EDISON

Cardio3 BioSciences

Far from the overvalued crowd

Strategic CAR and cardiac update, FY14 results

Pharma & biotech

Cardio3 has disclosed an aggressive and ambitious clinical trial programme to develop its novel Natural Killer CAR therapy. Currently starting a Phase I in AML and MM, Cardio3 aims to start one solid tumour trial per quarter once an initial AML/MM efficacy signal is detected. This potentially moves Cardio3 into large, valuable indications, well away from the crowded space around ALL. Cardio3's core value is based on C-Cure cardiac cell therapy. Adding CAR AML and MM therapies takes the indicative value to €985m, €121/share. Solid tumour indications might add €519m, €64/share, but are not currently included as still preclinical. Comparable US CAR companies have high valuations on limited clinical data: Juno $5.2bn; Kite $2.4bn. Cardio3 has announced a US IPO.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/13	0.0	(12.56)	(3.06)	0.0	N/A	N/A
12/14	0.1	(18.53)	(2.75)	0.0	N/A	N/A
12/15e	0.0	(21.24)	(2.71)	0.0	N/A	N/A
12/16e	0.0	(29.61)	(3.77)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding intangible amortisation, exceptional items and share-based payments. 2013 restated due to accounting treatment changes.

NKG2D- CAR potentially targets multiple cancers

The current dose-finding Phase I safety study is in Acute Myeloid leukaemia (AML) and Multiple Myeloma (MM). Results will be announced as each three-patient cohort completes dosing. If an efficacy signal without significant toxicology is seen, Cardio3 will both expand the study in AML and MM and start a series of solid cancer Phase II studies, aiming to start one new indication per quarter. Late 2014 data from other companies on CD19 CAR therapies showed complete response rates of around 90%; these were mostly in ALL with a US incidence of only 6,000.

Cardiac: C-Cure cells and surgical devices

The core of Cardio3's value remains the C-Cure autologous cell treatment for cardiac regeneration. CHART-1 could deliver data by mid-2016. The futility analysis determined that CHART-1 can meet its endpoint, so the probability has risen from 40% to 45%. CHART-2, a part-US Phase III study, is planned to start in H215; Cardio3 has applied to the FDA to use its Cath$_{ez}$ catheter delivery system. A manufacturing base in Minnesota is being established. Cath$_{ez}$ and CorQuest (acquired late 2014) are the basis for a high-value cardiac surgery device business.

Valuation: Dichotomy C-Cure core plus CAR potential

Edison's indicative value has risen to €985m, €121share (formerly €97/share) at the current $/€ rate of 1.09. The core value remains C-Cure with initial estimates for CAR in AML and MM at 15% probability added. Adding in up to six solid tumours might generate a further €519m of additional current value. A comparative value comparison is Juno, which has limited clinical data, a $5.2bn value and raised $304m. Cardio3 completed a €32m funding at €44.5/share in February 2015. This gives effective cash of €62m to fund through 2016, depending on the clinical trial investments made. Cardio3 has announced that it plans to undertake a US IPO.

8 April 2015

Price	**€45**
Market cap	**€352m**
Cash (€m) at 31 December 2014	30.3
Shares in issue	7.84m
Free float	45%
Code	CARD
Primary exchange	Euronext Brussels
Secondary exchange	Euronext Paris

Share price performance

%	1m	3m	12m
Abs	(4.0)	20.0	14.4
Rel (local)	(6.5)	(0.1)	(6.8)
52-week high/low		€47.0	€30.1

Business description

Cardio3 is developing C-Cure, an autologous Phase III stem cell therapy for chronic ischaemic heart disease. An innovative cell cancer CAR-T therapy, NKG2D, was acquired in 2015. Cardio3 is also developing high-value cardiac devices: Cath$_{ez}$ for cell delivery and CorQuest (mitral valve surgery).

Next events

Final results	26 March 2015
CAR first cohort	Mid-2015
CHART-2 start	Q215
Interim results	25 August 2015

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Edison profile page

Investment summary

Cardio3 has two core competences: autologous cell therapy development (in cancer and cardiac indications) and cardiac medical devices. Over 2014, the company boosted both these aspects.

Chimeric Antigen Receptor (CAR) cell cancer therapy was added to the autologous cell portfolio through an acquisition announced in early 2015. In general, antibody-based CAR approaches have showed outstanding Phase II results, notably form Novartis, but only in a rare, easily targeted blood cancer so far. The NKG2D CAR approach of Cardio3 is novel and potentially much more versatile as NKG2D binds to several ligands found on multiple tumour types including solid cancers like ovarian and colorectal. In preclinical work, NKG2D CAR gives a strong and lasting immunological response showing that it might generate sustained tumour immunity in patients. It might be developed into an allogenic therapy, which could vastly expand its affordability.

C-Cure (autologous cell therapy for chronic ischaemic heart failure) is in Phase III. The EU CHART-1 study enrolled its last patient in March 2015. This enables a possible direct marketed EU product from H217 assuming data by mid-2016. The part-US CHART-2 study is expected to start in H215 with data estimated by Edison perhaps in 2018 and US marketing from 2019. We estimate the targeted potential global market to be up to 40,000 cases per year.

In devices, Cardio3 acquired a cardiac surgical device, CorQuest, in Q414 (terms undisclosed) to facilitate mitral valve repair. CorQuest could be EU marketed under the CE system from 2017; the US approval route is not yet clear. C-Cath$_{ez}$, for cardiac cell injection, is CE marked. It is used in the CHART-1 study and is under FDA evaluation for use in CHART-2.

Valuation: Dichotomy with CAR-T or without

The Edison model indicates a core risk-adjusted 2015 value of €870m or €107/share. This has been increased from €97/ share to reflect the US$/€ rate of 1.09 and takes into account the C-Cure trial delay until H215 and a slightly higher CHART-1 probability of 45% (from 40%) after the futility analysis. It is based on 7.84m shares plus warrants and options after the February 2015 €32m gross funding at €44.5per share. Added to this core value is €15/share as a preliminary CAR T-cell therapy scenario for AML and MM. This gives an overall €121/share indicative value. Other CAR-based companies in the US have achieved valuations of multiple billions on limited clinical data.

Financials: Strong cash position after €32m February funding

Cash on 31 December 2014 was €30.3m boosted by €32m in Q115; a further $4m in equity was issued for the CAR acquisition (Cardio3 also paid $6m in cash). Cash operating expenditure in 2015 is likely to be about €21m, rising to about €29m in 2016 as CHART-2 gets underway. Although well-funded by European standards, Cardio3 is tightly funded relative to its US-based CAR competitors.

Sensitivities: Diversified risks, clear competences

Cardio3 has diversified its risk with a clear set of cell and cardiac device competences. CHART-1 data remain the major immediate sensitivity. C-Cure has the potential to be the first cardiac regenerative cell therapy in 2017 and could create a major new market. Both CHART studies are fully funded. NKG2D therapy still needs to be proven and clinical data will emerge steadily over 2015. The CAR programme opens a major long-term opportunity. The initial indications of AML and MM have clear market opportunities and the versatility of the technology potentially allows trials in solid tumours to start within six to 12 months; six indications are currently targeted, including ovarian cancer, which has strong preclinical data. The CAR sector might become the major value driver for the business as the clinical profile, still unknown, becomes better defined.

Company description: Cancer CAR adds to cardiac

Cardio3's expertise is in autologous cell therapies and cardiac surgical devices. Projects are shown in Exhibit 1. In cardiac regeneration, C-CURE (in Phase III) comprises harvested bone marrow stem cells reprogrammed to become heart muscle cells (cardiomyocytes). This remains the core value and focus with a possible EU-marketed product from 2017. The acquisition of the NKG2D CAR T-cell technology will enable the use of Cardio3's autologous cell therapy expertise in cancer therapy. NKG2D technology is potentially very versatile and could target multiple cancer types. It might be extendable into an allogenic therapy, which would vastly expand the commercial market. The Q414 CorQuest acquisition (preclinical) is a novel surgical device that could simplify mitral valve repair, an underserved market due to the complexity of current surgery. It fits alongside the $Cath_{ez}$ catheter (CE-marked, under FDA review) used to inject C-Cure into the heart.

