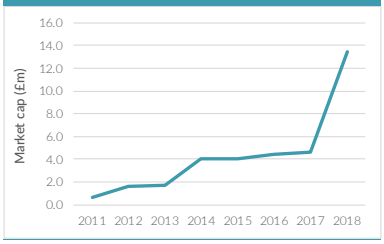
Pharmaceuticals & Biotechnology



Source: Hardman & Co Life Sciences Research

Market data

EPIC/TKR	**INC**
Last funding	2018
Price	550p
Shares in issue	2.43m
Pre-IPO capitalisation	£13.4m
IPO target raise	£4.0-£10.0m
Target market	AIM

Description

Incanthera is a specialist oncology company that uses novel, targeted, drug delivery systems to deliver cytotoxic warheads directly to cancer cells in the expectation that they will improve efficacy and have fewer side effects than conventional cytotoxic therapies.

Company information

Exec. Chairman	Tim McCarthy
CEO	Simon Ward
COO	Pawel Zolniercyk
CFO	Laura Brogden

www.incanthera.com

Key shareholders

Directors	7.8%
North West Fund	33.3%
Uni. of Bradford	15.4%
ImmuPharma plc	15.0%
Founders	2.7%
Maven Capital (NPIF NW)	1.9%

Diary

Nov'18	IPO
Nov'18	Interims
4Q'19	ICT01-2588 CTA submission

Analysts

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INCANTHERA LIMITED

Pre-IPO research – targeting the warheads

Incanthera is a spin-out from the Institute of Cancer Therapeutics at the University of Bradford to exploit development opportunities generated from this prestigious organisation. Key is a targeted pro-drug delivery platform, to which different cytotoxic warheads can be attached, activated only when enzymes are over-expressed by tumour cells. The specificity of this technology should improve efficacy and lower side effects, to give better patient outcomes. The diversity of uses means that its drugs will address a large segment of the $110bn cancer market. Incanthera will be seeking £4-£10m at IPO to progress three drugs into trials.

- **Strategy:** Incanthera is a specialist oncology company using a novel pro-drug approach to deliver cytotoxic warheads directly to tumour cells. It intends to develop drugs to a suitable valuation inflection point and then out-licence them for late-stage trials, in return for development milestones and royalties.

- **Focus:** Incanthera has expertise in developing a pipeline of anti-cancer pro-drugs that deliver cytotoxic warheads directly to the cancer cell environment. ICT01-2588, using a colchicine analogue warhead, has already been out-licensed and is expected to be Phase I ready by the end of 2019.

- **Valuation:** Incanthera has been compared with valuations afforded by stock markets for both UK and global peer groups, and with prices paid by major pharma/biotech to acquire novel oncology assets. The average EV for UK peers is £29.4m, and for global peers is £68.6m, suggesting strong upside potential.

- **Risks:** Investments in small, early-stage pharmaceutical companies carry a significant risk, and additional capital will be required in the future for further expansion of its clinical programmes. Management intends to undertake an IPO on AIM, but there is no guarantee on timing nor on the quantum of cash raised.

- **Investment summary:** Incanthera offers a novel approach to the concept of targeted cancer therapy which, when further de-risked, is likely to attract the attention of the majors, especially given management strategy to out-licence its drug candidates, at a suitable time point, for later-stage development. Our cashflow analysis, based on a raise of £7m at IPO with ca.£4m already approved by HMRC for VCT/EIS tax relief, indicates at least a two-year cash runway.

Financial summary and valuation

Year-end March (£000)	2016	2017	2018	2019E	2020E	2021E
Sales	0	0	603	0	1,000	1,800
SG&A	-615	-676	-1,223	-1,050	-1,280	-1,360
R&D	-451	-365	-143	-250	-2,000	-2,250
EBITDA	-946	-920	-832	-1,230	-3,210	-3,310
Underlying EBIT	-1,066	-1,041	-952	-1,350	-3,330	-3,430
Reported EBIT	-1,100	-1,075	-984	-2,158	-3,370	-3,474
Underlying PBT	-1,066	-1,041	-952	-1,346	-3,330	-3,430
Statutory PBT	-1,100	-1,075	-984	-2,155	-3,370	-3,474
Underlying EPS (p)	-104.7	-97.1	-55.7	-50.7	-72.9	-73.8
Statutory EPS (p)	-108.4	-100.7	-57.6	-82.7	-73.9	-75.0
Net (debt)/cash	43	88	143	6,879	3,703	840
Capital increases	0	309	1,021	9,064	0	0

Source: Hardman & Co Life Sciences Research

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Executive summary

Introduction

Incanthera provides the development platform for the UoB's Institute of Cancer Therapeutics…

Incanthera was incorporated in 2010 as a spin-out from the University of Bradford's Institute of Cancer Therapeutics to maximise the development opportunities being generated from this renowned organisation. To that end, in 2011, Incanthera entered into an exclusive technology agreement with the University of Bradford (UoB), which was crystallised at the end of 2012 when all the intellectual property (IP) rights in the relevant patents were fully assigned to Incanthera. This provided the company with its core pro-drug delivery platform technology, which has been armed with a known cytotoxic warhead to create its lead candidate, ICT01-2588, for solid tumours that will be Phase I ready by the end of 2019. Recently, the pipeline agreement with the UoB was extended for a further 10 years.

…boosted by a series of acquisitions and research agreements

Other technologies and products have been acquired through the acquisitions of Onco-NX (University of Salford spin-out) and Spear Therapeutics, both with an oncology focus, and an agreement with the Trustees of the Leland Stanford Junior University (Stanford) for tumour-targeted theranostics – a combined therapeutic/ diagnostic tool.

Originating from the universities of Bradford (UK), Salford (UK) and Stanford (US), all its technologies have very strong provenance, supported by a strong IP position.

History of Incanthera

Date	Event
2010	Incorporation of Incanthera Limited (no. 11026926)
2011	Funding round enabling technology licence from UoB
2012	Assignment of IP rights in the relevant patents from UoB
2014	Acquisition of Onco-NX to gain access to ICT03-Es5
2014	Acquisition of Spear Therapeutics Ltd to gain access to ICT04
2015	Agreement with Stanford University in respect of ICT02
2017	Licensing deal with Ellipses Pharma Ltd for initial ICT01-2588 clinical trial
2018	Funding round to raise £1.26m (gross) funds at 550p per share
2018	Head-of-Terms agreement with ImmuPharma plc to for Nucant licence
2018 tbc	IPO of Incanthera plc

Source: Incanthera, Hardman & Co Life Sciences Research

The last round of funding provides a pre-IPO capitalisation of £13.4m

To get Incanthera to where it is today, the company has raised gross funds of £7.42m through a series of funding rounds, the last round being between March and October 2018 to raise a total of £1.26m at a price of 550p per share. In addition, AIM-listed company, ImmuPharma plc (IMM), recently made an investment of £2.0m in the company as part of a Head-of-Terms agreement for the further development of its Nucant technology (see page 28). At the latest issue price, the outstanding share capital of Incanthera is valued at £13.4m.

Focus on cancer

Through its close relationship with the Institute of Cancer Therapeutics, Incanthera's focus is on finding new cancer treatments

Given the origins of Incanthera, coupled with a continuing close working relationship with the UoB's Institute of Cancer Therapeutics, which has a mission to research and develop new cancer treatments that harness the immune system to attack cancer, switch-off cancer by blocking gene transcription, or prevent cancer from spreading to other sites, the company is looking to develop chemotherapeutic medicines with improved efficacy through greater selectively towards cancer cells and to address the plethora of adverse side effects seen with current treatments.

In addition, through this relationship, Incanthera has access to oncologists and surgeons at The Bradford Royal Infirmary and St James's Hospital, Leeds, which

enables the company to address all the elements of the drug discovery process from conception through to clinical evaluation at these hospitals.

Rationale

Cytotoxic agents are still in use in cancer therapy, but their delivery to the cancer cells needs to be greatly improved

There are numerous cytotoxic agents with the ability to kill cancer cells by targeting the cell cycle. However, many of them are unable to discriminate between cancer cells and healthy cells, and rely on the fact that cancer cells, by their very nature, are proliferating at a much faster rate. The lack of specificity leads to poor efficacy rates – response rate frequently as low as 12%-25% – and the presence of severe side effects. Therefore, for the last 20 years, the pharmaceutical industry has attempted to discover and develop cancer therapies that are better directed towards cancer cells and leave healthy cells untouched, with the best examples being antibody-derived drugs that are targeted only to tumour cells. Other approaches include the targeting of specific enzymes over-expressed by cancer cells, or the alteration of T-cell responses. While there has been some improvement in outcomes, they are still well below what had been expected.

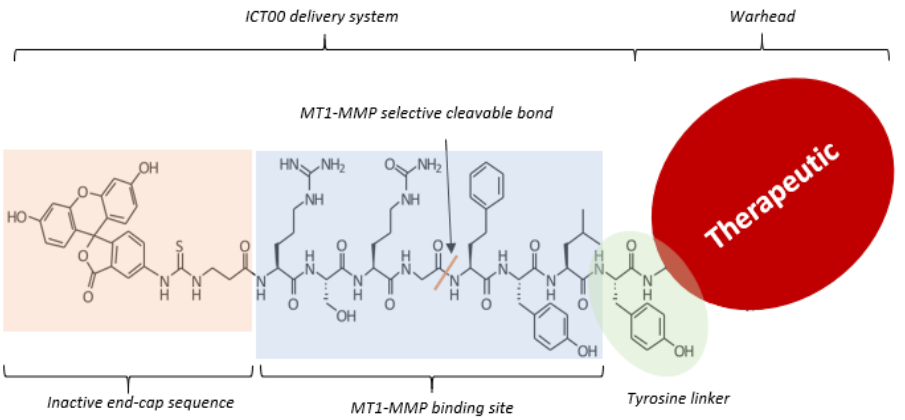
Incanthera aims to use the specificity of the cancer cells to deliver the cytotoxic agent …

Instead of inhibiting an enzyme that is over-expressed in cancer, Incanthera's strategy is to develop drugs that utilise over-expression of these enzymes to activate cancer specific drugs, leading to cell death. For example, matrix metalloproteinases (MMPs) are a group of endopeptidases enzymes that are responsible for the degradation of most extracellular proteins during organogenesis, growth and normal tissue turnover. They are essential for many physiological processes, such as wound healing, apoptosis (programmed cell death), cell migration, embryonic development, angiogenesis, cell migration, proliferation and invasion. The expression and activity of MMPs is normally quite low, but increases significantly in various pathological conditions such as tumour growth and metastasis.

… through the development of innovative pro-drugs

The focus of Incanthera is on pro-drug delivery platforms designed to be cleaved by a specific membrane-bound enzyme – the membrane-type I MMP (MT1-MMP, also known as MMP-14) present and over-expressed in many cancer cells. A cytotoxic warhead can then be attached to this, with the aim of releasing it only when the pro-drug sequence is cleaved by MMP-14 in the cancer cell. This platform provides a drug delivery system that is able to shield the toxic effects of a cytotoxic drug, acting as a vector to deliver the desired effect at the disease sites.

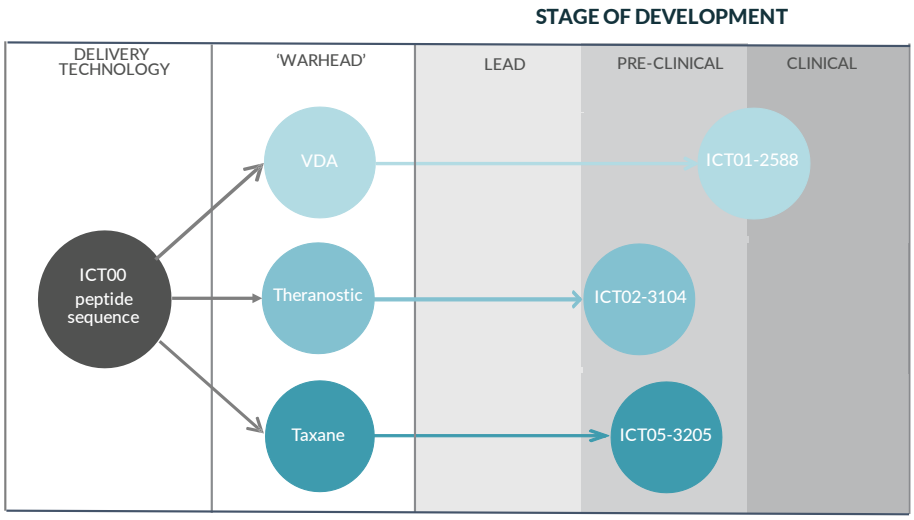
ICT00 platform technology



Source: Incanthera

This approach is highly targeted, and also very specific, because the warhead can only be released once the molecule is cleaved and this can only occur where there is overexpression of an active MT1-MMP binding site (cancer cells only). Sometimes described as a 'smart bomb', it provides a very versatile approach, as it can be combined with a number of cytotoxic drugs (warheads).

Multiple warhead drug delivery platform



ICT00: targeting, delivery vehicle.
Warhead: interchangeable active chemical.
Lead: chosen drug candidate.
Pre-clinical: regulatory safety assessment.
Clinical: patient trials.
VDA: Vascular Disrupting Agent.
Theranostic: Diagnostic tool.

Source: Incanthera

R&D pipeline

Incanthera has a rich pipeline of diverse pro-drugs targeting several types of cancer

Incanthera is developing a balanced portfolio of oncology products at different stages across a number of cancer indications, with its most advanced candidate set to be Phase I ready by the end of 2019. The UoB has identified already a rich and diverse pipeline of future products from which Incanthera could benefit given its ongoing relationship.

Incanthera pipeline

Platform	Product candidate	Indication	Lead optimisation	Pre-clinical	Phase I	Phase II
ICT00	ICT01-2588	Lung, breast, ovarian cancers				
	ICT02-3104					
	ICT05-3205	Ovarian, prostate cancers				
	ICT03-Es5	Liver, brain, paediatric cancers				
	ICT04-CYP	Bladder, colo-rectal cancers				

Product candidate	Indication	Lead optimisation	Pre-clinical	Proof-of-concept clinical trial
ICT07	Actinic keratinosis, melanoma			

Source: Incanthera, Hardman & Co Life Sciences Research

ICT01-2588

ICT01-2588 is expected to be Phase I ready by the end of 2019

ICT01-2588 is a novel peptide-conjugate of a VDA colchicine analogue 'warhead', linked to the ICT00 drug delivery platform technology described above. In pre-clinical studies, ICT01-2588 achieved tumour-selective delivery of the VDA, leading to reduced blood flow to the tumour and tumour shrinkage without significant toxicity. Clinical trials in solid tumours (lung, breast, ovarian) will be co-ordinated and paid for by Ellipses Pharma, and are set to commence late 2019.

ICT02-3104

Tumour-targeted theranostics comprise a VDA warhead (the therapeutic element) linked to both the ICT00 drug delivery platform technology and to an MRI contrast agent (the diagnostic element) to allow detection of its location. The lead theranostic compound is ICT02-3104, which is a construct comprising two main modules: ICT01-2588 and a CLIO nanoparticle for imaging.

ICT05-3205

ICT05-3205 and ICT03-Es5 are anticipated to enter the clinic in 2020

ICT05-3205 is a novel peptide-conjugate of a paclitaxel-related 'warhead linked to the ICT00 drug delivery platform. Taxol was a successful drug launched by Bristol-Myers Squibb (BMS) in 1993, reaching peak sales of $1.6bn in 2000 and cumulative ex-factory sales in excess of $13bn, despite the high level of side effects due to its lack of specificity.

ICT03-Es5

ICT03-Es5 is a quinone-based bio-reductive anti-cancer agent activated by the enzyme DT-Diaphorase (DTD), which is over-expressed in many solid tumours, including breast, colon, liver, bladder, stomach, the central nervous system (CNS), lung tumours, and in melanomas. Incanthera's approach is to use DTD to activate quinone-based pro-drugs to selectively target cancer cells that express DTD. It is a DNA cross-linking agent designed to overcome limitations associated with previously proposed bio-reductive agents, such as stability, solubility and poor efficacy.

ICT04-CYP

Know-how and early work at the UoB's Institute of Cancer Therapeutics targeted colo-rectal cancer using a catabolic enzyme (CYP2W1) to convert pro-drug to ultra-potent chemotoxins based upon the class of natural compounds known as the duocarmycins. Pre-clinical results with the lead compound have demonstrated successful delivery of ultra-potent agents with acceptable toxicity profiles. Current R&D programmes are vested within the UoB's Institute of Cancer Therapeutics, but are available to Incanthera, which is focusing on bladder and colo-rectal cancers.

ICT07

ICT07 is a topical formulation of a well-established product for skin solar keratosis treatment and prevention of skin melanoma. The active ingredient has been shown to be safe and effective in reducing the rate of new non-melanoma skin cancer and actinic keratoses following oral administration. With sun cream already effective in reducing the number of actinic keratoses and the incidence of squamous cell carcinoma, ICT07 would be targeting patients with nascent, pre-existing skin cancers. Given that various products are widely accessible and inexpensive, Incanthera will be targeting the high-end pharmaceutical market with a patent-protected formulation regulatory approved for a specific indication.

Nucant technology

As part of a corporate update announcement released via RNS on 7 September 2018, IMM provided details about a signed Heads-of-Terms agreement with Incanthera in order to progress its clinical-stage oncology asset, the Nucant programme. As part of the agreement, IMM has granted Incanthera a period of exclusivity until 31 December 2018 to finalise the terms of a Definitive Licence Agreement for the Nucant technology.

Business model

Incanthera has adopted an out-sourced business model with a pipeline generated from research institutes and acquisitions

Incanthera has adopted a lean out-sourced business model. Its pipeline is generated largely from research projects that are generated from partnerships with universities, for which it acts as the development and commercial outlet, or through acquisition. All of its development and clinical trial work is contracted out. For the foreseeable future, commercialisation will be achieved through out-licensing, with Incanthera receiving milestones and royalties. The company's HQ, management team, and all operational and finance activities are coordinated from modest offices based in Manchester.

Commercial opportunity

We estimate the global cancer market at $111bn in 2017…

Although Incanthera is operating in a very competitive environment, and despite all the research and commercialisation of new oncology therapies, there is still a desperate need for new, effective cancer drugs. Hardman & Co estimates that the global oncology market was worth ca.$111bn in 2017 and represented 9.9% growth over 2016 in $ terms. Given the incidence, the market is forecast to have 7%-8% CAGR and reach $155-$160bn in 2022.

…with a large proportion addressable by Incanthera's drugs

The development approach taken by Incanthera will address potentially a very large part of the market – up to 78%, or ca.$86bn in 2017. On the one hand it is developing small molecule cytotoxic drugs for the majority of solid tumours (ca.55% of cases), which implies that it would be competing with the $45bn small molecule segment of the market. On the other hand, it also has a highly targeted approach, which would both compete with and complement the antibody approach, which represented $41bn of in-market sales in 2017, especially given the multi-disciplinary approach adopted by oncologists.

