Turk Neurosurg 36(2):294-301, 2026
DOI: 10.5137/1019-5149.JTN.48543-25.1

Systematic Review

Neuro – Oncology

Received: 30.01.2025
Accepted: 27.05.2025

Published Online: 04.03.2026

Evaluation of Drugs with Selective Inhibitors Targeting the Anti-Apoptotic Protein B-cell Lymphoma 2 (BCL-2) with Pro-Apoptotic and Antineoplastic Activities in Grade IV Glioblastoma

Murat BALOGLU[1], Tamer TAMDOGAN[2], Sevim ONDUL[2], Mehmet BAKIRTAS[3], Ibrahim YILMAZ[4,5]

[1]Republic of Türkiye, Ministry of Health, Eskisehir City Hospital, Clinics of Neurosurgery, Eskisehir, Türkiye
[2]Giresun University School of Medicine, Department of Neurosurgery, Giresun, Türkiye
[3]Republic of Türkiye, Ministry of Health, Doctor Ismail Fehmi Cumalioglu City Hospital, Department of Hematology, Tekirdag, Türkiye
[4]Republic of Türkiye, Ministry of Health, Doctor Ismail Fehmi Cumalioglu City Hospital, Department of Pharmacovigilance, Tekirdag, Türkiye
[5]Istanbul Rumeli University, Vocational School of Health Services, Department of Medical Services and Techniques, Istanbul, Türkiye

Corresponding author: Ibrahim YILMAZ ✉ dryilmazi@yahoo.com

ABSTRACT

AIM: To systemically review the efficacy, safety, and clinical applications of B-cell lymphoma 2 (BCL-2) family inhibitors such as venetoclax (ABT-199), navitoclax (ABT-263), and obatoclax (GX15-070) across different malignancies.

MATERIAL and METHODS: A systematic search was conducted in the PubMed database following PRISMA guidelines. Studies evaluating the pharmacological effects, preclinical findings, and clinical trial data of venetoclax, navitoclax, and obatoclax were included in the analysis. Key outcomes, including efficacy, resistance mechanisms, and adverse effects, were synthesized from the analysis.

RESULTS: Venetoclax demonstrated significant efficacy and a favorable safety profile in hematologic malignancies, particularly chronic lymphocytic leukemia and acute myeloid leukemia; however, no positive safety profile was observed in glioblastoma grade IV (GBM). Navitoclax combination treatments showed potential in various malignancies but were used in a limited manner due to dose-related thrombocytopenia. However, no clear data were available regarding its efficacy against GBM. Obatoclax demonstrated efficacy in preclinical studies; however, off-target effects and limited clinical success hindered its development. No clear data were available regarding its effectiveness against GBM. Resistance mechanisms, including upregulation of MCL-1 and BCL-xL, were commonly observed among these agents, highlighting the need for combination strategies.

CONCLUSION: Venetoclax, navitoclax, and obatoclax represented significant advances in apoptosis-targeted therapy, with venetoclax emerging as the most clinically successful agent. However, resistance mechanisms and side effects were significant challenges, necessitating further preclinical and clinical studies to optimize the therapeutic potential of these agents.

KEYWORDS: Drug resistance, Glioblastoma, Navitoclax, Obatoclax, Pelcitoclax, Venetoclax

Murat BALOGLU : 0000-0001-7727-1982
Tamer TAMDOGAN : 0000-0002-0526-1459
Sevim ONDUL : 0000-0003-4219-4862
Mehmet BAKIRTAS : 0000-0003-3216-482X
Ibrahim YILMAZ : 0000-0003-2003-6337

INTRODUCTION

Despite treatment with surgery, radiation, and oncologic drugs such as temozolomide, Grade IV glioblastoma (GBM), the most common malignant tumor of the central nervous system, leads to poor overall survival outcomes due to factors such as the blood-brain barrier and/or the blood-tumor barrier, glioma stem-like cells, and genetic heterogeneity (39). A key factor contributing to drug treatment failure in GBM is the presence of mechanisms underlying treatment resistance and the insufficiency of strategies to overcome it (8).

Therefore, scientists continue to investigate treatments for GBM, as they do for many hematologic and oncologic malignancies. A prominent focus of these studies is the evaluation of pharmacological agents that induce cancer cell death by modulating interactions between key intracellular proteins. In this context, B-cell lymphoma 2 (BCL-2) family protein members have been extensively studied and remain a focus of ongoing research.

Historically, BCL-2 family proteins have been identified as regulators of programmed cell death. Some members, such as BCL-2 and BCL-extra large (BCL-XL), inhibit apoptosis, while others, such as BCL-2–associated X protein (Bax) and BCL-2 antagonist/killer (Bak), promote cell death (6,31). Bax and its homolog, Bak, are essential regulators of the mitochondrial apoptosis pathway (4).

In high-grade brain tumors such as GBM, overexpression of BCL-2 may contribute to tumor cells' escape from apoptosis and the development of treatment resistance (40).