Exhibit 1: Cardio3 pipeline

Product	Application (status)	Notes
Clinical-stage projects		
C-Cure	Chronic heart failure; two Phase IIIs: CHART-1 enrolled, data mid-2016 CHART-2 potential start Q215	CHART-1 (Congestive Heart Failure Cardiopoietic Regenerative Therapy) Phase III EU trial started April 2013 with 240 patients enrolled by December 2014; data mid 2016. CHART-2 part-US Phase III expected to start later in H215. Cardio3 will sell direct in Europe with a possible US marketing partner. Chinese and Asian rights sold to a JV with Medisun with royalties of 20-30% paid on sales.
CAR-T NKG2D	Acute Leukaemia, Multiple Myeloma and ovarian cancer. (Phase I)	Chimeric Antigen Receptor approaches use gene constructs to modify autologous T-cells. The Natural Killer Group 2D (NKG2D) ligand targeted by Cardio3 is found on haematological cancers and ovarian cancer, among others. It might be combined with chemotherapy.
Device projects		
$C\text{-}Cath_{ez}$	Specialist catheter for intraventricular injection of cells (CE-marked)	$C\text{-}Cath_{ez}$ use increases cell retention rates by 260%. It was CE marked in 2012 and is used in CHART-1. The FDA is expected to rule by mid-2015 on the use of the $C\text{-}Cath_{ez}$ in CHART-2.
CorQuest	Direct atrial access for mitral valve repair through chest wall (acquired late 2014)	This device gives direct surgical access to the atrium allowing easier work on the mitral valve (between the heart left atrium and ventricle). CE marking after EU trials in 2016, FDA approval route undisclosed.
Preclinical projects		
C3BS-GQR-4	Neutralising antibodies to prevent reperfusion injury (preclinical)	Reperfusion injury is a well-known, T-cell driven side effect of angioplasty. This is an early research-stage project that will be out-licensed or partnered. There is no news on any progression.
C3BS-PQR-1	A bioresorbable tube seeded with cells to replace defective blood vessels.	Repair of congenital cardiac vessel defects in young children as the implant grows with the child avoiding repeat operations. Cardio3 plans to develop and market this itself. No recent news.

Source: Edison Investment Research, Cardio3 reports

Chimeric Antigen Receptor (CAR) T-cell technology

In cancer, the immune system tolerates the cancer as it recognises it as healthy "self". CAR T-cell therapy uses modified white cells (killer T-cells) to recognise and attack the cancer and, ideally, to activate the endogenous immune system to generate persistent long-term immunity. The reason for this interest is that data from other companies at ASH 2014 on the CAR approach using a highly specific ligand (CD19) against cancerous antibody-producing while cells (B-cells) showed dramatic clinical efficacy. The lead candidate from Novartis, CTL-019, demonstrated 91% complete response (CR) in 39 paediatric Acute Lymphoblastic Leukaemia (ALL) patients. There was an overall six months survival rate of 78%.[1] Juno's candidate displayed 89% CR in 27 ALL patients plus some early good data in non-Hodgkin's Lymphoma. Kite's KTE-C19 CAR displayed 67% CR in a 21-patient adult and paediatric ALL group; Amgen did a deal with Kite in January 2015. In context, Amgen's recently approved Blincyto (blinatumomab) for the treatment of relapsed/refractory ALL displayed 42% CR. Blincyto approval was gained after a Phase II study.

The normal side effect seen with CAR therapy is cytokine-release syndrome (CRS), due to the strong immune response generated.[2] In the Novartis ALL study, for example, all patients showed CRS with, 27% displaying severe CRS. CRS can be controlled with Actemra (tocilizumab).[3] [4]

Given these clinical results and the customised therapy, very high prices are being postulated by some commentators; some press reports have suggested $350,000 per course. However, there is a

lot of research and clinical development needed. So far, CAR has shown efficacy in lymphoid (B-cell) cancers. However, there are only 6,000 new cases of ALL per year in the US. CAR use in late-stage solid cancers, the major commercial opportunity, is not proven. This is where Cardio3's approach may be more versatile with the potential for a leading position to be developed.

Cardio3 buys a CAR

In January 2015, Cardio3 bought the OnCyte business from the private US investment company Celdara Medical; an early-stage investor in new medical innovations located in Lebanon, New Hampshire. OnCyte has rights to Natural Killer Group 2D (NKG2D) CAR-T technology for cancer therapy from the group of Professor Charles Sentman at Dartmouth College, US. A product, CM-CS1, is ready to start a 21-patient Phase I US clinical study NCT02203825.

Cardio3 acquired the OnCyte CAR technology for an upfront fee of $10m, of which $4m was in equity. There are development and regulatory milestones of $50m, milestones on related products of $21m (such as solid tumour indications, reflecting the investment needed) and sales milestones of up to $80m on sales of over $1bn. The royalty rate is 5-8%. Cardio3 management has observed that the deal was agreed before the recent upsurge of interest in CAR therapies and that the upfront is part of an overall package including equity.

There are a number of patents. US7994298 B2, granted with priority on 31 August 2005, discloses the NKG2D technology. Note that there are general concerns over overlapping and infringing patents in the CAR area and not much IP has yet been granted or possibly yet published. A US patent application US20120302466 A1 filed on 30 April 2012 covers TCR-Inhibitor molecules (TIM, see Exhibit 2). The US government has some rights to this patent.

The OnCyte CAR: Natural Killer Group 2D (NKG2D)

NKG2D, a cell surface receptor, is found on various immune system cells, specifically on Natural Killer (NK) and often on activated killer T-cells. The diverse ligands recognised by NKG2D are commonly found on cancer cells, but are rare in normal tissues, although they seem to be more common in intestinal tissues.[5] Exhibit 2 discusses the biochemistry and cell biology. Cardio3 has two other targets in preclinical development (a receptor, NKp30 (also called CD37) and an antibody-derived CAR to the ligand of NKp30: B7H6 (R&D update 30 January 2015). The key aspect of using this set of receptors and legends is that they are versatile and potentially able to target a range of tumour types. Antibody approaches, like CD19, need a new, high-affinity antibody to be developed and validated for each new target that is likely to slow development.

Phase I/II

The Phase I trial (NCT02203825) in Acute Myeloid Leukaemia and Multiple Myeloma is a safety study aiming to find the maximum tolerated dose (MTD). Four dose cohorts are planned with a maximum dose of 30m cells. Each cohort involves three patients (at least one AML and one MM); if any patient shows any dose limiting toxicities, a further three patients are tested – this might involve between 12 and 24 patients. Each cohort is expected to take about three months and data will be reported at the end of each dose level. Once the MTD is found, an expansion phase then adds six AML and six MM patients. The initial endpoint is 28 days with three-, 12- and 24-month follow ups. The trial is now expected by management to complete recruitment and initial data reporting during H216. Cardio3 management notes that good preclinical responses have been seen in Multiple Myeloma.[6]

The full two-year CAR study will not complete before March 2019 (as of March 2015 from www.cliniclatrials.gov). The efficacy and persistence of the CAR T-cells will be assessed by a variety of clinical methods. Phase II should then follow. Other CAR companies have indicated that they are planning fast-track approvals in 2016-17 on the basis of Phase II data.