SWOT analysis

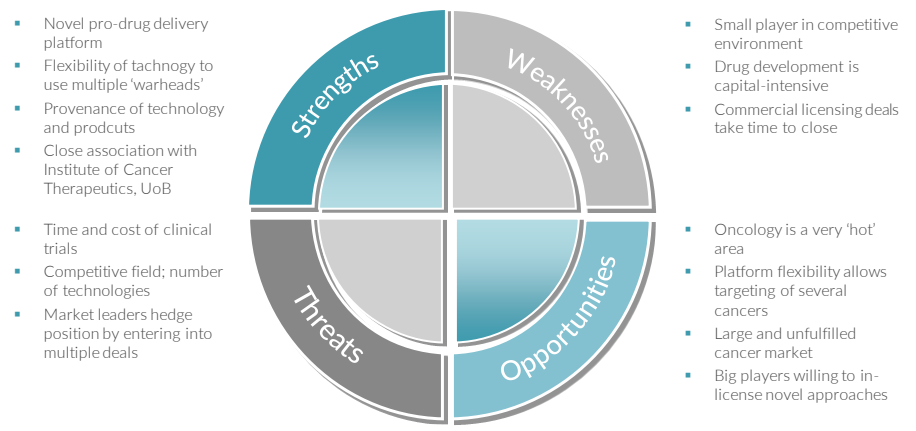
Incanthera addresses the vast majority of tumours…

Incanthera' strength is in using well-known cytotoxic 'warheads' in a controlled and highly selective manner. This is opening key opportunities, meaning that it is addressing the majority of tumours and would compete with and/or be complementary in the largest segments of the oncology drug market.

…in a competitive market

The key weakness and threat is that it is operating in a very competitive market place and will need to form partnerships and/or out-licensing agreements to fund late-stage trials and commercialise its drugs, in return for development milestones and royalties.

Incanthera – SWOT analysis



Source: Hardman & Co Life Sciences Research

Valuation

Incanthera has been evaluated against peer companies and through M&A analysis

Incanthera's strategy is to develop its assets through to value inflection points, preferably proof-of-concept clinical trials, and then to out-license them for large-scale, late-stage trials and commercialisation. In return, it will receive development milestones and royalties on net sales. This is consistent with several AIM-listed biotech companies. When this point has been achieved with the first few assets, it will be possible to prepare risk-adjusted discounted cashflow models of these milestone/royalty streams. However, at present, the assets are at too early stage to generate a meaningful outcome.

Using the last post-money valuation as a benchmark there is strong upside potential

Consequently, comparative valuation methodologies – M&A and peer group analyses –have been adopted. Our comments are based on a benchmark valuation of Incanthera obtained from the post-money valuation that the company commanded following the funding round in March 2018, together with the Subscription for shares by ImmuPharma, which values the group at £13.4m.

Licensing deals

- The median up-front licence deal value of pre-clinical compounds in the oncology space is $30m per target, with milestones of up to $562m; this compares with $17m and $357m, respectively, up to the end of 2015.
- The median up-front license deal value of Phase I clinical assets in oncology is $53m per target, with milestones of up to $511m; this compares with $45m and $628m respectively up to the end of 2015.

Peer group valuations

- From a group of AIM-listed UK peers, the average EV is £29.4m (range £4.5m-£143.5m). This sets the relative EV of these UK companies to the post-money valuation of Incanthera in the range of 0.3x to 12.2x, with an average of 2.3x.
- From a group of internationally-listed global peers, the average EV is £68.6m (range -£11.5m (i.e. trading below net cash) to £296.4m). This sets the relative EV of these global companies to the post-money valuation of Incanthera in the range of -0.9x to 22.9x, with an average of 5.3x. The best comparator for tumour directed technology is Alligator Bioscience (ATORX.ST), and the best comparator for VDA technology is Mateon (MATN.PK).

In our opinion, these peer group analyses suggest that there is scope for substantial upside in the valuation of Incanthera provided that the promise of its drug delivery technology in pre-clinical development work is borne out by clinical results in the upcoming trials.

Newsflow

Incanthera newsflow

Date	Event
4Q'18	Potential IPO on AIM
4Q'18	Completion of Nucant technology in-licensing deal
4Q'19	Submission of CTA for ICT01-2588 to MHRA for solid tumours
1Q'20	Submission of CTA for ICT07 to MHRA in actinic keratoses/melanoma
2020	Proof-of-concept trial results for ICT07
2020	Submission of CTA for ICT03-Es5 to MHRA
2020	Submission of CTA for ICT04-Cyp to MHRA
2020	Submission of CTA for ICT05-3205 to MHRA in ovarian/prostate cancer

Source: Hardman & Co Life Sciences Research

Investment conclusion

Incanthera has a well-diversified pipeline of targeted cytotoxic pro-drugs…

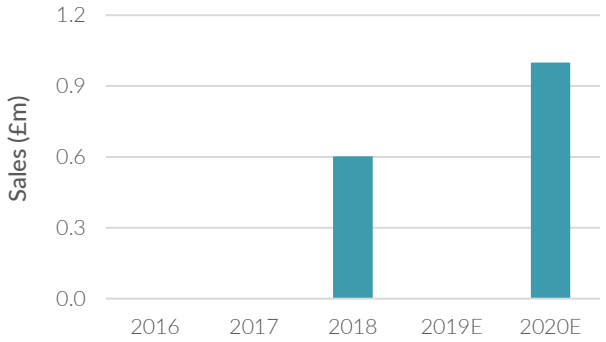
Incanthera represents a very interesting investment opportunity. For the last 20 years the pharmaceutical industry has been attempting to increase the specificity of cancer drugs in order to improve the efficacy and reduce the high incidence of quite severe side effects. Incanthera offers a completely novel approach to this concept, with its pro-drug targeting that only releases its cytotoxic warhead when cleaved only by cancer cells. This pro-drug technology can be applied to multiple warheads.

… with a strategy to licence-out when appropriate

In the near to medium term, management has adopted a licensing-out strategy whereby the company will benefit from development milestones and royalties on net sales when products are commercialised. The pharma/biotech majors are willing to pay handsome prices for such propositions.

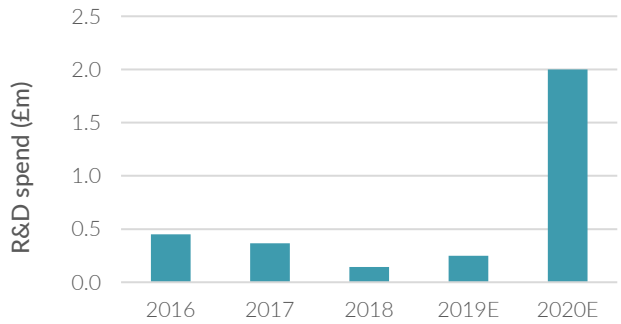
In the event that the company delivers against its goals in the upcoming clinical trials, peer group valuations suggest that there is scope for considerable upside. Part of the IPO funding, estimated to be in the range of £4-£10m, is eligible for VCT/EIS tax relief.

Sales



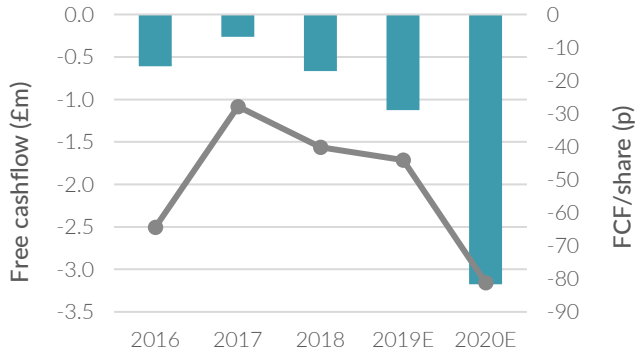
- Sales are related to services being provided by Incanthera to licensing partner Ellipses Pharma
- Work order #1 is almost complete and work order #2 will commence on completion, expected in 1H fiscal 2020
- Work order #3 will only be placed following a successful outcome with work order #2
- Sales are largely 'pass-through' costs and only carry a low margin

R&D spend



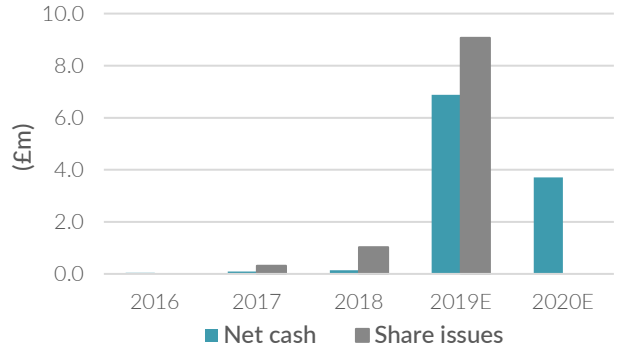
- R&D spend has been modest to date, aligned closely to the financial resources of the group, and does not allow for the unknown research costs by the universities, mostly grant funded
- The Phase I clinical trial with ICT01-2588 will be funded by Ellipses Pharma
- Conclusion of the in-licensing of Nucant technology will result in a significant increase in likely R&D investment
- Future R&D spend will be conditional on the level of funds raised at IPO

Cashflow



- The company has been operating with relatively modest financial resources to date
- Incanthera will be cash burn for the foreseeable future, as it pushes forward with its R&D programmes
- The level of R&D investment will be dependent on the quantum of funds raised at IPO
- Forecasts do not allow for any out-licensing income from its drug programmes

Net cash/(debt) and capital increases



- Total funds raised since inception are ca.£7.5m, plus an unquantifiable amount of research funding, mostly via grants
- The company raised £1.26m in pre-IPO funding during 2018, and £2.0m through a Subscription by IMM
- Forecasts are based on the assumption that the company will raise £7m (gross, and mid-point of target range) at IPO giving it at least a two-year cash runway

Source: Company data; Hardman & Co Life Sciences Research

Background

Introduction

Established in 2010 to exploit and commercialise opportunities from the Institute of Cancer Research at the UoB

Incanthera was established in 2010 as a spin-out from the Institute of Cancer Research, at the UoB to exploit and commercialise development opportunities in the field of oncology that were derived from this institution's globally-renowned research capability. In 2011, it raised its first funding and signed an exclusive IP and option agreement with the UoB, giving it access to its research pipeline. The option was exercised in 2012, crystallising assignment of all the IP rights to relevant patents to Incanthera. In February 2018, this pipeline agreement was extended for a further 10 years. In addition, a number of other complementary opportunities have been garnered from other world-leading universities.

Focus

Given its origins, Incanthera is focused on the field of oncology. The company's strategy is to identify and develop innovative solutions to address the well-known problems with many existing cancer drugs, namely a lack of specificity leading to severe adverse events and poor efficacy. Consequently, the pharmaceutical industry has spent the best part of 20 years, and taken many approaches, to specifically target drugs at cancer cells. Incanthera is providing a novel, alternative approach.

The initial focus is development of specific cancer-targeted pro-drugs

The original agreement with the UoB provided the company with its core pro-drug delivery platform technology which can be armed with any number of known cytotoxic warheads. This has generated a portfolio of specific cancer-targeted drugs designed to deliver cytotoxic drugs directly to solid tumours. Given that they are activated by enzymes over-expressed by cancer cells only, theoretically they will act specifically at cancer cells, thereby improving both the efficacy of the warhead and the side-effect profile. This has been borne out in extensive pre-clinical studies.

Key events

Incanthera has raised £7.51m (gross) capital, together with an unquantifiable amount of research funding largely through grants, to get the company to where it is today. This has been used primarily for R&D, IP and acquisitions, and has generated a portfolio of five products, with three expected to be in clinical trials within the next two years.

History of Incanthera

Date	Event
2010	Incorporation of Incanthera Limited (no. 11026926)
2011	Funding round enabling technology licence from UoB
2012	Assignment of IP rights in the relevant patents from UoB
2014	Acquisition of Onco-NX to gain access to ICT03-Es5
2014	Acquisition of Spear Therapeutics Ltd to gain access to ICT04
2015	Agreement with Stanford University in respect of ICT02
2017	Licensing deal with Ellipses Pharma Ltd for initial ICT01-2588 clinical trial
2018	Funding round to raise £1.26m (gross) funds at 550p per share
2018	Head-of-Terms agreement with ImmuPharma plc to for Nucant licence
2018 tbc	IPO of Incanthera plc
2018	Development agreement to be finalised with ImmuPharma plc for Nucant technology

Source: Incanthera, Hardman & Co Life Sciences Research

R&D pipeline

Incanthera has a solid pipeline of diverse products, from lead optimisation stage through to near Phase I ready

Most of the technology that is being developed by Incanthera originated from the UoB (Institute of Cancer Therapeutics, School of Pharmacy & Medical Sciences, Faculty of Life Sciences), the Leland Stanford University, and the University of Salford and, therefore, has good provenance. The preliminary proof-of-concept pre-clinical studies for the various technologies were completed prior to them being acquired through licensing deals by Incanthera. Using this approach, Incanthera has built a relatively solid pipeline of products for a company of its size.

Incanthera R&D pipeline

Platform	Product candidate	Indication	Lead optimisation	Pre-clinical	Phase I	Phase II
ICT00	ICT01-2588	Lung, breast, ovarian cancers				
	ICT02-3104					
	ICT05-3205	Ovarian, prostate cancers				
	ICT03-Es5	Liver, brain, paediatric cancers				
	ICT04-CYP	Bladder, colo-rectal cancers				

Product candidate	Indication	Lead optimisation	Pre-clinical	Proof-of-concept clinical trial
ICT07	Actinic keratinosis, melanoma			

Source: Hardman & Co Life Sciences Research

ICT00 – pro-drug delivery platform

Background

Presentation

The ICT00 platform aims to exploit the characteristics of cancer cells, to specifically bring cytotoxic warheads into the tumour environment

The ICT00 technology platform originated from research undertaken by Professor. Laurence Patterson at the UoB. It resulted from an understanding of the important role played by matrix metalloproteinases (MMPs) in cancer. However, in the early 1990's, the focus of the pharmaceutical industry was on small molecules that acted as broad-spectrum inhibitors of MMPs[1]. In contrast, the focus of Prof. Patterson was on a pro-drug delivery platform designed to be cleaved by a specific membrane-bound enzyme – the membrane-type I MMP (MT1-MMP, also known as MMP-14) present and over-expressed in many cancer cells.

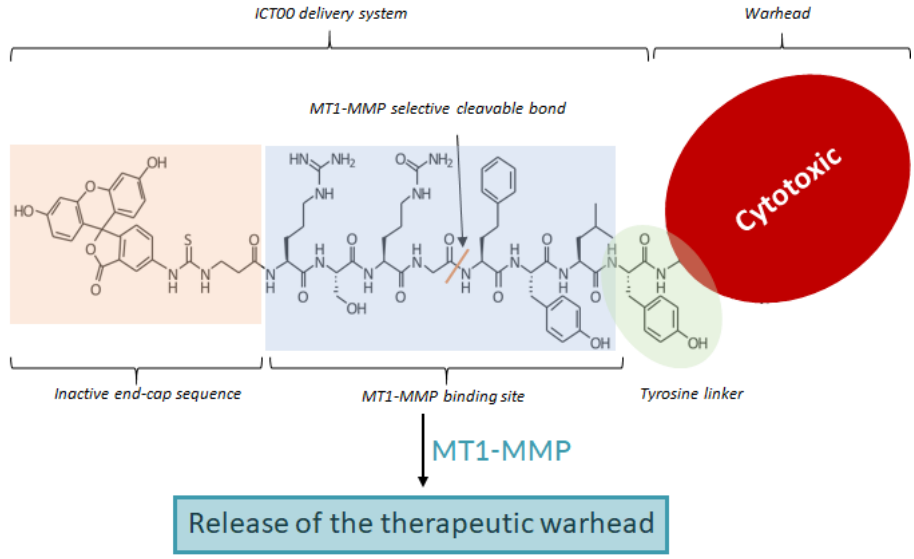
It consists of two parts:

- A selectively cleavable and non-natural peptide moiety with an MT1-MMP binding site.
- A cytotoxic therapeutic (warhead) or a diagnostic.

The goal was to obtain improved delivery of therapeutics directly to tumours using a membrane-type MMP (MT-MMP) targeted approach. This platform provides a drug delivery system that is able to shield the toxic effects of a cytotoxic drug, acting as a vector to deliver the desired effect at the disease sites. Sometimes described as a 'smart bomb', it provides a very versatile approach, as it can be combined with a number of cytotoxic drugs (warheads).

[1] Cathart et al., 2014.

ICT00 platform technology



Source: Adapted from Incanthera by Hardman & Co Life Sciences Research

The targeted action of the platform relies on the over expression of a specific enzyme seen only in cancer cells

The limitation with many cancer drugs is their lack of specificity. Although they are very effective at killing cancer cells, they are hampered by non-targeted toxicity of normal cells, leading to severe side effects. For many years, the pharmaceutical industry has searched for more targeted technologies to overcome these issues, resulting in commercially successful antibody-derived drugs, the advent of antibody-drug conjugates (ADCs) and therapeutic immuno-oncology. The approach adopted by Incanthera is highly targeted also, and very specific, because the warhead can only be released once the molecule is cleaved, and this can only occur where there is an MT1-MMP binding site (cancer cells only).

Mechanism of action

The delivery system is specifically an MMP14 hydrolysable peptide, which is activated by MMP14 expressed by the tumour cells, thus releasing the anti-cancer agent only in proximity of the target. Following the selective cleavage of the scissile peptide bond, a cascade of instant enzymatic events cleaves the remaining peptide bonds to ultimately free the therapeutic drug in a matter of seconds.

The pro-drug concept

Definition

Development of targeted therapy provides extensive possibilities in modern medicine. Numerous strategies have been explored with pro-drugs in cancer therapy to improve targeting and to increase the selectivity and efficacy of the warhead. A pro-drug is biologically inactive, only becoming effective following conversion into a pharmacologically active form by a specific bio-transformation (via chemical reaction or specific enzyme). Today, ca.10% of drugs used are administered as pro-drugs, and about half of these are hydrolysed to the active form, mainly by hydrolysis of esters.

The rationale for a pro-drug design is to:

- Overcome toxicity issues/problems
- Improve formulation and administration
- Enhance permeability and absorption
- Change the distribution profile
- Protect against rapid metabolism

Pro-drugs in cancer

Pro-drug strategies are particularly pertinent in cancer treatments to increase plasma exposure due to a very short half-life and to take advantage of particular enzymes/markers that are unique to cancer cells. Thus, inactive pro-drugs can be designed to target these markers, releasing active drugs to kill the cancer cells without damaging normal cells and tissues.

Incanthera lead candidates

Incanthera is currently developing three products using the ICT00 platform, with ICT01-2588 anticipated to be Phase I ready by the end of 2019

The strategy of Incanthera is to focus its resources on three MMP-activated pro-drug candidates each possessing a different warhead:

- **ICT01-2588:** First-in-man clinical trial in solid tumours anticipated late 2019.
- **ICT02-3205:** Pre-clinical stage using a derivative of the well-established warhead, paclitaxel (Taxol, BMS).
- **ICT05-3104:** Analogue of ICT01-2588 at discovery stage with potential as a theranostic (combines therapy and diagnostic in the same molecule).