The first proposed mechanism by which BCL-2 exhibits pro-apoptotic and antineoplastic activity in GBM involves its inhibition of apoptosis; BCL-2 localizes to the mitochondrial membrane, where it blocks pro-apoptotic signals (36). Additionally, high BCL-2 expression in GBM cells may allow them to evade apoptosis and proliferate uncontrollably (10). The second mechanism involves the development of treatment resistance. Overexpression of BCL-2 may contribute to GBM treatment resistance, particularly to chemotherapy and radiotherapy. This resistance facilitates the survival of tumor cells during treatment and reduces treatment effectiveness (12,41).

Many BCL-2 protein family inhibitors have been developed in recent years, including venetoclax (ABT-199) (13), navitoclax (ABT-263) (24), obatoclax (GX15-070) (42), pelcitoclax (APG-1252) (23), and oblimersen sodium (G3139) (14), among others. These inhibitors are primarily used in leukemia, lymphomas, and other hematologic malignancies. Venetoclax promotes apoptosis by selectively inhibiting BCL-2, thereby facilitating programmed cell death. Navitoclax is a small-molecule inhibitor that targets anti-apoptotic proteins of the BCL-2 family, including BCL-2, BCL-xL, and BCL-w. Obatoclax, in contrast, inhibits BCL-2, BCL-xL, and myeloid cell leukemia sequence 1 (MCL-1). These inhibitors function by targeting BCL-2 proteins, which are key regulators of apoptosis and are frequently overexpressed in cancer cells, leading to apoptotic resistance. Consequently, researchers have investigated the potential pro-apoptotic and antineoplastic effects of selective BCL-2 inhibitors in GBM.

A review of the literature revealed a lack of high-quality studies evaluating these inhibitors in combination. This study aims to evaluate the effects of selective BCL-2 inhibitors on GBM.

MATERIAL and METHODS

Search Strategy

This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (33). Searches were performed in PubMed, one of the electronic databases. Studies published up to January 26, 2025, were evaluated. Sequential searches were performed using the keywords "venetoclax (ABT-199)", "navitoclax (ABT-263)", "obatoclax (GX15-070)", "pelcitoclax (APG-1252)", "oblimersen sodium (G3139)" and "GBM" in the form of and/or.

Inclusion and Exclusion Criteria

Studies included in this systematic review met the following inclusion criteria:

- Articles written in the English language.
- This review aimed to include published clinical trials conducted in humans. However, if an insufficient number of clinical studies with high levels of evidence were available, data from preclinical studies, including *in-vivo* studies on mammalian subjects and *in-vitro* studies on cell cultures, were also considered.

Data Extraction and Synthesis

Three authors (MuB, TT, and SO) independently screened the articles to assess study eligibility. Inconsistencies were resolved through discussion. If consensus could not be reached, another author (MeB, IY) served as an arbitrator. The following data were extracted from the included studies: first author's name, year of publication, study design, drugs studied and their respective doses, and outcomes reported (Figure 1).

Statistical Analysis

"The results of the data analysis, conducted using Microsoft Excel (Version 10.0), are reported in appropriate units.

RESULTS

Initially, when only the words "glioblastoma", "GBM", or "glioblastoma multiforme" were used separately, 61.327, 25.390 and 59.140 studies were found, respectively.

A total of 3,769 studies were found for "Venetoclax"; 732 when using "Navitoclax"; 283 when using "Obatoclax."; There are five studies when "Pelcitoclax" is used and 246 when "Oblimersen sodium" is used. When the keywords "Glioblastoma AND/OR Venetoclax" were used, eight studies were found. Although 26 studies were found after consecutive screening using "Glioblastoma AND/OR Navitoclax", seven studies were found when screening was performed with "Glioblastoma AND/OR Obatoclax". However, no studies were found when screening with "Glioblastoma" AND/OR Pelcitoclax (APG-1252)" or "Glioblastoma AND/OR "Oblimersen sodium".

