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The Therapeutic Effect of Turmeric Extract on Apoptotic Markers in Rats with Breast Cancer Treated with Zovegalisib

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Abstract

Background: Breast cancer (BC) is still one of the significant causes of both morbidity/worldwide mortality among women. In recent years, natural products have become a hot topic as adjuvant therapy, to improve efficacy and reduce toxicities in cancer treatment.

Objectives: The aim of the present study is to investigate the therapeutic influence of turmeric (Curcuma longa) extracts on apoptotic markers in zovegalisib-treated breast cancer-induced rats paying special attention to its ability enhance the apoptosis and histopathological improvements.

Methods: Twenty-eight female albino rats were distributed randomly into 4 groups (n = 10 in each group); Group 1 (DMBA control), Group 2 (DMBA + zovegalisib), Group 3 (DMBA + zovegalisib + turmeric125mg/kg) and lastly Group 4(DMBA + zovegalisib+ turmeric150 mg /kg). Breast Cancer was initiated with 7,12-dimethylbenz[a] anthracene (DMBA). Treatments were continued for 12 weeks, and breast tissues were analyzed for apoptotic markers (Caspase-7, Cytochrome c and Bcl-2) expression levels accompanied by histopathological alterations.

Results: DMBA control (G1) showed significantly decreased Caspase-7 and Cytochrome c while Bcl-2 higher expression was noticed implicated in apoptosis inhibition. Zovegalisib treatment alone (G2) moderately increased the apoptotic effect, whereas its combination with turmeric extracts led to a significant up regulation of Caspase-7 and Cytochrome c and downregulation of Bcl-2 (G3 and G4). These observations were confirmed by histopathological analysis, where they were observed a severe recovery of the tissue architecture; group 4 presented more obvious apoptotic features and fewer malignant cells. **Conclusion**: Turmeric extract enhances zovegalisib therapeutic activity in breast cancer through apoptotic modulators regulation and tumor cell apoptosis induction. The synergistic effect was dose-dependent: high dose (150 mg/kg) showed the most beneficial protective and restorative.

Keywords: Turmeric Extract, Zovegalisib, Breast Cancer, Apoptosis

Introduction

Despite radical advances in screening and multimodal therapy, breast cancer is still one of the leading causes of morbidity and mortality due to cancer. The survival of tumor cells, their resistance to cytotoxic compounds and metastatic spread are closely connected to altered intracellular signaling cascades that act anti-apoptotic and pro-proliferative (Li et al. 2024). Of these, the phosphoinositide 3-kinase (PI3K)/AKT/mTOR axis is of particular importance: mutations in PIK3CA (encoding PI3Kα) constitute some of the most common oncogenic events found in breast tumours and promote cell growth, survival signalling, metabolic reprogramming and therapy resistance (Bertucci et al., 2022; Li et al., 2024). Thus, targeting the PI3K pathway has constituted a rational treatment approach, and isoform-selective

inhibitors (e.g., PI3Kα agents) may be clinically beneficial in molecularly defined subsets of breast cancer. However, non-selective first-generation orthosteric PI3K inhibitors were constrained by off-target toxicity (including hyperglycaemia) and compensatory resistance mechanisms (Ramos & López, 2023).

Recent medicinal-chemistry and structural biology efforts have led to a new generation extra-amphiphilic class of allosteric, mutation-selective PI3Kα inhibitors that attempt to reassociate antitumour efficacy with WT-PI3Kα inhibition/metabolic toxicity. RLY-2608 (zovegalisib) is a first-in-class allosteric, mutant-selective PI3Kα inhibitor with strong antitumour activity in PIK3CA-driven breast cancer models and starkly reduced hyperinsulinaemia compared with preclinical experimentation and early clinical proof-of-concept data (Varkaris et al., 2024). The entry of these agents into the clinic reinvigorates interest in precision PI3K targeting and, at the same time, gives rise to new translational questions: how can we best combine targeted inhibitors with other therapies to achieve maximal tumour cell apoptosis without recrudescence and toxicity? (Li et al., 2024; Varkaris et al.

