MDM2 inhibitors: Targeting p53-MDM2 interaction to anti-cancer

Xulin Zhang1, a, *

1Institute of Overseas Education, Nanjing Tech University, Jiangsu Province, China

Abstract. P53 is a recognized tumor suppressor gene, which mainly depends on the activity of its transfer factor to realize the tumor suppressor effect. Mouse two-minute 2 (MDM2) is an important inhibitor of p53. When combined with MDM2, the activity of p53 will be reduced, and the anti-cancer effect will be weakened. According to the mechanism between p53 and MDM2, researchers focus on the inhibitors to inhibit their binding. Through a large number of drug screening methods and means, this article has found many new inhibitors of p53-MDM2 interaction, most of which are still in the clinical research stage. Specifically, we classify the drugs based on their different action mechanisms. Firstly, some drugs combine with MDM2 to inhibit the p53-MDM2 interaction. They are Siremadlin (NVP-HDM201), RG7112, and NVP-CGM09. While some act on p53, they rely on their induction of p53 signalling and inhibition of tumour cell proliferation in p53 wild-type tumor cell lines, like MK-8242 and KRT-232(AMG-232). What’s more, one inhibitor’s action bases on P53 and MDM2 in T cells is APG-115. And last but not least, there are also several drugs that stable tumor suppressor TP53, leading to p53 activation and inducing cell cycle arrest and apoptosis, they are Idasanutlin (RG7388) and Milademetan (DS-3032/RAIN-32). Furthermore, clinical studies are finding that monotherapy does not deliver a powerful therapeutic effect. Various combination strategies are being explored with MDM2 inhibitors preclinically and in the clinic. This article will talk about some specific combinations: APG-115 combine with immune checkpoint inhibitor PD-1/PD-L1, MDM2 inhibitors combine with BCL-2 inhibitors, anti-CD20 therapeutic antibodies, and the last, combine with alkylating agents.

1 Introduction

In the current decades, the malignant tumor has been a serious threat to human health. According to TCGA data, more than 50% of tumor patients have changes in the P53 gene. Moreover, P53 variants are associated with more than half of all cancers, including lung, stomach, liver, bladder, esophagus, breast, cervical, and other cancers. P53 is a tumor suppressor gene that has the highest correlation with human tumorigenicity so far. In the cell cycle, normal p53 is activated at the time of DNA damage or hypoxia so that the cell cycle stops at the G1/S point for DNA repair. If the repair fails, the downstream genes are activated to cause cell apoptosis. So P53 has been called the "guardian of the genome" [1]. The p53 is a transcription factor encoded by the TP53 gene. One of the major functions of p53 is to induce apoptotic cell “suicide” and subsequently suppress tumor cells from proliferating. The TP53 gene was found mutated or deleted in around half of the human cancer cells, indicating the importance of p53 in suppressing tumors [2]. The p53 is known to be primarily inhabited by the murine double minute 2 (MDM2) oncogene.

Mouse double minute 2 (MDM2) is a vital negative regulator of the tumor suppressor p53. The p53 peptides possess three hydrophobic residues, Phe19, Trp23, and Leu26, which cluster together and bind to the MDM2 in a hydrophobic pocket. Its expression can up-regulate various cancers, leading to loss of p53-dependent activities, such as apoptosis and cell cycle arrest [3]. It plays a key role in controlling its transcriptional activity, protein stability, and nuclear localization. Specifically, MDM2 has the activity of E3 ubiquitin ligase and can mediate its ubiquitin and its substrate ubiquitin. The E3 ligase activity of MDM2 depends on its RING domain, and its E3 activity is eliminated by deletion of this domain or substitution of any amino acid within it [4, 5]. Therefore, MDM2 can regulate the balance between its ubiquitination and substrate ubiquitination through post-translational modifications. The main post-translational modifications include SUMOylation and phosphorylation. Once SUMO binds to MDM2, its E3 ligase activity changes towards ubiquitination of p53, with its ubiquitination being minimal. Stress such as DNA damage phosphorylates MDM2 and reduces the ability of MDM2 to bind p53, thus stabilizing and activating p53.

The MDM2 regulates p53 through three major mechanisms: (1) MDM2 binds directly to p53 and deprives its ability to bind with DNA, hence stopping the transcription pathway; (2) MDM2 induces ubiquitination on the p53 structure and renders p53 ineffective; (3) MDM2 exports p53 from the nucleus, making p53 unable to access the DNA [6-8], thus blocking p53 expression. (Figure 1)
In normal cells, these negatively regulatory pathways help remain p53 at a stable level. However, overexpression or amplification of MDM2 can significantly reduce the level of p53 expressed in cells, inhibiting the tumor suppression of p53 and lead to malignancies.

Recent research has focused on inhibiting this MDM2-p53 interaction, trying to find suitable agents that could selectively inhibit MDM2 and reactivate p53. A new therapeutic strategy of blocking the protein-protein interaction has been developed over the recent few years. Small molecules targeting the protein-protein interaction have been designed and developed swiftly through these years.