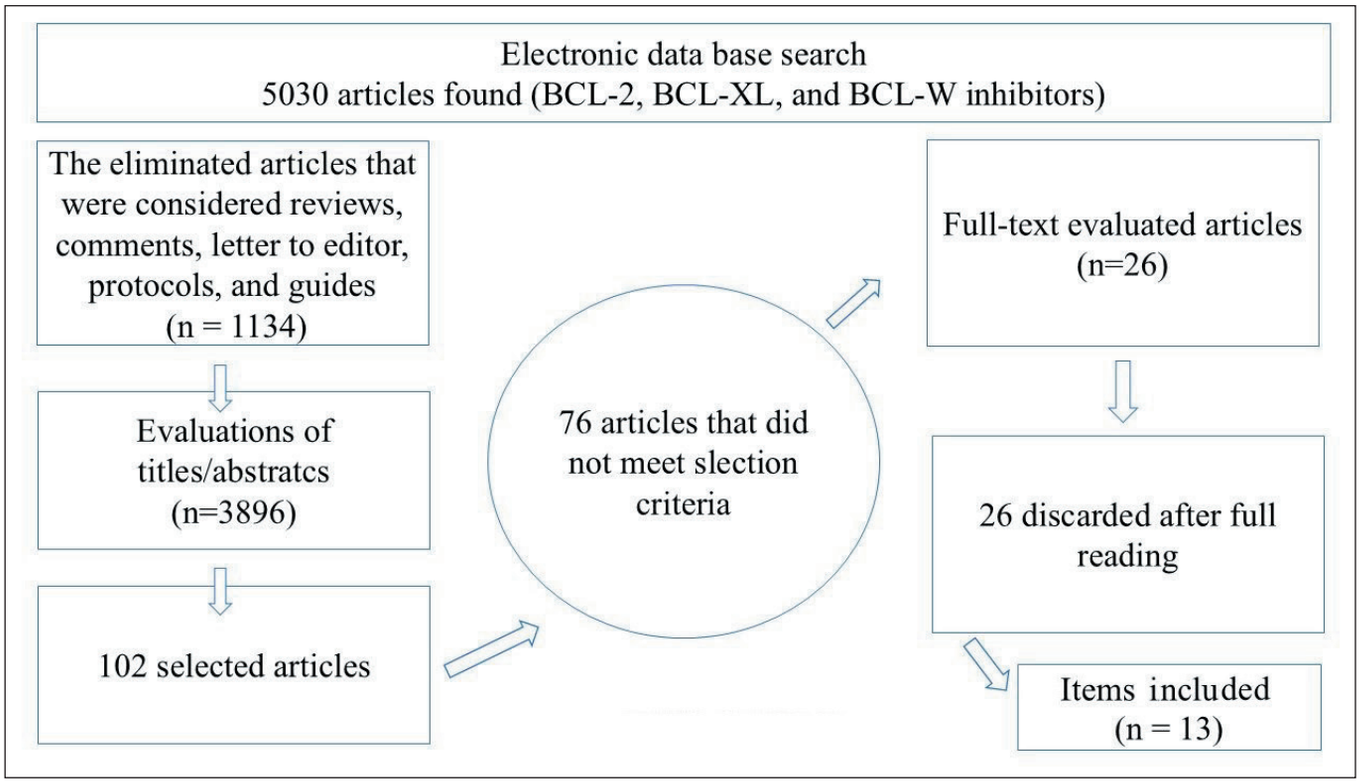

Figure 1: The process of article selection and the reasons for exclusion are shown in the PRISMA flowchart.

In addition to BS153 cells, GBM sphere cultures, and other GBM-derived cells (16), experiments were conducted using varying drug doses on cells obtained from different sources. (Table I).

DISCUSSION

Despite current treatment strategies, including pharmacological and surgical interventions, GBM remains the most aggressive and fatal type of brain tumor. Previous studies have reported that in GBM, overexpression of EGFR and its activated variant, EGFRvIII, resulted in increasing invasiveness and treatment resistance (27). Houweling et al. reported that screening for synergistic multitarget therapies in GBM predicted novel treatment strategies (16). BCL-2 plays a key role in inhibiting apoptosis, and its inhibition by venetoclax effectively kills senescent GBM cells (38).

Additionally, in mice with BCL-2 gene-silenced GBM tumors, taxol treatment significantly inhibited tumor growth and angiogenesis (12). More importantly, anti-apoptotic BCL-2 family members are now considered druggable targets, with specific BCL-2 antagonists such as venetoclax.

Lincoln et al. examined the sensitivity of GBM cell lines to a combination of the death ligand TRAIL and an IAP antagonist due to the lack of effective treatments for GBM. Their findings emphasized that a high caspase-8/Bid signature was associated with synergistic TRAIL- and IAP antagonist-induced apoptosis in GBM cells. Additionally, they highlighted BCL-2 antagonism as a highly effective approach to sensitizing TRAIL-resistant GBM cells to TRAIL and IAP antagonists (26).

Yu et al. reported that the prosurvival BCL-2 family proteins BCL-2 and BCL-xL are targets of both ABT-737 and navitoclax, whereas venetoclax is highly specific to BCL-2 (43). A study reported that eliminating radiation-induced senescence in the brain tumor microenvironment could reduce GBM recurrence. The study highlighted navitoclax, a senolytic drug that selectively kills senescent astrocytes *in-vivo*, as a potential treatment (11).

BH3 proteins contain BH3 motifs that bind and regulate BCL-2 homologs, playing a crucial role in cellular responses to stress-induced stimuli and apoptosis (9). Koessinger et al. reported that increased apoptotic sensitivity in GBM enables therapeutic targeting with BH3-mimetics. Venetoclax, a BH3-mimetic targeting BCL-2, has demonstrated significant efficacy in hematologic malignancies (22).

Similarly, one study reported that “BH3 mimetic drugs cooperate with temozolomide, JQ1 and inducers of ferroptosis in killing GBM cells” (30).

