ANI-624 for the Treatment of Non-Hodgkin's Lymphoma

Overview

Drug Name	ANI-624
Description	ANI-624 is an oral multi-target inhibitor against tumor angiogenesis, mitosis and chronic inflammation in phase I clinical trials for the oral treatment of patients with relapsed or refractory non-Hodgkin's lymphoma.
Target	VEGFR; PDGFR; AURK2; KIT
Drug Modality	Small Molecule
Indication	Non-Hodgkin's Lymphoma
Product Category	Angiogenesis Inhibitors
Mechanism of Action	Signal Transduction Modulators
Status	Phase I
Patent	Granted

Seeking Global Cooperation

Protheragen Inc. is actively seeking partnership for ANI-624. Potential collaboration can be strategic alliance, licensing, or marketing agreement.
We look forward to hearing from you.

Target

Vascular endothelial growth factor receptor (VEGFR)

VEGF receptors are receptors for vascular endothelial growth factor (VEGF). There are three main subtypes of VEGFR, numbered 1, 2 and 3. Depending on alternative splicing, they may be membrane-bound or soluble.

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All members of the VEGF family stimulate cellular responses by binding to the VEGFRs on the cell surface, causing them to dimerize and become activated through transphosphorylation. VEGFR-1 is required for the recruitment of haematopoietic stem cells as well as the migration of monocytes and macrophages while VEGFR-2 regulates vascular endothelial function and VEGFR-3 regulates lymphatic endothelial cell function. VEGFR-2 has been the focus of the most research as it is the major signal transducer of both physioligcal, and perhaps more importantly, pathological angiogenesis, especially in cancerous tumors.

Platelet-derived Growth Factor Receptor (PDGFR)

PDGFR (platelet-derived growth factor receptor) is a membrane receptor tyrosine kinase for the glycoprotein PDGF. The two receptor isoforms (PDGFRalpha and PDGFRbeta) regulate cellular proliferation, differentiation and migration in normal cells and are widely expressed in several malignancies. Extracellular binding of PDGF stimulates the intrinsic tyrosine kinase activity in the cytoplasmic portion of each subunit of the receptor resulting in transphosphorylation of specific tyrosine residues. These phosphotyrosines can then serve as binding sites for intracellular signaling molecules by means of their Src homology 2 domains, thus activating multiple downstream pathways, including phosphatidyl-inositol-3 (PI3)-kinase, phospholipase C (PLC)-gamma, Src kinase, Janus kinase (JAK)/Signal transducers and activators of transcription (STAT) and mitogen activated protein (MAP) kinase pathways. PDGFR inhibitors have been shown to inhibit malignant cell proliferation and survival.

Aurora kinase B (AURK2)

This gene encodes a member of the aurora kinase subfamily of serine/threonine kinases. The genes encoding the other two members of this subfamily are located on chromosomes 19 and 20. These kinases participate in the regulation of alignment and segregation of chromosomes during mitosis and meiosis through association with microtubules. A pseudogene of this gene is located on chromosome 8.

KIT proto-oncogene, receptor tyrosine kinase (KIT)

This gene encodes a receptor tyrosine kinase. This gene was initially identified as a homolog of the feline sarcoma viral oncogene v-kit and is often referred to as proto-oncogene c-Kit. The canonical form of this glycosylated transmembrane protein has an N-terminal extracellular region with five immunoglobulin-like domains, a transmembrane region, and an intracellular tyrosine kinase domain at the C-terminus. Upon activation by its cytokine ligand, stem cell factor (SCF), this protein phosphorylates multiple intracellular proteins that play a role in in the proliferation, differentiation, migration and apoptosis of many cell types and thereby plays an important role in hematopoiesis, stem cell maintenance, gametogenesis, melanogenesis, and in mast cell development, migration and function. This protein can be a membrane-bound or soluble protein.

Indication

Non-Hodgkin Lymphoma (NHL)

Of all the tumors, lymphoma is a highly heterogeneous malignant tumor. 90% of lymphomas are Non-Hodgkin Lymphomas (NHL) and the remaining 10% are Hodgkin's Lymphoma (HL). NHL is an umbrella term referring to various closely-related lymphoproliferative malignancies. According to the World Health Organization (WHO), there are more than 60 different types of cancer classified under the broader heading of NHL. Diffuse large B-cell lymphoma (DLBCL), of which more than a dozen subtypes exist, is the most common form of NHL in all countries and age groups, accounting for up to one-third of newly diagnosed cases. Follicular lymphoma is the second most common form, accounting for another 10-20% of all newly diagnosed cases of NHL in Western countries.

The International Agency for Research on Cancer estimates that in the year 2018, there were 284,713 cases of NHL diagnosed in men and 224,877 in women worldwide, yielding annual global incidence rates of 6.7 and 4.7 per 100,000, respectively. There were an estimated 249,000 deaths worldwide due to NHL that year, yielding an age-standardized mortality rate of 4.4 and 2.5 per 100,000 in men and women, respectively. Based on incidence data from the Globocan 2008 database and projected population increases, the World Economic Forum estimates that 583,681 new cases of NHL will be diagnosed worldwide in 2030.

Mechanism of Action

Signal Transduction Modulators

Molecular Mechanism	Inhibiting VEGFR, PDGFR, AURK2 and KIT

Status

The Status of ANI-624

The international patent applications under the PCT have been granted.

	Discovery/Optimization	Preclinical	Clinical
ANI-624			

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