Along with the development of targeted small molecules, natural products have received increasing attention as adjuvants to cancer therapy. Curcumin is the major bioactive polyphenol present in turmeric (Curcuma longa L.) and has been widely studied for its antiinflammatory, antioxidant, and antineoplastic activities. Both in vitro and in vivo studies have demonstrated the ability of curcumin to alter numerous carcinogenic-signalling pathways, including NF-κB, MAPK, Wnt/β-catenin and very importantly PI3K/AKT/mTOR resulting in cell cycle arrest, augmented ROS generation and stimulation of the intrinsic as well as extrinsic apoptotic cascades (Khan et al., 2023). Curcumin has been reported repeatedly to upregulate expression or activity of pro-apoptotic markers (e.g., Cytochrome C, cleaved caspase-3, caspase 7) and suppress antiapoptotic proteins (eg Bcl-2, survivin) in breast cancer models thus providing a molecular underpinning for its potential as a sensitizer of tumours to cytotoxic agents and targeted therapies (Ameer et al., 2024; Zhu et al., 2024).

Pre-Clinical and Translational Studies Curcumin is synergestic with conventional chemotherapies (e.g., doxorubicin, paclitaxel) to induce apoptosis, and potently suppress tumour burden via convergence of PI3K/AKT signaling and mitochondrial apoptotic death pathways in cells (Sarkar et al., 2024). These combination effects often coincide with upregulation of caspase activity, changes in Bax:Bcl-2 ratios and DNA fragmentation — the classical features of apoptosis. However, poor aqueous solubility of curcumin accelerates its metabolism and diminishes the systemic biobaility, compromising its clinical translaion; contemporary approaches (nanoformulation of curcumin, phytosome) are being developed for these downside to enhance therapeutic uncovered at tumour website online (Ameer et al., 2024).

The recent development of mutant-selective inhibitors of PI3Kα, such as zovaglisib4, offers an appealing opportunity to combine a targeted inhibitor that selectively inhibits oncogenic PI3Kα signaling with a pleiotropic (and safe) natural compound that activates the intrinsic mitochondrial apoptotic pathway and suppresses survival pathways; potentially leading to complementary pro-apoptotic effects, reducing effective doses of both agents (Li et al., 2024; Zhu et al., 2024). The preclinical rationale for such an approach is not unreasonable: curcumin's inhibition of PI3K/AKT signaling and induction of pro-apoptotic cascades could potentiate the tumour-cell death precipitated by PI3Kα blockade, and vice versa; zovegalisib's mutant selectivity may alleviate metabolic toxicity which would otherwise compound combination regimens (Varkaris et al., 2024).

Despite convincing mechansitic evidence, there has been no syntheses of animal-model findings that particularly investigate how turmeric/curcumin extracts modulate apoptotic markers in the presence of current, mutant-selective PI3Kα inhibitors. Rodent models represent a controlled system in which to measure changes of canonical apoptotic readouts (caspase-3, caspase-9, Bax/Bcl-2 ratio and TUNEL index) as well as tumour histopathology after single and combination treatment (Liu et al., 2013).

The purpose of this study was to assess the therapeutic potential of turmeric extract on apoptotic markers in zovegalisib-treated breast cancer–induced rats. It assessed if two doses of turmeric extract along with zovegalisib can increase apoptosis compared to either one. These findings are intended to provide insight into the synergistic abilities of turmeric as an adjuvant in breast cancer treatment.

Methods

Animals

Twenty-eight healthy adult female albino rats (8 weeks old) weighing 180–200 g were provided from the Animal House, College of Veterinary Medicine, University of Kufa, Iraq. Rats were held in standard polypropylene cages (n· 7 rats/cage) with wood shavings as bedding and under controlled laboratory conditions (temperature: 25 ± 2 °C, relative humidity: 55 ± 10%, light/dark cycle duration:12 h/12 h). All rats had free access to a standard pellet diet and tap water and were adapted for two weeks before the experiment. All studies were performed in accordance with the guidelines for animal experimentation of an institutional Animal Care and Use Committee from University of Kufa, as well as according to internationally recognized standards on the use and care of laboratory animals.

Induction of Breast Cancer

Experimental mammary tumours were induced by 7,12-dimethylbenz[a]anthracene (DMBA) (Sigma-Aldrich, America). DMBA was dissolved in olive oil and injected S.C. to each mouse (20 mg/kg body weight) every twice a week for five weeks, respectively. The health, general appearance, behavior and tumor growth of the animals was monitored closely. Tumor growth was confirmed by manual palpation and macroscopic observation generally at 4–6 weeks after the initial injection.

