Black Sea Journal of Engineering and Science
doi: 10.34248/bsengineering.1696059

Open Access Journal
e-ISSN: 2619 – 8991

Research Article
Volume 8 - Issue 5: 1450-1459 / September 2025

PRECLINICAL EVALUATION OF BRIGIMADLIN (BI 907828) AS A NOVEL MDM2 INHIBITOR IN ACUTE LYMPHOBLASTIC LEUKEMIA

Erhan APTULLAHOĞLU[1,2]*

[1]*Bilecik Şeyh Edebali University, Faculty of Science, Department of Molecular Biology and Genetics, 11100, Bilecik, Türkiye*
[2]*Bilecik Şeyh Edebali University, Biotechnology Application and Research Centre, 11100, Bilecik, Türkiye*

Abstract: Acute lymphoblastic leukemia (ALL) is a genetically heterogeneous malignancy that frequently retains wild-type *TP53* at diagnosis, rendering it a potential candidate for therapies targeting upstream regulators of p53 such as MDM2. Brigimadlin (BI 907828) is a next-generation, orally bioavailable MDM2-p53 antagonist with established activity in solid tumors, yet its therapeutic potential in hematologic malignancies remains underexplored. In this study, the *in vitro* effects of brigimadlin were investigated using a panel of ALL cell lines with a defined *TP53* status. Cell viability assays demonstrated potent, dose-dependent growth inhibition in *TP53* wild-type cell lines Nalm-6 and RS4;11, with low nanomolar IC_{50} values (38 nM and 18 nM, respectively). In contrast, the *TP53*-mutant CCRF-CEM line displayed resistance, with minimal viability loss even at micromolar concentrations. Microscopic analysis corroborated these findings, showing marked cytotoxicity in *TP53*-functional cell lines but not in *TP53*-deficient one. Quantitative RT-PCR analysis revealed strong induction of p53 target genes, including *CDKN1A*, *PUMA*, *BAX*, and *MDM2*, in wild-type Nalm-6 cells following treatment, consistent with reactivation of p53-mediated transcriptional signature. No gene induction was observed in the *TP53*-mutant cell line, supporting the specificity of brigimadlin's action. Taken together, these findings highlight brigimadlin's potential to selectively target p53-functional ALL cells and provide foundational preclinical evidence for its continued investigation. *In vivo* studies in *TP53* wild-type models are warranted to assess its translational relevance, and future research may explore its integration into combination regimens or biomarker-guided therapeutic strategies.

Keywords: Acute lymphoblastic leukaemia, MDM2-p53 antagonists, MDM2, p53, Brigimadlin (BI 907828)

***Corresponding author:** Bilecik Şeyh Edebali University, Faculty of Science, Department of Molecular Biology and Genetics, 11100, Bilecik, Türkiye
E mail: erhan.aptullahoglu@bilecik.edu.tr (E. APTULLAHOĞLU)
Erhan APTULLAHOĞLU https://orcid.org/0000-0002-9400-0938

Received: May 09, 2025
Accepted: August 06, 2025
Published: September 15, 2025

Cite as: Aptullahoğlu E. 2025. Preclinical evaluation of Brigimadlin (BI 907828) as a novel MDM2 inhibitor in acute Lymphoblastic Leukemia. BSJ Eng Sci, 8(5): 1450-1459.

1. Introduction

Acute lymphoblastic leukemia (ALL) is a heterogeneous hematologic malignancy with diverse genetic alterations and clinical outcomes (Terwilliger and Abdul-Hay, 2017). Despite advances in multi-agent chemotherapy (Specchia et al., 2005; Farooq et al., 2019), targeted agents (Malagola et al., 2016), immunotherapies (Maude et al., 2018; Chitadze et al., 2020), and stem cell transplantation (Thomas et al., 2004; Sun and Huang, 2022), treatment resistance and relapse remain significant challenges, especially in adult patients and those with high-risk features (Pulte et al., 2014; Schwartz and Muffly, 2024). While *TP53*, the gene encoding the tumor suppressor protein p53 (a key regulator of DNA repair, cell cycle arrest, and apoptosis), is typically intact in most ALL cases and generally associated with a more favorable prognosis, a subset of patients with wild-type *TP53* still exhibit resistance to standard therapies. In such cases, wild-type *TP53* may represent a therapeutic opportunity, as pharmacologic reactivation of p53 through MDM2 inhibition offers a mechanistically rational approach to overcoming treatment resistance.

The p53 protein orchestrates essential cellular processes, including DNA repair, cell cycle arrest, and apoptosis, in response to genomic stress (Ozaki and Nakagawara, 2011). Loss of p53 function, either through mutation (Chen et al., 2022) or regulatory inactivation (Kubbutat et al., 1997; Garcia-Cano et al., 2020; Chen et al., 2021), disrupts these pathways, thereby promoting unchecked cell proliferation and survival. Although *TP53* mutations are a defining feature in approximately half of all human cancers (Hollstein et al., 1991) and represent a well-established focus in cancer drug development (Wiman, 2006; Wu et al., 2022), they are relatively rare in ALL. These mutations are detected in fewer than 10% of cases at diagnosis (Chiaretti et al., 2013; Stengel et al., 2014) and rise to approximately 30-40% at relapse (Irving et al., 2016; Yu et al., 2020), with an especially low prevalence in pediatric cases. These data suggest that in ALL, particularly in the *TP53* wild-type subset, alternative mechanisms such as post-translational regulation of p53

may play a more critical role in leukemogenesis.

Among the primary regulators of p53 is MDM2, an E3 ubiquitin ligase that binds to p53, represses its transcriptional activity, and targets it for proteasomal degradation (Oliner et al., 1992). Overexpression of MDM2 has been documented in various malignancies (Hou et al., 2019), including hematologic cancers such as ALL (Zhou et al., 1995; Gustafsson et al., 1998), where it contributes to p53 inactivation (Nag et al., 2013) despite the absence of *TP53* mutations. This has catalyzed interest in pharmacologically targeting the MDM2-p53 interaction to restore p53's tumor suppressor function. The development of small-molecule MDM2 antagonists began with Nutlin-3 (Vassilev, 2004) and has extended to newer-generation compounds such as RG7388 (Ding et al., 2013), HDM201 (Furet et al., 2016), AMG232 (Rew and Sun, 2014), DS-3032 (Arnhold et al., 2018), ASTX295 (Willmore et al., 2024), and MI-77301 (Wang et al., 2014). These agents have demonstrated promising preclinical efficacy, including in models of leukemia and lymphoma (Ciardullo et al., 2016; Wu et al., 2018; Ciardullo et al., 2019; Ghotaslou et al., 2022; Aptullahoglu, Ciardullo, et al., 2023; Johansson et al., 2023; Bell et al., 2024; Gungordu and Aptullahoglu, 2024; Aptullahoglu et al., 2025). Many of these inhibitors are currently under investigation in clinical trials, both as single-agent therapies (Stein et al., 2022; Koyama et al., 2023) and in combination with other treatments (Abdul Razak et al., 2022; Daver et al., 2022; Konopleva et al., 2022).

While MDM2 inhibitors are supported by a strong mechanistic rationale, many early clinical candidates have failed to translate this promise into meaningful clinical efficacy and have been associated with significant hematologic toxicity (Pi et al., 2019). Thrombocytopenia and neutropenia, in particular, have been identified as dose-limiting toxicities that restrict their therapeutic potential (Pi et al., 2019). Moreover, clinical investigations have largely concentrated on solid tumors with high mutational burdens or refractory phenotypes. In contrast, leukemias may be more biologically suited to benefit from MDM2-targeted therapy due to the frequent retention of wild-type *TP53*. This positions these diseases as rational targets for MDM2 inhibition.