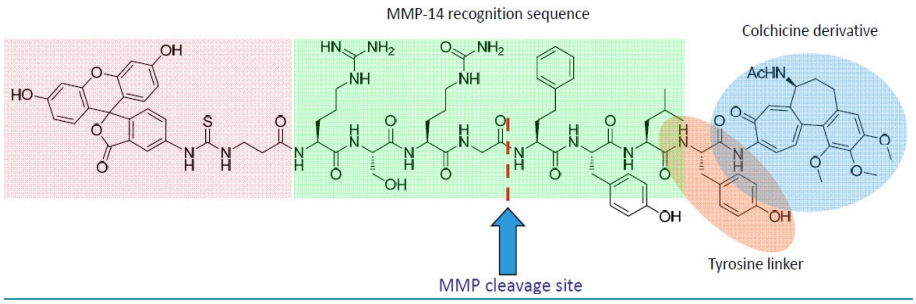
In addition, the intellectual property strategy around the ICT00 platform allows the company to patent each pro-drug separately, which adds to attractiveness for potential commercialisation partners.

ICT01-2588 – vascular disrupting agent

The lead compound ICT01-2588 possesses a colchicine derivative warhead

The peptide drug conjugate, ICT01-2588, combines the MT1-MMP peptide substrate with a warhead that is an analogue (aza-demethyl-colchicine (aza-d-colch)) of the well-known cytotoxic agent, colchicine. ICT01-2588 is designed to target selectively MMP being over-expressed by the tumour and release the warhead locally that targets the tumour vasculature. Initially, ICT01-2588 will be used against solid tumours, such as lung, breast, colon and prostate cancers.

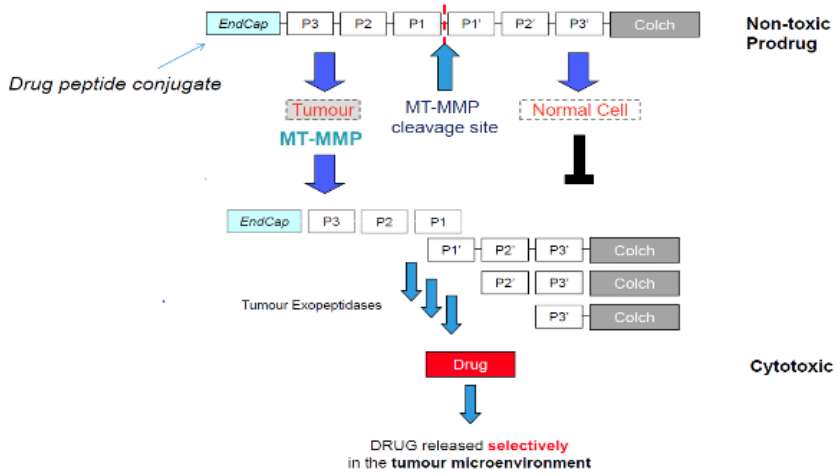
ICT01-2588 structure



Source: Incanthera

Following administration of ICT01-2588, normal cells will be unaffected because they are not expressing MT1-MMP. However, when the drug reaches cancer cells that are over-expressing MM1-MMP, the recognition sequence is cleaved and broken down by various tumour endopeptidases, releasing the colchicine analogue warhead, as shown in the following graphic. ICT01-2588 causes collapse of tumour vasculature, which leads to tumour starvation and death by necrosis.

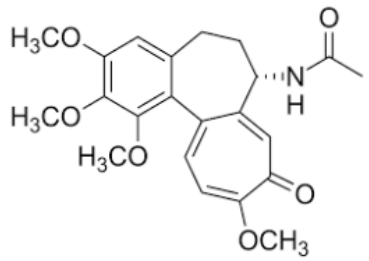
ICT01-2588 mode of action



Source: Incanthera

Warhead

Colchicine



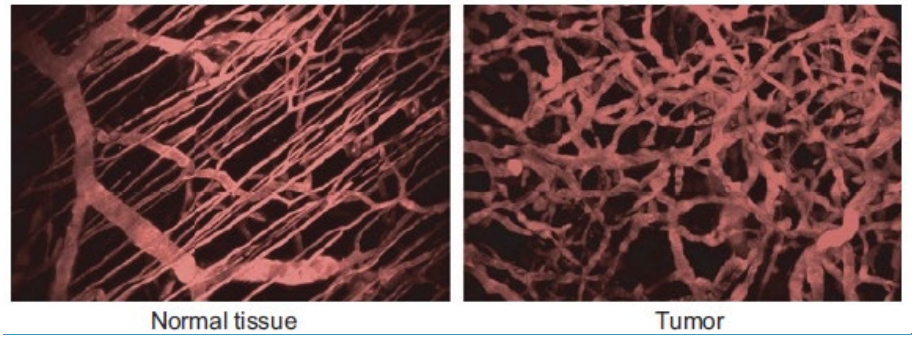
Source: Wikimedia Commons

Colchicine is a well-known anti-inflammatory drug derived from the autumn crocus (*colchicum autumnal*). Although it possesses potent anti-cancer activity, this drug is far too toxic for common usage in humans due to its lack of specificity. Its use is limited to the treatment of gout in very low doses. Colchicine inhibits microtubule polymerisation by binding to tubulin, essential in the processes of cell division (mitosis), providing the rationale for its use as an anti-cancer agent. However, it has a low therapeutic margin because it also affects the cell division of normal cells. In addition, the high concentrations needed for anti-cancer activity[2] lead to extreme vascular damage and fluid loss, which could result in multiple organ failure and is sometimes fatal. ICT01-2588 is using an analogue of colchicine as its warhead.

Tumour vasculature

During tumour development, the imbalance of angiogenic regulators drives tumour angiogenesis and causes the development of disorganised blood vessel networks that are fundamentally different from normal vasculature[3].

Normal vs. tumour vasculature



Source: J. C. Foster et al

It is common knowledge that cancers are typically more vascularised than the corresponding normal tissue. In addition, the generally observed chronic and acute hypoxia is due to high intra-tumour heterogeneity in microvascular density and lower-than-normal blood oxygenation levels through abnormally developed tumour

[2] Lin et al., 2016.
[3] Foster et al., 2017.

vasculature. Hypoxic regions are associated with decreased cell proliferation. Tumour vasculature is typified by aberrant structural dynamics and vessels that are:

- Immature
- Tortuous
- Hyperpermeable[4]

Vascular disrupting agents

Colchicine is a vascular disrupting agent with action in established tumour vasculatures, leading to necrosis

Targeting of established tumour vasculature has some potential advantages. Unlike conventional chemotherapy, which uses cytotoxic drugs to target every tumour cell, VDAs aim to disrupt relatively few vascular endothelial cells, leading to the blocking or collapsing of tumour vessels and ultimately provoking tumour necrosis and cell death. In contrast to the vasculature in normal tissues, tumour vasculature is more disorganised, proliferative, relatively immature and more permeable. Therefore, VDAs aim to make use of these characteristics, and have high selectivity towards tumour vasculature. However, VDAs cause necrosis only at the tumour core and leave, invariably, a viable rim in peripheral areas that could allow tumour re-growth. Therefore, combination with other chemotherapeutic agents would increase the overall anti-tumour effect.

VDA agents in clinical trials

Agent	Type	Company	Stage of development	Comments
Plinabulin (NPI-2358)	Tubulin	BeyondSpring	Multiple Phase I, II & III trials in combination with chemotherapy and CPI	Two Phase III and one Phase II are currently running in combination with docetaxel and the CPI PD-1 inhibitor nivolumab (Opdivo)
Vadimezan (ASA404)	Flavonoid	Novartis	Phase III (NSCLC) Phase II (HER2 -ve MBC)	Discontinued in 2010 due to lack of efficacy alone or in combination with paclitaxel and carboplatin
Ombrabulin (AVE8062)	Tubulin	Sanofi	Phase III (melanoma) Phase I (NSCLC)	Phase III discontinued in 2013 due to lack of efficacy, then discontinued in other studies
ABT-751 (E7010)	Tubulin	AbbVie	Phase II (paed. ALL, NSCLC, breast, colo-rectal, HRMPC, neuroblastoma, RCC)	Discontinued
Soblidotin (TZT-1027)	Tubulin	Daiichi	Phase II (sarcoma, NSCLC)	Discontinued in 2013
CYT997/Lexibulin	Tubulin	Cytopia	Phase II (multiple myeloma)	Acquired by Gilead, no news on the programme
Dolastatin 10	Tubulin		Phase II (RCC, sarcoma, pancreatic, HRMPC, liver/bile, duct/gall bladder, lymphoma, CLL)	Lack of significant clinical activity as a single agent
ZD6126	Tubulin	Angiogene	Phase II	Related to colchicine. The compound appeared to be too cardiotoxic
Verebulin/Azixa	Tubulin	Myriad/Myrexis	Phase II (melanoma, glioblastoma)	Lack of efficacy at tolerable dose
OXi4503 (CA41P)	Tubulin	Mateon	Phase I/II (AML, MDS)	Dose escalation study as single agent and in combination with cytarabine
Fosbretabulin (CA4P)	Tubulin	Mateon	Pre-clinical in combination with CTL-4 CPI	Previously in a Phase II/III in combination with Avastin for ovarian cancer, but was terminated due to lack of efficacy
Crinobulin (EPC2407)	Tubulin	Immune Pharmaceuticals	Phase I	Discontinued
MN-029	Tubulin	Medicinova	Phase I	Limited development effort
BNC105	Tubulin	Bionomics	Phase I	Change of indication

Note: this list is not exhaustive
Source: Company websites, Hardman & Co Life Sciences Research

[4] Siemann et al., 2011.

VDAs currently under investigation can be divided into two distinct families:

- **Flavonoid compounds**, which are related to flavone acetic acid.
- **Tubulin-binding agents**, which affect microtubule stability.

One of the main challenges for a VDA is to exhibit its disruptive action in established tumour vasculature without touching the healthy cardiovascular system. No drugs targeting VDA are available commercially because of the lack of efficacy due to, possibly, the low dose used before getting toxicity. Ombrabulin (Sanofi) was in multiple clinical studies, both alone and in combination with DNA-damaging agents. Following disappointing results in a Phase III trial in combination with cisplatin, this product was discontinued.

Today, the most promising agent is probably plinabulin, which is being investigated in multiple Phase I to Phase III clinical trials for multiple indications by the New York-based biotech company, BeyondSpring.

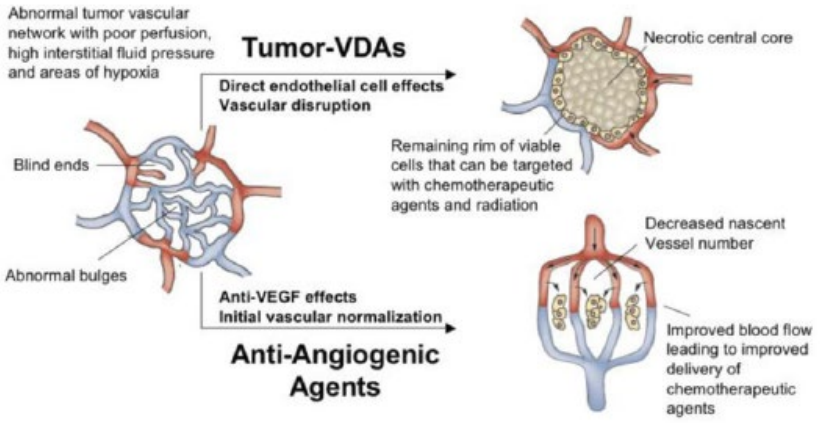
VEGF vs. VDA

Among the arsenal of existing anti-cancer agents, disruption of the tumour vasculature is a viable option, aiming to deplete the tumour of nutrients vital for their development and growth[5]. Two different approaches are employed, usually to disrupt tumour vasculature:

- Inhibition of new vessel growth with the anti-angiogenic approach through vascular endothelial growth factor (VEGF) inhibitors and the corresponding receptor (VGFR).
- Target pre-existing vasculature with vascular disrupting agents (VDA) to induce vascular failure, and ultimately cell death through apoptosis.

There is no competition between the use of VEGF/VGFR and VDA, as they have complementary actions. Targeting the formation of new vasculature leads to vessel normalisation, allowing efficient delivery of chemotherapeutic agents and increased oxygenation to aid radiotherapy/chemotherapy. This is in contrast to VDA treatment, which leads to vascular disruption and extensive central necrosis, leaving a thin rim of surviving viable cells that can be efficiently targeted with standard therapies.

Difference between VDA and anti-angiogenic agents



Source: D.W. Siemann

Key pre-clinical differences between the Tumour-Vascular Disrupting Agents (Tumour-VDAs) and anti-angiogenic drug classes are shown in the following table.

[5] Ji Y.-T et al., 2015.

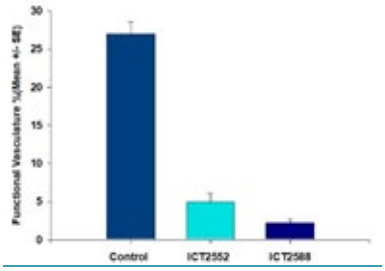
Normal vs. tumour vasculature	
Vascular-disruptive agents	**Anti-angiogenic agents**
Administered acutely	Administered chronically
Disrupt the established tumour vasculature	Inhibit neovascularisation
Cause vessel occlusion and inhibition of bloodflow	Induce vascular normalisation with initial improvement to tumour bloodflow
Cause extensive tumour necrosis	Prevent or limit tumour growth
Active against large tumour masses, causing extensive central necrosis	Active in peripheral tumour locations where nascent vessels are more predominant

Source: Adapted from D.W Siemann

Pre-clinical studies

ICT01-2588 has been investigated extensively in a number of pre-clinical cancer models. Of note, the biological effect on tumour vasculature and the level of haemorrhagic tumour necrosis was measured on HT1080 tumour-bearing mice. ICT01-2588 produced a 90% decrease in the level of functional tumour vasculature relative to solvent treated controls, 24 hours after treatment. This effect was greater than that observed following administration of aza-d-colchicine (ITC2552) at an equimolar concentration (80% reduction).

Functional vasculature



Source: J. M. Atkinson et al, 2010

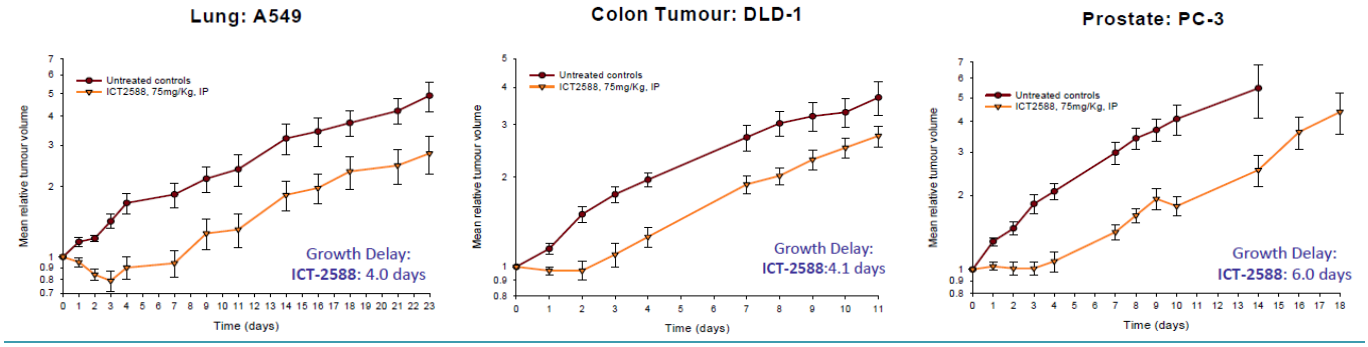
The distribution, activation and metabolism of ICT01-2588 and aza-d-colchicine were evaluated in mice bearing subcutaneous human HT1080 xenograft tumours. These studies showed that ICT01-2588 was widely distributed in the mouse, but concentrations of aza-d-colchicine were significantly lower in normal organs than in those with tumours.

Efficacy study

As a single agent, ICT01-2588 showed some efficacy and delay in tumour growth, without raising any cardiovascular toxicity

Greater anti-tumour activity was observed with ICT01-2588 (8.4 days' growth delay) compared with aza-d-colchicine (3.8 days' growth delay). Similar anti-tumour studies were conducted in mice bearing subcutaneous human A549 (non-small cell lung carcinoma), DLD-1 (colorectal carcinoma), PC3 (prostate carcinoma) and MCF7 (breast carcinoma) xenografts, with differential MMP-14 expression. Delays in tumour growth were observed across the panel of tumour types, with ICT01-2588 being significantly more efficacious than administration of aza-d-colchicine alone.

ICT01-2588 efficacy studies in cancer models



Source: Incanthera

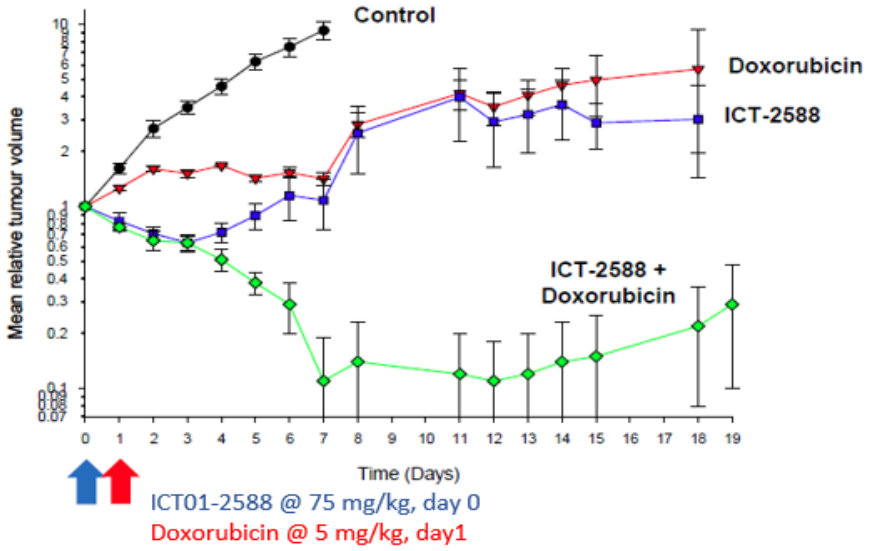
Combination study

Efficacy was enhanced when combined with the chemotherapeutic compound doxorubicin

The combination of ICT01-2588 and doxorubicin, a topoisomerase II inhibitor, has been performed in the HT1080 mouse model While doxorubicin and ICT01-2588 inhibited tumour growth by 6.3 days and 8.4 days, respectively, the synergistic effect of the combination resulted in a dramatic 22.6 days' delay in tumour growth[6] added to tumour cures in five out eight mice.

[6] Atkinson et al., 2010.

