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DISSERTATION TITLE: *Exploring Targeted Thorium Conjugate and Small Molecule Combinations: New Effective Treatments for Cancer*

The Targeted Thorium-227 Conjugates (TTCs) represent a novel class of cancer therapy currently in preclinical and clinical development at Bayer AS. The TTCs consist of the alpha emitter thorium-227 (^{227}Th) complexed to a 3,2-HOPO chelator conjugated to a tumor specific antibody. The high energy and short range of the alpha-particle induces a potent local irradiation of the tumor with limited damage to surrounding tissue, thus making them beneficial for treatment of cancer.

The cytotoxicity of the alpha particle is largely linked to their high potency of inducing complex DNA damage. This thesis describes the preclinical evaluation of TTCs in combination with small molecule DNA damage response (DDR) inhibitors. The DNA damage induced by the alpha-particle combined with the pharmaceutical or genetic inhibition of DNA repair was hypothesized to result in synergistic effects as fewer DNA breaks per cell would be required to trigger cell death. The overall aim with the combination therapy is to achieve an enhanced effect at lower doses and thereby an increased therapeutic window. The results presented in the thesis summarize *in vitro* and *in vivo* studies demonstrating synergistic effects achieved over a range of cancer indications, TTC targets and DDR inhibitors. Furthermore, mechanistic studies confirmed that the enhanced cytotoxic effect was linked to increased levels of DNA double strand breaks. In summary, this supports the further exploration of combination therapy with TTCs and DDR inhibitors for treatment of different cancer indications and investigation of defects in DDR genes as potential biomarkers for treatment with TTCs.

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