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Therapeutic focus – Competitors cycle in palbo's slipstream

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Inhibiting cyclin-dependent kinases had once held considerable promise owing to these enzymes' role in cell cycle control, and there are signs that after a cooling-off period the pharma industry might be willing to give the approach another look.

A recent hike in sellside forecasts for Pfizer's palbociclib is partly responsible for stimulating interest, though in the event this molecule generated mixed phase II results. While an early filing for palbo is now a long shot, the project is still in play and *EvaluatePharma* data reveal several competitors waiting in the wings (see table).

Palbo inhibits cyclin-dependent kinases (CDK) 4 and 6 – enzymes that normally allow cell division to start by inactivating the tumour-suppressor gene RB. Oestrogen receptor-positive breast cancers are associated with increased CDK4/6 activity, so these tumour types make a logical target for palbo and similarly acting molecules.

The current question for palbo is whether it can be filed on the mixed results of the Paloma-1 study alone (*Palbo bull case dissipates as Paloma fires blanks, April 7, 2014*). But even if the company has to wait until the end of 2015 for full phase III data, palbo will still be a year ahead of Novartis's LEE011 and Lilly's bemaciclib, says Mark Schoenebaum, an analyst from ISI Group.

LEE011 is being studied in a very similar patient population to palbo, but no previous clinical data have been revealed; a filing is planned for 2016. Lilly's bemaciclib, meanwhile, is at least a year behind that, having only reached phase II so far in mantle cell lymphoma.

However, Lilly recently upped its game, registering on clinicaltrials.gov a phase III breast cancer study that has yet to begin enrolment. This adds bemaciclib to fulvestrant – palbo is in one phase III trial with letrozole and another with fulvestrant – and doses bemaciclib continuously for 28 days, versus palbo's 21 days on and seven days off.

Considerable presence

The Novartis project is the result of work with Astex, a company that had a considerable presence in cell cycle inhibition and was acquired by Otsuka last year. A separate Astex-derived project, the CDK 1/2/9 inhibitor AT7519, is in phase II studies in haematological cancers.

The industry pipeline shows numerous other CDK inhibitors with specificity beyond the 4/6 subtype, though these have tended to be studied in other cancer types.

Cyclin-dependent kinase (CDK) inhibitors in development			
Status	**Project**	**Company**	**Pharmacology class**
Phase III	Palbociclib	Pfizer / Amgen	CDK 4 & 6 inhibitor
	LEE011	Novartis / Otsuka	CDK 4 & 6 inhibitor
	Dinaciclib	Merck & Co / Ligand	CDK 1, 2, 5 & 9 inhibitor
Phase II/III	P276-00	Piramal Enterprises	CDK 1, 4, & 9 inhibitor
Phase II	Bemaciclib (LY2835219)	Eli Lilly	CDK 4 & 6 inhibitor
	AT7519	Novartis / Otsuka	CDK 1, 2, 7 & 9 inhibitor
	BAY1000394	Bayer	CDK inhibitor
	Alvocidib	Sanofi / Tolero	CDK inhibitor
	NK-101 & NK-102	Neurokin	CDK inhibitor
Phase I/II	P16_37-63	Oryx	CDK inhibitor
Phase I	Seliciclib ((R)-roscovitine)	Cyclacel Pharmaceuticals	CDK 2, 7 & 9 inhibitor
	P1446A	Piramal Enterprises	CDK 1, 4 & 9 inhibitor
Preclinical	CYC065	Cyclacel Pharmaceuticals	CDK 2 & cyclin E inhibitor
	GZ38-1	G1 Therapeutics	CDK 4 & 6 inhibitor
	Senexin A	Senex Biotechnology	CDK 8 & 19 inhibitor
	CDK9 Inhibitor Research Project	AstraZeneca	CDK 9 inhibitor
	AT9311	Otsuka Holdings	CDK inhibitor
	CYC400	Cyclacel Pharmaceuticals	CDK inhibitor
	ON 123300	Onconova Therapeutics	CDK4 & ARK5 inhibitor
	ON 108600	Onconova Therapeutics	CDK9 & CK2 inhibitor

In addition to AT7519, Merck & Co's dinaciclib and Sanofi's alvocidib are also targeting haematological cancers, while lead indications for Piramal's P276-00, Bayer's BAY1000394 and Oryx's P16_37-63 are radiation-induced mucositis, small-cell lung cancer and genitourinary cancers respectively.

There are other important differences, too, such as the fact that P16_37-63 is a protein and not a small molecule. While the leading projects are dosed orally, P276-00 and AT7519 are delivered intravenously.

P276-00 has been studied in triple-negative breast cancer in phase I, while a phase II trial of dinaciclib ended two years ago with no further development. The specificity of targeting breast cancer with inhibitors of the CDK 4/6 subtype makes for a neat approach, especially considering broader inhibitors' propensity to cause off-target effects.

Beyond oncology

And the CDK inhibition story does not end with oncology. Neurokin, a private French group, is focusing on cerebrovascular ischaemia, based on the finding that CDK inhibitors can block stress-induced neuronal apoptosis, preventing proliferation of glial cells and exhibiting anti-inflammatory properties.

That said, investors' primary focus remains on breast cancer and palbociclib, whose consensus 2018 revenue forecasts have risen from $179m 18 months ago to the current $1.8bn. ISI's Mr Schoenebaum has trimmed his forecasts after the Paloma-1 readout, but he is still above consensus, modelling $2.8bn of revenue in 2018 and over $4bn in 2021.

It is also worth pointing out that the jump in palbo's consensus expectations was in no small part due to analysts trying to justify a top-tier valuation for its originator, Onyx, while that company was being bid for by Amgen. Beside palbo only LEE011 and bemaciclib feature in sellside consensus models, and that at a fraction

of the value of the Pfizer project.

Of course, as well as efficacy the safety of these projects will be closely watched. QTc interval prolongation could be a class effect, while neutropenia is palbo's dose-limiting toxicity. Bemaciclib has shown significantly less neutropenia than palbo, and if in bigger studies Lilly can reproduce Pfizer's efficacy at a fraction of the neutropenia this should prompt another sharp reassessment of the value of this drug class.

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