Brigimadlin (BI 907828) is a next-generation, orally bioavailable MDM2-p53 antagonist that has demonstrated potent antitumor activity in preclinical models, particularly in *TP53* wild-type, MDM2-amplified cancers such as dedifferentiated liposarcoma (DDLPS) (Rudolph et al., 2018; Cornillie et al., 2020; Gollner et al., 2024). The compound exhibits favorable pharmacokinetic characteristics, including high oral bioavailability and dose-proportional exposure (Sarkaria et al., 2024). The compound is presently undergoing evaluation in several phase I and II clinical trials, predominantly in patients with advanced solid tumors (Clinical Trial Identifiers: NCT05376800, NCT06619509, NCT03449381, and NCT05512377). Among the broad array of MDM2 inhibitors developed to date, BI 907828 stands out due to its optimized balance of pharmacologic efficacy and clinical tolerability. While first-generation compounds such as nutlin-3a were instrumental in elucidating the biological role of MDM2 inhibition, their clinical utility was limited by suboptimal pharmacokinetics. Similarly, second-generation agents like idasanutlin showed promising on-target effects but were hampered by gastrointestinal toxicity and limited clinical benefit in AML trials (Yee et al., 2021; Konopleva et al., 2022). In contrast, BI 907828 was specifically engineered to allow intermittent, high-dose administration, a strategy that enhances therapeutic impact while minimizing cumulative toxicity. Preclinical studies have demonstrated robust p53 pathway activation at nanomolar concentrations and significant tumor regression in xenograft models (Hao et al., 2023; Gollner et al., 2024). Early-phase clinical data further support its favorable safety, pharmacokinetic profile, and durable on-target activity under less frequent dosing regimens (LoRusso et al., 2023).

However, its efficacy in hematologic malignancies, and in ALL in particular, remains largely uncharacterized. This study was designed to assess the *in vitro* therapeutic potential of BI 907828 in ALL cells with defined *TP53* status.The findings may help inform the future clinical utility of MDM2 inhibition strategies in hematologic cancers.

2. Materials and Methods

2.1. Cell lines and Compound

The human ALL cell lines Nalm-6, RS4;11, and CCRF-CEM, sourced from authenticated cell line repositories (ATCC), were cultured in RPMI-1640 medium (Gibco), supplemented with 10% fetal bovine serum (FBS) (Gibco) and 100 U/mL penicillin/streptomycin (Sigma-Aldrich). The cells were maintained in appropriate culture vessels (Labselect) at 37°C in a CO2 incubator (Esco) with a 5% CO2 atmosphere. Cell viability, morphology, and potential contamination were carefully monitored on a daily basis. The cell panel included two cell lines with wild-type *TP53*, Nalm-6 and RS4;11, as well as one cell line with a mutated *TP53*, CCRF-CEM, which harbors missense mutations at codons 175 and 248. These mutations affect the DNA-binding domain of p53 in the CCRF-CEM cell line (Gungordu and Aptullahoglu, 2024). Brigimadlin (BI 907828), purchased from Selleckchem, was dissolved in dimethyl sulfoxide (DMSO, Sigma-Aldrich) and used at a final concentration of 0.5% (v/v) DMSO for experimental purposes.

2.2. Cell Viability Assay

Cells were plated in 96-well plates (Labselect) at a density of 100 µL of complete medium per well, 24 hours prior to treatment with the inhibitor. The optimal initial cell density of 2.5×10^5 cells/mL, established from growth curve analysis for each cell line, ensured at least two doubling times over the 72-hour treatment period, and was used in subsequent XTT assays. On the following day,

the cells were exposed to BI 907828, with the final concentration of DMSO maintained at 0.5% (v/v) across all treatment and control groups, and incubated for 72 hours. Treatment concentrations were selected based on preliminary optimization studies using a wide dose range to capture the sensitivity profiles of each cell line. Additionally, published IC_{50} values for brigimadlin in *TP53* wild-type and mutant tumor models were considered to define a relevant starting range (Gollner et al., 2024). A 72-hour incubation period was chosen to allow sufficient time for cumulative cytotoxic effects to manifest. Cell viability was evaluated using the XTT assay kit (Cayman Chemical Company), which quantifies mitochondrial activity (Scudiero et al., 1988). Viability percentages were calculated by comparing the treated cells to the DMSO control wells. The half-maximal inhibitory concentration (IC50) values were derived from at least three independent experiments, where IC50 is defined as the concentration required to inhibit mitochondrial activity by 50%.

2.3. Cell Imaging Post-Treatment with BI 907828

After a 72-hour incubation period following treatment with the vehicle control (VC), 50 nM, and 500 nM concentrations of BI 907828, cell morphology and confluence were assessed using an inverted phase-contrast microscope. Final DMSO concentration was maintained at 0.5% (v/v) across all treatment and control groups. Images were captured from multiple fields of view per well to ensure representative sampling of the entire well surface. For each condition, at least three independent replicate wells were imaged to ensure reproducibility. The captured images were analyzed qualitatively to evaluate cell confluence, indicative of cytotoxicity or treatment effects.

2.4. RNA Extraction and Quantitative Real-Time PCR (qRT-PCR) Analysis

Cells were seeded at a density of 1×10^6 cells/mL in 12-well plates (Labselect) and treated with BI 907828 for 24 hours. Final DMSO concentration was maintained at 0.5% (v/v) across all treatment and control groups. The 24-hour time point was selected based on previous studies (Ohtani et al., 2004; Ciardullo et al., 2019), which demonstrated that transcriptional changes in p53 pathway-associated downstream genes are most prominently captured at this interval, making it a suitable time frame for assessing p53-mediated gene expression responses. Total RNA was isolated using the Aurum™ Total RNA Mini Kit (Bio-Rad). RNA integrity and concentration were determined using a spectrophotometer. Complementary DNA (cDNA) synthesis was carried out with the Promega reverse transcriptase kit. Quantitative real-time PCR (qRT-PCR) was performed using SYBR Green Master Mix (Life Technologies, Thermo Fisher Scientific) according to the manufacturer's protocol. Each qRT-PCR reaction was carried out with 20 ng of cDNA in a final volume of 10 µL, employing standard cycling conditions. Amplification products were monitored in real-time using a Roche LightCycler 480® system. PCR primers (listed in Table 1) were designed based on cDNA sequences (GenBank™) to assess alterations in gene expression. Gene expression levels were quantified using the $2^{-\Delta\Delta CT}$ method (also known as the comparative CT method). In this approach, the threshold cycle (CT) values of target genes were first normalized to the CT value of the reference (housekeeping) gene GAPDH to obtain ΔCT ($\Delta CT = CT_{TARGET} - CT_{GAPDH}$). These ΔCT values were then compared between treated and corresponding untreated (DMSO control) samples to calculate ΔΔCT ($\Delta\Delta CT = \Delta CT_{TREATED} - \Delta CT_{CONTROL}$). Finally, the relative gene expression was calculated as $2^{-\Delta\Delta CT}$, representing the fold change in gene expression relative to the control group. A no-template control was included to rule out contamination with external DNA.

Table 1. Forward and reverse primer sequences used for quantitative real-time PCR.