ICT01-2588 efficacy study as a single agent and in combination with Doxo



Source: Incanthera

Regulatory compliance

Targeting the pre-existing vasculature may raise some concerns regarding potential toxicity of VDAs on a healthy vascular system, especially cardiotoxicity. Incanthera has commissioned (Covance) regulatory toxicity studies in both mice and dogs with up to 28 days of treatment on a twice-weekly dosing regimen. Additional cardiotoxicity parameters were included in the dog 28-day study to provide further evidence of the safety.

ICT01-2588 was proven to be safe in animals and did not cause cardiac anomalies. No significant drug-related toxicities were seen at maximum achievable dose levels in either species. Toxicokinetic analyses confirmed that only low levels of aza-demethylcolchicine (<5%) released from ICT01-2588 hydrolysis were seen in the plasma of mice or dogs and that ICT01-2588 and its active metabolite did not accumulate in tissue, but were cleared within 24 hours.

Phase I ready

CTA application to be submitted in 4Q'19, thereby making the product Phase I ready

Submission of the regulatory dossier is anticipated in 4Q'19, which will allow the commencement of a Phase I clinical trial in solid tumours shortly thereafter. The protocol is expected to consist of a standard dose-escalation study with safety and tolerability as primary end-points. Pharmacokinetic and pharmacodynamic data will also be collected. The trial will aim to demonstrate safety and tumour-selective activation of ICT01-2588, with potentially some early efficacy, and identify a recommended Phase II dose for further studies.

The trial will recruit approximately 40-60 patients with advanced cancer, including NSCLC, breast, colorectal and prostate cancers, and is expected to take up to 18-24 months. ICT01-2588 will be administered for six cycles, unless there is disease progression, unacceptable toxicity, withdrawal of consent or the responsible clinician judges it inappropriate to continue.

Following the out-licensing of ICT01-2588 in 2017 (see page 37), this trial will be funded by Ellipses Pharma and coordinated by the Phase I Clinical Unit at St. James' Hospital, Leeds. It will be run at two centres – St James's Hospital Leeds and Weston Park Hospital Sheffield – and led by Professor Christopher Twelves from the University of Leeds.

Manufacturing

In 2017, Ambiopharm was selected to manufacture a 1kg batch of ICT01-2588 to GMP standard for the clinical trial. This has been completed, and the API is now undergoing final formulation studies. Incanthera works closely with Ambiopharm, Ellipses Pharma and QRCC, its CMC (Chemistry, Manufacturing & Controls) regulatory advisors, to ensure the GMP manufacturing process is fully compliant with the relevant regulations.

ICT02-3104

Background

In 2013, while ICT01-2588 was being developed by the Institute of Cancer Therapeutics (UoB), the team of Professor Heike Daldrup-Link at the renowned Stanford University in California had the idea of attaching a magnetic cross-linked iron oxide nanoparticle (CLIO), which could be picked up via an MRI scan, thus generating a combined therapeutic/diagnostic ('theranostic') tool, otherwise known as ICT02-3104.

- Iron-based MRI contrast agent (ferumoxytol) in combination with ICT2588 construct to generate a 'theranostic'.
- Dual benefit of tumour targeting provided by the nanoparticle, with selective release in the tumour achieved by the MMP activated pro-drug.
- Expected to have improved pharmacokinetics.
- Enhanced permeability and retention – crosses blood-brain barrier that is compromised.

Theranostic dual effect

Source: A&G Pharmaceutica

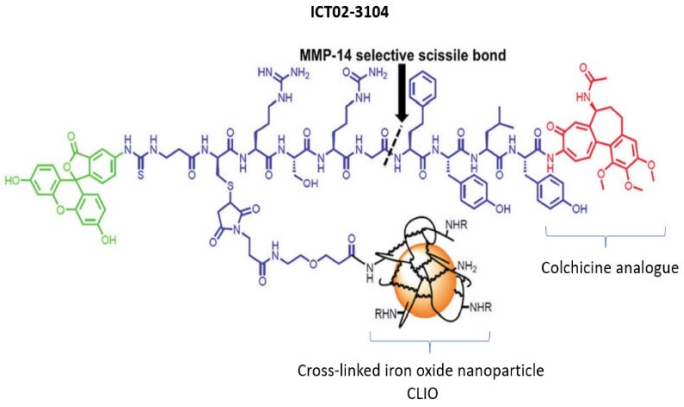
ICT02-3104 aims to harness the in vivo labelling of the solid tumour

The aim of the project is to allow *in vivo* labelling. ICT02-3104 is a novel tumour-targeted theranostic nanoparticle (TNP) activated by MMP-14. Theoretically, the technology allows a reduction in dose-limiting toxicities, thereby increasing the therapeutic index, which is a very attractive strategy for development of cancer therapeutics.

Synthesis

ICT02-3104 is a modified analogue of ICT01-2588 with an additional cysteine residue at the P5 position to allow conjugation to the nanoparticle via maleimide. It is synthesized by the conjugation of ferumoxytol, an FDA-approved iron oxide nanoparticle, to an MMP-activated peptide conjugate of aza-demethylcolchicine (ICT), creating CLIO-ICTs.

Structure of the theranostic compound ICT02-3104/CLIO-ICT



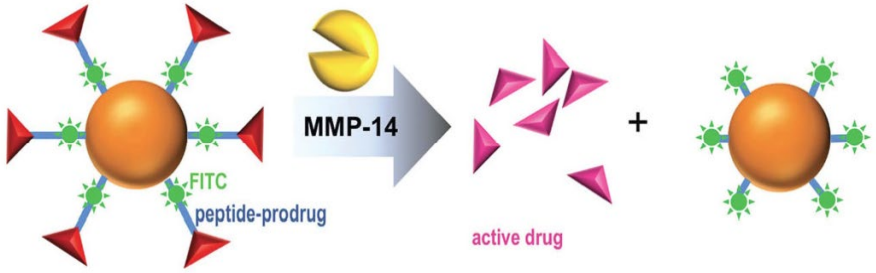
Source: Incanthera

The MoA is similar to ICT01-2588 with the release of the active drug and the nanoparticle in the tumour micro-environment

Mechanism of action

The mechanism of action is very similar to ICT01-2588. At the environment of the cancer cell, the MMP-14 enzymes cleave the peptide at its binding site, which, after a cascade of spontaneous enzymatic reactions, frees the active drug and the nanoparticle.

Mechanism of action



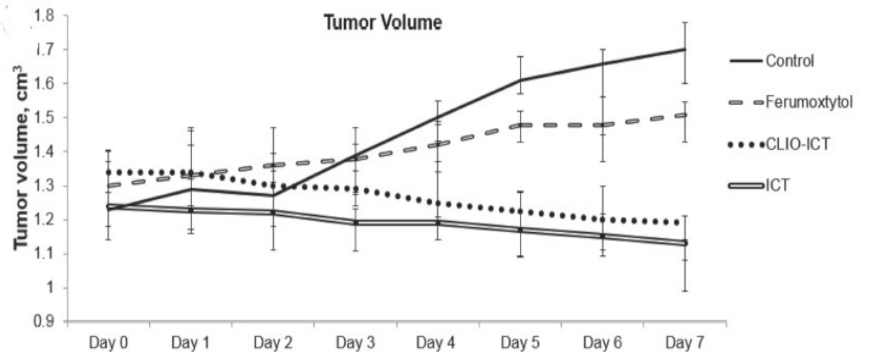
Source: Incanthera

Under normal circumstances, such a big molecule would have difficulty in crossing cell membranes or the blood-brain barrier. However, with glioblastoma (brain cancer), the concept of this theranostic is to exploit the fact that the brain barrier is compromised, making it unusually leaky/permeable compared with normal tissue. This is a principle called the enhanced permeability and retention (EPR) effect.

Pre-clinical studies

In vitro and *in vivo* studies have been carried out at Stanford. Tumour regression was observed with ICT02-3104 in a murine breast carcinoma MMTV-PyMT.[7] CLIO-ICT demonstrated both significant MRI effects and anti-cancer activity, with selective and effective delivery to the tumour site, and a consequential reduction in associated toxicity in normal organs.

ICT02-3104 efficacy study in MMTV-PyMT model

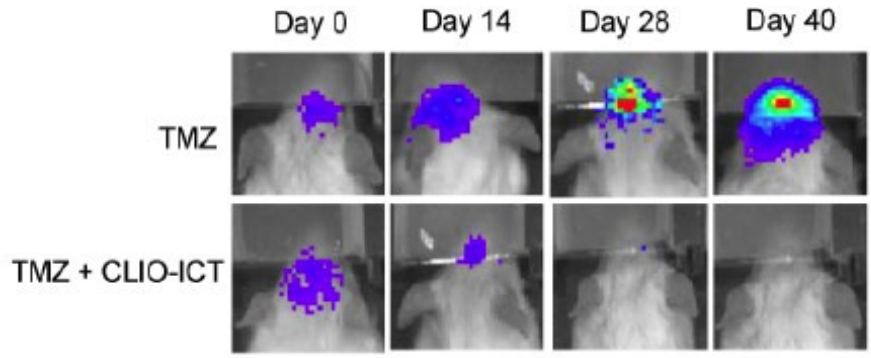


Source: C. Ansari et al

Similar efficacy was observed in an *in-vivo* human glioblastoma (GBM) cancer model where prolonged retention in the tumour tissue via VDA-initiated vasculature collapse was obtained following intravenous injection of ICT-CLIO.[8] The study also highlighted the improved therapeutic index when combined with the only approved drug for glioblastoma, temozolomide (TMZ), and achieved remission.

[7] Ansari et al., 2013.
[8] Mohanty et al., 2017.

ICT02-3104 efficacy study in a GBM model in combination with TMZ



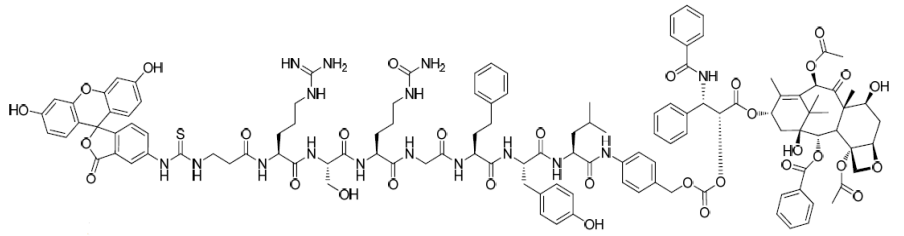
Source: Mohanty et al

ICT05-3205

ICT05-3205 uses the mitotic poison Taxol as its warhead

ICT05-3205 uses the same ICT00 drug delivery pro-drug platform, but with a different warhead, in this case paclitaxel (Taxol), a well-established anti-cancer therapy. This will be released in the same way by tumour cells expressing the MMP14 enzyme. ICT05-3205 is currently in late-stage pre-clinical development.

ICT05-3205 structure



Source: Incanthera

Cytotoxic cell activity

ICT05-3205 shows efficacy in cancer cells expressing MMP-14 …

The MTT assay is widely used to measure cell viability and metabolic activity when tested with a cytotoxic compound. The EC_{50} value refers to the half maximal effective concentration of a drug, antibody or toxicant, which induces a response halfway between the baseline and maximum after a specified exposure time. It is commonly used as a measure of a drug's potency.

Metabolic activity

Cell line	PNT2	PC3	LNCaP
Cell type	Normal cells	Prostate cancer cells	Androgen-sensitive human prostate adenocarcinoma cells
MMP-14	No	No	Yes
Paclitaxel EC_{50} (nm)	0.05	0.05	0.008
ICT05-3205 EC_{50} (nm)	>10	>10	0.05

Source: Incanthera

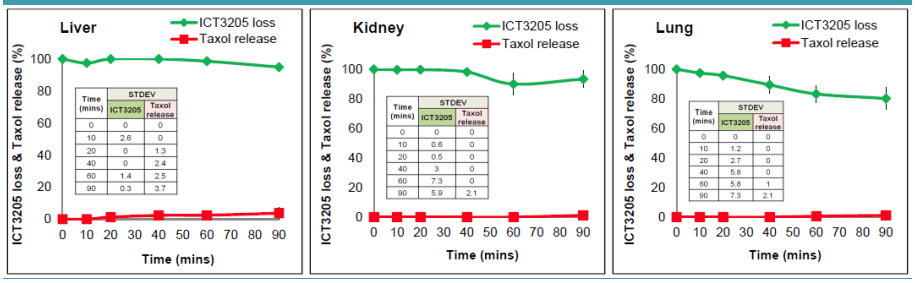
In the assay, EC_{50} values of ICT05-3205 were compared with the equimolar equivalent of its parent product paclitaxel in cell lines with different expression of the MMP-14 enzyme, and with a normal cell line. ICT05-3205 did not show any cell cytotoxicity in a normal, non-cancerous cell line, nor in a cancerous cell line unable to express MMP-14. However, in the prostate cancer cell line, which expresses MMP-14, both paclitaxel and ICT05-3205 were shown to have potent activity.

Ex vivo stability studies

… and good stability in vivo

It is important to assess the stability of the pro-drug in different organs. Equimolar doses of ICT05-3205 and Taxol were administered to mice in order to enable an *in vivo* comparison.

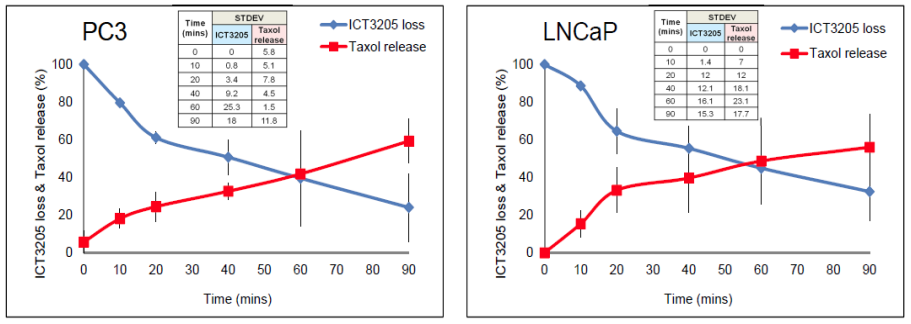
ICT05-3205 stability studies in normal tissues



Source: Incanthera

Minimal release of Taxol from ICT05-3205 was observed in plasma, liver, kidney, lung and heart. On the other hand, in PC3 and LNCaP tumour cell lines, ICT05-3205 was cleaved, releasing a large concentration of active drug. Interestingly, it is worth mentioning that, despite the PC3 cell line not expressing the MMP14 enzyme, its expression does appear in the newly created cancer vasculature.

ICT05-3205 stability in tumours



Source: Incanthera

In vivo efficacy

In vivo efficacy has been demonstrated in a mouse model…

ICT05-3205 has been compared with paclitaxel in prostate cancer PC-3 tumour-bearing mice. In this study, animals were treated with 7mg/kg of paclitaxel and 20mg/kg (equivalent of 7mg/kg of active paclitaxel) of ICT05-3205. Solvent alone was used as a control. Animals were dosed with paclitaxel and ICT05-3205 on days zero and four.

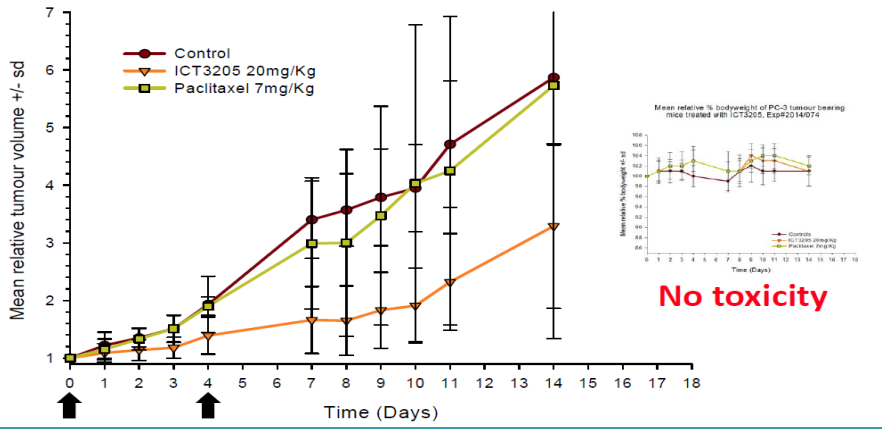
… with a better outcome compared to the parent therapeutic Taxol…

Interestingly, while there was very little difference in the Mean Relative Tumour Volume (MRTV) at 14 days between the control and paclitaxel arms at 5.8, those treated with ICT05-3205 had an MRTV of 3.2, indicating increased efficacy of the pro-drug compared with its parent therapeutic. This is probably due to the specific cancer targeting of the ITC00 platform. In this study, ICT05-3205 significantly slowed down tumour growth – thus indicating good potential efficacy against prostate cancer.

…added to a good tolerability and safety profile

Toxicity was assessed via measurement of animal weight. ICT05-3205 had no effect on mice weight providing grounds for a good tolerability and safety profile.

In vivo efficacy study with ICT05-3205 and paclitaxel

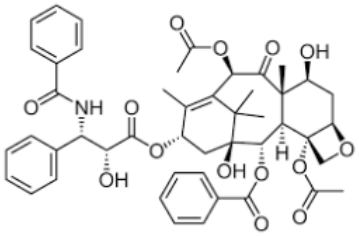


Arrows indicate dosing days
Source: Incanthera

Paclitaxel

Paclitaxel (Taxol, BMS) was isolated from the bark of the Pacific yew (*Taxus brevifolia*), and first discovered to possess anti-cancer activity during a screening programme funded by the US National Cancer Institute in 1971. It received regulatory approval in 1992 for the treatment of breast, ovarian, lung, bladder, prostate, melanoma, oesophageal, and other types of solid tumour cancers.

Structure of Taxol



Source: Bristol-Myers Squibb

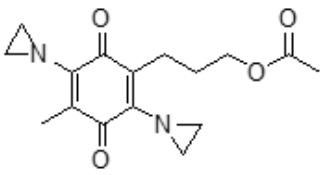
Paclitaxel is a mitotic poison that targets tubulin, meaning that it stabilises the microtubule assembly during the cell division, and protects it from disassembly. Cells are then unable to achieve division, resulting in apoptosis. Although cancer cells are known to proliferate faster than normal cells, paclitaxel has many side effects due to its lack of selectivity, which include an increased risk of getting an infection, alopecia, bruising, bleeding gums and nose bleeds, diarrhoea, and low blood pressure. Also, paclitaxel has extremely poor water solubility and needs a relatively higher dose compared with other anti-cancer drugs.

For these reasons, it is always administered with ethanol and Cremophor EL as vehicles to increase water solubility, which potentially was the cause of severe hypersensitivity in some patients. Many attempts[9] have been made to increase its water solubility in order to provide greater selectivity, some of which involved a pro-drug strategy. Therefore, Incanthera is surfing the wave with ICT05-3205.

