

ASX Release

## First Cohort Successfully Completed in PTX-200 Phase 1b/2 AML Trial

- No dose limiting toxicities - determined safe and tolerable at 25 mg/m<sup>2</sup>
- Next cohort at 35 mg/m<sup>2</sup> now open for enrollment

**Melbourne, Australia - (8 March, 2017):** Clinical-stage oncology company Prescient Therapeutics Ltd (ASX: PTX) announces that it has successfully completed the first cohort in its Phase 1b clinical trial of PTX-200 plus cytarabine in refractory or relapsed acute leukemias, namely acute myeloid leukemia (AML).

The first cohort treated three patients with relapsed or refractory AML using a dose of 25mg/m<sup>2</sup> of PTX-200 given as a one hour intravenous infusion on days 1, 8 and 15; in combination with 400mg/m<sup>2</sup> of cytarabine as continuous infusion on days 2 – 6 of each 21 day cycle.

The dose was found to be safe, with no dose limiting toxicities.

The trial's Principal Investigator, Professor Jeffrey Lancet, M.D., said "the trial is proceeding well to date, with no significant safety issues, along with some early signals of efficacy. We're looking forward to the next stage of dose escalation."

The trial now proceeds to the next dose level, being 35 mg/m<sup>2</sup> PTX-200. This second cohort is now open for enrollment.

### ENDS

#### About AML

AML is a form of cancer that affects the blood and bone marrow, resulting in the overproduction of immature white blood cells, preventing the sufferer from producing normal blood cells and therefore rendering them unable to fight infections, to prevent bleeding and may become anemic. AML remains a largely incurable illness, with 5 year survival rates of less than 30%.<sup>1</sup>

AML is the most common acute leukemia in adults, with an estimated 20,830 new cases diagnosed and an estimated 10,460 deaths in the US alone in 2015.<sup>2</sup> The projected number of new cases for 2015 increased by 7,000 (i.e. over 50%) from that in 2013.<sup>2,3</sup>

For relapsed AML, in general, remission rates are low (especially if the initial complete response (CR) duration is less than 1 year), remission duration is short (generally on the order of 3-6 months), and overall survival is less than 1 year.<sup>4</sup> Older individuals (>60 years) experience both inferior CR and survival rates following initial therapy.<sup>5,6</sup> Hence, newer, effective therapies are greatly needed for both older patients as well as those with relapsed or refractory disease. This is precisely the area that PTX-200 is targeting.

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## About PTX-200

PTX-200 is a novel and selective Akt activation inhibitor. It is both anti-proliferative and pro-apoptotic.

Most Akt inhibitors seek to work by mimicking ATP, a molecule used by all kinases in the cells, and therefore off target effects are likely to result in toxicities.

By contrast, the mechanism by which PTX-200 inactivates Akt is not by inhibiting its kinase, but rather by binding to the PH domain of Akt and preventing its binding to the plasma membrane where it must be localized to be phosphorylated and activated.<sup>7</sup> Therefore, by preventing Akt binding to the plasma membrane, PTX-200 inhibits Akt, but without the off-target toxic effects of typical kinase inhibitors.

Hyperactive Akt is a prominent feature of many human cancers and is correlated with resistance to chemotherapy.

## Rationale for Combined Therapy with PTX-200 and Cytarabine in AML

Signal transduction pathways play an important role in the homeostasis, growth, and survival of cells. One such signal transduction pathway, comprises the lipid kinase, phosphatidylinositol 3-kinase (PI3K), and the protein serine/threonine kinase, Akt. Persistent hyper-activation of the PI3K/Akt axis occurs frequently in human cancers, causing uncontrolled cell growth, survival, invasion and metastasis, and serving as an important mode of neoplastic propagation and resistance to cytotoxic therapies. As such, this pathway is an attractive target for the development of novel therapeutic strategies in many different malignancies.

In the setting of hematologic malignancies, particularly AML, the PI3K/Akt signaling pathway appears to be critical for cell survival. Several investigators have demonstrated that this pathway is hyper-activated in AML from cell lines and fresh biopsies.<sup>8-10</sup> In addition, the persistent activation status of this pathway positively affects leukemic cell survival and inhibition of this pathway including the use of PI3K inhibitors induces apoptosis.<sup>8,11</sup> The hyper activation of this pathway (high phosphor-Akt levels at baseline) is associated with poor overall survival of AML patients.<sup>10</sup>

Another intriguing aspect of the PI3K/Akt pathway is its potential role as a mediator of resistance to cytotoxic chemotherapy in many cancers, including AML. In primary patient AML cells and cell lines, it has been demonstrated that Akt activation is protective against chemotherapeutic agents, including cytarabine and etoposide.<sup>8</sup> When added to chemotherapeutic compounds, pharmacologic inhibitors of the PI3K/Akt pathway have been shown to synergize with chemotherapy in eliciting apoptosis within leukemic cells, suggesting the importance of this pathway in mediating chemotherapy resistance in AML.<sup>8,12,13</sup> Mechanistically, the importance of the PI3K/Akt pathway in chemotherapy resistance is becoming better understood. In AML, the cytoprotective effect induced by leukemic adherence appears to be mediated by PI3K/Akt activation, such that by pharmacologically inhibiting PI3K, the protective effect from adherence is abrogated.<sup>14</sup> Other recent evidence has also highlighted the importance of PI3K/Akt for the upregulation of multidrug resistance-associated protein 1, an important multidrug resistance modulator.<sup>15</sup> Taken together, these findings suggest a potential role for combining cytotoxic chemotherapy with pharmacologic inhibitors of PI3K/Akt in AML.

## About Prescient Therapeutics Limited (PTX)

PTX is a clinical stage oncology company developing novel compounds that show promise as potential new therapies to treat a range of cancers that have become resistant to front line chemotherapy.

PTX's lead drug candidate PTX-200 inhibits an important tumor survival pathway known as Akt, which plays a key role in the development of many cancers, including breast and ovarian cancer, as well as leukemia. Unlike other drug candidates that target Akt inhibition which are non-specific kinase inhibitors that have toxicity problems, PTX-200 has a novel mechanism of action that specifically inhibits Akt whilst being comparatively safer. This highly promising compound is now the focus of three current clinical trials. The first is a Phase 1b/2 trial evaluating PTX-200 as a new therapy for relapse and refractory Acute

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Myeloid Leukemia, being conducted at Florida's H. Lee Moffitt Cancer Center (Moffitt) and Yale Cancer Center in New Haven, Connecticut (Yale) under the leadership of Professor Jeffrey Lancet, MD.

PTX is also conducting a Phase 1b/2 study examining PTX-200 in breast cancer patients at the prestigious Montefiore Cancer Center in New York and the Moffitt. The third trial is a Phase 1b/2 trial of PTX-200 in combination with current standard of care is also underway in patients with recurrent or persistent platinum resistant ovarian cancer at the Moffitt.

PTX's second novel drug candidate, PTX-100, is a first in class compound with the ability to block an important cancer growth enzyme known as geranylgeranyl transferase (GGT). It also blocks the Ral and Rho circuits in cancer cells which act as key oncogenic survival pathways, leading to apoptosis (death) of cancer cells. PTX-100 was well tolerated and achieved stable disease in a Phase I trial in advanced solid tumors.

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