Background

DRP-104, a novel broad acting glutamine antagonist, has significant therapeutic potential in cancer via directly targeting tumor metabolism and inducing a potent antitumor immune response. Here we sought to elucidate the immunomodulatory effect of DRP-104 on tumor growth inhibition as a single agent and in combination with PO-D1-L1 checkpoint inhibitors in syngeneic models. We utilized multiple technologies to assess mechanistic effects on immune cells in vivo including flow cytometry, multiplex immunassay, gene expression profiling and GeoMx® digital spatial profiling.

DRP-104 mediated tumor growth inhibition was associated with increased tumor-infiltrating leukocytes (TIL) including T, NK, and NKT cells, M1-polarized tumor associated macrophages, and decreased immune-suppressive cells such as M2Cs. Nanosting® IO360 analysis revealed broad remodeling of the tumor microenvironment including up regulation of cytotoxic/antigen presentation score; increase in tumor metabolic stress/apoptotic score; and decrease in cell proliferation score. GeoMx® profiling also demonstrated increased tumor T cells and granzyme B expression. DRP-104 showed significant tumor growth inhibition and regressions as a single agent in mouse syngeneic tumor models, including those resistant to immune checkpoint inhibitors. Lastly, combination of DRP-104 with anti-PO D1 Ab or anti-PO-D1-L1 Ab further improved survival effect with long-term durable cure.

In summary, DRP-104 treatment resulted in broad remodeling of the tumor microenvironment including increased infiltration and function of multiple immune cells distinct from activities obtained by a checkpoint inhibitor treatment. Combination therapy of DRP-104 with anti-PO/D1-L1 achieved significantly improved anti-tumor efficacy including long-term durable cures even in checkpoint inhibitor resistant models. This unique and non-overlapping mechanism of action supports clinical development of DRP-104 alone and in combination with PO-D1-L1 checkpoint inhibitors.

Summary

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Conclusions

DRP-104 achieved a 66x tumor/plasma ratio for DON in MC38 bearing CES 1KO mice proving successful partitioning of protot to direct DON, the active moiety, to tumors. Combination of DRP-104 yielded dose-dependent changes in key tumor & plasma pharmacodynamic metabolites, broad metabolic reprogramming of the TME, and dramatic immune oncolysis related gene modulations. This was further supported by GeoMx® digital spatial profiling and Nanosting® gene expression analysis. Immuno-phenotypical analysis showed that DRP-104 induced substantial and varied changes in various immune cells infiltrates, such as increased TL, TN and NKT cells. T cells and NK cells were more proliferative, TAMs were polarized to M1 phenotype, and M2Cs were decreased. All of these changes suggest broad remodeling of the TME by DRP-104 treatment.

CD4+ and NK cell depletion reduced TGI of DRP-104, while CD8+ cell depletion enhanced anti-tumor efficacy of DRP-104 indicating an immune cell mediated anti-tumor mechanism of action.

DRP-104 monotherapy demonstrated a prolonged survival effect in both CT26 and H22 models compared to immune checkpoint inhibitors. Combination of DRP-104 with either anti-PO-D1 Ab or anti-PO-D1-L1 Ab significantly increased efficacy, leading to long-term durable cures.

These data support clinical development of DRP-104 as a single agent and in combination with immune checkpoint inhibitors - including in settings of non-response to IO therapies. An IND has been recently opened and clinical development is forthcoming.

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