



Alchemia Limited

ASX:ACL

Global Regulatory Strategy – Registration Studies
Ausbio 2010



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- Founded 1995, listed on ASX (ASX:ACL) Dec 2003
 - Small molecule biopharmaceutical company with 20 FTEs

- Two Promising Late Stage Assets
 - Generic fondaparinux – Filed for US approval March 2009
 - ANDA accepted with priority review May 2009
 - Manufacture and marketing agreement with Dr Reddy's
 - Commercial launch pending

 - Novel antibody-drug conjugate (ADC) platform for tumor-targeting technology
 - Phase II trial of HA-Irinotecan in colorectal cancer
 - Phase III study in colorectal cancer
 - Other potential clinical applications



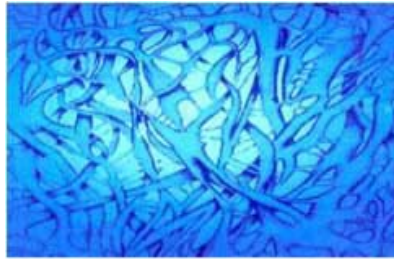
Alchemia Oncology

HyACT[®] and HA-Irinotecan

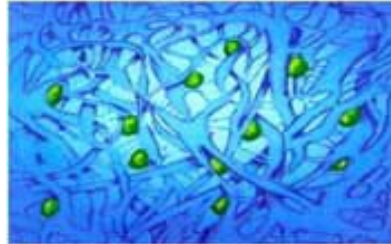
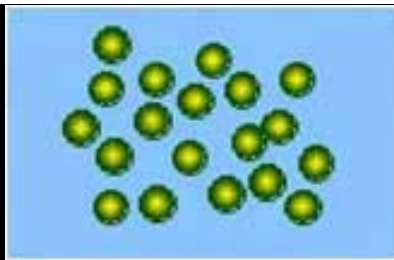
HyACT[®] Technology Platform



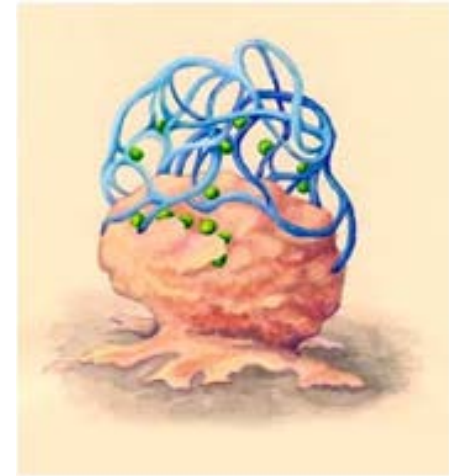
Hyaluronic acid (HA) used to target chemotherapy agents to tumors



Hyaluronate (HA)



The drug is formulated within HA matrix.



HA selectively binds to cancer cells via HA receptors (CD44) delivering more drug to tumor.



- Targeting drug to Hyaluronic Acid (HA) receptor (CD44)
 - Activated CD44 over-expressed in majority of tumor types
 - CD44 is an established marker for cancer stem-cells
 - Enhancement of activity is dependant on CD44 expression
- Hyaluronic acid is approved for human use
 - Used in eye and knee surgery and as dermal filler
 - Most abundant natural occurring polysaccharide
 - Available at scale from bacterial fermentation
- Tumor effects seen with multiple agents
 - Small-molecule drugs and biologicals

Regulatory Objectives for HyACT[®] Platform



- Hyaluronic Acid drug delivery vehicle must be considered as a novel excipient and not as a new chemical entity

A novel excipient is a compound that has the potential to impart an additive or synergistic effect on the intrinsic pharmacological activity of drug substance with which it is formulated, but lacks pharmacological activity at the levels used in the drug product.

- Registration route must adopt a 505(b)(2) approach

A section 505(b)(2) is relevant when changes are made to already approved drug products, variations that can range from route of administration, dosing regimen, formulation strength, ingredients such as the quality or type of excipients, changes to the active ingredient of drug product. Registration dossier relies on data from studies not required for the original applicant thereby reducing development costs and time.

