and chemotherapy with or without PI3K inhibitor GDC-0032 in HER2-overexpressing breast cancer: Primary results from the window of opportunity randomized phase II trial. Clin Cancer Res. 2017;23(13):3314–3325. https://doi.org/10.1158/1078-0432.CCR-16-2071

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