Genes	Forward Primers (5'-3')	Reverse Primers (5'-3')
GAPDH	CGACCACTTTGTCAAGCTCA	GGGTCTTACTCCTTGGAGGC
CDKN1A	TGTCCGCAGAACCCATGC	AAAGTCGAAGTTCCTCGCTC
BAX	CCCGAGAGGTCTTTTTCCGAG	CCAGCCCATGATGGTTCTGAT
PUMA (BBC3)	ACCTCAACGCACAGTACGA	CTGGGTAAGGGCAGGAGTC
CASP3	ATGGAAGCGAATCAATGGA	TGTACCAGACCGAGATGTC
BCL-2	GGTGGGGTCATGTGTGTGG	CGGTTCAGGTACTCAGTCATCC
MDM2	AGTAGCAGTGAATCTACAGGGA	CTGATCCAACCAATCACCTGAAT
TP53	TGCGTGTGGAGTATTTGGAT	GGTACAGTCAGAGCCAACCTC

2.5. Statistical Analysis

Data from the repeated experiments were presented as mean±standard error of the mean (SEM) unless otherwise stated. Statistical tests were carried out using GraphPad Prism 6 software (version 8.0.1). Comparisons between each treatment and its matched DMSO control were made using paired t-tests (*P<0.05; **P<0.01; ***P<0.001; ****P<0.0001*).* Given the limited number of biological replicates (n=3), formal normality testing was not performed; nevertheless, the paired t-test was chosen as a standard method for matched-sample comparisons in similar preclinical studies. qRT-PCR data were analyzed using the Roche LightCycler 480 Software (version 1.5), according to the manufacturer's instructions, and subsequently visualized using GraphPad Prism 6 software (version 8.0.1).

3. Results

Three ALL cell lines were treated with increasing concentrations of the MDM2 inhibitor BI-907828 to evaluate its cytotoxic effects. Cell viability was measured 72 hours post-treatment using the XTT assay, and results were normalized to the vehicle control (0 nM DMSO). BI-907828 treatment resulted in a dose-dependent reduction in viability in two *TP53* wild-type cell lines, Nalm-6 and RS4;11, with respective IC_{50} values of 38 ± 5 nM and 18 ± 7 nM (Figure 1, Table 2), indicating high sensitivity to MDM2 inhibition. In contrast, the CCRF-CEM cell line, which carries two missense mutations within the DNA-binding domain of the *TP53* gene, exhibited marked resistance to BI-907828, with an IC_{50} value exceeding 3000 nM (Figure 1, Table 2).

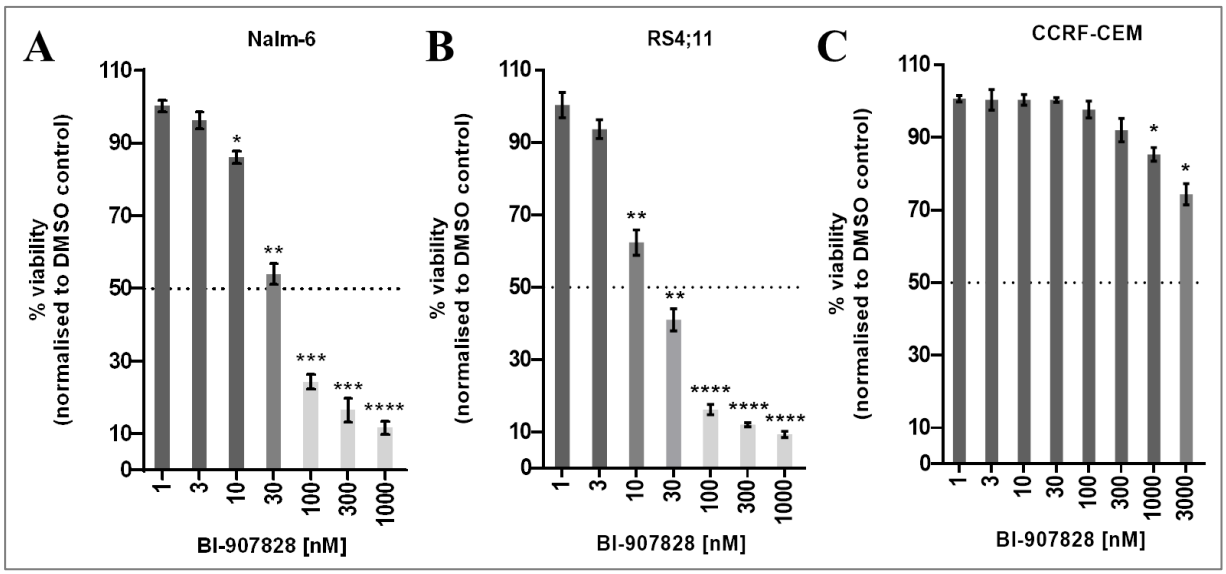

Figure 1. Dose-dependent reduction in cell viability induced by BI-907828 in three distinct ALL cell lines. The ALL cell lines Nalm-6 (A), RS4;11 (B), and CCRF-CEM (C) were exposed to increasing concentrations of BI-907828, ranging from 1 to 1000 nM (up to 3000 nM for CCRF-CEM). Following 72 hours of treatment, cellular metabolic activity was evaluated using the XTT assay. Viability was normalized to the DMSO-treated control and expressed as a percentage. Results are shown as the mean ± standard error of the mean (SEM) from three independent biological replicates. For each concentration, statistical comparison with the control was performed using paired t-tests. Statistically significant differences are indicated on the graphs as follows: **P*<0.05; ***P*<0.01; ****P*<0.001; *****P*<0.0001.

Table 2. *TP53* status and BI-907828 sensitivity in ALL cell lines used in this study.

Cell lines	Cell type	* *TP53* Status	** BI 907828 (nM)
Nalm-6	B cell ALL	WT	38 ± 5
RS4;11	B cell ALL	WT	18 ± 7
CCRF-CEM	T cell ALL	Mutant (Heterozygous) c.524G>A;p.R175H & c.743G>A;p.R248Q	>3000

**TP53* gene mutational status were taken from COSMIC (Catalogue of Somatic Mutations in Cancer) database. **The IC_{50} values shown represent the mean of at least n=3 independent repeats±SEM. WT: wild-type; nM: nanomolar; ALL: acute lymphoblastic leukemia.

Following a 72-hour incubation with vehicle control (VC), 50 nM, or 500 nM of BI-907828, cell morphology and confluence were examined using inverted phase-contrast microscopy. Qualitative analysis of the images revealed dose-dependent reductions in cell confluence for the *TP53* wild-type cell lines, Nalm-6 and RS4;11(Figure 2). Notably, RS4;11 cells showed a marked decrease in cell density even at 50 nM, which became more pronounced at 500 nM. A similar, though slightly less dramatic, effect was observed in Nalm-6 cells. In contrast, the *TP53*-mutant CCRF-CEM cell line exhibited no observable changes in cell confluence or morphology, even at the highest concentration tested, suggesting resistance to BI-907828–induced cytotoxicity (Figure 2).