Through many drug screening methods and means, we have found eight promising inhibitors and classified them into four distinct groups according to their different function mechanisms. They are Siremadlin (NVP-HDM201), RG7112, and NVP-CGM09; MK-8242 and KRT-232(AMG-232); Idasanutlin (RG7388) and Milademetan (DS-3032/RAIN-32); and the last, APG-115. Also, we conducted some further combination therapy research to enhance the inhibition effect on the cancer cell.

2 Research on MDM2 inhibition drugs

Compared with peptide inhibitors, small molecule inhibitors of MDM2-p53 interactions have lower molecular weight, higher specificity, and oral convenience. At recent, the specific amounts of small molecule target drugs have been discovered and put into clinical trials, ranging from preclinical to those approved by FDA. And we classify these inhibitors into four distinct groups which are based on their respective mechanisms. For a clear demonstration, we use a simple mind map below. (Figure 2)
2.1 Combined with MDM2 to inhibit the p53-MDM2 interaction

2.1.1 Siremadlin (NVP-HDM201)

HDM201 is a novel and highly effective MDM2-P53 interaction inhibitor. It binds to the p53 binding site of the MDM2 protein and disrupts the interaction between the two proteins, leading to activation of the p53 pathway. In human p53 wild-type tumor cells, HDM201 induces potent p53-dependent cell cycle arrest and apoptosis. HDM201 is highly selective in a variety of cancer cell lines.

Currently, HDM201 is under several clinical trials. We elucidate two of them which were more meaningful relatively. According to Seipel K team research and clinical trials, we can know that NVP-HDM201 is the most potent MDM2 inhibitor, which exhibited superior combinatorial effects on the cell viability of FLT3-ITD AML cells when taken with midostaurin, along with moderate combinatorial effects together with quizartinib and gilteritinib [9]. To specify, HL-60 cells with deleted TP53 were resistant to midostaurin and HDM201, indicating that these two compounds specifically target AML cells with functional p53 protein. This apparently distinguished the FLT3- inhibitor sorafenib and the MDM2 inhibitor nutlin-3, which promoted synergistic cytotoxicity irrespectively of FLT3 and p53 status via induction of the pro-apoptotic Bcl-2 family members Bax and Bak in p53 wild type and p53 deleted cells [10].

What’s more, the Centre Leon Berard has announced that they will make the clinical trials (Phase II) that focus on HDM201 and its matched targeted therapy, aiming to assess different Matched Targeted Therapy (MTT). They use the combination of HDM201 and Ribociclib. This clinical trial will be completed by November 2022. (ClinicalTrials.gov Identifier: NCT04116541)

2.1.2 RG7112

Another MDM2 inhibitor is RG7112, whose several safety issues have been worked out. As the potent, orally bioavailable MDM2 inhibitor, RG7112 displays antineoplastic activity. RG7112 is the first MDM2 inhibitor advanced into human clinical trials (Hoffmann La Roche RO5045337) [11]. It is the nutlin imidazoline compound. RG-7112 binds to MDM2, thereby preventing the binding of the MDM2 protein to the transcriptional activation domain of the tumor suppressor protein p53.

The clinical research of it still remained at phase I. Phase I clinical trials of RG7112 for the treatment of advanced solid tumors (Clinical Trials: NCT00559533) and hematologic neoplasms (Clinical Trials: NCT00623870) were completed [12]. The trial demonstrates that it is tightly bound to MDM2 and can displace P53 from the MDM2 surface, showing its potency is 4 and 200 times more than that of Nutlin-3a and the inactive enantiomer respectively [13]. Furthermore, it showed efficacy in both in vitro and in vivo studies and had a dose-dependent effect on tumor regression.

According to a deeper study in Phase I, RG7112 had evidenced on-target activity, resulting in p53 activation. After treatment with RG7112, there was an increased expression of downstream pro-apoptotic proteins [14, 15]. Especially in AML, RG7112 was studied both as monotherapy and in combination with low-dose cytarabine [16]. Some patients even achieved CR and were subsequently transplanted. The hematological toxicity with this drug was prolonged, as MDM2 plays a crucial role in hematopoiesis [17].

Furthermore, last few years, Obrador-Hevia and co-workers found that RG7112 can significantly enhance the
response of Trabectedin to MDM2-amplified liposarcoma cells [18]. Clinical pharmacological studies showed that high/low-fat food and new formulation could enhance bioavailability; high-dose consecutive daily dosing for 3–5 days can yield required high drug exposures and PD effects for cancer therapy [19]. However, P53 activation, induced by RG7112, caused thrombocytopenia [20], restricting its clinical use. Clinical trials of RG7112 in 20 patients indicated that all patients had at least one adverse event, 12 serious adverse events, particularly neutropenia and thrombocytopenia, observed in eight patients [21].

