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DRUG COMBINATIONS TO OVERCOME THERAPY RESISTANCE IN CANCER

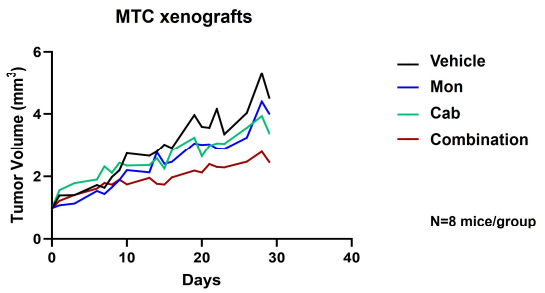
Keywords: Vandetanib, cabozantinib, monensin, clofilium tosylate, combination therapy, TKR inhibitor, RET inhibitor, MTC

INVENTION NOVELTY

In order to provide therapies for the treatment of diseases associated with tyrosine kinase receptor (TKR) activation, TKR inhibitors have been developed. Medullary Thyroid Carcinoma (MTC), a rare tumor of the thyroid gland, is an example for a disease associated with activation of a TKR, more exactly activation of the TKR RET. Targeted therapy with the multi-kinase inhibitors vandetanib (Van) and cabozantinib (Cab), which besides RET also inhibit other TKRs, has demonstrated clinical benefits for patients with progressive or metastatic MTC. However, these drugs associate with severe toxicities and patients almost invariably develop resistance over time. Also, the recently approved TKR inhibitors selpercatinib and pralsetinib associate with therapy resistance and some toxicity. The inventors found that the combination of the known TKR/RET inhibitors with monensin (Mon) or clofilium tosylate (Ct), respectively, resulted in an unexpected synergistic effect in the treatment of diseases associated with TKR activation beyond MTC.

VALUE PROPOSITION

The identification of the two novel agents Mon and Ct as drugs that synergize with known TKR/RET inhibitors leading to enhanced anti-proliferative effects against various cancer types associated with TKR/RET activation. This allows to lower the doses of the inhibitors thereby reducing unwanted toxicities. This effect may also reduce therapy resistance with a great benefit for the patients.



Efficacy of Mon and Cab alone or in combination on MTC cell-derived xenografts in mice (Source: N. Pellegata/I. Valenca, Helmholtz Munich).

TECHNOLOGY DESCRIPTION

The inventors have performed a drug screening and discovered two promising hits able to synergize with low dose of the multikinase inhibitors Cab and/or Van - the antibacterial Mon and the antiarrythmic agent Ct. The results showed that every combination was able to decrease the cell viability of human MTC cell lines as well as other tumor cell lines associated with TKR/RET activation in a more effective manner than the single drug treatment. The 2D cell monolayer effects have been validated in (i) 3D organotypic cultures, where the anti-proliferative effect of the combinations was stronger than with a single drug and (ii) *in vivo* in MTC xenograft models. The same synergistic effects could be demonstrated by combining Mon and Ct with different kinase inhibitors, e.g. alectinib, sunitinib, regorafenib, selpercatinib, and pralsetinib.

COMMERCIAL OPPORTUNITY

The recent work demonstrated that the results obtained with the drug combinations may suggest an extension also to other tumor entities besides MTC. It could be shown that the drug combinations also suppress the proliferation of pituitary, adrenal, and other neuroendocrine tumor cells (pancreatic, Small Cell Lung Cancer), and non-neuroendocrine tumor cells (Renal Cell Carcinoma). The technology is open for co-development as well as licensing.

DEVELOPMENT STATUS

In vivo studies in MTC xenograft mice with Mon and Cab combination showed a significant and effective inhibition in tumor growth compared to single compounds.

PATENT SITUATION

A European patent application has been filed in August 2023.

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