Pfizer Investigational Agents for Breast Cancer Now (BCN) Catalyst Program
Axitinib
RTKI including VEGFR-1,2,3
Axitinib
RTKI including VEGFR-1,2,3

Overview

• The vascular endothelial growth factor (VEGF) family of proangiogenic proteins are key regulators of many of the signaling networks contributing to angiogenesis

• The VEGF receptors are implicated in pathologic angiogenesis, tumor growth, and cancer progression

• Axitinib is a small molecule substituted indazole derivative that inhibits receptor tyrosine kinases, including VEGFR-1, VEGFR-2, and VEGFR-3, at therapeutic plasma concentrations

• VEGF-mediated endothelial cell proliferation and survival were inhibited by axitinib in vitro and in mouse models

• Axitinib was shown to inhibit tumor growth and phosphorylation of VEGFR-2 in tumor xenograft mouse models
**Stage of Development**

Axitinib is being investigated as a single agent or in combination with other agent(s) in the following tumor types. Axitinib is not approved for the uses listed below.

<table>
<thead>
<tr>
<th>Stage of Development</th>
<th>Adjuvant Renal Cell Carcinoma (RCC)</th>
<th>Advanced Renal Cell Carcinoma (RCC)</th>
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</thead>
<tbody>
<tr>
<td>Phase 3 *</td>
<td></td>
<td>Phase 3: Combination</td>
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</tbody>
</table>

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Bosutinib
ABL and Src Kinase Inhibitor
Overview

- The Philadelphia chromosome is a reciprocal translocation that fuses the Abl locus on chromosome 9 with the Bcr locus on chromosome 22, resulting in overexpression of the constitutively active protein tyrosine kinase Bcr-Abl, which is commonly associated with chronic myeloid leukemia (CML).
- The Src family of tyrosine kinases plays a role in a variety of normal cellular functions including proliferation, differentiation, survival etc. and are frequently overexpressed and/or aberrantly activated in many tumors.
- Bosutinib is a synthetic quinolone derivative and kinase inhibitor that targets both Abl and Src kinases with potential antineoplastic activity.
- Bosutinib inhibits Bcr-Abl in several CML cell lines and transfectants, with IC\textsubscript{50} values in the low nanomolar range and also inhibited Bcr-Abl kinase activity in CML CD34+ cells.
- Bosutinib inhibits Src in an enzyme assay with an IC\textsubscript{50} of 1.2 nM, inhibits anchorage-independent growth of Src-transformed fibroblasts with an IC\textsubscript{50} of 100 nM, and inhibits Src-dependent protein tyrosine phosphorylation.

References:
Stage of Development

Bosutinib is being investigated in the following tumor type. Bosutinib is not approved for the use listed below.

<table>
<thead>
<tr>
<th>Stage of Development</th>
<th>Phase 3*</th>
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</thead>
<tbody>
<tr>
<td>Newly Diagnosed</td>
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<tr>
<td>Chronic Phase (CP)</td>
<td></td>
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<tr>
<td>Chronic Myeloid</td>
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<tr>
<td>Leukemia (CML)</td>
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</table>

* Closed to enrollment

Gedatolisib
PI3K/mTOR Pathway Inhibitor

Gedatolisib is an investigational compound
Overview

- Phosphatidylinositol 3-kinases (PI3Ks) activate a signaling pathway which includes the protein kinases AKT and mTOR, leading to regulation of cell growth, cell cycle progression, apoptosis, migration, metabolism, and vesicular trafficking.
- The PI3K/AKT/ mTOR pathway is one of the most frequently mutated pathways in solid tumor malignancies, resulting in activation of PI3K and its downstream targets AKT and mTOR.
- PF-05212384 is a small molecule inhibitor of the PI3K/AKT/mTOR signaling pathway.
- *In vitro*, PF-05212384 has demonstrated suppression of PI3K (and mTOR) kinase activity in a diverse array of tumor cell lines, and *in vivo* the compound has inhibited tumor cell growth and induced tumor regression in human tumor xenograft models with select gene mutations.
- PF-05212384 shows antitumor activity in subcutaneous and orthotopic human xenograft tumor models when administered intravenously (iv) as a single agent.
Gedatolisib
PI3K/mTOR Pathway Inhibitor

Mechanism of Action

Adapted from Workman P, et al. Nat Biotech. 2006;24:794-796. Used with permission from AACR.
Gedatolisib
PI3K/mTOR Pathway Inhibitor

