

Advancing cancer treatment: Targeting the MDM2-p53 interaction in the clinic



Despite recent advances, cancer remains one of the biggest healthcare challenges we face today. It is a leading cause of death globally and, in 2020, accounted for an estimated 9.9 million deaths¹. Boehringer Ingelheim, through our 'Taking Cancer On' strategy, has a long-term commitment to deliver scientific breakthroughs and develop innovative cancer treatments to positively transform the lives of patients. Our commitment to innovation has resulted in pioneering treatments for lung cancer and we are now advancing a unique clinical development pipeline of new therapeutic agents, both cancer-cell directed agents and immunology therapies, to help combat many different types of cancer.

Evasion of apoptosis is a key hallmark of cancer - inactivation of p53 is a central mechanism by which tumours escape the body's control mechanisms and promote tumour growth and proliferation. In many cancer types, the *TP53* gene is often mutated or deleted, which inactivates the tumour suppression activity of the p53 protein. However, loss of p53 tumour-suppressor activity can also occur through amplification of MDM2. As MDM2 is a negative regulator of p53, this promotes p53 degradation and inhibits p53 tumour suppressor activity².

Overall, approximately 5–7% of tumours display *MDM2* amplifications³. However, such amplifications are more common in some tumour types than others, with an incidence of up to 90% in some types of advanced soft tissue sarcoma (STS). Despite advances in the treatment for other cancers over the past decade, the standard-of-care treatment

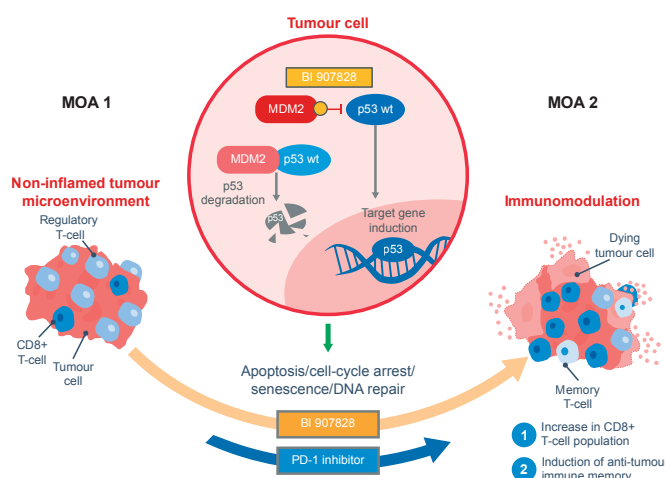


Figure 1. The MDM2-p53 antagonist BI 907828 has a dual mechanism of action (MOA), combining both direct cell-targeted and immune-modulatory activities.

for patients with advanced STS is still chemotherapy; hence, patient outcomes are poor and there is a clear need for new therapeutic options with improved efficacy and better tolerability. Blocking the MDM2-p53 interaction to reactivate wild-type p53 function is therefore a promising cancer therapeutic strategy, especially in this setting.

At Boehringer Ingelheim, we have developed a compound designed to target the MDM2-p53 interaction: the oral, small-molecule MDM2-p53 antagonist BI 907828. This novel agent has a dual mechanism of action: direct targeting of tumour cells and exertion of immune-cell modulatory effects (Fig. 1). BI 907828 binds directly to MDM2 and blocks its interaction with p53, leading to stabilization of p53, *TP53* target gene induction, cell-cycle arrest and apoptosis in tumour cells with wild-type *TP53* status. Activation of p53 also promotes an anti-tumour immune response by increased CD8+ T-cell infiltration in the

tumour and induces anti-tumour immune memory. Consequently, BI 907828 and immune checkpoint inhibitors targeting PD-1 may show synergistic activity in combination.

Based on encouraging preclinical activity⁴, BI 907828 is currently under clinical investigation in two ongoing phase I clinical trials in patients with advanced solid tumours:

- NCT03449381: 1403.1, a phase I trial of BI 907828 as monotherapy.
- NCT03964233: 1403.2, a phase I trial of BI 907828 in combination with the anti-PD-1 antibody ezabenlimab (BI 754091).

Building on these phase I trials, a global multicentre phase II/III trial, 'Brightline-1', comparing BI 907828 with doxorubicin in first-line treatment of patients with advanced dedifferentiated liposarcoma, will start recruiting in early 2022 (NCT05218499). The data from both ongoing and upcoming clinical studies with BI 907828 as monotherapy and in combination will provide

more evidence about the relevance of such an innovative, targeted therapy in various tumour types susceptible to MDM2-p53 blockade.

Over the past 20 years, many advances in cancer treatment have provided benefit to patients; however, there remain multiple areas of unmet medical need. Although further clinical investigation is needed, progress so far with the MDM2-p53 antagonist BI 907828 is just one example of the efforts being made in the fight against cancer. At Boehringer Ingelheim, we believe that our long-term focus on both cancer cell- and immune cell-directed therapies, together with our close collaboration with the oncology community, will continue to provide novel therapies and improved outcomes for cancer patients.

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