Radiotherapy (RT) plays a central role in cancer treatment. Despite the use of their treatment, nearly 30% of all cancer patients have indicators for radioresistance, particularly in the setting of primary or recurrent patients. KRAS\(^{G12C}\) mutations in approximately 3.5% of colorectal cancers (CRC). \(^{1}\) KRAS\(^{G12C}\) mutations act as an oncogenic driver and contribute to resistance in disseminated first in mouse cell lines transformed with SNAKE, SNAKE \(^{2}\) and MSKR A\(^{3}\) \(^{4}\). These results are in line with clinical observations in patients with KRAS mutated cancers, often showing overall response rates to therapies resulting in poor clinical outcomes. New KRAS covalent KRAS\(^{G12C}\) inhibitors are showing promising clinical activity (Krystal-1 trial); however, the new therapeutic combinations are needed due to the emergence of treatment resistance and limited efficacy as monotherapy.

OBJECTIVES

In this work, we explore the efficacy of the association between RT and MRTX1257, a selective and covalent potent KRAS\(^{G12C}\) inhibitor.

Additionally, we study the immunomodulatory effects of the association of RT and MRTX1257 by describing the immune changes reshaping the tumor immune microenvironment.

RESULTS

MRTX1257\(^{G12C}\) inhibits the effects of RT in immunocompetent BALB/c mice bearing CT26 KRAS\(^{G12C}\) tumors, and is able to induce durable responses in combination with RT.

CONCLUSION AND PERSPECTIVES

We achieved tumor shrinkage of 20% of the immunocompetent mice treated with the combination, in contrast with fast regrowth observed in mice, suggesting the involvement of the immune component in the efficacy of the combined treatment. However, MRTX1257 \(^{G12C}\) alone, significantly delayed tumor growth also in immunocompetent mice. Therefore, KRAS\(^{G12C}\) tumors, the anti-tumor immune response, cannot be considered the key pillar of the immunomodulatory outcomes observed in this work. One of the expected outcomes of both KRAS\(^{G12C}\) mutations in these cells is the expected increase in the proliferation of CD8+ T cells following the combined treatment.

- Flow cytometry experiments in CT26 KRAS\(^{G12C}\) tumor showed meaningful changes within the immune component, including downregulation of PD-1-L in myeloid cells, tumor and neuronal cells, increase in the proportion of infiltrating monocytes and conventional dendritic cell type 2 and 8, and the upregulation of the co-stimulatory marker CD86 within macrophages which is in line with a more pro-inflammatory phenotype of these cells following RT alone or RT with MRTX1257.

- The down-regulation of PD-1+ is a major positive effect of MRTX1257, and may be crucial for the efficacy of the combination as it counterbalances the upregulation of PD-1+ following RT.

- Our immunomodulatory outcomes are in phase with most of those presented in the work by Bracks et al. on MRTX649 used alone in preclinical models of KRAS\(^{G12C}\) mutated cancer, including increase in the proportion of CD8+ T cells, CD8+ helper cells and CD8+ T cells.

In this work, we first demonstrated the ability of MRTX1257 to enhance the effect of radiotherapy in both in vitro and in vivo. This effect depended on EGF mucin status, dose and timing of administration and was associated with a growth profile. Moreover, the use of RT and MRTX1257 led to a significant rate in BALB/c mice bearing CT26 KRAS\(^{G12C}\) tumors, but not in nude mice, highlighting the role of the tumor immune microenvironment in the radioresistant effect of MRTX1257. This work constitutes a first step towards the implementation of new combination approaches involving RT and MRTX1257 in KRAS\(^{G12C}\) mutated cancers, with the aim of providing new therapeutic strategies with a prolonged clinical benefit.

References


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