OncoSil Medical (OSL)

INITIATION OF COVERAGE

Another internal radiation success story

- **Company summary**: The Sydney-based OncoSil is developing a brachytherapy device that, implanted locally, can emit cancer-killing radiation into a tumour without damaging healthy surrounding tissues. The device, previously developed by the UK's Defence Evaluation and Research Agency, and then by a US biotech company called pSivida, was spun out into OncoSil in 2013. OncoSil's product is similar to Sirtex's SIR-Spheres product for the treatment of liver cancer. The OncoSil device has been trialled at Phase II in pancreatic cancer with favourable results. The company intends to file for CE Mark approval of the device this year as a pancreatic cancer treatment and is currently initiating a single pivotal study in pancreatic cancer for FDA approval, expected in 2016 or 2017.
- **OncoSil has good management.** We value Oncosil's leadership team highly. Chairman Martin Rogers brought the cancer immunotherapy company Prima Biomed (ASX: PRR) back from potential oblivion in 2007 and took it to Phase III in 2012. CEO, Dr Neil Frazer has a track record of clinical success gained at GSK and other companies working mainly on cancer.
- **OncoSil is undervalued on our numbers.** We value OncoSil using a probability-weighted DCF approach at $0.43 base case and $1.10 optimistic case. Our $0.45 target price sits at our base case. We see OncoSil being re-rated by the market as the pivotal study gets underway and CE Marking approaches.
- **OncoSil will file for CE Mark approval of its brachytherapy this year**, on the premise that the existing Phase II data is sufficient for approval.
- **OncoSil is initiating a single pivotal study trial for US approval**. The company is currently preparing its IDE submission for a 150-patient randomised controlled study in pancreatic cancer patients with planned interim analyses. The study commences this year and will likely conclude in 2016, which will set OncoSil on track for FDA approval in 2017. OncoSil understands that a two to three month improvement in 'Overall Survival' as well as lowered pain scores are both registrable endpoints.
- **OncoSil is funded to achieve a meaningful commercial outcome**, after a $10.3m placement and SPP in late 2013 at 12.5 cents per share, which brought cash as at December 2013 to $11.4m; this is more than enough to fund the pivotal study which we estimate will cost ~A$8m after R&D tax credits.

INVESTMENT SUMMARY

Year End: 30 June		2012 (A)	2013 (A)	2014 (E)	2015 (E)	2016 (E)
Revenue	$mn	0	0	0	0	0
EBITDA	$mn	-0.6	-1.0	-4.2	-6.3	-6.4
EBIT	$mn	-0.6	-1.0	-4.2	-6.3	-6.4
Reported Profit	$mn	-0.4	-0.9	-4.1	-6.3	-6.4
Adjusted Profit	$mn	-0.4	-0.9	-4.1	-6.3	-6.4
EPS (Reported)	¢	-0.4	-0.3	-1.1	-1.4	-1.5
EPS (Adjusted)	¢	-0.4	-0.3	-1.1	-1.4	-1.5
EPS Growth	%	N/A	N/A	N/A	N/A	N/A
PER (Reported)	x	N/A	N/A	N/A	N/A	N/A
PER (Adjusted)	x	N/A	N/A	N/A	N/A	N/A
Dividend	¢	0.0	0.0	0.0	0.0	0.0
Yield	%	0.0	0.0	0.0	0.0	0.0
Franking	%	0	0	0	0	0

RECOMMENDATIONS

Rating	**BUY** ▲
Risk	Speculative
Price Target	**$0.45**
Share Price	$0.13

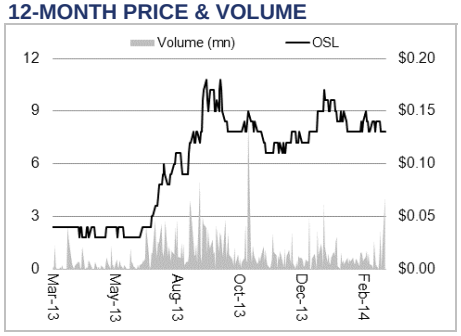
SNAPSHOT

Monthly Turnover	$1.7mn
Market Cap	$43mn
Shares Issued	346.4mn
52-Week High	$0.18
52-Week Low	$0.03
Sector	Health Care

BUSINESS DESCRIPTION

OncoSil is developing a brachytherapy device that can emit radiation locally into a tumour without damaging healthy surrounding tissues. OncoSil's product is similar to Sirtex's SIR-Spheres product for the treatment of liver cancer. The device has been trialled at Phase II in pancreatic cancer with favourable results.

12-MONTH PRICE & VOLUME



RESEARCH ANALYST

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Disclosure
The author owns no shares in OSL.

Baillieu Holst has acted in a corporate advisory role for OncoSil and earned fees in relation to that activity in the past twelve months.

Financial summary

Code	OSL
Analyst	Stuart Roberts
Date	17 March, 2014
Share price	$0.13
Market capitalisation	$43m
Year end	30 June

Rating	BUY
Price target	$0.45
Upside/downside	260.0%
Valuation	$0.434 / $1.102
Valuation method	Probability-weighted DCF
Risk	Speculative

PROFIT AND LOSS (A$m)

Y/e June 30 (A$m)	FY12A	FY13A	FY14E	FY15E	FY16E
Revenue	0	0	0	0	0
EBITDA	**-1**	**-1**	**-4**	**-6**	**-6**
D&A	0	0	0	0	0
EBIT	**-1**	**-1**	**-4**	**-6**	**-6**
Net interest	0	0	0	0	0
Pre-tax profit	**0**	**-1**	**-4**	**-6**	**-6**
Tax	0	0	0	0	0
NPAT	0	-1	-4	-6	-6
Minority interests	0	0	0	0	0
Net profit after minorities	0	-1	-4	-6	-6

BALANCE SHEET (A$m)

Y/e June 30	FY12A	FY13A	FY14E	FY15E	FY16E
Cash	2	4	5	9	3
Current receivables	0	0	0	0	0
Inventories	0	0	0	0	0
Other current assets	0	0	4	4	4
Current assets	**3**	**4**	**10**	**13**	**7**
PPE	0	0	0	0	0
Intangible assets	0	3	3	3	3
Other non-current assets	0	0	0	0	0
Non-current assets	0	3	3	3	3
Total assets	3	6	12	16	10
Payables	0	0	0	0	0
Debt	0	0	0	0	0
Other liabilities	0	0	0	0	0
Total liabilities	0	0	0	0	0
Shareholders' equity	2	6	12	16	10
Minorities	0	0	0	0	0
Total shareholders funds	**2**	**6**	**12**	**16**	**10**
Total funds employed	**3**	**6**	**12**	**16**	**10**
W/A shares on issue	97	126	321	341	401

CASH FLOW (A$m)

Y/e June 30	FY12A	FY13A	FY14E	FY15E	FY16E
NPAT plus discontinued ops.	0	-1	-4	-6	-6
Non-cash items	0	0	0	0	0
Working capital	0	0	0	0	0
Other operating cash flow	0	0	0	0	0
Operating cashflow	**0**	**0**	**-4**	**-6**	**-6**
Capex	0	0	0	0	0
Investments	0	0	-4	0	0
Other investing cash flow	0	0	0	0	0
Investing cashflow	**0**	**0**	**-4**	**0**	**0**
Change in borrowings	0	0	0	0	0
Equity raised	0	2	10	10	0
Dividends paid	0	0	0	0	0
Other financing cash flow	0	0	0	0	0
Financing cashflow	**0**	**2**	**10**	**10**	**0**
Net change in cash	**0**	**1**	**2**	**4**	**-6**
Cash at end of period	2	4	5	9	3

EARNINGS (A$m)

Y/e June 30	FY12A	FY13A	FY14E	FY15E	FY16E
Net profit ($m)	-0.4	-0.9	-4.1	-6.3	-6.4
EPS (c)	-0.4	-0.7	-1.3	-1.8	-1.6
EPS growth (%)	N/A	N/A	N/A	N/A	N/A
P/E ratio (x)	-28.1	-17.9	-9.8	-6.8	-7.9
CFPS (c)	-0.3	-0.4	-1.2	-1.7	-1.5
Price/CF (x)	-39.6	-33.3	-10.5	-7.2	-8.4
DPS (c)	0.0	0.0	0.0	0.0	0.0
Yield (%)	0.0%	0.0%	0.0%	0.0%	0.0%
Franking (%)	N/A	N/A	N/A	N/A	N/A
EV/EBITDA	-55.9	-32.6	-7.6	-5.1	-5.0
EV/EBIT	-55.9	-32.5	-7.6	-5.1	-5.0

PROFITABILITY RATIOS

Y/e June 30	FY12A	FY13A	FY14E	FY15E	FY16E
EBITDA/revenue (%)	N/A	N/A	N/A	N/A	N/A
EBIT/revenue (%)	N/A	N/A	N/A	N/A	N/A
Return on assets (%)	-17.1%	-14.1%	-33.0%	-39.4%	-64.0%
Return on equity (%)	-17.4%	-14.5%	-33.6%	-39.9%	-65.4%
Return on funds empl'd (%)	-17.4%	-14.5%	-33.6%	-39.9%	-65.4%
Dividend cover (x)	N/A	N/A	N/A	N/A	N/A
Effective tax rate (%)	0.0%	0.0%	0.0%	0.0%	0.0%

LIQUIDITY AND LEVERAGE RATIOS

Y/e June 30	FY12A	FY13A	FY14E	FY15E	FY16E
Net debt/(cash) ($m)	-2	-4	-5	-9	-3
Net debt/equity (%)	-97.1%	-58.0%	-43.9%	-56.7%	-29.9%
Net interest cover (x)	N/A	N/A	N/A	N/A	N/A
Current ratio (x)	61.5	18.6	46.3	63.4	34.7

INTERIMS

Y/e June 30 ($m)	1H13A	2H13A	1H14A	2H14F	1H15F
Revenue	0	0	0	0	0
EBITDA	**0**	**-1**	**-2**	**-2**	**-3**
D&A	**0**	**0**	**0**	**0**	**0**
EBIT	**0**	**-1**	**-2**	**-2**	**-3**
Net interest	**0**	**0**	**0**	**0**	**0**
Pre-tax profit	0	-1	-2	-2	-3
Tax	**0**	**0**	**0**	**0**	**0**
NPAT	0	-1	-2	-2	-3
Minority interests	**0**	**0**	**0**	**0**	**0**
Net profit after minorities	0	-1	-2	-2	-3

VALUATION

	Base	Optim.
OncoSil (A$m)	168.5	453.9
Value of tax losses	2.7	2.7
Underlying R&D cost	-9.6	-9.6
Cash now (A$m)	11.5	11.5
Cash from options and cash to be rai	12.4	12.4
Total value (A$m)	185.5	470.8
Total diluted shares (million)	427.1	427.1
Value per share	$0.43	$1.10
Valuation midpoint	$0.77	
Share price now (A$ per share)	$0.125	
Upside to midpoint	514.7%	

Introducing OncoSil (OSL)

- **OncoSil is developing a brachytherapy device for the treatment of pancreatic cancer.** Its origins herald back to the UK's Defence Evaluation and Research Agency where it was developed as a brachytherapy by US biotech company, pSivida[1]. The device was spun out into Sydney-based, OncoSil in 2013. OncoSil's product is similar to Sirtex's SIR-Spheres product for the treatment of liver cancer. The device has been trialled at Phase II in pancreatic cancer with favourable results. OncoSil intends to file for CE Mark approval of the device this year and is currently initiating a single pivotal study in pancreatic cancer for FDA approval, expected in 2016 or 2017.
- **What is brachytherapy?** Brachytherapy is a form of radiotherapy for the treatment of cancer. In radiotherapy, a tumour is exposed to radiation such as x-rays or gamma rays, which kills the cancer cells by breaking the DNA molecule inside those cells. Most radiotherapy is external radiation therapy, that is, the patient is placed under a source of radiation outside the body. However not all cancers are amenable to external radiation because the radiation tolerance of normal tissue around the tumour is too low. For such cancers, internal radiotherapy can sometimes be used. This is where a radioactive substance with a short range[2] is placed at the site of the tumour within the body for more favourable results. Internal radiotherapy effectively targets the tumour whilst exposing the normal tissue to low levels of radiation. Brachytherapy as a treatment approach is a century old, but is only now on the verge of mainstreaming.
- **What is pancreatic cancer?** The pancreas is the organ in the body which secretes hormones and enzymes to digest fats. One of the hormones it secretes is insulin. Cancer of the pancreas tends to kill quickly because the symptoms - mainly weight loss, abdominal and back pain and jaundice - don't become noticeable until the cancer has metastasised. This means that, more often than not, the cancer is detected too late[3]. Currently pancreatic cancer has a five-year survival rate of 6%; this is the lowest survival level of any of the 200-or-so kinds of cancer.

