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A novel, highly selective inhibitor of cyclin-dependent kinases 2, 7 and 9; in clinical development for Hereditary Breast and Ovarian Cancer, Cushing’s Disease and rheumatoid arthritis.

A Targeted Cell Cycle Inhibitor

Seliciclib is a novel, orally-available inhibitor of CDK2/E, CDK2/A, CDK7 and CDK9 - enzymes that are central to the process of cell division and cell cycle control and play pivotal roles in cancer cell growth and DNA damage repair. Inhibition of CDKs 2 and 9 may also correct aberrant cell cycle control in certain non-malignant diseases of proliferation. Seliciclib exerts an anti-proliferative effect via several key mechanisms:

- selective downregulation of proliferative and survival proteins and upregulation of p53, leading to growth arrest or apoptosis;
- decreasing phosphorylation of Rb and modulating E2F transcriptional activity leading to growth arrest or apoptosis;
- inhibiting HR and NHEJ DNA repair pathways, resulting in synergy with DNA damaging agents; and
- in sequence with chemotherapy, overcoming cell cycle related drug resistance.

Seliciclib has been evaluated in 16 clinical trials and administered to over 450 subjects including healthy volunteers. It is sparing to the bone marrow as observations of myelosuppression are rare. Major toxicities attributed to seliciclib include nausea, vomiting, fatigue, hypokalemia and liver enzyme elevation.

**BRCA mutated solid tumors:** Breast cancer susceptibility proteins BRCA1 and BRCA2 are tumor suppressors that ensure DNA stability and prevent uncontrolled cell growth in normal cells. BRCA gene mutations are common in Hereditary Breast and Ovarian Cancer (HBOC), but other defects, including suppression of BRCA1/2 expression by promoter hypermethylation, can produce DNA homologous recombination repair (HR) defects in these and other tumors, including NSCLC and AML. Around 50% of high grade serous ovarian cancers are reported to be HR-defective.

CDK2 and CDK9 have been shown to participate in DNA repair and to be a therapeutic target in BRCA-deficient cancers through inhibition of DNA repair pathway activity and reduction of DNA repair pathway protein expression. CDK inhibitor potentiation of DNA damaging agents is being explored in an all oral, two drug combination trial of seliciclib and sapacitabine.

Phase 1 enrolment is ongoing in patients with advanced solid tumors and gBRCA mutations.

At the MTD for sequential administration four patients with BRCA-deficient, breast, ovarian and pancreatic cancers achieved confirmed partial responses with promising durability, with the longest lasting more than 78 weeks. Stable disease of 12 weeks or more was observed in eight additional patients, including two with BRCA-deficient ovarian and breast cancers, lasting 64 weeks and 21 weeks respectively. Pharmacodynamic effects observed in skin biopsies demonstrated that seliciclib increased DNA damage induced by sapacitabine.

**Cushing’s Disease (CD):** A rare endocrine disorder in which a small tumor in the pituitary gland causes endogenous hypercortisolism predisposing patients to central obesity, diabetes, hypertension and osteoporosis. It also substantially increases risk of infection, thrombosis and psychiatric disorders. If inadequately controlled, CD is fatal, with an increased mortality rate that is 4 fold higher than controls and a median survival of 4.6 years.

Cell cycle dysregulation is strongly implicated in pituitary tumorigenesis, overexpression of cyclins, particularly cyclin E. Dysregulation of endogenous CDK inhibitors is frequently encountered. In CD models, seliciclib inhibited growth of mouse corticotroph adenomas. Seliciclib is being evaluated in a Phase 2, Investigator-Sponsored Trial funded by the US National Institutes of Health (NIH) to determine if the drug can safely normalize urinary free cortisol levels by reducing pituitary corticotroph tumor ACTH production in patients with CD.

**Rheumatoid Arthritis (RA):** Over the past 20 years, improved treatment strategies and better drugs have improved outcomes for RA patients. Currently available disease-modifying antirheumatic drugs (DMARDs) slow or halt disease progress by reducing joint inflammation or neutralizing immune cells. However, many patients do not recover and about one in ten do not respond at all to conventional treatments. Scientists believe that fibroblasts may be responsible and may be limiting response to conventional treatments. In RA these cells divide uncontrollably and produce chemicals that eat into cartilage and bone and cause inflammation. RA synovial fibroblasts (RA SF) are hyper-proliferative, in part due to decreased expression of p21, which is involved in cell cycle control, and overexpression of Mci-1, which blocks apoptotic cell death. CDK inhibitors, including seliciclib, have shown efficacy in arthritis models by mimicking cell cycle-dependent and -independent effects of p21 expression, and decreasing Mci-1 levels.

Seliciclib is being evaluated in RA patients in a Phase 1/2, Investigator-Sponsored Trial entitled “Targeting the RA synovial fibroblast via cyclin dependent kinase inhibition - a phase ib/lla study (TRAFIC)”. The trial uses a two stage design evaluating the safety and efficacy of seliciclib in participants who have active RA despite treatment with anti-TNF monotherapy. The trial is being conducted in the UK with funding from the UK Medical Research Council.

Seliciclib has shown clinical benefit as a single agent in Phase 1 and 2 clinical studies in Nasopharyngeal Cancer (NPC) and Non-Small Cell Lung Cancer (NSCLC). Interim Phase 2 data showed that 7 of 10 previously-treated NPC patients had stable disease with two staying on treatment for over 8 and one for over 24 months. In a Phase 1 NPC study significant transcriptional down-regulation of genes related to cellular proliferation and survival were shown in some patients post treatment. Tophline results from a double-blinded, randomized Phase 2b study in patients with at least two prior treatments for NSCLC showed no difference in progression free survival (PFS) but an increase in median overall survival favoring seliciclib over placebo.