- Clinical trial must be conducted with a Progression Free Survival end-point (not considered only as a surrogate end-point) required for registration in both USA and Europe

HyACT[®] – human experience



Test Compound	Patient Population	Number of patients	Safety
Phase I studies			
Hyaluronic acid (HA)	Healthy volunteers	8	√
Hyaluronic acid (HA)	Healthy volunteers	24	√
HA-fluorouracil	Metastatic Colorectal	14	√
HA-doxorubicin	Metastatic Cancers	16	√
	Metastatic Colorectal	13	Reduced diarrhea and neutropenia
	Metastatic Colorectal	80	Equivalent to irinotecan

HA-Irinotecan - Phase II trial summary



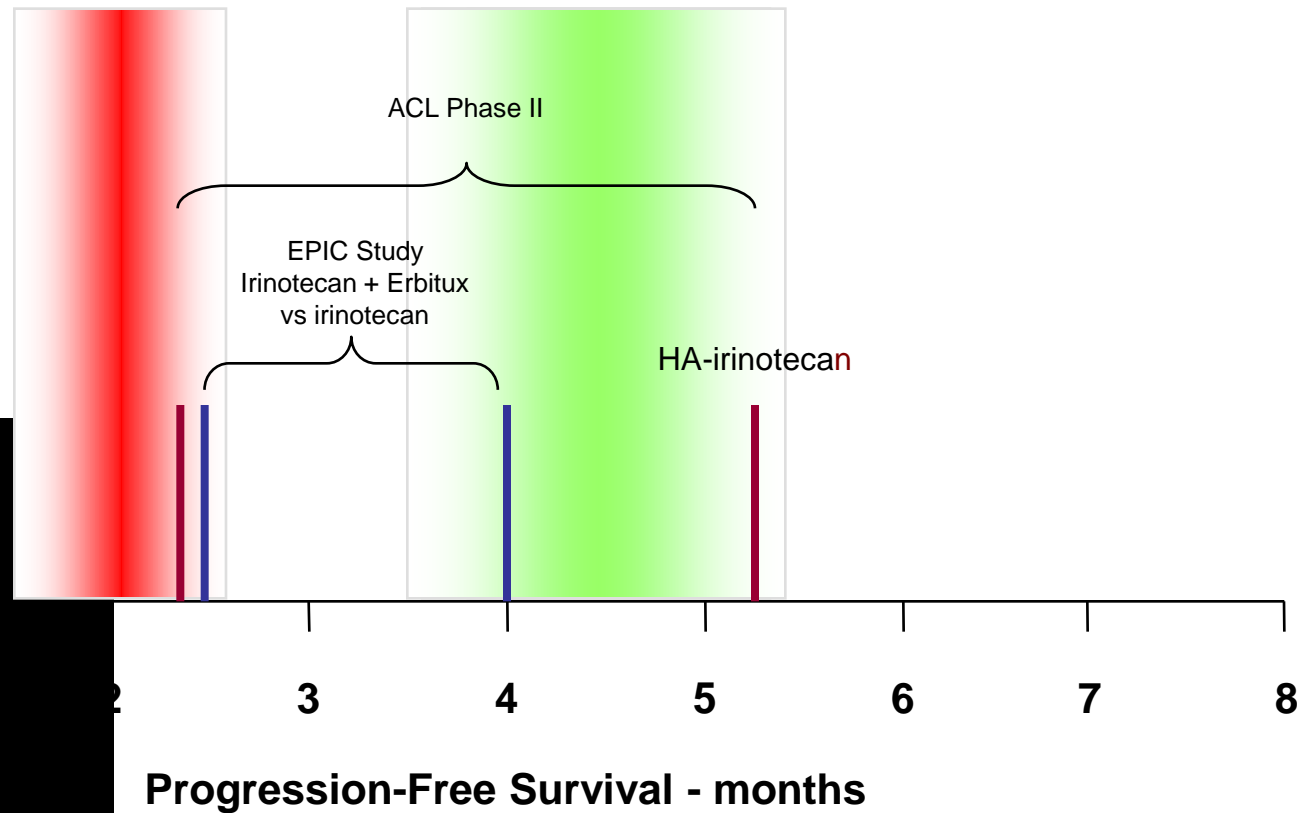
- 2nd line mCRC, 5FU failures (85% FOLFOX), ECOG 0-1
 - 80 patients, 1:1 randomization
 - irinotecan 350mg/m² vs HA-Irinotecan (350mg/m² irinotecan, 1000mg/m² HA) every 3 weeks
 - Well matched demographics and prior treatment
 - Significant increase in PFS (+116%, p=0.014)
 - Significant increase in TTF (+123%, p=0.007)
 - Significant increase in disease control by RECIST (76% vs 46%, p=0.05)
 - Significant increase in OS (10.0m vs 8.0m, p=0.20)
 - Similar toxicity
 - Similar plasma PK of irinotecan or SN-38
 - Similar dose intensity per patient per cycle