The higher dose to attain satisfactory p53 activation caused significant toxicities (cytopenias, diarrhea, sepsis, and deaths), and so the need for a more potent and less toxic agent was identified.

2.1.3 NVP-CGM097

Since RG7112 has been discovered that its toxicities can incur many health problems. So, we turned to another drug called NVP-CGM097, an effective and specific MDM2 inhibitor that binds to human MDM2 and shows high selectivity over MDM4. NVP-CGM097 is about four times more potent than Nutlin-3a. It can significantly inhibit the proliferation of cells expressing wild-type p53 while sparing the p53 null cells with a 35-a 58-fold difference.

Recently, the researchers have obtained that the small molecule MDM2 inhibitor NVP-CGM097 inhibits ER-positive breast cancer cells in a p53-dependent manner, and the combination of NVP-CGM097 and fulvestrant synergistically inhibits MCF-7 cells without increasing apoptosis. The combination of NVP-CGM097 with fulvestrant downregulates E2F and G2/M transcriptional programs in vitro. What is more, the combination NVP-CGM097/fulvestrant reduces tumor growth in an in vivo PDX model of endocrine resistance [22].

Besides, the first in human phase 1 study of single-agent CGM097 in patients with advanced solid tumors who have progressed despite standard therapy or for whom no standard therapy exists. The tumor must be characterized by p53wt status. The study consists of a dose-escalation part where patients will receive escalating doses of CGM097, and a dose expansion part in which patients are given CGM097 at the maximum tolerated dose (MTD) or Recommended Phase 2 Dose (RP2D). Each dose escalation step will be decided based on the recommendation from an adaptive Bayesian logistic regression model (BLRM). And this trial will not be finished until July 24, 2020. (ClinicalTrials.gov Identifier: NCT01760525)

2.2. Drug action bases on P53 and MDM2 in T cells

2.2.1 APG-115

APG-115 is a potent MDM2 inhibitor under clinical development for patients with solid tumors. It is an orally effective and highly selective small-molecule inhibitor targeting MDM2-P53 protein interaction. APG-115 is the first MDM2-p53 inhibitor that gained the FDA Orphan Drug Certification and simultaneously is the ace product developed by Yasheng Pharmaceutical. The drug action depends on P53 and MDM2 in T cells, which bind to the hydrophobic binding pockets where MDM2 binds to P53, allowing the protein to be released.

In TP53 wild-type AML lines, Sun’s team found that APG-115 exhibited potent antiproliferative and apoptotic activities, along with induced cell cycle arrest by activating the P53/P21 pathway. In vivo, APG-115 noticeably alleviated tumor burden and prolonged survival in TP53 wild-type AML xenograft models.

In 2019, the research trial gained the results showing that APG-115 in combination with PD-1 blockade enhances the antitumor immunity in the TME and the anti-PD-1-mediated antitumor effect in Trp53wt, Trp53mut, and Trp53−/− syngeneic mouse tumor models. Moreover, it can increase PD-L1 expression on tumor cells, suppress alternative (M2) macrophage polarization, and augment M1 macrophage polarization. It is quite meaningful that APG-115 has the co-stimulatory activity in effector T cells [23].

Moreover, the combinations of APG-115 with SOC treatments drew forth synergistic antileukemic activity. Similarly, APG-115 combines with either AZA or Ara-C cooperatively activating the P53 pathway and downregulating genes involved in cell cycle progression and mismatch repair in TP53 wild-type AML cells [24].

Evidence from the present study also suggests that the antileukemic activity of APG-115 is more potent than RG-7388 both in vitro and in vivo. When combined with SOC agents, APG-115 caused apoptosis more apparently, as evidenced by increased cleavage of PARP-1 protein. An ongoing Phase I trial of patients who have unresectable or metastatic melanoma or advanced solid tumors is evaluating the potential immunomodulatory effects of APG-115 in tandem. (NCT03611868)

2.3. Interrupt the p53-MDM2 interaction and lead to p53 activation

2.3.1 Idasanutlin (RG7388)

As a novel, potent, and selective small-molecule MDM2 antagonist with a pyrrolidine structure, Idasanutlin interrupts the p53–MDM2 interaction, leading to activation of p53. In contrast to other Nutlin family molecules, it has an identical cellular mechanism. It can enhance potency, selectivity, and bioavailability. By preventing the p53–MDM2 interaction, Idasanutlin allows for p53 activation, particularly in patients with TP53 wild-type (WT) status.

In combination with cytarabine, it showed reasonable safety and promising clinical activity in a Phase I/II study in patients with AML. In the study, researchers have identified the recommended dose for the Phase III evaluation of Idasanutlin. MIRROS (NCT02545283) is a randomized Phase III trial evaluating Idasanutlin + cytarabine versus placebo + cytarabine in R/R AML [25].