ICT03-Es5

Background

Structure of ICT03-Es5



Source: Incathera

ICT03-Es5 is a pro-drug of quinone and an analogue of the clinical product RH1[10], but with the terminal alcohol function protected by an acetyl (Ac) group. It needs an enzymatic reduction to become active. It was developed at the University of Colorado Health Sciences Center and the UoS by the former CRUK Patterson Institute, Manchester. In 2004, RH1 was licensed to the US biotech company, Allos Therapeutics, which was acquired by Spectrum Pharmaceuticals in 2012.

During 2007, RH1 underwent a Phase I clinical trial in patients with advanced solid tumours or non-Hodgkin's lymphoma. The dose-escalation study confirmed its overall safety and determined a maximum tolerated dose. While the recommendation was to progress RH1 to Phase II trials, Allos decided to discontinue the programme for a number of reasons, which included two deaths in the trial,

[9] Meng et al., 2016.
[10] Danson et al., 2011.

potentially related to the high dosage of RH1 needed, and also to a strategic decision due to a lack of cash at that point in time.

In order to improve the pharmacokinetic and pharmacodynamic parameters, such as solubility, stability and selectivity, which were believed to limit the potential of RH1, continuing work at the UoS resulted in the synthesis of a range of analogues. One of these molecules, ICT03-Es5, has been identified as a prospective development candidate. The improved characteristics of Incanthera's derivative product are expected to eliminate many of the issues experienced by Allos with RH1. Therefore, ICT03-Es5 provides an opportunity to 'resurrect' the RH1 approach, building upon a strong established base of pre-clinical and clinical data, and protected by a new patent that was filed in 2012.

The pro-drug ICT03-Es5 is an improved analogue of the clinical product RH1 developed by Allos Therapeutics

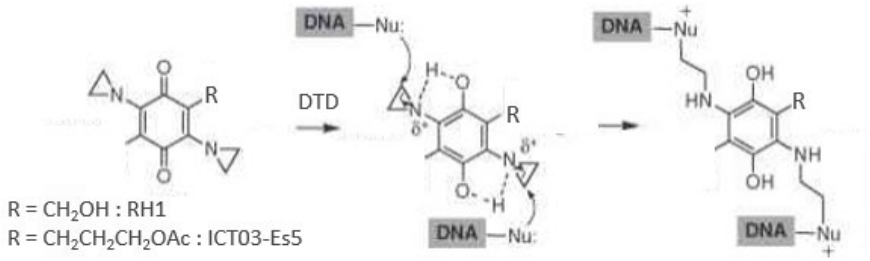
Mechanism of action

The ICT03-Es5 pro-drug is activated by the DTD enzyme and form a covalent adduct to the DNA

ICT03-Es5 is a quinone pro-drug and potent bio-reductive anti-cancer agent activated by the enzyme diphtheria toxin-diaphorase (DTD – also known as NAD(P)H: quinone oxidoreductase-1 NQO1), which itself is over-expressed in many solid tumours. Quinones are a source of active compounds in cancer medicine, which require bio-reduction to intermediates, which either generate toxic-free radical species or bind to DNA to form covalent adducts.

These pro-drugs are converted to active intermediates by enzymatic activity either in hypoxic areas of solid tumours or by increased activity of these enzymes in tumours compared with normal tissues and, therefore, should exhibit tumour-selective cytotoxicity.

ICT03-Es5 alkylating mechanism



Source: Adapted from www.drugtimes.org/anticancer-drugs-2/aziridines-ethyleneimines.html

ICT03-Es5 exhibits a similar mechanism of action to the potent chemotherapeutic agent Mitomycin C, with greater potential activity against cells expressing high DTD and a potentially more favourable safety profile. Mitomycin C is an antibiotic which, when activated, acts as a DNA alkylating agent. This results in mispairing of bases, DNA strand breakage, and cross-linking of complementary strands which prevents DNA synthesis that leads to cell death by apoptosis.

Hypoxia is a tumour-specific condition that is exploited in cancer therapy. Hypoxic cells are viable and resistant to some forms of chemotherapy and to radiotherapy. Also, hypoxia is able to drive genetic instability that is associated with an aggressive disease phenotype. [11]

Phase I clinical trial

CTA submission anticipated in 2020 for a Phase I trial

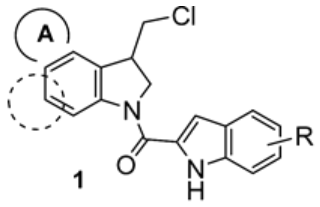
Incanthera expects to submit the Clinical Trial Application to the MHRA in 2020 for a Phase I trial with ICT03-Es5. It would be a dose escalation study to determine the maximum tolerated dose, identify any adverse events, and to determine the dose for subsequent Phase II studies. Typically, a trial of this nature would involve about 20-30 patients and take 12-18 months to complete.

[11] C.P. Guise et al., 2014.

ICT04-CYP

ICT04 is the pro-drug form of the DNA alkylating agent duocarmycin

Structure of ICT04-CYP



Source: Incanthera

Background

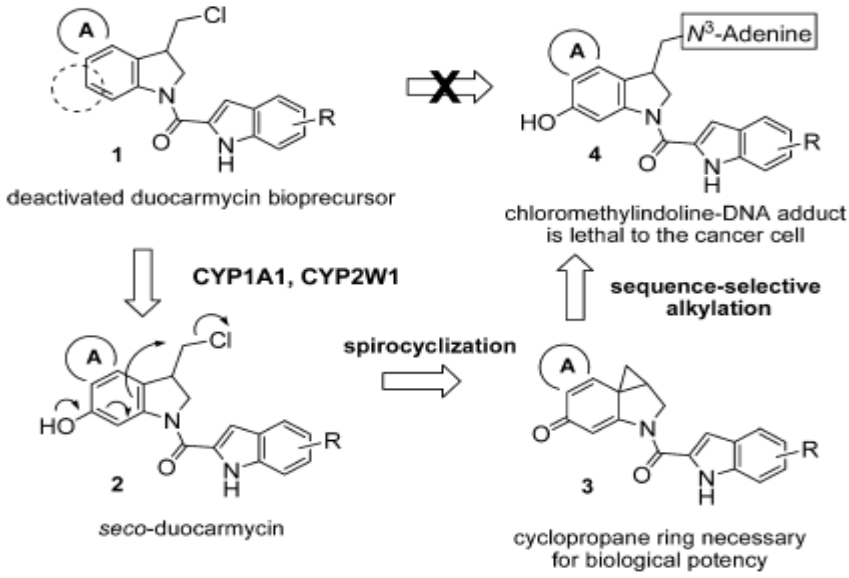
The ICT04-CYP programme was initiated at the Institute of Cancer Therapeutics, UoB. It is a pro-drug of a well-known cytotoxic compound, duocarmycin, and has been designed specifically to overcome its intrinsic toxicity.

The CYP super-family is a group of enzymes that are responsible for the metabolism of endogenous and exogenous chemicals, including therapeutic drugs, to facilitate their excretion from the body. The use of the CYP-mediated enzymatic oxidation to activate a prodrug is not new and has been used widely by the pharmaceutical industry to target the liver, tumours or hypoxic tissues[12].

Mechanism of action

ICT04-CYP belongs to the class of the alkylating anti-cancer agent, which, unlike the classical alkylating agents, requires an activation step. Activation of the pro-drug is performed by the site-specific mono-oxidation CYP2W1 enzyme, which triggers a cascade of events that ultimately result in DNA alkylation and cancer cell death. Whereas tubulin binders will only attack tumour cells when they are in mitosis, duocarmycin exerts its effect at any phase in the cellular cycle, suggesting that analogues might be more effective anti-cancer drugs, provided that their activity can be localised within the tumour.

Mechanism of action



Source: H.M. Sheldrake et al, J. Med Chem. 2013, 6273-6277

Competitive landscape

Due to non-specific toxicity, duocarmycin failed to progress to the clinic. The pro-drug strategy is considered to be a suitable way forward, and SYD985 (Synthon Biopharma), a duocarmycin-based HER2-targeting antibody-drug conjugate (ADC), is currently being evaluated in a Phase I trial (NCT02277717) in HER2-positive cancers, including (metastatic) breast, gastric, bladder (urothelial) and endometrial (uterine). Headline results are expected in 2H'18.

[12] Ortiz de Montellano, 2013.

Proof-of-concept studies

Pre-clinical development stage expected during 2018

Incanthera's pro-drug offers an alternative approach, being dependent only on the presence of the CYP2W1 enzyme. Laboratory experiments showed that cancer cells expressing CYP2W1 suffer substantial DNA damage, causing loss of viability. These experiments show promise for what would be a new class of drug. ICT04-CYP is currently in the late discovery stage and will enter pre-clinical development in 2018.

ICT07

In 2018, Incanthera entered into a product development and licensing agreement with a UK-based pharmaceutical design company, which is a specialist in the formulation of dermatological products and owns a specific dermatological drug delivery formulation and on which it has pending patents. Through this, Incanthera has acquired the ICT07 asset, which has potential in the treatment of solar keratosis and preventing it from eventually turning into skin melanoma.

ICT07 will be a topical formulation of an orally active product against solar keratosis

The ICT07 programme consists of a new formulation of a well-established skin care product that is generally used to treat acne and other skin-related problems, but with an improved trans-dermal delivery. When taken orally, this drug has been shown to prevent progression and recurrence of common solar keratosis to skin melanoma. The intention of Incanthera, is to re-formulate this product into the patent protected delivery technology in order to achieve active drug levels locally which are, at least, equivalent to those achieved following oral administration.

Incanthera intends ICT07 to be a topical application that offers the following additional benefits:

- Circumvention of first-pass metabolism.
- Ease of compliance.
- Direct targeting of sun-exposed skin tissues.

Incanthera's strategy

ICT07 topical formulation aims to improve the effect of the active compound

With sun cream already effective in reducing the number of actinic keratoses and the incidence of squamous cell carcinoma, ICT07 would be targeting patients with nascent, pre-existing skin cancers. The company will need to perform a proof-of-concept clinical trial, which is a relatively small and inexpensive bioequivalence/efficacy trial, and is expected to take approximately 18 months to complete – six-months pre-clinical work, six to eight months to run the trial, and four to six months data analysis.

Nucant technology

As part of a corporate update announcement released via RNS on 7 September 2018, IMM provided details about a signed Heads-of-Terms agreement with Incanthera in order to progress its clinical-stage oncology asset, the Nucant programme. As part of the agreement, IMM has granted Incanthera a period of exclusivity until 31 December 2018 to finalise the terms of a Definitive Licence Agreement for the Nucant technology. The final terms are expected to include, but will not be limited to the following:

- Incanthera will pay an up-front licence fee to IMM of £1m in the form of new Ordinary shares in Incanthera.
- Incanthera will be responsible for all the future development costs of the Nucant programme.
- All future commercialisation revenues will be shared equally between the two companies.

As part of the collaboration agreement, IMM has made a £2m investment in Incanthera by subscribing for 363,637 new Ordinary shares at a price of 550p per share, which is the same price as that used in a funding round completed in March 2018. This has given IMM a ca.16% shareholding in Incanthera. In addition, IMM was granted warrants to subscribe for shares in Incanthera with an aggregate exercise value of £2 million.

From Incanthera's perspective, in-licensing the Nucant technology will boost its R&D pipeline with an additional clinical-stage programme. Although the in-licensing deal is yet to be concluded, we do expect this to be closed shortly after Incanthera's IPO has been achieved.

History of the Nucant programme

IMM, in partnership with Centre National de la Recherche Scientifique (CNRS), has been developing a novel concept in the potential treatment of cancer. It centres on the modulating effect of the Nucants on angiogenesis, the mechanism which controls the formation of micro vessels. By and large, tumour generated micro vessels are of poor quality and offer only a poor supply of blood and oxygen to the tumour. Consequently, these tumours are much more resistant to cytotoxic drugs. By modulating the tumour micro vessels, Nucants improve the blood flow, allowing a better supply of oxygen, thereby increasing the concentration of cytotoxic drug within the tumour.

ImmuPharma – Nucant programme history

Date	Event
May 2011	Publication in *Cancer Research* on the potential use of Nucants to enhance the activity of existing cytotoxic drugs
June 2014	USPTO grant of patent covering the composition of matter for optically pure versions of the Nucant family
Oct 2014	The EU awarded a €7m grant to a number of EU partners to develop Nucants in combination with cytotoxic drugs linked to a solid support, of which €0.43m was for IMM
Feb 2015	Headline results from a Phase I dose-ranging clinical trial with lead compound IPP-204106 which identified the MTD at 9mg/kg
Nov 2016	Publication in *Cancer Research* on the mechanism of action of Nucants, entitled "Nucleolin targeting impairs the progression of pancreatic cancer and promotes the normalization of tumour vasculature"
Sept 2018	Heads of Terms agreement signed with Incanthera for the further development of the Nucant programme

Source: Hardman & Co Life Sciences Research

The main conclusions from the key publications were that Nucants represented a new strategy to improve the delivery and efficacy of chemotherapeutic drugs[13] and that Nucants had the potential to improve dramatically the delivery and efficacy of existing chemotherapeutic drugs, and in particular, for difficult-to-treat tumours such as pancreatic cancer[14]. The mode of action of Nucants fits well with the pro-drug strategy of Incanthera, and this in-licensing opportunity would boost its R&D pipeline significantly with a clinical-stage opportunity.

[13] A Simple Approach to Cancer Therapy Afforded by Multivalent Pseudopeptides That Target Cell-Surface Nucleoproteins. *Cancer Research*. http://www.ImmuPharma.co.uk/wp-content/uploads/2017/05/Cancer-Research-Publication-May-2011-with-cover1.pdf

[14] Nucleolin targeting impairs the progression of pancreatic cancer and promotes the normalization of tumour vasculature. *Cancer Research*. http://cancerres.aacrjournals.org/content/early/2016/10/15/0008-5472.CAN-16-0300

Drug discovery programmes

While Incanthera is aiming to progress the clinical and late-stage pre-clinical programmes, it will continue to work closely with, amongst others, the Institute of Cancer Therapeutics in Bradford, which is investigating a number of other novel targets that are at the drug discovery stage. Its close working relationship will put it in prime position to in-license any leads that are generated from these programmes.

Commercial opportunity

Background to cancer

Epidemiology

The toll of cancer – US

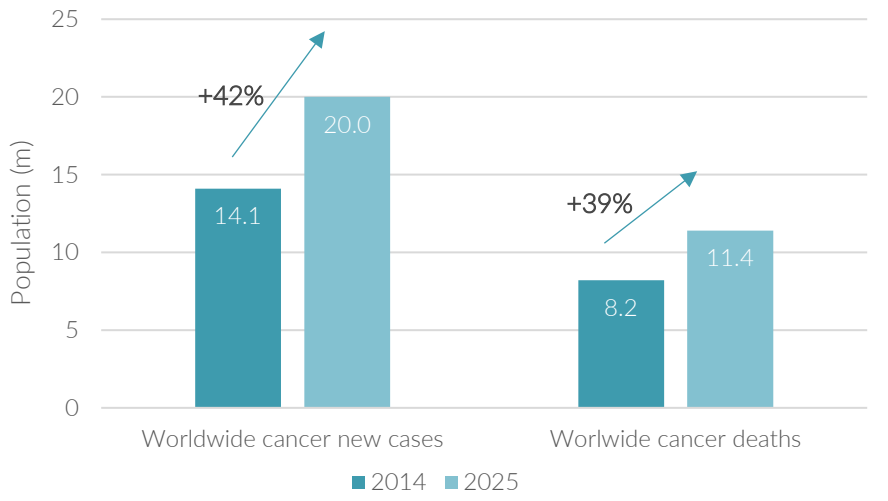
Source: American Cancer Society

Cancer is a worldwide problem, being the second leading cause of death globally, after cardiovascular diseases. There were an estimated 14.1 million new cases globally in 2014 associated with 8.2 million cancer-related deaths, and this number is forecast to rise to 24 million by 2035[15]. The increase is due mainly to the growing global population and increased life expectancy. In the US, the five most common cancers (breast, lung, prostate, colo-rectal, prostate and melanoma) are estimated to account for 55% of all cases in 2018.

The frequency of cancer increases with age, with relatively few people acquiring cancer before the age of 30 years. This is partly because it can take many years to acquire the multiple abnormalities that generate cancer cells. Furthermore, the probability of being exposed to the risk factors for cancer also increases with time.

An estimated[14] one-third of the world's population will develop cancer of some kind during their lifetime, and about 70% of those who do, will die from the disease. From 2014 to 2025, the anticipated rise of 42% in cancer new cases will be accompanied by an increase in cancer deaths of 39%, and most of the burden of the cancer incidence and mortality will be borne by low- and middle-income countries.

Impact of cancer worldwide



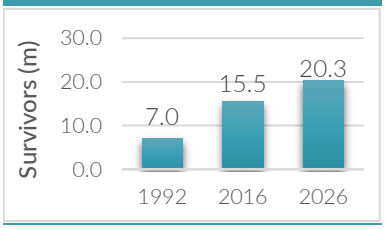
Source: World Cancer Report 2014, www.cancer.gov[2], Hardman & Co Life Sciences Research

Improving survival reates

Over the last 30 years, considerable progress has been made in the fight against cancer. The overall age-adjusted cancer mortality rates for most cancers has dropped steadily in the US and other developed countries[16]. This is due mainly to the reduction of tobacco consumption, an improvement of cancer diagnosis and the introduction of new drugs.

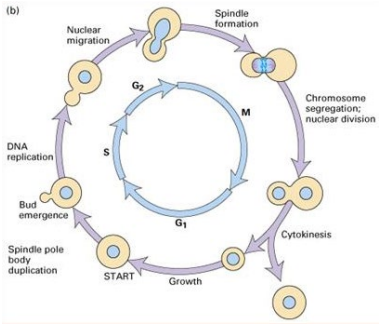
[15] www.wcrf.org
[16] www.cancer.gov

Cancer survival – US data



Source: www.cancer.gov

Cell cycle progression



Source: www.pha.jhu.edu

Early diagnosis is key

According to the American Cancer Society, the number of cancer survivors in the US, has increased from ca.3.0 million in 1971 to 13.7m in 2012[17] and 15.5m in 2016. Despite the great progress that has been, and continues, to be made against cancer, it remains the second most common cause of deaths in the US, accounting for nearly 1-in-4.

Cancer biology

Cancer is a term that describes a number of diseases in which abnormal cells grow and divide in an unregulated way. This malfunction is caused by damage to a number of regulatory mechanisms and genetic disorders within the cell which ultimately form a tumour, an abnormal mass of tissue that can be:

- **Benign** (non-cancerous): Does not have the ability to invade and metastasise.
- **Cancerous:** Unregulated cancer cells grow and multiply, with the aptitude to invade nearby tissues and spread around the body (metastasis).

Metastasis occurs when cells become detached from the initial tumour, and are carried through the bloodstream and lymphatic system to other parts of the body, forming a secondary cancer. This eventually interferes with the normal functioning of cells and organs, which can lead to the death of the patient. An estimated 60% of all cancer patients have some sort of metastasis at diagnosis.

