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Review

Advancements in MDM2 inhibition: Clinical and pre-clinical investigations of combination therapeutic regimens

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ABSTRACT

Cancer cells often depend on multiple pathways for their growth and survival, resulting in therapeutic resistance and the limited effectiveness of treatments. Combination therapy has emerged as a favorable approach to enhance treatment efficacy and minimize acquired resistance and harmful side effects. The murine double minute 2 (MDM2) protein regulates cellular proliferation and promotes cancer-related activities by negatively regulating the tumor suppressor protein p53. MDM2 aberrations have been reported in a variety of human cancers, making it an appealing target for cancer therapy. As a result, several small-molecule MDM2 inhibitors have been developed and are currently being investigated in clinical studies. Nevertheless, it has been shown that the inhibition of MDM2 alone is inadequate to achieve long-term suppression of tumor growth, thus prompting the need for further investigation into combination therapeutic strategies. In this review, possible clinical and preclinical MDM2 combination inhibitor regimens are thoroughly analyzed and discussed. It provides a rationale for combining MDM2 inhibitors with other therapeutic approaches in the management of cancer, taking into consideration ongoing clinical trials that evaluate the combination of MDM2 inhibitors. The review explores the current status of MDM2 inhibitors in combination with chemotherapy or targeted therapy, as well as promising approach of combining MDM2 inhibitors with immunotherapy. In addition, it investigates the function of PROTACs as MDM2 degraders in cancer treatment. A comprehensive examination of these combination regimens highlights the potential for advancing MDM2-inhibitor therapy and improving clinical outcomes for cancer patients and establishes the foundation for future research and development in this promising area of study.

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1. Introduction

It is widely acknowledged that most tumors rely on multiple pathways to grow and survive. Cancer treatments often modulate proteins that are involved in complex growth pathways and mechanisms of drug resistance (Huang et al., 2020). Therapeutic resistance and cancer progression are driven by heterogeneity among cancer cells within a tumor, which limits the number of patients who experience meaningful clinical improvement and optimal treatment outcomes. Cancer molecular characteristics and medication pharmacokinetics may vary among individuals and tumors, providing a biological explanation for the observed variation. Single-cell sequencing has shown that cancer genomes evolve rapidly and diversely in response to treatment (Kuipers et al., 2017; Maynard et al., 2020). The effectiveness of cancer therapy is also hindered by the disease's ability to evolve through genetic and nongenetic processes. Even highly effective targeted therapies that aim to treat specific genetic mutations exhibit variability in drug response in clinical studies. Combining different therapeutic approaches such as surgery, chemotherapy, radiation, or targeted treatments can offer significant curative advantages in treating cancer by increasing efficacy and reducing acquired treatment resistance and toxic adverse effects (Plana et al., 2022; Strebhardt and Ullrich, 2008).

Many solid tumors are primarily treated with surgery, which is frequently accompanied by neoadjuvant and adjuvant therapies. Although systemic therapy is often a favored approach, the effectiveness of cytotoxic drugs has been limited for specific types of cancer including non-solid tumors (Italiano et al., 2012). Similarly, ionizing radiation is a frequently utilized modality in the treatment of childhood sarcoma, commonly associated with elevated MDM2, either during the initial diagnosis or in cases of disease recurrence. It has been observed that a significant proportion of sarcomas occurring in children demonstrate a p53 wild-type phenotype (Phelps et al., 2015). MDM2 inhibitors commonly disrupt the binding between MDM2 and p53, thereby activating wild-type p53. However, the cellular response to MDM2 inhibition can differ significantly depending on both the type of tumor and the dosage administered (Jeay et al., 2018; Ray-Coquard et al., 2012). On the other hand, the efficacy of using MDM2 inhibitors as a single therapy remains inconclusive owing to many circumstances, including the existence of non-functional p53 mutations and the development of resistance mechanisms. Idasanutlin, known as RG7388, is a second-generation MDM2 inhibitor and a member of the nutlin family. Compared to the first-generation MDM2 inhibitors, idasanutlin has demonstrated higher efficacy and selectivity (Ding et al., 2013). However, recent findings revealed that long-term exposure to idasanutlin led to the emergence of resistance, which was attributed to the activation of the extracellular signal-regulated kinases 1/2 (ERK1/2)insulin growth factor binding protein 1 (IGFBP1) signaling pathway (Berberich et al., 2019). The incidence of primary resistance or acquired resistance to several MDM2 inhibitors remains prevalent in a wide variety of malignancies. Although poorly understood, acquired resistance to MDM2 inhibitors might develop through a number of pathways, one of which is the acquisition of p53 mutations (Aziz et al., 2011; Hata et al., 2017; Jung et al., 2016). These obstacles reinforce the need to integrate MDM2 inhibitors with other pharmacological anticancer agents. Therefore, profiling tumor genotypes could enhance MDM2 inhibition effectiveness and inform combination therapy design. In addition, identifying broader criteria beyond p53 status is crucial to predicting treatment response. Also, optimized treatment schedules and dosages are potentially essential to address toxicity and resistance challenges (Haronikova et al., 2021). The purpose of this review is to discuss the advantages of targeting the MDM2 pathway with the objective of improving the effectiveness of cancer therapies while simultaneously mitigating the risk of adverse effects. The key focus of such a strategy is to highlight the substantial advantages of employing a synergistic approach to advance cancer therapy outcomes, particularly in the context of malignancies linked to the dysregulation of MDM2.

To fully leverage the potential benefits of combining treatments, it is imperative to conduct a comprehensive assessment that includes both clinical and preclinical studies (Konopleva et al., 2020a). This comprehensive evaluation carefully examines the advantages and disadvantages associated with applying combined therapeutic approaches, with the primary objective being to ensure that the combination of diverse therapeutic approaches does not result in increased toxicity or the occurrence of severe adverse effects that outweigh the predicted positive effects (Burgess et al., 2016). This review further examines the molecular mechanisms of the MDM2 pathways and explores potential combination strategies to enhance their tumorigenic effects.

2. MDM2 and its detrimental role in cancer progression

The MDM2 gene was identified in 1987 using RNA screening in a spontaneously transformed mouse 3 T3 cell (Cahilly-Snyder et al., 1987). Further investigation found that this evolutionarily conserved gene was important in controlling cellular development and had tumorigenic potential (Fakharzadeh et al., 1991; Momand et al., 1992). Elevated levels of MDM2 have been observed in certain human malignancies, resulting in reduced p53 function. Subsequently, it was discovered that the N-terminal domain of MDM2 inhibits the activity of p53, and it was also demonstrated that MDM2 facilitates the degradation of p53 through an E3 ligase proteasomal mechanism (Fig. 1) (Chen et al., 1993; Fang et al., 2000; Honda et al., 1997; Oliner et al., 1993). Mounting data suggests that the oncogenic role of MDM2 extends beyond its well-known function as a negative regulator of the p53 tumor suppressor. MDM2 has been found to control the cell cycle, apoptosis, differentiation, and genomic stability in a p53-independent fashion (Bohlman and Manfredi, 2014; Jones et al., 1998; Wu and Levine, 1997). For instance, Arena et al. demonstrate that p53 is not required for MDM2 recruitment to mitochondria to regulate respiration and mitochondrial dynamics (Arena et al., 2018). Werner Syndrome (WS) is an autosomal recessive disorder characterized by premature aging, and it is caused by mutations in the WRN gene. A study showed that MDM2-mediated degradation of WRN plays a role in cellular aging through a mechanism that operates independently of the p53 tumor suppressor pathway (Liu et al., 2019). Similarly, MDM2 has been shown to be critical in circumventing cell cycle checkpoints, essential mechanisms for maintaining cellular equilibrium and preventing uncon-