In the trials, participants received induction therapy idasanutlin and cytarabine. The evaluation of Idasanutlin
in combination with cytarabine in R/R AML in the Phase III MDM2 Inhibitor in R/R AML for Overall Survival (MIRROS) trial (NCT02545283) is continuing [25]. The antitumor activity was observed with Idasanutlin’s combination therapy with cytarabine in xenograft models [26]. This information is all provided by (Responsible Party): Hoffmann-La Roche. Extensively, RG7388 is also being explored in that it can combine with other apoptotic agents such as the BCL-2 inhibitor venetoclax. It was synergistic that the combination of RG7388 and venetoclax in preclinical studies in p53 wild-type AML tumor models [27]. Similar results were seen in WT-p53 AML cell lines treated with the MDM2 inhibitor SAR405838 and BCL-2 inhibitor ABT-263 (navitoclax) [28]. Interestingly, RG7388 induced G1 arrest and caused nuclear fragmentation in the G1 phase of the second cycle, while the BCL-2 inhibitor caused apoptosis in G1 compartments. The BCL-2 inhibitor hit cells that were transiently missed by RG7388 from apoptosis. Further studies with the combination suggest that each agent can reciprocally overcome the apoptotic resistance to either agent alone [29, 30]. The RG7388 and venetoclax combination is being evaluated in Phase I/ib trial for patients 60 years and older with R/R AML who are not candidates for cytotoxic therapy (NCT0267044).

2.3.2 Milademetan (DS-3032/RAIN-32)

Another drug with a similar action mechanism is Milademetan. It is an orally available MDM2 antagonist with potential antineoplastic activity due to increased p53 activity through interruption of the MDM2-p53 interaction. Milademetan inhibits the growth of cancer cells harboring wild-type p53 across six human cancer cell lines and also suppresses tumor growth of human osteosarcoma xenografts in nude mice [31].

The recent trial called “Milademetan tosylate and low-dose cytarabine in treating participants with recurrent or refractory acute myeloid leukemia” is the phase I/II trial that studies the side effects and best dose of Milademetan tosylate. Additionally, they also research to see how well it works with cytarabine with or without venetoclax in treating participants with acute myeloid leukemia who has come back (recurrent) or that does not respond to treatment (refractory) [14]. Milademetan tosylate and venetoclax may stop the growth of cancer cells by blocking some of the enzymes needed for cell growth. This information is provided by M.D. Anderson Cancer Center.

2.4 Regulate the p53 signaling pathway for inhibiting tumor cell proliferation

2.4.1 MK-8242

MK-8242 (formerly SCH 900242) is a potent, orally bioavailable, small-molecule inhibitor of the HDM2/p53 protein-protein interaction [32]. It can activate the p53 pathway with an acceptable safety and tolerability profile. Wanger AJ and the project teams carried out the phase I dose-ranging study designed to establish the recommended phase II dose (RP2D) of MK-8242 based on safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) in adults with advanced solid tumors with WT TP53 gene [33].

Additionally, a study of MK-8242 alone and in combination with cytarabine in adult participants with refractory or recurrent acute myelogenous leukemia (AML) was carried out by Merck Sharp & Dohme Corp. The study had 2 arms. Arm A was for participants with refractory or recurrent AML who were considered ineligible for standard chemotherapy. Arm B was for participants with recurrent AML following an initial complete remission (CR) or CR with incomplete marrow recovery (CRI) of 6 to 12 months duration. The pharmacokinetics of MK-8242 was studied in both arms. With Amendment 4 (22 August 2013), a 21-day dosing cycle was added, with MK-8242 being given on Days 1-7 of each 21-day cycle in both the monotherapy and combination therapy arms; data from Arm A was used to determine whether a participant receives 21-day or 28-day therapy in Arm B. This clinical trial has been done by August 27, 2018. (ClinicalTrials.gov Identifier: NCT01451437)

2.4.2 KRT-232(AMG-232)

Similarly, AMG 232 is an investigational oral, selective MDM2 inhibitor that restores p53 tumor suppression by blocking the MDM2-p53 interaction with picomolar affinity. The treatment with AMG 232 resulted in tumor growth inhibition and caused regression of MDM2-amplified tumors by inducing growth arrest and apoptosis [34]. This article noticed that, to some extent, the therapeutic effectiveness of KRT-232 can be improved when the patient is treated with MEK inhibitor trametinib and BCL-XL/BCL-2 inhibitor navitoclax. Combination therapies of trametinib plus KRT-232 led to improved partial response rates over single-agent activity in a subset of PDX models [35].

In a word, trametinib plus KRT-232 or navitoclax led to greater in vivo anti-cancer activity than did single-agent therapy, whereas KRT-232 plus navitoclax did not result in improved activity. We did not observe obvious weight loss in any of the treatment groups and tested models, suggesting that all treatment regimens were not toxic. To note, we found that one trial study on phase III evaluates KRT-232 for the treatment of patients with myelofibrosis (MF) who no longer benefit from treatment with a JAK inhibitor. Inhibition of MDM2 is a novel mechanism of action in MF.

