Evaluate Vantage

January 16, 2013

Twilight of the vascular disrupting agents

Jacob Plieth

Sharp-eyed industry watchers will have noted the significance of the quiet discontinuation of Sanofi's tumour vascular disrupting agent ombrabulin, announced at a pipeline presentation amid the fanfare of this month's JP Morgan conference.

The project's scrapping in phase III comes after numerous other failures for this drug class, and leaves Oxigene and Bionomics as the only remaining companies with small-molecule vascular disrupting agents (VDAs) in mid-stage development. It could presage a sorry end for a mechanism of action that had once been heralded as a highly promising anticancer strategy, and had attracted the attention of several big pharma groups (see table below).

Among the big pharmas, AstraZeneca and Abbott had dabbled in VDAs, with ZD6126 and ABT-751 respectively, but neither is now in development. Sanofi says it canned ombrabulin after a phase III study in sarcoma had failed to show sufficient clinical benefit – despite hitting its primary endpoint of progression-free survival.

And even the few remaining companies battling on face a far from certain future. Australia's Bionomics is conducting phase II studies on BNC105 combined with chemotherapy in both renal cell and ovarian cancers, with results due in June 2013 and October 2014 respectively. Should these be positive a partnering deal will be necessary to fund further development.

Oxigene, meanwhile, has gone as far as designing a phase III study combining its fosbretabulin (Zybrestat) with carboplatin and paclitaxel in thyroid cancer, and this is apparently scheduled to start this June. However, with an $8m market cap it is hard to see the US company raising sufficient cash to run such a trial.

Attacking the vasculature

Tumour VDAs work by attacking the vasculature of solid tumours and thus restricting their blood supply – in contrast to angiogenesis inhibitors, for instance, which prevent the growth of new blood vessels.

Thus the concept is somewhat similar to Roche's blockbuster Avastin, whose VEGF-targeting mode of action has some anti-vascular (as well as anti-angiogenic) effects. Most of the small-molecule approaches, including imbrabulin, fosbretabulin, plinabulin, verubulin and ZD6126, cause destabilisation of microtubules.

Summary of small-molecule tumour VDA projects				
Project	**Status**	**Company**	**Cancer type**	**Notes**
Fosbretabulin	Phase II	Oxigene	Thyroid cancer	300-pt phase III study to start June 2013.
Vadimezan	Discontinued	Antisoma	NSCLC	Failed in phase III. Was licensed to Novartis.
Ombrabulin	Discontinued	Sanofi	Soft tissue sarcoma	Phase III study failed to show sufficient efficacy.
BNC105	Phase II	Bionomics	Renal and ovarian cancers	Data in mid-2013 and mid-2014 respectively.
ZD6126	Discontinued	AstraZeneca	various	Scrapped after phase II. Now owned by AngioGene.
Plinabulin	Not known	Nereus	NSCLC	172-patient phase I/II study was due to yield results due June 2011.
Verubulin	Discontinued	Myrexis	Glioblastoma	Mixed phase II data in 2011. Company being liquidated. Molecule handed back to EpiCept.
ABT-751	Not known	Abbott	various	No active trials ongoing.
Crolibulin	Phase I/II	EpiCept	Solid tumours	70-pt, NCI-sponsored trial to complete in Sep 2013. Company being merged with Immune Pharmaceuticals.
Denibulin	Phase I	MediciNova	various	Completed phase I. Licensed from AngioGene.

UK investors will surely recall Antisoma's vadimezan (ADA404), which was once the most advanced tumour VDA and attracted Novartis, no less, as a licensing partner. But failure in two phase III studies precipitated not only the end of vadimezan but also of Antisoma, one of the UK's brightest biotech prospects.

Robin Davison, an analyst with Edison Investment Research, which has covered Antisoma and Bionomics, told *EP Vantage*: "This was once a very prominent idea ... but small molecules haven't come very far. [The ombrabulin discontinuation] effectively leaves Bionomics as the last man standing."

The long wait for data

Other small molecules whose future is uncertain are Nereus's plinabulin and EpiCept's crolibulin. The former was due to yield data from a phase I/II docetaxel combination trial in 172 non-small-cell lung cancer patients almost two years ago, but none were revealed, suggesting that this too was a failure.

EpiCept, meanwhile, says it is still developing crolibulin, although the compound's only study is being conducted by the US National Cancer Institute. The company itself has run out of cash and is being merged with the private Israeli biotech Immune Pharmaceuticals.

EpiCept also recently regained rights to another tumour VDA, verubulin (Azixa), which had been discontinued by Myrexis, a company formerly known as Myriad Pharmaceuticals. All manner of setbacks had befallen Myrexis, including the suspension of all development activities and the death of its chief executive, Richard Brewer, and as of last November it was being liquidated.

While some of these small biotechs and academic groups might well press on with the handful of remaining VDAs, it is hard to see a realistic way forward without big pharma's endorsement.

It looks like the sun is slowly setting on what was once a highly promising anticancer drug class.

To contact the writer of this story email Jacob Plieth in London at jacobp@epvantage.com or follow @JacobEPVantage on Twitter

44-(0)20-7377-0800

Evaluate Americas
+1-617-573-9450

Evaluate APAC
+81-(0)80-1164-4754