Clinical Outcomes in mCRC



Irinotecan or
FOLFIRI

Irinotecan
+ Erbitux



Regulatory Strategy – Mark I



- Clinical Advisory Board recommended HA-Irinotecan + Erbitux for Phase III study
 - Current standard of care in 2nd line metastatic CRC
 - Would be difficult to recruit single agent irinotecan study
- 2008 - difference between EMA and FDA on Erbitux use
 - EMA mandated Kras gene testing and Erbitux use only in Kras wild-type tumors
 - FDA approved Erbitux use in Kras mutant and wild-types
 - FDA focused on acceptability and breadth of label

Regulatory Strategy – Mark I



- 740 patient study proposed, 2nd line mCRC, Kras wild type only
- IND filed at end Phase II
 - Proposal accepted for Phase III study in combination with Erbitux
- Sought scientific advice in Europe
 - (as) EU rapporteur for Camptosar (irinotecan)
 - (as) EU rapporteur for Erbitux (cetuximab)



➤ ASCO June 2008

- Analysis of CRYSTAL study in mCRC evaluated role of Kras gene
- 1200 patients, 1st line mCRC, FOLFIRI +/- Erbitux
- Retrospective analysis of 587 pts with known Kras status showed...
 - Patients with wild-type Kras gained significant benefit from Erbitux
 - Patients with mutant Kras gained no benefit from Erbitux

➤ FDA did not immediately change label on Erbitux/Vectibix

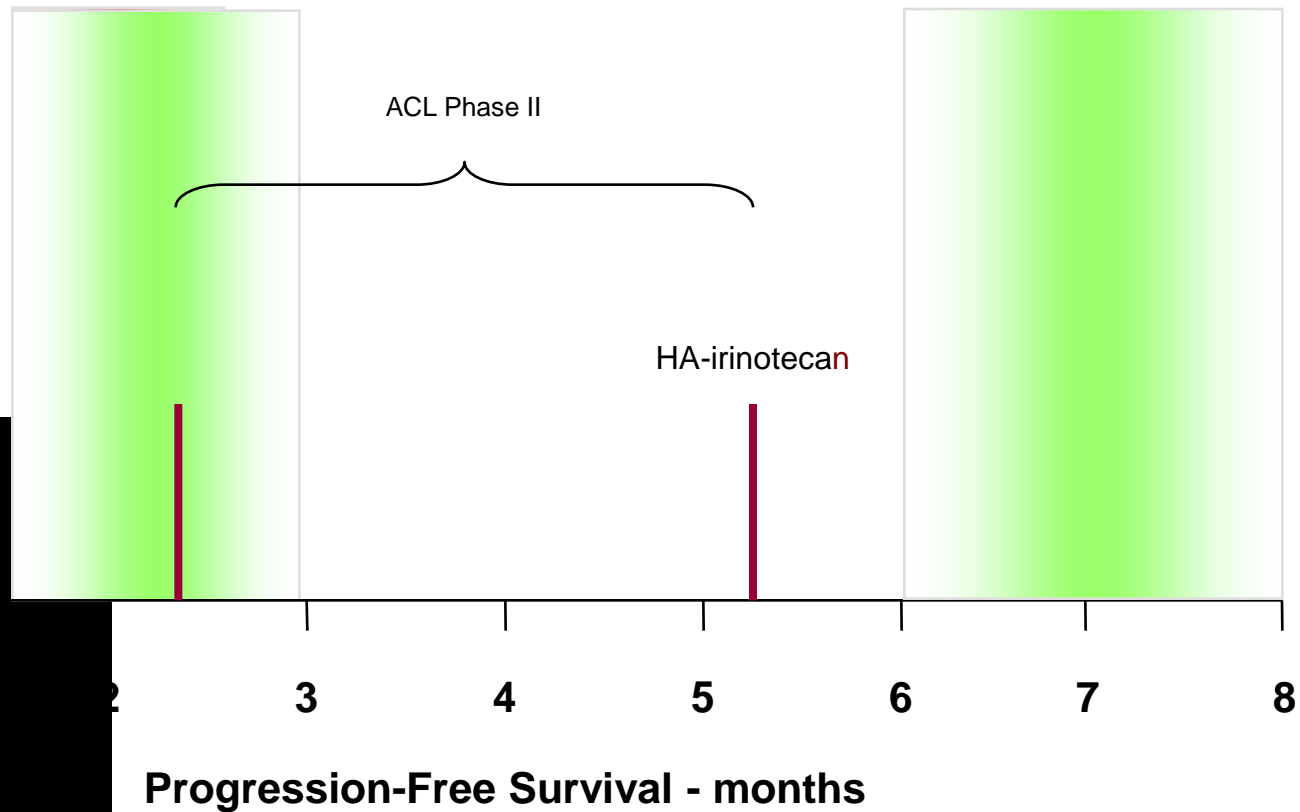
- Clinical trials prospectively stratified for Kras status
- FDA recommended use of EGFR mAbs in Kras wt
- Bristol-Myers Squibb and Amgen (Vectibix) requested label change
- FDA 'recommends' Kras testing