This trial will not be completed until 2023 and will be conducted in 2 phases (phases 2 and 3). Phase 2 will determine the KRT-232 recommended dose and dosing schedule; Phase 3 will test KRT-232 vs. Best Available Therapy (BAT). The treating physician will determine the BAT administered, with the option to “cross-over” to KRT-232 treatment after 6 months of BAT or if the disease worsens at any time. Information provided by (Responsible Party): Kartos Therapeutics, Inc.
3 Combination therapy

3.1 Combine with PD-1/PD-L1

The successful development of immune checkpoint inhibitors, such as monoclonal antibodies against programmed cell death 1 (PD-1) and PD-1 ligand (PD-L1), is revolutionizing cancer therapy. While some patients treated with anti-PD-(L)1 agent have experienced dramatic tumor regressions, a significant subset of patients failed to respond to anti-PD-(L)1 immunotherapy. Moreover, 9–29% of patients may develop a hyper progressive disease [36]. MDM2 amplification identified in some of these patients indicates that the genetic alteration may contribute to hyper progressive disease [37] and raises the possibility that a combination strategy with MDM2 inhibitors could limit hyperprogression on immunotherapy [38]. In trials NCT02935907 and NCT03611868, promoting an antitumor microenvironment with an MDM2 antagonist such as APG-115 may enhance the efficacy of PD-1 blockade in the clinic. The research found that APG-115 upregulates PD-L1 expression on tumor cells [39], and APG-115 enhances the anti-PD-1-mediated antitumor effect [40]. Interestingly, APG-115 in combination with PD-1 blockade enhances antitumor immunity in the TME. And the results demonstrate that the combination treatment reverses the immunosuppressive TME into antitumor immunity, leading to enhanced therapeutic benefit in mice. APG-115-stimulated immunity is able to sensitize resistant tumors to PD-1 blockade into sensitive tumors, and such a therapy approach may apply to both Trp53wt and Trp53mut tumors, creating a significant impact [41].

3.2 Combine with BCL-2 inhibitors

Bcl-2 gene is a kind of oncogene, which has an obvious inhibitory effect on cell apoptosis. Whose inhibitors are also the hot topic being researched and developed currently. The BCL-2 inhibitor called APG-2575 showed a strong synergic effect with mouse double minute 2 (MDM2)–p53 inhibitor APG-115[42]. So current research focuses on combining APG-115 with APG-2575, which demonstrated synergistic activity, leading to reduced cell viability, increased apoptosis, and tumor regression in TP53-wild-type diffuse large B-cell lymphoma cell lines and xenograft models (NCT04496349).

Additionally, another BCL-2 inhibitor called venetoclax, whose combination therapy with idasanutlin is being evaluated in elderly patients with relapsed/refractory or previously treated secondary AML (NCT012670044). Wild-type p53 is expressed in over 80% of AML cases; thus, inhibition of the interaction between MDM2 and p53 can re-establish the p53 pathway in AML cells resulting in cell cycle arrest and induction of apoptosis [43].

And the clinical trial that is researching for Siremadlin (NVP-HDM201) in combination with venetoclax in patients with acute myeloid leukemia (AML) (NCT03940352), while the clear result will come out till December 29, 2021.

3.3 Combine with Anti-CD20 therapeutic antibodies

The CD20 target is found on the surface of many types of lymphoma cells and on normal B cells, but not on hematopoietic stem cells, some pre-mature B cells, and plasma cells. Obinutuzumab and rituximab are anti-CD20 mAbs that are human-designed. Through the clinical study data, we can get to know that the obinutuzumab is more efficient than rituximab in depleting B cells [44] and has a lower toxin. In contrast, rituximab therapy causes increased resistance generation [45]. Phase 1b/2 clinical trials of rituximab and obinutuzumab in combination with idasanutlin have been conducted by Hoffmann-La Roche. The first study started in 2015 and involved treating idasanutlin and obinutuzumab in the FL patients and the idasanutlin/rituximab combination in DLBCL patients (NCT03135262).

In addition, the synergistic effect on cell death induction has been shown for obinutuzumab and nutlin-3 in the preliminary in vitro studies with chronic lymphocytic leukemia cell lines [46]. Roche has strengthened the idea of combination therapy with anti-CD20 mAbs and HDM2 antagonists for patients with CD20-positive B-cell malignancies. The study reported the combined obinutuzumab/idasanutlin treatment to be superior to single therapy with mAb in mantle cell lymphoma (MCL) and DLBCL xenograft models [47].

