ASX Release

First Patient Dosed on Phase 1b/2 AML Trial

Melbourne, Australia - (14 December, 2016) – Clinical-stage oncology company Prescient Therapeutics Ltd (ASX: PTX) announces that H. Lee Moffitt Cancer Centre (Moffitt) in Florida has dosed the first patient to PTX's Phase 1b/2 clinical trial in refractory or relapsed acute leukemias, namely acute myeloid leukemia(AML).

The clinical trial is being led by Principal Investigator, Jeffrey Lancet, M.D., Professor of Oncologic Sciences at the Moffitt and University of South Florida. He is Chair of the Department of Malignant Hematology at Moffitt. Moffitt is the third largest cancer center in the US and is an NCI-designated comprehensive cancer center.

The encouraging results from earlier Phase 1 studies in acute leukemias with PTX-200, conducted at MD Anderson and Moffitt clearly showed that further AML trials with PTX-200 were warranted.

The clinical trial will be conducted with PTX's Akt inhibitor, PTX-200, plus cytarabine in refractory or relapsed AML. Approximately 18 patients will be recruited in the Phase 1b stage of the trial.

Professor Lancet, an internationally recognized hematologist with extensive clinical and research experience in AML said "I am excited to commence recruitment on this important trial. PTX-200 has shown some promising activity and the proposed study will frame our direction as we progress further down the clinical trial process with PTX-200."

PTX's CEO and Managing Director Steven Yatomi-Clarke said "Professor Lancet is an authority on AML with deep clinical experience across many AML treatment regimes. We are pleased to be working so closely with him." Professor Lancet was the Principal Investigator on Celator Pharmaceuticals successful AML trial, following which Celator was acquired by Jazz Pharmaceuticals for US$1.5 billion this year.

PTX's Phase 1b study will enroll 15-18 patients and is an open-label, dose escalation study, using a standard design for dose escalation and for determining the safe dose to be used in combination with cytarabine in the Phase 2 part of the study. Up to four dose levels will be evaluated, with the initial dose level of 25 mg/m^2 PTX-200. Each dose level will be increased by 10 mg/m^2. Doses will be administered for a maximum of four 21-day cycles. Safety and clinical activity will be evaluated at the end of each cycle. PTX will also be evaluating the effect of PTX-200 on Akt signaling, inhibition of proliferation (growth) and induction of apoptosis (cell death).

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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%.[1]

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 in 2015.[2] The projected number of new cases for 2015 increased by 6,240 (i.e. 42%) above estimates of incidence in 2013.[2,3]

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.[4] Older individuals (>60 years) experience both inferior CR and survival rates following initial therapy.[5,6] 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.

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.[7] 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.[8-10] 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.[8,11] The hyper activation of this pathway (high phosphor-Akt levels at baseline) is associated with poor overall survival of AML patients.[10]

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.[8] 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.[8,12,13] 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.[14] 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.[15] 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 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.

References

1. Tallman MS, Gilliland DG, Rowe JM. Drug therapy for acute myeloid leukemia. Blood 2005; 106(4):1154-1163.
2. Siegel, R., Miller, K.D., and Jemal, A. (2015). Cancer Statistics, 2015. CA Cancer J Clin 2015;65:5-29.
3. Siegel R., Naishadham, D., Jemal, A.(2013). Cancer Statistics, 2013. CA Cancer J Clin 2013; 63(1):11-30.
4. Litzow MR. The therapy of relapsed acute leukaemia in adults. Blood Reviews 2004; 18(1):39-63.
5. Appelbaum FR, Gundacker H, Head DR et al. Age and acute myeloid leukemia. Blood 2006; 107(9):3481-3485.
6. Juliusson G, Antunovic P, Derolf A et al. Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry. Blood 2009; 113(18):4179-4187.
7. Berndt N, Yang H, Trinczek B et al. The Akt activation inhibitor TCN-P inhibits Akt phosphorylation by binding to the PH domain of Akt and blocking its recruitment to the plasma membrane. Cell Death Differ 2010.
8. Grandage VL, Gale RE, Linch DC, Khwaja A. PI3-kinase//Akt is constitutively active in primary acute myeloid leukaemia cells and regulates survival and chemoresistance via NF-kB, MAPkinase and p53 pathways. Leukemia 2005; 19(4):586-594.
9. Kubota Y, Ohnishi H, Kitanaka A, Ishida T, Tanaka T. Constitutive activation of PI3K is involved in the spontaneous proliferation of primary acute myeloid leukemia cells: direct evidence of PI3K activation. Leukemia 2004; 18(8):1438-1440.

10. Min YH, Eom JI, Cheong JW et al. Constitutive phosphorylation of Akt//PKB protein in acute myeloid leukemia: its significance as a prognostic variable. Leukemia 2003; 17(5):995-997.
11. Xu Q, Simpson SE, Scialla TJ, Bagg A, Carroll M. Survival of acute myeloid leukemia cells requires PI3 kinase activation. Blood 2003; 102(3):972-980.
12. O'Gorman DM, McKenna SL, McGahon AJ, Knox KA, Cotter TG. Sensitization of HL60 human leukaemic cells to cytotoxic drug-induced apoptosis by inhibition of PI3-kinase survival signals. Leukemia 2000; 14(4):602-611.
13. Papa V, Tazzari PL, Chiarini F et al. Proapoptotic activity and chemosensitizing effect of the novel Akt inhibitor perifosine in acute myelogenous leukemia cells. Leukemia 2007; 22(1):147-160.
14. Matsunaga T, Takemoto N, Sato T et al. Interaction between leukemic-cell VLA-4 and stromal fibronectin is a decisive factor for minimal residual disease of acute myelogenous leukemia. Nat Med 2003; 9(9):1158-1165.
15. Tazzari PL, Cappellini A, Ricci F et al. Multidrug resistance-associated protein 1 expression is under the control of the phosphoinositide 3 kinase//Akt signal transduction network in human acute myelogenous leukemia blasts. Leukemia 2007; 21(3):427-438.

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