Pancreatic cancer survival rates are tiny, at only 6%

- **What is OncoSil's brachytherapy product?** OncoSil's brachytherapy is tiny particles of porous nano-engineered silicon around 30 microns in size[4] containing radioactive phosphorus-32 (^{32}P) isotopes with a half-life of 14.3 days. They are delivered using endoscopic ultrasound directly into the pancreatic tumours in a short (ie: half an hour) procedure that takes place under general anaesthetic. Beta radiation given off by the ^{32}P travels through tissue no further than 7.6 mm[5], which minimises the damage that the radiation can do to healthy pancreatic tissue and to the rest of the body.
- **How well do pancreatic cancer patients do on OncoSil's brachytherapy product?** In an open-label Phase IIa clinical study, pancreatic cancer patients registered a median Overall Survival of 10.2 months. That compares favourably with the 5.7 months expected of gemcitabine, and the 8.5 months expected of gemcitabine plus Abraxane from the Phase III studies that gained pancreatic cancer indications for those drugs. Also, patients experienced reduced abdominal pain, which can be serious in pancreatic cancer. OncoSil believes that in the upcoming randomised controlled pivotal trial, the device is well placed to gain two-to-three months (or more) survival over gemcitabine plus Abraxane, as well as reduced abdominal pain. Either of these favourable outcomes is understand to be a registrable endpoint.
- **If OncoSil's brachytherapy product is so good, how come OncoSil is only capitalised at ~A$40m?** We believe that OncoSil is currently undervalued by the market because the relevant Phase II data we cited above is six years old from an uncontrolled trial. pSivida reported the data in early 2008 but instead chose to focus on its ophthalmic drug delivery technologies and allowed the brachytherapy opportunity to languish. Subsequently, nothing much was expected by the market from this technology. By contrast, we believe the time is right for the technology to go forward. Moreover Sirtex has grown considerably since 2008, further mainstreaming the idea of brachytherapy. Abraxane has shown that progress is possible in pancreatic cancer in terms of survival. And OncoSil is now funded through to a pivotal trial result, probably in 2016.

[1] See Appendix IV for the background to the technology.
[2] Hence the name - 'brachytherapy' comes from the Greek word brachys, meaning 'brief' or 'short'.
[3] Gene Upshaw (1945-2008), the NFL Hall of Fame Guard, died only four days after his diagnosis.
[4] Around a third less than the average width of a strand of human hair.
[5] See Zhang et. al., Clin Cancer Res. 2005 Oct 15;11(20):7532-7.

Ten reasons to buy OncoSil

- **The OncoSil brachytherapy works in pancreatic cancer**. Under pSivida the OncoSil technology was tried in four Phase I/II clinical trials, all with solid results. Phase IIa saw pancreatic cancer patients register a median overall survival of 10.2 months versus just 5.7 months with gemcitabine. The product also lowered abdominal pain in the patients. Phase IIb, which tested up to four times the dose of Phase IIa, had too few patients for survival data to be meaningful, but that study did show an improvement in the disease control rate from 82% to 100%, with all doses well tolerated.

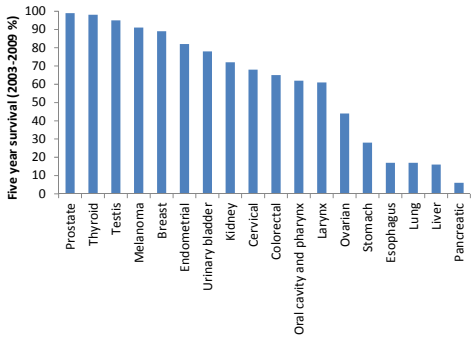
At Phase IIa OncoSil boosted median overall survival in pancreatic cancer by ~80%

- **There is demand for new pancreatic cancer therapies**. Around 46,000 Americans and 85,000 Europeans will be diagnosed with pancreatic cancer this year. The median Overall Survival after treatment with gemcitabine and Abraxane for these patients is only 8.5 months. There remains demand for new products that can extend this life expectancy still further, opening up the potential of a >US$1.0bn market.
- **OncoSil will file for CE Mark approval of its brachytherapy this year**, on the view that the Phase II data that has been generated its sufficient for approval. This nearness of first regulatory approval is likely to appeal to Life Science investors who prefer technologies that have been clinically de-risked.
- **OncoSil initiating a single pivotal study ahead of US approval**. The company is currently preparing its IDE submission for a 150-patient randomised controlled study in pancreatic cancer patients, with interim analyses. This study is likely to conclude in 2016, seeing OncoSil on track for FDA approval in 2017. OncoSil understands that a two to three month improvement in Overall Survival and lowered pain scores are registrable endpoints.

About A$25m has been invested in OncoSil's development to date

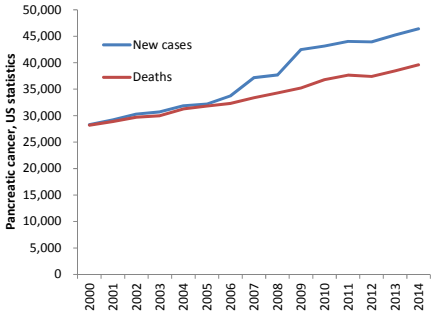
- **OncoSil is funded to achieve a meaningful commercial outcome** after a $10.3m placement and SPP in late 2013 at 12.5 cents per share. We believe this was more than enough to fund the pivotal study. As at December 2013 OncoSil held A$11.4m cash. We estimate that the pivotal study, to be called ONC-301, will cost ~A$8m to complete after R&D tax credits.
- **The development of OncoCal provides OncoSil with a good second generation technology**. OncoSil is currently developing a calcium-based delivery system to replace the current silicon-based system presently used for ^{32}P delivery. Amongst other benefits, this technology brings outright ownership by the company, so that OncoSil's Next Generation brachytherapy product will be royalty-free.
- **OncoSil is trading at not much above replacement level**. OncoSil estimates that ~A$25m has been invested in the development of its brachytherapy technology. OncoSil's current market capitalisation is ~$40m. This means that OncoSil is trading at only a small premium over replacement value in spite of the favourable clinical data, the ONC-301 registration study initiation, and the imminence of CE Marking.
- **Sirtex Medical has helped grow market acceptance for brachytherapy**, with SIR-Spheres now a >US$100m pa business at the revenue line and growing rapidly thanks to excellent clinical outcomes in liver cancer. We think the success of Sirtex, and its current market capitalisation of ~$850-900m, provides a good benchmark for OncoSil to aspire to.
- **OncoSil has good management**. We value OncoSil's leadership team highly. Chairman, Martin Rogers brought the cancer immunotherapy company, Prima Biomed (ASX: PRR) back from potential oblivion in 2007 and took it to Phase III in 2012. Meanwhile, CEO, Dr Neil Frazer has a track record of clinical success gained at GSK and other companies, working mainly on cancer.
- **OncoSil is undervalued on our numbers**. We value OncoSil using a probability-weighted DCF approach at $0.43 base case and $1.10 optimistic case. Our $0.45 target price sits at our base case. We see OncoSil being re-rated by the market as the ONC-301 study begins and CE Marking approaches.

FIG.1: PANCREATIC CANCER HAS A LOW SURVIVAL RATE…



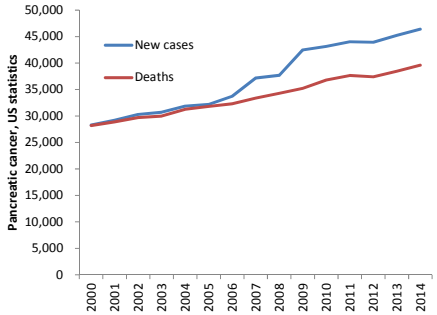
Source: Cancer Facts and Figures 2014

FIG.2: …EVEN THOUGH SURVIVAL IS IMPROVING



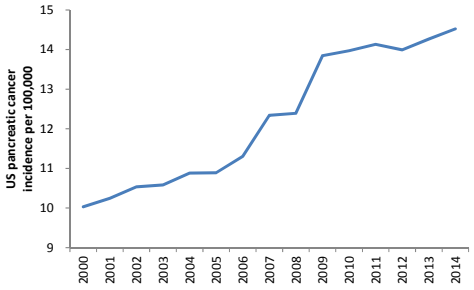
Source: Cancer Facts and Figures 2014

FIG.3: THE DEATH RATE FROM PANCREATIC CANCER IS RISING…



Source: Cancer Facts and Figures 2014

FIG.4: …BECAUSE PER-CAPITA INCIDENCE IS INCREASING



Source: Cancer Facts and Figures 2014

OncoSil can be game-changing in pancreatic cancer

Background to pancreatic cancer

- **Pancreatic cancer is the cancer you *really* don't want to get**. Of all the cancers a patient could be diagnosed with, probably the worst cancer to get is pancreatic. Consider a cross section of 18 cancers that represents ~82% of all cancer incidence in America[6]. For that cross section, measured through all stages of the relevant disease, the average five year survival rate in the 2000s was ~67%. For pancreatic cancer it was 6%. Well-managed patients typically only live ~8-9 months after diagnosis and a mere 20% of patients will live longer than a year[7]. For those 10-15% of patients diagnosed when surgery is an option[8], the five year survival rate improves to ~20%[9], but that still isn't great.

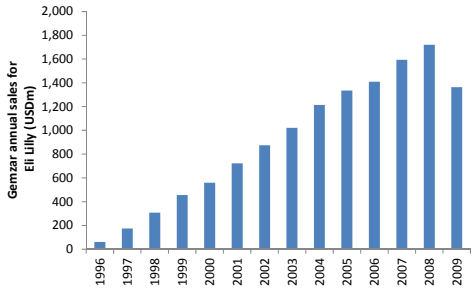
Median Overall Survival in pancreatic cancer today is 8-9 months

[6] In order of five year survival, the 18 are prostate, thyroid, testicular, skin, breast, endometrial, bladder, kidney, cervical, colorectal, laryngeal, ovarian, stomach, esophageal, lung, liver and pancreatic. Source: American Cancer Society, *Cancer Facts and Figures 2014*, page 17.
[7] The Apple founder Steve Jobs (1955-2011) lived after his diagnosis for seven years, but that was because he had a neuroendocrine form of pancreatic cancer, and these kinds are more amenable to surgery than most. However neuroendocrine tumours account for less than 5% of all pancreatic tumours. The other 95% of pancreatic cancers are exocrine tumours, most of them adenocarcinomas. These cancers generally kill quickly. For example, Luciano Pavarotti (1935-2007), the Italian operatic tenor, lived for 14 months post-diagnosis. The American actor Patrick Swayze (1952-2009) got 19 months of life after his diagnosis. Randy Pausch (1960-2008), professor of computer science at Carnegie Mellon University but famous for his 2008 book *The Last Lecture*, lived for 22 months.
[8] In America around 9% of all pancreatic cancer is local at the time of diagnosis and 24% is regional (see J Gastrointest Surg. 2006 Nov;10(9):1212-23; discussion 1223-4). Some regional cancer can be treated with surgical resection. For estimates of the percentage of patients eligible for resection, see Surgery. 1996 Oct;120(4):680-5; discussion 686-7 and Med J Aust. 2012 May 7;196(8):511-5.
[9] See Ann Surg. 2008 Mar;247(3):456-62 and World J Surg. 2003 Mar;27(3):324-9. Epub 2003 Feb 27. The US Supreme Court Justice Ruth Bader Ginsburg (1933-) had pancreatic cancer surgery in early 2009 but has remained alive and active on the Court since then.

