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Therapeutic focus - Votrient a blazing trail in soft tissue sarcoma

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Soft tissue sarcoma patients in the US may have their first targeted agent in May if the FDA follows its expert panel in supporting Votrient. Sarcoma has so far been missed by the evolution in oncology drugs and remains treated primarily with surgery, radiation and chemotherapy.

This may begin to change in the near future if the agents in a fairly healthy pipeline begin to show success. Four drugs are in phase III trials, three of which have not been approved in any indication, with the first two expected to report phase III results this year. Phase II has some familiar names in Avastin and Nexavar; thus it is likely that patients and specialists will have some new choices in coming years.

Success wanted

First, of course, the FDA will have to give its stamp of approval to Votrient. An advisory committee gave the GlaxoSmithKline compound an 11-2 positive vote in patients with advanced sarcomas who have previously undergone chemotherapy. In a phase III trial patients taking Votrient survived 4.6 months without their disease worsening, compared to 1.6 months for patients in an arm taking a placebo; no difference in overall survival could be measured.

With approval, Votrient would have a clear first-mover advantage in a disease that could do with some attention. Soft-tissue sarcomas represent only about 1% of all new cancer cases, around 11,000 patients and 4,000 deaths annually in the US. If approved, Votrient will probably be well ahead of Ariad and Merck & Co's ridaforolimus, if indeed the drug ever gets approved following its 13-1 negative vote.

Patients in the European Union and some other non-US jurisdictions have Johnson & Johnson and Grupo Zeltia's Yondelis as an option. However, the FDA has taken a sceptical view of that drug, demanding additional trials in ovarian cancer, and it does not appear that the drug derived from a sea squirt will make it to the US market anytime soon (*Therapeutic focus - Disappointment a recurring theme in ovarian cancer pipeline, December 20, 2011*).

Late stage soft tissue sarcoma pipeline

	Product	Generic Name	Company	Originator	Pharmacological Class	Trial ID
Filed	Ridaforolimus	ridaforolimus	Merck & Co	ARIAD Pharmaceuticals	Rapamycin analogue (mTOR inhibitor)	NCT0053823
	Votrient	pazopanib hydrochloride	GlaxoSmithKline	GlaxoSmithKline	Multi-kinase inhibitor	NCT0075368
Phase III	TH-302	-	Merck KGaA	Threshold Pharmaceuticals	Hypoxia selective alkylating agent	NCT0144008
	Ombrabulin	ombrabulin	Sanofi	Ajinomoto	Combretastatin derivative	NCT0069951
	Zymafos	palifosfamide	ZIOPHARM Oncology	Dekk-Tec	Alkylating agent	NCT0116879
	Halaven	eribulin mesylate	Eisai	Eisai/National Cancer Institute (NCI; USA)	Microtubule/tubulin inhibitor	NCT0132788

New agents

The first signs of an emerging pipeline of new agents could come around the beginning of 2013 with some important phase III trials reporting. The first one expected to read out is ZioPharm's Oncology's Zymafos, also known as palifosfamide, a stabilised metabolite of the chemotherapy agent ifosfamide, already used in soft tissue sarcoma treatment. The Massachusetts company reckons Zymafos will have fewer side effects because it will not have the toxic byproducts of its pro-drug.

ZioPharm expects its phase III Picasso 3 trial to complete enrolment of 424 patients by the end of this month and will be able to report toplines on its primary endpoint for accelerated approval, progression free survival, by the end of the year.

If successful, decent revenues are being forecast for this drug - $112m by 2016, according to EvaluatePharma forecasts - and it may spark some partnering interest. The net present value of Zymafos is $520m, although expectations appear to have been dampened since it appeared as one of the top unpartnered drugs in the R&D pipeline (*What partnering hopes for the industry's biggest unpartnered R&D assets?, August 6, 2010*).

Also likely to report soon after the new year is Sanofi's ombrabulin, the next true targeted agent in the pipeline in that it has been shown to attack blood vessel growth in tumour cells. Analysts estimate the French group will report results in the population of patients who have progressed following chemotherapy sometime in the second quarter of 2013.

If successful in the clinic and with the regulators, the compound is expected to ramp up sales slowly, reaching $88m in 2016, although analysts from JP Morgan Cazenove estimate it could achieve peak sales of $500m.

A better idea of the potential of Threshold Pharmaceuticals' TH-302 in soft tissue sarcomas will also become clearer in early 2013 when the independent data monitoring committee reports an interim analysis of its pivotal trial in combination with doxorubicin in advanced disease. The hypoxia-targeted agent has had unexpected success in the difficult-to-treat pancreatic cancer, so expectations may begin building for this Merck KGaA partnered drug (*Threshold's hypoxia success is notable for field that has disappointed, February 22, 2012*).