3.4 Combine with alkylating agents:

Alkylating agents, also known as alkylating agents. They are the earliest cytotoxic drugs, mainly used for malignant lymphoma and chronic lymphocytic leukemia but also for malignant tumors. Especially small cell lung cancer caused by the superior vena cava syndrome. Temozolomide (TMZ) is one of the alkylating agents, which delivers methyl groups to purine bases of DNA, resulting in the formation of N7-methylguanine N3-methyladenine [48]. TMZ was evaluated in combination with RG7775 (idasanutlin prodrug) to treat neuroblastoma [49]. The combined treatment has led to tumor growth inhibition, which was correlated with the upregulation of genes involved in apoptosis and signals transduction and downregulation of genes involved in DNA replication, mitosis, cell cycle progression, and cell division [49]. In another study, TMZ showed an additive antiproliferative effect with HDM2 antagonist CGM097 in the neuroendocrine tumor model [50]. Furthermore, idasanutin was combined with another alkylating agent—busulfan, resulting in consolidation during frontline treatment in neuroblastoma cells [51].
4 Conclusions

All in all, from the perspective of mechanism and inhibition of p53-MDM2 interaction, the development, and research of MDM2 inhibitors is a very promising medical research and development project. The current clinical trials elaborate that many drugs have passed Phase III and even FDA approval, which means their potency and therapeutic efficiency are excellent and satisfying and their toxicology and side effects are within clinical limits. Simultaneously, we must recognize that some novel drugs still have many indispensable defects, which means these MDM2 inhibitors show action mechanisms and interferential function ideally just in theory. In contrast, when they are applied to the patients, the facts always show the less-than-ideal result. So, we believe that combination therapy is a wise and meaningful category. In this way, it is possible that we can make the drug toxicity to the lowest level and enhance the efficacy to the maximum in a variety of cancer types. Similar to other drug classifications, reasonable combination strategies may implement the adverse effect, like hyper progressive disease after taking anti-PD-(L)1 agents. In fact, several combination studies are underway, and data are becoming available. As a result, MDM2 inhibitors do play an important role in cancer treatment. And in the future, they have a lot of room to develop and advance.

References

1. M. Lacroix, R. Riscal, G. Arena, et al. (2020) Metabolic functions of the tumor suppressor p53: Implications in normal physiology, metabolic disorders, and cancer. Mol Metab, 33: 2-22.
2. A. Feki and I. Irminger-Finger. (2004) Mutational spectrum of p53 mutations in primary breast and ovarian tumors. Crit Rev Oncol Hematol, 52, (2): 103-16.
3. J. D. Oliner, A. Y. Saiki, and S. Caenepeel. (2016) The Role of MDM2 Amplification and Overexpression in Tumorigenesis. Cold Spring Harb Perspect Med, 6, (6).
4. S. Fang, J. P. Jensen, R. L. Ludwig, et al. (2000) Mdm2 is a RING finger-dependent ubiquitin protein ligase for itself and p53. J Biol Chem, 275, (12): 8945-51.
5. R. Honda and H. Yasuda. (2000) Activity of MDM2, a ubiquitin ligase, toward p53 or itself is dependent on the RING finger domain of the ligase. Oncogene, 19, (11): 1473-6.
6. X. Wu, J. H. Bayle, D. Olson, et al. (1993) The p53-mdm-2 autoregulatory feedback loop. Genes Dev, 7, (7A): 1126-32.
7. D. A. Freedman, L. Wu, and A. J. Levine. (1999) Functions of the MDM2 oncoprotein. Cell Mol Life Sci, 55, (1): 96-107.
8. T. Juven-Gershon and M. Oren. (1999) Mdm2: the ups and downs. Mol Med, 5, (2): 71-83.
9. K. Seipel, M. A. T. Marques, C. Sidler, et al. (2018) MDM2- and FLT3-inhibitors in the treatment of FLT3-ITD acute myeloid leukemia, specificity and efficacy of NVP-HDM201 and midostaurin. Haematologica, 103, (11): 1862-1872.
10. G. Zauli, C. Celeghini, E. Melloni, et al. (2012) The sorafenib plus nutlin-3 combination promotes synergistic cytotoxicity in acute myeloid leukemic cells irrespectively of FLT3 and p53 status. Haematol-Hematol J, 97, (11): 1722-1730.
11. B. Vu, P. Woykulich, G. Pizzolato, et al. (2013) Discovery of RG7112: A Small-Molecule MDM2 Inhibitor in Clinical Development. ACS Med Chem Lett, 4, (5): 466-469.
12. Y. Fang, G. Liao, and B. Yu. (2020) Small-molecule MDM2/X inhibitors and PROTAC degraders for cancer therapy: advances and perspectives. Acta Pharm Sin B, 10, (7): 1253-1278.
13. C. Tovar, B. Graves, K. Packman, et al. (2013) MDM2 small-molecule antagonist RG7112 activates p53 signaling and regresses human tumors in preclinical cancer models. Cancer Res, 73, (8): 2587-97.
14. M. Andreeff, K. R. Kelly, K. Yee, et al. (2016) Results of the Phase I Trial of RG7112, a Small-Molecule MDM2 Antagonist in Leukemia. Clin Cancer Res, 22, (4): 868-876.
15. I. Ray-Coquard, J. Y. Blay, A. Italiano, et al. (2012) Effect of the MDM2 antagonist RG7112 on the P53 pathway in patients with MDM2-amplified, well-differentiated or dedifferentiated liposarcoma: an exploratory proof-of-mechanism study. Lancet Oncol, 13, (11): 1133-1140.
16. R. Kurzrock, J. Y. Blay, B. B. Nguyen, et al. (2012) A phase I study of MDM2 antagonist RG7112 in patients (pts) with relapsed/refractory solid tumors. J Clin Oncol, 30, (15).
17. E. Mahfoudhi, L. Lordier, C. Marty, et al. (2016) P53 activation inhibits all types of hematopoietic progenitors and all stages of megakaryopoiesis. Oncotarget, 7, (22): 31980-31992.
18. A. Obrador-Hevia, E. Martinez-Font, I. Felipe-Abrío, et al. (2015) RG7112, a small-molecule inhibitor of MDM2, enhances trabectedin response in soft tissue sarcomas. Cancer Invest, 33, (9): 440-50.
19. A. Patnaik, A. Tolocher, M. Beeram, et al. (2015) Clinical pharmacology characterization of RG7112, an MDM2 antagonist, in patients with advanced solid tumors. Cancer Chemother Pharmacol, 76, (3): 587-95.
20. C. Iancu-Rubin, G. Mosoyan, K. Glenn, et al. (2014) Activation of p53 by the MDM2 inhibitor RG7112 impairs thrombopoiesis. Exp Hematol, 42, (2): 137-45 e5.
21. I. Ray-Coquard, J. Y. Blay, A. Italiano, et al. (2012) Effect of the MDM2 antagonist RG7112 on the P53 pathway in patients with MDM2-amplified, well-differentiated or dedifferentiated liposarcoma: an exploratory proof-of-mechanism study. Lancet Oncol, 13, (11): 1133-40.
22. N. Portman, H. H. Milioli, S. Alexandrou, et al. (2020) MDM2 inhibition in combination with endocrine therapy and CDK4/6 inhibition for the treatment of ER-positive breast cancer. Breast Cancer Res, 22, (1): 87.