Exhibit 2: CAR-T terms and biology

Term	Definition and biochemical role
MHCI	Major Histocompatibility Complex type I is genetically inherited (there are many types and subtypes).The centre of each MHCI holds a peptide: a short, randomly selected fragment of a normal cell protein but this could also be a fragment of virus or a mutated protein.
Self vs non-self	The immune system distinguishes between self and non-self. Self-cells are protected from immune attack as they display the right MHCI. Non-self is recognised and attacked. If self-cells display an abnormal peptide in the MHCI, the killer T-cells destroy them.
Tolerance	In cancer, as the MHCI is "self" and if the displayed the peptides are normal, killer T-cells tolerate the cancer. New types of T-cells are always being produced but they are deactivated and destroyed if they recognise self-signals, the regulatory T-cells control this process. To break tolerance, the cancer MHCI signal needs to be recognised as non-self. Once this happens, new lines of T-cell that bind the cancer MHCI signal survive and grow generating a powerful response. It takes some days to produce a new set of T-cell lines against a new threat, so a full immune response is not immediate. Tolerance is tightly maintained so it is hard to generate immune responses against cancer.
CD8 T-cells	These are killer T- cells. (There are many types of T-cells, so called as they mature in the thymus gland.). T-cell check that cells are "self" by testing the MHCI type and that the embedded peptide fragments are "self". If either of these signals is wrong, they attack. MHCI is recognised by the T-cell receptor Complex (TCR).
TCR	The T-cell receptor has several subunits, some external, some internal. They are highly polymorphic to bind a huge variety of targets - although any one T-cell linage only binds one specific target. The TCR signalling subunit inside the cell is CD3 zeta (CD3ζ). CD3ζ transmits the signal from the TCR into the cell to trigger an attack. CD3ζ is used in the OnCyte NKG2D CAR construct.
CD4 T-cells	These are "helper" T-cells. They would be involved in generating a long-lasting immune response to the cancer, regulating the CD8 killer T-cell response and retaining a long-term memory of the cancer. Destroyed cancer fragments are processed by Antigen Presenting Cells and these programme the helper T-cells to recognise the cancer. Any long-term immune response needs to involve these cells.
Natural Killer cells	NK cells are part of the fast response, innate immune system. They do not recognise specific abnormal signals but generally attack any cells with low or no MHCI and distress markers – protein signals on the cell surface. There is a balance between the level of distress markers like NKG2D ligands and the MHCI level which determines if NK cells kill or not.
NKG2D	Natural Killer Group 2D (NKG2D) receptors are found on many immune cells including Natural Killer cells and stimulated CD8 T-cells. NKG2D binds MICA, MICB and ULBP ligands. On the outside of the cell membrane, NKG2D is linked to a costimulatory protein called DAP10. DAP10 transmits the signal when the NKG2D receptor binds to a ligand. This is slightly unusual in that the pathway triggered is different to those in other CAR approaches by also activating PI3K (Phosphatidylinositol-4,5-bisphosphate 3-kinase) that increases cell survival.
NKG2D ligands	The ligands (distress markers) bound by NKG2D in humans are MICA and B (MHC Class I chain related protein A or B) and the UL16 binding protein family, there are six ULBP forms (UL16 is a virus protein not relevant to cancer). These markers are higher in cells after treatment with drugs like Velcade (bortezomib), HDAC inhibitors, chemotherapy and radiation. They seem to be naturally found on many cancer types.
Role of NGK2D	The receptor enables natural killer cells to recognise distressed cells without any other stimulus. In T-cells, it acts alongside the TCR as a co-stimulatory signal. T-cells need two different activating signals to attack. In the OnCye CAR, these are provided by CD3ζ and DAP10.]
Other ligands	Natural killer cells have a variety of receptors and Cardio3 is developing some of these in addition to NKG2D. These are a receptor, NKp30 (also called CD37) and its B7H6, the ligand to NKp30. Cardio3 has made preclinical CAR constructs using either the NKp30 receptor (instead of NKG2D) or using an antibody fragment against B7H6. There is literature evidence that these can be active against tumours. [7]
Killer in action	Killer T-cells work by binding tightly to their victims. They activate the death receptor system carried by all normal cells to trigger apoptosis: a. caspase enzyme cascade that internally digests the cell. To make sure of the victim, T-cells also pass a package of lethal enzymes into the other cell. These are more proteases (Grannzymes) and Perforin (a protein that punches holes in the cell membrane damaging its integrity)
Co-effector	Other CAR-T candidates need to have an extra co-effector, like CD28, since T-cells only active if they get two signals. This is one way of optimising a CAR-T therapy and an area of active research. This does not seem to be the case with NKG2D CAR since it activates the T-cell response and the natural DAP10 ligand found naturally in active T-cells. This might be a big advantage, it is not yet clear.
Transforming the T-cells	To get the chimeric CAR into T-cells, a viral vector is used. Most competitors (Novartis) use lentivirus as this integrates into the genomic structure of the cells. OnCyte uses a retroviral approach: T-cells are isolated from patients, transformed using a retrovirus, cultured and transfused into the patient. This currently an autologous process and so expensive. Transfection efficiencies range form 20-70%.
NKG2D CAR-Therapy	Professor Sentman and his colleges linked the NKG2D receptor to part of the T-cell receptor in a genetic construct packaged in a retrovirus. By infecting young killer T-cells with this virus, modified cells are produced that recognise and kill target cells carrying natural NKG2D ligands. Note that some normal cells may carry NKG2D markers so this approach might be less specific than the CD19 based approach specifically targeting antibody-producing B-cells. This might be positive (broader range of targets) and may be problematic (potential side effects).
Persistence of response and cancer immunity	Activated T-cell produce powerful cytokines (hormone like chemical messengers) to stimulate other T-cells. The debris of the destroyed cancer cells is cleaned up and processed by other immune cells and this might then enable unaltered young T-cells to recognise the cancer and proliferate. If this happens, a major and sustained endogenous immune response can be mounted against the cancer even if is heterogeneous. This effect needs to be seen and quantified in clinical studies. Preclinical work shows that animals that clear a tumour after NKG2D CAR-T treatment are then "resistant" if more cancer cells are injected.
Resistance and relapse	Cancers can lose the targeted ligand, for example, by no longer displaying CD19, called "antigen escape". This makes the cancer invisible again. So called "Positive relapses" occur when the CAR-T cells cease to attack the cancer even when the ligand (like CD19) is present.
Allogeneic NKG2D therapy with TIM	TCR-Inhibitory Molecules (TIMs) are an approach used by Cardio3, currently in early preclinical, to obtain T-cells that will not attack the host tissue triggering Graft vs Host (GvH) disease. A random assortment of T-cells from another person, injected (grafted) into a cancer patient, might attack the patient's healthy tissues as they are recognised as non-self by the graft TCR. Autologous therapy avoids this, but is expensive. Allogenic T-cells would be cheaper to produce and could be "out of the freezer" enabling rapid treatment. TIMS are either short hairpin RNA or dominant negative proteins. These genes for these are linked to the CAR gene construct used to transfect the cells. ShRNA stop the production of TCR proteins; dominant negative proteins are synthesised by the T-cell and assembled into non-functional TCR. These T-cells now only attack patient tumour cells as they cannot "see" any healthy tissue. The CAR-T cells may themselves be recognised as foreign by the host (Host vs Graft) and eliminated. This could reduce efficacy but TIMs do not prevent this.
Which cancer types	NKG2D ligands (MICA) are particularly found in leukaemia, glioma, melanoma myeloma ovarian and cancers. The exact type of ligand will vary and not all cells in a cancer express them. For example, 80% of ovarian cancers have some NKG2D ligand, 50% of metastatic melanoma and 75% of primary melamine cancers have MICA. The ligands have been reported in bladder, breast, lung, liver. colorectal, kidney and prostate cancers. They might be upregulated in response to chemotherapy.

Source: Edison Investment Research, Spear, P. *et al* 2013.

Solid tumours

Cardio3 intends to look for initial signs of efficacy in each cohort. If an efficacy signal is seen in a cohort (criteria undisclosed), solid tumour Phase II trials at that dose will be started. Cardio3 plans to start one per quarter with six indications cited: breast, colorectal, pancreatic, ovarian, melanoma and renal. The level of NKG2D ligand expression in these tumours is not statistically well determined in published literature, with few patient samples per indication.[8] Because of these uncertainties, solid CAR therapy is treated as a scenario rather than a clear value parameter.