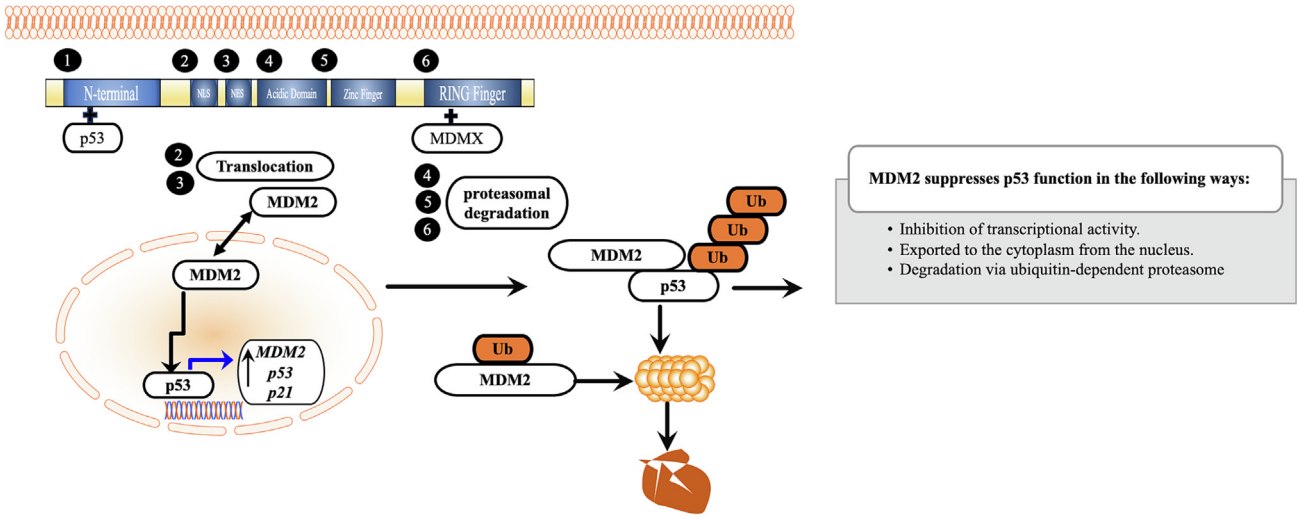

Fig. 1. Illustrates the protein structure of mdm2 and the inhibitory effect of mdm2 on p53 function. mdm2 consists of distinct domains, including an n-terminal p53-binding domain, nuclear export signal, nuclear export signal, a central acidic domain, a zinc finger domain, and a c-terminal ring finger domain. mdmx, a homolog of mdm2, forms a dimeric complex with the n-terminal domain of mdm2. ub stands for ubiquitin binding, which is necessary for ubiquitination to take place.

trolled growth, specifically in estrogen-dependent breast cancer cells. Estrogen promotes cell growth via an MDM2-regulated pathway that not only functions independently of the p53 tumor suppressor but also has the capacity to impair the activity of wild-type p53 (Brekman et al., 2011).

MDM2 amplification or overexpression has been reported in 40% to 60% of human sarcomas. In addition, late-stage solid and hematological malignancies exhibit increased expression of MDM2. The MDM2 gene has been observed in more than 28 types of tumors, which account for approximately 17% of all cancer types (Araki et al., 2010).These aggressive tumors are associated with poor clinical outcomes and inadequate diagnostic tools. As a result, MDM2 overexpression has been associated with a poorer clinical prognosis, a lower possibility of an effective therapeutic response, and an increased risk of distant metastases. Since the identification of the MDM2 and p53 interaction configuration in 1996, several small-molecule MDM2 inhibitors have been developed and are currently being evaluated in clinical trials to assess their effectiveness in treating cancer (Fig. 2) (Haupt et al., 1997; Tortora et al., 2000). Nutlin, the first MDM2 inhibitor, was developed in 2003 and has been extensively used to study MDM2 function (Vassilev et al., 2004). MDM2 has emerged as a potential target for cancer therapy, with the inhibition of the proteinprotein interaction between MDM2 and p53 being recognized as an effective treatment strategy (Li and Lozano, 2013). MDM2 genomic profiling and protein structure: implications for cancer treatment.

Extensive research has been conducted on the MDM2 protein structure and chromosomal location of its gene. The MDM2 gene, also known as HDM2, is located on chromosome 12q14.3-q15 and has two promoters (P1 and P2). It is regulated at multiple levels, including transcriptional, translational, and post-translational, by various cellular signals that govern protein accumulation and activity (Barak et al., 1993; de Oca Luna et al., 1996). The MDM2 gene consists of 12 exons, each capable of producing distinct spliced variants and isoforms of the MDM2 protein. MDM2 expression is constitutively regulated by the P1 promoter, while the P2 promoter is responsible for inducing the gene expression in response to stressors such as radiation. The translational functionality of the MDM2 protein may differ depending on the promoter, despite both P1 and P2 MDM2 promoters producing full-length MDM2 proteins.

On the other hand, recent research indicates that aberrant regulation of splicing plays a role in carcinogenesis and the development of cancer. The molecular mechanisms by which cancer cells modify their splicing ability to facilitate tumor growth and treatment resistance are poorly understood. Notably, unlike solid tumors, hematological tumor cells frequently carry mutations in genes involved in splicing (Kitamura and Nimura, 2021). Numer-

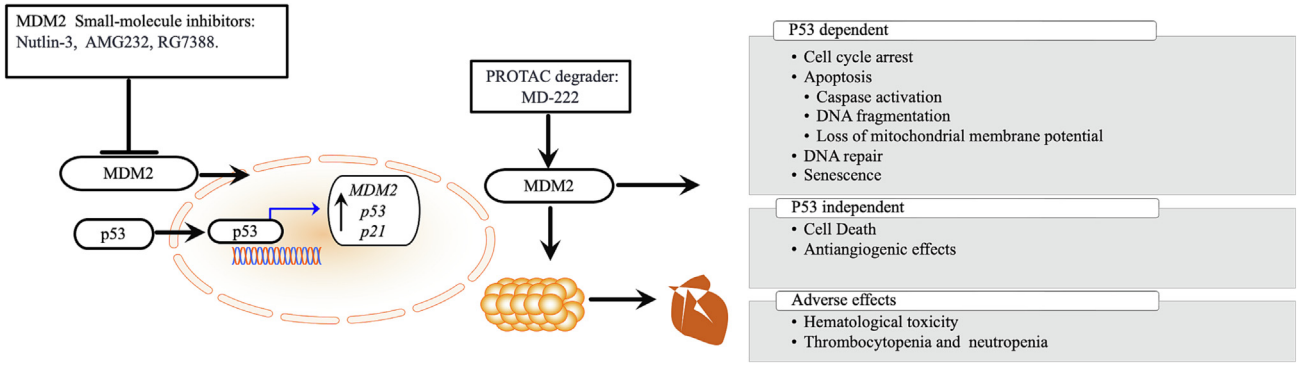

Fig. 2. Illustrates the primary mechanism of action for mdm2 inhibitors and mdm2-targeted protacs. Small molecules disrupt the interactions between p53 and mdm2, leading to the subsequent release of p53. Protacs also possess the ability to degrade mdm2 protein. Inhibiting mdm2 will lead to many p53-dependent and independent effects.

ous splice variants of MDM2 have been identified in both normal and malignant cells, but their impact and functional characteristics in response to chemotherapy treatment remain unclear (Huun et al., 2017). The first alternatively spliced MDM2 transcript has been observed in human malignancies for more than twenty years. A total of 72 distinct MDM2 splice variants have been identified in both human cancer and normal tissue (Bartel et al., 2002).The elevated expression of MDM2 splice variants has been observed in response to genotoxic stress caused by chemotherapy (Bartel et al., 2004). The existence of extensive genomic profiling databases, such as The Cancer Genome Atlas Research Network, has facilitated the examination of the effects of MDM2 amplification and single nucleotide polymorphisms (SNP) inheritance in diverse high-quality tumor samples from various cancer origins.

MDM2 consists of three distinct domains, including the N-terminal domain, the C-terminal domain, and the acidic domain (Fig. 1). Numerous studies have provided evidence indicating that distinct regions of MDM2 engage in interactions with p53, resulting in the suppression of its transcriptional activity. In addition, the MDM2 domains serve to enhance the E3 ligase function of MDM2, resulting in the degradation of proteins targeted by MDM2, such as p53, through the proteasomal pathway. During cellular stress, the transportation of MDM2 between the cytoplasm and the nucleus is facilitated by the presence of additional domains, namely a nuclear localization signal (NLS) and a nuclear export signal (NES) (Fig. 1) (Li and Lozano, 2013). The RING finger region is essential for localizing the p53 protein, in addition to its potential role in ubiquitin ligase-mediated activities (Fig. 1) (Boyd et al., 2000).