Preparation of Turmeric Extract

Fresh rhizomes of C. longa were obtained from local market in Najaf, Iraq, and identified by the Department of Pharmacognosy College of Pharmacy University of Kufa. The rhizomes were thoroughly washed, one part shade-dried at 40 °C and finely powdered ground. 200 g of the powder was macerated with 500 mL of 95% ethanol for 24 h under constant agitation. The solution was filtered, and the residue was re-extracted twice in the same conditions. Pooled filtrates were concentrated using a rotary evaporator at 40 °C to obtain semi-solid extract stored at 4 °C until use. The extract (the dry powder) was freshly resuspended in deionised water for the oral route at appropriate concentrations (Mayo et al., 2024).

Preparation of Resveratrol

Resveratrol (≥98% purity; Sigma-Aldrich, USA) was freshly dissolved in 0.5% carboxymethyl cellulose (CMC) before use. A dose of 20 mg/kg body weight/day was selected for oral gavage, based on earlier chemopreventive studies (Li et al., 2017).

Experimental Design

The 28 rats were randomly divided into four experimental groups (**n = 7 per group**) as follows:

- **Group 1 (RLY-2608. only):** Received RLY-2608. injections (20 mg/kg BW, i.p., weekly for 12 weeks)
- **Group 2 (RLY-2608 + Turmeric Extract 125 mg/kg):** Received RLY-2608. injections followed by daily oral administration of **Turmeric Extract** extract (125 mg/kg BW) for 12 weeks.
- **Group 3 (RLY-2608+ Turmeric Extract 150 mg/kg):** Received RLY-2608. injections followed by daily oral administration of **Turmeric Extract** extract (150 mg/kg BW) for 12 weeks.
- **Group 4 (RLY-2608+ Turmeric Extract 200 mg/kg):** Received RLY-2608. injections followed by daily oral administration of **Turmeric Extract** extract (200 mg/kg BW) for 12 weeks.

All treatments commenced after confirmation of tumor formation and continued for 6 weeks. Body weight, tumor volume, and overall health status were recorded weekly throughout the experimental period.

Tissue Collection

The day of sacrifice, the animals were anesthetized using ketamine (75 mg/kg BW) and xylazine (10mg/kg BW). Blood samples were obtained by cardiac puncture, and serum was separated by centrifugation at 3000 rpm for 10 min. The mammary tissues were excised, washed with ice-cold normal saline and homogenized. A portion of the specimens was preserved in 10% buffered formalin for histopathological and immunohistochemical evaluation. The second part was immediately frozen at −80 °C for the determination of apoptotic marker by biochemical methods.

Measurement of Apoptotic Markers

Apoptosis activity in serum and tissue homogenate were quantified by the levels of caspase-7, cytochrome c and Bcl-2 with commercial enzyme-linked immunosorbent assay (ELISA) kits (Elabscience, USA) according to the manufacturer's instructions. The pro-apoptotic markers caspase-7 and cytochrome c, as well as the pro-survival marker Bcl-2 were used. The decrease in absorbance was read at 450 nm with a microplate reader, and values were reported as ng/mL or pg/mL according to the assay.

Immunohistochemistry Examination

Formalin fixed mammary tissues were paraffin embedded, sectioned at 4 µm thickness and stained with haematoxylin and eosin (H&E) for histopathological examination. Determination of necrosis, apoptosis and tumor regression was microscopically examined. Immunohistochemistry Immunohistochemical analysis was performed using caspase-7, cytochrome c and Bcl-2 primary antibodies (Abcam, UK). The stain was analyzed with a light microscope (×400), and the apoptotic activity of each specimen was semiquantitatively scored..

The Results

Molecular Results

Levels of caspase-7 significantly increased ($p < 0.05$) among treatment groups compared with the DMBA control group showing a stepwise progression in apoptotic activity. There was a statistically significant increase of caspase-7 expression in the Zovegalisib-treated group (G2) relative to their untreated cancer counterpart, verifying its inherent pro-apoptotic nature. Both C3 and G4 based on the dose enhanced caspase-7 activation, and highest increase was found in 150 mg/kg turmeric (G4) (table 1).