NKG2D CAR has been shown, in an ovarian preclinical model,[9] to activate the endogenous immune system against solid cancers, a major advance if validated in a clinical trial. Management notes that 100% survival is found for NKG2D-treated animals versus zero survival for those treated with non-CAR T-cells. Further, treated animals are protected against further inoculation with the same tumour line, but not against different tumours. This shows that the immune response generated is protective, long term and cancer specific. NKG2D has also shown preclinical efficacy in heterogeneous tumours; these are inherently more intractable but more "real world".[10]

Driving a CAR business

CAR-T therapy uses a defined gene construct and gives a known dose of modified cells. Currently, the gene treatment is applied to patient cells (autologous) or matched donors in a laboratory and then cultured to get enough modified cells for a therapeutic dose. This needs excellent process control and hygiene and is expensive. Novartis gained a head start in CAR development by buying a specialist former Dendreon facility for about $43m. Cardio3 has a Belgium manufacturing facility and is one of the few companies with the ability to develop autologous cell therapies from preclinical to Phase III, including manufacturing and logistics optimisation. A Rochester, Minnesota (US) facility is being built with local grant support.

Although this is not known for NKG2D cells, other CAR therapies show the cells growing and dividing as they attack the tumour, standard T-cell behaviour so long as allowed by regulatory T-cells. In the Novartis ALL study, CTL019 CAR-expressing cells proliferated; after six months, the probability of detecting CTL019 was 68%. Consequently, as this treatment reproduces itself,[i] there is no simple relationship between dose and efficacy.

Breaking tolerance is potentially dangerous. The CIDeCAR technology (preclinical) from Bellicum aims to be able to control the administered cells. It is not certain if this is needed as NKG2D CART-T has been well tolerated in preclinical models.

The NKG2D ligands seem to be widespread across tissue types; this may give versatility, but could run the risk of more widespread side effects. Cardio3 notes that NKG2D ligands are present only in "stressed" cells such as tumour cells or infected cells and at very low levels in the intestinal

[i] A normal small molecule or antibody drug is administered at a fixed dose and is destroyed or excreted. This is easy to track with laboratory blood tests and blood amount falls over time to zero. Other cell therapies being developed seem to find that the cells die or cannot be detected after a few days. Cardio3's C-Cure might be exceptional here as the cells have been treated to have the potential to integrate into heart muscle.

CAR therapies are different since modified T-cells reproduce if they detect their cancer target. It is as if one could take a smart headache pill that grew into two or three pills if the headache was bad and persistent but became half a pill if the headache was minor and that lasted for months. Much clinical development focuses on finding a reproducible dose-response relationship and, in cancer, a maximum tolerated dose, but these calculations assume a fixed dose and that the amount of drug decreases in a known pattern over time. Further, as CAR therapy triggers a natural immune response, the overall patient response is the sum of the dose and the endogenous immune response, which will vary with patient and tumour burden.

This is a very new paradigm for the industry, doctors and regulators. Because these cells can persist (this is not known as yet for NKG2D CAR in humans), some companies have developed suicide switches, like CIDeCAR, so that a small molecule drug can be given to the patient to cause a cell suicide reaction in the CAR T-cells. This will allow, in theory, control of the therapy if it should generate long-term undesirable side effects such as autoimmune reactions or over-strong anti-tumour reactions, which can be fatal. These suicide switches are biochemically complicated and add to the level of genetic manipulation and clinical testing needed, so whether they are needed, and will work if needed, is not clinically established.

epithelial tract and the endometrium at the time of menstruation. Cardio3 therefore anticipates that NKG2D CAR-T therapy will be very safe. While Cardio3 also anticipates that NKG2D therapy will be effective on its own, there are literature reports that cancer cells produce NKG2D ligands in response to chemotherapy, such as Velcade. This may enable future combination strategies

An advantage of the DAP10 and NKG2D system seen by management is that any long-term effect is generated by the endogenous immune response and probably not due to the NKG2D modified cells that triggered the initial response. This could become a differentiating element of huge importance as it may give a major safety advantage with potential long-term efficacy.

Exhibit 3 shows an overview of CAR competition by indication (rather than company) indicating the focus on rare lymphoid cancers. The tumours initially targeted by NKG2D, AML and MM, are competitive but there has been little CAR activity in them so far.

Exhibit 3: T-cell anti-cancer therapies by indication

Standard Indication	Target	Stage of development	Company	Name	Description
Acute lymphoblastic leukemia (ALL)	CD19	Phase I	Juno Therapeutics	JCAR015	Autologous CAR-T cells
	CD19	Phase II	Novartis	CTL019	Autologous CAR-T cells
	CD19	Phase I/II	Kite Pharma	KTE-C19	Autologous CAR-T cells
Acute myelogenous leukemia (AML)	Wilms tumor 1	Phase I/II	Cell Therapy Catapult	WT1	Autologous CAR-T cells
	NKG2D ligands	Phase I	Cardio3	CM-CS1	Autologous CAR-T cells
B cell lymphoma	CD19	Phase I/II	Kite Pharma	KTE-C19	Autologous CAR-T cells
	CD19	Phase II	Novartis AG	CTL019	Autologous CAR-T cells
	CD20	Phase I	Unum Therapeutics Inc.	ATTCK20	Autologous CAR-T cells
Chronic lymphocytic leukemia (CLL)	CD19	Phase I	Juno Therapeutics Inc.	JCAR015	Autologous CAR-T cells
	CD19	Phase II	Novartis AG	CTL019	Autologous CAR-T cells
Chronic myelogenous leukemia (CML)	Wilms tumor 1	Phase I/II	Cell Therapy Catapult	WT1	Autologous CAR-T cells
Glioblastoma	EGFRvIII	Phase I/II	Kite Pharma Inc.	EGFRvIII CAR	Chimeric antigen receptor (CAR)
Haematological cancers	CD19	Preclinical	Bellicum	BPX401	CIDeCAR
	CD19	Preclinical	Blueird / Celgene	NA	NA
Liver cancer		Phase I	NeoStem Inc.	NBS-20	dendritic cell therapy
Metastatic Melanoma		Phase II	Lion Biotechnologies Inc.	LN-144	Autologous tumour lymphocytes
		Phase II	NeoStem Inc.	NBS-20	Tumour cell-specific dendritic cell
Multiple Myeloma	NKG2D ligands	Phase I	Cardio3	CM-CS1	Autologous CAR-T cells
non-Hodgkin's lymphoma (NHL)	CD19	Phase I/II	Kite Pharma Inc.	KTE-C19	Autologous CAR-T cells
	CD19	Phase I	Juno Therapeutics Inc.	JCAR015	Autologous CAR-T cells
	CD19	Phase I/II	Kite Pharma Inc.	KTE-C19	Autologous CAR-T cells
Ovarian cancer		Pilot	Lion Biotechnologies Inc.	LN-144	Autologous tumour lymphocytes
	Peritoneal cancer	Phase II	Wistar Institute	TALL-104	Patient derived Cytotoxic T cell
Not disclosed	NA	Preclinical	Intrexon and Merck		Uses Rheoswitch to control CAR
	NA	Preclinical	Intrexon and Ziopharm		Sleeping Beauty gene transfer
	NA	Preclinical	Transposagen /J&J		PiggyBack gene transfer
	NA	Preclinical	Cellectis/Pfizer		Allogeneic

Source: Edison Investment Research

C-Cure

C-CURE has been extensively reviewed (2014 outlook note); trials are summarised in Exhibit 4.

The CHART-1 Phase III has enrolled the final patient; the 240 minimum was reached in late 2014. This individual will be treated, once the harvested cells have been processed, in Q315. The endpoint is a composite measure of heart function. Management expects overall data to be available by mid-2016.