Pancreatic cancer is now America's fourth biggest cancer killer

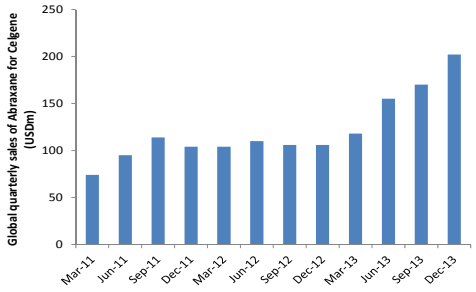
- **Around 46,000 Americans will be diagnosed with pancreatic cancer this year, and 40,000 will die from it.** Thankfully pancreatic cancer is only around 2-3% of all cancer incidence in America, however the incidence rate has steadily increased since the turn of the century, from around 10 per 100,000 in 2000 to 14.5 per 100,000 now. Since the disease generally kills quickly, the number of pancreatic cancer deaths is always close to the number of new cases. It is now the fourth biggest cancer killer in America. Since 2003 more people have died every year from pancreatic cancer than prostate cancer, and these days only slightly less people die from breast cancer.

FIG.5: GEMZAR WAS A US$1.8BN BLOCKBUSTER FOR ELI LILLY



Source: Eli Lilly

FIG.6: CELGENE HAS BEEN GROWING ABRAXANE STRONGLY



Source: Celgene

- **Survival has improved – a little - thanks mainly to gemcitabine and Abraxane**. The 6% survival rate may be small but there has been improvement. In the mid-1970s five year survival was 2% and in the late 1980s it was 4%[10]. In recent years there have been five important developments in pancreatic cancer:
  - **Better surgery**. The standard surgical treatment of pancreatic cancer is the 'Whipple pancreaticoduodenectomy', where the head of the pancreas, a portion of the bile duct, the gallbladder and the duodenum are all cut out in order to get at the cancer. This procedure originated from the 1930s, but even in the 1980s it was associated with perioperative mortality higher than 15%. Nowadays such unfavourable outcomes are rare[11].
  - **Gemcitabine**. This drug, which Eli Lilly marketed as Gemzar[12] and which is now generic[13], gained its first FDA approval in May 1996 with a pancreatic cancer indication. As a first-line monotherapy at that time, the drug generated median overall survival of 5.7 months - 1.3 months better than the 4.4 months for the previous standard of care drug, 5-FU[14]. Gemzar did US$1.7bn peak net sales in 2008.
  - **Tarceva**[15]. This Roche drug gained FDA approval for a pancreatic cancer indication in November 2005[16]. The drug works in pancreatic cancer, but not fantastically so. In a Phase III study, Tarceva plus gemcitabine improved median overall survival from 5.9 months to 6.2 months. However this study was the first to show that gemcitabine could combine with another drug to improve survival in advanced pancreatic cancer[17]. Tarceva, a US$1.4bn drug for Roche in 2013, generally only gets used as a 'last line' therapy in pancreatic cancer these days.
  - **Folfirinox**. This drug combination of 5-FU, leucovorin, irinotecan and oxaliplatin was shown in 2011 to be superior to gemcitabine in pancreatic cancer, with median overall survival of 11.1 months versus 6.8 months for gemcitabine. It was more toxic however, with more than twice the degradation in Quality of Life[18].

[10] The improvement in the 1980s was mainly due to better surgical techniques. See Ann Surg. 1987 Sep;206(3):358-65.
[11] See Am Surg. 1999 Sep;65(9):889-93.
[12] See www.gemzar.com.
[13] The drug went generic in Europe in 2009 and in the US in 2010.
[14] See Burris et. al., J Clin Oncol. 1997 Jun;15(6):2403-13.
[15] Generic name erlotinib, see www.tarceva.com.
[16] Tarceva was first FDA-approved in 2004, for Non-Small Cell Lung Cancer.
[17] See J Clin Oncol. 2007 May 20;25(15):1960-6. Epub 2007 Apr 23.
[18] See N Engl J Med. 2011 May 12;364(19):1817-25.

- **Abraxane**[19]. This Celgene drug[20] gained FDA approval for a pancreatic cancer indication, in conjunction with gemcitabine, in September 2013, off the back of outstanding Phase III data reported in January 2013. Abraxane is simply paclitaxel bound to the blood plasma protein albumin for better half-life in the bloodstream. In Phase III it increased median overall survival by a massive (by pancreatic cancer survival standards) 1.8 months, from 6.7 months for gemcitabine alone to 8.5 months for the gemcitabine/Abraxane combination[21]. That's a 27% increase. Abraxane did US$645m in net sales for Celgene in 2013.

As of 2013 Abraxane is the current star of the pancreatic cancer treatment show

OncoSil works as a pancreatic cancer therapy

- **Most drug candidates haven't worked in pancreatic cancer**. For only two drugs to have made significant improvements in pancreatic cancer in 16 years shows how difficult it is to come up with new chemotherapies in this setting. That, however, is not without many drug developers trying. The attraction of pancreatic cancer for an emerging company is the traditionally low survival rates, which makes the hurdle for success a 'mere' two or three months extra Overall Survival beyond gemcitabine (and now Abraxane), in studies that are small and (regrettably for the patients), relatively quick to run. That fatal attraction has turned pancreatic cancer into a drug development graveyard, as the list of failed compounds in Appendix II will attest[22]. Basically, pancreatic cancer cells are tougher than just about all others in terms of resistance to chemotherapy[23], in part because mutations of the K-Ras gene, a well-known oncogene (ie: cancer causing gene), occur in over 90% of pancreatic carcinomas[24]. Also, most pancreatic cancers (ie adenocarcinomas) are 'hypovascular', meaning they have fewer blood vessels that can feed drug into the tumour. All of which begs the question as to why OncoSil should succeed when Roche's Avastin, BMS and Merck KGaA's Erbitux and Sanofi's Zaltrap didn't.
- **It's not clear whether external beam radiation plus chemotherapy works in pancreatic cancer**, because the clinical evidence swings either way. The FFCD-SFRO trial from 2008, in 1,900 locally advanced unresectable pancreatic cancer patients, said 'no' because patients who got both external radiation plus gemcitabine only had 8.6 months median survival versus 13 months for gemcitabine alone (p=0.03)[25]. However the 74-patient ECOG study from 2011, in a comparable group of patients, said 'yes', with 11.1 months for chemoradiation versus 9.2 months with gemcitabine (p=0.034)[26]. Consequently, external beam radiation in pancreatic cancer is seen as 'controversial'[27]. We argue that the ECOG trial points to the usefulness of chemoradiotherapy on the grounds that the survival numbers for the gemcitabine-only army in the FFCD-SFRO trial were unusually high, and also because patients in the chemoradiation arm started on F-5U and cisplatin before switching to maintenance gemcitabine. However the radiation used was necessarily low in each case – 60 Gy for FFCD-SFRO and 50.4 Gy for ECOG.
- **OncoSil has what the conventional chemotherapy and chemoradiotherapy approaches haven't had – effective localised radiation.** OncoSil originates from the mid-1990s invention of a nano-porous silicon material called BioSilicon by the British physicist Professor Leigh Canham[28]. Canham's technology allows differently sized porous silicon particles with variable biodegradation rates[29] to be nano-engineered, and a decade ago this permitted the Canham laboratory and its commercial collaborator, pSivida to design a ^{32}P-carrying BioSilicon particle optimally sized to localise irremovably within a tumour and not degrade until the radiation had been spent. Given how readily radiation kills cancers, even those riddled with K-Ras mutations, a product like ^{32}P BioSilicon should be highly effective because:

[19] Generic name nab-paclitaxel, see www.abraxane.com.
[20] Abraxane was first FDA-approved in 2005, for breast cancer. Celgene paid US$2.9bn in mid-2010 in order to buy Abraxis Bioscience, primarily because of Abraxane.
[21] See N Engl J Med. 2013 Oct 31;369(18):1691-703. Epub 2013 Oct 16. Celgene significantly overpowered this study, recruiting 861 patients in order to be able to gain a low p value on any survival advantage for its drug, and came back with p<0.001. The company was willing to make this investment because success in pancreatic cancer would show the power of the drug across a range of solid tumours.
[22] Failure in pancreatic cancer, however, need not be a long-term setback. Consider the Bay Area biotech SuperGen. This company's Orathecin drug, a camptothecin like the old Wyeth drug Camptosar, was only good in Phase II for 6 months median survival with gemcitabine, as per an April 2006 interim analysis. However as Astex Pharmaceuticals, this company was ultimately bought by Otsuka in 2013 for US$886m, with Otsuka mainly wanting Astex's first drug, Dacogen for the treatment of myelodysplastic syndrome.
[23] A good parallel can be made here to primary liver cancer. No drug was successful here until the Bayer/Onyx drug Nexavar (sorafenib) in 2007 (see See N Engl J Med. 2008 Jul 24;359(4):378-90), but Sirtex's SIR-Spheres brachytherapy had a long track record of success in this indication stretching back to the late 1990s.
[24] See Science. 2008 Sep 26;321(5897):1801-6. Epub 2008 Sep 4.
[25] See Ann Oncol. 2008 Sep;19(9):1592-9. Epub 2008 May 7.
[26] See J Clin Oncol. 2011 Nov 1;29(31):4105-12. Epub 2011 Oct 3.
[27] It's also worth noting that it's long, given five days a week for 3-6 weeks. This allows various kinds of rapidly dividing cells with different cycle times to be captured by the radiation.
[28] We understand that Leigh Canham still consults to OncoSil as well as to pSivida.
[29] The degradation rate being controllable by the porosity of the BioSilicon.

- The ability for the BioSilicon to stay in place – the porous nature of the silicon gives it more chance to embed in tumour tissue than a product with a smooth surface - should mean that radiation is focused more or less where the product is placed (ie. on the tumours), and not on healthy tissue;
- The use of ^{32}P means that only short-travelling beta radiation is being emitted, further limiting the potential for healthy tissue damage;
- The long 14.3 day half-life of ^{32}P increases the chances that cancer cells are killed by the radiation; and
- The localised nature of the therapy means that whereas 50-60 Gy is about has high as external beam radiation can go in pancreatic cancer. OncoSil can be effective at much higher doses.

