SELICICLIB

Summer 2016

A highly selective inhibitor of cyclin-dependent kinases 2, 7 and 9; in clinical development for hereditary breast and ovarian cancers, Cushing's Disease and rheumatoid arthritis.

A Targeted Cell Cycle Inhibitor

Seliciclib[1] is a novel, orally-available inhibitor of CDK2, 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. CDK2/9 inhibition may also correct aberrant cell cycle control in certain non-malignant diseases of proliferation. Seliciclib exerts an anti-proliferative effect via the following 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 cancers, 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.

Seliciclib is being investigated in the following clinical trials:

BRCA mutated tumors (*sapacitabine combination*)	**Phase 1**
Cushing's Disease	**Phase 2**
Rheumatoid Arthritis	**Phase 1/2**
Cystic Fibrosis	**Phase 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. A Phase 1 clinical trial of seliciclib in healthy volunteers and patients with IgA nephropathy has been completed.*

CDK2/9 have been shown to participate in DNA repair and are therapeutic targets in BRCA-deficient cancers through inhibition of DNA repair pathway activity and reduction of BRCA protein expression. CDK inhibitor potentiation of DNA damaging agents is being explored in a Phase 1/2, all-oral combination of seliciclib and sapacitabine. Data were presented at an oral presentation at the 2016 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago.[2] The regimen was administered as sequential (Part 1) or concomitant (Part 2) treatment to 67 heavily-pretreated patients. Antitumor activity was demonstrated in a subgroup of 45 patients with breast, ovarian and pancreatic cancers who tested positive for BRCA mutations (44 germline and 1 sporadic) with a 35.6% disease control rate (1 CR, 5 PR and 10 SD). Treatment durations in responders ranged between 16 and over 240 weeks. No CR or PR was observed in BRCA negative patients. Pharmacodynamic effects observed in skin biopsies demonstrated that seliciclib increased DNA damage induced by sapacitabine. Based on the data from the Phase 1/2 study, an expansion cohort has been initiated in an enriched population of BRCA positive patients with breast cancer.

Clinical Activity in other Solid Tumors

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.[3] In a Phase 1 NPC study transcriptional downregulation of genes related to cellular proliferation and survival were shown in certain patients post treatment.

Despite recent immuno-oncology advances NSCLC remains challenging and is ultimately fatal after failure of 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. 218 days respectively).[4]

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 four prior regimens had stable disease that lasted for 14 and 18 months respectively.[5]

Results from 2 previously reported Phase 2 studies of seliciclib in combination with either gemcitabine/cisplatin or docetaxel in 52 patients with NSCLC showed that 9 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.[6]

Clinical Activity in Non-Malignant Proliferative Diseases

Cushing's Disease (CD) is 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, and dysregulation of endogenous CDK inhibitors is frequently encountered. In CD models, seliciclib inhibited growth of mouse corticotroph adenomas.[7] Seliciclib is being evaluated in a Phase 2, Investigator-Sponsored Trial (IST) 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, as they divide uncontrollably and produce chemicals that eat into cartilage and bone and cause inflammation. RA synovial fibroblasts are hyper-proliferative, in part due to decreased expression of p21, which is involved in cell cycle control, and overexpression of MCL-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 MCL-1 levels.[8,9]

Seliciclib is being evaluated in RA patients in a Phase 1/2 IST entitled "Targeting the RA synovial fibroblast via cyclin dependent kinase inhibition" (TRAFIC). TRAFIC uses a 2-stage design evaluating 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.

Cystic Fibrosis (CF): Cystic Fibrosis is a life-threatening inherited genetic disease that primarily affects the lungs and digestive system. Patients with CF suffer from extensive inflammatory and chronic infectious injury to the lung airway. It was recently recognized that immune system defects, and in particular macrophage function, play a key role in disease initiation. It has been discovered that seliciclib may have "corrector" activity in the most prevalent CF mutation, F508del[10], anti-inflammatory properties which may also help reduce inflammatory injury in patients with CF [8,11] and may help restore the defective bactericidal activity of macrophages in CF.[12] Under a collaboration, licensing and supply agreement between Cyclacel and Manros Therapeutics, seliciclib is being evaluated in a Phase 2 tolerability and efficacy clinical study of adult patients with cystic fibrosis.

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.

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These characteristics support data showing that seliciclib is synergistic in combination with targeted signal transduction inhibiting agents, such as HDAC inhibitors and EGFR inhibitors.[13] In preclinical and clinical studies, seliciclib has also shown synergy in combination with chemotherapies, such as gemcitabine, platinums 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.[14] Consistent with its mechanism of action, seliciclib treatment delayed lung tumor development in mice with tumors which were overexpressing cyclin E.[15] 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.[15] Overexpression of full length and truncated cyclin E could be a marker for sensitivity to CDK2 inhibitors in drug resistant tumors. Correlation of cyclin E expression with resistance to trastuzumab and letrozole, and resulting increased sensitivity to seliciclib or its more potent derivative, CYC065, has been shown in breast cancer *in vitro* and *in vivo*.[16,17,18]

Endnotes:

1. *An experimental drug under clinical investigation. Not approved for human use.*
2. *Tolaney, S, et al,J Clin Oncol 34, 2016 (suppl; abstr 2503).*
3. *Yeo, et al, 2009 J Clin Oncol 27-15s (Suppl abstr 6026) and Cyclacel data on file.*
4. *Cyclacel Press Release December 21, 2010.*
5. *Faivre, et al, 2003 Clin Cancer Res 2003, 9 Suppl Abs. A154.*
6. *Siegel-Lakhai, et al, 2005 ASCO Proceedings, Abs. 2060 and Cyclacel data on file.*
7. *Liu, et al, 2011 PNAS 108 8414*
8. *Rossi et al. 2006 Nat. Med. 12:1056*
9. *Sekine, et al, 2008 J. Immunol. 180:1954*
10. *Norez et al 2014 BJP 171 4849*
11. *Moriceau et al 2010 J. Innate Immunity 2:260*
12. *Riazanski et al 2015 PNAS 112:E6486*
13. *Fleming, et al, 2008 Clin Cancer Res 14 4326.*
14. *Ma, et al, 2007 PNAS 104 4089.*
15. *Galimberti, et al, 2010 Clin Cancer Res 16 1 109-20.*
16. *Scaltriti, et al, 2011 PNAS 108:3761.*
17. *Akli, et al, 2010 Clin Cancer Res 16:1179.*
18. *Akli, et al, 2011 Cancer Res 71:3377.*

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