A study on neurosphere GBM cultures and xenografts suggested that combined inhibition of BCL-xL and disruption of the tricarboxylic acid cycle could serve as a treatment strategy for GBM using the clinically validated drug CPI-613. The study found that BCL-xL inhibition prevented OGDH loss-of-function in patients. Additionally, it genetically and clinically confirmed that OGDH is synthetically lethal with its BH3 mimetic, navitoclax (32).

Table I: Application Dose and Site of Application of Bcl-2 Protein Family Inhibitors Identified in the Literature Review

Origin of the Cell Used or Living Mammalian Subject Species	Drug Administration/Dose	Efficiency	Reference No.
U87MG, U251 cells	Venetoclax / 10 μM	Venetoclax is effective when used in combination with Temozolomide, Methotrexate, and Cytarabine.	44
Patient-derived GBM stem-like cells	Venetoclax / 1 μM	BCL-xL and MCL-1 prosurvival function is important for GBM survival and can be therapeutically exploited by BH3 mimetics.	22
U87MG, U251, SNB-19, SNB-75, SF268, SF295, and SF539 cells	Venetoclax / 1 μM	Dual targeting of distinct programmed cell death signaling pathways in GBM may enhance the utility of BCL-xL inhibitors and ferroptosis inducers, in combination with standard-of-care treatment, for improved GBM therapies.	30
U87MG, LN-229 (RRID: CVCL_0393), A172 (RRID: CVCL_0131)	Venetoclax / 50 μM	BV6 and venetoclax act as senolytic agents in glioblastoma cells following temozolomide exposure.	38
A172, U251, U343, U373, MZ18, and MZ304	Venetoclax / 0.1 μM, 5μM, and 10 μM	Antagonizing Bcl-2 by venetoclax allowed TRAIL/Birinapant response synergies to manifest in otherwise TRAIL-resistant cell lines.	26
Human GBM xenografts obtained from patients	Venetoclax / 10 μM	*In-vitro* cytotoxicity assays demonstrated that ABT-737, Navitoclax, and Venetoclax—specifically ABT-737—sensitized different tumors to immunotoxin treatment.	43
U373, Patient-derived glioblastoma stem-like cell cultures	Obatoclax / 225nM	Obatoclax overcomes resistance to histone deacetylase inhibitors as radiosensitizers in patient-derived GBM stem-like cells.	2
U87MG, HEK293, HEK293T, NIH/3T3, LM8, HCT116, SW480, SW620, and EL4 cell lines	Obatoclax / 1 μM	Cucurbitacin B, gossypol, and obatoclax exhibit broad cellular specificity across different cell lines by regulating extracellular vesicles.	28
U251, LN229, U87MG, A375, or A375R cells were implanted subcutaneously into mice	Navitoclax / 25–50 mg/kg Obatoclax / 5 mg/kg Venetoclax / 1 μM	Combining Navitoclax and Obatoclax or Venetoclax with gamitrinib-TPP suppressed cellular proliferation synergistically through massive activation of intrinsic apoptosis.	21
Syngeneic mouse glioma model that constituted immunocompetent C57BL/6J mice implanted with luciferase-tagged GL261 mouse glioma cells (immun competan mice)	Navitoclax / 50 mg/kg	Navitoclax treatment selectively eliminated senescent astrocytes in vivo, significantly attenuating glioma cell growth in preirradiated brains.	11
U87, U343, and U251 cells	Navitoclax /1 μM	Acriflavine has MCL-1 inhibitory function and synergistic antitumor effects with Navitoclax..	29

Table I: Cont.

Origin of the Cell Used or Living Mammalian Subject Species	Drug Administration/Dose	Efficiency	Reference No.
LN229, A172 (human glioblastoma cell lines)	ABT-737 / 2.5 μM	ABT-737 and Navitoclax selectively eliminated senescent astrocytes in vivo, significantly reducing glioma cell growth in preirradiated brains.	1
Human glioblastoma cell lines (p53 wild-type, PTEN-mutated LN229, U87, and U373 [p53-mutated, PTEN-mutated])	Navitoclax / 1 μM - 4μM	GDC-0941 enhances Navitoclax-mediated cell death by modulating BAD phosphorylation.	35

BV6: *A potent and specific antagonist of at least three inhibitors of apoptosis proteins (IAPs);* ***TRAIL:*** *Tumor necrosis factor-related apoptosis-inducing ligand;* ***MCL-1:*** *Myeloid leukemia 1.*

A study evaluating the synergy of acriflavine with navitoclax, an MCL-1 downregulator, against triple-negative breast cancer, lung adenocarcinoma, and GBM demonstrated that acriflavine exhibits MCL-1 inhibition and a synergistic antitumor effect with navitoclax (25). The inhibition of MEG3, whose aberrant expression is implicated in various cancers, has been suggested to enhance the chemosensitivity of glioma cells to 5-fluorouracil but not to navitoclax (7).