**Seliciclib is being investigated in the following clinical trials:**

- **combination with sapacitabine in gBRCA mutated tumors**  
  Phase 1

- **Investigator-sponsored trial - Cushing’s disease**  
  Phase 2

- **Investigator-sponsored trial - rheumatoid arthritis**  
  Phase 1/2

**Completed clinical trials with seliciclib:**

- **nasopharyngeal cancer (NPC)**  
  Phase 2

- **non-small cell lung cancer (NSCLC)**  
  Phase 2

- **solid tumors**  
  Phase 1

- **hematological malignancies**  
  Phase 2

- **combination studies**  
  Phase 2

* Oncology only. Phase 1 clinical trials of seliciclib in healthy volunteers and in patients with IgA nephropathy have also been completed.*
The Function of Cyclin Dependent Kinases

The cell cycle is comprised of a series of events culminating in cell growth and division. Cell cycle check points are used to detect flaws in cell DNA that lead to cell proliferation in diseases such as cancer. CDKs regulate and drive cell cycle progression. Cancer cells frequently have deregulated CDK activity and in such cases selective CDK inhibition can cause cell cycle arrest and force cells into apoptotic cell death. CDKs were first thought to be regulators of the cell cycle, but are now understood to include proteins with pivotal functions in the control of proliferation such as the regulation of transcription and DNA repair. The precise selectivity of an individual CDK inhibitor molecule for certain preferred CDKs is key to targeting particular tumor types and avoiding undesirable side effects through non-specific antiproliferative activity.

Mechanism of Action

Different CDKs are responsible for control of different aspects of proliferation, and when dysregulated can be drivers of particular cancer sub-sets. Seliciclib selectively inhibits:

- CDK2, which drives cell cycle transition and activates major DNA double-strand break repair pathways;
- CDK7 and CDK9, which regulate transcription of genes (incl. cyclins, MCL-1, etc.) through phosphorylation of RNA polymerase II.

These characteristics support data showing that seliciclib is synergistic in combination with targeted signal transduction inhibiting agents, such as HDAC inhibitors and EGFR inhibitors. In preclinical and clinical studies, seliciclib has also shown synergy in combination with chemotherapies, such as gemcitabine, platinum and taxanes, which inhibit adjacent or sequential phases of the cell cycle.

During tumorigenesis, negative and positive cellular regulators of CDKs are inactivated or overexpressed. Consistent with its mechanism of action, seliciclib treatment delayed lung tumor development in mice with tumors which were overexpressing cyclin E. Seliciclib was effective in killing lung cancer cells through anaphase catastrophe. Among 52 cell lines of NSCLC origin tested, 2 (4%) were insensitive to seliciclib, 21 (40%) were modestly sensitive and 29 (56%) markedly sensitive. Of 13 lung cancer cell lines with the highest sensitivity, 12 (92%) had Ras-activating mutations, including KRAS and NRAS. None of the 15 least sensitive cell lines had Ras-activating mutations. Overexpression of full length and truncated cyclin E could be a marker for sensitivity to CDK2 inhibitors in drug resistant tumors.

Seliciclib has also been shown to synergize in combination with chemotherapies, such as gemcitabine, platinum and taxanes, which inhibit adjacent or sequential phases of the cell cycle.

Clinical Results to Date

Nasopharyngeal cancer (NPC) is associated with deregulated CDK activity and infection with Epstein-Barr virus. In the lead-in portion of a randomized Phase 2 study, 23 patients with advanced solid tumors including 10 with NPC were randomized between 400 mg twice a day or 800 mg once a day for 4 days per week. 7 out of 10 NPC patients had stable disease with 2 lasting over 8 months and one over 2 years. The observation of prolonged stable disease suggests that seliciclib inhibits tumor growth in patients with previously-treated NPC.

NSCLC remains a very challenging disease and is ultimately fatal after failure of the three available lines of treatment. The APPRAISE, double-blinded, randomized discontinuation Phase 2b study compared single agent seliciclib vs. best supportive care (BSC) in patients with advanced NSCLC as a third, fourth or fifth line treatment. 187 patients were given three 2-week cycles of seliciclib, following which 53 patients with stable disease were randomized to seliciclib treatment or placebo with BSC.

Topline unblinded results showed no difference in progression free survival (PFS) but an increase in median overall survival favoring the seliciclib arm over placebo (388 vs. 213 days respectively). Cyclacel collected and analyzed biopsy samples from APPRAISE for K-Ras mutational status, cyclin D1 and cyclin E1 protein levels to test correlation with tumor sensitivity to seliciclib. As only 30 patient samples were retrospectively available, a meaningful correlation could not be drawn.

In Phase 1 dose escalating trials, 77 patients with various solid tumors who had failed multiple regimens were treated with seliciclib. One patient with liver cancer had a partial response that lasted 7.5 months at a dose of 800 mg twice daily. Ten patients had stable disease that lasted at least 4 months. Notably, two patients with advanced NSCLC who had failed prior regimens had stable disease that lasted for 14 and 18 months respectively.

Results from two previously reported Phase 2 studies of seliciclib in combination with either gemcitabine/cisplatin or docetaxel in 52 patients with NSCLC showed that nine patients treated with seliciclib/gemcitabine/cisplatin exhibited partial response and 21 stable disease. Two patients treated with seliciclib/docetaxel had a partial response and 1 stable disease.

Endnotes:


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