mCRC after CRYSTAL



Irinotecan or
FOLFIRI or
Iri+Erbitux KRAS mutant

Irinotecan
+ Erbitux
KRAS wild type



Regulatory Strategy – Mark II



➤ Changes in treatment after CRYSTAL

- FOLFIRI or irinotecan now standard of care for large patient population
 - Kras mutant (~40%)
 - EGFR –(ve)
 - Where Erbitux/Vectibix not available/unaffordable
 - Intolerant of EGFR mAb toxicities

➤ Phase III ready to enrol Q1 2011

- FOLFIRI (HA)-Iri*, 1:1 randomization
- 100 patients, 2nd line mCRC
- Kras mutant
- Primary endpoint = PFS

Irinotecan + 5FU + irinotecan vs leucovorin + 5FU + HA-Irinotecan

Alchemia interactions with FDA



Pre-IND Meeting - Aug 2004:

- Pre-IND meeting where a 505(b)(2) route registration route was agreed if it could be demonstrated that HA was “inert” when not combined with a drug.

Second Pre-IND Meeting – Jan 2008:

- FDA agreed that HA could be considered as a novel excipient.

IND Filing - Sep 2008

Open IND - Oct 2008

Phase 1 (Feb 2009):

- Overall survival as the primary end-point for the HA-Irinotecan trial.

Phase 2 (2009):

- Reached agreement on Progression Free Survival
- Trial may be eligible for full or conditional approval in US
- Trial design acceptable for US registration.



Scientific Advice Procedure Meetings (MPA & AFSSAPS) - Jan 2008:

- Primary objective to harmonize the US and European registration strategy
- Interaction with Swedish (MPA) and French (AFSSAPS) regulatory authorities to evaluate dossier and suitability of HA-Irinotecan/Cetuximab Phase III clinical trial.
- Agree that the proposed Phase III clinical trial would be suitable for registration in Europe.

Scientific Advice Request (EMA, UK) - Jan 2010:

- Met and obtained scientific advice

- obtained on the current (FOLFIRI) /Phase III clinical trial design the current non-clinical and manufacturing data dossiers.
- acceptable in EU for registration submission (including OS as trial endpoint).

Outcomes from Regulatory Negotiations



- Hyaluronic acid drug delivery vehicle considered as a **novel excipient**
 - 505(b)(2) route adopted
- **Progression Free Survival** accepted as a drug approval end-point for the Phase III clinical trial
- Phase III clinical trial is the **pivotal** registration trial
- Comparison of US and European regulatory strategies.

Tips/Recommendations



- Must have clear regulatory objectives and be willing to persist and negotiate with regulatory agencies.
- Harmonize regulatory strategies in key markets where possible.