

## Therapeutic focus - PI3Ks in the spotlight in 2012



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By the end of 2012, oncologists will know much more about the potential of PI3K inhibitors in treating a variety of haematological cancers and solid tumours. With one big phase III trial about to report and as many as eight phase II trials nearing completion this year, the sector will know if its hopes of phosphatidylinositol 3-kinase as a useful target in restraining tumour cell growth and proliferation are well placed.

First up will be Keryx Biopharmaceuticals with pivotal data on its PI3K/Akt kinase inhibitor perifosine, or KRX-0401, in advanced refractory colorectal cancer. Whilst an extremely important event for the New York company, the trial's outcome will be a sign of the drug class's clinical promise and whether the investment of big pharma players such as Novartis, Pfizer, Roche and Sanofi will pay off, not to mention Merck's \$251m deal in December to lock up a preclinical candidate from Exelixis and Takeda's \$190m takeover of Intellikine (see tables).

	Product	Pharmacological Class	Company	Originator	Trial IDs
Phase III	KRX-0401	Akt kinase/PI3K inhibitor	Keryx Biopharmaceuticals/Æterna Zentaris	Asta Medica	NCT01002248 NCT01097018
Phase II	TORKi/CC-223	PI3K & mTOR inhibitor	Celgene	Celgene	NCT01177397
	GS 1101/CAL101	PI3K inhibitor	Gilead Sciences	ICOS	NCT01393106 NCT01282424 NCT01306643 NCT01203930
	BEZ235	PI3K & mTOR inhibitor	Novartis	Novartis	NCT01471847 NCT01495247 NCT01288092 NCT01453595 NCT01337765 NCT01508104
	BGT226	PI3K inhibitor	Novartis	Novartis	NCT00600275 NCT00742105
	BKM120	PI3K inhibitor	Novartis	Novartis	NCT01289041 NCT01297491 NCT01339052 NCT01501604
	RG7321	PI3K inhibitor	Roche	Piramed	NCT01493843 NCT01437566
	RG7422	PI3K inhibitor	Roche	Roche	NCT01455493 NCT01485861 NCT01442090 NCT01437566
	SAR245408	PI3K inhibitor	Sanofi	Exelixis	NCT01013324 NCT01082068 NCT01042925
	SAR245409	PI3K & mTOR inhibitor	Sanofi	Exelixis	NCT01403636 NCT01082068
	PF-05212384	PI3K & mTOR inhibitor	Pfizer	Wyeth	NCT01420081
	PF-04691502	PI3K & mTOR inhibitor	Pfizer	Pfizer	NCT01430585 NCT01420081
	PX-866	PI3K inhibitor	Oncothyreon	Burnham Institute/U. of Arizona/U. of Pittsburgh	NCT01259869 NCT01331083 NCT01204099 NCT01252628

### Key moment

PI3K lies upstream of such well-known targets as mTOR, which has produced a cancer treatment in Afinitor, and Akt, which has proven less successful so far but in which many drug developers remain interested. In the body, the kinase is linked to a number of cell growth, proliferation, differentiation, motility, survival and intracellular trafficking functions; as such, genetic mutations that trigger aberrant signalling are believed to be involved in tumour development and drug-resistant cancers.

The number of clinical stage candidates and trials underway are evidence of the importance placed on PI3K in

disease origin, as well as its relative novelty as a target. According to EvaluatePharma data, more than 60 trials are underway on 29 molecules, some of which are pure PI3K inhibitors and others that have additional action on mTOR and Akt.

For those with an interest in the space, the pivotal study of perifosine will be a key moment. The trial in colorectal cancer is expected to report sometime in the first quarter; being conducted under a special protocol assessment with the FDA, it tests perifosine plus capecitabine against the chemotherapy alone in 430 patients with overall survival as a primary endpoint and progression free survival as a secondary. Patients in the trial must have failed chemotherapy and targeted therapies, so it is a very sick population in need of another option.

Trial success would be an important catalyst for Keryx, which has partnered the drug with Aeterna Zentaris in Europe; it has a net present value of \$308m for the group, well above its market capitalisation. However, there is some scepticism about its chance of success – shares have fallen by one-third in the last six months and more than 10% of its shares are held in short positions. Thus, a successful trial result would likely see a significant ramping up of the share price.

A second phase III, in multiple myeloma, could wrap up by the end of the year.

### **Following in the footsteps**

Several phase II trials are expected to report this year. Gilead Sciences' GS 1101, which it brought on board with its purchase of Calistoga Pharmaceuticals in a push into the oncological space, is expected to wrap up a single agent trial sometime around the middle of the year in relapsed or refractory Hodgkin lymphoma. Around the same time, Novartis' BKM120 is expected to wrap up mid-stage trials in three different cancers: a 70-patient phase I/II trial in combination with Herceptin in breast cancer patients with relapsing HER2-overexpressing disease who have become resistant to Herceptin; a trial of 65 glioblastoma patients both eligible and ineligible for surgery; and a 93-patient trial in glioblastoma multiforme in combination with Avastin.

By the end of the year, BKM120 also may have completed a 140 patient trial in advanced endometrial cancer. It may be joined by Celgene's TORKi, being tested in 120 non-Hodgkins lymphoma patients, which could report in the third quarter; and Oncothyreon's PX-866 in non-small cell lung cancer and glioblastoma multiforme.

Another 15 mid- and late-stage trials are likely to report in 2013, including candidates from Sanofi, Pfizer and Roche. Thus, the next 24 months will be a defining moment for the drug class.

	Product	Pharmacological Class	Company	Originator	Trial ID
<b>Phase I</b>	AMG 319	PI3K delta inhibitor	Amgen	Amgen	NCT013
	BAY80-6946	PI3K inhibitor	Bayer	Bayer	NCT013
	MSC1936369B + SAR245408	MEK & PI3K inhibitor	Merck KGaA/Sanofi	Exelixis/Santhera Pharmaceuticals	NCT013
	MSC1936369B + SAR245409	MEK, PI3K/mTOR inhibitor	Merck KGaA/Sanofi	Exelixis/Santhera Pharmaceuticals	NCT013
	BYL719	PI3K inhibitor	Novartis	Novartis	NCT013
	RG7604	PI3K inhibitor	Roche	Genentech	NCT012
	IPI-145	PI3K inhibitor	Purdue Pharma/Infinity Pharmaceuticals/Intellikine	Intellikine	NCT014
	INK1117	PI3K inhibitor	Intellikine	Intellikine	NCT014
	ZSTK474	PI3K inhibitor	Zenyaku Kogyo	Zenyaku Kogyo	NCT012
	PWT33597	PI3K alpha/mTOR inhibitor	Pathway Therapeutics	Pathway Therapeutics	NCT014
	P529 intravitreal	PI3K/Akt/mTOR antagonist	Paloma Pharmaceuticals	Paloma Pharmaceuticals	NCT010
	GSK2126458	PI3K inhibitor	GlaxoSmithKline	GlaxoSmithKline	NCT009
	INK128	TOR kinase inhibitor	Intellikine	Intellikine	NCT013
	DS-7423	mTOR/PI3Kinhibitor	Daiichi Sankyo	Daiichi Sankyo	NCT013
	Carboxyamidotriazole Orotate	VEGF-1 & PI3K inhibitor	Tactical Therapeutics	Tactical Therapeutics	NCT011
	RG7603	PI3K inhibitor	Roche	Roche	NCT013

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