The CHART-2 study could start in H215, management indicates probably in the autumn. This is an FDA approved, part-US trial with a six-minute walk primary endpoint; this is simpler that the CHART-1 endpoint. The FDA is expected to rule in Q315 on whether C-Cath$_{ez}$ use in CHART-2 will be allowed. As the dose range is believed to be very wide, enough cells can, in theory, be delivered

by existing catheters. However, it would be advantageous, and give comparability to CHART-1, to use C-Cath$_{ez}$.

The planned futility analysis reported in late March that CHART-1 could potentially meet its planned endpoint and had no safety issues which required a trial halt. Note that the analysis did not determine efficacy; just that the trial is worth running to completion. The result of the futility analysis is hard to assess on CHART-1 probability, but a small increase seems justified from 40% to 45%. The US success probabilities remain at 30%.

In China, Hong Kong and Taiwan, Cardio3 has gained potential upside at no cost through the €25m Medisun joint venture deal announced mid 2014 (see the June 2014 update note). Medisun will invest a further €20m to fund the JV, which will be owned 40:60 with Cardio3 dropping to 30:70. The royalty will be 20-30%. Manufacturing will be in China; clinical material will be prepared in Belgium.

C-Cure and C-Cath$_{ez}$ technology

Cardio3 uses a specific cell programming technique as its core platform. This was developed at the Mayo Clinic in Minnesota (Behfar et al, 2010[11]). The approach isolates the patient's bone marrow stem cells and directs them, in a laboratory culture, to develop into cardiac progenitor cells through a cocktail of signalling agents. The cells are not genetically altered; this is an important safety feature in chronic disease. When injected into the heart, these programmed cardiac progenitors form fully integrated and functional heart muscle cells (cardiomyocytes). These regenerate damaged heart muscle by the formation of new blood vessels and by stimulating endogenous cells through long-lasting paracrine[ii] effects. The company has good Phase II data reported in 2013.[12] This was discussed in depth in the 2014 outlook note.

The specialised catheter, C-Cath$_{ez}$, can be used to inject cells into the wall of the heart with a curved, perforated needle. This gives a more efficient dosing as up to 260% more cells are retained than with current straight-tipped catheters, as used in the Phase III clinical study. The therapeutic advantage is assumed but not proven and the cell dose range seems to be wide.

Exhibit 4: CHART map

Parameter	CHART-1	CHART-2
Centres	European up to 55 centres.	Europe plus US (ideally 55).
Dose	600m standard cell dose. Cells shipped frozen, thawed and processed in operating theatre with Biosafe Sepax device for maximum viability and consistency.	
Administration	Uses C-Cathez catheter with 36% cell retention vs 10% for straight-needle alternatives.	MyoStar (default) with C-Cathez as a possible alternative if FDA approval granted.
Design	240-patient, randomised and placebo control.	240-patient, randomised and placebo control.
Entry criteria	NYHA class III or IV; LVEF≤30%. Note that patients can be Class IIb on entry if they have previously been classed as Class III or IV. This group has a high risk of progression.	
Power	90% powered	
Start	Trials started April 2013.	Planned for Q215
End	Data assumed by mid-2016.	2018 possible
Primary endpoints	Hierarchical primary endpoint at one year. Mortality, worsening heart failure, LVEF, 6MW, ESV, QoL.	Six-minute walk test showing an improvement of 40 metres or more after nine months.

Source: Edison Investment Research based on Cardio3 announcements

Manufacturing

Currently, Cardio3 has a 250-dose per year GMP certified clean room facility at its Belgian headquarters with a further 250-patient capacity facility being set up in Rochester, US. These could be expanded to 500 doses by using a new self-contained, cassette-based culture system. We have assumed a cassette-based cost of €8,000 per dose with a 95% experience curve effect since a cassette process should have scale economies.

[ii] Paracrine means that the injected cells secrete a mix of cytokines and factors that trigger the natural repair systems into activity and serve to dampen any inflammation at the injury site.

C-Cure and Cath$_{ez}$ market estimates

C-CURE is a bespoke therapy. Management does not expect it to be administered to more than 30-50,000 patients per year across North America and Europe, Exhibit 5.

Exhibit 5: Market sizes (000s)

Category	Percentage used	US	EU	Total
Heart failure	N/A	5,100	6,500	11,600
Access to high-level care and funding	75%	3,800	4.,900	8,700
Classes III and IV	30%	1,140	1,470	2,610
Systolic failure	60%	680	880	1,560
Ischaemic m	60%	410	530	940
Patients assumed in Edison forecast 2030	3.8%	20.1	15.3	35.4

Source: Cardio3 estimates, Edison Investment Research, literature sources including 2013 AHA data.
Note: Only Class III and IV patients are included, Class IIb patients potentially double the market size, but might be a more price-sensitive and competitive market segment.

Cardio3 will accrue a substantial share of the profits if C-Cure is approved due to direct marketing. The Medisun deal gave Cardio3 the cash to fund CHART-2 without giving a substantial part of the US profits to a partner. We assume a price for treatment of $90,000 in the US, €55,000 in the EU.

The market could be in excess of these numbers if it expands, for example into Class IIb patients or takes share from competing therapies. The EU market share is assumed to be lower than in the US due to price and the likelihood of the need for results-based pricing or national discounting.

The only comparison catheter to C-Cath$_{ez}$ is MyoStar for cell injection. MyoStar sells for about $4,350 with additional imaging equipment needed, costing $3,650 per use; standard coronary artery catheters for angioplasty sell for under $150. We assume that Cath$_{ez}$ is priced at around €2,000 in the EU and $3,500 in the US. As Cath$_{ez}$ and C-Cure would be approved as a package by the FDA, US C-Cure users would have to buy C-Cath$_{ez}$. We assume a €300 cost of goods.

Competition

Comparable cardiac stem and gene cell therapies in cardiac ischaemia are shown in Exhibit 6. The lack of large-scale Phase IIb and III data means that definitive conclusions about what works, and what does not, are not yet possible. Cardio3 is now at the leading edge of the clinical work in this area. Cardio3 sees its main competitor as Mesoblast's allogeneic, stem cell line Revascor, licensed to Teva, but Cardio3 might enter the EU market in advance of Mesoblast/Teva. Capricor/Jansen data in late Q415 should be very interesting with an allogeneic approach. Celladon has a Phase IIb in situ gene therapy. Vericel, in Phase II, targets a highly focused small orphan indication.

Exhibit 6: Chronic ischaemia cardiac stem cell and gene therapy trials

Company (product)	Indication	Stage	Dose	Notes on trial	Method
Cardio3 (C-Cure)	Chronic advanced ischemic heart failure	CHART-1 Phase III 240 patients; data by mid-2016 CHART-2, 240 patients start Q215	600m cells injected with high retention rate	CHART-1 change in hierarchical composite endpoint at 39 weeks. CHART-2 – US and EU centres; six-minute walk endpoint required by FDA.	Cultured bone marrow cells, programmed to become heart muscle progenitor cells before injection with a proprietary catheter.
Vericel ex Aastrom) (Ixmyelocel-T)	Ischaemic dilated cardiomyopathy	Phase II 108 patients. Data due late 2015.	About 125m cells	Injection into heart. Endpoint is change in of clinical events over 12 months.	Bone marrow (about 50ml) is cultured (14 days) and injected.
Mesoblast/ Teva	Congestive heart failure	Phase III 1,730-patient trial. Data Q318.	150m cells	Allogeneic therapy. Placebo controlled. A MACE endpoint is being used.	A single injection of allogeneic STRO+ precursor cells (MPC).
Capricor/ Janssen (J&J)	Regeneration after infarct	ALLSTAR Phase II 274 patients, Data Q415	25m	Cardiosphere culture of allogeneic cardiac cells	Given by intracoronary infusion so retention may be an issue
Celladon (Mydicar)	Advanced heart failure	250 patient Phase IIb. Data due Q116.	1x1013 DNA particles	CUPID-2b trial with endpoint of time to recurrent clinical cardiac events.	Gene therapy. Given by single intracoronary infusion.