Eisai's breast cancer drug Halaven rounds out phase III. The Japanese group initiated its trial in advanced disease a year ago, with completion expected in 2015; patients will be randomised to a treatment arm of Halaven or dacarbazine, with overall survival the primary endpoint.

Further back

Whilst the presence of Roche's powerhouse Avastin, Pfizer's Torisel and Bayer's Nexavar in phase II should give all competitors some pause, there are a number of other interesting agents. Expectations in general have been building for Keryx BioPharmaceuticals and Aeterna Zentaris' KRX-0401, or perifosine, the most advanced candidate in the PI3K inhibitor class (*Therapeutic focus - PI3Ks in the spotlight in 2012, January 27, 2012*). Its trial in advanced colorectal cancer could report in coming weeks, giving the field some idea of the potential of the agent and the class.

Pfizer's recently approved drug axitinib, being marketed as Inlyta, is being tested in a trial being sponsored by Sheffield Teaching Hospitals NHS Foundation Trust in the UK, with Cancer Research UK and Pfizer listed as collaborators. Given that the VEGF-targeting tyrosine kinase inhibitor is the fourth drug in that class and the seventh targeted agent to be approved in renal cell carcinoma, Pfizer would do well to find success in less competitive spaces.

Bristol-Myers Squibb's brivanib is being tested in a phase II trial that encompasses sarcoma and a number of other types of cancer, including non-small cell lung cancer and pancreatic cancer. If it proves effective in sarcoma, further mid-stage work would probably be necessary; the drug is more likely to be filed in liver cancer where phase III work is underway.

Options have been few for soft-tissue sarcoma patients. However, the next year or so should reveal whether the most-advanced candidates in the space can build on the success of Votrient, and with a fairly rich phase II pipeline it is clear that drug developers have their eyes on this space.

Phase II soft tissue sarcoma pipeline					
	Product	**Generic Name**	**Company**	**Originator**	**Pharmacolo Class**
Phase II	INNO-206	doxorubicin (conjugated)	CytRx	KTB Tumorforschungs	Anthracycline
	GPI-101		Genelink BioPharm	Genelink BioPharm	G-protein cou

	CBI-101	-	Carolina BioPharm	Carolina BioPharm	receptor (GP agonist
	Trivalent Ganglioside Vaccine	-	MabVax Therapeutics	Memorial Sloan-Kettering Cancer Center	Cancer vacci
	Sarcodoxome	doxorubicin hydrochloride	GP Pharm	Farmitalia	Anthracycline
	Axitinib	axitinib	Pfizer/Cancer Research Technology	Agouron Pharmaceuticals	VEGFr 1-3 tyrosine kina inhibitor
	LY573636	tasisulam sodium	Eli Lilly	Eli Lilly	Mitochondria enzyme modulator (A
	Torisel	temsirolimus	Pfizer	Wyeth	FKBP-Rapam associated pr (mTOR inhibi
	PD-0332991	-	Pfizer/Onyx Pharmaceuticals	Onyx Pharmaceuticals/Warner-Lambert	CDK4/6 dual inhibitor
	Doxorubicin	doxorubicin	Delcath Systems	BiOrion Technologies	Anti-cancer a
	KRX-0401	perifosine	Keryx Biopharmaceuticals/Æterna Zentaris	Asta Medica	Akt kinase/PI inhibitor
	ARQ 197	tivantinib	Daiichi Sankyo	ArQule	c-Met tyrosin kinase inhibit
	Sabarubicin	sabarubicin hydrochloride	Menarini	Menarini	Anthracycline
	Reolysin	-	Oncolytics Biotech	University of Calgary	Oncolytic viru Ras activated
	Belinostat (PXD101) IV	belinostat	Celldex Therapeutics/Spectrum Pharmaceuticals/TopoTarget	Prolifix	Histone deacetylase (HDAC) inhib
	Brivanib	brivanib	Bristol-Myers Squibb	Bristol-Myers Squibb	FGFR & VEGF kinase inhibit
	IMC-3G3	olaratumab	Eli Lilly	ImClone Systems	Anti-platelet-derived grow factor recept (PDGFr) MAb
	IMC-A12	cixutumumab	Eli Lilly	ImClone Systems	Anti-insulin li growth factor receptor (IGF MAb
	RG4733	-	Roche	Roche	Gamma secr inhibitor
	Arenegyr (NGR-hTNF)	-	MolMed	San Raffaele Scientific Institute	CD13 aminopeptida (APN) inhibito
	Nexavar	sorafenib tosylate	Bayer	Onyx Pharmaceuticals	Multi-kinase inhibitor
	Avastin	bevacizumab	Roche	Genentech	Anti-VEGF MA