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RESEARCH PAPER

CD19-Targeted Lipid Nanoparticles for Delivering Venetoclax and BCL2 siRNA in B-Cell Acute Lymphoblastic Leukemia

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ABSTRACT

B-cell acute lymphoblastic leukemia (B-ALL) is an aggressive hematologic malignancy characterized by uncontrolled proliferation of immature B lymphocytes. Current therapeutic approaches, including chemotherapy and monoclonal antibodies, face challenges such as drug resistance and systemic toxicity. CD19-targeted lipid nanoparticles (LNPs) represent a promising strategy for precision medicine by enhancing drug delivery specificity and overcoming apoptotic resistance. Venetoclax, a potent BCL-2 inhibitor, and BCL2 siRNA, a gene-silencing agent, offer a synergistic approach to combat leukemic cell survival mechanisms. By co-delivering these therapeutic agents through LNPs, the targeted modulation of apoptotic pathways can improve treatment efficacy while minimizing off-target effects. This review explores the rationale, formulation, and clinical prospects of CD19-targeted lipid nanoparticles for co-delivery of Venetoclax and BCL2 siRNA in B-ALL therapy, highlighting their potential to revolutionize leukemia treatment.

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INTRODUCTION

B-cell acute lymphoblastic leukemia (B-ALL) is a hematologic malignancy characterized by the uncontrolled proliferation of immature B lymphocytes, often driven by genetic mutations and aberrant signaling pathways. Despite advancements in chemotherapy and targeted therapies, drug resistance remains a significant barrier to successful treatment [1]. A key factor contributing to therapeutic failure is the dysregulation of apoptosis, particularly via overexpression of B-cell lymphoma 2 (BCL-2), which promotes leukemic cell survival and limits the efficacy of cytotoxic agents [2]. CD19, a transmembrane glycoprotein exclusively expressed on B lymphocytes, has emerged as an important therapeutic target in B-ALL [3]. Monoclonal antibodies and chimeric antigen receptor (CAR) T-cell therapies directed against CD19 have demonstrated clinical success, yet limitations such as relapse due to antigen loss and off-target toxicity necessitate alternative drug delivery strategies [4]. Lipid nanoparticles (LNPs) have gained attention as promising carriers for precise drug targeting due to their ability to encapsulate both small molecules and nucleic acids, thereby enhancing therapeutic stability and reducing systemic side effects [5]. Venetoclax, a potent BCL-2 inhibitor, has been widely studied for its pro-apoptotic effects in hematologic malignancies, yet drug resistance mechanisms often hinder long-term efficacy [6]. Co-delivery of Venetoclax with BCL2-targeted siRNA through CD19-functionalized LNPs represents a synergistic approach to overcome apoptotic resistance by simultaneously inhibiting BCL-2 protein function and suppressing its transcriptional expression [7].

This review explores the rationale for CD19-targeted LNPs as a co-delivery platform for Venetoclax and BCL2 siRNA, highlighting their therapeutic implications in B-ALL. By examining key molecular pathways, formulation strategies, and clinical advancements, we aim to provide insights into the future of nanoparticle-based precision medicine in hematologic oncology.

CD19 AS A THERAPEUTIC TARGETED

Biological Significance of CD19 in B-ALL

CD19 is a transmembrane glycoprotein expressed exclusively on B-cell precursors and mature B lymphocytes, making it a crucial marker for B-cell malignancies such as B-cell acute lymphoblastic leukemia (B-ALL) [3]. It plays a fundamental role in regulating antigen receptor signaling, influencing survival and proliferation through interactions with intracellular pathways [8]. One of its major functions involves amplifying B-cell receptor-mediated signaling by recruiting kinases such as Lyn and PI3K, leading to enhanced cellular activation and proliferation. This makes CD19 an essential component of B-cell maturation and immune function [9]. However, in leukemic B cells, aberrant CD19 signaling contributes to uncontrolled proliferation and therapy resistance [10]. Has shown that CD19 expression remains consistent across different disease stages, including relapse, making it a reliable therapeutic target [11]. Unlike other B-cell surface proteins that may be lost due to immune escape mechanisms, CD19 persistence ensures a prolonged window for targeted interventions [12]. Additionally, its absence in hematopoietic stem cells and non-B-lineage tissues minimizes the risk of off-target toxicity, an essential consideration in precision medicine approaches [13]. Dysregulation of CD19-mediated signaling cascades, including the PI3K-AKT and MAPK pathways, enhances leukemic cell survival, reducing the efficacy of conventional therapies [14]. Targeting CD19 therapeutically disrupts these oncogenic networks and restores apoptosis, thereby improving treatment outcomes. Given its widespread presence in malignant B cells and its role in disease progression, CD19 remains an ideal molecular target for antibody-based, cell-mediated, and nanoparticle-driven interventions in B-ALL [15].

