

targeting drugs to tumours – HyACT®

HyACT® (Hyaluronic Acid Chemotransport Technology) is Alchemia's proprietary technology used to reformulate cancer drugs and enhance their activity against tumours. The transportation works through a 'receptor-based' targeting mechanism in which the hyaluronic acid (HA) binds to tumour cells that express HA receptors on their surface. The HyACT® product HA-Irinotecan successfully completed Phase II clinical trials and the final preparations for the pivotal Phase III trial are underway. The technology has been applied to the anti-cancer drugs 5-fluorouracil and doxorubicin, to produce HyFIVE and HyDOX, both of which have undergone Phase I clinical trials. Preclinical studies have been conducted on many other anti-cancer drugs, including monoclonal antibodies.

Progress over the last year

One of the primary objectives of Alchemia's clinical team over the last year has been to continue to develop and confirm the global regulatory strategy for HA-Irinotecan, ensuring that one final pivotal trial will provide a clear and rapid route to market using a 505(b)(2) NDA (New Drug Application). In September 2008, Alchemia obtained an open Investigative

New Drug Application (IND) from the US FDA which translates into a clinical 'go-ahead'. During the last twelve months there have been landmark changes to the way in which metastatic colorectal cancer is treated, where it has been identified that only 60% of colorectal tumours contain the normal form of the Kras gene which means that the remaining patients do not respond to Erbitux®, which until recently was the best standard of care. This discovery has highlighted the need for more effective therapies in the 40% of patients who are ineligible to receive Erbitux® due to their Kras status. Alchemia believes that this represents a significant opportunity for HA-Irinotecan.

The Phase II clinical testing of Alchemia's lead oncology drug HA-Irinotecan demonstrated that it could significantly delay the progression of advanced colon cancer when compared to irinotecan alone, a drug widely used in the treatment of colorectal cancer. The trial also provided evidence that HA-Irinotecan provides comparable efficacy to a combination of the monoclonal antibody, Erbitux® in combination with chemotherapy, and it became apparent that HA-Irinotecan could fulfil the significant unmet clinical need in patients who do not respond to Erbitux® treatment regimens.

Metastatic Colorectal Statistics

USA*

Colorectal cancer is the third most common cancer in both men and women.

An estimated 106,100 cases of colon and 40,870 cases of rectal cancer are expected to occur in 2009.

An estimated 49,920 deaths from colorectal cancer are expected to occur in 2009, accounting for almost 9% of all cancer deaths.

globally*

Colorectal cancer is the fourth most common cancer in men and the third most common cancer in women worldwide.

In all countries other than the United States the incidence of colorectal cancer is increasing which may be due to obesity, physical inactivity, smoking, heavy alcohol consumption, a diet high in red or processed meats, and inadequate consumption of fruits and vegetables, which are also factors associated with economic development or westernization.

* 1. Center et al. *International Trends in Colorectal Cancer Incidence Rates*. /Cancer Epidemiology Biomarkers & Prevention/, 2009; 18 (6): 1688 DOI: 10.1158/1055-9966.EPI-09-0090. 2. Umar et al. *Alarming Colorectal Cancer Incidence Trends: A Case for Early Detection and Prevention*. /Cancer Epidemiology Biomarkers & Prevention/, 2009, 18 (6): 1672 DOI: 10.1158/1055-9966.EPI-09-0320.

Plans for Phase III

As a result of the Phase II findings, the HA-Irinotecan Phase III clinical trial was re-designed to address the significant therapeutic changes that occurred after the American Society of Clinical Oncologists (ASCO) meeting in mid 2008 and to meet the resulting unmet clinical need that exists in a large proportion of colorectal cancer patients.

The modified Phase III trial is expected to be as follows:

- Randomised and double-blinded; both the patient and clinician will not know which treatment is being administered
- 330 second-line metastatic colorectal cancer patients
- Half of the patients will receive Alchemia's HA-Irinotecan in combination 5-fluorouracil and leucovorin (test arm) and half will receive unmodified irinotecan with 5-fluorouracil and leucovorin (control arm)
- To be conducted over several sites and regions including the US, Europe and Australia
- The primary endpoint will be progression-free survival (PFS).

In June 2009, Alchemia's medical team met with the FDA and presented the modified Phase III study where it was agreed that the trial design was acceptable and if successful, one trial would be required before it was possible to obtain market approval for HA-Irinotecan. In addition to gaining further support of Alchemia's clinical and regulatory route to market, the extensive planning and implementation of the pivotal clinical trial is in the final stages of preparation.

Research in this area was supported through a Commercial Ready Grant from the Federal Government.

Broad application – small molecules and monoclonal antibodies

Alchemia's HyACT® technology is versatile and has the potential to enhance the activity of products that are already on the market including generics, patented products or those near patent expiration. The technology is patent protected and can potentially extend the lifecycle of many different therapeutics from small molecule cytotoxic agents to large antibodies. Furthermore, because of its unique ability to enhance targeting and reduce the toxic effects of chemotherapeutic agents, hyaluronic acid can be trialled with potentially efficacious therapeutics that have failed clinical trials for toxicity reasons.

Super generics

New products typically proceed through a sequence of stages including introduction, growth, maturity and decline, a process described as the product life-cycle. Life-cycle management involves reformulating a therapeutic, before it reaches generic status, producing a new proprietary product with renewed and full patent protection and greater earnings potential than commodity generics. Alchemia expects the HyACT® platform to generate a sustainable pipeline of patented therapeutics with improved safety and efficacy profiles. HyACT® products will be well placed to avoid generic pricing pressure, as they are proprietary products with superior therapeutic profiles. This will enable them to attract premium pricing.

Improving safety and efficacy

In preclinical studies using multiple cancer drugs, HyACT® has been shown to deliver more than double the dose of drug to the tumour compared with the drug injected alone. Research has demonstrated that this is due to an accumulation of the HyACT® drug at the tumour site due to the over expression of a receptor (activated CD44) that binds HA on tumour cells. HyACT® offers the potential for reformulation of compounds that have failed clinical trials due to efficacy or toxicity reasons. HyACT® reformulation offers this class of drugs a pathway to improved efficacy and safety, which may see them pass through further clinical trials to market. For other cancer drugs, HyACT® may sustain or build upon a drug's market value.

Outlook – versatility expands potential

In regulatory terms Alchemia's HyACT® technology,

- is ready to enter a Phase III trial in combination with the cancer drug irinotecan;
- has received FDA support for a single Phase III trial;
- will require just one successful Phase III trial to gain approval.

Furthermore, HyACT®,

- has the potential to improve the safety and efficacy of cancer drugs
- can help extend the product lifecycle of cancer drugs
- will have greater earnings potential than commodity generics
- has patents around formulation which are protected until 2020.