- **For OncoSil, the clinical data has borne out the theory.** After favourable pre-clinical work reported in September 2003[30], pSivida took its ^{32}P brachytherapy product into the clinic in mid-2004 for an initial Phase II trial in liver cancer patients, which demonstrated that the product was safe and could engineer tumour regression[31]. Then came two open-label Phase II trials, run between 2006 and 2008, demonstrating that OncoSil had the goods in pancreatic cancer:
  - An initial Phase IIa recruited 17 patients with local and metastatic pancreatic cancer. These patients received a single intra-tumoral implantation of OncoSil particles, delivered in a liquid suspension using a fine-gauge needle guided into place by endoscopic ultrasound. The OncoSil particles emitted 100 Gy of radiation – double those used in the ECOG trial cited above – and were delivered in combination with gemcitabine. The result was disease control (ie: a complete or partial response) in 82% of patients. Median Progression-Free Survival of 121 days represented a 71% improvement over gemcitabine alone (ie: 4.0 months versus 2.3 months[32], a gain of 1.7 months) while median Overall Survival of 309 days was 80% better (ie: 10.2 months, versus the expected 5.7 months for gemcitabine, a 4.5 month gain). This data, which clearly warranted further clinical work, was presented at the ASCO-GI meeting in January 2008[33].
  - A six-patient Phase IIb dose-escalation study, again conducted with gemcitabine, commenced in July 2008 to find the optimal dose of radiation. This study showed that 400 Gy, four times the dose from Phase IIb, was optimal, with a disease control rate of 100%[34].

OncoSil delivered twice the radiation of previous chemoradiotherapy strategies

- **OncoSil's brachytherapy was probably synergistic with chemotherapy**. While there is no hard data on this from OncoSil, it's reasonable to suggest that in the two studies the gemcitabine was softening up the cancers so that radiation could work more effectively:
  - Gemcitabine has long been known *in vitro* as one of the more potent radiosensitisers[35]
  - This radiosensitising effect has been shown *in vivo* to be enhanced by fixed-dose-rate infusion rather than bolus delivery of gemcitabine[36]
  - The pre-clinical evidence on combining gemcitabine and radioimmunotherapy is encouraging[37]
  - The ECOG findings cited above have borne out earlier evidence from other, smaller clinical studies[38].
- **OncoSil was also able to reduce abdominal pain in pancreatic cancer**. Probably 40-50% of all pancreatic cancer patients experience severe abdominal pain[39] due to the pancreas lying in an area of the abdomen crisscrossed with nerves and wedged up against various other organs. Oncologists have long known that external radiation can bring about pain relief in pancreatic cancer[40], and OncoSil's investigators observed average pain

[30] See pSivida's market releases of 11 September 2003 and 6 April 2004. The *in vivo* studies were published in 2005 – see Zhang et. al., op. cit. These studies, established, in porcine models, that the BioSilicon beads would stay in place.
[31] See pSivida's market releases of 7 October 2004, 15 February 2005 and 21 June 2005.
[32] See Burris et. al., op. cit.
[33] Source: pSiVida market release dated 29/1/2008. ASCO-GI is a meeting of the American Society of Clinical Oncology focused on gastrointestinal cancers, taking place every January. At the time of the Phase IIa data pSivida stock was capitalised at A$66m.
[34] Source: pSiVida market release dated 22/10/2009.
[35] See Invest New Drugs. 1996;14(3):257-63 and Cancer. 2002 Aug 15;95(4 Suppl):933-40.
[36] See Transl Oncol. 2008 Mar;1(1):44-9.
[37] See Int J Cancer. 2002 Jan 20;97(3):386-92.
[38] See, for example, Clin Cancer Res. 2001 Aug;7(8):2246-53, where 30 Gy were used, and J Clin Oncol. 2008 Feb 20;26(6):942-7, where 36 Gy were used.
[39] See J Clin Oncol. 1992 Jan;10(1):149-55.
[40] See J Pain Symptom Manage. 1988 Fall;3(4):199-205.

reduction in the Phase IIa study of 35%. OncoSil believes that pain reduction, as measured by an easy-to-administer questionnaire such as the Brief Pain Inventory, would be an approvable endpoint for its device, since it would reduce the use of potentially dangerous opioid drugs in pain management[41], as well as improve Quality of Life in what is a relatively short life expectancy. In the upcoming pivotal study a reduction in pain will represent a secondary endpoint in the trial, but OncoSil believes that pain reduction data could be used in the design of a second pivotal trial in the event that Overall Survival in the current pivotal doesn't come in with a statistically significant improvement.

- **OncoSil won't be the first brachytherapy to be studied in pancreatic cancer, but it will be the first to go to a pivotal trial**. Doctors have been trying brachytherapy of radioactive particles in pancreatic cancer for some time now. Back in 2006 doctors at Sheng Jing Hospital in the Chinese city of Shenyang gained 10.6 months median survival using iodine-125 seeds implanted as a monotherapy[42] however the addition of gemcitabine to the therapy in a subsequent trial didn't seem to work, bringing survival back to 9.0 months[43]. We believe the issue was not enough I-125 seeds staying in place. What the Sheng Jing studies clearly showed however, is serious reduction in pain scores; and this bodes well for OncoSil as it moves into its pivotal study.
- **The regulatory pathway for OncoSil is reasonably straightforward**. OncoSil's brachytherapy is regarded by regulators as a 'Class III' medical device rather than a drug with potential to enter systemic circulation. This means that for FDA approval, a single pivotal trial is probably all that is required, while the Phase IIa data is sufficient for the company to move to CE Marking. Late in 2013, OncoSil decided that it would go for PMA approval in the US rather than the less onerous 510(k).
- **OncoSil's pivotal study has good prospects**. OncoSil is currently preparing its IDE submission[44] for a 150-patient controlled study in locally advanced as well as metastatic pancreatic cancer patients, where the tumour is not amenable to surgical resection[45]. The patients will randomise 2:1 to OncoSil plus gemcitabine/Abraxane versus gemcitabine/Abraxane alone[46]. The OncoSil patients will receive a single intra-tumoural implantation dosing to 400 Gy and the study will measure Overall Survival as a primary endpoint and PFS and Quality of Life as secondary endpoints. This study is now getting underway, initially in sites outside the US, and will likely conclude in 2016, with interim analyses planned[47]. This sets OncoSil on track for FDA approval in 2017. There is the risk that there will be too few patients to recruit quickly, however we expect that the Phase II data can attract sites into the trial. OncoSil believes the study is powered to show statistical significance on a >30% improvement in Overall Survival (ie: 2.6 months, from the 8.5 months of gemcitabine+Abraxane alone to 11.1 months with OncoSil) as well as lowered pain scores, two potentially registrable endpoints. We believe this expectation is reasonable, since:
  - Like gemcitabine, Abraxane is known to be a radiosensitiser[48], suggesting the synergism noted with gemcitabine can be continued with this drug;
  - The delivery system – ie: in 'sticky' silicon - suggests a better way to site radioactivity in a tumour than straight-out radioactive beads; and
  - 400 Gy, which as we noted is tolerated by patients, is a powerful radiation dose.
- **There is potential for OncoSil's brachytherapy to be useful in other cancers** since the stickiness of the silicon makes them relatively easy to implant in any solid tumour. Consequently if the pancreatic cancer pivotal study works, we expect the market will value OncoSil for more than just this indication.
- **Are there future therapies that could displace OncoSil's brachytherapy?** We expect that other drugs will be able to build on Abraxane's success and further enhance survival. We also expect good things from immunotherapy in this space. However we expect that OncoSil will be able to take advantage of its data and build a sizeable business before any of these prospects becomes a clear threat to OncoSil.

Incyte's Jakafi may be the next drug to put the spotlight on pancreatic cancer

[41] That pancreatic cancer pain is difficult to control is suggested by a randomised control study showing that oxycodone doesn't work any better than morphine in this setting – see Clin J Pain. 2010 Nov-Dec;26(9):794-7.
[42] See Endoscopy. 2006 Apr;38(4):399-403.
[43] See Endoscopy. 2008 Apr;40(4):314-20. Epub 2008 Feb 19.
[44] We understand a meeting was held with the FDA after Phase II trials several years ago in which the Agency gave pSivida some guidance on the path to approval for BrachySil. Material from this meeting is now being used in the trial design and IDE submission.
[45] We understand that for metastatic patients there can be no more than three lesions in either the lung or liver, with maximum lesion size 5 cm.
[46] OncoSil envisages around 20 trial sites globally - in Australia, the US, Singapore and Europe.
[47] OncoSil will conduct interim analyses once 30 patients are recruited, as well as at the six and twelve month milestones after commencement of the study. A 15% or greater improvement in PFS for the OncoSil patients would support study continuation.
[48] See Clin Cancer Res. 2007 Mar 15;13(6):1868-74.

- Probably the next drug to watch in pancreatic cancer is a twice daily pill called Jakafi[49], now a US$400m drug for Novartis and the American drug developer, Incyte (see Appendix III). Jakafi is notable as the first approved drug to target the JAK kinases, part of the signalling pathways known to go wrong in cancers and inflammation. Jakafi plus the Roche drug Xeloda[50] has shown promise in refractory metastatic pancreatic cancer. Phase II data in August 2013 showed that 42% of patients prospectively identified as most likely to benefit from JAK pathway inhibition lived longer than six months, versus only 11% for placebo;
- Cancer immunotherapy will be an area to watch given its progress in recent years. Ralph Steinman (1943-2011), the Canadian immunologist who was a co-recipient of the 2011 Nobel Prize in Physiology or Medicine for his 1973 discovery of the dendritic cell, lived a remarkable 4.5 years after his pancreatic cancer diagnosis in part because of the dendritic cell therapy he devised in his Rockefeller University lab and then tried on himself. He died just before the Nobel Prize was awarded[51]. Companies working on immune-based approaches to pancreatic cancer include Aduro BioTech[52] and Globeimmune[53] from the US, Ganymed Pharmaceuticals[54] and Isarna Therapeutics[55] from Germany, and Norway's Targovax[56].

OncoSil will address a large market opportunity in pancreatic cancer

- **Pancreatic cancer is an 'orphan' disease**. In the US an Orphan Drug, as per the Orphan Drug Act of 1983, is one that treats a disease affecting < 200,000 Americans pa. This roughly equates to one-in-1,600 people. The comparable figures in the EU would be <250,000 patients or one-in-2,000. OncoSil doesn't have an Orphan Drug since devices don't fit in that category. However we think the company will benefit from a recent trend in which drug and medical device players have focused more on orphan diseases, where reimbursement prospects are often better than would be the case with mainstream products[57].
- **Even $12,000 per patient has potential to be cost-effective**. OncoSil has talked about a pricing of ~US$15,000 per dose for its brachytherapy[58], which would be roughly comparable with SIR-Spheres. There is debate in US healthcare circles as to where the cut-off should be in terms of cost effectiveness. Traditionally it was US$50,000 per Quality-Adjusted Life Year[59]. These days it is US$100,000[60]. A two month survival advantage priced at US$12,000 – and we believe there will be more survival than just two months - would suggest a cost effectiveness of US$100,000 per QALY for OncoSil[61].
- **For a new company, the market is large even with small patient numbers.** ~46,000 patients at US$12,000 per patient results in a US$550m opportunity for the US alone, while the comparable European figure is more like US$1.02bn (ie ~85,000 patients at US$12,000). OncoSil is arguing that perhaps only 15% of First World patients would represent its addressable market. However, as we show later in this note, this opportunity still provides a lot of upside.

The US market for OncoSil is worth > US$500m

- **We believe that OncoSil can control its own sales destiny**, growing usage of its brachytherapy through its own sales force, as Sirtex has done with SIR-Spheres. This would further enhance the company's long-run profitability.