Zhao et al. stated in their study that adjuvant treatment of GBM with temozolomide inevitably failed due to therapeutic resistance, necessitating new treatment approaches. They also reported that apoptosis induction in GBM cells was inefficient due to an excess of anti-apoptotic XPO1/BCL-2 family proteins. Based on the findings obtained from *in-vitro* and *in-vivo* research, they deduced "optimal drug combinations were. In response to inhibitors Eltanexor (XPO1), Venetoclax (Bcl-2), and Mcl-1, genes encoding for the corresponding proteins were upregulated in a compensatory manner" (44). One study, identified obatoclax among potential drugs for treating refractory GBM based on drug sensitivity patterns of different immune subtypes (3).

As a result, the BCL-2 protein family inhibitors venetoclax, navitoclax, and obatoclax have been investigated in GBM treatment; however, no studies have reported the effects of pelcitoclax or oblimersen sodium against GBM. These findings suggest that ionizing radiation, a standard treatment for GBM, may contribute to radioresistance by inducing the expression of anti-apoptotic BCL-2 proteins in tumor cells. Venetoclax, in combination with radiotherapy, increases tumor cell death by inhibiting radiation-induced BCL-2 activity and promoting apoptosis. This combination showed a significant increase in survival in orthotopic animal models of diffuse midline glioma, a variant of GBM (29).

Navitoclax selectively induces apoptosis in senescent GBM cells by targeting BCL-xL, potentially reducing tumor recurrence (37). Obatoclax can overcome this resistance by inhibiting BCL-2 proteins, thereby enhancing the effectiveness of treatments such as suberoylanilide hydroxamic acid and radiotherapy. Specifically, obatoclax sensitizes patient-derived GBM stem-like cells to these treatments, leading to increased apoptosis (2). Additionally, the combination of obatoclax with the EGFR inhibitor lapatinib was reported to show synergistic effects in inducing cell death in central nervous system tumor cells, including GBM. This combination promoted apoptosis by effectively blocking survival signaling pathways (5).

A review of the literature indicates that studies have been conducted on commercial cell lines, patient-derived GBM stem-like cells, human GBM xenografts, and immune-competent mice. In *in-vivo* studies, navitoclax was administered at 25–50 mg/kg, while obatoclax was given at 5 mg/kg in mammalian subjects. Studies reported that the *in-vitro* dose of venetoclax ranged from 0.1μM and 50μM. Studies found that the *in-vitro* dose of obatoclax ranged from 225 nM and 1μM. Navitoclax was administered at doses ranging from 1 μM and 4 μM.

These studies commonly use commercial cell lines and animals. However, the sensitivity of animal tissue differs from that of human tissue (19,20). Results from animal tissue analyses may differ from those using human tissues, potentially leading to misleading conclusions (19,20). This may lead to misleading results. Additionally, commercial cell lines contain only a single cell type and lack the complex coordination mechanisms of the tumor microenvironment (19,20). They do not exhibit the same genotypic or phenotypic characteristics as tumor cells in the human body. For this reason, the results of studies using cell lines may be misleading (19,20).

Systematic reviews are valuable tools for synthesizing evidence, but they also have limitations. One major challenge is the heterogeneity among studies (15). Another limitation is publication bias (34). Moreover, despite existing guidelines, decisions regarding study inclusion, exclusion, and data interpretation can introduce subjective bias, particularly if pre-registration or protocols are not followed (17,18). These limitations apply to our study. However, we believe it contributes to the literature by collectively evaluating preclinical data on these drugs tested against GBM.

CONCLUSION

Although these preclinical findings are promising, clinical trials are necessary to assess the safety and efficacy of venetoclax, navitoclax, and obatoclax in GBM patients. To date, all of these inhibitors are under investigation in combination with other treatments for a variety of solid tumors, but specific clinical studies for GBM remain extremely limited. Equally important, the complex biology of GBM and the incomplete understanding of therapeutic resistance necessitate the discovery of novel antigens or targeted pharmacological strategies.

Declarations

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

Ethics approval and consent to participate: This study is a systematic review based solely on previously published studies. No new human participants were enrolled, and no individual patient data were collected. Therefore, ethical approval and informed consent were not required.

AUTHORSHIP CONTRIBUTION

Study conception and design: MuB, IY

Data collection: MuB, TT

Analysis and interpretation of results: MeB, SO

Draft manuscript preparation: MuB, TT, SO

Critical revision of the article: MeB, IY

Other (study supervision, fundings, materials, etc...): MuB, MeB, IY

All authors (MuB, TT, SO, MeB, IY) reviewed the results and approved the final version of the manuscript.