CD19-Targeted Therapies (CAR-T, Monoclonal Antibodies)

CD19-targeted therapies have become a cornerstone in B-ALL treatment, utilizing mechanisms that selectively recognize and eliminate malignant B cells [16]. Among these, chimeric antigen receptor T-cell (CAR-T) therapy has gained prominence as a highly personalized approach. CAR-T cells are engineered by modifying patient-derived T lymphocytes to express a synthetic receptor capable of binding to CD19-expressing cells [4, 16]. Upon recognition, CAR-T cells activate intracellular cytotoxic pathways, leading to rapid tumor elimination. Clinical trials evaluating CD19-directed CAR-T products such as Tisagenlecleucel (Kymriah) and Axicabtagene Ciloleucel (Yescarta) have demonstrated significant remission rates in

relapsed B-ALL cases [17]. Monoclonal antibodies represent another targeted strategy, leveraging biologically engineered proteins to engage CD19 on leukemic cells [18]. Blinatumomab, a bispecific T-cell engager (BiTE), connects CD19-positive B cells with cytotoxic T lymphocytes, enhancing immune-mediated cell killing [19]. Unlike CAR-T therapy, monoclonal antibodies do not require patient-specific manufacturing, making them more accessible [20]. Despite their efficacy, monoclonal antibodies exhibit limitations such as short half-life, rapid clearance, and potential neutralization by host immune responses [21].

Rationale for Using CD19-Targeted Lipid Nanoparticles

Despite the success of CD19-directed therapies, significant challenges persist in B-ALL treatment, including drug resistance, immune escape, and systemic toxicity [22]. Lipid nanoparticles provide a novel solution by enabling precise drug delivery with minimal off-target effects. These nanoscale carriers enhance therapeutic bioavailability, ensuring optimal drug stability and sustained release [23]. One of the most compelling reasons to incorporate CD19-targeted lipid nanoparticles is their ability to encapsulate both small-molecule inhibitors and RNA-based therapeutics, facilitating synergistic drug mechanisms [24]. Venetoclax, a potent BCL-2 inhibitor, effectively induces apoptosis but suffers from resistance mechanisms driven by compensatory survival pathways [6]. Co-delivery of BCL2-targeted small interfering RNA (siRNA) via lipid nanoparticles enhances Venetoclax's apoptotic efficacy by silencing anti-apoptotic gene expression at the transcriptional level [25]. CD19-functionalized nanoparticles further refine this approach by specifically binding to leukemic B cells, reducing systemic drug exposure and minimizing adverse effects [26]. Some studies indicate that lipid nanoparticle formulations improve cellular uptake and intracellular drug release, enhancing treatment response. Additionally, nanoparticle-mediated delivery circumvents issues such as short antibody half-life and immune-mediated neutralization, ensuring prolonged therapeutic activity[27]. By integrating CD19-targeted lipid nanoparticles into B-ALL treatment, researchers can leverage nanotechnology to overcome existing challenges, providing a precision-based approach to improving patient outcomes while maintaining treatment specificity and tolerability [28].