Rationale for a Cancer Target

Overview

Mechanism of Action

Stage of Development

Gedatolisib is an investigational compound

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Stage of Development

Metastatic HR+ Breast Cancer (MBC)  Phase 1 Combination

Metastatic Triple Negative Breast Cancer (TNBC)  Phase 1 Combination

Glasdegib
Smoothened (SMO) Inhibitor

Glasdegib is an investigational compound
Overview

- The Hedgehog (Hh) signal transduction pathway is essential for the patterning and development of tissues in metazoan organisms
- The hedgehog receptor, patched homologue 1 (PTCH1), inhibits smootherned (SMO), a key activator in the pathway
  - During physiologic signaling, Hh binds to PTCH1 on neighboring cells, thereby allowing SMO to activate hedgehog signaling.
  - SMO activation results in activation of target proteins, such as GLI transcription factors, which can cause proliferation, survival, and differentiation of cells.
- PF-04449913 is an orally bioavailable small-molecule inhibitor of the Hedgehog (Hh) signaling pathway with potential antineoplastic activity
  - In vivo, PF-04449913 was shown to revert multidrug resistance (MDR) by down-regulation of ABCA2 and BCL2 on leukemia stem cells in acute myeloid leukemia and chronic myeloid leukemia
  - PF-04449913-treated medulloblastoma allografts had reduced levels of GLI1 gene expression and downregulation of genes linked to the Hh signaling pathway

Papayannidis, C., Cancer Research: April 15, 2012; Volume 72, Issue 8, Supplement 1
Mechanism of Action

- The Hedgehog pathway is expressed in all 3 germ layers throughout embryogenesis
- The Hedgehog pathway is repressed in adult tissues but, if aberrantly reactivated, can induce neoplasia
- Soluble Hh binds PTCH1 to release SMO and activate GLI signaling
- Inappropriate SMO signaling is implicated in multiple human malignancies
- The Hedgehog pathway regulates cancer stem cell maintenance and activity

# Stage of Development

<table>
<thead>
<tr>
<th>Disease</th>
<th>Stage</th>
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</thead>
<tbody>
<tr>
<td>Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)</td>
<td>Phase 2 *</td>
</tr>
<tr>
<td>Myelofibrosis</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Myelodysplastic Syndrome (MDS)</td>
<td>Phase 1b/2 Combination</td>
</tr>
</tbody>
</table>

* Closed to enrollment

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**Glasdegib**
Smoothened (SMO) Inhibitor

**Overview**

**Mechanism of Action**

Glasdegib is an investigational compound

Pfizer Oncology Development.com

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Lorlatinib
ALK/ROS1 Inhibitor

Lorlatinib is an investigational compound
Overview

- A variety of human malignancies have anaplastic lymphoma kinase (ALK) translocations, amplifications, or oncogenic mutations, including non-small cell lung cancer (NSCLC), anaplastic large cell lymphoma, inflammatory myofibroblastic tumors, and neuroblastoma.
- ROS1 is a receptor tyrosine kinase (RTK) implicated in tumor progression, and the first oncogenic fusion of ROS1 (FIG-ROS1) was discovered in glioblastoma.
  - Elevated ROS expression has also been observed in cholangiocarcinoma, NSCLC, and breast cancer.
- PF-06463922 is an ATP-competitive small molecule inhibitor of both ALK and ROS1, created through structure-based drug design (SBDD), with specific considerations such as a low efflux in cell lines overexpressing P-glycoprotein and breast cancer resistance protein, providing blood-brain barrier and cell penetration properties.
- PF-06463922 shows antitumor activity in preclinical models which harbor the resistant mutations ALK-G1202R and ROS1-G2032R.
- Single-dose preclinical rat in vivo studies of PF-06463922 showed oral bioavailability and CNS availability, with brain levels approximately 30% of that in the plasma.

References:
Lorlatinib
ALK/ROS1 Inhibitor

Rationale for a Cancer Target

Overview

Stage of Development

Mechanism of Action

Stage of Development

ALK+ Non-Small Cell Lung Cancer (NSCLC)  Phase 3

ALK+/ROS1+ Non-Small Cell Lung Cancer (NSCLC)  Phase 2 *

NOVEMBER 2017  NPU00667_25c

Lorlatinib is an investigational compound

PfizerOncologyDevelopment.com


* Closed to enrollment
Palbociclib
CDK 4/6 Inhibitor
Overview

- Cyclin-dependent kinases (CDKs) are small serine/threonine kinases that play a key role in regulating cell cycle progression and to a large degree govern cellular transitions from growth phases (G1 and G2) into phases associated with DNA replication (S) and mitosis (M).

- Progression through the G1-S phase requires phosphorylation of the retinoblastoma (Rb) protein by CDK4 or CDK6 in complex with their activating subunits, the D-type cyclins.
  - Components of this pathway, particularly cyclin D1 and Rb, are frequently altered in sporadic human cancers to promote deregulated cellular proliferation.

- Palbociclib is an orally active inhibitor of CDK4 and CDK6 kinases. Inhibition results in decreased phosphorylation of the CDK4/6 target retinoblastoma protein.
  - Blocking Rb phosphorylation prevents cell cycle progression in sensitive cell lines.

- Palbociclib has been shown, in vitro, to induce growth arrest in the G1 phase of the cell cycle in multiple Rb+ tumor cell line models. Palbociclib causes a specific cell cycle arrest in G1 phase and inhibits proliferation in cultured and xenografted leukemia, myeloma, breast cancer, colon cancer, and lung cancer cells.