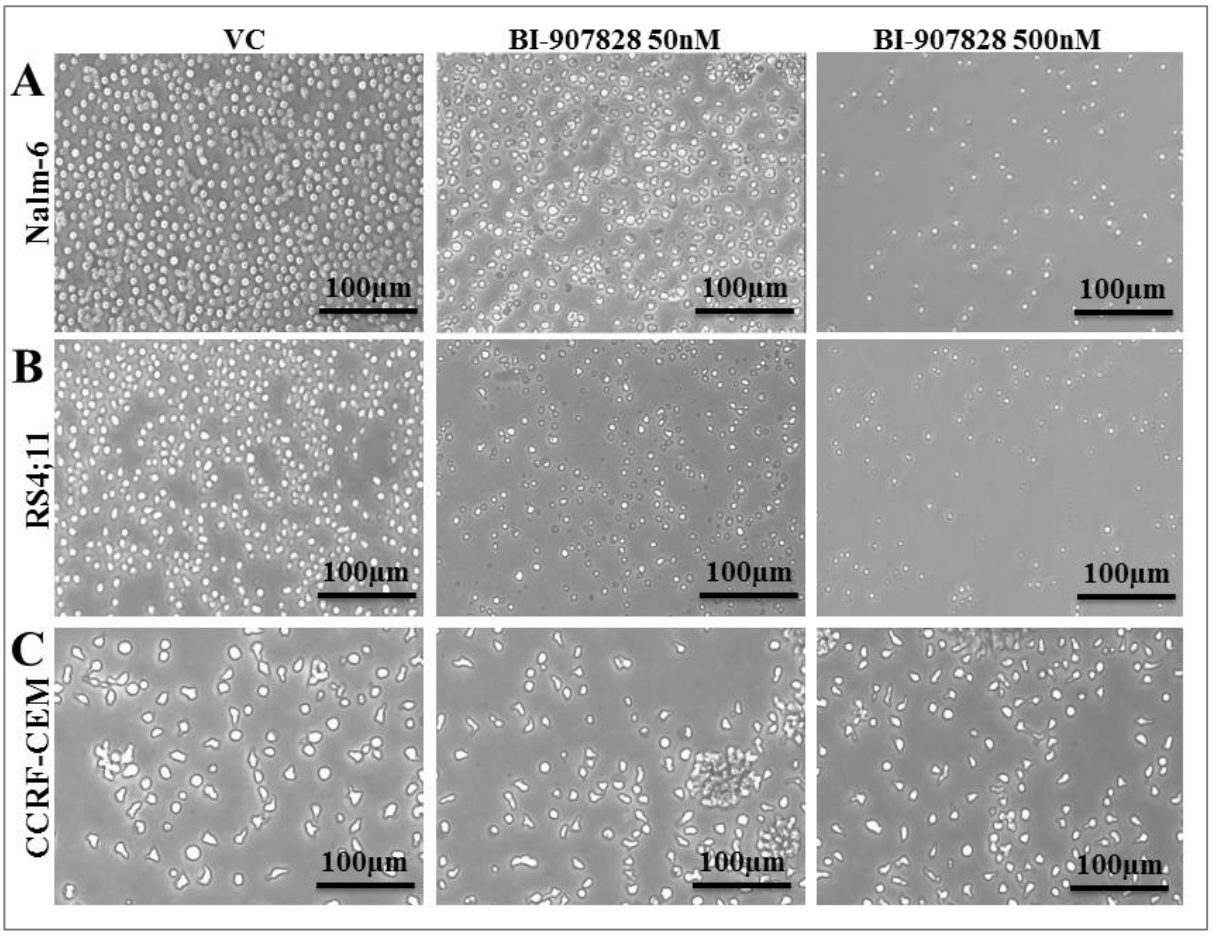

Figure 2. Effects of BI-907828 on the proliferation of Nalm-6 (A), RS4;11 (B), and CCRF-CEM (C) cells. Changes in cell density were observed following treatment with BI-907828. Cells were incubated for 72 hours with 0 nM (vehicle control, VC), 50 nM, or 500 nM of BI-907828 and imaged using phase-contrast microscopy. Imaging was performed in three independent biological replicates, and representative images are presented. Scale bar: 100 µm. nM: nanomolar.

To test the hypothesis that inhibition of the p53 negative regulator MDM2 activates p53-dependent signaling pathways leading to cell death in ALL cells, the mRNA expression levels of several canonical p53 target genes involved in cell cycle arrest, apoptosis, and auto-regulation were quantitatively assessed using qRT-PCR. Quantitative RT-PCR was performed on two ALL cell lines treated with 100 nM and 300 nM of BI-907828, with an additional 1000 nM dose included for the CCRF-CEM cell line. Gene expression was normalized to GAPDH and compared to the DMSO-treated control.

In the *TP53* wild-type Nalm-6 cell line, BI-907828 treatment significantly upregulated multiple p53 transcriptional targets. Among these, *CDKN1A* (encoding p21), a key mediator of p53-induced cell cycle arrest, and *MDM2*, which participates in the negative feedback regulation of p53, showed robust increases in expression (Figure 3A). Furthermore, treatment with 300 nM BI-907828 induced marked upregulation of pro-apoptotic genes, including *PUMA* (7.3-fold), *BAX* (3.4-fold), and *CASP3* (2.2-fold), indicating activation of the apoptotic pathway. Concurrently, a modest downregulation of the anti-apoptotic gene *BCL2* was observed, supporting a shift toward a pro-apoptotic transcriptional profile. As expected, no significant changes in *TP53* mRNA levels were detected, consistent with the mechanism of MDM2 inhibitors, which stabilize existing p53 protein rather than increasing its transcription.

In contrast, the CCRF-CEM cell line, which harbors two missense mutations in the DNA-binding domain of *TP53* and was previously shown to be resistant to BI-907828-induced cytotoxicity (Figure 1C), did not exhibit any significant transcriptional activation of p53 target genes at any tested concentration (Figure 3B).

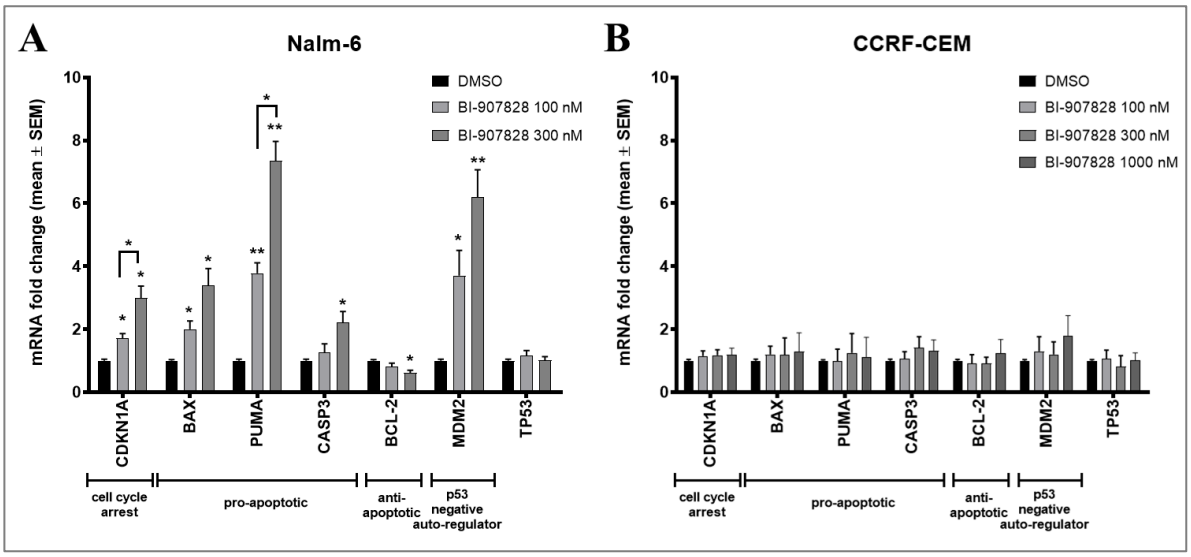

Figure 3. Fold change in mRNA expression of p53 target genes following BI-907828 treatment, measured by qRT–PCR. mRNA levels of p53-regulated target genes were quantified after 24-hour treatment with 100 nM or 300 nM of the MDM2 inhibitor BI-907828 (with an additional 1000 nM dose applied in CCRF-CEM cells). Gene expression was normalized to GAPDH and compared to the DMSO vehicle control in Nalm-6 (A) and CCRF-CEM (B) cell lines. Statistical significance was determined using paired t-tests (*P<0.05; ** P<0.01) and is indicated above the bars for comparisons versus the DMSO control. Differences between BI-907828 doses are marked above the horizontal lines, with only statistically significant values (P<0.05) shown. Data represent the mean ± standard error of the mean (SEM) from three independent biological replicates. nM: nanomolar.