REFERENCES

1. Beltzig L, Christmann M, Kaina B: Abrogation of cellular senescence induced by temozolomide in glioblastoma cells: Search for senolytics. Cells 11:2588, 2022. https://doi.org/10.3390/cells11162588.
2. Berghauser Pont LM, Spoor JK, Venkatesan S, Swagemakers S, Kloezeman JJ, Dirven CM, van der Spek PJ, Lamfers ML, Leenstra S: The Bcl-2 inhibitor Obatoclax overcomes resistance to histone deacetylase inhibitors SAHA and LBH589 as radiosensitizers in patient-derived glioblastoma stem-like cells. Genes Cancer 5:445-459, 2014. https://doi.org/10.18632/genesandcancer.40.
3. Chen W, Chen L, Guo L, Liu N, Wu T, Cheng Y, Xu P, Li Y, Yang X, Xu R, Chen B: The signature of immune-subtype specific driving transcription factors suggest potential drugs for refractory glioblastoma. Am J Cancer Res 13:1278-1294, 2023. https://doi.org/10.1016/j.ajcr.2023.04.015.
4. Cosentino K, García-Sáez AJ: Bax and Bak pores: Are we closing the circle? Trends Cell Biol 27:266-275, 2017. https://doi.org/10.1016/j.tcb.2016.12.005.
5. Cruickshanks N, Hamed HA, Bareford MD, Poklepovic A, Fisher PB, Grant S, Dent P: Lapatinib and obatoclax kill tumor cells through blockade of ERBB1/3/4 and through inhibition of BCL-XL and MCL-1. Mol Pharmacol 81:748-758, 2012. https://doi.org/10.1124/mol.111.076976.
6. D'Aguanno S, Brignone M, Scalera S, Chiacchiarini M, Di Martile M, Valentini E, De Nicola F, Ricci A, Pelle F, Botti C, Maugeri-Saccà M, Del Bufalo D: Bcl-2 dependent modulation of Hippo pathway in cancer cells. Cell Commun Signal 22:277, 2024. https://doi.org/10.1186/s12964-024-01467-1.
7. Degirmenci Z, Unver S, Kilic T, Avsar T: Silencing of the MEG3 gene promoted anti-cancer activity and drug sensitivity in glioma. J Cell Mol Med 27:2603-2613, 2023. https://doi.org/10.1111/jcmm.17891.
8. Dogra N, Singh P, Kumar A: A multistep in silico approach identifies potential glioblastoma drug candidates via inclusive molecular targeting of glioblastoma stem cells. Mol Neurobiol 61:9253-9271, 2024. https://doi.org/10.1007/s12035-024-04067-3.
9. Elkholi R, Floros KV, Chipuk JE: The role of BH3-only proteins in tumor cell development, signaling, and treatment. Genes Cancer 2:523-537, 2011. https://doi.org/10.1177/1947601911411088.
10. Fels C, Schäfer C, Hüppe B, Bahn H, Heidecke V, Kramm CM, Lautenschläger C, Rainov NG: Bcl-2 expression in higher-grade human glioma: A clinical and experimental study. J Neurooncol 48:207-216, 2000. https://doi.org/10.1023/A:1006414918451.
11. Fletcher-Sananikone E, Kanji S, Tomimatsu N, Di Cristofaro LFM, Kollipara RK, Saha D, Floyd JR, Sung P, Hromas R, Burns TC, Kittler R, Habib AA, Mukherjee B, Burma S: Elimination of radiation-induced senescence in the brain tumor microenvironment attenuates glioblastoma recurrence. Cancer Res 81:5935-5947, 2021. https://doi.org/10.1158/0008-5472.CAN-21-0483.
12. George J, Banik NL, Ray SK: Bcl-2 siRNA augments taxol mediated apoptotic death in human glioblastoma U138MG and U251MG cells. Neurochem Res 34:66-78, 2009. https://doi.org/10.1007/s11064-008-9757-6.
13. Goulart H, Kantarjian H, Pemmaraju N, Daver N, DiNardo CD, Rausch CR, Ravandi F, Kadia TM: Venetoclax-based combination regimens in acute myeloid leukemia. Blood Cancer Discov 6:23-37, 2025. https://doi.org/10.1158/2643-3230.BCD-24-0001.
14. Herbst RS, Frankel SR: Oblimersen sodium (Genasense bcl-2 antisense oligonucleotide): A rational therapeutic to enhance apoptosis in therapy of lung cancer. Clin Cancer Res 10:4245s-4248s, 2004. https://doi.org/10.1158/1078-0432.CCR-03-0806.
15. Hoffmann F, Eggers D, Pieper D, Zeeb H, Allers K: An observational study found large methodological heterogeneity in systematic reviews addressing prevalence and cumulative incidence. J Clin Epidemiol 119:92-99, 2020. https://doi.org/10.1016/j.jclinepi.2019.10.012.