LIPID NANOPARTICLES AS DRUG DELIVERY SYSTEMS

Structural and Functional Properties of Lipid Nanoparticles

Lipid nanoparticles (LNPs) are nanoscale drug delivery systems composed of biocompatible lipid materials, designed to enhance the stability, bioavailability, and targeted delivery of therapeutic agents [29]. These nanoparticles typically consist of a lipid bilayer or core-shell structure that encapsulates drugs, nucleic acids, or biologics, providing controlled release and improved cellular uptake [30]. Structurally, LNPs are categorized into solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and liposomes, each with distinct compositions and therapeutic advantages [31]. SLNs contain a solid lipid matrix that remains intact at body temperature, reducing drug degradation and enhancing stability. NLCs, in contrast, incorporate both solid and liquid lipids, improving drug loading capacity and release kinetics[32]. Liposomes, composed of phospholipid bilayers, mimic biological membranes, making them ideal for delivering hydrophilic and hydrophobic drugs while minimizing systemic toxicity [33]. Functionally, LNPs improve drug solubility, protect encapsulated therapeutics from enzymatic degradation, and facilitate cellular uptake through endocytosis. The inclusion of surface ligands or functional moieties enhances target specificity, reducing off-target effects [34]. Additionally, LNPs enable co-delivery of multiple agents, allowing synergistic treatment approaches in cancer and other diseases. Their adaptability, biocompatibility, and ability to cross biological barriers underscore their importance in modern drug delivery applications [35].

Current Applications of Lipid Nanoparticles in Oncology

One of the most notable applications of LNPs in oncology is the delivery of nucleic acid-based therapies, including small interfering RNA (siRNA) and messenger RNA (mRNA), which regulate gene expression in tumor cells [36]. Lipid nanoparticles have been successfully utilized in siRNA-based treatments to silence oncogenes, thereby inhibiting tumor growth and progression. Additionally, LNPs facilitate mRNA-based cancer immunotherapies by encoding tumor antigens, stimulating immune responses against malignant cells [37]. Chemotherapeutic

drug delivery using lipid nanoparticles has significantly improved therapeutic indices. Liposomal formulations of doxorubicin (Doxil) and cisplatin have demonstrated enhanced efficacy and reduced systemic toxicity compared to free drug administration. These formulations leverage lipid nanoparticles to enhance drug stability and prolong circulation time, ensuring more precise tumor targeting [38]. Moreover, lipid nanoparticles enable combination therapies, where multiple agents are co-encapsulated for synergistic effects. This approach is particularly beneficial for overcoming multidrug resistance in tumors. The integration of targeting ligands, such as antibodies or peptides, further refines nanoparticle-based delivery, improving treatment specificity and minimizing off-target effects [39].

VENETOCLAX MECHANISM OF ACTION

Venetoclax is a potent, selective inhibitor of B-cell lymphoma 2 (BCL-2), a protein that plays a crucial role in regulating the intrinsic apoptotic pathway. Apoptosis is a programmed cell death mechanism essential for maintaining cellular homeostasis and preventing uncontrolled proliferation [40]. In many hematologic malignancies, including B-cell acute lymphoblastic leukemia (B-ALL), BCL-2 is overexpressed, allowing leukemic cells to evade apoptosis and persist despite cytotoxic therapies [41]. Venetoclax works by targeting the BH3-binding groove of BCL-2, displacing pro-apoptotic proteins such as BIM, BAX, and BAK. This displacement leads to mitochondrial outer membrane permeabilization (MOMP), cytochrome c release, and subsequent activation of caspase cascades, ultimately resulting in cell death [42]. The specificity of Venetoclax for BCL-2 is a key advantage in leukemia therapy, as it minimizes off-target effects associated with broader-spectrum apoptosis modulators [43]. However, its action is largely dependent on the BCL-2 dependency of the cancer cells, meaning that leukemic cells with upregulated alternative anti-apoptotic proteins, such as myeloid cell leukemia 1 (MCL-1) or BCL-XL, may develop resistance [44]. Studies have demonstrated that resistance mechanisms involve either increased transcriptional expression of these compensatory proteins or post-translational modifications that inhibit apoptotic signaling. Furthermore, genetic alterations in BCL-2, such as point mutations in the BH3 domain, may diminish Venetoclax's binding affinity, reducing its therapeutic efficacy [2, 45]. To counteract these resistance mechanisms, combination strategies integrating Venetoclax with agents targeting complementary apoptotic pathways are being explored [46]. One promising approach is co-delivery of Venetoclax with small interfering RNA (siRNA) targeting BCL2 mRNA, effectively silencing its expression at the genetic level while simultaneously inhibiting the protein function [47]. Lipid nanoparticle-based delivery of Venetoclax and siRNA provides additional benefits, including improved drug stability, enhanced intracellular uptake, and sustained apoptotic modulation [48]. Given its mechanism of action and resistance factors, optimal Venetoclax dosing regimens must be carefully tailored to patient-specific leukemic profiles [49]. Pharmacokinetic studies highlight the need for dose titration to prevent tumor lysis syndrome (TLS), a severe complication arising from the rapid destruction of leukemic cells [50]. Drug metabolism is primarily mediated via the CYP3A pathway, meaning co-administration with CYP3A inhibitors or inducers necessitates dosage adjustments to maintain efficacy while avoiding toxicity [51].

