Evaluate Vantage

March 31, 2010

# Therapeutic focus - Late stage set backs sharpen focus on earlier lung cancer candidates

Amy Brown

Encouraging results from a mid-stage lung cancer trial with a novel tyrosine kinase inhibitor (TKI), ARQ 197, provided some rare positive news today from a field that has suffered a depressingly large number of late-stage set backs so far this year.

Shares in the developer of the drug, Massachusetts-based ArQule, almost doubled in value in early trading on the news, but a look at recent progress of the industry's late-stage pipeline suggests that enthusiasm is probably best tempered. Of the 26 products identified by *EP Vantage* in February as promising phase III candidates, seven have since failed or stalled; perhaps not surprising for such a hard-to-treat cancer. Still, on a more positive note ARQ 197 is one of 125 phase II candidates under development, a healthy sized mid-stage pipeline, of which kinase inhibitors appear to be attracting the most attention (see tables below).

**No such thing as early stage**

Because the lung has no pain fibres, patients have few signs early on and tend to present with symptoms due to metastatic spread to other regions such as the brain, bone and liver.

By this stage the tumour in the lung is often too large to operate on. Professor Stephen Spiro, vice chairman of the British Lung Foundation, says that the average size of a tumour when it presents in the lung is 3-4cm in diameter. Halfway through the life of a solid tumour it is typically 1mm in diameter, meaning lung cancer tumours can be 7/8ths of the way through their natural history by the time a patient is identified.

"There's really no such thing as early lung cancer and the tests we have don't pick up disease under 1cm in size reliably. So it's very difficult to catch it when it's still operable and therefore many people just receive drug treatment," he says.

Add to this the fact that the average age of the lung cancer patient is 71 years old.

"It's an elderly population, they tend to present late, they have a lot of co-morbidities, and they are very hard to treat because of all that," he says.

**Recent setbacks**

Recent progress of the industry's late-stage pipeline certainly supports this bleak outlook. The most recent setback was the termination of a phase III trial of Antisoma's ASA404, a vascular targeting agent licensed to Novartis, after an interim read out revealed little chance of the study succeeding. Although a second phase III study is still ongoing the future of the compound is looking very uncertain (*Antisoma rethinks strategy after lung cancer drug fails pivotal trial, March 29, 2010*).

The table below is an update of the full phase III table presented in February (*Therapeutic focus - Shots on goal could be the key for lung cancer, February 10, 2010*). Only one candidate, Abraxis' Abraxane, has managed to generate positive news.

| Update on selected Phase III Candidates for Lung Cancer | | | |
|---|---|---|---|
| **Product** | **Company** | **Pharmacological Class** | **Update note** |
| ASA404/AS1404 (DMXAA) | Novartis/Antisoma | Vascular targeting agent | 29 Mar: first PIII trial terminated on efficacy grounds |
| CP-751871 | Pfizer | Anti-IGF-1R MAb | 11 Mar: second phase III trial terminated on efficacy grounds |
| Stimuvax | Merck KGaA/Oncothyreon | Anti-MUC1 vaccine | 23 Mar: PIII suspended after serious adverse event. |
| Picoplatin | Poniard Pharmaceuticals/Genzyme | Platinum compound | 24 Mar: company suspends further development |
| NOV-002 | Purdue Pharma/Novelos Therapeutics | Chemotherapy protector | 24 Feb: PIII fails to meet survival endpoint |
| Erbitux | Merck KGaA/Eli Lilly/Bristol-Myers Squibb | Anti-EGFr MAb | 19 Nov 09: refused EU approval, re-filing in US awaited |
| Zactima | AstraZeneca | EGFr & VEGFr inhibitor | 28 Oct 09: US and EU filings withdrawn |
| | | | |
| *Abraxane* | *Abraxis BioScience* | *Taxane* | *10 Mar: +ve phase III data, filing planned 2011* |

The set back with ASA404 was particularly disappointing given the hugely encouraging phase II results the compound generated. The survival benefit in a randomised, mid-stage study in patients with previously untreated, advanced NSCLC was amongst the best seen in lung cancer: median survival of 14 months compared with 8.8 months in patients given chemotherapy alone was reported.