16. Houweling M, Giczewska A, Abdul K, Nieuwenhuis N, Küçükosmanoglu A, Pastuszak K, Buijsman RC, Wesseling P, Wedekind L, Noske D, Supernat A, Bailey D, Watts C, Wurdinger T, Westerman BA: Screening of predicted synergistic multi-target therapies in glioblastoma identifies new treatment strategies. Neurooncol Adv 5:vdad073, 2023. https://doi.org/10.1093/noajnl/vdad073.
17. Ioannidis JP: The mass production of redundant, misleading, and conflicted systematic reviews and meta-analyses. Milbank Q 94:485-514, 2016. https://doi.org/10.1111/1468-0009.12210.
18. Karaarslan N, Yilmaz I, Ozbek H, Caliskan T, Topuk S, Sirin DY, Ates O: Systematic evaluation of promising clinical trials-gene silencing for the treatment of glioblastoma. Turk Neurosurg 29:328-334, 2019. https://doi.org/10.5137/1019-5149.JTN.25656-19.2.
19. Karaarslan N, Yilmaz I, Ozbek H, Yasar Sirin D, Kaplan N, Caliskan T, Ozdemir C, Akyuva Y, Ates O: Are radio-contrast agents commonly used in discography toxic to the intact intervertebral disc tissue cells? Basic Clin Pharmacol Toxicol 124:181-189, 2019. https://doi.org/10.1111/bcpt.13179.
20. Karaarslan N, Yilmaz I, Sirin DY: Toxicity of the acetyl-para-aminophenol group of medicines to intact intervertebral disc tissue cells. Exp Ther Med 21:147, 2021. https://doi.org/10.3892/etm.2020.9549.
21. Karpel-Massler G, Ishida CT, Bianchetti E, Shu C, Perez-Lorenzo R, Horst B, Banu M, Roth KA, Bruce JN, Canoll P, Altieri DC, Siegelin MD: Inhibition of mitochondrial matrix chaperones and antiapoptotic Bcl-2 family proteins empower antitumor therapeutic responses. Cancer Res 77:3513-3526, 2017. https://doi.org/10.1158/0008-5472.CAN-16-2636.
22. Koessinger AL, Cloix C, Koessinger D, Heiland DH, Bock FJ, Strathdee K, Kinch K, Martínez-Escardó L, Paul NR, Nixon C, Malviya G, Jackson MR, Campbell KJ, Stevenson K, Davis S, Elmasry Y, Ahmed A, O'Prey J, Ichim G, Schnell O, Stewart W, Blyth K, Ryan KM, Chalmers AJ, Norman JC, Tait SWG: Increased apoptotic sensitivity of glioblastoma enables therapeutic targeting by BH3-mimetics. Cell Death Differ 29:2089-2104, 2022. https://doi.org/10.1038/s41418-022-01002-4.
23. Lakhani NJ, Rasco D, Wang H, Men L, Liang E, Fu T, Collins MC, Min P, Yin Y, Davids MS, Yang D, Zhai Y: First-in-human study with preclinical data of BCL-2/BCL-xL inhibitor pelcitoclax in locally advanced or metastatic solid tumors. Clin Cancer Res 30:506-521, 2024. https://doi.org/10.1158/1078-0432.CCR-23-2047.
24. Lazaro-Navarro J, Alcon C, Dorel M, Alasfar L, Bastian L, Baldus C, Astrahantseff K, Yaspo ML, Montero J, Eckert C: Inhibiting H3K27 demethylases downregulates CREB-CREBBP, overcoming resistance in relapsed acute lymphoblastic leukemia. Cancer Med 14:1-7, 2025. https://doi.org/10.1002/cam4.6425.
25. Lee A, Jin HO, Masudul Haque M, Kim HY, Jung H, Park JH, Kim I, Song JY, Yoon HK, Kim HK, Han J, Park IC, Kim KS, Park SG: Synergism of a novel MCL 1 downregulator, acriflavine, with navitoclax in triple negative breast cancer, lung adenocarcinoma and glioblastoma multiforme. Int J Oncol 60:2, 2022. https://doi.org/10.3892/ijo.2021.5299.
26. Lincoln FA, Imig D, Boccellato C, Juric V, Noonan J, Kontermann RE, Allgöwer F, Murphy BM, Rehm M: Sensitization of glioblastoma cells to TRAIL-induced apoptosis by IAP- and Bcl-2 antagonism. Cell Death Dis 9:1112, 2018. https://doi.org/10.1038/s41419-018-1125-5.
27. Lo HW: EGFR-targeted therapy in malignant glioma: novel aspects and mechanisms of drug resistance. Curr Mol Pharmacol 3:37-52, 2010. https://doi.org/10.2174/1874467211003030037.
28. Ma Y, Yoshida T, Matoba K, Kida K, Shintani R, Piao Y, Jin J, Nishino T, Hanayama R: Identification of small compounds regulating the secretion of extracellular vesicles via a TIM4-affinity ELISA. Sci Rep 11:13471, 2021. https://doi.org/10.1038/s41598-021-92744-9.
29. Madhavan K, Balakrishnan I, Lakshmanachetty S, Pierce A, Sanford B, Fosmire S, Elajaili HB, Walker F, Wang D, Nozik ES, Mitra SS, Dahl NA, Vibhakar R, Venkataraman S: Venetoclax cooperates with ionizing radiation to attenuate diffuse midline glioma tumor growth. Clin Cancer Res 28:2409-2424, 2022. https://doi.org/10.1158/1078-0432.CCR-21-3533.
30. Moujalled D, Southon AG, Saleh E, Brinkmann K, Ke F, Iliopoulos M, Cross RS, Jenkins MR, Nhu D, Wang Z, Shi MX, Kluck RM, Lessene G, Grabow S, Bush AI, Strasser A: BH3 mimetic drugs cooperate with temozolomide, JQ1 and inducers of ferroptosis in killing glioblastoma multiforme cells. Cell Death Differ 29:1335-1348, 2022. https://doi.org/10.1038/s41418-021-00917-3.
31. Nachmias B, Aumann S, Haran A, Schimmer AD: Venetoclax resistance in acute myeloid leukaemia-clinical and biological insights. Br J Haematol 204:1146-1158, 2024. https://doi.org/10.1111/bjh.18921.
32. Nguyen TT, Torrini C, Shang E, Shu C, Mun JY, Gao Q, Humala N, Akman HO, Zhang G, Westhoff MA, Karpel-Massler G, Bruce JN, Canoll P, Siegelin MD: OGDH and Bcl-xL loss causes synthetic lethality in glioblastoma. JCI Insight 9:e172565, 2024. https://doi.org/10.1172/jci.insight.172565.
33. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al: The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372:n71, 2021. https://doi.org/10.1136/bmj.n71
34. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, McKenzie JE. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ 372:n160, 2021. https://doi.org/10.1136/bmj.n160.
35. Pareja F, Macleod D, Shu C, Crary JF, Canoll PD, Ross AH, Siegelin MD: PI3K and Bcl-2 inhibition primes glioblastoma cells to apoptosis through downregulation of Mcl-1 and Phospho-BAD. Mol Cancer Res 12:987-1001, 2014. https://doi.org/10.1158/1541-7786.MCR-13-0686.
36. Qian S, Wei Z, Yang W, Huang J, Yang Y, Wang J: The role of BCL-2 family proteins in regulating apoptosis and cancer therapy. Front Oncol 12:985363, 2022. https://doi.org/10.3389/fonc.2022.985363.