Diagnosis

Early diagnosis is a key factor for obtaining a positive prognosis – the earlier that the cancer is diagnosed, the better chance of a successful outcome. It is essential to identify the problem before it has had the chance to metastasise and spread to other parts of the body. Great strides have been made in recent years with the advent of molecular diagnostics, which allow genotyping to identify 'at risk' patients, and early diagnosis using DNA-based tests can detect the presence of cancer from a very small number of cells.

Treatment

Treatment of cancer relies on three core approaches:

- **Surgery:** Ablation of the tumour.
- **Radiation:** Ionising radiation or more recent approaches e.g. proton therapy.
- **Chemotherapy:** Use of cytotoxic drugs.

Depending on the type of cancer, treatment is often in the form of a multi-disciplinary approach. This is increasingly the case as new options have emerged, making the chemotherapeutic tactic much more refined than simply blasting cells with very toxic drugs in an unspecific manner.

Targeted approaches

Approach	Comment
Hormonotherapy	For hormone-sensitive or hormone-dependent cancers
Immunotherapy	Use own immune system to fight the disease
Precision medicine	Tailored patient treatment based on genotyping
Stem cell transplant	Allows higher doses of chemotherapy

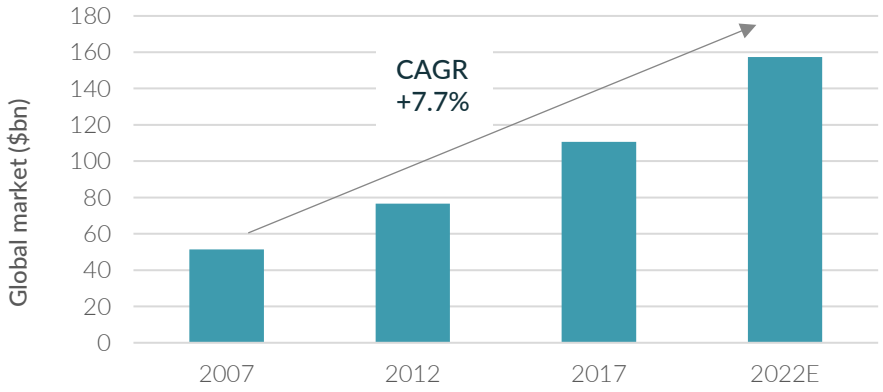
Source: Hardman & Co Life Sciences Research

[17] www.pha.jhu.edu

Market opportunity

Hardman & Co estimates that the global oncology market was worth ca.$111bn in 2017 and represented 9.9% growth over 2016 in $ terms. Our analysis is based on the ex-factory sales for the leading 110+ branded drugs on the market, to which a modest figure representing the plethora of small/old/generic cancer drugs has been added. Our data indicates that the global oncology market has seen 8.0% CAGR over the last 10 years (2007-17).

Global oncology market

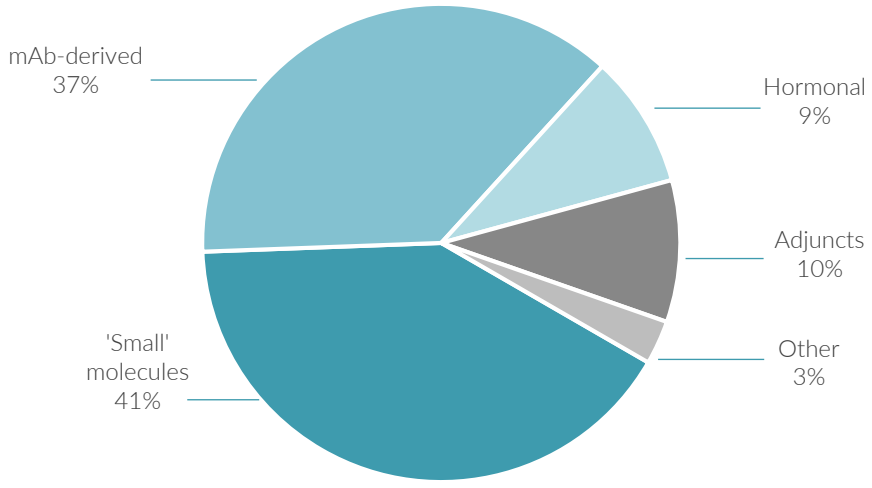


Source: Hardman & Co Life Sciences Research

Cancer drugs derived from targeted antibodies represented 37% of the market in 2017

Over the last decade, the global oncology market has been driven by sales of drugs derived from antibodies[18], which represented an estimated 37% of the market in 2017, at $41.3bn (including ADCs). Given the enormity of current development programmes for targeted immunotherapies, this status is unlikely to change in the next decade. This suggests that the historical growth rate of 7%-8% compound will be maintained, such that Hardman & Co is forecasting the oncology market will grow to $155-$160bn in 2022.

Oncology market by drug class – 2017



Source: Hardman & Co Life Sciences Research

[18] Chang, 2015

Incanthera opportunity

Incanthera's pipeline is addressing a large spectrum of solid tumours...

The approach taken by Incanthera addresses potentially a very large part of the market. On the one hand it is developing small-molecule cytotoxic drugs for the majority of solid tumours, which implies that it would be competing with the $45bn small-molecule segment of the market. On the other hand, it also has a highly targeted approach, which would both compete with and complement the antibody approach, especially given the multi-disciplinary approach adopted by oncologists.

...and could be expanded

Moreover, as can be seen in the following table, Incanthera's drugs are attempting to address the very largest segments of the cancer market, which account for the majority of tumour cases, as highlighted earlier in the epidemiology section (page 30).

Incanthera targets – US data

Site	Estimated new cases 2018	Estimated deaths	Survival rate 2008-14	ICT addressable market
Breast	268,670	41,400	89.6%	ICT01, ICT02
Lung and bronchus	234,030	154,050	18.6%	ICT01, ICT02, ICT03
Prostate	164,690	29,430	98.2%	ICT01, ICT05
Colon and rectum	140,250	50,630	64.5%	ICT04
Skin melanoma	91,270	9,320	91.8%	ICT07
Bladder	81,190	17,240	76.8%	ICT07
Non-Hodgkin lymphoma	74,680	19,910	71.4%	
Kidney/renal pelvis	65,340	14,970	74.5%	
Uterus	63,230	11,350	81.1%	
Leukaemia	60,300	24,370	61.4%	
Pancreas	55,440	44,330	8.5%	
Thyroid	53,990	2,060	98.1%	
Oral cavity/pharynx	51,540	10,030	64.8%	
Liver/bile duct	42,220	30,200	17.7%	ICT03
Myeloma	30,770	12,770	50.7%	
Stomach	26,240	10,800	31.0%	
Brain/nervous system	23,880	16,830	33.2%	ICT03
Ovary	22,240	14,070	47.4%	ICT01, ICT05
Oesophagus	17,290	15,850	19.2%	
Cervix/uterus	13,240	4,170	66.2%	
Larynx	13,150	3,710	60.9%	
Small intestine	10,470	1,450	67.6%	
Testis	9,310	400	95.3%	
Anus	8,580	1,160	67.4%	
Hodgkin lymphoma	8,500	1,050	86.6%	
Vulva	6,190	1,200	71.0%	
Bone and joint	3,450	1,590	66.9%	
Total	**1,640,150**	**544,340**		

Source: adapted from SEER, www.cancer.gov; Hardman & Co Life Sciences Research

In conclusion, Incanthera would be very well positioned in the large and growing oncology market:

- Addresses solid tumours which represent the majority of cases.
- Established 'warheads' with well-known cytotoxic properties.
- Targeted approach that only releases the warhead at the required site of action.
- Compete with the established 'small' molecule cytotoxic segment of the market.
- Multi-disciplinary approach means that its drugs would also compete with and/or complement the targeted antibody approach.

Intellectual property

Incanthera employs the services of Haseltine Lake LLP, one of the largest and longest-established firms of Patent and Trade Mark Attorneys in Europe, for all of its IP requirements. A full report will be provided in the prospectus at the time of the company's IPO. A summary of the more important patents is discussed below, based on information provided by the management team. Incanthera has registered the rights to protect its inventions against unauthorised commercialisation in the most relevant international jurisdictions.

Overview of patents

Patents grant the proprietor a monopoly right to prevent others from carrying out the invention claimed in the patent. Once granted, the right may be kept in force for the patent term (normally 20 years from the date of application) by payment of periodic (normally annual) renewal fees.

Patents are territorial rights that are effective within a given jurisdiction, usually a single country. For example, a UK patent is recognised only in the UK. An initial national patent application will usually serve as a 'priority application' for further filings up to one year later in other countries and also for European and international patent applications. Presently, 38 countries are party to the European Patent Convention, and applications are searched and examined by the European Patent Office (EPO). An International application will designate all countries party to the Patent Cooperation Treaty at the time of its filing (currently 152 countries). This generally covers most territories of commercial importance, including the US, Europe and Japan.

Certain patent offices are considered to be strict examining offices, notably the United Stated Patent and Trademark Office (USPTO), the UK Intellectual Property Office (UKIPO), the EPO and the Japanese Patent Office (JPO). Granting of a patent by one of these strict examining offices affords a strong IP position on the discovery and increases the likelihood that a corresponding patent on the same technology in the same patent family will be granted in other jurisdictions.

Freedom to operate (FTO)

The granting of a patent does not provide the patentee with a right to use the claimed invention. The exclusive rights conferred by the patent are rights to stop others. Therefore, consideration of third-party patent rights is necessary regardless of Incanthera's own patent position. It is not always practical to perform FTO analysis when a product is at an early stage of development, but it becomes more practical and relevant during later stages of development, and before commercialisation.

Individuals in the management team, together with the named inventors on its patent portfolio and the group's scientific and clinical advisors, are well versed in the relevant fields and therefore they have a good insight into the work of other research and development groups in the same fields. Given that development is at a relatively early stage, full FTO analysis has not been performed yet. It is intended that abbreviated FTO analyses will be performed on each product on entry into clinical trials.

Patent strategy

Protection of property rights is at the heart of the group's activities, with regular face-to-face meetings with patent attorneys from Haseltine Lake to review high-level IP approaches, new developments and forthcoming deadlines. To date, initial patent filings have been made to the UKIPO, and Incanthera takes advantage of the information available by requesting an early search report during the priority year.

Towards the end of the priority year, continued interest in an innovation is confirmed and then a priority claiming international patent application (PCT) is filed.

Summary of patent families				
Family	PCT number	Ownership	Priority date	PCT date
1	PCT/GB2008/001043	International	12 Apr 2007(UK)	27 Mar 2008
2	PCT/GB2009/002484	International	22 Oct 2008 (UK)	20 Oct 2009
3	PCT/EP2014/066087	International	2 Aug 2013 (UK)	25 Jul 2014
4	PCT/GB2016/053745	International	1 Dec 2015 (UK)	29 Nov 2016
5	PCT/EP2013/065968	International	30 Jul 2012 (UK)	30 Jul 2013
6/7	PCT/GB02/00801	International	22 Feb 2001	22 Feb 2002

Source: Incanthera

Summary of Incanthera's patents

- 23 granted patents.
- 24 pending applications in seven patent families.

Summary of Incanthera's IP position			
Project	Covering	Ownership	Family
ICT00	Delivery platform technology	Incanthera	1,2
ICT01	ICT01-2588 and other VDA-based pro-drugs	Incanthera	1,2
ICT02	Tumour-targeted theranostics	Incanthera and Leland Stanford University	3
ICT03	Es5 and related pro-drugs	Onco-NX	5
ICT04	CYP programme	Incanthera	6,7
ICT05	ICT05-3205 and other taxane-based pro-drugs	Incanthera	1,4
ICT07	Topical formulation to treat skin solar keratosis and prevent skin melanoma	Incanthera	8

Source: Incanthera

Project ICT00 – drug delivery platform

This is a broadly applicable anti-cancer warhead delivery vehicle provided by a stable peptide chain with its sequence optimised to be specifically and selectively cleaved by MT1-MMP-14, an enzyme over-expressed in many solid human cancers. Incanthera is not aiming to inhibit the MMPs *per se*, but to exploit the functional activity of MT1-MMP to hydrolyse a peptide-conjugated anti-cancer agent and release that cytotoxic drug directly into the tumour. The key development area is the optimised peptide chain, which comprises a specific sequence of seven amino acids of -Arg-Ser-Cit-Gly-Hof-Tyr-Leu-.

Project ICT01, ICT01-2588 and related VDA-based prod-drugs

ICT01-2588 is a novel peptide-conjugate of a VDA "warhead", which is aza-demethylcolchicine, linked to the ICT00 drug delivery platform technology described above. In pre-clinical studies, ICT01-2588 achieved tumour-selective delivery of the VDA leading to reduced blood flow to the tumour and tumour shrinkage without significant toxicity. This patent family also covers pro-drugs comprising a VDA other than aza-demethylcolchicine linked to the drug delivery platform technology. These may include the key specific peptide sequence or may involve certain modifications to that key specific peptide sequence.

Project ICT02, ICT02-3104 and related tumour-targeted theranostics

Tumour-targeted theranostics comprise a VDA warhead (the therapeutic element) linked to both the ICT00 drug delivery platform technology and to an MRI contrast agent (the diagnostic element) to allow detection of its location. This patent family is a collaboration with the University of Stanford and, therefore, is not under the

exclusive control of Incanthera. The key discovery is the lead theranostic ICT02-3104, which is a construct comprising two main modules: ICT01-2588 and a CLIO nanoparticle for imaging.

Project ICT03, ICT03-Es5 and related pro-drugs

ICT03-Es5 is a quinone-based bio-reductive anti-cancer agent activated by the enzyme, DT-Diaphorase (DTD), which is over-expressed in many solid tumours including: breast, colon, liver, bladder, stomach, the central nervous system (CNS), lung tumours, and in melanomas. Incanthera's approach is to use DTD to activate quinone-based pro-drugs to selectively target cancer cells that express DTD. ICT03-Es5 is a DNA cross-linking agent and has been designed to overcome limitations associated with previously proposed bio-reductive agents including, stability, solubility, poor efficacy and unsuitable clinical regimes. In pre-clinical studies, ICT03-Es5 showed promising efficacy and an improved pharmacokinetics (PK) profile. Other development areas covered by this family are pro-drugs with structures related closely to Es5.

Project ICT04 – CYP Programme.

This is based on know-how and earlier work from Prof. Laurence Patterson at the Institute of Cancer Therapeutics, UoB. Early work focused on targeting colo-rectal cancer using CYP2W1, a catabolic enzyme, to convert pro-drug to ultra-potent chemotoxins based upon the class of natural compounds known as the duocarmycins. Pre-clinical results to date with the lead compound show promising prospects for this new class of drug, demonstrating successful delivery of ultra-potent agents with acceptable toxicity profiles. Incanthera is maintaining the previous lead compound patent protection in key territories (US and UK) via patent families 6 and 7. Current R&D programmes are vested within the Institute of Cancer Therapeutics, UoB, but available to Incanthera.

Project ICT05, ICT05-3205 and related taxane-based pro-drugs

ICT05-3205 is a novel peptide-conjugate of a paclitaxel "warhead", linked to the ICT00 drug delivery platform technology. Other development areas are pro-drugs comprising a taxane other than paclitaxel, linked to the delivery platform, which may be the key specific peptide sequence or may involve certain modifications to that key specific peptide sequence.

Project ICT07

This covers a topical formulation for skin solar keratosis treatment and prevention of skin melanoma. In 2018, Incanthera entered into a product development and licensing agreement with a UK-based pharmaceutical design company, which owns a specific dermatological drug delivery formulation and on which it has pending patents and specialises in dermatological drug formulations. The strategy is to develop an improved topical skin formulation for delivery of a known agent which has proven oral activity. The agreement also provides the group with a licence to use the specific dermatological drug delivery formulation for the purposes of ICT07.

Material agreements

University of Salford

On 14 July 2011, Onco-NX Ltd (see below) entered into an exclusive licence agreement with the UoS in respect of substituted stilbenes and their reactions (US patent 7220784B2). The consideration was satisfied with shares in Onco-NX, and subsequently replaced (10 January 2014) by 499 Ordinary shares in Incanthera. The licence in relation to the patent applications expires on the latest date of expiry of such patents, and the tenth anniversary of the licence in relation to the know-how.

University of Bradford

On 19 December 2011, Incanthera entered into an exclusive licence for certain intellectual property and option to assign with the UoB. Under the terms of this agreement, in the event of an assignment event occurring within [the initial term], UoB would automatically assign all rights, title and interest in the relevant IP to Incanthera. An assignment event occurred on 18 December 2012 (being the investment by a third party of £1,000,000 or more in Incanthera). Accordingly, the relevant IP, including international patents, has now been fully assigned to Incanthera by UoB.

In February 2018, the original agreement was extended for a further 10 years.

Onco-NX Ltd

On 10 January 2014, Incanthera acquired the entire issued share capital of Onco-NX Ltd. The consideration of £150,000 was satisfied by the issue of 35,294 Ordinary shares of Incanthera Ltd to the Onco-NX vendors. The Onco-NX sellers gave various warranties and restrictive covenants for a period of three years from completion. There are no outstanding liabilities or obligations on the group in favour of the Onco-NX sellers.

Spear Therapeutics Ltd

On 12 December 2014, Incanthera acquired the entire issued share capital of Spear Therapeutics, mostly held by De Montfort University. The consideration of £337,943 was satisfied by the issue of 79,516 Ordinary shares of Incanthera Ltd to the vendors. The vendors and certain other parties gave various warranties and restrictive covenants for a period of three years from completion. There are no outstanding liabilities or obligations on the group in favour of the Spear Therapeutics vendors.

Duocarmycin assignment

On 12 December 2014, Incanthera entered into a licence agreement with UoB in respect of the IP associated with the duocarmycin programme. In return, UoB received 39,758 'A' Ordinary and 39,758 Ordinary shares of Incanthera.

Theranostics assignment

On 27 January 2015, UoB and the Trustees of the Leland Stanford Junior University (Stanford), as co-applicants for the patent in respect of ICT02 (tumour-targeted theranostics), assigned all rights in the patent to Incanthera. In return, Stanford received £1.00 as consideration for the assignment.

Pro-drug assignment

On 10 June 2017, UoB assigned all rights in the patents relating to ICT00 to Incanthera in return for 54,546 Ordinary shares of Incanthera.

Ellipses Pharma Ltd

On 16 July 2017, Incanthera entered into a series of agreements with Ellipses Pharma Ltd, a company established by biopharmaceutical entrepreneur, Sir Christopher Evans, to provide a source of capital to fund clinical trials of innovative cancer drugs. The deal covers a number of areas:

- Patent assignment and development agreement.
- Patent licence.
- Clinical services framework.
- Work order no.1.

Patent assignment and development agreement

Specified IP of Incanthera, as defined in the agreement including the rights to ITC01-2588, passed to Ellipses for commercial exploitation. The consideration for these patent and commercial rights will be a share of the rewards of this exploitation, including milestones and royalties. The assignment automatically becomes effective once Ellipses has satisfied certain conditions.