2.1. The MDM2-p53 axis as a therapeutic target in cancer

MDM2 inhibits p53 through multiple mechanisms. The functions of this protein include acting as an E3 ubiquitin ligase, which leads to the degradation of p53 (Fig. 1). It also inhibits the transcriptional activation domain of p53 and plays a role in the transportation of p53 from the nucleus to the cytoplasm. By disrupting the interaction between MDM2 and p53, it is possible to inhibit all three pathways (Fig. 1). The prevalence of p53 mutations varies significantly among different types of tumors. For example, more than 90% of ovarian cancers have been found to contain p53 mutations, whereas in acute myeloid leukemias (AML), these mutations are present in less than 15% of cases (ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium, 2020). P53 gene mutations have a wide variety of effects on the development and progression of cancer. Some mutations can lead to a functional deficit, while others might bring novel functionalities or have dominant-negative consequences. This adds to the complexity of the cancer biology associated with p53. The disparity in the frequency of p53 mutations between various cancer types suggests tissue-specific requirements, which could determine the necessity for normal p53 function loss or aberrant mutant p53 functions (Kennedy and Lowe, 2022). The p53 gene is responsible for encoding p53, a transcription factor and tumor suppressor that is widely recognized as the guardian of the genome. P53 is the most frequently mutated gene in various types of cancer, with mutations present in nearly 50% of malignancies. The prevalence of p53 mutations varies significantly across different cancer types, with rates as low as less than 5% in cervical cancer and as high as 80% to 90% in small-cell lung cancer and ovarian cancer. The majority of p53 mutations (73%) are missense substitutions, while frameshift insertions and deletions (9%), nonsense mutations (8%), silent mutations (4%), and other less common modifications make up the remaining mutations (Dembla et al., 2018; Joerger and Fersht, 2016).

Compared to MDM2, p53 is activated and stabilized in the cell when there is cellular stress and DNA damage, indicating its important function as a tumor suppressor (Joerger and Fersht, 2016; Vassilev, 2007). In these circumstances, p53 triggers the activation of specific genes that result in cell cycle arrest, DNA repair, and apoptosis. These processes facilitate the repair or elimination of damaged cells, thus preventing the development of tumors. Activating p53 in human malignancies has been a longstanding therapeutic priority, and despite recent progress, it remains a challenging task (Saiki et al., 2014). Numerous studies have demonstrated that inhibiting MDM2 effectively stimulates p53 activation and promotes apoptosis in cancer cells in preclinical in vitro and animal models. Elevated levels of p53 can hinder the proliferation and differentiation of healthy cells. Under normal and unstressed circumstances, p53 levels are tightly controlled through rapid degradation by the proteasome (Levine and Oren, 2009). The later hypothesis suggests that MDM2 facilitates the activation of wild-type p53 in a manner that does not involve genetic damage, resulting in a more advantageous therapeutic result (Chen et al., 2015). Thereby, restoring p53 signaling is approached cautiously in practice due to its potential impact on healthy cells.

The MDM2-p53 axis is a crucial pathway in the development of tumors and has been extensively researched as a potential target for cancer treatment. This intervention could potentially be used in most cancers that have wild-type p53. The primary focus of recent research has been directed towards the development of therapeutic agents that exhibit synergistic effects when used in combination with MDM2 inhibitors. In vitro and in vivo studies have demonstrated the promising antiproliferative effects of small-molecule inhibitors of MDM2 on tumors (Saiki et al., 2014). The primary objectives of targeting the MDM2 pathway are to reduce the regulatory impact of MDM2 on p53 and restore its function as a tumor suppressor to effectively impede tumor growth and mitigate the emergence of resistance to these inhibitors. Several molecular strategies have been developed to achieve this objective, including inhibiting the expression of MDM2, inhibiting the interaction between MDM2 and p53, modifying the E3 ubiquitin ligase activity of MDM2, and targeting the MDM2-p53 proteinprotein complex (Fig. 2).

Significant evidence supports the existence of an auto-regulatory feedback loop between MDM2 and p53. The p53-binding site interacts with the MDM2 P2 promoter in this loop, leading to an increase in both MDM2 gene expression and protein levels. MDM2 inhibits the transactivation domain of p53 upon binding, resulting in reduced transcriptional activity of p53 on MDM2 and other genes. MDM2 functions as an E3 ubiquitin ligase, promoting the ubiquitination of p53 and consequently accelerating its degradation (Karni-Schmidt et al., 2016; Konopleva et al., 2020b; Vassilev, 2007). The presence of an auto-regulatory loop between MDM2 and p53 suggests that the efficacy of MDM2 inhibitors may be limited due to the buildup of MDM2 protein, which in turn facilitates the later degradation of p53. On the other hand, MDMX, an MDM2 homolog, can interact with both p53 and MDM2, complicating the interaction between p53 and MDM2. MDMX binds to the N-terminal transactivation domain of p53, leading to the inhibition of its transcriptional activity. Nevertheless, it is important to acknowledge that MDMX does not exhibit direct E3 ligase activity and lacks p53-responsive elements (Shvarts et al., 1996). In contrast, MDMX possesses a RING domain that facilitates its interaction with MDM2, leading to the formation of RING-mediated heterodimers (Leslie et al., 2015; Sharp et al., 1999; Tanimura et al., 1999; Tisato et al., 2017).

The initial discovery involved the identification of the nutlins, which are the first low molecular weight inhibitors that exhibit potent and selective properties in their ability to disrupt the bind-

ing between MDM2 and p53 (Kirkpatrick, 2004; Vassilev, 2004). These first-generation compounds activate the p53 pathway and inhibit tumor growth in vitro and in vivo. The mechanism of action of these compounds involves binding to the hydrophobic cleft at the N-terminus of MDM2, which mimics the p53 residues Trp23, Leu26, and Phe19 (Fig. 2) (Vassilev et al., 2004). Several preclinical studies have evaluated the efficacy of nutlin-3 in hematologic cancers with MDM2 amplification, such as acute myeloid leukemia, chronic lymphocytic leukemia, and multiple myeloma. Nutlin-3a has been found to induce cell death independently of p53 by stabilizing p73, a pro-apoptotic tumor suppressor belonging to the p53 family (Fig. 3). RG7112, a second-generation MDM2 inhibitor, has been shown to inhibit cell-cycle progression in a dose-dependent manner and increase the expression of the p53 protein. This medication was the first MDM2 inhibitor to enter clinical trials, with the primary goal of treating MDM2-amplified liposarcoma. Both nutlin and RG7112 exhibited clinical limitations in terms of their effectiveness (Duffy et al., 2022; Konopleva et al., 2020b; Wade et al., 2013).

MDM2 amplification is frequently observed in patients with advanced dedifferentiated liposarcomas (DDLPS). As a result, exploring different oncogenic signaling pathways linked to sarcoma tumorigenesis via the MDM2-p53 loop may present potential targets for combination therapy in DDLPS. Until recently, none of the developed MDM2 inhibitors had progressed beyond early-phase clinical trials for solid tumors (Iancu-Rubin et al., 2014). However, a recent trial evaluating the preliminary efficacy of milademetan (DS-3032b) in patients with advanced malignancies, including DDLPS, yielded inconclusive outcomes (Gounder et al., 2023a, 2023b). Another recent report indicated that patients with advanced well-differentiated LPS or DDLPS had a feasible and early anti-tumor response when administered with siremadlin and ribociclib (Abdul Razak et al., 2022). Milademetan is a small molecule inhibitor that selectively targets the MDM2-p53 interaction by activating p53 function at low concentrations and has also been shown to induce apoptosis in wild-type p53 cancer cell lines (Ishizawa et al., 2018). The first clinical investigation evaluating milademetan in patients with advanced solid tumors or lymphomas assessed the safety and tolerability of milademetan using various dosing regimens. The disease control rate for all cohorts (N = 107) was 45.8% (95% CI, 36.1 to 55.7), and the median progression-free survival was 4.0 months (95% CI, 3.4 to 5.7). The study population demonstrated that milademetan had a 46% disease control rate (DCR) when used as a monotherapy. This is comparable to the DCR of milademetan in Japanese patients with solid tumors, which was 44% in a phase I study. (Takahashi et al., 2021). The observed monotherapy results of milademetan in DDLPS have led to the initiation of a randomized phase III trial (MANTRA) comparing milademetan to standard care in DDLPS (Gounder et al., 2023a, 2023b).

