

# SELICICLIB

Fall 2011

**A novel, orally available, CDK (cyclin-dependent kinase) inhibitor with efficacy in lung cancer & development potential in breast cancer sub-groups.**

### A Targeted Cell Cycle Inhibitor

Seliciclib<sup>1</sup> is a novel, orally-available inhibitor of CDK2/E, CDK2/A, CDK7 and CDK9 (in declining order of potency)–enzyme complexes that are central to the process of cell division and cell cycle control. In breast and lung tumors overexpression of cyclin E is associated with poor prognosis and drug resistance. Resistant breast and lung tumor cell lines overexpressing cyclin E are resensitized to apoptotic cell killing by seliciclib. NSCLC cell lines with Ras-activating mutations, such as KRAS and NRAS, have been found to be sensitive to seliciclib-induced apoptosis.

Seliciclib has shown clinical benefit as a single agent in Phase 1 and 2 clinical studies in Non-Small Cell Lung Cancer (NSCLC) and Nasopharyngeal Cancer (NPC). Topline 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 the seliciclib arm over placebo (388 vs. 218 days respectively). 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.<sup>2</sup>

Seliciclib has been evaluated in 16 clinical trials and administered to over 450 subjects. 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.

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

- non-small cell lung cancer (NSCLC) **Phase 2**
- nasopharyngeal cancer (NPC) **Phase 2**
- combination with sapacitabine nucleoside analogue **Phase 1**

#### Seliciclib completed clinical trials:\*

- solid tumors (n=103) **Phase 1**
- hematological malignancies (n=38) **Phase 2**
- combination studies (n=70) **Phase 2**

\* Oncology only. Seliciclib has also completed a Phase 1 clinical trial in a proliferative disease indication outside oncology.

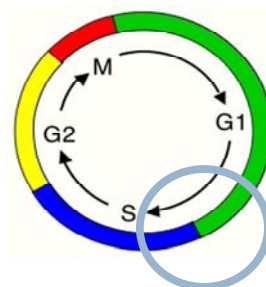
### The Cell Cycle

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. CDK inhibition causes cell cycle arrest, forcing cells into apoptotic cell death.

### Mechanism of Action

Different CDKs are responsible for each critical transition. Seliciclib selectively inhibits two CDKs driving cell cycle transitions and two CDKs involved in transcription of genes (cyclins, MCL-1 etc.)

associated with cancer cell progression or resistance. These characteristics support data showing that seliciclib is synergistic in combination with targeted signal transduction inhibiting agents, such as HDAC inhibitors and EGFR inhibitors.<sup>3</sup>



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.<sup>4,5</sup>

Consistent with its mechanism of action, seliciclib treatment delayed lung tumor development in mice with tumors which were over-expressing cyclin E.<sup>6</sup> 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.<sup>6</sup> Overexpression of full length and truncated cyclin E could be a marker for sensitivity to CDK2 inhibitors in drug resistant tumors. Correlation 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*.<sup>7,8,9,10</sup>

### Clinical Results to Date

NSCLC remains a very challenging disease and is ultimately fatal after failure of the three available lines of treatment.

187 patients were enrolled in the APPRAISE, double-blinded, randomized discontinuation Phase 2b study comparing single agent seliciclib vs. best supportive care (BSC) in patients with advanced NSCLC as a third, fourth or fifth line treatment. The study's main objective is to learn the anti-tumor activity of seliciclib as a single agent in refractory NSCLC and determine further development strategies. 187 patients were given three 2-week cycles of seliciclib, following which 53 patients achieving stable disease were randomized to receive continued seliciclib treatment or placebo with best supportive care.

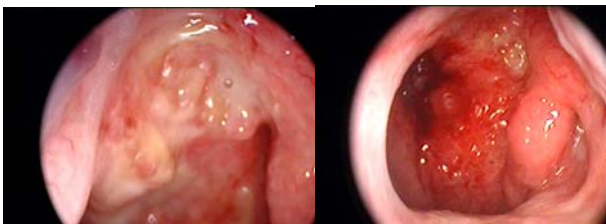
Topline unblinded results, showed no difference in progression free survival (PFS) but an increase in median overall survival favoring the seliciclib arm over the placebo arm (388 versus 218 days respectively).<sup>14</sup> Of the randomized patients, 85% received 3 or more prior therapies and 85% also previously received at least one EGFR inhibitor. 14 patients were crossed-over to the seliciclib arm whose cancer progressed after randomization to placebo. Seliciclib was determined to be safe at the recommended dose.

Cyclacel is collecting and analyzing biopsy samples from APPRAISE. Investigating a correlation between clinical outcomes and Ras mutation status as well as other biomarkers may provide a rationale to select patients for targeted treatment with seliciclib.



Nasopharyngeal cancer (NPC) is associated with deregulated CDK activity and possibly infection with the Epstein-Barr virus.

Interim results from the lead-in portion of a randomized Phase 2 study were reported at ASCO 2009. 23 previously-treated patients with NPC were randomized between 400 mg twice a day or 800 mg once a day both for four days per week. Seven out of ten NPC patients had stable disease with two 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.<sup>2</sup>



Images courtesy of Dr. BC Goh, National University Hospital.

*This document contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995 about financial results and estimates, business strategy, clinical trial plans and research and development programs of Cyclacel Pharmaceuticals, Inc. By their nature, forward-looking statements and forecasts involve risks and uncertainties because they relate to events and depend on circumstances that will occur in the future. A number of factors could cause actual results and developments to differ materially and are discussed under "Risk Factors" in the Annual Report on Form 10-K for the year ended December 31, 2010, as supplemented by the interim quarterly reports, filed with the SEC. The information in this presentation is current as of this date. Cyclacel does not take any responsibility to update such information.*

In an investigator-sponsored Phase 1 study in untreated patients with NPC, seliciclib had antitumor activity (decrease in size of primary tumor size and involved lymph nodes and increase in tumor cell death). Endoscopic images from a patient in this study before (left) and after (right) treatment with seliciclib are shown below.<sup>11</sup>

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.<sup>12</sup>

### Combinations

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.<sup>13</sup>

Phase 1 enrolment is ongoing in patients with advanced solid tumors who are receiving treatment with a combination of seliciclib and sapacitabine, Cyclacel's orally-available nucleoside analogue.

### Endnotes:

1. An experimental drug under clinical investigation. Not approved for human use.
2. Yeo, et al, 2009 J Clin Oncol 27-15s (Suppl abstr 6026) and Cyclacel data on file.
3. Fleming, I. et al, 2008 Clin Cancer Res 14 4326.
4. Akli S. et al, 2007 Cancer Res 67 7212.
5. Ma Y. et al, 2007 PNAS 104 4089.
6. Galimberti et al 2010 Clin Cancer Res 16 1 109-20.
7. Scaltriti et al., AACR 2010
8. Scaltriti M., et. al., 2011. PNAS 108:3761
9. Akli et al., 2010. Clin. Cancer Res. 16:1179
10. Akli et al., 2011. Cancer Res. 71:3377
11. Hsieh, W-S. et al, 2009 Clin Cancer Res 15 1435.
12. Faivre, S. et al, 2003 Clin Cancer Res 2003, 9 (16; Suppl.), Abs. A154.
13. Siegel-Lakhai, W. et al, 2005 ASCO Proceedings, Abs. 2060 and Cyclacel data on file.
14. Cyclacel Press Release December 21, 2010.

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