BCL2 SIRNA AND RNA-BASED THERAPEUTICS

Gene Silencing as a Therapeutic Approach in B-ALL

Gene silencing via RNA interference has emerged as a precise molecular tool for targeting disease-associated genes in various malignancies, including B-cell acute lymphoblastic leukemia [52]. Unlike conventional therapies that broadly affect cellular pathways, RNA interference-based approaches specifically inhibit the expression of oncogenic or survival-promoting genes at the messenger RNA level, thereby reducing the production of pathological proteins [53]. Small interfering RNA is one of the most widely studied RNA interference mechanisms, where synthetic, short double-stranded RNA molecules bind to complementary messenger RNA sequences, triggering degradation through the RNA-induced silencing complex. This process prevents translation of the targeted gene, effectively suppressing its biological activity [54]. In B-cell acute lymphoblastic leukemia, dysregulated apoptotic signaling and uncontrolled proliferation are key drivers of disease progression [1]. Many leukemic cells evade programmed cell death by upregulating anti-apoptotic genes, including BCL2, MCL1, and BCL-XL, making RNA interference-based therapeutics an attractive strategy to

counteract these survival mechanisms [55]. By silencing oncogenic transcripts, small interfering RNA therapy provides a molecular precision approach that minimizes off-target effects compared to systemic chemotherapy [56]. Despite its potential, clinical translation of small interfering RNA therapy faces significant obstacles, primarily concerning stability, delivery efficiency, and immune recognition [57]. Free small interfering RNA molecules are highly vulnerable to enzymatic degradation and have poor bioavailability due to their inherent hydrophilicity [58]. To overcome these challenges, advanced delivery platforms such as lipid nanoparticles have been employed to encapsulate and transport small interfering RNA to target tissues [59]. Lipid nanoparticles protect small interfering RNA from degradation, enhance intracellular uptake, and enable targeted release at disease sites [60]. CD19-functionalized lipid nanoparticles provide an additional layer of specificity, ensuring selective binding to leukemic B cells while avoiding healthy tissues [26].

Role of BCL2 siRNA in Apoptotic Resistance Modulation

B-cell lymphoma 2 is a central regulator of apoptotic resistance in hematologic malignancies, playing a key role in maintaining the survival of leukemic cells [2]. Its overexpression prevents mitochondrial-mediated apoptosis by inhibiting the activation of pro-apoptotic proteins such as BAX and BAK, leading to persistent tumor growth and chemotherapy resistance [61]. In B-cell acute lymphoblastic leukemia, high levels of B-cell lymphoma 2 are associated with poor treatment response and increased risk of disease relapse, necessitating targeted therapeutic strategies to suppress its activity [1, 62]. BCL2-targetedsmall interfering RNA offers a genetic level approach to overcoming apoptotic resistance by silencing BCL2 messenger RNA, thereby reducing the production of the anti-apoptotic protein. Unlike pharmacologic BCL2 inhibitors such as Venetoclax, which competitively bind to the BCL-2 protein, small interfering RNA therapy eliminates BCL2 expression at the transcriptional level, preventing the synthesis of new BCL-2 molecules [40]. This dual mechanism—functional inhibition through small-molecule drugs and genetic suppression via RNA-based therapeutics—represents a powerful strategy for enhancing leukemic cell death and reducing resistance [63]. One of the primary challenges in BCL2 small interfering RNA therapy is efficient intracellular delivery. Naked small interfering RNA molecules face rapid degradation in circulation and exhibit poor cellular uptake due to their negative charge and hydrophilic nature [63]. To address this, lipid nanoparticles have been developed as nanocarriers for small interfering RNA encapsulation and delivery, ensuring protection against enzymatic degradation and improving intracellular transport [64]. Functionalized lipid nanoparticles incorporating CD19-targeting ligands further enhance specificity, directing small interfering RNA molecules to malignant B cells while sparing healthy hematopoietic cells [65].