Ellipses is obliged to develop certain drugs through clinical trials to a valid licensing point post a Phase I trial and both parties were obliged to enter into the framework services agreement described below to facilitate Incanthera undertaking any agreed development tasks.

Patent licence

Under this agreement, Ellipses is permitted to use the specified IP pending the patent assignment referred to above becoming effective.

Clinical services framework agreement

The framework by which Incanthera undertakes certain development work for Ellipses was established. This agreement contains a change control procedure, which enables alterations to be made to work orders, but the amount payable may not be increased unless the scope of the services to be provided has changed.

Work Order No 1

This is the first work order under the clinical services framework agreement above, and is intended to cover the preparation work required for the proposed phase I clinical trial with ICT01-2588. Incanthera is providing project management services including the delivery of appropriate authorisation and the manufactured product needed for that trial.

The total cost of the services to be provided is £1.4m of which £640,000 is being paid directly to sub-contractors by Ellipses for the provision of GMP-manufactured active pharmaceutical ingredient (API). Up-front and monthly payments have been received already by Incanthera, with a final balance of £160k to be paid by Ellipses on receipt of the clinical trial authorisation (CTA) from the regulators (MHRA).

ImmuPharma plc

Incanthera has signed a Heads-of-Terms agreement with IMM to acquire the development rights to progress its clinical stage oncology asset, the Nucant programme. Incanthera has an exclusive period until 31 December 2018 to to finalise the terms of a Definitive Licence Agreement for the Nucant technology. Given that The Nucant programme would greatly enhance the R&D propfile of Incanthera and several of the likely final terms have been disclosed, we expect this deal to be concluded shortly after a successful IPO of Incanthera.

Financials and valuation

Funding history

The last funding round provides a benchmark valuation of £13.4m

Since incorporation, Incanthera has raised a total of £7.51m, including equity issued in exchange for acquired IP, at an average price of 307p per share (taking into account the bonus issue that was used to re-configure the share structure into a unified Ordinary share), to get the company to where it is today. The most recent funding was earlier in 2018, through the issue of 240,845 Ordinary shares at a price of 550p to raise gross new capital of £1.26m and the Subscription for shares by IMM, also at 550p, giving the company a post-money valuation of £13.4m.

Incanthera share issues

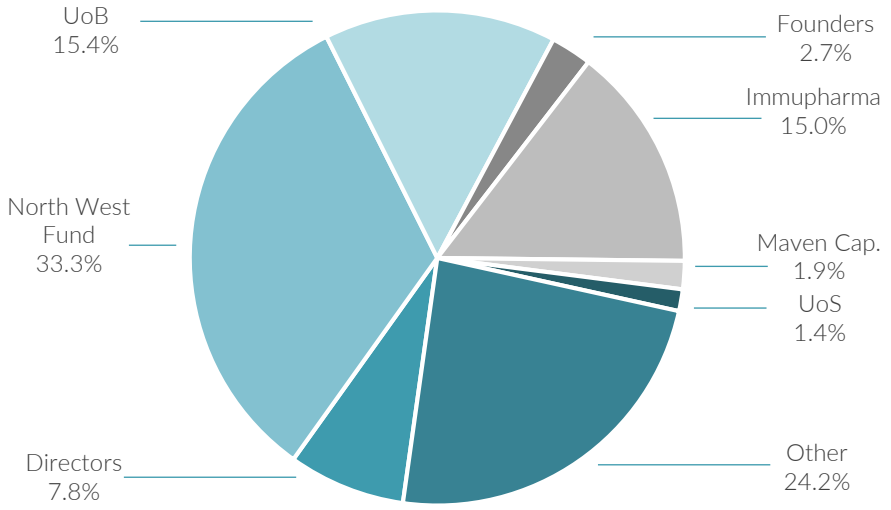
Date	Shares issued	Price (p)	Funds (£)	Total shares in issue	Post-money valuation (£)
2011	415,781	160	667,075	415,781	667,075
2012	248,850	242	603,198	664,631	1,611,028
2013	45,759	242	110,925	710,390	1,722,066
2014	806,263	263	2,122,444	1,516,653	3,992,507
2016	62,837	279	175,032	1,579,490	4,399,658
2017	80,114	279	223,132	1,659,604	4,622,288
2018	195,391	550	1,014,617	1,854,995	10,202,473
2018	363,637	550	2,000,004	2,218,632	12,202,476
2018	*145,951	100	145,951	2,364,583	13,005,207
2018	18,182	550	100,001	2,382,765	13,105,208
2018	45,454	550	249,997	2,428,219	13,355,205
Totals	**2,428,219**	**305**	**7,412,375**	**2,428,219**	**13,355,205**

**Exercise of options*

Source: Incanthera, Hardman & Co Life Sciences Research

- Acquisitions of product/technology for shares have been included as if the vendor(s) had received cash and concomitantly made as investment in the company.
- At 30 September 2018, there were 2,428,219 Ordinary 1p shares in issue.
- Any outstanding options will lapse at the time of the IPO, and be replaced by a new option scheme after Incanthera is listed on AIM.

Shareholders



Source: Incanthera

Profit & Loss

Forecasts are based on the assumption that Incanthera raises £7m at IPO, which represents the middle of its £4.0-£10.0m target range.

- **Sales:** Solely 'work orders' (w/o) from Ellipses in relation to ICT01-2588. w/o #1 for pre-clinical work is nearing completion, which will trigger a much larger w/o #2 which, on successful completion will lead to w/o #3. The timing of this work is in the hands of Elipses.
- **Gross margin:** The initial gross margin on w/o #1 was at a good margin (ca.69%), however, this is not yet complete and there will be much greater direct costs associated with subsequent work, such that the margin will be nearer 30%.
- **SG&A:** The addition of a few permanent staff after IPO for a full-year contribution, coupled with some increased sponsorship costs for the 10-year UoB research extension, will lead to higher SG&A, then rising with inflation.
- **R&D:** Closure of the Heads-of-Terms agreement with IMM will result in expansion of the R&D portfolio. This, in turn, will raise the level of R&D investment needed. However, investment in R&D will depend largely on the quantum of new capital raised at the time of IPO. On the basis that the company raises £7m (see cashflow, page 41), much of this will be ear-marked for R&D over the forecast period.

Profit & Loss account						
Year-end March (£000)	2016	2017	2018	2019E	2020E	2021E
Sales	0	0	603	0	1,000	1,800
COGS	0	0	-189	-50	-1,050	-1,620
Gross profit	0	0	414	-50	-50	180
Gross margin	-	-	68.7%	-	-5.0%	10.0%
SG&A	-615	-676	-1,223	-1,050	-1,280	-1,360
R&D	-451	-365	-143	-250	-2,000	-2,250
EBITDA	-946	-920	-832	-1,230	-3,210	-3,310
Depreciation	-9	-10	-9	-9	-9	-9
Amortisation	-111	-111	-111	-111	-111	-111
Licensing/Royalties	0	0	0	0	0	0
Underlying EBIT	**-1,066**	**-1,041**	**-952**	**-1,350**	**-3,330**	**-3,430**
Share-based costs	-34	-34	-32	-35	-40	-45
Exceptional items	0	0	0	-773	0	0
Statutory EBIT	-1,100	-1,075	-984	-2,158	-3,370	-3,474
Net financials	0	0	0	4	0	0
Underlying pre-tax profit	**-1,066**	**-1,041**	**-952**	**-1,346**	**-3,330**	**-3,430**
Reported pre-tax	-1,100	-1,075	-984	-2,155	-3,370	-3,474
Tax liability/credit	117	120	41	63	500	563
Tax rate	0	0	0	0	0	0
Underlying net income	**-949**	**-921**	**-911**	**-1,284**	**-2,830**	**-2,867**
Statutory net income	-983	-955	-943	-2,092	-2,870	-2,912
Ordinary 1p shares:						
Period-end (m)	0.92	0.98	1.85	3.88	3.88	3.88
Weighted average (m)	0.91	0.95	1.64	2.53	3.88	3.88
Fully-diluted (m)	1.27	1.31	2.00	2.89	4.25	4.25
Underlying basic EPS (p)	**-104.7**	**-97.1**	**-55.7**	**-50.7**	**-72.9**	**-73.8**
Statutory basic EPS (p)	-108.4	-100.7	-57.6	-82.7	-73.9	-75.0
U/l fully-diluted EPS (p)	-74.8	-70.2	-45.6	-44.4	-66.7	-67.5
Stat. fully-diluted EPS (p)	-77.5	-72.8	-47.2	-72.3	-67.6	-68.6
DPS (p)	0.0	0.0	0.0	0.0	0.0	0.0

Source: Hardman & Co Life Sciences Research

Balance sheet

- **Cash position:** Incanthera undertook a small pre-IPO funding round in March 2018 – last month of fiscal year – to satisfy short-term funding requirements in the run-up to IPO. At 31 March 2018, Incanthera had £0.14m cash.
- **Working capital:** Incanthera operates largely as a virtual company, out-sourcing most of the R&D functions – therefore, the working capital requirement is modest, often reflecting timing differences, e.g. tax credits from HMRC.
- **Tax credits:** Increasing investment in R&D will be associated with a rising level of Research and Development Expenditure Credit (RDEC) available from HMRC, which is usually received in the following fiscal period.
- **Cash runway:** Forecasts have been prepared on the basis that Incanthera raises £7m at IPO. The eventual figure will dictate the investment that will be made in R&D. The cash raised is expected to be sufficient to support a cash runway of over two years.

Balance sheet						
@31 March (£000)	2016	2017	2018	2019E	2020E	2021E
Shareholders' funds	789	185	236	7,952	5,122	2,255
Cumulated goodwill	0	0	0	0	0	0
Total equity	789	185	236	7,952	5,122	2,255
Share capital	9	10	19	39	39	39
Reserves	780	175	217	7,913	5,083	2,216
Provisions/liabilities	0	0	0	0	0	0
Long-term loans	0	0	0	0	0	0
Short-term debt	0	0	0	0	0	0
less: Cash	43	88	143	6,879	3,703	840
less: Deposits	0	0	0	0	0	0
Invested capital	**746**	**97**	**93**	**1,073**	**1,419**	**1,415**
Fixed assets	21	11	10	10	12	16
Intangible assets	871	760	949	2,150	2,150	2,150
Inventories	0	0	0	0	0	0
Trade debtors	*3*	*5*	*5*	*5*	*5*	*5*
Other debtors	*62*	*66*	*235*	*235*	*235*	*235*
Tax credit/liability	*117*	*120*	*41*	*63*	*500*	*563*
Trade creditors	*-54*	*-74*	*-331*	*-331*	*-331*	*-331*
Other creditors	*-274*	*-791*	*-816*	*-1,059*	*-1,152*	*-1,223*
Debtors less creditors	-146	-674	-866	-1,087	-743	-752
Invested capital	**746**	**97**	**93**	**1,073**	**1,419**	**1,415**
Net cash/(debt)	**43**	**88**	**143**	**6,879**	**3,703**	**840**

Source: Hardman & Co Life Sciences Research

Cashflow

- **Model:** The cashflow model for Incanthera is very simple. Underlying EBIT reflects the R&D investment and the corporate overhead (SG&A), with an adjustment for the actual cash received from HMRC for tax credits accrued in the previous financial year.
- **Pre-IPO funding round:** During 2018, Incanthera raised £1.26m (before expenses) through the issue of 241k shares at 550p per share to satisfy its short-term needs in the run-up to IPO.

- **ImmuPharma deal:** On signing the Heads-of-Terms agreement for the Nucant technology, IMM made a £2.0m investment in Incanthera via a Subscription for shares. Definitive agreement for the Nucant licensing deal with IMM will result in a payment of £1m to the licensor, which will be in the form of new Ordinary shares. Incanthera will be responsible for all future development costs in the Nucant technology.
- **IPO funding:** Forecasts assume that the company raises gross funds of £7.0m at IPO, with associated costs of ca.7%. Apart from the corporate overhead, this will be used primarily to drive forward its R&D programmes and get three products into human trials by the end of 2020.
- **Runway:** The discretionary element to the forecasts is the rate of investment in R&D. In the event that a figure lower than £7m is raised, then R&D forecasts would be scaled back, and vice-versa. However, whatever the level of new capital, management is likely to adjust the spending plans so that Incanthera has a clear two-year cash runway.

Cashflow						
Year-end March (£000)	2016	2017	2018	2019E	2020E	2021E
Underlying EBIT	-1,066	-1,041	-952	-1,350	-3,330	-3,430
Depreciation	9	10	9	9	9	9
Amortisation	111	111	111	111	111	111
Inventories	*0*	*0*	*0*	*0*	*0*	*0*
Receivables	*42*	*-6*	*-169*	*-186*	*-195*	*-201*
Payables	*208*	*545*	*282*	*254*	*178*	*160*
Change in working capital	250	539	113	68	-18	-41
Other	0	0	0	0	0	0
Company op. cashflow	**-696**	**-381**	**-719**	**-1,162**	**-3,227**	**-3,351**
Net interest	0	0	0	4	0	0
Tax paid/received	112	117	61	41	63	500
Operational cashflow	-584	-264	-658	-1,118	-3,165	-2,851
Capital expenditure	-26	0	-8	-9	-11	-13
Free cashflow	**-610**	**-264**	**-666**	**-1,127**	**-3,176**	**-2,863**
Dividends	0	0	0	0	0	0
Acquisitions	0	0	-300	-1,201	0	0
Disposals	0	0	0	0	0	0
Cashflow after invests.	**-610**	**-264**	**-966**	**-2,328**	**-3,176**	**-2,863**
Share repurchases	0	0	0	0	0	0
Share issues	0	309	1,021	9,064	0	0
Change in net debt	**-614**	**45**	**55**	**6,736**	**-3,176**	**-2,863**
Hardman FCF/share (p)	-64.4	-27.8	-40.2	-44.1	-81.1	-73.1
Opening net cash/(debt)	657	43	88	143	6,879	3,703
Closing net cash/(debt)	**43**	**88**	**143**	**6,879**	**3,703**	**840**

Source: Hardman & Co Life Sciences Research

Valuation

The best approach to valuing biopharmaceutical companies is to prepare detailed discounted cashflow analyses of key products through to patent expiry, and then to risk-adjust the NPV based upon industry standards for the probability of the product reaching the market. In the case of Incanthera, the assets are at too early a stage in the development process to be able to undertake a DCF valuation without exhaustive analysis of the market opportunities, penetration rates and potential milestones and royalty payments. However, this situation looks set to change over the next two years, by which time Incanthera will have three products in clinical trials and a better understanding of its commercialisation strategy will be known, although this will almost certainly be via out-licensing deals.

Suffice to say, Incanthera has a novel approach, with potential to target the biggest segments of a very large market, suggesting that these assets will all be attractive to big pharma and/or biotech companies. To that extent it is probably more relevant to look at what large pharma is prepared to pay to gain access to such molecules.

Comparative valuation – M&A

Incanthera aims to out-license its asset at an appropriate time point

Incanthera's strategy is to develop its assets through to proof-of-concept clinical trials and then to out-license them. The following table provides some indication of the value that big pharma and biotech are willing to place on novel clinical and pre-clinical assets in the field of oncology. The list is not exhaustive but investigates transactions where financial terms were disclosed. There are many more deals where financial terms have not been disclosed. Our focus has been on a number of transactions where assets were in late-stage pre-clinical development or early-stage clinical development to better illustrate the value inflection points.

Median up-front payments for pre-clinical assets are $25m…

- The median up-front licence deal value of pre-clinical compounds in the oncology space is $25m per target, with milestones of up to $433m; this compares with $17m and $357m, respectively, up to the end of 2015.

…rising to and $53m for Phase I

- The median up-front licence deal value of Phase I clinical assets in oncology is $53m per target with milestones of up to $628m; this compares with $45m and $628m, respectively, up to the end of 2015.

Selected Phase I oncology deals

Licensor	Licensee	Type	Date	Up-front ($m)	Milestones ($m)	Comment
Sierra Oncology	Gilead/Kite	Lic.	Aug-18	3	185	Failed two Ph.III trials in 2016
Eli Lilly	AurKa Pharma	Acqn.	May'18	110	465	Acquisition of the Aurora kinase inhibitor
Incyte	MacroGenics	Lic.	Oct'17	150	750	Worldwide rights to PD-1 drug
Merck & Co	Rigontec	Acqn.	Sep'17	137	415	Company buy-out
Celgene	Beigene	Lic.	Jul'17	263	1,000	Worldwide ex-Asia rights to BGB-A317
Incyte	Calithera Bio.	Lic.	Jan'17	53	430	Global collab. & licensing for CB-1158
Five Prime Ther.	BMS	Lic.	Oct'16	350	1,390	Anti-CSF1R for oncology/non-oncology uses
Sierra Onc.	Sareum/CRT	Lic.	Sep'16	7	322	Sareum has rights over 27.5% of all income
Celgene	Juno	Lic.	Aug'16	50	1,000	CD19 programme ex-N.America and China
Novartis	Xencor	Lic.	Jun'16	150	2,410	Access to bi-specific antibodies: XmAb5871
CANbridge LS	Aveo Onc.	Lic.	Mar'16	1	132	World, excl North America, rights to AV-203
Alligator Bio.	Janssen	Lic.	Aug'15	U/D	700	$700m deal size, incl. up-front payments, dev./reg. & sales milestones, plus royalties
Newlink Gen.	Genentech	Lic.	Oct'15	150	1,000	>$1bn. US co-promote option
			Average	**101.6**	**701.5**	
			Median	**53.0**	**510.5**	

Acqn.= Acquisition; Lic. = Licensing deal; U/D = undisclosed; Reg.= regulatory; DD = double-digit royalties
This table should not be considered comprehensive
Source: Hardman & Co Life Sciences Research