2.2. The rationale for combining MDM2 inhibitors with other cancer-treatment approaches

In recent years, numerous research efforts have concentrated on the advancement of selective MDM2 inhibitors and their potential combination treatments. (Traweek et al., 2022) Notably, MDM2 is crucial in hematopoiesis, and inhibiting MDM2 can lead to hematological complications. It is widely accepted that treatment with MDM2 inhibitors stimulates the activation of various signaling pathways that trigger apoptosis, including caspase activation, DNA fragmentation, and loss of mitochondrial membrane potential (Fig. 2) (Balayssac et al., 2018; Kojima et al., 2005a; Pant et al., 2012). MDM2 inhibitors have the potential to enhance therapeutic effectiveness and reduce the possibility of chemotherapy resistance. However, it appears that the exclusive targeting of MDM2 has limited potential for consistent and effective suppression of tumor proliferation. Prior research, on the other hand, has shown that suppressing MDM2 might possibly increase the development of tumor cells with rare incidences of p53 inactivation. Therefore, it is essential to employ a synergistic therapeutic strategy in order to eradicate tumors completely (Fig. 3) (Aziz et al., 2011; Martins et al., 2006).

Historically, early clinical trials of MDM2-p53 pathway inhibitors have not demonstrated significant clinical efficacy (Andreeff et al., 2016; de Jonge et al., 2017). The optimal effectiveness of MDM2 in the treatment of solid tumors, as compared to non-solid tumors, remains to be definitively established. This disparity is attributed to numerous factors, including the presence of inactive p53 mutations, the upregulation of coactivators such as MDMX, and other unknown resistance mechanisms (Jung et al., 2016). Previous clinical studies identified two main concerns related to MDM2-targeted agents. The first main problem is p53 activation in the bone marrow, which causes hematological toxicity, particularly thrombocytopenia and neutropenia (Fig. 2). Therefore, these toxicity concerns are widely recognized as major dose-limiting concerns, necessitating the adjustment of an optimal dosing regimen. The second concern pertains to the identification of p53 mutations in numerous cancer patients. This underscores the significance of combining MDM2 inhibitors with drugs that can effectively reduce tumor growth, regardless of the patient's p53 status. Given the importance of p53 in cancer development, the

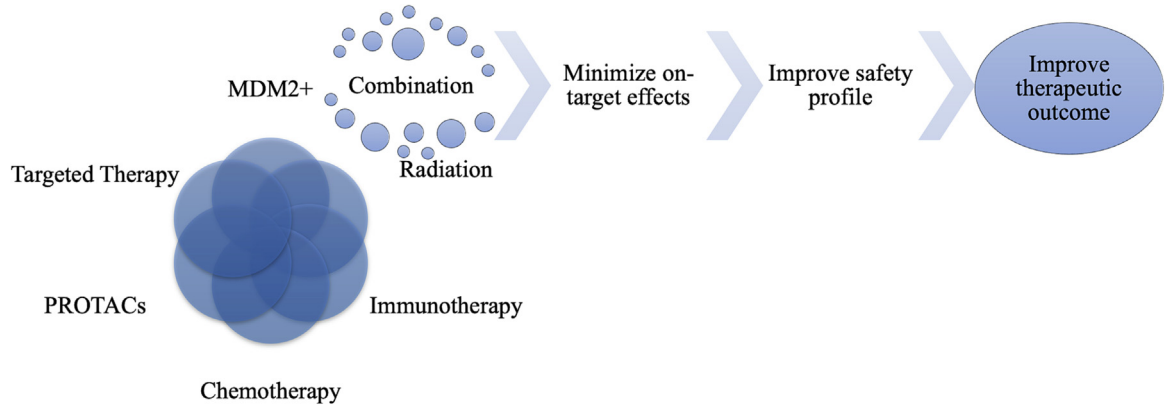

Fig. 3. Demonstrates the benefits of combining mdm2 with diverse cancer therapies. This combined approach enhances the effectiveness of cancer treatments as it synergistically reduces tumors and induces cancer cell death, potentially overcoming treatment resistance.

existing paradigm has encountered significant challenges over the past two decades (Fig. 2) (Hoffman-Luca et al., 2015; Wang et al., 2017).

Combined therapies can offer advantages to patients by either restoring their antitumorigenic activity or slowing the development of treatment resistance. It is therefore important to prioritize patient safety when considering combining modalities to avoid undesirable side effects (Rusiecki et al., 2019). Wang HQ and colleagues found that inhibiting MDM2 can enhance the antitumor effects in cancer cells with wild-type p53 by influencing the immune and stromal microenvironments. These results provide evidence for the potential effectiveness of combining MDM2 inhibitors with checkpoint-blocking antibodies in the treatment of patients with p53 wild -type tumors (Wang et al., 2021). Additionally, experimental studies utilizing human tumor cell lines have demonstrated that the addition of MDM2 inhibitors to radiation therapy can enhance radiation response (Werner et al., 2015). Fig. 3 highlights the potential advantages that can be achieved through the synergistic combination of MDM2 with various therapeutic cancer modalities. Through collaborative efforts, the combination of MDM2 and various therapeutic interventions exhibits a synergistic effect, leading to enhanced tumor suppression and the induction of cancer cell death. The integration of this combined strategy exhibits considerable potential for the advancement of cancer therapeutics, with a particular emphasis on enhancing efficacy and tailoring treatments to individual patients. This review focuses on the potential of MDM2 inhibitors in combination with other tumorigenic signaling pathways, as well as the preclinical and clinical use of PROTAC (proteolysis targeting chimeras) (Khurana and Shafer, 2019).

2.3. Investigating the role of PROTACs MDM2 degraders in cancer management

MDM2 inhibitors function by inhibiting the degradation of MDM2, resulting in the accumulation and activation of the p53 protein. This process enhances the transcription of MDM2 mRNA, leading to an elevation in MDM2 protein levels. One drawback of MDM2 inhibitors is that the removal of these inhibitors can lead to the rapid degradation of p53 by the increased MDM2 protein, thereby restricting their therapeutic efficacy. In this regard, prior research has demonstrated that the accumulation of p53 protein in xenograft tumor tissues is transient following a single administration of an MDM2 inhibitor, highlighting the short-term efficacy of the treatment. Moreover, the presence of an elevated level of MDM2 protein in healthy tissues, given its carcinogenic properties, could potentially lead to undesirable consequences (Fig. 2). It is therefore necessary to develop innovative approaches for more efficient targeting of MDM2. These approaches should aim to optimize therapeutic outcomes by addressing issues related to transient p53 accumulation and potential adverse effects in normal tissues (Li et al., 2019). For instance, exploring the potential of PROTACs MDM2 degraders as a substitute for combination therapy in cancer treatment presents promising prospects. PROTACs present an intriguing therapeutic option due to their ability to target multiple pathways simultaneously, exhibit enhanced specificity, potentially overcome resistance, and demonstrate synergistic effects with other treatments (Fig. 2).

