of endocrine therapeutics, treatment-resistant relapse is a significant problem that affects 30-50% of patients who initially respond to endocrine therapy. Therefore, studying resistance to endocrine therapy is critical for breast cancer research.We have shown that invasive lobular breast cancer (ILC) cells resistant to the anti-estrogen tamoxifen increase their expression of metabotropic glutamate receptors (GRMs/mGluRs). GRMs are well-known to play important roles in learning and memory in the brain and protect neurons from excitotoxicity (cell death caused by prolonged exposure to neurotransmitters). It is now appreciated that this pro-survival function of GRMs can be highjacked by cancer cells, including breast cancer. Thus, targeting GRM signaling could prove a valuable therapeutic strategy. We chose to target the GRM signaling pathway with the FDA-approved drug Riluzole currently being used to treat amyotrophic lateral sclerosis.In this study, we test the ability of Riluzole to reduce cell growth, alone and in combination with endocrine therapy, in a diverse set of ER+ invasive ductal and lobular breast cancer-derived cell lines, primary breast tumor explant cultures, and the estrogen-independent, ESR1-mutated, ILC-derived patient-derived xenograft model HCI-013EI. In addition to measuring tumor growth rate and size, primary tumors and organs were collected for immunohistochemistry analysis.Riluzole as a single agent suppressed the growth of ER+ invasive ductal and lobular breast cancer cell lines in vitro, inducing differential histologic subtype-associated cell cycle arrest (G0-G1 for ductal, G2-M for lobular). In tamoxifen-resistant ILC cells, Riluzole induced apoptotic and ferroptotic cell death, and inhibited phosphorylation of focal adhesion kinase. Riluzole combined with either fulvestrant or 4-hydroxytamoxifen additively or synergistically suppressed ER+ breast cancer cell growth in vitro. Using proliferating cell nuclear antigen (PCNA) staining as a proxy for cell proliferation, the combination of Riluzole plus Fulvestrant significantly reduced PCNA in a patient-derived explant model (t-test $p = 0.013$). The in vivo experiment showed reduced tumor size and growth between the control and combination treatments. However, unlike in the in vitro experiment, there was little difference between the single-agent fulvestrant and the combination groups. The observed difference between the in vitro and in vivo study may be attributed to the bioavailability of Riluzole in mice.In conclusion, our results show that Riluzole enhances response to endocrine therapy in ER + breast cancer.

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Riluzole suppresses growth and enhances response to endocrine therapy in ER+ breast cancer

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Approximately 75% of breast cancers are classified as hormone receptor-positive, most of which are estrogen receptor alpha-positive (ER+), which is the primary driver of growth in these tumors. Consequently, endocrine or anti-estrogen therapy is used for treatment. However, despite the benefits