23. D. D. Fang, Q. Q. Tang, Y. H. Kong, et al. (2019) MDM2 inhibitor APG-115 synergizes with PD-1 blockade through enhancing antitumor immunity in the tumor microenvironment. J Immunother Cancer, 7, (1).

24. H. Sun, Q. Q. Tang, D. Fang, et al. (2021) MDM2 Inhibitor APG-115 Suppresses Cell Proliferation and Tumor Growth in Preclinical Models Of NSCLC Harboring STK11 Mutations. J Thorac Oncol, 16, (3): S132-S133.

25. P. Montesinos, B. M. Beckermann, O. Catalani, et al. (2020) MIRROS: a randomized, placebo-controlled, Phase III trial of cytarabine ± idasanutlin in relapsed or refractory acute myeloid leukemia. Future Oncology, 16, (13): 807-815.

26. B. Higgins, C. Tovar, K. Glenn, et al. (2013) Antitumor activity of the MDM2 antagonist RG7388. Mol Cancer Ther, 12, (11).

27. M. Dangl, Y. C. Chien, C. Lehmann, et al. (2014) Synergistic anticancer activity of clinical stage, non-genotoxic apoptosis inducing agents RG7388 (MDM2 antagonist) and ABT-199 (GDC-0199, BCL2 inhibitor) in p53 wild-type AML tumor models. Cancer Res, 74, (19).

28. C. G. Hoffman-Luca, D. Dizazadeh, D. McEachern, et al. (2015) Elucidation of Acquired Resistance to Bcl-2 and MDM2 Inhibitors in Acute Leukemia In Vitro and In Vivo. Clin Cancer Res, 21, (11): 2558-2568.

29. R. Q. Pan, V. Ruvolo, H. Mu, et al. (2015) BCL-2 Inhibition By ABT-199 (Venetoclax/GDC-0199) and p53 Activation By RG7388 (I dasanutilin) Reciprocally Overcome Leukemia Apoptosis Resistance to Either Strategy Alone: Efficacy and Mechanisms. Blood, 126, (23).

30. R. Q. Pan, K. Kojima, Z. Z. Zheng, et al. (2014) Activation of p53 By Novel MDM2 Antagonist RG7388 Overcomes AML Inherent and Acquired Resistance to Bcl-2 Inhibitor ABT-199 (GDC-0199). Blood, 124, (21).

31. V. Arnhold, K. Schmelz, J. Proba, et al. (2018) Reactivating TP53 signaling by the novel MDM2 inhibitor DS-3032b as a therapeutic option for high-risk neuroblastoma. Oncotarget, 9, (2): 2304-2319.