[49] Generic name ruxolitinib, see www.jakafi.com.
[50] Generic name capecitabine, see www.xeloda.com. Xeloda, a prodrug of 5-FU, was a US$1.6bn drug for Roche in 2013.
[51] For Steinman's story see *Is the Cure for Cancer Inside You?* by Daniel Engber, New York Times, 21/12/2012.
[52] Berkeley, Ca., privately held, www.adurobiotech.com. This company is working on a number of cancer vaccine approaches, including GVAX (irradiated tumour cell lines engineered to recruit immune cells by expressing GM-CSF) and Listeria (live attenuated Listeria bacterium engineered to express tumour-specific proteins). In January 2014 Aduro announced results from a Phase II trial in metastatic pancreatic cancer patients showing that a GVAX and a Listeria vaccine together could enhance survival outcomes.
[53] Louisville, Co., privately held, www.globeimmune.com. This company's cancer vaccine uses yeast as the vector to deliver the cancer-specific target to the dendritic cells. In 2012 Globeimmune reported that its GI-4000 vaccine, in combination with gemcitabine, improved Overall Survival by 2.6 months in Ras-mutation positive pancreatic cancer patients.
[54] Mainz, Germany, privately held, www.ganymed-pharmaceuticals.de. This company specialises in antibodies for targets specific to cancer cells. The company's IMAB362 antibody, now in Phase II in gastroesophageal cancer, has been granted Orphan Drug status in pancreatic cancer. The drug targets CLDN18.2, expressed in ~60% of all pancreatic cancers
[55] Munich, Germany, privately held, www.isarna-therapeutics.com. This company is working on inhibitors to the cytokine TGF-B as a way to restore cancer immunovigilance. Trabedersen, an antisense molecule targeting TGF-B2, has been granted Orphan Drug status in pancreatic cancer.
[56] Oslo, Norway, privately held, www.targovax.com. This company has developed a peptide vaccine called TG-01 for Ras-positive pancreatic cancer. TG01 is now in Phase I/II in surgically resected pancreatic cancer patients.
[57] Basically because orphan diseases often have few or no treatment alternatives, making what therapies there are cost effective by definition, and also because high prices for small patient populations are less noticeable in the contact of the larger healthcare system.
[58] See the company's 25/2/2014 presentation, slide 9.
[59] See Expert Rev Pharmacoecon Outcomes Res. 2008 Apr;8(2):165-78.
[60] The US$50,000 cost per QALY was first discussed around 1992. Typical US consumer prices for medical care have risen 2.2 times since then (source: US Bureau of Labor Statistics). Consequently an appropriate cost per QALY today would be more like US$111,000.
[61] Estimated with a 0.7 utility, derived from a survey of medical oncologists in Canada related to various pancreatic cancer therapies - see Cancer. 2012 Feb 15;118(4):1119-29. Epub 2011 Jul 19.

OncoSil is working towards European approval this year

- **>80,000 people in the EU will be diagnosed with pancreatic cancer this year**. In the 28 countries of the EU the incidence rate for pancreatic cancer is around 15% higher than the US, at ~16.1 per 100,000 in 2012[62], with Germany and Italy representing the two large markets with higher than average incidence. Indeed, at 20.2 per 100,000, Germany has one of the highest pancreatic cancer incidence rates in the world. The EU as a whole represents a patient population around 85% higher than the US, at ~81,000 patients in 2012 and perhaps 85,000 this year.
- **OncoSil believes that its data will be sufficient for European approval**. As a general rule developers of drugs and medical devices find it easier to gain approval in Europe than to have the product reimbursed, while in the US the opposite is true. OncoSil has had guidance from its Notified Body that the data from the Phase IIa and IIb studies is sufficient for approval, and will look to file for CE Mark this year. We do not expect that OncoSil will necessarily build a big business in Europe ahead of US approval, but rather will see CE Mark as adding to its credibility.
- **Reimbursement will be an issue, but one that can ultimately be overcome**. Obviously most EU member states are suffering budget constraints that hamper the ability of governments to fund new therapies. However we think the fact that the NHS reimburses SIR-Spheres in the UK suggests that the health economics of brachytherapy stack up, and that good data can ultimately prevail with payors, even in a climate of austerity.

OncoSil's COGS for its brachytherapy are likely to be favourable

Germany's Eckert & Ziegler is working on manufacture of OncoSil

- **OncoSil knows how to manufacture its brachytherapy.** With pSivida having worked on the product since the early 2000s, OncoSil inherited a large body of knowledge on how to make ^{32}P BioSilicon beads. The process is relatively straightforward – mix silicon and phosphorus at 1,480 degrees Celsius, atomise the mixture with water to create silicon/phosphorus microparticles, grade the particles to 30 microns, make them porous through acid etching, and then render the phosphorus radioactive in a high neutron reactor. In July 2013, OncoSil established a 'global strategic manufacturing alliance' with Eckert & Ziegler[63], a German maker of isotope technology components; and the two companies are currently validating the manufacturing process, ahead of E&Z manufacturing product for the ONC-301 study. OncoSil will use the study to test the feasibility of device supply logistics, where the 32P particles are manufactured on demand, then packaged and shipped in lead-covered Perspex containers to the hospital for reconstitution by the local hospital pharmacist.
- **We expect high gross margins.** Sirtex currently enjoys >80% gross margins on its SIR-Spheres[64]. We believe that OncoSil can move towards similar cost of goods with its brachytherapy once the technology has transitioned into clinical use.
- **OncoSil is working on a Next Generation product called 'OncoCal'**, so-called because it replaces silicon with calcium as the delivery material for ^{32}P. OncoCal, which was unveiled by OncoSil in February 2014, was invented by OncoCil's current Chief Scientific Officer, Dr Peter Knox, before he joined the company; and the relevant intellectual property was acquired by OncoSil[65]. OncoCal works by reacting with interstitial fluid to form an insoluble salt, which ensures that the ^{32}P remains where it is placed at the time of injection. A major benefit of OncoCal is that it replaces the royalty which OncoSil currently has to pay to pSivida as the licensor of the technology. OncoSil believes that OncoCal can bring about a cost reduction of as much as 75% in terms of cost of goods and nuclear reactor time. Another benefit will be the ability to gain 510(k) approval for the new OncoCal products.

[62] Presumably because of higher risk factors such as smoking and alcohol consumption. Incidence estimates come from Globocan 2012 data. Interestingly, for the globe as a whole the incidence rate is around 4.8 per 100,000, pancreatic cancer being primarily a disease of the First World. 4.8 per 100,000 suggests ~340,000 patients worldwide.
[63] Berlin, Germany, Xetra: EUZ, www.ezag.com.
[64] The average since the December 2011 half has been 82%.
[65] See WO/2012/143713, expiring April 2033. This patent application was vended into Enigma Therapeutics in 2012.

Sirtex has laid the groundwork for OncoSil

- **Sirtex has been a great brachytherapy success story**. Sirtex Medical is a Sydney-based company which gained FDA and CE Mark approval in 2002 for a brachytherapy product called SIR-Spheres, for the treatment of both primary and secondary liver cancer. The company has enjoyed considerable growth over the last decade, with SIR-Spheres dose sales increasing from around 500 in FY03 to 7,300 in FY13, and revenue growing A$9.5m in FY03 to A$96.8m in FY13. Driving this expansion has been:
  - **Evidence of favourable patient outcomes** - A patient with metastatic colorectal cancer (mCRC) where the tumour has metastasised to the liver can expect to live around 26 months if he or she receives FOLFOX plus Avastin[66]. FOLFOX without Avastin is probably good for 20 months of overall survival[67]. By contrast SIR-Spheres with FOLFOX has been shown to achieve overall survival in the order of 30-38 months, albeit in small studies[68]
  - **Evidence of cost effectiveness** - At ~US$14,000 per dose, all the evidence suggests that SIR-Spheres represent a highly cost effective treatment option for liver cancer.
  - **A sales force increasing reaching more oncologists**. SIR-Spheres are now administered to +750 hospitals worldwide, as against ~600 just two years ago.
- **Sirtex believes that market penetration for its product is only around 1%.** There is a simple reason for this. Up until now, all the clinical studies on SIR-Spheres, including those that allowed marketing approval to be obtained, were only conducted with 50 patients or less. Without large studies that recruit hundreds of patients, the product can't 'mainstream' and move from 'salvage therapy' (as it stands at present) to a first line treatment, which is where Sirtex would like it to go. Sirtex is now rectifying this situation with five large studies ongoing. The first of these, called SIRFLOX, reads out data in 2015[69]. We think that this, and subsequent studies will lay the groundwork for a step-change in SIR-Spheres usage.
- **The market is now starting to capitalise Sirtex's growing user base.** In late November 2011 Sirtex was briefly capitalised at just A$229m. It has since grown to A$850-900m as the market has started to factor in continued growth in usage as well as step-change from SIRFLOX and other studies. The growing investor recognition of Sirtex in Australia bodes well for OncoSil's reception as it moves into its pivotal.

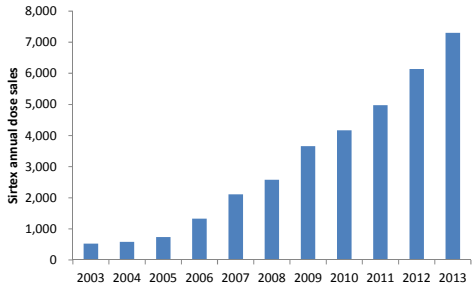
Sirtex is now capitalised at >A$800m

- **Sirtex's commercial success lays the groundwork for OncoSil, by helping to 'mainstream' brachytherapy**. Sirtex didn't invent brachytherapy. Various physicians experimented with it since shortly after the discovery of radioactivity in 1896[70], most notably the English surgeon, Sir Geoffrey Keynes[71] who tried it out in breast cancer in the late 1920s. However, brachytherapy only started to attract widespread attention in the 1990s when imaging technologies became good enough to properly site and dose brachytherapy seeds at the site of tumours. Sirtex, the first major company in the world to have been built around a brachytherapy product, was able to take advantage of this trend when it developed SIR-Spheres in the late 1990s. It is now helping to 'mainstream' brachytherapy and overcome the traditional gap in which medical oncologists have to refer their patients to an interventional radiologist, something that is harder than just prescribing drugs in terms of the bureaucracy involved. We see OncoSil as being well placed to benefit from the mainstreaming of brachytherapy when it launches in the US around 2017.
- **There are three main differences between SIR-Spheres and OncoSil's brachytherapy product**, namely
  - **Half-life** – The Yttrium 90 isotopes in SIR-Spheres have a half-life of 64 hours versus ^{32}P's half-life of 14.3 days;
  - **Radiation dose** – The clinical data has suggested that OncoSil's brachytherapy is safe and effective at a 400 Gy dose. By contrast SIR-Spheres are only designed to deliver around 120-130 Gy[72];

[66] See Ann Oncol. 2009 Nov;20(11):1842-7. Epub 2009 Apr 30. Foxfox is a chemotherapy regimen made up of folinic acid (FOL) plus 5-fluorouracil (F) and Oxaliplatin (OX).
[67] See J Clin Oncol. 2004 Jan 1;22(1):23-30. Epub 2003 Dec 9.
[68] See Kosmider et. al., J Vasc Interv Radiol. 2011 Jun;22(6):780-6 (19 patients). Epub 2011 Apr 22; and Tie et. al., Ann Oncol 2010; 21 (Suppl 8) (31 patients).
[69] Sirtex had been expecting late 2014 but the large volume of work related to crunching the SIRFLOX data has pushed out the data availability to 2015.
[70] By the Frenchman Henri Becquerel (1852-1908), Nobel laureate for physics in 1903.
[71] Brachytherapy. 2011 Sep-Oct;10(5):427-31. Epub 2011 Mar 11. Sir Geoffrey Keynes (1887-1982) was a younger brother of the economist Maynard Keynes. For a good account of Keynes' brachytherapy see *The Emperor of All Maladies: A Biography of Cancer* by Siddhartha Mukherjee (New York: Simon & Schuster, 2011).
[72] See Br J Cancer. 1994 November; 70(5): 994–999.