Certain proteins have proven difficult to target due to their broad, shallow active sites, which pose challenges when binding with small molecules. Protein degraders represent a category of molecules that have the potential to selectively degrade particular proteins. Clinical studies using PROTAC molecules began in 2019, and by 2020, these trials had provided the first clinical evidence demonstrating the efficacy of this novel therapeutic approach, providing proof-of-concept for two challenging oncogenic targets: the estrogen receptor and the androgen receptor (BÕkÕs et al., 2022). PROTACs have a heterobifunctional structure, consisting of two distinct ligands. One ligand binds to a specific protein of interest (POI), while the other ligand binds to an E3 ubiquitin ligase. The two ligands are covalently bonded together through a linker. PROTACs enhance the recruitment of the ubiquitinproteasome system (UPS), allowing the POI to be brought into close proximity with the E3 ligase. Consequently, the specific protein undergoes ubiquitination and subsequent degradation by the proteasome, facilitated by the UPS (Khan et al., 2020a; Li et al., 2022). On the other hand, MDM2 can independently target other tumorigenic proteins through its E3 ligase activities. The first MDM2-based PROTAC has effectively degraded the androgen receptor by utilizing nutlin-3a as the MDM2 ligand and a non-steroidal selective androgen receptor modulator (SARM) as the AR ligand (Khan et al., 2020b; Wang et al., 2020).

The inconsistent response rates shown in clinical studies with MDM2 inhibitors have prompted concerns about whether PROTACs degraders can provide better effectiveness without noticeably raising toxicity. In theory, PROTACs have the potential to overcome the limitations of current MDM2 inhibitors; hence, many MDM2 inhibitors have incorporated PROTACs approach to target endogenous MDM2 (Han et al., 2022). MS3227 was designed to target MDM2 and recruit Von Hippel-Lindau E3 ligase, leading to the proteasomal degradation of MDM2. It has been shown that MS3227 activates p53 targets such as p21, PUMA, and MDM2 in leukemia cells, resulting in cell cycle arrest, apoptosis, and decreased cell viability and demonstrates effectiveness in primary patient samples. Predominantly, targeting leukemic blasts and boosting the efficacy of other anti-leukemic drugs such as azacytidine, cytarabine, and venetoclax have been demonstrated (Marcellino et al., 2023). Similarly, the IMiD-based MDM2 PROTAC 8 effectively reduces MDM2 protein levels in the RS4;11 xenograft model. MDM2 PROTAC 8 demonstrates superior efficacy when compared to MI-1061, a non-degrading MDM2-p53 inhibitor. IMiD-MDM2 PROTAC 8 demonstrates efficient degradation of MDM2 both in vitro and in vivo (Ryan P. Wurz and Cee, 2019). MD-224, another example of MDM2 PROTAC degraders, has shown potential as a cancer treatment by using the cullin 4A E3 degradation system (Li et al., 2019).

A recent study showed that targeting MDM2 degradation using PROTACs represents a promising and innovative therapeutic approach with significant potential for the treatment of triple-negative breast cancer (TNBC) that surpasses the efficacy of current MDM2 inhibitors. TNBC is a highly aggressive, therapy-resistant, and often fatal subtype of breast cancer characterized by the inactivation of the p53 tumor suppressor protein. It has been shown that MDM2-targeted degrader effectively eliminates p53-inactivated TNBC cells, underscoring the critical role of MDM2 in the survival of TNBC cells and establishing it as a promising new therapeutic target for this disease (Adams et al., 2023). As a consequence, using a targeted degradation strategy to block the MDM2-p53 proteinprotein interaction might lead to increased efficacy and a long-term pharmacological impact that is significantly different from that of conventional inhibitors.

In normal cells and tissues such as bone marrow, spleen, and small intestine, small-molecule MDM2-p53 inhibitors are already linked to clinical dose-limiting toxicities. This is thought to be due to the on-target activation of p53, which can be eliminated when using this approach (Fig. 2) (Ryan P Wurz and Cee, 2019). New PROTAC degraders show promise for cancer therapy due to their potential to address the limitations of MDM2 inhibitors, such as limited efficacy, drug resistance, and undesirable toxicities. However, the effectiveness and toxicity of PROTAC in human cancer patients remain unclear, given the mixed response rates in clinical trials (Fang et al. 2020a). PROTACs can be used in combination

with various chemotherapeutic drugs, but this approach is still in its early stages and has the potential to alter current cancer management practices. To determine whether PROTAC MDM2 degraders can enhance therapeutic outcomes while maintaining an acceptable safety profile, more studies are needed (Fang et al., 2020b).

2.4. Combination of MDM2 inhibitors with targeted therapy

The limitations of current cancer therapies in terms of effectiveness and drug resistance are widely acknowledged, prompting researchers to constantly explore new strategies for targeting proteins that facilitate tumor growth. In recent decades, targeted therapies have made significant advancements in improving cancer treatment outcomes **(**Fig. 3**)**. The potential of combining MDM2 inhibitors with other medications, including phosphoinositide 3-kinases /mitogen-activated protein kinase (PI3K/MAPK) inhibitors, Bcl-2 homology 3 (BH3) mimetics, Histone Deacetylases (HDAC) inhibitors, and BCR-ABL kinase blockers, has been explored and shows promise as a treatment option for different types of cancer. Clinical studies have demonstrated that the use of triple combination inhibitors targeting MDM2, PI3K, and BRAF/MEK leads to significant inhibition of cancer cell growth when compared to the outcomes achieved with dual inhibition (Saiki et al., 2014) Therefore, the implementation of a simultaneous targeting strategy for multiple pathways could potentially be an effective method to overcome signaling redundancies and improve the effectiveness of MDM2-targeted treatment. These research findings emphasize the complex interactions between tumorigenic pathways that influence MDM2-p53 signaling in various types of cancer. As a result, the simultaneous inhibition of these pathways emerges as a promising approach to address these challenges.

It is believed that focal adhesion kinase (FAK) plays non-canonical roles in cancer cells under cellular stress, in addition to its nuclear functions related to regulating p53 degradation and cytokine expression. A recent study presented evidence supporting the combination of an MDM2 inhibitor and a FAK inhibitor as a potential therapeutic approach for mesothelioma (Lim et al., 2008; Serrels et al., 2015). FAK, a non-receptor tyrosine kinase, is typically involved in transmitting signals from cellular adhesions to regulate various biological activities such as cancer cell survival, migration, and invasion. The objective of utilizing a combination therapy involving MDM2 and FAK inhibitors is to concurrently target multiple pathways, with the goal of possibly enhancing treatment outcomes for this specific cancer type as well as perhaps other types of cancer (Dawson et al., 2021). A study showed that the FAK inhibitor (CP-31398) exhibited significant inhibition of mesothelioma tumor growth, and when combined with nutlin-3a, synergistic effects were observed. This suggests that the combination of CP-31398 with nutlin-3a may provide enhanced therapeutic benefits for mesothelioma treatment compared to using either agent alone. These findings suggest that targeting multiple pathways, including FAK, could potentially offer a more effective treatment strategy for mesothelioma (Zhong et al., 2020).