Source: Edison Investment Research

Patents, IP and Mayo royalties

The core IP on the cardiogenic mix of signalling agents (owned by the Mayo Foundation) has a priority date of 29 July 2005. Cardio3 will pay 2% of in-market sales to the Mayo Foundation until summer 2025. A 2 December 2010 patent filed by Cardio3 covers the C-Cure process. Cardio3 should be able to defend its market till at least 2030 if this second patent is granted.

CorQuest

CorQuest, founded in 2012, is a virtual US company developing a device to make repair or replacement of the mitral valve easier to perform, details in Exhibit 7. The CorQuest device is designed to simplify and improve surgical access to the atrium. The CorQuest acquisition was announced in November 2014. Terms were not disclosed.

The product was developed by Dr Didier De Canniere, a professor of surgery in Brussels and formerly director of Minimally Invasive and Robotic Cardiothoracic Surgery at the University of Miami. It is in late preclinical testing. A patent application is in progress (US20130041395 A1).

Exhibit 7: Heart access and valve repair

Aspect	Commentary
Heart structure	The heart has four chambers. The right atrium fills the right ventricle which pumps venous blood around the lungs. The left atrium takes oxygenated blood from the lung circuit and fills the left ventricle. The left ventricle pumps blood into the aorta, the main artery, and so around the body and is the most powerful chamber. The passage of blood between the left atrium and ventricle is regulated by the mitral valve. As the ventricle relaxes and fills, the mitral valve is open allowing blood to flow passively into the empty left ventricle. Only the last 20% of blood in the atrium is actively pushed into the ventricle so the atrium wall is relatively thin and less muscular.
Mitral Valve	The mitral valve has two flaps held in place by chords attached to the interior wall of the ventricle. This makes the valve relatively complex and its location makes access difficult. The tricuspid value is between the right atrium and ventricle with a similar structure.
Valve action and common problems	Once full, the left ventricle contracts strongly pushing blood round the circulation. The mitral valve stops this pressurised blood flowing back into the atrium. This is particularly an issue with the left ventricle as any backflow reduces the amount of blood reaching the main circulation and can lead to lung congestion (fluid build-up). Regurgitation is the commonest mitral problem, due to the flaps not sealing properly, and is treated by surgery. The procedure is offered by leading clinics, like the leading US Cleveland clinic. Prolapse is when the valve flaps are not held securely by the chords. This causes the flaps to invert, also allowing blood to flow back into the artium.
Repair or replace?	Repair of the valve is better than implantation of an artificial valve since the mitral valve structure is complex and integral with the ventricle due to the chords that hold the valve closed. Patients with metal artificial valves need chronic anti-clotting therapy; animal-based valves wear out. The biggest replacement valve market is for the tricuspid aortic valve that stops blood flowing back into the left ventricle from the aorta after the heart has contracted. This is relatively easy to access and has a less complicated overall structure.
Gaining access	Open heart surgery requires sawing through the breastbone, with very long recovery times. Minimally invasive and robotic surgery is now preferred. Both these need a heart and lung bypass machine. The mitral valve is accessed by an incision in the left atrium.
MitraClip	The latest FDA approved innovation is a procedure from Abbott for regurgitation: MitraClip. This avoids chest incisions and heart and lung bypass. A catheter is inserted into the femoral artery (leg) and threaded up to the heart where it is pushed across the atrium wall to access the mitral valve. A clip is then positioned to secure the area of distorted valve lips together.
Other problems for valve repair	The mitral valve can suffer from stenosis when it does not open fully; this reduces the blood flow into the left ventricle again reducing the circulated blood flow. Stenosis is commonly caused by rheumatic fever (an adverse immune reaction to bacterial infection now rare in the developed world) or, less often, by calcification. A balloon valvuloplasty can help by expanding the opening or the valve is replaced. Valvuloplasty does not need surgery and is done with transarterial catheters.
Prevalence and market size estimates	Mitral valve regurgitation occurs in about 2% of the US population: 6m cases. Most will be mild cases. Mitral valve prolapse is the most common valvular disorder in the United States, occurring in 2.4% of the general population. Age is the main risk factor, data on prevalence is limited. The biggest study is from the 1990s as part of the Framlington study.[13] The Medicare database identified 47,279 primary isolated mitral valve repair or replacements from 2000 to 2009.[14] Another study showed that most hospitals do few operations with only 9% doing more than 40 per year.[15] A survey in 910 hospitals over eight years found 58,370 patients undergoing primary mitral valve operations (7,300 per year); 80% were for regurgitation.[16] European figures are hard to ascertain.
Regulation and approval	Under the EU rules, the device would be CE-marked. The CE mark is a manufacturing and quality standard. As a transient (under one hour) surgical device for use on the central circulatory system it will be in the high-risk Class III category. This means that the regulatory file is assessed by a Notified Body, such as the UK MHRA. A clinical trial will be required but in surgical devices this could be small and open label. Cardio3 hopes to gain EU regulatory approval for the device in 2016. FDA regulatory approval might be sought later but is not currently forecast. Device studies are typically small. It is also common to run a registry, a database of patients, to track long-term side effects.

Source: Edison Investment Research

Market

Abbott's Mitraclip sells for $30,000, but the procedure is not fully reimbursed under Medicare where the payment is based on a standard, fast, PCI coronary angioplasty. MitraClip is limited to patients who are too ill for open heart surgery. A November 2014 published clinical overview report states

that 10,000 procedures had used the device and that implantation now tales about 100 minutes. [17] Edison assumes a price of €5,000, but this could be higher or lower; management has given no guidance. The potential value on 10,000 procedures could be about €50m per year.

The product could be distributed directly, but Cardio3 will need to run training courses and support opinion leaders to promote the product. The device might be EU marketed from 2017. The timing of launches in the US is not yet known as the FDA approval strategy is still being developed.

Sensitivities

Cardio3 has diversified its risk with major cardiac and cancer programs based on its autologous cell competences. Both Phase III CHART studies are fully funded. Valuations are highly sensitive to the changed $/€ rate as the US is the most valuable market and Cardio3 plans to sell direct.

CHART-1 data in mid-2016 remains the major sensitivity. C-Cure has the potential to be the first cardiac regenerative cell therapy in 2017 and could create a major new market with direct EU sales. The clinical benefit will need to justify a high price for C-Cure as autologous therapies are expensive to manufacture. Hence, commercial success is not necessarily automatic. The C-CURE Phase II offers support but was not an exact parallel to CHART-1 as the Phase III uses a complex hierarchical endpoint. CHART-2 results by H118 assume that CHART-2 starts by Q415 and recruits fully by late 2016. There may be further delays depending on the FDA view of C-Cath$_{ez}$ use.

The CAR programme opens a major long-term opportunity. The initial indications of AML and MM have clear market opportunities but moving into sold tumours, perhaps within 6-12 months. will be a major change possible due to the versatility of the technology. NKG2D therapy data will emerge steadily over 2015. The CAR sector might become the major value driver for the business as the clinical profile, still unknown, becomes better defined. Cardio3 has the autologous cell skills to make this therapy area work and is setting up the US infrastructure required. Adding allogenic versions of CAR products will cut costs, make them easier to use and extend biological exclusivity.

The CorQuest acquisition is intriguing but relatively minor relative to CAR and C-Cure. Although a small trial should enable CE marking and EU sales; the FDA registration process is still not clear. Device markets are often slow to develop and can be price sensitive.

Valuation

The immediate value rests on the outcome of the C-Cure trials at €107 per share including dilution from issued warrants and options. This is slightly higher (formerly €97) due to the gains in the USD/€ rate but offset by the delay in starting CHART-2. This is based on sales to 2030 based on the 2010 patent filed by Cardio3. Until 2025, a 2% royalty on net worldwide sales is paid.

