BPR5K230: Small Molecule AXL and MERTK Dual Kinase Inhibitor as Anticancer and Immunomodulatory Agent

INDICATIONS:

- ✓ AXL and MERTK over-expression solid tumors
- ✓ Tumors relapsed or resistant to chemotherapy, molecular targeted agents or immune checkpoint inhibitors

PATENTS:

PCT patent applications

DEVELOPMENT STATUS:

Lead optimization to candidate

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INVENTION DESCRIPTION

AXL and MERTK are members of TAM (TYRO3, AXL and MERTK) receptor tyrosine kinases. Both AXL and MERTK play important roles in tumor progression, metastasis, drug resistance and immune evasion. Thus, dual AXL and MERTK inhibition in the tumor and tumor immune microenvironment would enhance anti-tumor efficacy and boost anti-tumor immune responses. Utilizing our proprietary small molecule tyrosine kinase inhibitors compound library, we identified BPR5K230 with potent AXL and MERTK kinase inhibitory activities and selectivity over TYRO3. BPR5K230 produced *in vivo* anti-tumor efficacy, alone or in combination with immune checkpoint inhibitors, induced tumor regression and prolonged median survival days in mice. In multiple preclinical models evaluated, the anti-tumor effect of BPR5K230 was more efficacious than the clinical stage agent Ono-7475 (Tumor growth inhibition TGI, % of Control: BPR5K230: 44–86%; Ono-7475: 10–45%). As an immunotherapeutic agent, BPR5K230 decreased M2 tumor-associated macrophages (TAM) in the tumor and increased effector T cells in the spleen. As a molecular-targeted agent, BPR5K230 produced greater anti-tumor efficacy than either AXL or MERTK mono-targeted agent used alone, verifying BPR5K230's dual AXL and MERTK inhibitory activities. Importantly, BPR5K230 in combination with erlotinib overcame erlotinib-resistant tumors. BPR5K230 exhibited good oral bioavailability (F = 60%) in mice. US patent has been filed including 174 examples of a series of pyrimidine-like heterocyclic derivatives as potent AXL/MERTK dual kinase inhibitors.

COMPETITIVE ADVANTAGES OF BPR5K230

- ➤ Novel AXL and MERTK dual kinase inhibitors use one single chemical entity with dual functions to simultaneously inhibit AXL and MERTK signaling in the tumor and tumor immune suppressive microenvironment, thereby enhancing anti-tumor efficacy and boosting anti-tumor immune responses.
- ➤ Dual AXL and MERTK kinase inhibitors have advantages over AXL and MERTK-selective agents for their broader clinical indications, preventing treatment resistance and reducing overlapping/multiple side effects caused by mono-target agents.
- ➤ BPR5K230 dual AXL and MERTK kinase inhibitors are best used for patients who fail current therapies and whose tumors and immune cells overexpress AXL and MERTK.

MARKET POSITIONING/OPPORTUNITY

- ➤ BPR5K230 with anti-tumor and immune modulatory activities would expect to drive global kinase inhibitors markets, targeted cancer therapy market and immuno-oncology market.
- ➤ Drug and companion diagnostics (CDx) co-development would identify patients who are likely to benefit from BPR5K230, alone or in combination with other agents, including chemotherapeutic agents, target agents or immune checkpoint inhibitors.

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