- **Indication** – SIR-Spheres are useful in liver cancer and have been tried with some success in pancreatic cancer liver metastases[73], but aren't considered useful in pancreatic cancer because they work by embolisation – embedding in the blood vessels that feed the tumours after being dosed into the hepatic artery – whereas OncoSil's ^{32}P beads are directly implanted at the site of the pancreatic tumour.
- **Intellectual property** – SIR-Spheres are primarily protected by trade secrets whereas OncoSil's product is protected by patents granted and pending.

FIG.7: SIRTEX HAS GROWN USAGE STRONGLY SINCE 2003



Source: Sirtex

FIG.8: SIRTEX STOCK HAS PERFORMED STRONGLY SINCE 2011

Source: ASX

[73] See Tumori. 2010 Nov-Dec;96(6):955-8.

Valuing OncoSil – How we get $0.45 per share

- **Our probability-weighted DCF of OncoSil was built as follows**:
  - Our WACC was 16.7% (appropriate in our view for a 'Speculative' risk rating[74]);
  - We assume a 50% probability of clinical success in the upcoming ONC-301 study;
  - We assume global launch of OncoSil in mid-2017;
  - We modelled revenue out to FY30 and then used FY31 as a terminal year. This is conservative since the OncoCal intellectual property provides coverage for the business out to ~2033;
  - We used a population model for pancreatic cancer using 27 First World jurisdictions in which the OncoSil brachytherapy is likely to be used in the future[75]. This model suggests around 164,000 new cases pa currently, rising to 253,000 by 2030. OncoSil has suggested, for conservatism's sake, take-up by only 15% of First World pancreatic cancer patients, the other 85% being either suitable for surgery or otherwise refusing treatment[76]. We assume that 15% of patients are eligible for surgery. That leaves 70% of patients that OncoSil can provide some benefit for, beginning with locally advanced patients and moving on to patients with metastatic disease, but that OncoSil doesn't think it can immediately address. We assume a gradual increase in OncoSil's total patient pool, to around ~17-18% of all new cases by 2030;
  - Our assumptions on pricing and patient numbers suggest peak sales of US$670m (base case) to US$1.16bn (optimistic case);
  - We assume that OncoSil initially sells at US$12,000 per dose (base case) to US$15,000 (optimistic case), with prices increasing 2-4% pa;
  - We assume 75-85% gross margins for OncoSil at launch, alongside SG&A expenses equal to 20-25% of sales. We assume both COGS and SG&A decline by 0.1%-0.2% of revenue annually;
  - We assume an 8% royalty to pSivida for the technology, which OncoSil ceases to pay after the fifth year post product launch due to the introduction of OncoCal; and
  - We assume negative terminal growth of 3-5% after 2030, which we think is conservative but allows for the risk of alternative brachytherapies that could reasonably emerge by this time.

We model peak sales for OncoSil of >US$1bn optimistic case

- **We assume a further A$10m capital raising** in order to fund the field force which would launch OncoSil globally around 2017.
- **OncoSil is undervalued on our numbers.** Our model result is a probability-weighted DCF valuation of $0.43 base case and $1.10 optimistic case. Our $0.45 target price sits at our base case.
- **We see a number of events helping to re-rate the stock towards $0.45:**
  - Filing for CE Mark approval and subsequent receipt of CE Mark;
  - First recruitment into the ONC-301 study;
  - Clearance of the IDE for ONC-301;
  - The first interim analysis from ONC-301;
  - Full patient accrual for ONC-301;
  - Granting of further patent protection over the OncoSil brachytherapy product;
  - Presentations of the OncoSil approach at various scientific meetings around the world.

[74] For a relevant discount rate, we use WACCs of between 12.3% and 16.7% depending on the risk for Life Science companies. This is derived from a RFR of 4.1%; a MRP of 7.5%-11.5% (7.5% for 'medium risk' companies, 9.5% for 'high risk' companies and 11.5% for 'speculative' companies like OncoSil); and an ungeared beta of 1.1 . We regard Life Science companies with existing businesses, or who have enough capital to reach the market with their products, as 'Medium' risk. Companies that have small revenue streams from marketed products but that are still potentially in need of capital are 'High' risk. Everything else is 'Speculative'.
[75] The countries were Australia, Austria, Belgium, Canada, the Czech Republic, Denmark, Finland, France, Germany, Hong Kong, Ireland, Israel, Italy, Japan, Korea, the Netherlands, New Zealand, Norway, Saudi Arabia, Singapore, Spain, Sweden, Switzerland, Taiwan, the United Arab Emirates, the UK and the US.
[76] See the company's 25/2/2014 presentation, slide 9.

Good leadership – The Prima band is back together

- Chairman, Martin Rogers came to OncoSil with a significant 'Life Sciences' success under his belt – the transformation of the cancer immunotherapy company, Prima Biomed[77] from near oblivion to its entry into Phase III in just four years. Rogers achieved this by acquiring the right people, and the right capital partners for that company's Cvac technology. As a result, Prima stock re-rated 19-fold between December 2007 and April 2011, creating a company with a market value of ~A$300m[78]. Prior to Prima, Rogers helped incubate technology for UNSW and gained valuable experience as an entrepreneur and investor.
- CEO, Dr Neil Frazer brings to OncoSil many years of experience conducting clinical studies of new drugs, which have led to product registrations in Europe and the US. At GSK, for example, programmes on which Frazer worked have yielded 10 FDA approvals. Frazer was Primo Biomed's Chief Medical Officer before joining OncoSil, and before this was CMO of antiviral drug developer, Chimerix[79].
- Non-Executive Director, Dr Roger Aston brings years of experience as a bio-entrepreneur with involvement in companies such as Peptech[80], Cambridge Antibody[81], Cambridge Drug Discovery[82], Clinuvel[83], pSivida, Halcygen[84] and Ascent Pharmaceuticals[85].
- Non-Executive Director, Lawrence Gozlan brings a track record of success as an analyst and fund manager participating in the growth of emerging Life Sciences companies.
- CSO, Dr Peter Knox brings strong knowledge of radiopharmaceuticals from his time as CSO of industry leader, Amersham[86]
- Head of European Operations, Dr Drew Ferguson has developed and launched products for companies such as Murex[87], Serono[88], MediSense[89] and Celsis[90].
- VP of Clinical Research, Natalie Ruffles brings experience managing clinical trials for the medical device major, Medtronic as well as various Contract Research Organisations.

Martin Rogers previously helped re-rate Prima Biomed

[77] Redwood City, Ca., Nasdaq: PMBD, www. primabiomed.com.au.
[78] From A$6.3m to A$314.6m. The stock has since eased back, and took a hit in September 2013 due to an interim analysis of Canvas, an ovarian cancer Phase III, that did not show clinical benefit to all comers but did show benefit to patients that had previously experienced two relapses.
[79] Now a >US600m company (Durham, NC, Nasdaq: CMRX, www.chimerix.com).
[80] An Australian antibody drug developer which as Arana was sold in 2009 to Cephalon for A$318m. Cephalon was bought by Teva in 2011.
[81] A UK antibody company bought by AstraZeneca for £702m in 2006.
[82] A UK developer of biological assay systems for drug discovery, CDD was bought in 2001 for £27.5m by BioFocus, which was in turn bought by Belgium's Galapagos in 2005.
[83] An Australian developer of dermatology drugs (Melbourne, , ASX: CUV, www.clinuvel.com).
[84] A developer of generic drugs which bought the oral pharmaceutical group of Mayne Pharma from Hospira in 2009 and changed its name to Mayne Pharma in 2010.
[85] An Australian generic drug company bought by Watson in 2012 for A$375m. Watson was bought by Actavis later that year.
[86] Bought by GE for US$9.5bn in 2004.
[87] A Canadian diagnostics developer bought by Abbott in 1998.
[88] A Swiss pharmaceutical company bought by Merck KGaA in 2006 for US$13bn.
[89] A maker of blood glucosde test kits bought by Abbott in 1996 for US$876m.
[90] A US developer of microbial detection systems.

The risks

- We see four major risks for OncoSil:
  - Delays or slowness in recruitment for the ONC-301 study – OncoSil are expecting the study to take about a year to recruit, and are arguing that it will benefit from the completion of earlier studies that had taken up a lot of patients;
  - Clinical risk for the ONC-301 study;
  - Lack of clinical acceptance for the brachytherapy product; and
  - Lack of reimbursement for the product.

Major shareholders

- Neil Frazer (7.6%).
- Webinvest (Otto Buttula) 5.5%. OttoButtula founded and built the online broker IWL, sold in 2007 to CBA for A$350m.

Appendix I – An OncoSil glossary

^{32}P – Radioactive phosphorus, where the nucleus contains 15 protons and 17 neutrons. ^{32}P has a half-life of 14.3 days. OncoSil delivers ^{32}P for localised radiotherapy. ^{32}P is a beta emitter. ^{32}P has been used in medicine since it was first synthesised in the 1930s.

510(k) – Regulatory approval for a medical device in the US where the device has been found to be functionally equivalent to one that was on the market before 1976.

5-fluorouracil (5-FU) – A systemic chemotherapy drug introduced by Roche in the late 1950s and sometimes used in treating pancreatic cancer. 5-FU is generally administered with leucovorin (LV). The drug works by blocking thymidylate synthetase, which interferes with DNA synthesis.

Adenocarcinoma – A cancer of the glandular tissues. Most exocrine tumours in pancreatic cancer are adenocarcinomas.

Beta radiation – Radiation is the stream of electrons given off by radioactive material. The three most important kinds of nuclear radiation are alpha, beta and gamma, with alpha having the shortest tissue penetration (only 0.1mm, unsuitable for radiation therapy) and gamma the longest. Radioactive substances like ^{32}P that produce only beta radiation are called beta emitters.

BrachySil – The old name for the OncoSil device.

Brachytherapy – Internal radiation treatment given by placing radioactive material at the site of the tumour.

Brief Pain Inventory – A short, self-administered questionnaire that evaluates the pain experience of cancer patients.

CE mark – European approval for a medical device.

Class III medical device – A medical device that involves significant risk to the patient and therefore warrants more scrutiny of the clinical and pre-clinical data. Class III is the highest of three classes in terms of the risks. Dental floss is Class I and a condom is Class II.

Cohort – A group of patients in a clinical trial with features in common such as dose.

Disease control rate – The percentage of patients with advanced or metastatic cancer who have achieved complete response (eradication of tumour), partial response (tumour reduction <=30%) or stable disease (no change in tumour size), as measured by the RECIST criteria.

Endoscopic ultrasound – The insertion of a probe into a hollow organ in order to obtain images of that organ.

Endpoint – The outcome, either primary of secondary, a clinical trial is designed to evaluate.

Erlotinib – A drug used as the 'last line' therapy in pancreatic cancer. The innovator brand is Roche's Tarceva. Erlotinib works by targeting the epidermal growth factor receptor (EGFR) tyrosine kinase.

Exocrine tumours – Pancreatic tumours of the exocrine glands, which secrete pancreatic enzymes into ducts.

External beam radiation therapy – Radiotherapy where the radiation source is outside the body.

FDA – The Food and Drug Administration, the American government agency which regulates drugs and medical devices.

Gemcitabine – A cancer drug often used to treat pancreatic cancer. The innovator brand was Eli Lilly's Gemzar. Gemcitabine is a nucleoside analogue which, by replacing cytidine during DNA replication, triggers cancer cell apoptosis (ie 'programmed' cell death).