32. F. Ravandi, I. Gojo, M. M. Patnaik, et al. (2016) A phase I trial of the human double minute 2 inhibitor (MK-8242) in patients with refractory/recurrent acute myelogenous leukemia (AML). Leuk Res, 48: 92-100.

33. A. J. Wagner, U. Banerji, A. Mahipal, et al. (2017) Phase I Trial of the Human Double Minute 2 Inhibitor MK-8242 in Patients With Advanced Solid Tumors. J Clin Oncol, 35, (12): 1304-1311.

34. W. L. Gluck, M. M. Gounder, R. Frank, et al. (2020) Phase 1 study of the MDM2 inhibitor AMG 232 in patients with advanced P53 wild-type solid tumors or multiple myeloma. Invest New Drugs, 38, (3): 831-843.

35. X. Zhang, R. Zhang, H. Chen, et al. (2020) KRT-232 and navitoclax enhance trame tinib's anti-Cancer activity in non-small cell lung cancer patient-derived xenografts with KRAS mutations. Am J Cancer Res, 10, (12): 4464-4475.

36. S. Champiat, L. Dercle, S. Ammari, et al. (2017) Hyperprogressive Disease Is a New Pattern of Progression in Cancer Patients Treated by Anti-PD-1/PD-L1. Clin Cancer Res, 23, (8): 1920-1928.

37. S. Kato, A. Goodman, V. Walavalkar, et al. (2017) Hyperprogressors after Immunotherapy: Analysis of Genomic Alterations Associated with Accelerated Growth Rate. Clin Cancer Res, 23, (15): 4242-4250.

38. M. Konopleva, G. Martinelli, N. Daver, et al. (2020) MDM2 inhibition: an important step forward in cancer therapy. Leukemia, 34, (11): 2858-2874.

39. M. A. Cortez, C. Ivan, D. Valdecanas, et al. (2016) PDL1 Regulation by p53 via miR-34. J Natl Cancer Inst, 108, (1).

40. D. D. Fang, Q. Tang, Y. Kong, et al. (2019) MDM2 inhibitor APG-115 synergizes with PD-1 blockade through enhancing antitumor immunity in the tumor microenvironment. J Immunother Cancer, 7, (1): 327.

41. M. Olivier, M. H ollstein, and P. Hainaut. (2010) TP53 mutations in human cancers: origins, consequences, and clinical use. Cold Spring Harb Perspect Biol, 2, (1): a001008.

42. Q. Y. Luo, W. T. Pan, S. N. Zhou, et al. (2020) A Novel BCL-2 Inhibitor APG-2575 Exerts Synthetic Lethality With BTK or MDM2-p53 Inhibitor in Diffuse Large B-Cell Lymphoma. Oncol Res, 28, (4): 331-344.

43. N. Cancer Genome Atlas Research, T. J. Ley, C. Miller, et al. (2013) Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. N Engl J Med, 368, (22): 2059-74.

44. A. L. Gagez and G. Cartron. (2014) Obinutuzumab: a new class of anti-CD20 monoclonal antibody. Curr Opin Oncol, 26, (5): 484-91.

45. T. Pirich, E. Zwickl-Traxler, M. Pecherstorfer, et al. (2018) Tolerability of obinutuzumab therapy in patients with rituximab-relapsed/refractory B-cell malignancies - a retrospective single center cohort study. Oncotarget, 9, (52): 29944-29956.

46. M. Jak, G. G. van Bochove, E. A. Reits, et al. (2011) CD40 stimulation sensitizes CLL cells to lysosomal cell death induction by type II anti-CD20 mAb GA101. Blood, 118, (19): 5178-88.

47. F. Hertzing, S. Herter, T. Friess, et al. (2016) Antitumour activity of the glycoengineered type II anti-CD20 antibody obinutuzumab (GA101) in combination with the MDM2-selective antagonist idasanutlin (RG7388). Eur J Haematol, 97, (5): 461-470.

48. J. Kocik, M. Machula, A. Wisniewska, et al. (2019)
Helping the Released Guardian: Drug Combinations for Supporting the Anticancer Activity of HDM2 (MDM2) Antagonists. Cancers (Basel), 11, (7).

49. L. Chen, F. Pastorino, P. Berry, et al. (2019) Preclinical evaluation of the first intravenous small molecule MDM2 antagonist alone and in combination with temozolomide in neuroblastoma. Int J Cancer, 144, (12): 3146-3159.

50. D. Phelps, K. Bondra, S. Seum, et al. (2015) Inhibition of MDM2 by RG7388 confers hypersensitivity to X-radiation in xenograft models of childhood sarcoma. Pediatr Blood Cancer, 62, (8): 1345-52.

51. D. Bocangel, S. Sengupta, S. Mitra, et al. (2009) p53-Mediated down-regulation of the human DNA repair gene O6-methylguanine-DNA methyltransferase (MGMT) via interaction with Sp1 transcription factor. Anticancer Res, 29, (10): 3741-50.