Based on evidence indicating that mutations or deletions of p53 were present in less than 20% of patients with hematologic malignancies at the time of diagnosis, the rationale for exploring combination therapy in AML and other leukemic cells has been established. (Mitani et al., 2007). Furthermore, several studies have shown that nutlin-3, when used alone or in combination with chemotherapy, can enhance the cytotoxicity of AML (Kojima et al., 2005b; Long et al., 2010; Secchiero et al., 2007). It has also been suggested that there is a reciprocal interplay between MDM2 and FMS-like tyrosine kinase-3-internal tandem duplication (FLT3) in AML cells. In this context, the combined use of sorafenib and nutlin-3 drugs has demonstrated synergistic cytotoxic effects on both primary acute myeloid leukemia blasts and acute myeloid leukemia cell lines, leading to an increased level of apoptosis and autophagy. (G. Zauli et al., 2012) However, the effectiveness of venetoclax (a B-cell lymphoma-2 inhibitor) and idasanutlin (2nd generation MDM2 inhibitor) as monotherapies has been limited in individuals with relapsed or refractory acute myeloid leukemia (R/R AML). In a similar vein, studies have demonstrated that combining BCL-2 and MDM2 inhibitors exhibits synergistic apoptotic effects both in vitro and in vivo (Kojima et al., 2006; Pan et al., 2017). Furthermore, simultaneous p53 activation and BCL-2 suppression were effective in reducing apoptotic resistance in drug-resistant AML animal models. In AML cell lines with wild-type p53, the combination of venetoclax and idasanutlin displayed synergistic antitumor activity. In AML models, this combination treatment demonstrated greater effectiveness and improved survival outcomes as compared to either drug alone. These data suggest that combining p53 activation with BCL-2 suppression as a treatment method for AML has promise (Lehmann et al., 2016; Pan et al., 2017). The synergistic mechanism of venetoclax and idasanutlin may involve the upregulation of proapoptotic proteins (BAX, BIM, and PUMA) through p53 activation, which leads to the inactivation of myeloid cell leukemia 1 (MCL-1) and BCL-extra-large (BCL-xL), along with the simultaneous degradation of MCL-1 via dual phosphorylation. MCL-1 is markedly elevated in AML, especially during relapse, and plays a significant role in the progression of AML. Hence, the combined use of venetoclax and idasanutlin may improve the effectiveness of venetoclax in combination therapy by indirectly targeting MCL-1 (Daver et al., 2023; Xiang et al., 2010). Another study group investigated the use of an MDM2 inhibitor in conjunction with a BH3 mimic to boost p53-mediated Bax activation. A BH3 mimetic is a small-molecule drug that mimics the activity of pro-apoptotic proteins BH3-only domain. The combination of MI-63 (an MDM2 inhibitor) and ABT-737 (a BH3 mimic) reduced cellular viability and enhanced apoptosis in multiple myeloma mice with mutant p53. These findings suggest that this combination therapy could be beneficial for patients with both wild-type and mutant p53. Additionally, it has been reported that the MDM2 inhibitor nutlin can bind to anti-apoptotic Bcl-2 family proteins, indicating that the benefits of the combination therapy which may be attributed to the off-target effects of the MDM2 inhibitor. These findings propose that combining an MDM2 inhibitor with a BH3 mimetic could serve as a promising therapeutic strategy for multiple myeloma. Moreover, MI-63 has shown the ability to overcome lenalidomide resistance and can be combined with other approved agents like bortezomib or lenalidomide to enhance activity against both myeloma cell lines and primary samples (Gu et al., 2014).

2.5. Combination of MDM2 inhibitors with chemotherapy in solid tumors

The current focus of scientific investigation lies in the comprehensive assessment of the therapeutic potential of combining MDM2 inhibitors with chemotherapy for the treatment of solid tumors. Although MDM2 inhibitors have exhibited promising results as single-agent therapies in preclinical studies, their efficacy as monotherapy in clinical trials has been limited. In 2006, investigators made the initial effort to combine MDM2 inhibitors and chemotherapy in order to stabilize wild-type p53, activate p53 activity, decrease proliferation, and enhance the vulnerability of cells to chemotherapy-induced apoptosis. In a preclinical study, it was observed that the combination of MDM2 inhibition with doxorubicin resulted in a considerable decrease in tumor growth compared to doxorubicin alone (Bill et al., 2019; Cassinelli et al., 2022). A previous investigation has revealed that neuroblastoma tumors often retain functional downstream p53 signaling path-

ways and exhibit wild-type p53 expression. Based on this observation, investigations have been conducted to explore the potential of combining MDM2 inhibitors with conventional chemotherapy regimens, with the aim of enhancing the efficacy of these therapeutic interventions. In this regard, three neuroblastoma cell lines treated with cisplatin, etoposide, and nutlin were used to examine the effect of combining MDM2 inhibitors with chemotherapy. The addition of nutlin-3a to etoposide or cisplatin consistently and significantly reduced proliferation while increasing apoptosis across all three cell lines. The findings suggest that inhibiting MDM2 could be a beneficial boost to chemotherapy for neuroblastoma and other solid tumors with wild-type p53 (Barbieri et al., 2006). Although p53 mutations are uncommon in neuroblastoma, MDM2 genetic changes are common. This makes MDM2 inhibitors targeting the P14 Alternate Reading Frame (ARF)-MDM2-p53 axis a possible therapeutic strategy (Van Maerken et al., 2009). Clinical studies with MDM2 inhibitors, such as MI-773, have shown encouraging results in the treatment of neuroblastoma. One study revealed that MI-773 induced an apoptotic effect in a p53-wild-type neuroblastoma and demonstrated comparable efficacy in combination with doxorubicin, highlighting the potential of combination therapies in overcoming chemotherapy resistance (Lu et al., 2016). A further investigation was conducted to explore the possibility that combining MDM2 inhibitors with other chemotherapeutic agents would be beneficial for neuroblastoma tumors lacking functional p53. The study focused on examining the potential of nutlin-3a to increase the sensitivity of a neuroblastoma cell line that lacks p53 and is resistant to doxorubicin. The results suggest that nutlin-3a can augment apoptosis induced by chemotherapy in cells lacking functional p53 through the activation of E2F1. This activation leads to the transcriptional activation of p73 and Noxa in the presence of DNA damage, thereby promoting apoptosis (Ambrosini et al., 2007). It was revealed that administering nutlin-3 resulted in increased levels of Tap73 and E2F proteins, both of which play critical roles in the doxorubicin-resistant phenotype. Consequently, this enhanced the ability of doxorubicin to inhibit cell growth and induce apoptosis. Notably, the sensitivity was reduced when Tap73 was deleted, indicating the significance of Tap73 in the process. The study revealed the p53-independent mechanism of nutlin-3 in addressing chemoresistant neuroblastoma, particularly in combination with other chemotherapeutic agents **(**Fig. 2**)** (Peirce and Findley, 2009).

Breast cancer stem cells are distinguishable through the presence of the side population (SP) marker ATP-binding cassette sub-family G member 2 (ABCG2). In breast cancer cell lines that exhibit high expression levels of ABCG2, the combined treatment of nutlin-3a and mitoxantrone demonstrated synergistic effects, as indicated by combination index estimates. Notably, the introduction of nutlin-3a was observed to restore sensitivity to mitoxantrone by inhibiting the transport function of ABCG2. Notably, the introduction of nutlin-3a was perceived to restore sensitivity to mitoxantrone by inhibiting the transport function of ABCG2. These findings suggest that the concurrent use of nutlin-3a and mitoxantrone holds promise as a therapeutic approach in breast cancer with high levels of ABCG2 expression and associated stem cell-like properties (Zhang et al., 2011). Efflux transporters, such as P-glycoprotein, multidrug resistance proteins, and breast cancer resistance proteins, are present on the luminal side of endothelial cells and contribute to drug resistance in breast cancer cells (Gadysz et al., 2022). A different study revealed that nutlin-3 demonstrates greater effectiveness compared to previously documented inhibitors of drug efflux proteins. As a result, cells become more vulnerable to cytotoxic drugs that are recognized as substrates of these specific efflux proteins. Michaelis et al. demonstrated the potential of nutlin-3 in inhibiting the functionality of ABC transporters, including P-glycoprotein and multidrug resistance protein 1 (MRP1; ABCC1) (Michaelis et al., 2009). Similarly, in vitro studies have shown that nutlin-3 can effectively overcome drug resistance in neuroblastoma and rhabdomyosarcoma cells when used in combination with cytotoxic agents that are substrates of P-glycoprotein and MRP1 (Zhang et al., 2011). Amplifications of the MDM2 and MYCN genes, which both control the p53 signaling pathway, have been seen in testicular cancer (TC) patients who are resistant to chemotherapy or have refractory disease (Bagrodia et al., 2016; Barrett et al., 2019). Preclinical studies have demonstrated that targeting MDM2 is a promising strategy for TC, as evidenced by synergistic effects on cell viability when combining the nutlin-3 with cisplatin (de Vries et al., 2020).