37. Rahman M, Olson I, Mansour M, Carlstrom LP, Sutiwisesak R, Saber R, Rajani K, Warrington AE, Howard A, Schroeder M, Chen S, Decker PA, Sananikone EF, Zhu Y, Tchkonia T, Parney IF, Burma S, Brown D, Rodriguez M, Sarkaria JN, Kirkland JL, Burns TC: Selective vulnerability of senescent glioblastoma cells to BCL-XL inhibition. Mol Cancer Res 20:938-948, 2022. https://doi.org/10.1158/1541-7786.MCR-21-0931.

38. Schwarzenbach C, Tatsch L, Brandstetter Vilar J, Rasenberger B, Beltzig L, Kaina B, Tomicic MT, Christmann M: Targeting c-IAP1, c-IAP2, and Bcl-2 eliminates senescent glioblastoma cells following temozolomide treatment. Cancers (Basel) 13:3585, 2021. https://doi.org/10.3390/cancers13143585.

39. Sherman JH, Bobak A, Arsiwala T, Lockman P, Aulakh S: Targeting drug resistance in glioblastoma (Review). Int J Oncol 65:80, 2024. https://doi.org/10.3892/ijo.2024.5723.

40. Thomas S, Quinn BA, Das SK, Dash R, Emdad L, Dasgupta S, Wang XY, Dent P, Reed JC, Pellecchia M, Sarkar D, Fisher PB: Targeting the Bcl-2 family for cancer therapy. Expert Opin Ther Targets 17:61-75, 2013. https://doi.org/10.1517/14728222.2013.741589.

41. Weller M, Malipiero U, Aguzzi A, et al: Protooncogene bcl-2 gene transfer abrogates Fas/APO-1 antibody-mediated apoptosis of human malignant glioma cells and confers resistance to chemotherapeutic drugs and therapeutic irradiation. J Clin Invest 95:2633-2643, 1995. https://doi.org/10.1172/JCI117936.

42. Wu R, Deng X, Wang X, Li S, Su J, Sun X: Prognostic model for hepatocellular carcinoma based on necroptosis-related genes and analysis of drug treatment responses. Heliyon 10:e36561, 2024. https://doi.org/10.1016/j.heliyon.2024.e36561.

43. Yu X, Dobrikov M, Keir ST, Gromeier M, Pastan IH, Reisfeld R, Bigner DD, Chandramohan V: Synergistic antitumor effects of 9.2.27-PE38KDEL and ABT-737 in primary and metastatic brain tumors. PLoS One 14:e0210608, 2019. https://doi.org/10.1371/journal.pone.0210608.

44. Zhao K, Braun M, Meyer L, Otte K, Raifer H, Helmprobst F, Möschl V, Pagenstecher A, Urban H, Ronellenfitsch MW, Steinbach JP, Pesek J, Watzer B, Nockher WA, Taudte RV, Neubauer A, Nimsky C, Bartsch JW, Rusch T. A novel approach for glioblastoma treatment by combining apoptosis inducers with targeted inhibitors. Cells 13:632, 2024. https://doi.org/10.3390/cells13070632.