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.