Background

The potency and selectivity of APL-102 against CSF1R kinase was evaluated in a cell free system where the enzyme activity was evaluated with Eurofins standard KinaseProfiler™ system. Cell growth inhibition was evaluated in the Ba/F3-BSCF1R cell line by the CellTiter-Glo (CTG) method. Engineered cell line Ba/F3/IC5SF1R was treated with APL-102 and control compounds for 3 days at 37°C, 5% CO₂, and 95% humidity.

Materials and Methods

In vivo efficacy studies of APL-102 in combination with an anti-PD-1 antibody were performed in two immunotherapy sensitive syngeneic models, a subcutaneous MC-38 colon model in C57BL/6J mice and a CT-26 colon model in BALB/c mice. Treatment with APL-102 and anti-PD-1 antibody was started after tumor establishment. The experiments were performed as per the guidelines of institutional protocols and the National Institute of Health (NIH) guidelines.

Results

The results demonstrated that APL-102 inhibits CSF1R in a radiometric enzyme activity assay with an IC50 of 43 nM. APL-102 demonstrated growth inhibition in cell dependent on CSF1-CSF1R signaling.

Discussion

The results demonstrated that APL-102 inhibits CSF1R in a radiometric enzyme activity assay with an IC50 of 43 nM. APL-102 demonstrated growth inhibition in cell dependent on CSF1-CSF1R signaling. We demonstrated a mechanism of action for APL-102 anti-tumor activity, the inhibition of CSF1R-dependent tumor associated macrophages in the tumor microenvironment.

Summary

We demonstrated a mechanism of action for APL-102 anti-tumor activity, the inhibition of CSF1R-dependent tumor associated macrophages in the tumor microenvironment. APL-102 treatment with 10 mg/kg APL-102 and 10 mg/kg anti-PD-1 antibody. The results demonstrated that APL-102 increased the total T cells (CD4, CD8+), and ISG80 markers in tumor tissues tested by IHC in the MC-38 efficacy study. Group 1 was treated with vehicle, Group 2 was treated with 5 mg/kg of APL-102, Group 3 was treated with 10 mg/kg of APL-102, Group 4 was treated with 10 mg/kg anti-PD-1 antibody, Group 5 was combined treatment with 5 mg/kg APL-102 and 10 mg/kg anti-PD-1 antibody. Group 6 was combined treatment with 10 mg/kg APL-102 and 10 mg/kg anti-PD-1 antibody. APL-102 showed significant inhibition on MC-38 tumor growth as a single agent. Anti-PD-1 antibody also showed inhibition as a single agent. The combination of APL-102 with anti-PD-1 antibody showed improved efficacy.

Contact / Further Information

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ABSTRACT:

APL-102, an oral small molecule multi-kinase inhibitor, demonstrates favorable CSF1R activity, offering a means for controlling tumor associated macrophages.

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Abstract No.: #2205

Background

The role of the tumor microenvironment (TME) in fostering the development of malignancies is prompting the pursuit of anticancer therapies that target its components as opposed to the tumor itself. As part of their immune surveillance duties, immune cells form part of this microenvironment, and yet, cancer cells have devised means to downplay their tumoricidal capabilities. Colony stimulating factor 1 receptor (CSF1R) may offer such a means of controlling tumor associated macrophages in the tumor microenvironment.

Materials and Methods

The potency and selectivity of APL-102 against CSF1R kinase was evaluated in a cell free system where the enzyme activity was evaluated with Eurofins standard KinaseProfiler™ system. Cell growth inhibition was evaluated in the Ba/F3/CSF1R cell line by the CellTiter-Glo (CTG) method. Engineered cell line Ba/F3/IC5SF1R was treated with APL-102 and control compounds for 3 days at 37°C, 5% CO₂, and 95% humidity.

Results

The effect of APL-102 was further evaluated in murine myelogenous cell lines and human monocytes. Two murine cell lines M-NFS-60 and RAW264.7 were starved and then treated with APL-102 or comparator test articles for 3 days at 37°C, 5% CO₂, and 95% humidity. The results demonstrated that APL-102 and anti-PD-1 antibody significantly inhibited tumor cell proliferation and showed inhibition as a single agent. The combination of APL-102 with anti-PD-1 antibody showed improved efficacy.

Discussion

The results demonstrated that APL-102 inhibits CSF1R in a radiometric enzyme activity assay with an IC50 of 43 nM. APL-102 demonstrated growth inhibition in cell dependent on CSF1-CSF1R signaling. We demonstrated a mechanism of action for APL-102 anti-tumor activity, the inhibition of CSF1R-dependent tumor associated macrophages in the tumor microenvironment. APL-102 treatment with 10 mg/kg APL-102 and 10 mg/kg anti-PD-1 antibody. The results demonstrated that APL-102 increased the total T cells (CD4, CD8+), and ISG80 markers in tumor tissues tested by IHC in the MC-38 efficacy study. Group 1 was treated with vehicle, Group 2 was treated with 5 mg/kg of APL-102, Group 3 was treated with 10 mg/kg of APL-102, Group 4 was treated with 10 mg/kg anti-PD-1 antibody, Group 5 was combined treatment with 5 mg/kg APL-102 and 10 mg/kg anti-PD-1 antibody. Group 6 was combined treatment with 10 mg/kg APL-102 and 10 mg/kg anti-PD-1 antibody. APL-102 showed significant inhibition on MC-38 tumor growth as a single agent. Anti-PD-1 antibody also showed inhibition as a single agent. The combination of APL-102 with anti-PD-1 antibody showed improved efficacy.

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