October 12, 2009

Pfizer halts trial of industry's most advanced IGF-1R antibody

Amy Brown

News that Pfizer has had to halt a phase III trial of experimental cancer therapy, figitumumab, is a disappointing set back for a new class of antibody that has until now shown great promise in attacking tumours via a novel pathway.

The product, also called CP-751871, is an insulin-like growth factor receptor antagonist (IGF-1R), which has been implicated in the growth and proliferation of a variety of human cancers. A number of companies are working on compounds to inhibit this pathway (see table) although Pfizer was by far the most advanced in the field; no doubt this news will prompt concern elsewhere. For the US drugs giant itself, which only recently stated grand ambitions for the oncology space, this is a particularly unwelcome development from one of its brightest pipeline candidates (*Pfizer might achieve No.3 in cancer but needs deals to hit $25bn sales target*, July 14, 2009).

The trial that was halted was being carried out in patients with non-small cell lung cancer. An independent monitoring board found that there were more serious adverse events, including deaths, among patients in the figitumumab arm, than those given chemotherapy. A review is ongoing, whilst another lung cancer trial with the drug in combination with Roche's Tarceva will continue.

Although this is not Pfizer's only shot on goal for figitumumab, it is the most advanced indication. Whilst the drug is far from over, some financial analysts took dramatic action in response.

Leerink Swann removed the drug from its sales model, saying lung cancer had appeared to hold most hope. The bank's analysts had previously forecast global revenues of $1.2bn by 2015, certainly one of the highest numbers out there. *EvaluatePharma* has consensus of $580m by 2014, with most analysts pencilling in a launch in 2012, although a couple of banks have sales starting in 2011.

This could well be pushed back now, as this news could cause a fairly sizeable delay. Data from the other phase III lung cancer trial is not due until late 2011.

Clinical programmes targeting IGF-1R					
	Pharmacological Class	**Product**	**Generic Name**	**Company**	**Indication Summary**
Phase III	Anti-IGF-1R MAb	CP-751871	figitumumab	Pfizer	Non-small cell lung cancer (NSCLC) [Phase III]; Prostate cancer [Phase II]; Breast cancer [Phase II]; Bone cancer [Phase II] and other phase II studies
	IGF-1R antagonist	OSI-906	-	OSI Pharmaceuticals	Solid tumour indications [Phase III]; Ovarian cancer [Phase II]; Non-small cell lung cancer (NSCLC) [Phase I]
Phase II	Anti-IGF-1R MAb	AMG 479	-	Amgen	Bone cancer [Phase II]; Small cell lung cancer (SCLC) [Phase II]; Pancreatic cancer [Phase II] and other phase II and phase I studies
	Anti-IGF-1R MAb	MK-0646	-	Merck & Co	Colorectal cancer [Phase II]; lung cancer [Phase II]; other phase I studies
	Anti-IGF-1R MAb	IMC-A12	cixutumumab	Eli Lilly	Colorectal cancer [Phase II]; Prostate cancer [Phase II]; Head & neck cancers [Phase II]; Hepatoma, liver cancer [Phase II] and other phase II and phase I studies
	Anti-IGF-1R MAb	RG1507	-	Roche	Soft tissue sarcoma [Phase II]; Breast cancer [Phase II]; Non-small cell lung cancer (NSCLC) [Phase II
	Anti-IGF-1R MAb	SCH 717454	robatumumab	Schering-Plough	Bone cancer [Phase II]; Lung cancer [Phase II]
Phase I	Anti-IGF-1R MAb	Anti IGF-IR/BIIB022	-	Dyax	Solid tumour indications [Phase I]
	IGF-1R, BCR-ABL & SRC tyrosine kinase inhibitor	XL228	-	Exelixis	Leukaemia, chronic lymphocytic (CLL) [Phase I]; Leukaemia, acute lymphocytic (ALL) [Phase I] and other phase I indications
	Anti-IGF-1R MAb	RG1507	-	Chugai	Solid tumour indications [Phase I]
	Anti IGF-1 & IGF-2 MAb	MEDI-573	-	AstraZeneca	Solid tumour indications [Phase I]
	Anti-IGF-1R MAb	Anti IGF-IR/BIIB022	-	Biogen Idec	Solid tumour indications [Phase I]

Also in phase III, but not an antibody, is OSI Pharmaceuticals with OSI-906, a small molecule approach to IGF-1R inhibition which it believes could prove effective in combination with targeted therapies like Tarceva as well as a monotherapy.

Last month, OSI announced the start of a phase III trial in patients with locally advanced or metastatic adrenocortical carcinoma (ACC). OSI-906 inhibits the signalling response of IGF-1R, specifically blocking the activation of the AKT and MAP kinase downstream pathways and causing inhibition of tumour cell growth and survival in animal models. The IGF/IGF-1R signalling pathway has also been implicated in protecting tumour cells from cell death induced by a number of cytotoxic agents as well as molecular targeted therapies

including EGFR inhibitors, hence the interest in combining the drug with Tarceva.

The ACC trial is a monotherapy trial, currently the only drug available to treat ACC is mitotane, a derivative of the pesticide DDT which acts as an adrenocortical suppressant, illustrating the need for more treatment options. The study will seek to recruit 135 patients, with overall survival the primary endpoint. OSI is seeking orphan drug status in this setting.

Another trial, this time phase I/II, has been started in combination with paclitaxel, primarily in ovarian cancer, whilst another registration orientated study in combination with Tarceva is planned for NSCLC, potentially starting next year. Therefore robust clinical data on this candidate is not going to be available for a couple of years yet.

Waiting game

In terms of the antibody approach to IGF-1R, Pfizer is definitely leading the pack.

Eli Lilly is conducting a very broad phase II programme with its candidate IMC-A12, which it gained from ImClone, and a stretch of data is due towards the end of this year. Breast cancer is a particular area of focus, with the company working on the premise that the growth factor receptor modulates the responsiveness of hormone receptor expressing breast cancers to anti-oestrogen therapy, as well as the development of resistance to anti-oestrogens.

Roche is a bit further back with its product and is testing it in fewer indications, although some data in sarcoma could be available in the final quarter of this year, and from a trial in NSCLC next year.

Schering-Plough could have data in a couple of years for Ewing’s sarcoma, or bone cancer, but is also planning trials in other solid tumours, whilst Amgen probably will not have phase II data due on its candidate AMG 479 in bone cancer until the end of next year.

As such, there will be many parties hoping that the side effects seen in Pfizer’s trial turn out to be unrelated to the drug.