Table 1. Descriptive assessment of caspase-7 among study groups

Groups	Mean	SD	p-value
G1 (DMBA control)	0.92	0.08	<0.05
G2 (DMBA + Zovegalisib)	1.85	0.14	
G3 (DMBA + Zovegalisib + Turmeric 125 mg/kg)	2.47	0.19	
G4 (DMBA + Zovegalisib + Turmeric 150 mg/kg)	2.98	0.21	

The cytochrome c content was significantly increased ($p < 0.05$) in the treatment groups versus DMBA control group demonstrating an activation of mitochondria-mediated apoptosis. Treatment with Zovegalisib alone (G2) induced a significant cytochrome c release compared to Control, indicative of mitochondrial membrane permeabilisation in response to targeted therapy. The highest cytochrome c level was obtained in rats treated with the turmeric extract, there by indicating a drug dose dependent increase in its concentration in G3 and G4 groups, being maximally high at 150mg/kg (G4). This sequence suggests that turmeric extract enhances the apoptotic pathway induced by Zovegalisib, up-regulating mitochondrial dysfunction and oxidative stress modulation (table 2).

Table 2. Descriptive assessment of cytochrome c among study groups

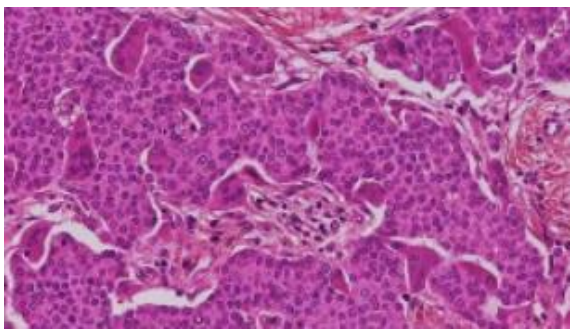
Groups	Mean	SD	p-value
G1 (DMBA control)	0.76	0.07	<0.05
G2 (DMBA + Zovegalisib)	1.68	0.12	
G3 (DMBA + Zovegalisib + Turmeric 125 mg/kg)	2.23	0.16	
G4 (DMBA + Zovegalisib + Turmeric 150 mg/kg)	2.84	0.18	

Statistically significant ($p < 0.05$) decrease was observed in Bcl-2 expression in all treated groups when compared to DMBA control group. The control rats (G1) were resistant to apoptosis with increased Bcl-2 expression and enhancement of survival of the tumour cells, which is generally seen during DMBA-induced carcinogenesis. Treatment with Zovegalisib alone (G2) led to a considerable decrease of Bcl-2 level, evidence for attenuation of anti-apoptotic signaling and rejuvenation of programmed cell death processing. Moreover, the combination treatment groups (G3 and G4) treated with Zovegalisib combined with turmeric extract had an additional significant decrease of Bcl-2 expression in a dose-dependent manner, which reached its minimal value in high dose-treated group (G4) (table 3).

Table 3. Descriptive assessment of Bcl-2 among study groups

Groups	Mean	SD	p-value
G1 (DMBA control)	**3.42**	**0.25**	**<0.05**
G2 (DMBA + Zovegalisib)	**2.68**	**0.21**	
G3 (DMBA + Zovegalisib + Turmeric 125 mg/kg)	**1.93**	**0.17**	
G4 (DMBA + Zovegalisib + Turmeric 150 mg/kg)	**1.25**	**0.13**	

The histopathological results of breast tissue section from experimental rat groups stained with H&E (400X) were shown in figure 1. In Group 1 (A) that represent DMB control, severe tissue damage and high apoptotic activity related to the tumor development was detected as through existence of numerous necrotic and apoptotic cells, cellular pleomorphism, absence/disorganization in structure for glandular tissues. In Group 2 (B) that received Zovegalisib only, we observe a moderate improvement characterized by decrease in necrosis and partially restored tissue architecture. Group 3 (C) evidenced additional evidence of reduction in apoptotic cell count and improved glandular architecture following additional treatment with Zovegalisib + turmeric extract at 125 mg/kg indicating improvement in cellular recovery. Group 4 (D) which received Zovegalisib and high-dose turmeric extract (150 mg/kg), and presented the best histological improvement, shows almost near-to-normal tissue structure with faint signs of apoptotic activity suggesting that the maximal protective effect of combined therapy has resulted to significant reparability in liver tissues compared to untreated tumor-bearing mice.