4. Discussion

This study evaluated the anti-leukemic efficacy of the novel, orally bioavailable MDM2-p53 antagonist brigimadlin in a panel of ALL cell lines with defined *TP53* status. The results provide compelling evidence that brigimadlin exerts potent cytotoxic activity in *TP53* wild-type ALL cells by reactivating p53-dependent signaling pathways, while *TP53*-mutant cells remain largely unresponsive, underlining the importance of functional p53 in mediating the therapeutic response to MDM2 inhibition.

The dose-dependent inhibition of proliferation observed in Nalm-6 and RS4;11 cells—both harboring wild-type *TP53*—with IC_{50} values in the low nanomolar range, highlights brigimadlin's high potency and therapeutic potential in p53-intact leukemic contexts. These results align with prior studies of MDM2 inhibitors such as RG7388 and HDM201, which similarly demonstrated selective cytotoxicity in p53-functional hematologic malignancies (Ciardullo et al., 2019; Gungordu and Aptullahoglu, 2024; Aptullahoglu et al., 2025). Notably, RS4;11 cells exhibited particularly high sensitivity, suggesting possible cell line–specific factors that enhance responsiveness, such as MDM2 amplification or differences in basal p53 activity. In contrast, CCRF-CEM cells, which harbor dual missense mutations in the DNA-binding domain of *TP53* (R175H and R248Q) (see Table 2), exhibited profound resistance to brigimadlin, consistent with a loss of transcriptionally active p53 and impaired engagement of downstream apoptotic pathways.

Microscopy-based morphological assessments corroborated these findings, revealing clear reductions in confluence in *TP53* wild-type cells following treatment, while *TP53*-mutant cells remained morphologically unchanged with no alteration in cell density. These phenotypic observations reinforce the central role of functional p53 in mediating the biological response to MDM2 antagonism and are consistent with brigimadlin's mechanism of action: disrupting the MDM2-p53 interaction, thereby stabilizing and activating endogenous p53.

Mechanistically, quantitative real-time PCR analyses further confirmed the activation of canonical p53 transcriptional targets following brigimadlin treatment in *TP53* wild-type cells. Upregulation of *CDKN1A* (encoding p21 protein) and *MDM2* indicates intact p53-mediated cell cycle regulation and autoregulatory feedback loops. Additionally, the significant induction of apoptotic effectors such as *PUMA*, *BAX*, and *CASP3*, coupled with the downregulation of anti-apoptotic *BCL2*, suggests a robust pro-apoptotic transcriptional shift, consistent with p53-driven intrinsic apoptosis. These transcriptional changes were completely absent in CCRF-CEM cells at all tested concentrations, supporting the idea that p53 functionality is essential for brigimadlin's activity.

Collectively, these data position brigimadlin as a promising candidate for targeted therapy in *TP53* wild-type ALL. Given the relatively low prevalence of *TP53* mutations in newly diagnosed ALL (Stengel et al., 2014; Irving et al., 2016) and the increasing interest in precision oncology, brigimadlin may represent a viable therapeutic strategy for a substantial subset of ALL patients.

Importantly, the differential sensitivity observed based on *TP53* mutational status supports the development of predictive biomarkers to guide patient selection in future clinical trials.

Combination strategies may further enhance the therapeutic impact of brigimadlin. For instance, MDM2 inhibitors have previously been shown to synergize with DNA-damaging agents such as cytarabine (Shabashvili et al., 2022) or with other targeted therapies (Aptullahoglu, Ciardullo, et al., 2023; Bell et al., 2024) by enhancing p53-mediated apoptosis. Similarly, co-targeting anti-apoptotic BCL2 with agents like venetoclax has demonstrated synergism with p53 reactivation in lymphoid and myeloid malignancies (Lehmann et al., 2016; Hohtari et al., 2022), potentially lowering the apoptotic threshold in resistant clones. Furthermore, given p53's emerging role in modulating immune checkpoint expression and tumor immunogenicity (Munoz-Fontela et al., 2016), combining MDM2 inhibitors with immunotherapeutic agents (Fang et al., 2019; Tolcher et al., 2019) may provide additional clinical benefit, particularly in settings where immune evasion contributes to disease persistence.

To better understand both sensitivity and potential resistance, comprehensive molecular profiling including whole transcriptome and exome sequencing should be employed. These approaches may uncover predictive biomarkers of response or resistance (e.g., *MDM2* amplification, alternative splicing (Aptullahoglu, Wallis, et al., 2023), or deregulation of p53 co-factors) and inform patient stratification in future clinical trials.

Nonetheless, certain considerations should be acknowledged. This study was limited to *in vitro* analyses of established ALL cell lines and may not fully reflect the heterogeneity of patient-derived leukemias or the influence of the bone marrow microenvironment. The lack of *in vivo* validation restricts the clinical applicability of these findings, particularly with respect to drug absorption, distribution, metabolism, and potential immunological interactions. Although the current study did not identify any acquired resistance, the scope was limited to a small panel of established cell lines. It remains possible that in a more heterogeneous patient-derived setting, intrinsic or adaptive resistance mechanisms could emerge as observed in some preclinical studies based on MDM2 inhibition (Aptullahoglu et al., 2024). Additionally, although the study clearly demonstrates that brigimadlin's activity is p53-dependent, the molecular underpinnings of the differential sensitivity between Nalm-6 and RS4;11 warrant further investigation. Factors such as MDM2 expression levels, alterations in upstream regulators (e.g., ARF, ATM), or differential expression of pro-survival factors may modulate the cellular response and should be systematically evaluated. Also, reliance on single end-point measurements of gene expression precludes insight into temporal response dynamics; incorporating longitudinal sampling or single-cell transcriptomic approaches in future work would provide a more detailed understanding of treatment kinetics. Lastly, although the data emphasize a strict requirement for functional p53 in mediating brigimadlin's cytotoxicity, possible off-target effects were not systematically evaluated, which merits further investigation through comprehensive mechanistic assays or high-throughput combination screens. Finally, while gene expression changes were evaluated at the mRNA level via qRT-PCR, corresponding protein-level analyses were not performed. Given that mRNA abundance does not always correlate with protein expression due to post-transcriptional and translational regulation, validating key findings at the protein level (e.g., via western blot or flow cytometry) would strengthen the biological relevance of the results.

5. Conclusion

This study provides the first comprehensive preclinical evidence of brigimadlin's potent and selective anti-leukemic activity in *TP53* wild-type ALL cells. Using a combination of viability assays, morphological assessments, and transcriptional profiling, this study demonstrates that brigimadlin effectively suppresses proliferation and activates canonical p53 target genes involved in cell cycle arrest and apoptosis, in a strictly p53-dependent manner. The complete absence of transcriptional responses in *TP53*-mutant cells confirms the compound's on-target mechanism and underscores the critical role of functional p53 in mediating its cytotoxic effects. These findings highlight the therapeutic potential of brigimadlin as a precision medicine targeting the MDM2–p53 axis in genetically defined subsets of ALL and support its further clinical investigation in hematologic malignancies characterized by intact p53 signaling.

Author Contributions

The percentages of the author' contributions are presented below. The author reviewed and approved the final version of the manuscript.

	E.A.
C	100
D	100
S	100
DCP	100
DAI	100
L	100
W	100
CR	100
SR	100
PM	100
FA	100

C=Concept, D= design, S= supervision, DCP= data collection and/or processing, DAI= data analysis and/or interpretation, L= literature search, W= writing, CR= critical review, SR= submission and revision, PM= project management, FA= funding acquisition.