Palbociclib is being investigated as a single agent or in combination with other agent(s) in the following tumor types. Palbociclib is not approved for the uses listed below.

- **HR+/HER2- Adjuvant Breast Cancer**: Phase 3: Combination*
- **HR+/HER2 normal Adjuvant Breast Cancer**: Phase 3: Combination**
- **HR+/HER2- Metastatic Breast Cancer**: Phase 3: Combination†
- **HR+/HER2+ Metastatic Breast Cancer**: Phase 3: Combination◊

* Sponsored by Alliance Foundation Trials, LLC.
Sponsored for Stage II or III breast cancer patients

** Sponsored by German Breast Group.
For high risk breast cancer patients. No longer screening

† Sponsored by Spanish Breast Cancer Group

◊ Sponsored by Alliance Foundation Trials, LLC.

Stage of Development

Palbociclib is being investigated as a single agent or in combination with other agent(s) in the following tumor types. Palbociclib is not approved for the uses listed below.

<table>
<thead>
<tr>
<th>Recurrent/Metastatic Squamous Cell Carcinoma of the Head &amp; Neck (SCCHN)</th>
<th>Phase 2: Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic Pancreatic Ductal Adenocarcinoma (PDAC)</td>
<td>Phase 1: Combination</td>
</tr>
<tr>
<td>Relapsed/Refractory Mantle Cell Lymphoma</td>
<td>Phase 1: Combination*</td>
</tr>
</tbody>
</table>

* Sponsored by National Cancer Institute (NCI). Closed to enrollment

Sunitinib
Multiple RTK Inhibitor
Overview

- Tyrosine kinases are enzymes which phosphorylate tyrosine residue on targeted proteins. They stimulate cellular pathways involved in such functions as growth, proliferation, migration, synthesis, and apoptosis.
- Sunitinib is an orally administered small molecule that inhibits multiple receptor tyrosine kinases (RTKs), some of which are implicated in tumor growth, pathologic angiogenesis, and metastatic progression of cancer.
- Sunitinib was identified as an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2, and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony-stimulating factor receptor Type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET).
- Sunitinib inhibition of the activity of these RTKs has been demonstrated in biochemical and cellular assays, and inhibition of function has been demonstrated in cell proliferation assays.

Stage of Development

Sunitinib is being investigated as a single agent in the following tumor type. Sunitinib is not approved for the use listed below.

| Pediatric Advanced Gastrointestinal Stromal Tumor (GIST) | Phase 2 * |

* Closed to enrollment

Talazoparib
PARP Inhibitor

Talazoparib is an investigational compound
Overview

• Poly (ADP-ribose) polymerase (PARP) enzymes are associated with DNA repair, specifically base excision repair, a key pathway in the repair of DNA single-strand breaks (SSB). They are thought to play a role in repair of damaged DNA and in stabilization of the genome

• Talazoparib is a dual inhibitor of the nuclear enzyme PARP with potential antineoplastic activity
  • Talazoparib is designed to inhibit PARP and trap PARP on DNA, with the goal of preventing PARP-mediated DNA damage repair thereby inducing tumor cell death in BRCA1/2-mutated tumor cells

• Talazoparib selectively binds to PARP and is thought to prevent PARP mediated DNA repair of single strand DNA breaks via the base-excision repair pathway
  • This enhances the accumulation of DNA strand breaks, promotes genomic instability and eventually leads to apoptosis. PARP catalyzes post-translational ADP-ribosylation of nuclear proteins that signal and recruit other proteins to repair damaged DNA and is activated by single-strand DNA breaks

Wainberg et al. AACR 2016 Abstract CT011.
Medivation Brochure CTSITE-MULTI-TALA-0001 03/16
Possible dual cytotoxic mechanisms of PARP inhibitors:

1: Catalytic inhibition (upper pathway) is thought to interfere with the repair of SSBs, leading to replication fork damage that requires homologous recombination (HR) repair

2: Trapping of PARP-DNA complexes may also lead to replication fork damage but utilizes additional repair pathways including Fanconi pathway (FA), template switching (TS), ATM, FEN1 (replicative flap endonuclease) and polymerase β.

Figure adapted from Cancer Res. 2012. 72:5588-5599. Murai J et al. Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors, with permission from AACR.
Talazoparib is an investigational compound*

**Rationale for a Cancer Target**

**Overview**

**Mechanism of Action**

**Stage of Development**

<table>
<thead>
<tr>
<th>Locally Advanced or Metastatic Breast Cancer with Germline BRCA mutations</th>
<th>Phase 3 *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic Castration-Resistant Prostate Cancer (MCRPC)</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Locally Advanced or Metastatic Solid Tumors</td>
<td>Phase 1b Combination</td>
</tr>
</tbody>
</table>

* Closed to enrollment