2.6. Effects of MDM2 inhibitors on the immune system and their potential use in combination with immunotherapy

The existing body of evidence suggests that the effectiveness of both conventional and targeted anticancer agents extends beyond their direct cytostatic and cytotoxic effects. It appears that these cancer therapeutic modalities also play a crucial role in stimulating or reactivating immune responses **(**Fig. 3**)**. It has been demonstrated that the activation of p53 not only modifies the TME but also plays a crucial role in facilitating immunogenic cell death in response to chemotherapy or radiotherapy (Moore et al., 2018; Zitvogel et al., 2013). Emerging evidence suggests that p53 dysfunction can contribute to the promotion of inflammation and facilitate the evasion of the immune system by tumors. Consequently, p53 dysfunction may serve as a driving force in the initiation and progression of tumorigenesis from an immunological perspective. Targeting p53 in the tumor microenvironment (TME) is consequently an immunologically appealing approach for reversing immunosuppression and increasing antitumor immunity (Guo and Cui, 2015; Muþoz-Fontela et al., 2016). Earlier investigations have indicated that nutlin-3 treatment may render tumor cells more vulnerable to immune-mediated killing through mechanisms including an elevated expression of CD80 in these tumor cells, indicating the possibility of an alternative mechanism for immune activation in tumors mediated by the MDM2/p53 axis (Scarpa et al., 2021). It has been suggested that the induction of effective antitumor immunity by nutlin-3a is mechanistically dependent on two distinct yet immunologically synergistic p53-dependent processes. First, it is dependent on the activation of p53, which results in tumor immunogenic cell death (ICD) and the induction of antigen-specific immune responses, activation, and proliferation of polyfunctional CD8 CTLs. Second, it requires an increase in infiltrating dendritic cells (DC) and a reduction in immunosuppressive MDSCs to produce the observed immunomodulatory effects; this is accomplished through the p53-mediated reversal of immunosuppression within the TME. On the other hand, it has been indicated that an immune-based approach requires only limited local p53 activation to change the immune landscape of TME and subsequently enhance the immune response to systemic antitumor immunity. Notably, while traditional tumoricidal therapies heavily depend on targeting the p53 protein in every individual tumor cell and frequently result in systemic toxicity, immune-based strategies necessitate only minimal local activation of p53 to modify the immune environment within the TME. This localized activation of p53 has been shown to have a significant impact on the promotion of systemic adaptive immunity. Additionally, the activation of p53 in tumor-infiltrating lymphocytes (TILeus) within the TME has been found to impact the behavior and function of myeloid subpopulations, leading to sustained activation of T-cells. Both of these processes are dependent on ensuring effective T-cell infiltration into the TME in order to achieve successful tumor elimination (Guo et al., 2017).

It has been indicated that the combination of MDM2 inhibition with immunomodulatory agents shows promise for enhancing the immune response against cancer cells and potentially improving treatment outcomes. In a recent study, it was revealed that APG-115, an MDM2 inhibitor, can enhance the immune response against tumors within the tumor microenvironment (TME) when combined with PD-1 inhibition. Notably, this effect was observed regardless of the p53 status of the tumor. As a result, a phase 1b clinical trial is presently in progress to examine the potential of combining APG-115 and pembrolizumab in patients with solid tumors, including those harboring p53 mutations (Fang et al., 2019). The potential immunomodulatory effects of MDM2/p53 inhibitors can be harnessed when used in combination with immune checkpoint blocking antibodies, thereby offering additional antitumor advantages. Through the use of syngeneic models, the study findings indicate that HDM201 use resulted in a significant upregulation of CD80 expression in tumor cells. Furthermore, it has been observed that there is a significant enhancement in T-cell stimulation and an enhanced percentage of CD8 + T cells within the overall CD45 + population. Furthermore, it has also been found that there is an upregulation of PD-L1 expression on CD45-negative cells, as well as an increase in the frequency of PD-1-positive cells within the T-cell populations. The blockade of the PD-1/PD-L1 interaction has been shown to enhance the activity of HDM201 specifically in tumors with wild-type p53, while no significant effect has been detected in tumors with mutant p53 or p53 knockout. These findings suggest that MDM2 inhibition promotes adaptive immunity, which is further enhanced by the addition of antibodies that block checkpoint proteins. Therefore, the combination of MDM2 inhibitors and checkpoint blockade antibodies displays therapeutic potential for patients with p53 wild-type tumors (Wang et al., 2021).

In both endocrine-resistant and endocrine-sensitive models of breast cancer, the effectiveness of NVP-CGM097, an MDM2 inhibitor, is currently being studied. Endocrine therapy combined with suppression of CDK4/6 and MDM2 has shown promising outcomes in the treatment of estrogen receptor positive (ER +) breast cancer. A recent investigation has shown that combining MDM2 inhibitors with ER degraders or CDK4/6 inhibitors provides an appealing approach for treating advanced, endocrine-resistant, ER-positive breast cancer. The study concluded that this combination activates cell cycle co-regulatory pathways in a synergistic manner (Portman et al., 2020). In the case of dedifferentiated liposarcomas, the combination of RG7388 (an MDM2 inhibitor) and palbociclib (a CDK4-targeting agent) showed greater antitumor efficacy when used together compared to either drug used alone, both in in vitro and animal models. In an animal model of dedifferentiated liposarcoma, the combined regimen significantly improved the median progression-free survival rate and reduced tumor progression rates when compared to the use of either drug individually (Laroche-Clary et al., 2017).

An alternative perspective suggests that combining MDM2 inhibition with an immunomodulatory agent like lenalidomide, despite its lack of specificity, could enhance the immune response against cancer cells. Lenalidomide has demonstrated the ability to activate T cells, promote cytokine production, and augment the expression of MHC class I molecules on tumor cells. As a result, lenalidomide may improve the recognition of tumor cells by the immune system, thereby potentially enhancing the immune-mediated antitumor response when used in combination with MDM2 inhibitors. The combination of MDM2 inhibition and lenalidomide offers a dual approach that can potentially target cancer cells directly and simultaneously activate and enhance the immune response. The combined strategy has the potential to improve treatment outcomes, particularly for patients with multiple myeloma who have developed resistance to lenalidomide or other immunomodulatory agents (Gu et al., 2014). Another study examined the effectiveness of a combined treatment using the glycoengineered type II anti-CD20 antibody obinutuzumab (GA101) and the MDM2-selective inhibitor idasanutlin (RG7388) in facilitating antitumor effects. The results revealed that this combination treatment exhibited an enhanced cytotoxic effect specifically on p53 wild-type mantle cell lymphoma (MCL) and diffuse large B-cell lymphoma (DLBCL) tumor cell lines. The combination therapy did not affect obinutuzumab-mediated antibody-dependent cellular cytotoxicity or B-cell depletion in samples from healthy donors. Furthermore, significant antitumor effectiveness was observed in vivo studies utilizing xenograft models with wild-type p53. The results indicate that the combination of obinutuzumab and idasanutlin may be an effective therapeutic strategy for p53 wild-type MCL and DLBCL, showing promise for targeted therapies in lymphoma treatment (Herting et al., 2016). Given the previously conflicted conclusions, the interaction between the effectiveness of immune-modulating agents and the status of p53 demonstrates variability depending on the specific context. The variability observed implies that the impact of p53 on the efficacy of immune-modulating agents may not be a universal phenomenon, but rather dependent on factors such as the type of immune-modulating agent and type of cancer. Further studies are necessary to better understand the complex relationship between immunomodulators and p53 due to the variability in the observed responses. These investigations can elucidate the relationship between the status of p53 and the response to immunomodulatory treatments, specifically identifying the conditions or contexts in which this influence occurs. Moreover, a comprehensive understanding of this correlation can facilitate customized treatment strategies, individualized medicine, and the advancement of more efficient therapies for different types of cancer.