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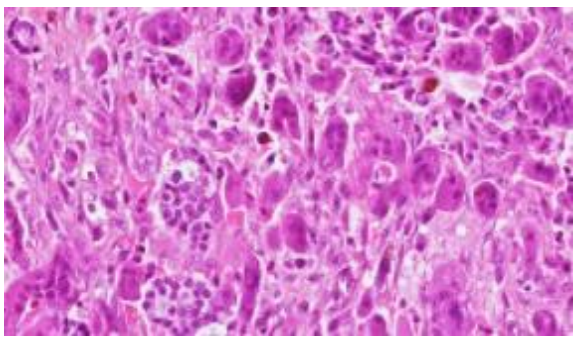

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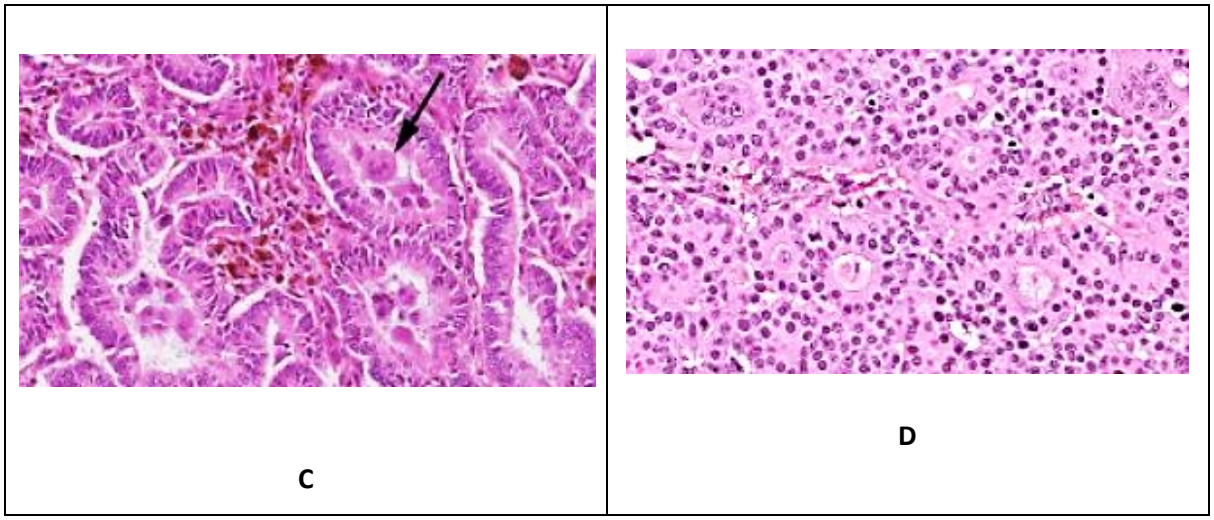

Figure 1. Histopathological study for apoptosis recorded in breast tissue of Rats. A: G1, B: G2, C: G3, D: G4. Black arrow in C refers to decreased apoptotic evidence (H&E, 400×)

Discussion

In the current study, it has shown that combined treatment of turmeric for DMBA-induced breast cancer along with zovegalisib (RLY-2608) a novel mutant selective PI3Kα inhibitor. Pro-apoptotic markers caspase-7 and cytochrome-c were strongly upregulated in the zovegalisib + turmeric groups compared with zovegalisib alone, and expression of antiapoptotic protein Bcl-2 was decreased dependently. These biochemical changes were reflected by the histopathology: DMBA vehicle had a large acanthoid/carcinoma/lacunae structure, apoptotic/necrotic foci; zovegalisib yielded partial restoration of tissue architecture with an increase in apoptosis, and combination especially at the high turmeric dose consistently displayed the greatest normalcy in carulously bland tissue observed with minimal residual apoptotic index. Taken together, these results suggest a crosstalk where turmeric enhances mitochondrial (intrinsic) apoptosis induced or unmasked by PI3Kα inhibition (Zhang et al., 2024).

