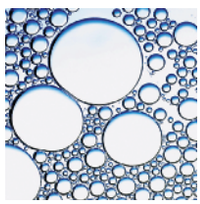
Drug Discovery

Major finding: Vacquinol-1 is a small molecule that kills glioblastoma cells by causing extreme vacuolization.

Concept: Vacquinol-1 induces membrane ruffling and massive macropinocytosis that eventually ruptures cells.

Impact: Compounds that induce catastrophic vacuolization in cancer cells may be therapeutically effective.

A SMALL MOLECULE INDUCES CATASTROPHIC VACUOLIZATION IN GLIOBLASTOMA



The genomic complexity and diversity of glioblastoma multiforme (GBM), a highly malignant and currently incurable form of brain cancer, have hindered efforts to develop targeted therapies. Hypothesizing that GBM may acquire unique alterations to cellular functions not directly involved in cell growth or transformation that could be exploited for the development of novel therapeutic approaches, Kitambi and colleagues tested a library of compounds for their ability to selectively retard the growth of patient-derived GBM cell lines. Candidate compounds were evaluated for *in vivo* toxicity and efficacy in a zebrafish GBM model. The most potent compound, dubbed "Vacquinol-1" because of its quinolone-alcohol scaffold, rapidly induced ATP loss and GBM cell death, but not through apoptotic or autophagic mechanisms. Instead, Vacquinol-1 induced cell rounding, membrane ruffling, and widespread macropinocytosis, or fluid internalization, that subsequently led to massive vacuolization, cell rupture, and necrotic-like cell death. A short hairpin RNA screen revealed that Vacquinol-1–induced cell death was dependent on activation of MAP kinase kinase 4 (MKK4), though the mechanism of MKK4 activation and the role of MKK4 in vacuolization remain unclear. Preclinical profiling of Vacquinol-1 predicted high membrane permeability and metabolic stability in liver cells; accordingly, the compound showed rapid *in vivo* tissue dispersal, high stability, and low plasma clearance in mice, raising the possibility that Vacquinol-1 could be used in treatment of GBM. Indeed, Vacquinol-1 strongly inhibited growth of patient-derived GBM xenografts in zebrafish, and orally administered Vacquinol-1 dramatically attenuated tumor growth and prolonged survival in tumor-bearing mice that had been intracranially injected with patient-derived GBM cell lines. Together, these data suggest that GBM cells are distinguished by their sensitivity to excessive vacuolization, and that targeting this vulnerability with compounds such as Vacquinol-1 may have clinical benefit. ■

Kitambi SS, Toledo EM, Usoskin D, Wee S, Harisankar A, Svensson R, et al. Vulnerability of glioblastoma cells to catastrophic vacuolization and death induced by a small molecule. Cell 2014;157: 313–28.

Clinical Trials

Major finding: The combination of an antiestrogen and a PI3K inhibitor is safe, well tolerated, and active.

Concept: The combination of buparlisib and letrozole had activity regardless of *PIK3CA* hotspot mutation status.

Impact: Combination PI3K and aromatase inhibitor therapy may have clinical benefit in ER-positive breast cancer.

BUPARLISIB AND LETROZOLE HAVE ACTIVITY IN METASTATIC BREAST CANCER

Preclinical studies have indicated that phosphoinositide-3-kinase (PI3K) signaling contributes to endocrine therapy resistance and estrogen-independent growth of estrogen receptor (ER)–positive breast cancer cells, suggesting that the combined use of PI3K inhibitors and antiestrogens would be beneficial. Mayer and colleagues performed a multicenter, open-label phase Ib trial of buparlisib, an oral pan-PI3K inhibitor, in combination with the oral aromatase inhibitor letrozole in patients with metastatic ER-positive breast cancer. The study had two arms, with 20 patients receiving continuous buparlisib treatment and 31 patients receiving buparlisib intermittently, and almost every patient had previously received endocrine therapy. The primary objective was to assess the safety and tolerability of buparlisib plus letrozole and the secondary objectives were to evaluate antitumor activity and tumor metabolic responses. Buparlisib and letrozole combination therapy was well tolerated, with few serious adverse events; the most commonly observed adverse events were gastrointestinal disorders, transaminitis, hyperglycemia, and mood disorders. In the continuous arm, 1 (5%) patient had a complete response and 1 (5%) patient had a partial response, and 11 (55%) had stable disease. In the intermittent arm, 14 (45%) patients had stable disease. Of 7 patients with stable disease lasting a year or longer, 3 (43%) had tumors with hotspot mutations in the PI3Kα catalytic subunit gene *PIK3CA*. Additionally, 3 of 9 (33%) patients who had a metabolic partial response as measured by [^{18}F]fluorodeoxyglucose uptake had *PIK3CA* mutations. Although the clinical activity of buparlisib and letrozole was not limited to breast cancers with *PIK3CA* mutations, it remains possible that other alterations in the PI3K pathway in these tumors conferred buparlisib sensitivity. Collectively, these findings indicate that combined use of a PI3K inhibitor and an antiestrogen is safe and effective in patients with endocrine therapy–refractory metastatic ER-positive breast cancer and support further evaluation of buparlisib and letrozole combination therapy in larger clinical trials. ■

Mayer IA, Abramson VG, Isakoff SJ, Forero A, Balko JM, Kuba MG, et al. Stand up to cancer phase Ib study of pan-phosphoinositide-3-kinase inhibitor buparlisib with letrozole in estrogen receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol 2014 Mar 24 [Epub ahead of print].