The C-Cure opportunity has a high value because Cardio3 is funding fund these trials directly following the $25m Asian Medisun venture deal. This captures most of the profits. A 50:50 marketing joint venture is assumed in the US with direct sales in Europe; a regional southern European marketing partner might be used but should be profit neutral. However, C-Cure is still relatively high risk. Phase II data was excellent but the trial was small. Edison uses a slightly raised 45% CHART-1 and an unchanged 30% CHART-2 success probability. The CHART-2 trial has been delayed from H214 to H215 (probably autumn) start so the Edison model timing has been pushed back by a year to 2019. All other parameters are as previously discussed.

The CAR therapies for AML and MM, as designated Phase I indications, are added to the indicative value on an indicative basis as the detailed value parameters and development costs and times are still unclear. These indications add €120m or €14 per share taking the total value to €121per share.

This is well above the $10m upfront paid in January 2015. However, the full deal includes milestones and royalties so the NPV (not estimated) will be much higher than the upfront value.

Exhibit 8: Cardio3 indicative value based on revenues and profits to 2030

	Product	Price (2015 value)	2030 market sales ($m)	Revenue share	Probability	Probability adjusted	
						$m	€m
US	C-Cure	90,000	1974	50%	30%	296	272
	C-Cath$_{ez}$	2,625	57			9	8
EU	C-Cure	55,000	1080	100%	45%		486
	C-Cath$_{ez}$	2,000	38				17
China	Nominal			20%	25%	18	16
RoW	Combined	as US	955	50%	30%	143	131
Total revenues			2540				931
CoG							-51
Gross Margin							880
R&D							-176
Sales							-88
Admin							-220
Operating margin							396
Interest							10
Tax							-138
Profit projection 2030							268
Value of C-Cure							870
Shares							7.85
Warrants and options							0.30
Core value per share							**107**
CAR Values	AML	150,000	566	100%	15%	78	72
	MM	150,000	608	100%	15%	90	82
	Nominal development						-39
Additional CAR value							115
CAR value per share							14
Value of C-Cure plus CAR							985
Indicative value per diluted share							**121**

Source: Edison Investment Research. Cash flows discounted at 12.5%

Solid cancer indications: a scenario approach to value

The NKG2D CAR products have a potentially huge market if they extend into solid tumour therapy. Exhibit 9 shows a simple scenario which could be regarded as additive to the values in Exhibit 8. Note that the timing and value of all these indications is still highly uncertain so they are not included in the core valuation estimate in Exhibit 8. The crucial assumption underlying Exhibit 9 is that in each case a similar response is seen to that observed with CD19 in lymphoma. There is, apart from published work on an ovarian cancer model, no data to support this premise. Consequently, these values will be adapted as data emerges and timelines resolve. For example, a CAR that gave a 90%+ complete response in pancreatic cancer would have a big market but pancreatic is a notoriously difficult indication so only a 2.5% preclinical probability is assigned.

Exhibit 9: Potential value of preclinical solid tumour CAR indications

Indication	US deaths	Peak share	Potential sales US $	Probability	NPV (US)	Global €	Notes
Ovarian	14,180	69%	1464	10.0%	81	100	Preclinical data, frequent late diagnosis means higher death rate
Breast	40,000	36%	2163	7.5%	88	108	Late diagnosis an issue, younger women particular target
Colorectal	50,310	36%	2721	7.5%	111	136	Note NKG2D ligands found in gut tissue, risk of higher side effects?
Pancreatic	39,590	69%	4086	2.5%	57	69	Lower probability as known difficult clinical target, but huge need.
Melanoma	9,710	13%	190	10.0%	11	13	Known immunogenicity but other immunotherapies like Yervoy (BMS)
Renal	13,860	69%	1430	7.5%	75	92	Little evidence, poor survival in metastatic disease
Total						**519**	

Source: Edison Investment Research, SEER data Price assumed €150,000 with US 75% of world market.

Exhibit 9 is based on US mortality, rather than incidence: it is assumed that other therapies may be preferred as first line due to price and complexity. The price used is based on that used by Dendreon (about $100,000) but with the added complexities of gene transfection and subsequent cell selection requiring a 50% premium. The US market is assumed to be 75% of the global figure for autologous therapies due to pricing and logistics.

A further simplifying assumption is made that these indications have a 35% cash profit margin. This may be too low but covers production, marketing and an implicit element for development amortisation. Alternatively, this could be a 35% royalty and milestone value after a deal.

Solid cancer indications with FDA fast-track approvals could reach patients by 2022-23 and allogeneic perhaps from 2023-24; dates and indications are very uncertain at this time.

Allogeneic versions of these products (not specifically valued as too early in development) could have longer biological protection if classed as new products and could extend the profitability by cutting the price, making the therapies easier to use and greatly expanding sales. Allogeneic therapies might be 50% US/ 50% EU, Japan and RoW.

Comparable companies

Note that Exhibit 9 is not a forecast. Nonetheless, Exhibits 8 and 9 combined compared to the value of Juno and Kite illustrate a valuation dichotomy. CAR T-cell cancer therapy has become one of the most active areas of cancer research and investment activity. Juno, which completed its IPO in December 2014, is now valued at $5.2 billion. Another prominent listed CAR specialist is Kite Pharma ($2.4 billion) now linked to Amgen.

In a December 2014 deal, two US companies (Intrexon ($2.8bn) and Ziopharm ($700m)) jointly paid $100m upfront (plus $15-20m per year of research funding) for a set of five preclinical candidates and the “sleeping beauty” gene transfer technology. Merck –Serono did a March 2015 deal to gain access to part of Intrexon’s technology portfolio to develop controllable CAR therapies. This deal had a $115m upfront with $826m of various milestones and tiered (undisclosed) royalties.

There seems to be little CAR premium in the Cardio3 share price; Exhibit 8 does not indicate a huge premium on standard criteria is needed at this stage. Yet clinical CAR data could rapidly emerge and this could alter market value perceptions, particularly of US investors, very quickly. Cardio3 has announced its intention to conduct a US IPO so will become more prominent to US investors as a result.

Devices

No specific value has been given to CorQuest at this stage. The project is early to properly value at this time. It could become peripheral if the CAR business develops quickly. C-Cath$_{ez}$ is valued as part of the C-Cure opportunity.

Financials

Cardio3’s cash use of 2015 and 2016 depends of the range of clinical trials undertaken itself affected by short-term data, for example, CAR therapies and solid tumours. Cash on 31 December was €30.3m with €32m gross raised in Q115; effectively €62m cash. This is stated by management to be sufficient to at least H216 .No further Walloon region loans are assumed see 2014 outlook note. There is a Belgium patent related tax exemption till 2025. Local funding in the US is supporting the establishment of the new manufacturing facility in Rochester. Edison has not assumed any significant C-Cure marketing investment in 2016 but a successful CHART-1 study

would need pre-launch investment although this could then be raised from various sources. Exhibit 10 shows the projected costs and cash flow using Cardio3's reporting categories.

Exhibit 10: Cardio3 expenditure and cash use

Summary	2014	2015	2016
Revenues	€0.15	€0.00	€0.00
CoG	-€5.25	-€3.00	-€6.00
Clinical	-€7.75	-€11.00	-€15.00
R&D	-€2.98	-€3.08	-€3.44
Admin	-€5.02	-€6.00	-€ .00
Other	€4.41	€0.00	€0.00
Operating profit (EBIT))	**-€16.44**	**-€23.08**	**-€31.44**
Dep, Amort	-€0.86	-€0.69	-€0.67
Share based payments	-€1.10	-€1.00	-€1.00
Net non-cash income	€1.85		
Other income	€2.00		
EBITDA (ex other income)	-€18.32	-€21.38	-€29.77
Operating cash flow	**-€17.41**	**-€20.02**	**-€29.41**
cash flow	€8.58	€3.53	-€30.66
Year end cash	**€30.30**	**€33.84**	**€3.18**

Source: Company data, Edison Investment Research

Although well-funded by European standards, Cardio3 is minimally funded relative to its US-based CAR therapy competitors. Juno, for example, raised $304m in December 2014. The proposed US IPO might alter that discrepancy. Exhibit 11 shows financial projections to 2016.