Conflict of Interest

The author declared that there is no conflict of interest.

Ethical Consideration

Ethics committee approval was not required for this study because of there was no study on animals or humans.

Acknowledgements

This study was supported by the TÜBİTAK R&D projects numbered 121S986 and 323S070, both led by the author. We gratefully acknowledge Prof. Şehime Gülsün Temel and Adem Alemdar from Bursa Uludağ University for conducting the STR profiling of the ALL cell lines.

References

Abdul Razak AR, Bauer S, Suarez C, Lin CC, Quek R, Hutter-Kronke ML, Cubedo R, Ferretti S, Guerreiro N, Jullion A, Orlando EJ, Clementi G, Sand Dejmek J, Halilovic E, Fabre C, Blay JY, Italiano A. 2022. Co-targeting of MDM2 and CDK4/6 with siremadlin and ribociclib for the treatment of patients with well-differentiated or dedifferentiated liposarcoma: results from a proof-of-concept, phase Ib study. Clin Cancer Res, 28: 1087-1097.

Aptullahoglu E, Ciardullo C, Wallis JP, Marr H, Marshall S, Bown N, Willmore E, Lunec J. 2023. Splicing modulation results in aberrant ısoforms and protein products of p53 pathway genes and the sensitization of B cells to non-genotoxic MDM2 Inhibition. Int J Mol Sci, 24(3): 2410.

Aptullahoglu E, Howladar M, Wallis JP, Marr H, Marshall S, Irving J, Willmore E, Lunec J. 2025. Targeting the MDM2-p53 ınteraction with siremadlin: a promising therapeutic strategy for treating TP53 wild-type chronic lymphocytic leukemia. cancers (Basel), 17(2): 274.

Aptullahoglu E, Nakjang S, Wallis JP, Marr H, Marshall S, Willmore E, Lunec J. 2024. RNA sequencing reveals candidate genes and pathways associated with resistance to MDM2 antagonist ıdasanutlin in TP53 wild-type chronic lymphocytic leukemia. Biomedicines, 12(7): 1388.

Aptullahoglu E, Wallis JP, Marr H, Marshall S, Bown N, Willmore E, Lunec J. 2023. SF3B1 Mutations are associated with resistance to non-genotoxic MDM2 ınhibition in chronic lymphocytic leukemia. Int J Mol Sci, 24(12): 11335.

Arnhold V, Schmelz K, Proba J, Winkler A, Wunschel J, Deubzer HE, Kunkele A, Eggert A, Schulte JH, Hundsdoerfer P. 2018. Reactivating TP53 signaling by the novel MDM2 inhibitor DS-3032b as a therapeutic option for high-risk neuroblastoma. Oncotarget, 9: 2304-2319.

Bell HL, Blair HJ, Jepson Gosling SJ, Galler M, Astley D, Moorman AV, Heidenreich O, Veal GJ, van Delft FW, Lunec J, Irving JAE. 2024. Combination p53 activation and BCL-x(L)/BCL-2 inhibition as a therapeutic strategy in high-risk and relapsed acute lymphoblastic leukemia. Leukemia, 38: 1223-1235.

Chen X, Zhang T, Su W, Dou Z, Zhao D, Jin X, Lei H, Wang J, Xie X, Cheng B, Li Q, Zhang H, Di C. 2022. Mutant p53 in cancer: from molecular mechanism to therapeutic modulation. Cell Death Dis, 13: 974.

Chen Y, Hao Q, Wang S, Cao M, Huang Y, Weng X, Wang J, Zhang Z, He X, Lu H, Zhou X. 2021. Inactivation of the tumor suppressor p53 by long noncoding RNA RMRP. Proc Natl Acad Sci, 118(29): e2026813118.

Chiaretti S, Brugnoletti F, Tavolaro S, Bonina S, Paoloni F, Marinelli M, Patten N, Bonifacio M, Kropp MG, Sica S, Guarini A, Foa R. 2013. TP53 mutations are frequent in adult acute lymphoblastic leukemia cases negative for recurrent fusion genes and correlate with poor response to induction therapy. Haematologica, 98: e59-61.

Chitadze G, Laqua A, Lettau M, Baldus CD, Bruggemann M. 2020. Bispecific antibodies in acute lymphoblastic leukemia therapy. Expert Rev Hematol, 13: 1211-1233.

Ciardullo C, Aptullahoglu E, Woodhouse L, Lin WY, Wallis JP, Marr H, Marshall S, Bown N, Willmore E, Lunec J. 2019. Non-genotoxic MDM2 inhibition selectively induces a pro-apoptotic p53 gene signature in chronic lymphocytic leukemia cells. Haematologica, 104: 2429-2442.

Ciardullo C, Woodhouse L, Aptullahoglu E, Wallis JP, Marr HJ, Marshall SR, Bown N, Willmore E, Lunec J. 2016. The p53-MDM2 antagonist RG7388 activates p53 and ınduces a predominantly pro-apoptotic gene expression signature in chronic lymphocytic leukemia. Blood, 128(22): 893.

Cornillie J, Wozniak A, Li H, Gebreyohannes YK, Wellens J, Hompes D, Debiec-Rychter M, Sciot R, Schoffski P. 2020. Anti-tumor activity of the MDM2-TP53 inhibitor BI-907828 in dedifferentiated liposarcoma patient-derived xenograft models harboring MDM2 amplification. Clin Transl Oncol, 22: 546-554.

Daver NG, Dail M, Garcia JS, Jonas BA, Yee KWL, Kelly KR, Vey N, Assouline S, Roboz GJ, Paolini S, Pollyea DA, Tafuri A, Brandwein JM, Pigneux A, Powell BL, Fenaux P, Olin RL, Visani G, Martinelli G, Onishi M, Wang J, Huang W, Green C, Ott MG, Hong WJ, Konopleva MY, Andreeff M. 2022. Venetoclax and idasanutlin in relapsed/refractory AML: a non-randomized, open-label phase 1b trial. Blood, 141(11): 1265-1276.

Ding Q, Zhang Z, Liu JJ, Jiang N, Zhang J, Ross TM, Chu XJ, Bartkovitz D, Podlaski F, Janson C, Tovar C, Filipovic ZM, Higgins B, Glenn K, Packman K, Vassilev LT, Graves B. 2013. Discovery of RG7388, a potent and selective p53-MDM2 inhibitor in clinical development. J Med Chem, 56: 5979-5983.

Fang DD, Tang Q, Kong Y, Wang Q, Gu J, Fang X, Zou P, Rong T, Wang J, Yang D, Zhai Y. 2019. MDM2 inhibitor APG-115 synergizes with PD-1 blockade through enhancing antitumor immunity in the tumor microenvironment. J Immunother Cancer, 7: 327.

Farooq MU, Mushtaq F, Farooq A, Khan DH, Mir MA. 2019. FLAG vs FLAG-IDA: outcomes in relapsed/refractory acute leukemias. Cancer Chemother Pharmacol, 83: 1191-1193.

Furet P, Masuya K, Kallen J, Stachyra-Valat T, Ruetz S, Guagnano V, Holzer P, Mah R, Stutz S, Vaupel A, Chene P, Jeay S, Schlapbach A. 2016. Discovery of a novel class of highly potent inhibitors of the p53-MDM2 interaction by structure-based design starting from a conformational argument. Bioorg Med Chem Lett, 26: 4837-4841.

Garcia-Cano J, Sanchez-Tena S, Sala-Gaston J, Figueras A, Vinals F, Bartrons R, Ventura F, Rosa JL. 2020. Regulation of the MDM2-p53 pathway by the ubiquitin ligase HERC2. Mol Oncol, 14: 69-86.

