Evaluate Vantage

March 22, 2011

Therapeutic focus – Cephalon buy points to rare win in small cell lung cancer

Amy Brown

Cephalon has gained a high risk lead compound from Gemin X, which the US biotech bought for $225m upfront this week. Obatoclax, a pan Bcl-2 inhibitor, is due to report phase II data in small cell lung cancer in the coming months, a very aggressive and tough to treat tumour type.

No targeted agents have proved effective in treating small cell lung cancer to date, although several are advancing through mid-stage trials alongside obatoclax. In fact, very few novel compounds have made it into phase III and only two agents outside of the therapies already on the market – a new chemotherapy called amrubicin and Avastin – are currently in late-stage testing (see table below). Still, the Cephalon deal suggests obatoclax data is going to be positive – welcome news for a disease with very poor prognosis.

Few options

Small cell lung cancer is a disease of smokers, accounting for around 15% of cases of lung cancer overall. It spreads more quickly than non-small cell and is much more aggressive. The cells grow quickly to form large tumours which often spread to the brain, liver and bone. Depending on how extensive the disease is, patients may live for a couple of years, although for some survival is a matter of months.

As such, in most cases the disease is not curable, and is treated with surgery where possible, then chemotherapy. Radiation therapy is also sometimes used.

There are no targeted agents on the market to treat small cell lung cancer, only chemotherapy agents, including topoisomerase inhibitors, anthracyclines and platinum compounds. Highlighting the challenges in developing effective treatment, there have not even been any notable late-stage disappointments.

Emphasising this paucity, perhaps the biggest disappointment in recent years was the failure in 2004 of Merck KGaA and ImClone's mitumomab (IMC-BEC2). Development of the antibody, which was designed to work like a cancer vaccine, was terminated after a phase III trial missed its primary endpoint of improving survival. Just prior to this setback some analysts had pencilled in a launch in 2005 and for sales to exceed $200m by 2007.

Like many of the agents currently being tested for small cell lung cancer, development of mitumomab was supported by a not-for profit agency, in this case the European Organisation for Research and Treatment of Cancer (EORTC). The analysis below reveals that few commercial outfits are putting their pipeline assets through later-stage studies in small cell lung cancer, chosing to pursue other indications instead.

Late-stage options

One of the most advanced new agents in the pipeline is Celgene with a new chemotherapy, a third-generation anthracycline, amrubicin, which was granted orphan drug designation by the FDA in 2008 for small cell lung cancer. The agent has been on the market in Japan since 2002, and came with Celgene's acquisition of Pharmion.

A phase III study has completed recruiting, pitting the drug against a widely used chemo agent for this disease, topotecan, measuring overall survival after the failure of first-line chemotherapy. Top line results are due any time now and could well be presented in full at the cancer conference Asco this year. Given the lack of treatment options for this disease, a strong result would generate a lot of interest.

Topotecan was approved on an overall survival benefit of 25 weeks in a similar patient population, according to JP Morgan analysts. They reckon the study has a 25% chance of success. They do not currently model any sales, but believe amrubicin has the potential to generate $184m in the US by 2015, assuming it reaches the market next year.

The only other novel agent in a late-stage study is Avastin, although the trial is not being run by Roche. The Intergroupe Francophone de Cancerologie Thoracique is running the study, testing Avastin in combination with chemotherapy, and should yield results next year. Genentech did run phase II studies in this setting, but never

pushed on to pivotal trials.

Mid-stage

The table below reveals a mixed mid-stage pipeline, although the Bcl-2 inhibitors are the most common approach.

Bcl-2 derives its name from B-cell lymphoma 2; the Bcl-2 family is a group of proteins that are involved in a number of cancers, including melanoma, breast, prostate and lung carcinomas, and are also thought to be involved in resistance to conventional cancer treatment.

Obatoclax is active across all Bcl-2 proteins, including the dominant protein Mcl-1 and has demonstrated efficacy in re-initiating programmed cell death, or apoptosis, and activity in inducing cancer cell self-digestion, or autophagy.

In March 2009, Gemin X launched a Phase 2 study of obatoclax in combination with carboplatin and etoposide for the potential first-line treatment of small cell lung cancer. Results are due – again likely to be presented at Asco – and given Cephalon's move it will be surprising if these are not positive.

This will be encouraging news for the other Bcl-2 inhibitors in development.

For example Ascenta Therapeutics has conducted a phase II study with AT-101, although the private company does not appear to be running any trials currently.

ABT-263, being developed by Abbott, completed a phase I/IIa study recently, and the company is currently recruiting for a phase I study to look at the safety of the agent in combination with chemotherapy. Trials in lymphoma and leukaemia are slightly more advanced, suggesting small cell lung cancer is not a priority.

