Dual SMG5/SMG7 NMD Inhibition Enhances Immunotherapy with Reduced Toxicity in Mutation-Rich Tumors

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Immune checkpoint blockade has transformed cancer treatment, yet conventional biomarkers such as tumour mutation burden (TMB) are not fully accurate in predicting response. Here we investigate whether pharmacological inhibition of nonsense-mediated mRNA decay (NMD), a pathway that limits neoantigen presentation by degrading mutant transcripts, can enhance anti-tumour immunity across multiple murine tumour models. We developed dual small-molecule inhibition of the NMD factors SMG5 and SMG7 and evaluated its therapeutic activity in vivo in a panel of murine syngeneic models with distinct genomic features: lung and breast cancer models with high and low TMD. NMD inhibition (NMDi) primarily reduced tumour burden in highly mutated models, whereas less mutated models showed only modest responses, establishing a positive relationship between mutation burden and NMDi responsiveness. Compared with the clinical-stage NMD inhibitor that targets SMG1 factor (KVS0001), our SMG5/SMG7-directed NMDi achieved similar anti-tumour efficacy with markedly reduced systemic toxicity on pathological assessment, supporting a more favorable therapeutic index as an NMD-targeting strategy. Combining NMDi with anti–PD-1 further improved tumour control, particularly in tumors with high TMB. Collectively, these data indicate that dual SMG5/SMG7 inhibition is a broadly immunostimulatory and pathologically less toxic NMD inhibition strategy whose efficacy scales with tumour mutational burden, and support the use of genomic and transcriptomic features, including MMR status, as biomarkers to guide its clinical deployment.

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