Ghotaslou A, Samii A, Boustani H, Kiani Ghalesardi O, Shahidi M. 2022. AMG-232, a New Inhibitor of MDM-2, enhance doxorubicin efficiency in pre-B acute lymphoblastic leukemia cells. Rep Biochem Mol Biol, 11: 111-124.

Gollner A, Rudolph D, Weyer-Czernilofsky U, Baumgartinger R, Jung P, Weinstabl H, Ramharter J, Grempler R, Quant J, Rinnenthal J, Perez Pitarch A, Golubovic B, Gerlach D, Bader G, Wetzel K, Otto S, Mandl C, Boehmelt G, McConnell DB, Kraut N, Sini P. 2024. Discovery and characterization of brigimadlin, a novel and highly potent MDM2-p53 antagonist suitable for ıntermittent dose schedules. Mol Cancer Ther, 23: 1689-1702.

Gungordu S, Aptullahoglu E. 2024. Targeting MDM2-mediated suppression of p53 with idasanutlin: a promising therapeutic

approach for acute lymphoblastic leukemia. Invest New Drugs, 42: 603-611.

Gustafsson B, Stal O. 1998. Overexpression of MDM2 in acute childhood lymphoblastic leukemia. Pediatr Hematol Oncol, 15: 519-526.

Hao X, Bahia RK, Cseh O, Bozek DA, Blake S, Rinnenthal J, Weyer-Czernilofsky U, Rudolph D, Artee Luchman H. 2023. BI-907828, a novel potent MDM2 inhibitor, inhibits glioblastoma brain tumor stem cells in vitro and prolongs survival in orthotopic xenograft mouse models. Neuro Oncol, 25: 913-926.

Hohtari H, Kankainen M, Adnan-Awad S, Yadav B, Potdar S, Ianevski A, Dufva O, Heckman C, Sexl V, Kytola S, Mustjoki S, Porkka K. 2022. Targeting apoptosis pathways with BCL2 and MDM2 ınhibitors in adult B-cell acute lymphoblastic leukemia. Hemasphere, 6: e701.

Hollstein M, Sidransky D, Vogelstein B, Harris CC. 1991. p53 mutations in human cancers. Science, 253: 49-53.

Hou H, Sun D, Zhang X. 2019. The role of MDM2 amplification and overexpression in therapeutic resistance of malignant tumors. Cancer Cell Int, 19: 216.

Irving JA, Enshaei A, Parker CA, Sutton R, Kuiper RP, Erhorn A, Minto L, Venn NC, Law T, Yu J, Schwab C, Davies R, Matheson E, Davies A, Sonneveld E, den Boer ML, Love SB, Harrison CJ, Hoogerbrugge PM, Revesz T, Saha V, Moorman AV. 2016. Integration of genetic and clinical risk factors improves prognostication in relapsed childhood B-cell precursor acute lymphoblastic leukemia. Blood, 128: 911-922.

Johansson KB, Zimmerman MS, Dmytrenko IV, Gao F, Link DC. 2023. Idasanutlin and navitoclax induce synergistic apoptotic cell death in T-cell acute lymphoblastic leukemia. Leukemia, 37: 2356-2366.

Konopleva MY, Rollig C, Cavenagh J, Deeren D, Girshova L, Krauter J, Martinelli G, Montesinos P, Schafer JA, Ottmann O, Petrini M, Pigneux A, Rambaldi A, Recher C, Rodriguez-Veiga R, Taussig D, Vey N, Yoon SS, Ott M, Muehlbauer S, Beckermann BM, Catalani O, Genevray M, Mundt K, Jamois C, Fenaux P, Wei AH. 2022. Idasanutlin plus cytarabine in relapsed or refractory acute myeloid leukemia: results of the MIRROS trial. Blood Adv, 6: 4147-4156.

Koyama T, Shimizu T, Kojima Y, Sudo K, Okuma HS, Shimoi T, Ichikawa H, Kohsaka S, Sadachi R, Hirakawa A, Yoshida A, Ando RM, Ueno T, Yanagaki M, Matsui N, Nakamura K, Yamamoto N, Yonemori K. 2023. Clinical activity and exploratory resistance mechanism of milademetan, an MDM2 ınhibitor, in ıntimal sarcoma with MDM2 Amplification: An open-label phase Ib/II study. Cancer Discov, 13: 1814-1825.

Kubbutat MH, Jones SN, Vousden KH. 1997. Regulation of p53 stability by Mdm2. Nature, 387: 299-303.

Lehmann C, Friess T, Birzele F, Kiialainen A, Dangl M. 2016. Superior anti-tumor activity of the MDM2 antagonist idasanutlin and the Bcl-2 inhibitor venetoclax in p53 wild-type acute myeloid leukemia models. J Hematol Oncol, 9: 50.

LoRusso P, Yamamoto N, Patel MR, Laurie SA, Bauer TM, Geng J, Davenport T, Teufel M, Li J, Lahmar M, Gounder MM. 2023. The MDM2-p53 Antagonist brigimadlin (BI 907828) in patients with advanced or metastatic solid tumors: results of a phase ıa, first-in-human, dose-escalation study. Cancer Discov, 13: 1802-1813.

Malagola M, Papayannidis C, Baccarani M. 2016. Tyrosine kinase inhibitors in Ph+ acute lymphoblastic leukaemia: facts and perspectives. Ann Hematol, 95: 681-693.

Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, Bader P, Verneris MR, Stefanski HE, Myers GD, Qayed M, De Moerloose B, Hiramatsu H, Schlis K, Davis KL, Martin PL, Nemecek ER, Yanik GA, Peters C, Baruchel A, Boissel N, Mechinaud F, Balduzzi A, Krueger J, June CH, Levine BL, Wood P, Taran T, Leung M, Mueller KT, Zhang Y, Sen K, Lebwohl D, Pulsipher MA, Grupp SA. 2018. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med, 378: 439-448.

Munoz-Fontela C, Mandinova A, Aaronson SA, Lee SW. 2016. Emerging roles of p53 and other tumour-suppressor genes in immune regulation. Nat Rev Immunol, 16: 741-750.

Nag S, Qin J, Srivenugopal KS, Wang M, Zhang R. 2013. The MDM2-p53 pathway revisited. J Biomed Res, 27: 254-271.

Ohtani S, Kagawa S, Tango Y, Umeoka T, Tokunaga N, Tsunemitsu Y, Roth JA, Taya Y, Tanaka N, Fujiwara T. 2004. Quantitative analysis of p53-targeted gene expression and visualization of p53 transcriptional activity following intratumoral administration of adenoviral p53 in vivo. Mol Cancer Ther, 3: 93-100.

Oliner JD, Kinzler KW, Meltzer PS, George DL, Vogelstein B. 1992. Amplification of a gene encoding a p53-associated protein in human sarcomas. Nature, 358: 80-83.

Ozaki T, Nakagawara A. 2011. Role of p53 in cell death and human cancers. Cancers (Basel), 3: 994-1013.

Pi L, Rooprai J, Allan DS, Atkins H, Bredeson C, Fulcher AJ, Ito C, Ramsay T, Shorr, Stanford WL, Sabloff M, Christou G. 2019. Evaluating dose-limiting toxicities of MDM2 inhibitors in patients with solid organ and hematologic malignancies: A systematic review of the literature. Leuk Res, 86: 106222.

Pulte D, Jansen L, Gondos A, Katalinic A, Barnes B, Ressing M, Holleczek B, Eberle A, Brenner H, Group GCSW. 2014. Survival of adults with acute lymphoblastic leukemia in Germany and the United States. PLoS One, 9: e85554.