Targeted approach

In terms of other targeted agents, Synta's heat shock protein 90 inhibitor ganetespib is undergoing a phase II study, sponsored Dana-Farber Cancer Institute. Results are unlikely to emerge until next year.

And Polaris recently saw the Ludwig Institute for Cancer Research start a phase II trial with ADI-PEG 20, or arginine deiminase. The microbial enzyme degrades arginine, an amino acid crucial to tumor cell metabolism and growth of certain cancers. Recruiting patients with relapsed sensitive or refractory small cell lung cancer, results are likely to emerge next year.

Amgen meanwhile has completed enrolment of a phase I/II study with the antibody AMG 479, although clinicaltrials.gov indicates data may not be available for some time. The compound is an insulin-like growth factor receptor antagonist (IGF-1R) – Pfizer suspended pivotal trials of its IGF-1R candidate figitumumab in non-small cell lung cancer, so it will interesting to see how Amgen gets on with this novel mechanism of action (*Pfizer halts trial of industry's most advanced IGF-1R antibody, October 12, 2009*).

The same Amgen study is also examining an anti-hepatocyte growth factor called AMG 102.

In turn, Pfizer has completed enrolling patients in a phase II trial with figitumumab, in patients with extensive stage small cell lung cancer, although results are not due until 2013, according to clinical trials.gov.

Another novel targeted agent trials is Roche and Curis' hedgehog pathway inhibitor GDC-0449, which is being trialled in an extensive phase II study being run by the Eastern Cooperative Oncology Group. The study is also looking at cixutumumab, an anti-IGF-1R antibody being developed by Eli Lilly. Recruitment of a targeted 170 patients is ongoing, according to clinicaltrials.gov.

Others to watch

Other agents in the pipeline to watch include ImmunoGen's IMGN901, which entered a phase I/II study last November. Results are not expected until late 2012; the study is primarily measuring dosage and safety.

The targeted agent is designed to kill cancer cells that express the protein CD56, and consists of a CD56-binding antibody with a potent cancer-cell killing agent, DM1, attached to it using an engineered linker.

Meanwhile, Neotropix's novel oncolytic virus, NTX-010, is currently undergoing a phase II trial being run by the National Cancer Institute, in patients with extensive stage disease, who have responded to chemotherapy. Results are due next year.

Much of the mid-stage pipeline investigating small cell lung cancer is still some way from yielding results. Nearer term, obatoclax and amrubicin hold the most promise for a well needed advance.

Small cell lung cancer pipeline						
	Product	**Generic Name**	**Pharmacological Class**	**Company**	**Clinical trial ID**	**First Introduction (any indication)**
Phase III	Calsed	amrubicin hydrochloride	Anthracycline	Celgene	NCT00547651	30/06/2012
	Avastin	bevacizumab	Anti-VEGF MAb	Roche	NCT00930891	26/02/2004
Phase II	Sabarubicin	sabarubicin hydrochloride	Anthracycline	Menarini	-	
	Obatoclax	obatoclax mesylate	Pan-Bcl-2 inhibitor	Cephalon/GeminX	NCT00682981	-
	huN901-DM1	lorvotuzumab mertansine	Anti-CD56 MAb-DM1 maytansinoid conjugate	ImmunoGen	NCT01237678	31/12/2014
	NTX-010		Oncolytic virus	Neotropix	NCT01017601	-
	Ganetespib	ganetespib	Heat shock protein 90 (Hsp90) inhibitor	Synta Pharmaceuticals	NCT01173523	30/06/2014
	AMG 479	ganitumab	Anti-IGF-1R MAb	Amgen	NCT00791154	-
	ADI-PEG 20	arginine deaminase	Arginine inhibitor	Polaris Group	NCT01266018	-
	AT-101		Bcl-2 inhibitor	Ascenta Therapeutics	-	-
	ABT-263	navitoclax dihydrochloride	Bcl-2 inhibitor	Abbott Laboratories	NCT00878449	31/12/2015
	Arenegyr (NGR-hTNF)		CD13 aminopeptidase N (APN) inhibitor	MolMed	-	31/12/2013
	AMG 102	rilotumumab	Anti-hepatocyte growth factor (HGF) MAb	Amgen	NCT00791154	31/12/2013
	RG3616 (GDC-0449)	vismodegib	Hedgehog protein antagonist	Roche/Curis	NCT00887159	30/06/2012
	Yervoy	ipilimumab	Anti-CTLA4 MAb	Bristol-Myers Squibb	NCT00527735	30/06/2011
	CP-751871	figitumumab	Anti-IGF-1R MAb	Pfizer	NCT00977561	-
	IMC-A12	cixutumumab	Anti-IGF-1R MAb	Eli Lilly	NCT00887159	31/12/2013

Source: EvaluatePharma

+81-(0)80-1164-4754