Good Manufacturing Practice (GMP) – The set of standards laid down by regulators for the production of drugs and medical devices.

Gy – Short for 'Gray', Gy is the standard unit of absorbed ionising-radiation dose. The name comes from the British physicist L.H. Gray (1905-1965), who pioneered the field of radiobiology.

IDE – Short for Investigational Device Exemption, FDA approval of a medical device clinical trial.

Interim analysis – An analysis of clinical data before all the patients have been recruited in order to ascertain that the treatment is safe and (apparently) effective.

Intra-tumoral – A therapy placed within a tumour.

Isotope – Any of various forms of the same element that contain equal numbers of protons but different numbers of neutrons in their nuclei.

Leucovorin – A form of folic acid used in combination with 5-fluorouracil in order to restore red and white blood cell counts.

Line – The order in which a therapy is used, from 'first line' at the beginning of treatment down to 'last line' for patients at death's door.

Micron – One millionth of a metre.

Monotherapy – Treatment of a disease with a single drug rather than a drug combination.

Nab-paclitaxel – The cancer drug paclitaxel bound to albumin for better half-life in the bloodstream. Nab-paclitaxel is often used in pancreatic cancer treatment. The innovator brand is Celgene's Abraxane drug.

Neurodocrine tumours – Pancreatic tumours of the endocrine glands, which secrete hormones into the bloodstream.

Notified Body – An organisation accredited by an EU Member state to assess products for CE Marking.

OncoSil – A product that locally delivers ^{32}P for cancer treating using nano-engineered porous silicon.

Open-label – A clinical trial in which both patients and doctors know what treatment is being administered.

Paclitaxel – A chemotherapy drug obtained from the Pacific yew tree, *Taxus brevifolia*. Paclitaxel works by stabilising microtubules in their polymerised form, leading to cell death. The innovator brand was BMS's Taxol drug, FDA approved in 1992. Taxol had peak sales of US$1.6bn in 2000.

Pancreas – A gland organ located in the abdomen that produces various enzymes and hormones, including insulin.

Phase – A stage of the clinical trialling process for a drug candidate. Phase I tests for safety. Phase II tests for efficacy in a small sample (Phase IIa trials test primarily for safety while Phase IIb are more focused on efficacy). Phase III studies, also called pivotal studies, test for efficacy in a large sample.

Pivotal study – A large clinical trial intended for registration of a drug or medical device.

Overall Survival (OS) – The length of time a cancer patient can live after receiving treatment.

PMA – Short for Pre-Market Approval, FDA approval to market a drug or device for which there was no functional equivalent approved prior to 1976.

Progression Free Survival (PFS) – The length of time a cancer patient undergoing treatment can see no increase in tumour size.

Radiotherapy – Cancer treatment that attacks tumours using X-rays or similar forms of radiation.

RECIST – Short for the Response Evaluation Criteria in Solid Tumours, the rules that define when a tumour has responded to treatment, is stable, or has progressed. See Disease Control Rate.

Registration study – The final clinical study before marketing approval can be sought from the FDA and other bodies.

Resection – Surgical removal of a tumour.

Standard of care – The set of therapies that are generally regarded as the best treatment available for a particular disease conditions.

Whipple – The standard surgical procedure to treat pancreatic cancer. It is named for the American surgeon Allen Whipple (1881-1963), who first described it in the mid-1930s.

Appendix II – Failed pancreatic cancer studies

- **Avastin, June 2006**. This Roche anti-angiogenesis antibody[91], while it had succeeded in colorectal cancer in 2003 and went on to be a US$6.7bn drug in 2013, failed at Phase III in pancreatic cancer. Median overall survival was 5.8 months for gemcitabine/Avastin and 5.9 months for gemcitabine alone[92].
- **Erbitux, April 2007**. This BMS/Merck KGaA antibody drug[93] may have worked in colorectal cancer and went on to do US$1.9bn in 2013 net sales, but with gemcitabine in pancreatic cancer the 6.3 months median overall survival in Phase III didn't cut it against the 5.9 months for gemcitabine. This study had a p value of 0.23[94].
- **Inlyta, January 2009**. This Pfizer drug, a VEGF inhibitor[95] gained its first approval in renal cell carcinoma in 2012, and did US$319m in 2013 net sales. However prior to the renal cell success in had failed at Phase III in pancreatic cancer, recording 8.5 months median overall survival with gemcitabine versus 8.3 months for gemcitabine[96].
- **Zaltrap, September 2009**. This anti-VEGF drug[97], from Sanofi and Regeneron[98], managed 6.5 months of median survival with gemcitabine while gemcitabine alone got 7.8[99]. Zaltrap didn't gain its first FDA approval until 2012, in metastatic colorectal cancer. 2013 net sales were US$70m.
- **RP101, October 2009**. The Bay Area specialty pharma company, SciClone[100] discontinued work on this nucleoside analogue drug during Phase II on safety concerns. The early clinical data had shown one-year survival rate of 33% with gemcitabine[101].
- **TNFerade, March 2010**. This product, from GenVec[102], is an adenovector carrying the TNF-α gene. When combined, external beam radiation and 5-FU in Phase III, it did no better than chemoradiation alone, with median survival in both groups of 10 months[103].
- **Saridegib, January 2012**. This compound, from Boston's Infinity Pharmaceuticals[104], failed in a Phase II trial with gemcitabine in spite of evidence that the 'hedgehog' pathway which it targets is re-activated in pancreatic cancer.
- **Ganitumab, August 2012**. This Amgen/Takeda antibody, targeting the IGF-1 receptor, failed at Phase III in conjunction with gemcitabine in spite of encouraging Phase II data[105].
- **CP-4126, November 2012**. This fatty acid derivative of gemcitabine, from the Norwegian biotech, Clovis Oncology, failed to beat regular gemcitabine in Phase III even though it was designed for patients low in levels of hENT1, the dominant transporter for gemcitabine[106].
- **Nexavar, November 2013**. This kinase inhibitor drug[107] from Bayer and Onyx[108] may have worked in advanced renal cell carcinoma and hepatocellular carcinoma but it failed at Phase III in pancreatic cancer when tried with gemcitabine[109].
- **Rigosertib, December 2013**. This kinase inhibitor drug, from Philadelphia drug developer, Onconova Therapeutics[110] failed at Phase III with gemcitabine on an interim analysis in spite of demonstrated antitumor efficacy in patients[111]. Baxter had taken the European rights for rigosertib in September 2012 for US$50m upfront and US$515m in milestones. The indications licensed were myelodysplastic syndrome and pancreatic cancer.

[91] Generic name bevacizumab, see www.avastin.com.
[92] J Clin Oncol. 2010 Aug 1;28(22):3617-22. Epub 2010 Jul 6.
[93] Generic name Cetuximab, see www.erbitux.com.
[94] J Clin Oncol. 2010 Aug 1;28(22):3605-10. Epub 2010 Jul 6.
[95] Generic name Axitinib, see www.inlyta.com.
[96] See Lancet Oncol. 2011 Mar;12(3):256-62.
[97] Generic name Aflibercept, see www.zaltrap.com. Zaltrap is a VEGF trap.
[98] Tarrytown, NY, Nasdaq: REGN, www.regeneron.com.
[99] See Eur J Cancer. 2013 Aug;49(12):2633-42. Epub 2013 Apr 30.
[100] Foster City, Ca., SciClone Pharmaceuticals, www.sciclone.com.
[101] Anticancer Drugs. 2006 Oct;17(9):1045-56.
[102] Gaithersburg, Md,, Nasdaq: GNVC, www.genvec.com.
[103] See J Clin Oncol. 2013 Mar 1;31(7):886-94. Epub 2013 Jan 22.
[104] Cambridge, Ma., Nasdaq: INFI, www.infi.com.
[105] See Ann Oncol. 2012 Nov;23(11):2834-42. Epub 2012 Jun 13.
[106] J Clin Oncol. 2013 Dec 10;31(35):4453-61. Epub 2013 Nov 12.
[107] Generic name sorafenib, see www.nexavar.com.
[108] Which got bought by Amgen in mid-2013 for US$10bn primarily because of Nexavar.
[109] See Dig Liver Dis. 2014 Feb;46(2):182-6. Epub 2013 Nov 2.
[110] Newtown, Pa., Nasdaq:ONTX, www.onconova.com.
[111] See Clin Cancer Res. 2012 Apr 1;18(7):2048-55. Epub 2012 Feb 14.

Appendix III – Comparable companies

FIG.9: COMPANIES DEVELOPING PANCREATIC CANCER TREATMENTS

Incyte	Wilmington, De	Nasdaq: INCY	10,167	www.incyte.com	Jakafi
Halozyme Therapeutics	San Diego, Ca.	Nasdaq: HALO	1,637	www.halozyme.com	PEGPH20
OncoMed	Redwood City, Ca.	Nasdaq: OMED	926	www.oncomed.com	OMP-54F28
NewLink Genetics	Ames, Ia	Nasdaq: NLNK	859	www.linkp.com	Algenpantucel-L
Momenta Pharmaceuticals	Cambridge, Ma.	Nasdaq: MNTA	802	www.momentapharma.com	M402
Merrimack Pharmaceuticals	Cambridge, Ma.	Nasdaq: MACK	581	www.merrimackpharma.com	MM-398
Immunomedics	Morris Plains, NJ	Nasdaq: IMMU	380	www.immunomedics.com	Clivatuzumab Tetraxetan
Sorrento Therapeutics	San Diego, Ca.	Nasdaq: SRNE	305	www.sorrentotherapeutics.com	Cynviloq
Threshold Pharmaceuticals	South San Francisco, Ca.	Nasdaq: THLD	296	www.thresholdpharm.com	TH-302
Nuvilex	New York, NY	OTCBQ: NVLX	232	www.nuvilex.com	Live-cell encapsulated ifosfamide
CytRx	Los Angeles, Ca.	Nasdaq: CYTR	231	www.cytrx.com	Aldoxorubicin
Oncogenex	Bothell, Wa.	Nasdaq: OGXI	174	www.oncogenex.com	apatorsen
Celsion	Lawrenceville, NJ	Nasdaq: CLSN	67	www.celsion.com	ThermoDox
Sunshine Biopharma	Montreal, Qc	OTCBQ: SBFM	10	www.sunshinebiopharma.com	Adva-27a