Selected pre-clinical oncology deals

Licensor	Licensee	Type	Date	Up-front ($m)	Milestones ($m)	Comment
Gilead/Kite	HiFiBiO	Option	Oct-18	10	U/D	Access to TCR platform
Roche	GO Therapeutics	Lic.	Oct-18	9	186	Glycoprotein bi-specific mAb platform
Merck & Co	Dragonfly	Lic.	Oct-18	U/D	700	Proteins on naturak killer (NK) cells
Roche	Tusk Therapeutics	Acqn.	Sep-18	81	0	Anti-CD25 antibody
Bluebird Bio	Gritstone Oncology	Lic.	Aug-18	20	Significant	Access to 10 x TCRs
Loxo Oncology	Redx Pharma	Acqn.	Jul-17	40	0	Assets and IP of BTK programme
Celgene	Dragonfly	Lic.	Jun-17	33	0	Option to license up to four I-O assets
Novo Nordisk	Innate Pharma	Lic.	Jun-17	45	415	Global rights to IPH5401; double-digit royalties
Merck KGaA	F-Star	Lic.	Jun-17	30	1,000	Upfront of €115 includes R&D and first 2-yr milestones
BioLineRx	AgaImmune	Acqn.	Mar-17	6	U/D	Significant R&D spend required
Amgen	Inmatics	Lic.	Jan-17	30	1,000	Bi-specific antibodies
Servier	Pieris Pharma	Lic.	Jan-17	32	1,900	Access to PRS-332 + stake in four other assets
Pfizer	BioInvent	Lic.	Dec-16	16	500	Research collab + commercialisation of up to five antibody drugs
Bristol-Myers	Enterome	Lic.	Nov-16	15	N/A	Microbiome expertise to boost cancer immontherapies
Bluebird	Medigene	Lic.	Sep-16	15	1,000	Milestones and tiered royalties
Amgen	Advaxis	Lic.	Aug-16	40	475	Access to ADXS-NEO cancer immunotherapy
Celgene	Jounce Ther.	Lic.	Jul-16	225	2,300	Access to JTX-2011 and up to four other assets
Servier	Sorrento Ther.	Lic.	Jul-16	28	785	Access to anti-PD-1 STI-A1110
Ono	Celyad	Lic.	Jul-16	12	306	Rights to NKR-2 T-cell immunotherapy in SE Asia
JNJ	MacroGenics	Lic.	May-16	75	665	Global rights to MGD015 bi-specific
AbbVie	Argenx	Lic.	Apr-16	40	625	ARGX-115 + milestone + dd royalties
Merck & Co	Iomet Pharma	Acqn.	Jan-16	U/D	400	$400m acquisition
Novera Ther.	JanssenJNJ	Lic.	Sep-15	U/D	345	$344.5m in dev/reg & sales milestones
Gencia	Takeda	Lic.	Sep-15	U/D	500	$500m in dev/reg and sales milestones
Xencor	Amgen	Lic.	Sep-15	45	1,700	$1.7bn in clinical, regulatory and sales milestones
Jiangsu Hengrui	Incyte	Lic.	Sep-15	25	770	$770m ($90m regulatory; $150m development; $530m commercial)
Heptares	AstraZeneca	Lic.	Aug-15	10	500	$500m in dev/reg and sales milestones, plus double-digit royalties
Inhibrx	FivePrime Therapeutics	Lic.	Jul-15	10	380	up to $380m
Sprint Bio.	Bayer	Lic.	Jul-15	U/D	U/D	Undisclosed milestone payments
Globavir	Sorrento Therapeutics	Lic.	Jul-15	Zero	80	$80m in dev/reg and sales milestones, plus royalties
Almac Discovery	Genentech	Lic.	Jun-15	14.5	349	$349m in dev/reg & sales milestones, plus royalties
Curadev	Roche	Lic.	Apr-15	25	530	$530m in dev/reg & sales milestones, plus tiered DD royalties
Checkpoint Therapeutics	TG Therapeutics	Lic.	Mar-15	0.5	164	$164m in development and sales based milestones, plus tiered single digit royalties
NeuPharma	Coronado Biosciences	Lic.	Mar-15	1		Undisclosed dev/reg and sales milestones, plus tiered single digit royalties
Sorrento Therapeutics	NantWorks	Lic.	Mar-15	10	100	$100m in milestone payments, 5% royalties
Flexus Bio.	BMS	Acqn.	Feb-15	800	450	$450m. Just IDO/ TDO acquired
Aurigene	Curis	Lic.	Jan-15	U/D	52.5	$52.5m/ programme
			Average	**40.1**	**680.9**	
			Median	**30.0**	**562.5**	

Acqn.= Acquisition; Lic. = Licensing deal; U/D = undisclosed; Reg.= regulatory; DD = double-digit royalties
This table should not be considered comprehensive
Source: Hardman & Co Life Sciences Research

Comparative valuation – peer group analysis

Another approach to valuation is to undertake a peer group comparison, whereby the value of Incanthera can be put into context against the valuations afforded to a group of similar companies by the stock market. However, while this is a sound approach to take, in practise it is much less straight-forward for a number of reasons:

- Companies are all at slightly different stages of development.
- Few companies take the same technological approach.
- Even using the same approach, different targets/indications are being tackled.
- It is well known that the UK stock market affords lower valuations to companies compared with similar companies quoted on other stock markets.

Therefore, to provide readers with as much information as possible and allow them to make their own judgement, the peer group analysis has been divided into two tables – one consists of a group of AIM-listed UK oncology-focused peers, all broadly at a similar stage of development; the second is a group of internationally quoted peers that are at the same stage of development, but some are less focused on the field of oncology.

UK peer group analysis

Peer group analysis suggests that there is scope for an upside potential

Most of the companies listed below are close peers of Incanthera, and all are developing new cancer drugs. Although most of them are at very similar stages of development, Diurnal (DNL) would be the anomaly with its first drug, a small molecule, having just been launched in Germany. Tiziana also stands out as an anomaly for different reasons – the enterprise value afforded to this company by the market looks out of synchronisation compared with the other companies at a similar stage of development; unusually for a biopharmaceutical company it has debt on its balance sheet in the form of a convertible loan note (out of the money) and, at this point in time, on our calculations, it has very little cash. However, the company is in the process of listing its shares on NASDAQ and in a Form-1 Registration Statement with the SEC, it has stated that it anticipates issuing 1.01m ADSs at a price of $9.90 (equivalent to 75p per Ordinary share), raising $10m gross new funds.

The share price of Diurnal has reacted negatively following release of headline data from a Phase III trial which generated unexpected results. Also, valuations for other companies (e.g. Evgen) are slightly depressed because the market is aware that clinical trial data with binary outcomes are about to be released, at a time when the companies are also running very low on cash. Positive news is likely to be accompanied by a valuation uplift and a capital increase.

Peer group valuations – UK quoted

Company	Evgen	Diurnal	Incanthera	Redx	Sareum	Scancell	Tiziana	ValiRx
Ticker	EVG	DNL	-	REDX	SAR	SCLP	TILS	VAL
Local currency	£	£	£	£	£	£	£	£
Share price	13.5	31.0	550.0	7.3	0.8	8.0	93.0	1.5
Shares in issue (m)	93.3	61.3	2.4	126.5	2,645.2	374.5	126.9	531.6
Market cap. (£m)	12.6	19.0	13.4	9.2	21.7	30.0	118.0	8.0
Cash (£m)	2.2	16.7	0.5	5.0	2.3	9.8	0.0	0.4
Debt (£m)	0.0	0.0	0.0	0.0	0.0	0.0	-14.0	0.0
EV (£m)	**10.4**	**2.3**	**12.9**	**4.2**	**19.4**	**20.2**	**132.0**	**7.5**
Relative EV (x)	0.8	0.2	-	0.3	1.5	1.6	10.3	0.6
Dev. Stage	Ph.I/II	Appr.	PC/Ph.I	PC/Ph.I	PC/Ph.I	Ph.I/II	PC/Ph.I	PC/Ph.I/II
Licensing deals	0	0	2/3	0	1	0	0	0

Prices taken at close of business on 2 November 2018
Source: Hardman & Co Life Sciences Research

- The average EV of UK peers is £26.1m (range £4.2m-£132.0m).
- The relative EV of peers to the post-money valuation of Incanthera at its last funding round is in the range of 0.2x to 10.3x, with an average of 2.0x.

Global peer group analysis

Interestingly, although the valuations afforded to the global peers by international stock markets are generally higher, our selected group of companies, all at similar stages of development and having made at least one licensing deal/partnership, have an unusually broad range. Again, there might be specific circumstances for this.

- The average EV of global peers is £68.2m (range £2.8m to £275.6m).
- The relative EV of peers to the post-money valuation of Incanthera at its last funding round is in the range of 0.2x to 21.4x, with an average of 5.3x. Alligator Bioscience is considered to be a good comparator to Incanthera, given its approach of tumour-directed immuno-oncology (with bi-specific antibodies) whereas Incanthera is using a non-antibody approach of tumour-directed warheads. It has a major licensing deal with Johnson & Johnson and is about to enter the clinic with its next product. Alligator has an EV of £121m.
- Mateon (formerly Oxigene) is an extremely good comparator from a scientific point of view, given that it is focused on the development of VDA drugs. However, the company has a bad history from its days as Oxigene, and recently terminated a late-stage product because of a failed trial (lack of clear efficacy). Both of these reasons are reflected in its share price and valuation.
- Advaxis is an immunotherapy company and also a good comparator in terms of stage of development and licensing deals. However, even after a recent capital increase and a strong balance sheet, it is currently trading at a market capitalisation that is very close to its net cash level (ca.$26m).

Peer group valuations – global quoted

Company	Addex	Advaxis	Alligator	Mateon	Bionomics	Incanthera	Inovio	OncoSec	Palatin
Ticker	ADXS	ADXS	ATORX	MATN	BNO	-	INO	ONCS	PTN
Local currency	CHF	$	SEK	$	AUD	£	$	$	$
Share price	2.3	0.6	27.7	0.2	0.14	550.0	5.2	1.88	0.9
Shares in issue (m)	28.6	52.8	71.4	41.4	431.5	2.4	91.5	52.3	202.0
Market cap. (lc)	66.6	29.6	1,977.5	7.5	60.4	13.4	471.2	98.4	185.9
Market cap. (£m)	50.9	22.8	167.4	5.7	33.4	13.4	362.4	75.7	142.9
Cash (lc.m)	45.0	25.9	548.6	2.6	37.1	0.5	112.8	17.9	25.7
Debt (lc.m)	0.0	0.0	0.0	0.0	-18.6	0.0	0.0	-1.1	-6.9
EV (lc)	21.5	3.6	1,428.9	4.8	41.9	12.9	358.4	81.7	124.1
EV (£m)	**16.5**	**2.8**	**121.0**	**3.7**	**23.2**	**12.9**	**275.6**	**62.8**	**95.4**
Relative EV (x)	1.3	0.2	9.4	0.3	1.8	-	21.4	4.9	7.4

Note: this peer group should not be considered comprehensive
Prices taken at close of business on 2 November 2018
lc = local currency
Source: Hardman & Co Life Sciences Research

Conclusion

These peer group analyses suggest that there is scope for substantial upside in the valuation of Incanthera provided that the promise of its drug delivery technology in pre-clinical development work is borne out by clinical results in the upcoming trials.

Company matters

Registration

Incorporated in the UK with company registration number: 11026926

Registered Office
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www.incanthera.com

Board of Directors

Board of Directors			
Position	**Name**	**Remuneration**	**Audit**
Executive Chairman	Tim McCarthy		
Chief Executive Officer	Simon Ward		
Chief Operating Officer	Pawel Zolnierczyk		
Chief Financial Officer	Laura Brogden		
Non-executive director	Dr Tom Morris	M	M
Senior independent NED	Douglas Quinn*	M	C
Non-executive director	Dr Alan Warrander	C	M

**Proposed*
M = member; C = chair
Source: Company reports

Tim McCarthy – Executive Chairman

Tim joined Incanthera in 2014, bringing more than 35 years' senior-level business experience in the Healthcare, Biotech and Technology sectors. He is non-executive Chairman of ImmuPharma plc and a supervisory member of Expedeon AG, an international molecular biology products company. He is a former CEO and Finance Director of a number of public and private companies, including Alizyme plc and Peptide Therapeutics Group plc. He has also co-founded a number of healthcare and biotechnology companies. A Fellow of the Association of Chartered Certified Accountants, he also has an MBA from Cranfield School of Management.

Simon Ward – Chief Executive Officer

Simon was instrumental in establishing Incanthera in March 2010 as a vehicle to commercialise and seek development funding for, the intellectual property being created by the ICT, part of the UoB. Previously, he founded and was appointed CEO of Molecular SkinCare Limited, a pioneer and developer of novel dermatology products for the prevention and management of skin diseases, which was acquired by York Pharma plc in 2005, becoming Chief Scientific Officer (2005 to 2009). From 2003 to 2011, Simon served as chairman of South Yorkshire Bioscience Enterprise Network (SYBEN). During part of this period, he was a non-executive director (and eventually deputy chairman) of Medipex, a healthcare innovation hub for NHS organisations across the Yorkshire & Humber and East Midlands regions and worked in industry and academia internationally. Simon graduated in 1990 from the School of Pharmacy, University of London with a Joint Honours Degree in Pharmacology and Toxicology, and in 1994 was awarded a DPhil in the Department of Human Anatomy, Oxford University, under a Glaxo Group Research Studentship.

Pawel Zolnierczyk – Chief Operating Officer

Pawel joined Incanthera in 2014, bringing over 10 years' experience in research commercialisation in the life sciences sector. He has successfully managed IP exploitation projects toward licences and spin-offs. A graduate of Gdansk University of Technology, Pawel has held industry appointments with CEMA Consulting including as CEO of iTech Innovations Ltd. He was formerly IP Manager for the UoS. Pawel has successfully negotiated deals with corporate partners including Reckitt Benckiser plc and Novartis AG. He has wide experience of managing the creation of wealth from academic IP and managing sub-contractors including the creation of Onco-NX spin-offs from DiviRNA, and CarbonAir which successfully secured seed stage investments. Before joining Incanthera, Pawel was managing director of Onco-NX which was acquired by Incanthera in 2014.

Laura Brogden – Chief Financial Officer

Laura Brogden was appointed by Incanthera in October 2017, having provided accountancy services to the company for six years through her role as a senior accountant with 'summ.It assist' LLP, a firm that provides outsourced finance staffing to UK companies. Laura has been with summ.It for 11 years, gaining extensive experience heading up the finance function for SMEs across a diverse range of industries. Laura is an Associate of the Chartered Institute of Management Accountants, and is contracted to Incanthera on a part-time basis.

Doug Quinn – Senior independent non-executive director (proposed)

Doug Quinn is an ACMA qualified, commercially-focused business manager, and has spent the last 16 years involved in start-up and early-stage businesses helping to guide them through their various phases of growth and to secure the requisite funding requirements. Mr Quinn has operational experience both within finance and across other business functions as well as considerable corporate finance experience, including in public markets. He is currently CFO of Aim-listed Skin Biotherapeutics plc, and regenerative medicine company Videregen Ltd. Previous appointments include CFO at AIM-listed Arthro Kinetics Plc, and University of Manchester spinout, Gelexir Healthcare Ltd. The proposal is that Doug will join the Incanthera Board in 2018 as senior independent non-executive director.

Dr Tom Morris – non-executive director

Dr Morris has 25 years' experience in drug development, much of which was specialising in oncology at AstraZeneca, where he was senior medical director (Oncology) until 2015. Since then, he has acted as a consultant to a number of companies, and is a director and chief medical officer at OncoTherics Limited. His expertise is in the clinical aspects of drug development, having overseen all phases of clinical trial programmes. This has included interacting with external academic groups and regulatory agencies worldwide, including the writing and review of regulatory documents to support scientific advice, multinational clinical trial applications, and marketing authorisation applications. Thomas is a graduate in physiology and medicine from the University of Wales, and received a Master of Laws degree from Cardiff Law School. He is also a Fellow and board member of The Faculty of Pharmaceutical Medicine, a former member of its Professional Standards Committee and a former chair of its Ethical Issues Committee.

Dr Alan Warrander – non-executive director

Since 2008, Alan has been an independent consultant in Pharma and Biotech. He joined Incanthera in 2012 as a Consultant, and also became a board member. His expertise is in the fields of partnering and licensing, with significant experience of global pharma drug discovery and drug development processes. Alan is a director of both Oncolytics Biotech (U.K.) Ltd and Oncolytics Biotech (Barbados) Inc. From 2005 until the end of 2007, he was SVP, Life Sciences at Wood Mackenzie, the global consultancy firm that provided advice and expert scientific opinion to pharma

and biotech companies, finance groups and law firms. Prior to this he spent over 20 years in various drug companies including AstraZeneca, Sterling Winthrop and Hoechst working in drug development and a further eight years at AstraZeneca in Licensing and Partnering, primarily covering the therapeutic areas of oncology and infection.

Scientific advisors

Scientific advisors		
Advisor	**Affiliation**	**Specialty**
Prof. Laurence Patterson	University of Bradford	Scientific
Prof. Alan McGown	University of Salford	Scientific
Dr John Hadfield	University of Salford	Scientific
Prof Paul Loadman	University of Bradford	Scientific
Dr Robert Falconer	University of Bradford	Scientific
Dr Kevin Adams	University of Bradford	Pre-clinical
Dr Murray Yule	Clinical Trials & Research Unit, Leeds	Clinical
Dr Gerard Costello	Ex-AstraZeneca	Commercial Project Management
Dr Jim Rennie	Chemistry, Manufacturing & Controls consultant	Pre-clinical
Dr Graham Allen	Analytical services	Pre-clinical

Source: Incanthera

Service providers

Drug development service providers	
Service provider	**Competence**
QRCC	Quality and regulatory affairs
Covance Laboratories	Animal studies
Symbiosis Pharma	Pharmacy specialists
Cyprotex	ADME in vitro studies
Ambiopharm	GMP manufacturer
Catalent Inc	Clinical formulations and analytical services

Source: Incanthera

Corporate advisors

Corporate advisors	
Role	**Advisor**
Solicitor	Gateley plc
Auditor	RSM LLP
Patent lawyer	Haseltine Lake LLP
NOMAD	Cairn Financial Advisers LLP
Broker	Turner Pope Investments Ltd
Technical expert	PharmaVentures Ltd

Source: Incanthera

Risks

Investments in small, early-stage pharmaceutical companies carry a significant risk, and investors must be aware of this fact. In our opinion, the following risks are particularly relevant. Each of them could have an impact on time to reach market, cashflow breakeven and profitability.

IPO

Forecasts have been made on the assumption that Incanthera undertakes an IPO ahead of summer 2018 and raises £7m (gross) – target range £4.0-£10.0m – which would provide sufficient cash for a runway of at least two years to fund its clinical development programme. However, there is no guarantee that an IPO will take place, on the quantum of new capital raised, or on the timing of an IPO.

Financial/dilution risk

Even in the event of a successful IPO, Incanthera will require additional capital in the future for further expansion of its clinical programmes. There is no guarantee that the company will be successful in raising such funds, nor on the terms that such capital is raised, which could be dilutive to shareholders.

Commercialisation

Given the precedent of the out-licensing deal with lead candidate ICT01-2588, it is reasonable to assume that the company intends to advance products to certain valuation inflection points and then out-license them for large-scale late-stage trials and commercialisation. However, there is no guarantee that this would be on terms that would be beneficial to shareholders.

Patent robustness

As with all IP-rich companies, there is a risk that the intellectual property is insufficiently covered by the global patents, allowing a competitor to gain market access. Any litigation could involve significant costs and uncertainties. At this point in time, no freedom-to-operate assessment has been undertaken.

Regulatory

It is important for companies to liaise with regulators on a regular basis throughout the development programme. Any inadequacies could lead to regulatory action, such as cessation of product development and loss of manufacturing or product licences.

Competition

The company operates in a market dominated by larger multinational competitors, most of which have significant financial resources to fund development programmes, marketing activities, etc.

Share liquidity

On the assumption that Incanthera has a successful IPO, as seen with many small-cap companies listed on AIM, there can be difficulty in buying and selling shares in volume. Market-makers only guarantee prices in a very small number of shares

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Notes

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