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Synergistic Effect of a HER2 Targeted Thorium-227 Conjugate in Combination with olaparib in a BRCA2 Deficient Xenograft Model

Targeted thorium conjugates (TTCs) represent a new class of therapeutic radiopharmaceuticals with the capability of targeting multiple cancer types. The TTCs are comprised of the alpha particle emitter thorium-227 complexed to a 3,2-hydroxypyridinone chelator conjugated to a tumor-targeting monoclonal antibody. When coupled to a suitable targeting moiety the radiation dose can be preferentially delivered to the surface of the tumor cell minimizing unwanted effects on the normal surrounding tissue. This study reports the pre-clinical evaluation of combination therapy comprising a HER2-TTC and the PARP inhibitor olaparib in the human cancer model DLD-1 and the knockout version DLD-1 BRCA2 -/-. As the mode of action of the TTC is based on the induction DNA damage we hypothesized that BRCA2 deficiency would sensitize to TTC treatment, and that the combination with PARP inhibitors would be synergistic.
Methods: The combination treatment was first evaluated in in vitro cytotoxicity assays, followed by analysis of the combination index according to the median-effect model of Chou-Telalay. Next, the HER2 expression and biodistribution of HER2-TTC was determined in DLD-1 xenograft bearing nude mice after a single intravenous dose administration (600 kBq/kg, 0.14 mg/kg, i.v.). In the same models we evaluated the in vivo anti-tumor efficacy of HER2-TTC ± olaparib and the combination effect was analyzed according to the Bliss additivity model. Results: In vitro, HER2-TTC and olaparib induced significantly increased cytotoxicity in the BRCA2 -/- cell line as compared to the parental and the combination treatment was determined to be synergistic in DLD-1 BRCA2 -/- and additive in DLD-1 parental.
The xenograft models DLD-1 parental and DLD-1 BRCA2 -/- were both determined to be HER2 low expressing and the biodistribution demonstrated significant and specific uptake of HER2-TTC (40-60 % ID/g) as compared to the isotype control (5 % ID/g). The monotherapy treatment with HER2-TTC induced significant and dose dependent tumor inhibition in both xenograft models. Furthermore, based on treatment-over-control ratio the DLD-1 BRCA2 -/- model was more sensitive to the highest dose of HER2-TTC (600 kBq/kg) compared to the DLD-1 parental. The in vivo combination efficacy was determined to be synergistic only in the DLD-1 BRCA2 -/- xenograft model, demonstrating significant tumor growth inhibition from a TTC dose of 120 kBq/kg and 50 mg/kg olaparib (daily, i.p. for 4 weeks), with comparable tumor growth inhibition to a single dose of 600 kBq/kg HER2-TTC. Conclusion: This study supports the further investigation of DNA damage response inhibitors in combination with TTCs as a new strategy for the effective treatment of mutation-associated cancers. Acknowledgments: We would like to thank the Research Council of Norway for funding this study. We would like to thank Pharmatest Services for conducting the animal studies.

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