Source: Company data

- **Celsion** is a liposomal drug delivery company. Liposomes are tiny bubbles of fatty acids. Celsion's Lysolipid Thermally Sensitive Liposome technology allows the targeted delivery of conventional chemotherapy drugs by encapsulating them in heat-sensitive liposomes; that is, liposomes that dissolve over a certain body temperature. The liposomes allow the chemotherapy to get inside tumours via the leaky blood vessels that feed those tumours, after which an external heating device allows drugs to be released into the tumour. Data released in January 2013 showed that Celsion's Phase III trial of ThermoDox, which is heat-activated liposomal delivery of doxorubicin, missed its primary endpoint of PFS in primary liver cancer. However the therapy may improve overall survival for some patients[112].
- **CytRx**. This company's lead product is aldoxorubicin, which is doxorubicin attached to the linker chemical EMCH for better targeting of the drug. Aldoxorubicin is now being prepared for a Phase III study in soft tissue sarcoma and is also in Phase II in glioblastoma and Kaposi's sarcoma. In soft tissue sarcoma at Phase IIb aldoxorubicin as a first-line therapy doubled median PFS, from 2.8 months to 5.7 months.
- **Halozyme Therapeutics**. This company's Enhanze drug delivery technology, based on the hyaluronidase enzyme which degrades hyaluronic acid in connective tissue, allows subcutaneous delivery of large molecule drugs such as antibodies as well as IVIG and insulin. Roche has gained EU approval for Enhanze-delivered Herceptin, while Baxter has gained EU approval for Enhanze-delivered IVIG. Halozyme has Phase I data showing that its hyaluronidase formulation, called PEGPH20, can improve the delivery of gemcitabine to tumours. PEGPH20 is now in Phase II[113].
- **Immunomedics**. This antibody drug developer's lead product is epratuzumab, now in Phase III for lupus and Phase II for lymphoma[114]. Clivatuzumab tetraxetan, an antibody attached to the radioactive isotope yttrium-90, is in Phase III for pancreatic cancer, while veltuzumab is in Phase II for Non-Hodgkin's Lymphoma[115]. At Phase Ib in relapsed pancreatic cancer, clivatuzumab tetraxetan with gemcitabine brought about 4 months of median PFS versus 2.8 months for gemcitabine alone (p=0.021).
- **Incyte**. This is the company which first developed Jakafi, the JAK kinase inhibitor that gained FDA approval in November 2011 for the treatment of the bone marrow disease myelofibrosis. Jakafi is currently in Phase III in polycythemia vera and in Phase II in pancreatic cancer, with favourable results to date (as we noted earlier in this report).
- **Merrimack Pharmaceuticals**. This company has used the tools of network biology to create new maps of various intracellular signal pathways, and used these maps to identify drug targets of interest. Merrimack's lead candidate, MM-121, is a HER2 antibody that has been partnered with Sanofi and is being trialled in breast and ovarian cancer as well as NSCLC. Outside network biology Merrimack is trialling MM-398, which is nanoliposomal irinotecan, in a Phase III study in metastatic pancreatic cancer where patients have failed gemcitabine. In a Phase II single-arm study median overall survival was 5.2 months.

[112] Namely, where there is a single liver cancer lesion that is also treated with Radio Frequency Ablation for more than 45 minutes. In Radio Frequency Ablation a needle electrode is inserted into a tumour, after which high-frequency electrical currents are passed through the electrode, creating heat that destroys the cancer cells.
[113] By degrading the hyaluronan protective matrix that often surrounds pancreatic tumours.
[114] USB have the global rights for all non-cancer indications for epratuzumab.
[115] Global rights for veltuzumab for all subcutaneous non-cancer indications are with Takeda. That company is in Phase II in Rheumatoid Arthritis and ITP.

- **Momenta Pharmaceuticals**. This company has been built on technologies to understand the structure and activity of complex molecules, allowing cheaper manufacturing processes to be developed. Momenta has a pipeline of complex generics and biosimilars (its first marketed product was a generic version of the Sanofi anticoagulant drug, Lovenox) as well as some novel products. The lead novel product is M402, a heparin sulphate mimetic with anti-cancer properties. The pre-clinical data in pancreatic cancer animal models is encouraging – the drugs seems to prevent the 'epithelial-to-mesenchymal transition' that creates cancer stem cells - and the drug is now in Phase I/II.
- **NewLink Genetics**. This cancer immunotherapy company takes tumour-specific cell lines and modifies them to express alpha-gal, the idea being that when the patient's immune system responds to the alpha-gal it will also learn to attack the tumour cells. Algenpantucel-L, built from the HAPa-1 and HAPa-2 pancreatic cancer cell lines, is in Phase III in resected and borderline resectable pancreatic cancer. Three year survival in resected patients at Phase II was 39%. The Phase III passed its first interim analysis in March 2014 without terminating, indicating that more patients are needed for statistical significance.
- **Nuvilex**. This company has been built on live-cell encapsulation technology, allowing cells of therapeutic value to be enclosed in a cellulose-based protective barrier so that they can be transplanted into patients and not be thrown out by the immune system of the recipient. Nuvilex uses this technology for targeted delivery of ifosfamide, a cancer prodrug that is activated by liver enzymes. Nuvilex has encapsulated a cell that produces the relevant enzyme, allowing it to be produced by the pancreas instead. The potential utility of this approach was demonstrated in a Phase I/II trial in advanced pancreatic cancer, which showed a doubling of one-year survival to 36%, versus 18% with gemcitabine.
- **OncoGenex**. This company works on drugs that overcome cancer treatment resistance, targeting proteins such as clusterin and HSP27. The anti-clusterin drug, custirsen, is in Phase III in prostate and NSCLC cancer, while apatorsen, targeting HSP27, is in various Phase II studies. Apatorsen has generated favourable pre-clinical data in pancreatic cancer and the drug went to Phase II in this indication in 2013.
- **OncoMed**. This cancer stem cell company, which has registered some serious partnering deals with GSK, Celgene and Bayer, is in early stage pancreatic cancer studies with its first three products - OMP-59R5 (GSK), demcizumab (Celgene) and vantictumab (Bayer). The data from these studies have been favourable.
- **Sorrento Therapeutics**. This company is mainly focused on antibody therapies, but it has as its lead compound, a new formulation of paclitaxel called Cynviloq. This product is similar to Abraxane in that, with Abraxane, paclitaxel is solubilised by being bound to albumin[116], whereas with Cynviloq paclitaxel is solubilised by being formulated in polymeric spheres called 'micelles'. Phase I work on Cynviloq with gemcitabine in pancreatic cancer has been promising. Cynviloq may be approvable using the FDA's 505(b)(2) route.
- **Sunshine Biopharma**. This company has been built on technology to strengthen the diester bonds in drug compounds, allowing stabler drugs with novel properties. Sunshine's Adva-27a drug, like irinotecan a topoisomerase inhibitor, has shown activity against various multidrug resistant cancer cells. Clinical work in pancreatic cancer is anticipated.
- **Threshold Pharmaceuticals**. This company's TH-302 drug has been designed to selectively activate in hypoxic conditions where cancer thrives but where conventional chemotherapy can be ineffective. Merck KGaA licensed the drug in February 2012 for US$25m upfront and US$525 in milestones. TH-302 is in Phase III in soft tissue sarcoma and in pancreatic cancer. At Phase II in pancreatic cancer the median PFS with gemcitabine was 5.6 months versus 3.6 months for gemcitabine alone.

[116] Since albumin is the body's natural carrier of molecules that are poorly soluble in water.

Appendix IV – A history of OncoSil's technology

OncoSil's enabling technology was developed as part of the UK's Defence R&D effort

- **OncoSil's enabling technology was originally developed by the UK taxpayer**. As we note in this report, OncoSil's brachytherapy originates from a technology called BioSilicon, a nano-engineered porous silicon which was created in 1996 as part of the British government's defence R&D effort, in the laboratory of Professor Leigh Canham at the Royal Signals and Radar Establishment in Malvern, Worcestershire. The technology was progressed from 2001 by pSivida, now a US developer of ophthalmic drug delivery systems[117].
- **What is BioSilicon?** BioSilicon is a porous silicon that is engineered by acid etching of the pure element. Canham's BioSilicon is so porous that a single cubic centimetre of the material can be engineered with a total surface area in excess of 500 square metres. Combined with silicon's natural biodegradability and biocompatibility[118], this make BioSilicon a potentially great scaffold for localised drug delivery and brachytherapy[119], and the Canham team used it early in the 2000s to design the ^{32}P-carrying brachytherapy product which OncoSil is now taking forward.
- **pSivida became the main commercial proponent of BioSilicon in 2000/01**, when a new company called pSiMedica was formed by DERA, the UK Government's Defence Evaluation and Research Agency (DERA)[120], in order to commercialise the medical uses of BioSilicon. pSimedica got a royalty-free, global exclusive licence from DERA to develop BioSilicon applications in human and animal healthcare. pSivida, then based in Perth and an ASX-listed Life Sciences company from mid-2001, became part of an investor group that funded pSiMedica. By early 2004, pSivida owned 40% of pSiMedica and in mid- 2004 it went up to 100% in a transaction that valued pSimedica at US$75m[121].
- **BioSilicon was pSivida's main technology from 2001 to 2005.** During this period the company mainly focused on the ^{32}P-based brachytherapy, which it called 'BrachySil'. However pSivida also initiated various collaborations and did internal work on BioSilicon applications in orthopaedics, drug delivery, wound healing, tissue engineering, diagnostics and food. However no products ever emerged from these collaborations. In 2005, pSivida acquired another company called Controlled Delivery Systems, a US specialist in controlled release technologies for ophthalmic drugs. The projects that came with Controlled Delivery Systems became the main focus of pSivida, but the Global Financial Crisis limited the amount of capital that could be devoted to BioSilicon and to BrachySil after the Phase II pancreatic cancer results came in.
- **pSivida continues to develop BioSilicon**, which it now calls Tethadur. The company believes that fully bioerodible Tethadur implants can be used to deliver therapeutic proteins useful in ophthalmology[122], and has generated proof of concept in animal models showing that Tethadur can improve the release profile of the cancer antibody, Avastin[123]. In July 2012, pSivida announced that a 'leading global biopharmaceutical company' was evaluating Tethadur for the delivery of large molecule ophthalmology drugs.
- **The OncoSil brachytherapy came to OncoSil Medical via Enigma Therapeutics.** In 2012 the English bio-entrepreneur Dr Roger Aston, together with Peter Knox and Drew Ferguson, founded Enigma Therapeutics[124] in order to take an exclusive global licence to the brachytherapy applications of BioSilicon[125]. Aston had a long history with pSivida, having helped put together pSiMedica back in 2000. Enigma Therapeutics was back-doored into Neurodiscovery, formerly an ASX-listed developer of CNS drugs, in 2013 (for 75 million shares), with Neurodiscovery changing its name in May 2013 to OncoSil.

[117] Watertown, Ma., Nasdaq: PSDV and ASX:PVA, www.psivida.com.
[118] It dissolves to yield harmless silicic acid as the sole degradation product.
[119] There are, however, numerous other uses of BioSilicon, including as a scaffold for tissue engineering, in skin care, in medical diagnostics, in food and in personal care products.
[120] At the time DERA was the UK's largest science and technology organisation, with a proud history of invention that included liquid crystal displays, carbon fibre, flat panel speakers, infrared sensors and radar. In 2001 DERA was split into QinetiQ, a commercial firm (www.qinetiq.com), and the Defence Science and Technology Laboratory (www.dstl.gov.uk), which remained focused on military R&D.
[121] At the time pSivida owned 46.26% of pSimedica (see pSivida's 3/10/2003 market release) and acquired the rest of the company for A$57.8m in cash and stock. The AUD/USD exchange rate at the time was 0.696.
[122] See, for example, Biomaterials. 2009 May;30(15):2873-80. Epub 2009 Feb 28.
[123] See the presentation entitled 'Drug Delivery and Nanostructuring: Divergent Effects', presented by pSivida's Dr Hong Guo at the 10th Annual NanoBusiness Conference in Boston in September 2011.
[124] Possibly Aston et. al. regarded pSivida's neglected, albeit clinically relevant, brachytherapy the way Winston Churchill regarded Russia: 'It is a riddle, wrapped in a mystery, inside an enigma'.
[125] Specifically, Enigma licensed WO/2002/067998 and WO/2005/066073 and the relevant national phase granted and pending patents. WO/2002/067998, expiring Feb 2022, covers the use of BioSilicon in cancer therapy, either through delivery of cancer drugs or radionuclides like ^{32}P. It has been granted as US Patent 8,097,236 (January 2012) and US Patent 8,647,603 (February 2014). WO/2005/066073, expiring Dec 2025, covers the combination of BioSilicon with phosphorus in order to create a ^{32}P delivery vehicle. It has been granted in Europe as EP 1 704 118 (April 2012) and as US Patent 8,293,630 (October 2012).

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