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Note: further material on C-cure is provided in earlier reports.

Exhibit 11: Financial summary

€000s	2013	2014	2015e	2016e
Year end 31 December	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS				
Revenue	0	146	0	0
Cost of Sales	(2,415)	(5,251)	(3,000)	(6,000)
Gross Profit	(2,415)	(5,105)	(3,000)	(6,000)
EBITDA	(10,815)	(18,322)	(21,385)	(29,769)
Operating Profit (before amort and except)	(11,025)	(18,515)	(21,409)	(29,769)
Intangible Amortisation	(670)	(670)	(670)	(670)
Other income and charges	0	3,846	0	0
Share-based payments	(1,258)	(1,098)	(1,000)	(1,000)
Operating Profit	(12,953)	(16,437)	(23,079)	(31,439)
Net Interest	(1,535)	(16)	171	158
Profit Before Tax (norm)	(12,560)	(18,531)	(21,238)	(29,611)
Profit Before Tax (FRS 3)	(14,488)	(16,453)	(22,908)	(31,281)
Tax	0	0	0	0
Profit After Tax (norm)	(12,560)	(18,531)	(21,238)	(29,611)
Profit After Tax (FRS 3)	(14,488)	(16,453)	(22,908)	(31,281)
Average Number of Shares Outstanding (m)	4.1	6.7	7.8	7.8
EPS - normalised (€)	(3.06)	(2.75)	(2.71)	(3.77)
EPS - (IFRS) (€)	(3.53)	(2.44)	(2.92)	(3.99)
Dividend per share (c)	0.0	0.0	0.0	0.0
Gross Margin (%)	N/A	N/A	N/A	N/A
EBITDA Margin (%)	N/A	N/A	N/A	N/A
Operating Margin (before GW and except) (%)	N/A	N/A	N/A	N/A
BALANCE SHEET				
Fixed Assets	9,783	11,041	19,971	19,451
Intangible Assets	9,400	10,266	19,120	18,450
Tangible Assets	243	598	674	824
Investments	140	177	177	177
Current Assets	22,602	32,935	35,460	4,800
Stocks	0	0	0	0
Debtors	421	1,839	830	830
Cash	22,058	30,304	33,838	3,178
Other	123	792	792	792
Current Liabilities	(3,390)	(6,053)	(6,215)	(6,276)
Creditors	(2,961)	(5,276)	(5,276)	(5,276)
Deferred revenue	0	0	0	0
Walloon loans for cash payment	(428)	(777)	(939)	(1,000)
Long Term Liabilities	(12,099)	(11,239)	(9,439)	(9,479)
Walloon loans (non-current)	(12,072)	(10,778)	(9,240)	(9,280)
Other long term liabilities	(27)	(461)	(199)	(199)
Net Assets	16,897	26,684	39,776	8,496
CASH FLOW				
Operating Cash Flow	(10,637)	(17,398)	(20,186)	(29,567)
Net Interest	(1,535)	(16)	171	158
Tax	0	0	0	0
Capex	(531)	(640)	(100)	(150)
Acquisitions/disposals	0	(1,550)	(5,714)	0
Financing	30,873	26,417	32,000	0
Dividends	0	0	0	0
Other	1,585	2,379	(1,261)	(1,202)
Net Cash Flow	19,754	9,192	4,909	(30,761)
Opening net debt/(cash)	10,197	(9,557)	(18,749)	(23,659)
HP finance leases initiated	0	0	0	0
Walloon loan recognition (non-cash)	0	0	(0)	0
Closing net debt/(cash)	(9,557)	(18,749)	(23,659)	7,102

Source: Edison Investment Research estimates, Cardio3 Bioscience announcements. Note: 2013 results restated due to accounting policy changes.

Contact details	Revenue by geography
Rue Edouard Belin 12 1435 Mont-Saint-Guibert Belgium +32(0)10 39 41 00 www.c3bs.com/en	N/A

CAGR metrics		Profitability metrics		Balance sheet metrics		Sensitivities evaluation	
EPS 2010-14e	N/A	ROCE 13e	N/A	Gearing 13e	N/A	Litigation/regulatory	●
EPS 2012-14e	N/A	Avg ROCE 2010-14e	N/A	Interest cover 13e	N/A	Pensions	○
EBITDA 2010-14e	N/A	ROE 13e	N/A	CA/CL 13e	N/A	Currency	◖
EBITDA 2012-14e	N/A	Gross margin 13e	N/A	Stock days 13e	N/A	Stock overhang	◖
Sales 2010-14e	N/A	Operating margin 13e	N/A	Debtor days 13e	N/A	Interest rates	○
Sales 2012-14e	N/A	Gr mgn / Op mgn 13e	N/A	Creditor days 13e	N/A	Oil/commodity prices	○

Management team

Chairman: Michel Lussier

Mr Lussier is a co-founder of Cardio3 and has been chairman since its foundation in 2007. He has held senior European marketing roles at Volcano, a US device company, since 2002. In 2002, he founded Medpole, a distribution incubator for medical device start-up companies. He was a VP at Novoste from 1998 to 2002 .Before Novoste, he was at InControl and with Medtronic in cardiac devices. He holds a BS in electrical engineering and an MS in biomedical engineering from Montreal University and an MBa from INSEAD.

CEO: Dr Christian Homsy

Dr Homsy has been the CEO of Cardio3 since its foundation. Before joining Cardio3 BioSciences, he was general manager of Medpole. He was previously at Guidant Corporation working in cardiovascular disease, where he founded the Guidant Institute for Therapy Development, a facility for healthcare professional education. Dr Homsy is a physician and received an MBA from IMD.

CFO: Patrick Jeanmart

Mr Jeanmart joined Cardio3 in 2007. He was previously at Ion Beam Applications (Belgium), where he was vice president of finance of IBA Molecular. He holds a Master in Economics degree from the University of Namur, Belgium.

VP Research & Development: Dr Peter de Waele

Dr De Waele joined Cardio3 in Nov. 2010. He was previously a consultant. Until 2006, he was COO at XCELLentis, a stem cell company. He was formerly at Innogenetics and holds an MSc and a PhD from Ghent University.

VP Business Development: Georges Rawadi

Prior to joining Cardio3 in June 2014, Dr. Georges Rawadi was VP Business Development with Cellectis. He has held business development positions at Galapagos, ProStrakan France and Sanofi-Aventis France. Dr. Rawadi holds a PhD in Microbiology from the Pierre et Marie Curie University (France), and a Masters in Management and Strategy from the ESSEC Business School.

Vice President Immuno-oncology: Vincent Brichard

Dr Vincent Brichard is an oncologist with a PhD in tumour immunology. Before joining Cardio3 in January 2015, he was the Senior Vice President of the Immunotherapeutics Business Unit at GSK Biologicals and former head of the Cancer Vaccines Business Unit (from 2002). He has held academic positions at the Ludwig Institute for Cancer Research, Brussels, Institut Curie Cancer Center, Paris, and the University of Louvain.

Principal shareholders (as of 7 April 2015 as supplied by Cardio3)	(%)
Tolefi SA (Company controlled by Mr Goblet, a Director)	28.90
Medisun (Asian JV partner)	7.24
PMV NV	5.46
SRIW Group (Wallonian Investment organisation)	5.10
Founders and Management	4.25
Mayo Foundation	2.69
Celdara	1.19
Others	45.17

Companies named in this report

Mesoblast, J&J, Juno, Kite, Merck-Serono, Bellicum, Neostem, Novartis, Intrexon, Ziopharm, Cellectis, Pfizer

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