2.7. Ongoing clinical trials assessing the combination of MDM2 inhibitors

Current clinical trials are being conducted to investigate the potential of combining MDM2 inhibitors as a novel treatment approach for cancer patients. The trials aim to improve the efficacy of MDM2 inhibitors in combating cancer, address drug resistance, and enhance treatment outcomes for individuals with various cancer types. Investigators aim to achieve synergistic effects and target multiple pathways simultaneously by combining MDM2 inhibitors with other therapies, such as chemotherapy drugs or targeted agents. These trials offer valuable insights into the potential benefits and challenges of combining MDM2 inhibitors with other therapies, aiming to develop more effective treatment regimens in the future. For instance, concurrent use of the multi-kinase inhibitor sorafenib and the small molecule inhibitor nutlin-3 against AML cells showed promising anti-leukemic potential. These findings prompted an initial study to investigate the potential benefits of combining sorafenib and nutlin-3 for AML treatment (Giorgio Zauli et al., 2012). While initial clinical data appeared promising, recent research indicates that some patients may experience a temporary positive response followed by subsequent non-responsiveness. This observation implies that sorafenib's efficacy may not be fully accomplished when used as a monotherapy, thus underscoring the necessity of investigating combination therapies as an alternative solution (Rahmani et al., 2012). In terms of efficacy, an early-phase clinical study (phase 1/1b) on individuals with AML (NCT01773408) demonstrates the success of this strategy. A combination of idasanutlin, an MDM2 inhibitor, and cytarabine was used in this experiment, which demonstrated both safety and beneficial therapeutic effects. The combined treatment exhibited composite rates of 27% (n = 20/75) for complete remission (CR) and 28% (n = 21/75) for overall CR. The findings of this study indi-

cate that the utilization of idasanutlin and cytarabine in combination exhibits potential as a therapeutic strategy for AML (Yee et al., 2021). Consistently, the efficacy of combining venetoclax, a BCL-2 inhibitor, with idasanutlin was evaluated in a phase 1b clinical trial (NCT02670044), which was intended for patients with relapsed or refractory AML who were not eligible for conventional cytotoxic chemotherapy. Venetoclax and idasanutlin as single-agent therapies demonstrated limited efficacy in patients with relapsed or refractory AML. During the dose escalation phase of the trial, the composite complete remission rate was 26.0% and the morphologic leukemia-free state rate was 12%. Despite not demonstrating improved overall survival compared to cytarabine alone, the rationale for combining venetoclax and idasanutlin in the trial was based on preclinical synergistic effects. The trial results demonstrated that the combination therapy of venetoclax and idasanutlin exhibited promising efficacy and acceptable safety in unfit patients with relapsed or refractory AML. Even though there was no significant improvement in overall survival, the combination of venetoclax and idasanutlin showed sensible clinical effects. This is particularly encouraging for individuals with relapsed or refractory AML who are unfit, have previously received low-intensity treatments, and have limited treatment options. The combination therapy demonstrated acceptable safety and promising initial efficacy in this challenging individual group, indicating the necessity for further investigation into the simultaneous inhibition of BCL-2 and MDM2 in AML (Daver et al., 2023).

The efficacy of the combination of cytarabine and idasanutlin was further evaluated in patients diagnosed with relapsed/refractory AML in the Phase 3 MIRROS trial (NCT02545283). The trial findings demonstrated that the incorporation of idasanutlin in combination with intermediate-dose cytarabine did not yield a statistically significant improvement in the median overall survival of the participants. Although the combination therapy exhibited increased response rates, the therapeutic effectiveness of idasanutlin was limited by its myelosuppressive effects. The trial participants frequently reported gastrointestinal AEs, such as diarrhea and nausea, as well as hematological AEs. The results of the study revealed a remission rate of 28% (n = 21/75) and a composite remission rate of 27% (n = 20/75). It was noted that modifying the treatment regimen or adjusting the dosage of MDM2 inhibitors might be necessary to alleviate myelosuppression and fully control the benefits of MDM2 inhibition (Montesinos et al., 2020). These observations highlight the need for further investigation and optimization of the treatment approach to enhance the therapeutic outcomes in patients with relapsed/refractory AML.

Single-agent MEK inhibitors have demonstrated limited clinical benefits in treating NRASQ61-mutant melanoma, which represents the second most common somatic mutation in melanoma. Currently, there are no established treatments specifically targeting NRASQ61-mutant melanoma. To overcome this challenge, an alternative treatment approach involves targeting essential proteins involved in intact and non-mutated cell death pathways (Dummer et al., 2017; Shattuck-Brandt et al., 2020). In the context of melanoma, the upregulation of the MDM2 protein is often observed due to the reduced or absent expression of MDM2 inhibitors like p14ARF (Fig. 1) (Polsky et al., 2001). It is important to note that the majority of melanomas exhibit wild-type p53 expression. A clinical trial (NCT02110355) assessed the safety, tolerability, pharmacokinetics, and maximum tolerated dose of AMG 232 (an MDM2 inhibitor) in combination with dabrafenib-trametinib or trametinib alone in patients with melanoma, with or without BRAFV600 mutations, respectively. Significantly, the patients included in the study had no prior exposure to BRAF or MEK inhibitors. The co-administration of AMG 232 with either trametinib alone or trametinib plus dabrafenib at the standard dose was generally well tolerated, especially at lower doses of AMG 232 (Moschos et al., 2022). Melanoma patients could experience improved outcomes and enhanced therapeutic efficacy by combining MDM2 inhibitors with established treatment modalities. Table 1 presents a comprehensive review of combined pharmacological agents for cancer treatment as assessed in various clinical trials.

3. Discussion and conclusion: future direction

Inhibition of MDM2 offers a potential therapeutic strategy for restoring p53 function and reducing tumor development across various types of cancer. Nonetheless, there are significant challenges associated with this approach. Drug-related toxicity poses a major drawback, as altering the treatment schedule alone may not adequately control adverse effects on the gastrointestinal, hematologic, and cardiac systems. To achieve better tolerability, it is crucial to explore and improve drug delivery approaches. One additional challenge pertains to the emergence of drug resistance, which can limit the effectiveness of MDM2 inhibitors in clinical settings. Notably, Jung et al. conducted a phase I study in which they observed clinical evidence of resistance to an MDM2 inhibitor (SAR405838) in individuals with de-differentiated or MDM2-amplified liposarcoma. Analysis of cell-free DNA revealed the emergence of p53 mutations during therapy, which correlated with tumor size. This finding underscores the importance of gaining a comprehensive understanding of the mechanisms underlying acquired resistance in both preclinical models and patients (Jung et al., 2016). Improving the efficacy of MDM2 combination regimens can be achieved by utilizing novel biomarkers to identify patients who would benefit from personalized therapeutic

Table 1
Overview of combined pharmacological anti-cancer agents evaluated in clinical trials.

Therapeutic Modality	Combined treatment	Disease	Observed Outcomes	ClinicalTrials.gov Identifier
Chemotherapy	Idasanutlin, + cytarabine	Relapsed or refractory (r/r) acute myeloid leukemia	The composite complete remission rates were 18.9% for monotherapy Vs. 35.6% for combination therapy	NCT01773408
	Idasanutlin, + cytarabine (Phase 3 MIRROS trial)	Relapsed or refractory (r/r) acute myeloid leukemia	Failed to produce a statistically significant enhancement in the participants' median overall survival	NCT02545283
Targeted Therapy	Venetoclax, a BCL-2 inhibitor + idasanutlin	Relapsed or refractory (r/r) acute myeloid leukemia	The combined rates show a complete remission of 34.3% and an anti-leukemic response of 48.5% vs. venetoclax (complete remission rate of 19%, and idasanutlin (anti-leukemic response of 21%)	NCT02670044
	AMG 232 (MDM2 inhibitor) + Trametinib (MAPK inhibitors)	Metastatic cutaneous melanoma	The combination treatment failed to demonstrate a noticeable increase in clinical efficacy	NCT02110355

approaches. Such an approach could significantly enhance the effectiveness of MDM2 combination approaches (Tisato et al., 2017). MDM2 inhibitors might be used in combination with other cancer treatment approaches, including chemotherapy, radiation therapy, or immunotherapy, to provide a more potent and thorough strategy. The combination of medications may function synergistically to target several pathways involved in tumor growth and survival, resulting in increased effectiveness and perhaps overcoming drug resistance. To comprehensively evaluate the therapeutic potential and safety profile of combining MDM2 inhibitors, additional studies, including preclinical models and clinical trials with a larger sample size, are required. These studies will shed light on their mechanism of action, optimal dosage, duration of treatment, and potential adverse effects. The efficacy of combining MDM2 inhibitors in the fight against cancer will be determined by the findings of careful scientific studies and the collection of solid clinical data. Such research activities are essential for guiding the development of targeted and personalized therapeutic strategies for cancer patients, with the ultimate goal of improving patient outcomes and survival rates.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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