Today, ArQule reported results from a trial in phase II patients with advanced, refractory NSCLC, with ARQ 197 appearing to work best in a subgroup of patients with non-squamous cancer. Given in combination with Tarceva, the drug generated median progression free survival of 18.9 weeks compared with 9.7 weeks in patients given Tarceva plus placebo in this group.

The results are certainly interesting and no doubt ArQule and its partner Daichii Sankyo will be hoping they have a new phase III candidate in their hands. However, as ASA404 demonstrated, positive phase II data is no guarantee of positive phase III data.

**Encouraging class**

Specifically, ARQ 197 is a c-met inhibitor. C-Met is a member of a class of enzymes known as receptor tyrosine kinases, which mediate cell signals involved in tumour growth and proliferation.

As the table below shows, kinase inhibitors represent a big area of research for lung cancer.

| Popular classes of lung cancer products in R&D | Product Count |
|---|---|
| Monoclonal antibodies | 56 |
| *of which...* | |
| *Anti-EGFr MAb* | *6* |
| *Anti-IGF-1R MAb* | *6* |
| | |
| Kinase inhibitors | 32 |
| *of which...* | |
| *tyrosine kinase inhibitors* | *12* |
| *multi-kinase inhibitors* | *11* |
| | |
| Vaccines | 23 |
| Topoisomerase inhibitors | 15 |
| Taxanes | 12 |
| Platinum compounds | 9 |
| Antisense agents | 6 |

TKIs in particular appear to hold much promise, and the two kinase inhibitors so far to gain approval in lung belong to this group, Roche's Tarceva and AstraZeneca's Iressa.

The most advanced in development are Pfizer’s Sutent and Bayer/Onyx’s Nexavar, both multi kinase inhibitors already on the market for other cancers. Both should generate phase III data this year and next in lung cancer, and there are high hopes for success.

**Targeted options**

The appearance of targeted agents such as Avastin, Tarceva and Iressa and the newer chemotherapy agent Alimta has certainly provided more options in treating lung cancer. However doctors would no doubt appreciate a couple more targeted agents in their lung cancer armoury.

With an ever increasing appreciation of the importance of genetics, in terms of the susceptibility of different tumours to different agents, it seems likely that treating lung cancer, as in other solid tumour types, will increasingly become patient, or tumour, specific.

Iressa, for example, after initially being deemed a failure is now approved in a subset of patients with a specific tumour mutation. The drug, which targets the epidermal growth factor receptor (EGFR) to block the transmission of signals involved in the growth and spread of tumours, has been shown to have specific efficacy in this group of patients, with the mutation occurring much more frequently in East Asia.

Only today AstraZeneca announced a deal with a UK diagnostics group, Source BioScience, to develop a companion diagnostic genetic testing service which will allow clinicians to identify whether lung cancer sufferers have activating mutations in their tumours, to help determine the most appropriate therapy regime; and no doubt help capture Iressa patients.

**Small steps**

Still, given the specific challenges of lung cancer, like most developments in oncology further progress is likely to happen slowly, in small incremental steps.

“It’s not going to be penicillin for pneumonia,” Professor Spiro says. “It’s always been that a new drug or a new combination of drugs gives you 3-5% improvement (in survival) at 5 years, which doesn’t sound like a lot but if it's thousands of people that is a lot of lives saved or extended,” he says.

With 219 candidates in active clinical development, hopefully the sheer volume of shots on goal and wide range of therapeutic approaches will eventually deliver these incremental improvements in treating lung cancer.

| Lung cancer - count of active products | |
|---|---|
| **Status** | **Count** |
| Marketed | 22 |
| | |
| Filed | 3 |
| Phase III | 39 |
| Phase II | 125 |
| Phase I | 55 |
| Pre-clinical | 73 |
| Research project | 19 |
| | |
| **Total** | **336** |

*All data provided by EvaluatePharma.*