CD19-TARGETED LIPID NANOPARTICLES FOR CO-DELIVERY

Formulation Strategies for Co-Encapsulation of Venetoclax and BCL2 siRNA

The co-encapsulation of Venetoclax and BCL2 siRNA within CD19-targeted lipid nanoparticles requires a meticulously designed formulation to enhance therapeutic efficacy, maintain drug stability, and ensure precise delivery to leukemic cells [66]. Lipid nanoparticles are widely utilized in drug delivery due to their biocompatibility, ability to protect fragile therapeutic agents, and capacity to improve systemic circulation [67]. For optimal formulation, several key parameters must be considered, including lipid composition, particle size, surface charge, and the incorporation of targeting ligands to facilitate specific uptake by B-cell acute lymphoblastic leukemia cells [68]. The encapsulation of Venetoclax, a hydrophobic BCL-2 inhibitor, and BCL2 siRNA, a hydrophilic genetic silencing agent, requires a structural configuration that accommodates both molecules within a single delivery system [69]. Venetoclax is typically incorporated into the lipid core or bilayer, where hydrophobic interactions stabilize the molecule, preventing premature degradation and ensuring sustained release [70]. BCL2 siRNA, due to its negative charge and susceptibility to enzymatic degradation, is formulated with cationic or ionizable lipids that electrostatically bind to siRNA, stabilizing the complex during systemic circulation and facilitating intracellular delivery [71]. To enhance cellular uptake, the lipid nanoparticles are functionalized with CD19-targeting ligands, ensuring preferential binding to leukemic B cells [67]. These ligands can be monoclonal antibodies, aptamers, or other surface modifications that

enhance nanoparticle internalization via receptor-mediated endocytosis [72]. The nanoparticle formulation also includes helper lipids such as cholesterol, which contributes to membrane stability, and polyethylene glycol, which prolongs circulation time by reducing immune system recognition and clearance [73]. The ratio of Venetoclax to BCL2 siRNA within lipid nanoparticles must be carefully balanced to achieve synergistic therapeutic effects without compromising drug activity or delivery efficiency [74].

Synergistic Effects in Overcoming Apoptotic Resistance

Apoptotic resistance represents a significant challenge in the treatment of B-cell acute lymphoblastic leukemia, where leukemic cells evade programmed cell death through the overexpression of anti-apoptotic proteins such as BCL-2 [75]. Venetoclax, a selective BCL-2 inhibitor, directly blocks the protein's function by disrupting its interactions with pro-apoptotic regulators such as BAX and BAK. This restores the apoptotic cascade, leading to mitochondrial outer membrane permeabilization and caspase activation [40]. However, despite its effectiveness, leukemic cells can compensate for BCL-2 inhibition by upregulating alternative survival proteins such as MCL-1 and BCL-XL, leading to acquired resistance. To address this limitation, the co-delivery of Venetoclax with BCL2-targeted siRNA provides a synergistic approach to combating resistance mechanisms by simultaneously inhibiting BCL-2 protein activity and silencing its gene expression [76]. This dual mechanism prevents leukemic cells from synthesizing new BCL-2 proteins, ensuring sustained apoptosis and reducing the likelihood of therapeutic escape [77]. Unlike Venetoclax monotherapy, which depends on continued drug exposure for effectiveness, BCL2 siRNA offers a prolonged regulatory effect by suppressing BCL2 transcription, effectively lowering protein levels over time [40, 78]. Lipid nanoparticle-mediated co-delivery enhances therapeutic efficacy by improving drug and siRNA stability, increasing cellular uptake, and promoting controlled release within malignant cells [79]. CD19-targeted nanoparticles ensure selective accumulation in leukemic B cells, minimizing off-target effects while maximizing apoptotic induction. By leveraging lipid nanoparticle encapsulation, Venetoclax achieves higher intracellular concentrations, reducing the need for excessive systemic dosing and mitigating toxicity risks associated with traditional administration methods [80].

