

BR101801 STIMULATES ANTI-TUMOR IMMUNITY AND ENHANCES THE EFFICACY OF RADIATION IN A SYNGENEIC MODEL

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Background BR101801 is an inhibitor of PI3K γ/δ and DNA-PK. It has received clinical approval from the U.S. FDA as an anticancer drug candidate, and phase 1a/1b is ongoing in the U.S. and South Korea. According to the prior studies PI3K γ/δ inhibition exhibits anticancer immune effects by changing the tumor microenvironment [1]. In addition, ionizing radiation (IR) activates the immune response by causing the destroyed cells to act as antigens [2]. Therefore, the combination of BR101801 and IR can induce cancer cell death and amplify anticancer immune effects. This study aims to demonstrate efficacy of the BR101801 as a potent cancer immunotherapy.

Methods The enzymatic potency of PI3K isotype and DNA-PK was analyzed by Eurofins. The effects of BR101801 on cell viability were evaluated in 4T1 (breast cancer) and CT-26 (colon cancer) cells for 72 h using WST-8 assay. For in vivo studies, the tumor (4T1 or CT-26)-bearing syngeneic mice were treated with BR101801. To evaluate the synergistic effect, CT-26 tumor-bearing syngeneic mice were treated with vehicle, BR101801, IR (2 Gy or 7.5 Gy), and BR101801 + IR. Immune cells from the spleen or tumor were quantified by flow cytometry.

suppressor cells (MDSC) were decreased and CD8+ T cells were increased in the spleens isolated from the tumor-bearing mice. Compared with other PI3K inhibitors, BR101801 had the highest efficacy, confirming that it changes the immune microenvironment. Moreover, BR101801 was synergistic in combination with 2 Gy or 7.5 Gy of IR in the syngeneic model. Notably, Tregs & Macrophage2 were decreased and CD8+ T cells were increased in the tumor tissue, confirming that the anticancer efficacy.

The combination of BR101801 and ionizing radiation showed synergistic effects in the CT-26 Syngeneic model. BR101801 increases anti-cancer immune cells, CD8 + T cells, and decreases immune suppressor cells Tregs and macrophages through a combination of radiation, resulting in immuno-cancer effects.

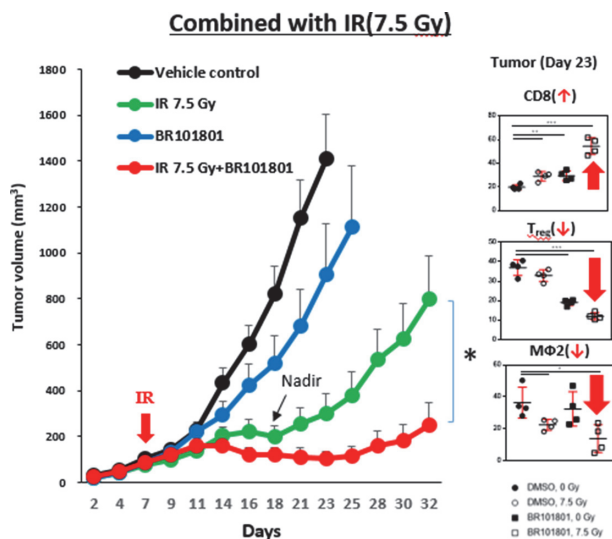
Conclusions BR101801 demonstrated an anticancer immune effect by changing the tumor microenvironment and showed synergistic effects with radiation combination therapy. We will confirm the anticancer immunity effect in ongoing clinical trials.

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Ethics Approval The protocol and any amendment(s) or procedures involving the care and use of animals in this study were reviewed and approved by the Institutional animal Care and Use Committee (IACUC) of BoRyung Pharm. prior to conduct.[Approval number:BR18130]

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Abstract 600 Figure 1 Synergistic effect with ionizing radiation In Vivo

Results In vitro selectivity and target potency of BR101801 on different PI3K isotypes and DNA-PK were studied in a cell-free system. The biochemical IC₅₀ values of BR101801 for PI3K γ , δ , and DNA-PK were 15 nM, 2 nM, and 6 nM, respectively. In vitro 50% of maximal inhibition of cell proliferation (GI₅₀) in 4T1 and CT26 cell lines were both above 10 μ M. In 4T1 and CT-26 syngeneic models, BR101801 showed the highest tumor inhibitor efficacy (Figure 1). In particular, regulatory T cells (Tregs) & Myeloid derived