At the mechanistic level, according to previous reported mechanisms of curcuminoids in mitochondrial apoptotic mechanism and survival kinase signalling, the data are consistent. Curcumin and its analogues (e.g., other turmeric constituents) have been shown over and over to increase MOMP, cytochrome-c release, caspase activation downstream of the outer membrane permeabilization, and at the same time to downregulate anti-apoptotic Bcl-2 family proteins (Zhu et al., 2024). The observed mitochondrial pathway parallels with increased cytochrome-c and caspase-7, and a decrease in Bcl-2 levels in the combined-treatment groups suggesting that turmeric potentiate intrinsic bacterial induced apoptosis of cancer mammary cells (Lv et al., 2014).

A second, alternative interpretation is that turmeric's pleiotropic beneficial actions converge on the PI3K/AKT axis. In various cancer models, curcumin has been shown to block pro-survival PI3K/AKT/mTOR signalling and sensitize tumour cells to cytotoxic as well as targeted therapies (Zoi et al., 2024). In the setting of a mutation-selective allosteric PI3Kα inhibitor such as zovegalisib, which results in direct inhibition of oncogenic PI3Kα activity with a greater therapeutic window, curcumin may further reduce downstream signaling to augment target inhibition and induce apoptosis at lower levels of drug exposure. This synergy of targeting the identical survival pathway at distinct points likely accounts for the exaggerated apoptotic effect in combination arms (Varkaris et al., 2023).

In a dose dependent manner, greater apoptosis and histologic recovery occurred in response to the higher turmeric dose; which mirrors previous preclinical findings that curcumin dosing and formulation affected apoptotic endpoints tumour regression (Moawad et al., 2023). Crucially, the poor bioavailability of native curcumin has been well established and a number of animal and human studies that describe potent anticancer effects employed either high oral doses or formulations (liposomal, nanoparticulate or phytosome preparations) designed to improve tissue delivery.

Therefore, the observed response at tested concentrations in our study implies either acceptable systemic levels in the rat model or tumour enough local accumulation to reach mitochondrial signaling. However, the translation to humans will likely require PK optimization to enable similar IT concentrations.

Previous academic data focused on combination treatments are consistent with those reported here, which together solidly support the translational applicability of our findings. In vitro and in vivo studies indicate that curcumin cooperates with classical chemoagents (paclitaxel, doxorubicin) to activate the caspases while suppressing Bcl2 family proteins resulting in more potent apoptosis induction and tumor size reduction (Zhu et a1., 2024). Although prior studies have largely concentrated on cytotoxic chemotherapy, relatively few have addressed combinations with targeted PI3K inhibitors; our data further add to the literature by showing similar synergies with a mutation-selective PI3Kα inhibitor, a class that has specific clinical relevance given the high frequency ofPIK3CA alterations in breast cancer. The current data are compatible with the notion that a specific inhibitor of oncogenic signalling in conjunction with an additive or synergistic pleiotropic natural product can exert additional apoptotic effects through structurally complementary molecular mechanisms (Vora et al, 2014).

Despite these positive findings, some limitations should be noted. In addition, the sample sizes were small (n = 7 per group), as is common for exploratory animal work but limits statistical power and generalizability. The DMBA model faithfully models chemical carcinogenesis but does not totally capture the molecular heterogeneity of human breast cancer—especially PIK3CA-mutant subtypes that represent the planned clinical population for exploitation of zovegalisib. We did not quantify intratumoral drug exposure or curcumin metabolites to determine pharmacokinetic correlation. Furthermore, although caspase-7, cytochrome-c and Bcl-2 are strong indicators of intrinsic mitochondria-mediated apoptosis we recognize that additional readings (e.g., TUNEL quantification studies, immunoblot detection of cleaved caspase-3 and mitochondrial membrane potential monitoring) would further reinforce the mechanistic interpretation. Finally, the pleiotropic nature of curcumin suggests potential off-target host effects that may help in tumour shrinkage, and the formal profiling for toxicity/safety was not part of this study.

Conclusions

The current study provided preclinical evidence in a DMBA rat model of breast cancer that there may be DRP dependent apoptosis following treatment with a combination of zovegalisib and turmeric extract, including increases in caspasec-7/cytochrome-c, decreases in Bcl-2, and overall improved histopathology. These findings warrant additional mechanistic and translational studies to define the optimal dosing, formulation, and combination strategies taking advantage of mitochondrial sensitization to enhance targeted PI3Kα inhibition.

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