CLINICAL STUDIES

Zhaozhao Chen et al [81], introduced an innovative CAR-T engineering technique the use of mRNA delivered thru lipid nanoparticles (LNPs), aiming to reduce fees and decorate safety even as retaining strong anti-tumour efficacy. advanced an LNP-based transfection protocol for efficient transport of mRNA encoding complete-human CAR constructs, attaining high CAR expression and sizable cytotoxicity in opposition to leukaemic cells in vitro. Co-subculture with Raji engraftment showed increased cytokine secretion and tumour cellular killing via mRNA-LNP CAR-T cells. therapeutic efficacy turned into similarly demonstrated in an NOD-scid-IL2Rγnull (NSG) mouse version with Raji engraftment, wherein dealt with mice exhibited marked tumour regression and prolonged survival. these findings underscore the capability of mRNA-LNPs as a non-viral, powerful CAR-T engineering platform, supplying a promising alternative to standard techniques that might enhance CAR-T protection, efficacy and accessibility in scientific cancer immunotherapy.

Chipeng Guo et al [82], developed lipid nanoparticle-encapsulated mRNA-encoding antibodies (mRNab-LNPs) focused on CD19, and evaluated their healing efficacy in lupus and RA mice. mRNab-LNPs enabled robust manufacturing of anti-CD19 antibodies in multiple cellular lines in vitro. apparently, intramuscular injection of mRNab-LNPs led to excessive and sustained production of anti-CD19 antibodies in mice. mainly, the numbers of CD19+ circulating B cells and tissue-resident plasma cells are extensively decreased with the aid of mRNab-LNPs in mice. As a result, mRNab-LNPs notably decreased the histopathological changes and tissue injuries in each lupus and RA mice. together, those findings reveal the therapeutic and translational ability of mRNab-LNPs in the treatment of SLE and RA.

CONCLUSION AND FUTURE PERSPECTIVES

The development of CD19-targeted lipid nanoparticles for co-delivery of Venetoclax and BCL2 siRNA represents a significant advancement in precision medicine for B-cell acute lymphoblastic leukemia. By addressing

the limitations of conventional chemotherapy and targeted biologics, lipid nanoparticles offer a platform for enhanced drug stability, improved bioavailability, and selective targeting of malignant B cells. The synergistic mechanism of combining a pharmacologic BCL-2 inhibitor with genetic silencing through siRNA enables a dual therapeutic approach that maximizes apoptotic induction while minimizing resistance. The integration of nanoparticle-mediated delivery systems enhances intracellular uptake, optimizes therapeutic exposure, and provides sustained leukemic cell elimination.

Current preclinical research suggests that this strategy has the potential to significantly improve treatment efficacy by overcoming apoptotic resistance mechanisms commonly observed in relapsed and refractory leukemia cases. However, successful clinical translation requires further optimization of nanoparticle formulations, dosing strategies, and delivery efficiencies. Addressing pharmacokinetic challenges such as siRNA degradation, immune clearance, and nanoparticle circulation time will be crucial for advancing this approach toward human trials.

The future of CD19-targeted lipid nanoparticles in leukemia therapy lies in continued refinement of nanoparticle engineering to enhance delivery precision and therapeutic potency. Ongoing research will explore modifications in lipid compositions, encapsulation efficiencies, and ligand targeting strategies to improve specificity and therapeutic outcomes. Additionally, combination approaches integrating CD19-targeted nanoparticles with immunotherapies, such as CAR-T cells or immune checkpoint inhibitors, may further enhance treatment efficacy by modulating the tumor microenvironment. Advancements in RNA-based therapeutics will continue to refine siRNA stability and delivery platforms, ensuring prolonged gene silencing effects with minimal off-target interactions. The exploration of next-generation nanocarriers, such as exosome-based delivery systems or biodegradable lipid formulations, may further improve biocompatibility and enhance clinical applicability. Furthermore, real-time monitoring systems, including nanoparticle-based imaging and biomarker-driven adjustments in treatment protocols, will contribute to a more personalized and adaptive leukemia treatment strategy.

By integrating nanotechnology, targeted gene silencing, and apoptotic modulation, the application of CD19-targeted lipid nanoparticles holds immense potential for transforming leukemia therapy. With continued research, clinical validation, and technological innovations, this approach could pave the way for highly precise, minimally toxic, and highly effective therapeutic strategies for hematologic malignancies.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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