Evaluate Vantage

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Keryx blazing a trail with promising Akt inhibitor

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Keryx Biopharmaceuticals reported further steady progress last week with a novel anti-cancer compound, KRX-0401, in the shape of FDA fast track designation. Signs are that the drug should continue to attract attention in the coming months.

The compound, generically called perifosine, inhibits a couple of crucial cell signalling pathways, including Akt, and last year generated very encouraging results in mid-stage studies carried out in multiple myeloma and colorectal cancer. Of course, caution is always recommended at this stage, but with pivotal programmes agreed with the FDA under special protocol assessments, orphan drug status already granted and enough money in the bank to see two phase III trials to the end, Keryx has quietly been laying the groundwork for an interesting period.

Survival, growth, death

KRX-0401 specifically inhibits the phosphoinositide 3-kinase (PI3K)/Akt pathway, which is largely associated with cell survival, growth and death.

The Akt protein family play an important role in cellular signalling. Three genes, Akt1, 2 and 3 code for specific enzymes which are respectively involved in cellular survival pathways and the insulin signalling pathway, whilst the role of Akt3, predominantly expressed in the brain, is less clear.

Akt1, sometimes just referred to as Akt, has been implicated as a major factor in many types of cancer, regulating survival and metabolism, hence it is a target for anti-cancer therapies. It is believed that so-called activated Akt, or pAkt, may enable proliferation and survival of cells, and this pathway is often activated in tumours that are resistant to other forms of anticancer therapies, and associated with poor prognosis.

Challenging group

As such, both pivotal trials, in multiple myeloma and colon cancer, will be conducted in highly refractory patient groups.

Already underway is the myeloma trial, which will enrol approximately 400 patients with relapsed/refractory disease, who have already been treated with both Velcade and an immunomodulatory agent such as Revlimid and/or Thalomid, and been previously treated with one to four prior lines of therapy.

They will either receive Velcade, dexamethasone and KRX-0401, or Velcade, dexamethasone and placebo, and the primary endpoint is progression free survival. Results are expected towards the end of 2011.

The trial in metastatic colorectal cancer is due to start in the next couple of months, and should also yield results around the same time. The study will pit KRX-0401 in combination with capecitabine (Roche's Xeloda) against capecitabine plus placebo in around 430 patients. They must have failed pretty much all therapies available, including 5-fluorouracil, Eloxatin, irinotecan, Avastin and, if K-Ras wild-type, with prior Erbitux or Vectibix.

The primary endpoint is overall survival. The median survival for this patient group is five months and based on previous trials Keryx is expecting to see survival of seven-eight months for the perifosine arm.

Rising hopes

Clearly, these are challenging patient populations, but efficacy seen in phase II studies is building hopes, in colon cancer particularly. In the phase II study, which the phase III will essentially repeat, but on a much larger scale, overall survival in the perifosine arm was 18 months versus 11 in the placebo group, whilst time to progression was also significantly longer, more than double.

The compound's side effect profile is also relatively moderate, compared with other cytotoxic agents. To date, over 1,800 patients have been treated, with no evidence of flu-like symptoms, thrombocytopenia or alopecia.

On the downside, this is the first time an agent like KRX-0401 will be tested in large late stage studies and as

the table below shows, compounds targeting Akt are few and far between.

Rexahn expects to complete phase II trials for Archexin by the end of 2010 in renal cell carcinoma, which will probably provide the next important data for this class of drug. Although Exelixis did have a similar compound in development, XL418, this no longer features in the company's pipeline chart so has possibly been abandoned.

Blazing a trail

As such, Keryx and partner, Aeterna Zentaris, which owns rights to the drug outside of the US, Canada and Mexico, are blazing a trail in this area.

On the stock market Keryx has not really recovered from the failure of its previous lead compound, Sulonex, in phase III in 2008, an event which almost spelled the end for the New York-based company. However, progress with KRX-0401 has led a revival over the last 12 months, and its shares are currently trading at $3.14, up from 16 cents 12 months ago.

With a market value of $176m and $35m in the bank, enough to last at least 18 months, the company is in an interesting position. On a conference call last month, Ron Bentsur, the company's chief executive, admitted that partners were already paying an interest in perifosine, but hinted that nothing is on the horizon. A bit more data will probably be required before money changes hands over what is still a high risk project, but Keryx could well have a valuable asset in its hands.

Akt inhibitors				
	Pharmacological Class	**Product**	**Company**	**Indication Summary**
Phase III	Akt kinase inhibitor	KRX-0401	Keryx Biopharmaceuticals/Æterna Zentaris	Multiple myeloma [Phase III]; Prostate cancer [Phase II]; Soft tissue sarcoma [Phase II]; Melanoma [Phase II]; Breast cancer [Phase II]; Non-small cell lung cancer (NSCLC) [Phase II]; and other cancer types
Phase II	Akt-1 kinase inhibitor	Archexin	Rexahn Pharmaceuticals	Pancreatic cancer [Phase II]; Renal cell carcinoma (RCC) [Phase II];
Phase I	Akt kinase & S6 kinase (S6K) inhibitor	XL418	Exelixis	Solid tumour indications [Phase I]
Pre-clinical	Akt kinase inhibitor	KRX-0404	Keryx Biopharmaceuticals	General cancer indications [Pre-clinical]
	Akt kinase inhibitor	AT13148	AstraZeneca	Solid tumour indications [Pre-clinical]
	Akt kinase inhibitor	PX-316	Oncothyreon	Solid tumour indications [Pre-clinical]
	PI3K & Akt kinase inhibitor	AEZS-126	Æterna Zentaris	General cancer indications [Pre-clinical]
	Akt kinase inhibitor	RX-0201-Nano	Rexahn Pharmaceuticals	General cancer indications [Pre-clinical]
	Akt kinase inhibitor	RX-0183	Rexahn Pharmaceuticals	Solid tumour indications [Pre-clinical]
	Rapamycin analogue (mTOR inhibitor) & Akt inhibitor	BN108	Bionovo	General cancer indications [Pre-clinical]
	Akt kinase inhibitor	EM370	Emiliem	Solid tumour indications [Pre-clinical]

Source: EvaluatePharma