Rew Y, Sun D. 2014. Discovery of a small molecule MDM2 inhibitor (AMG 232) for treating cancer. J Med Chem, 57: 6332-6341.

Rudolph D, Gollner A, Blake S, Rinnenthal J, Wernitznig A, Weyer-Czernilofsky U, Haslinger C, Garin-Chesa P, Quant J, McConnell DB, Moll J, Norbert K. 2018. A novel, potent MDM2 inhibitor that is suitable for high-dose intermittent schedules. Cancer Research, 78(13_Supplement): 4868-4868.

Sarkaria JN, Mrugala MM, Jaeckle KA, Burns TC, Vaubel RA, Parney IF, Chaichana K, Clement PM, Martinez-Garcia M, Sanchez JMS, Omuro AMP, Pronk L, Ross H, Teufel M, Hesse R, Grempler R, Galanis E. 2024. A phase (Ph) 0/Ia study of brigimadlin concentration in brain tissue and a non-randomized, open-label, dose escalation study of brigimadlin in combination with radiotherapy (RT) in patients (pts) with newly diagnosed glioblastoma (GBM). 19th Meeting of the European Association of Neuro-Oncology, October 17-20, Glasgow, UK, pp: 42.

Schwartz MS, Muffly LS. 2024. Predicting relapse in acute lymphoblastic leukemia. Leuk Lymphoma, 65: 1934-1940.

Scudiero DA, Shoemaker RH, Paull KD, Monks A, Tierney S, Nofziger TH, Currens MJ, Seniff D, Boyd MR. 1988. Evaluation of a soluble tetrazolium/formazan assay for cell growth and drug sensitivity in culture using human and other tumor cell lines. Cancer Res, 48: 4827-4833.

Shabashvili DE, Feng Y, Kaur P, Venugopal K, Guryanova OA. 2022. Combination strategies to promote sensitivity to cytarabine-induced replication stress in acute myeloid leukemia with and without DNMT3A mutations. Exp Hematol, 110: 20-27.

Specchia G, Pastore D, Carluccio P, Liso A, Mestice A, Rizzi R, Ciuffreda L, Pietrantuono G, Liso V. 2005. FLAG-IDA in the treatment of refractory/relapsed adult acute lymphoblastic leukemia. Ann Hematol., 84: 792-795.

Stein EM, DeAngelo DJ, Chromik J, Chatterjee M, Bauer S, Lin CC,

Suarez C, de Vos F, Steeghs N, Cassier PA, Tai D, Kiladjian JJ, Yamamoto N, Mous R, Esteve J, Minami H, Ferretti S, Guerreiro N, Meille C, Radhakrishnan R, Pereira B, Mariconti L, Halilovic E, Fabre C, Carpio C. 2022. Results from a first-in-human phase I study of siremadlin (HDM201) in patients with advanced wild-type TP53 solid tumors and acute leukemia. Clin Cancer Res, 28: 870-881.

Stengel A, Schnittger S, Weissmann S, Kuznia S, Kern W, Kohlmann A, Haferlach T, Haferlach C. 2014. TP53 mutations occur in 15.7% of ALL and are associated with MYC-rearrangement, low hypodiploidy, and a poor prognosis. Blood, 124: 251-258.

Sun W, Huang X. 2022. Role of allogeneic haematopoietic stem cell transplantation in the treatment of adult acute lymphoblastic leukaemia in the era of immunotherapy. Chin Med J, 135: 890-900.

Terwilliger T, Abdul-Hay M. 2017. Acute lymphoblastic leukemia: a comprehensive review and 2017 update. Blood Cancer J, 7: e577.

Thomas X, Boiron JM, Huguet F, Dombret H, Bradstock K, Vey N, Kovacsovics T, Delannoy A, Fegueux N, Fenaux P, Stamatoullas A, Vernant JP, Tournilhac O, Buzyn A, Reman O, Charrin C, Boucheix C, Gabert J, Lheritier V, Fiere D. 2004. Outcome of treatment in adults with acute lymphoblastic leukemia: analysis of the LALA-94 trial. J Clin Oncol, 22: 4075-4086.

Tolcher AW, Karim R, Tang YF, Ji J, Wang HB, Meng LC, Kaiser A, Coe J, Liang E, Rosas C, Yang DJ, Zhai YF. 2019. Phase Ib study of a novel MDM2 inhibitor APG-115, in combination with pembrolizumab in patients with metastatic solid tumors in US. Molec Cancer Therap, 18(12): A086-A086.

Vassilev LT. 2004. Small-molecule antagonists of p53-MDM2 binding: research tools and potential therapeutics. Cell Cycle, 3: 419-421.

Wang SM, Sun W, Zhao YJ, McEachern D, Meaux I, Barrière C, Stuckey JA, Meagher JL, Bai LC, Liu L, Hoffman-Luca CG, Lu JF, Shangary S, Yu SH, Bernard D, Aguilar A, Dos-Santos O, Besret L, Guerif S, Pannier P, Gorge-Bernat D, Debussche L. 2014. SAR405838: An optimized ınhibitor of MDM2-p53 ınteraction that ınduces complete and durable tumor regression. Cancer Res, 74: 5855-5865.

Willmore E, Ahn M, Kyle S, Zhao Y, Thomas H, Rankin KS, Bevan L, Fazal L, Hearn K, Wilsher N, Kucia-Tran J, Ferrari N, Wallis N, Thompson N, Lyons J, Miller D, Cano C, Noble ME, Hardcastle IR, Howard S, Chessari G, Lunec J, Newell DR, Wedge SR. 2024. Targeting the MDM2-p53 interaction: Time- and concentration-dependent studies in tumor and normal human bone marrow cells reveal strategies for an enhanced therapeutic index. Cancer Res, 84: 3333.

Wiman KG. 2006. Strategies for therapeutic targeting of the p53 pathway in cancer. Cell Death Differ, 13: 921-926.

Wu CE, Chen CP, Huang WK, Pan YR, Aptullahoglu E, Yeh CN, Lunec J. 2022. p53 as a biomarker and potential target in gastrointestinal stromal tumors. Front Oncol, 12: 872202.

Wu CE, Esfandiari A, Ho YH, Wang N, Mahdi AK, Aptullahoglu E, Lovat P, Lunec J. 2018. Targeting negative regulation of p53 by MDM2 and WIP1 as a therapeutic strategy in cutaneous melanoma. British J Cancer, 118: 495-508.

Yee K, Papayannidis C, Vey N, Dickinson MJ, Kelly KR, Assouline S, Kasner M, Seiter K, Drummond MW, Yoon SS, Lee JH, Blotner S, Jukofsky L, Pierceall WE, Zhi J, Simon S, Higgins B, Nichols G, Monnet A, Muehlbauer S, Ott M, Chen LC, Martinelli G. 2021. Murine double minute 2 inhibition alone or with cytarabine in acute myeloid leukemia: Results from an idasanutlin phase 1/1b study small star, filled. Leuk Res, 100: 106489.

Yu CH, Chang WT, Jou ST, Lin TK, Chang YH, Lin CY, Lin KH, Lu MY, Chen SH, Wu KH, Wang SC, Chang HH, Su YN, Hung CC, Lin DT, Chen HY, Yang YL. 2020. TP53 alterations in relapsed childhood acute lymphoblastic leukemia. Cancer Sci, 111: 229-238.

Zhou M, Yeager AM, Smith SD, Findley HW. 1995. Overexpression of the MDM2 gene by childhood acute lymphoblastic leukemia cells expressing the wild-type p53 gene. Blood, 85: 1608-1614.